International Society for VACCINES

2024

ISV ANNUAL CONGRESS

21-23 October 2024

SEOUL, SOUTH KOREA

https://isv-online.org/

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Dear Vaccinologists,

Welcome to Seoul and the 2024 ISV Annual Congress! On behalf of the International Society for Vaccines (ISV), the Scientific Committee, and our partners, donors, sponsors, we are pleased by your attendance and enthusiastic engagement.

ISV members come from the diverse fields related to vaccines and from the spectrum of institutions around the globe. The Annual Congress is the world's largest non-profit conference dedicated to all aspects of vaccines providing opportunities to present and learn the latest developments of the many disciplines of vaccine R&D, regulation, deployment, and access. The Congress is designed to both have high profile speakers present, while also providing the opportunity for many attendees to present their work both as talks and posters, increasing your visibility and opportunities for establishing collaborations.

Thanks to the generous support of the US NIH, the Gates Foundation, the International Veterinary Vaccinology Network (IVVN), the many public and private sponsors, and personal donations from ISV board members and participants, the ISV Congress provides an unusually large number of scholarships and grants to enable scientists from LMICs and early career stages to attend, both in person and virtually. The ISV Congress also has a special emphasis on supporting and developing the careers of trainees and Early Career Researchers with special sessions and prizes awarded to them.

ISV is dedicated to increasing interactions, collaborations, and mentorship for scientists globally. Sessions are designed to facilitate networking to foster collaborations. While the Congress has all speakers in person, it is also a hybrid meeting to enable people to view the lectures remotely, and even providing scholarships for remote attendees from LMICs. Throughout the year, ISV also has a virtual lecture series, with participants able to both ask questions live, during the presentation, and able to view the lectures at their convenience on the ISV YouTube channel. https://www.youtube.com/@internationalsocietyforvac7634

Huge thanks are due to the ISV Officers, Board Members, and Scientific Committee Members for their year-round dedication to the preparation of the Congress. We are indebted to the Scientific Committee members who provided ideas for sessions and speakers in addition to spending so much time reviewing the record number of abstracts and award applications. The Congress and ISV's year-round activities would not be possible without the heroic dedication of Edward (Ted) Gibson from the ISV Congress Secretariat as well as Anna Taliadoros who has likewise enabled all of ISV activities.

We particularly thank the International Vaccine Institute (IVI) for the assistance in securing the venue and in facilitating visas for attendees. Please attend the ISV Annual General Meeting, 2 p.m. Tuesday in Hanra 1. Everyone is welcome to both attend and to participate in the various ISV activities- a great way to increase your impact and visibility.

More satellite activities have been added to this year's congress: a China Day mini symposium (3F Shilla 1+2) in the afternoon of Oct. 20 to introduce vaccine landscape in China and a half-day tour to IVI the morning of Oct. 24.

With all best wishes for a productive and enjoyable time at the ISV Congress and in Seoul.

2024 Congress Co-Chairs

Joon Haeng Rhee, Chonnam National University Medical School, South Korea
Margaret Liu, ProTherImmune, USA, and Karolinska Institutet, Sweden
Shan Lu, University of Massachusetts, USA
Ken Ishii, University of Tokyo, Japan
Jerome Kim, International Vaccine Institute, South Korea

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2024 CONGRESS CO-CHAIRS

Joon Haeng Rhee
Chonnam National University Medical School, South Korea

Margaret Liu
ProTherImmune, USA
Karolinska Institutet, Sweden

Shan Lu
UMASS Chan Medical School, USA

Ken Ishii
University of Tokyo, Japan

Jerome Kim
IVI , South Korea

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WEBSITES

Conference Website: https://isv-online.org/congress/

ISV Congress Virtual Platform: https://2024isvannualcongress.vfairs.com
Enter email you used to register

ISV LinkedIn: https://www.linkedin.com/company/international-society-for-vaccines/posts/?feedView=all

ISV YouTube: https://www.youtube.com/channel/UC9_-f8tDAqOmVEZWqGeuFo

Contact: info@isv-online.org
info@isvcongress.org

RECOGNITION FOR EXTERNAL FINANCIAL SUPPORT TO THE ISV

ISV acknowledges the following partners, companies, donors, foundations, and supporters for their generous contribution to the Society's mission to engage, support, and sustain the professional goals of a diverse membership in all areas relevant to vaccines and immunotherapeutics. Funds are used to support the Society's initiatives of scientific information exchange, education, mentorship, networking and collaboration directed through the activities of the ISV Board Committees on Awards & Prizes, Education & Mentorship, Global Equity & Engagement, Outreach & Public Engagement, and Vaccine Industry Interactions.

PARTNERS:
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IBS Korea Virus Research Institute
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US FEDERAL INSTITUTE SUPPORT:

Funding for this conference was made possible [in part] by **1R13AI186468-01** from the **National Institute of Allergy and Infectious Diseases**. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

Information

REGISTRATION DESK

The ISV Registration/Information desk is located in the Hanra Foyer and will remain open throughout the conference and staffed during the following times:

- Monday 21 October 07:30-20:00
- Tuesday 22 October 07:30-17:30
- Wednesday 23 October 07:30-17:00

BADGES

For security reasons, please wear your conference name badge at all times. Replacements for lost badges are available from the registration desk.

DELEGATE BOOKS

Please write your name in your delegate book; if misplaced, we'd like to ensure that yours can be returned.

ORAL ABSTRACT PRESENTATION INSTRUCTIONS

Oral presentations are allocated a total of 15 minutes, including time for questions, so please keep the actual talk to 10-12 minutes.

Bright Sparks presentations are a total of 10 minutes, so aim for 8 minutes to present. Chairpersons will eliminate questions for speakers whose talks run the maximum minutes.

All presenters: At least 2 hours prior to your presentation, please take your presentation on a USB flash drive directly to the registration desk. Staff will direct you to the VIP Room where the A/V technicians will load your presentation, and you will be able to make any last minute edits if needed. ISV staff will be available if you have any questions with the process.

POSTER SESSION INSTRUCTIONS

Poster presenters are asked to set up posters anytime between 08:00-10:00 on Monday, 21 October prior to the start of the opening remarks. If this is not possible, presenters may do so during the coffee breaks.

Poster stands will be set in the Shilla 1-5 rooms with poster numbers posted on each stand. Please refer to the poster index of this program book to check poster designation numbers. Supplies to attach posters to boards are provided.

The dedicated poster sessions will take place on Monday, 21 October from 17:30-20:00 as well as Tuesday, 22 October from 13:30-15:00. Poster presenters may stand by their posters during this time.

Note: PhD student and Early Career Researcher posters will be judged between 18:30-19:30 on Monday, 21 October. We ask you please stand by your posters during the judging.

Posters may be removed by 23 October, at the conclusion of the program to bring home. Any posters left after 17:00 Tuesday will be discarded.

WELCOME RECEPTION

A welcome reception will take place on Monday, 21 October, 18:00-20:00 in the Shilla 1-5 rooms, Hanra and Shilla foyers, and Hanra 1. Complimentary hors d'oeuvres and drinks will be provided.

LUNCH

Lunch will be provided on Monday, Tuesday, and Wednesday in Hanra 1,2,3. Bento boxes will be brought to you at your seat. Anyone who wishes to attend the Lunch Workshops should move to Hanra 3 and may have lunch during the workshop.

COFFEE BREAKS

Coffee breaks are included for all attendees Monday, Tuesday, Wednesday in the Hanra Foyer.

WI-FI

Wi-Fi will be available throughout the hotel free of charge.
Network name: PUBLIC_SEOUL DRAGON CITY
No password is required.

NO RECORDING OF SESSIONS

Please be advised that no photography or video/sound recording of conference presentations can take place during the conference.

VIRTUAL SESSIONS

All presentations, abstracts, exhibits, and special virtual presentations and sessions will be uploaded to the ISV vFairs virtual platform. All congress delegates receive access to the content.

To access, please go to: https://2024isvannualcongress.vfairs.com/

- enter the email address you used to register for Congress.

EVALUATION FORM

Delegate views and feedback on the content and organization of the conference are highly valued. We encourage you to complete the evaluation form that will be emailed after the congress.

GENERAL INFORMATION

Congress Location: Seoul Dragon City, 95, Cheongpa-ro 20-gil, Yongsan-gu, Seoul 04372, Korea
ISV Website: www.isv-online.org
ISV Virtual Platform: https://2024isvannualcongress.vfairs.com/

2024 ISV ANNUAL CONGRESS SATELLITE CONFERENCE: CHINA DAY PROGRAM
会议议程

Onsite Registration (Maximum 70 participants)
现场注册（限 70 人）

Conference Hotel: SEOUL DRAGON CITY **Room: Shilla 1 + 2** 호텔：서울드래곤시티 会议酒店： 首尔龙城酒店		**Address: 95 CHEONGPA-RO 20-GIL, YONGSAN-GU** ㈜서부티엔디 / 서울시 용산구 청파로 20 길 95 地址：韩国首尔市龙山区青坡路 20 街 95 号
Date	**Time**	**Onsite Check-in**
2024-10-20	13:30 -17:00	Registration starts at 12:30 Entrance of Shilla 1 + 2

组委会（Organizing Committee）: Anna Du, Baomin Jiang, Qihan Li, Sam Li, Shan Lu, Bin Wang, Yuan Yuan, Tao Zhu.

主办单位：上海市生物医药科技产业促进中心，International Society for Vaccines

Organizer: Shanghai Center of Biomedicine Development, International Society for Vaccines

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Co-organizer：Nanjing Bosnan Health Technology Co., Ltd.

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ISV 2024 ANNUAL CONGRESS CHINA DAY

PROGRAM

Sunday, 20th October 2024	
Room Shilla 1 + 2, Dragon City Hotel, Seoul, South Korea	
12:30-17:30	**REGISTRATION** **现场注册**
13:30-13:45	**WELCOME BY ISV PRESIDENT: Linda Klavinskis,** *King's College London, UK* **欢迎致辞：琳达·S·克拉文斯基，** *ISV 主席,伦敦国王学院*
	Organizers Remarks: Anna DU, *Bill & Melinda Gates Foundation*; **Shan LU,** *UMASS Chan Medical School, USA*; **组委会致辞：Anna Du，** *比尔及梅琳达·盖茨基金会*；**卢山，** *马萨诸塞州陈医学院*；
	Session One **Chairs: Bin WANG,** *Fudan University;* **Sam LI,** *ChStone* ;
13:45	Overall introduction of SCBD and Shanghai Biomedical industry **Xiao SUN**, *Senior Director of Platform Partnership Department, Shanghai Center of Biomedicine Development (SCBD)*
14:05	Introduction of Shanghai Center for Drug Evaluation and Inspection **Gang LI,** *Shanghai Center for Drug Evaluation and Inspection*
14:20	China Vaccine Landscape **Yuan YUAN**, *China Country Representative, Business & Alliance Management, PATH*
14:40	Pathogen Distribution And Pneumococcus Disease Burden Of Clinical Diagnosed Pneumonia Among Children, A Multi-Center Case-Control Study **Yi ZHANG**, *Huashan Hospital Affiliated with Fudan University*
14:55	Next Peumoccocal Disease Vaccines **Tao ZHU**, *Co-founder, Executive Director and CSO, CanSino*
15:10	Thermo-stable mRNA Vaccine **Yuanqing LIU**, *CSO, Immorna*
15:25-16:00	**Tea Break**
	Session Two **Chairs: Tao ZHU,** *Co-founder, Executive Director and CSO, CanSino;* **Baoming JIANG,** *US Centers for Disease Control and Prevention (US CDC)*
16:00	The Technical Design Of Vaccine With Virus-Like Structure (VlS) Against Sars-Cov-2 Variants **Jingjing ZHANG**, *Professor, Wei Rui Biotechnology(Kunming)/Shandong Weigao Litong Biological Products(Weihai)*
16:15	Rapid Evaluation of Potency of Vaccine Adjuvants Using a Photoconversion Mouse Model **Bin WANG**, *Fudan University*
16:30	Novel Adjuvant Vaccine Development And Large Scale-Up Production **Dexiang CHEN**, *Founder, Maxvax*
16:45	Integrated mRNA Product Development-A Collaborative Way to Deliver **Hang YU**, *Co-founder, CEO, RNACure*
17:00	To be added
17:15	**Group Photo and Closing OF China Day CONFERENCE**

ISV ANNUAL CONGRESS, 21-23 OCTOBER 2024
DRAGON CITY HOTEL, SEOUL, SOUTH KOREA
ORAL PROGRAM
MONDAY 21 OCTOBER 2024

08:00-10:00	**REGISTRATION**	**(Hanra Foyer)**
09:00-10:00	**WELCOME COFFEE *Sponsored by Afrigen Biologics & Vaccines***	**(Hanra Foyer)**
10:00-10:10	**OPENING SESSION:** **Session Chair: Joon Haeng Rhee,** *Chonnam National University, South Korea* **INTRODUCTION OF THE 2024 ISV ANNUAL CONGRESS & CO-CHAIRS:** **Margaret Liu,** *ProTherImmune & Karolinska Institutet, USA & Sweden* **Shan Lu,** *UMASS Chan Medical School, USA*; **Jerome Kim,** *International Vaccine Institute (IVI), South Korea;* **Ken Ishii,** *University of Tokyo, Japan* **WELCOME BY ISV PRESIDENT: Linda Klavinskis,** *King's College London, UK*	**(Hanra 1 & 2)**
10:10-10:40	**STANLEY PLOTKIN LECTURE:** **Session Chair: Joon Haeng Rhee,** *Chonnam National University, South Korea* **INTROUCTION OF STANLEY PLOTKIN LECTURE & 2024 SPEAKER:** **Linda Klavinskis,** *King's College London, UK* **STANLEY PLOTKIN LECTURE 2024 SPEAKER:** Advancing Vaccine End-to-End Capabilities (AVEC) in Africa: A Model for Sustainable Regional Vaccine Manufacturing **Jerome Kim,** *International Vaccine Institute (IVI), South Korea*	**(Hanra 1 & 2)**
10:40-12:00	**PLENARY SESSION 1: CLIMATE CHANGE AND EMERGING INFECTIONS** **Session Chairs: Jeffrey Ulmer,** *TechImmune LLC, USA*; **Ken Ishii,** *University of Tokyo, Japan*	**(Hanra 1 & 2)**
10:40-11:05	Climate and Infectious Diseases: Past, Present and Future **Axel Timmermann,** *Pusan University, South Korea*	
11:05-11:30	Clinical Advances in Vaccines for Blood-Stage Malaria **Simon Draper,** *University of Oxford, UK*	
11:30-11:45	Lung Eosinophil Recruitment and Type 2 Host Immune Responses in Vaccinated Mice is Non-Pathological and Correlates with Protection During Influenza Infection in Mice with Infection Permissive or Sterilizing Immunity **Michael Schotsaert,** *Icahn School of Medicine at Mount Sinai, USA*	
11:45-12:00	Peripheral Co-Delivery of Plasmid-Encoded Mucosal Chemokine CCL27 Enhances Mucosal Immunity and Supports Protection from Heterologous SARS-CoV-2 and H5N1 Influenza Challenges in Vivo **Ebony N. Gary,** *The Wistar Institute, USA*	
12:00-13:30	**LUNCH *Sponsored by Pfizer***	**(Hanra 1 & 2)**
12:15-13:25	**Cutting Edge: AI/ML and Computational Vaccinology Workshop** ***Organized by EpiVax, Inc.*** **Session Chairs: Joon Haeng Rhee,** *Chonnam National University, South Korea*; **Manon Cox,** *NextWaveBio, USA* **Yoshimasa Takahashi,** *Director of the Research Center for Drug and Vaccine Development at NIID Japan* **Anne De Groot,** *Founder and CSO of EpiVax, Inc.* **Chaok Seok,** *Professor in the Department of Chemistry, Seoul National University / CEO of Galux Inc.*	**(Hanra 3)**

13:30-14:50	**PLENARY SESSION 2: VACCINES WITH BROAD IMPACT** **(Hanra 1 & 2)** **Session Chairs: Margaret Liu,** *ProTherImmune & Karolinska Institutet, USA & Sweden;* **Lars Frelin,** *Karolinska Institutet, Sweden*		
13:30-13:55	Vaccines for TB and HIV: Opportunity and Access **Nina Russell**, *Gates Foundation, USA*		
13:55-14:20	A Vaccine to Prevent Congenital CMV: How Close Are We? **Sallie Permar,** *Weill Cornell Medicine, USA*		
14:20-14:35	Development of Parenteral Vaccines for Global Control of Rotavirus Diarrhea in Children: Progress and Update **Baoming Jiang,** *Centers for Disease Control and Prevention, (CDC), USA*		
14:35-14:50	Long-Term Impact of Rotavirus Vaccination on All-Cause and Rotavirus-Specific Gastroenteritis and Strain Distribution in Central Kenya: An 11-Year Interrupted Time-Series Analysis **Ernest Wandera**, *Kenya Medical Research Institute, (KEMRI), Kenya*		
15:00-15:30	**COFFEE BREAK *Sponsored by Arcturus Therapeutics*** **(Hanra Foyer)**		
15:30-17:20	**Concurrent Session: Bright Sparks in Vaccinology: PhD Students** **Location: Rendezvous Room 2nd Floor** **Session Chairs:** **Linda Klavinskis,** *King's College London, UK* **Jean Boyer,** *Agenta Therapeutics, USA* **(See pages following program for details)**		
15:30-17:30	**CONCURRENT SESSION 1** **(Hanra 1)** **VIRAL VACCINES OF CONTEMPORARY INTEREST** **Session Chairs:** **Mark Connors,** *NIH/NIAID, USA* **Danilo Casimiro,** *Sanofi, USA*	**CONCURRENT SESSION 2** **(Hanra 2)** **STRATEGIES FOR IMPROVED PROTECTION** **Session Chairs:** **Kai Dallmeier** *KU Leuven, Belgium* **Simon Draper,** *University of Oxford, UK*	**CONCURRENT SESSION 3** **(Hanra 3)** **VACCINES AGAINST CHALLENGING TARGETS** *Sponsored by Pfizer* **Session Chairs:** **Petro Terblanche,** *Afrigen Biologics & Vaccines, South Africa* **Tim Hirst,** *GPN Vaccines, Australia*
15:30-15:55	PIV5-Vectored RSV and COVID-19 Intranasal Vaccines Show Great Promise in Clinical Studies **Hong Jin,** *Blue Lake Biotechnology, USA*	Enhancing HIV Broadly Neutralizing Antibodies Through Multistate Affinity Optimization **Joseph Jardine,** *Scripps Research Institute, USA*	Progress Toward Development of a Human Lyme Disease Vaccine **James Baber,** *Pfizer Vaccine Research and Development, Australia*
15:55-16:10	Safety and Immunogenicity of Ad5-nCoV Given as the Second Booster Following Three Doses of CoronaVac: A Multicentre, Open-label, Phase 4, Randomised Trial **Hui Zheng,** *Southeast University, China*	Controlling Antibody Breadth to Viral Antigens **Yoshimasa Takahashi** *National Institute of Infectious Diseases, Japan* *(15:55-16:20)*	Development of an Anti-Tauopathy Mucosal Vaccine Specifically Targeting Pathologic Conformers **Shee Eun Lee,** *Chonnam National University, South Korea* *(15:55-16:20)*
16:10-16:25	Analysis of Adverse Events in Immunocompromised Individuals Following Moderna COVID-19 Vaccination: Insights From 701,070 Reported Cases (December 2020 to June 2023) **Veronica Urdaneta,** *Moderna, Inc., USA*	K3-SPG-Mediated Long-Term Protection Against Viral Infection **Asuka Tobuse** *University of Tokyo, Japan* *(16:20-16:35)*	Transfection of the Apicomplexan Parasite Theileria Parva Sporozoites: Towards CRISPR/Cas Gene Editing for Vaccine Development **Ethel Webi,** *University of Nairobi, Kenya* *(16:20-16:35)*

16:25-16:40	A First-In-Man Placebo Controlled, Randomized, Double-Blind, Phase I Clinical Trial of a Multi Antigen SARS-CoV DNA Vaccine Delivered by In Vivo Electroporation as a Booster Dose, Following Three Doses of Spike-Based mRNA Vaccines **Soo Aleman** *Karolinska Institutet, Sweden*	Broad Filovirus Protection via NK Cell Activation and Neutrophil Phagocytosis in Mice Induced by a YF17D-Vectored Sudan Virus Vaccine **Lara Kelchtermans**, *KU Leuven, Belgium* *(16:35-16:50)*	Vaccine Development Against Multidrug Resistant A. baumannii Infection **Yun Shi** *West China Hospital, China* *(16:35-16:50)*
16:40-16:55	Increased Potency and Breadth of Protection Conferred by a Next-Generation Pre-Emptive SARS-CoV-2 Vaccine Targeting both B and T Cell Responses **Jeffrey Ulmer,** *TechImmune LLC, USA*	A VLP-like Polio Vaccine Candidate Produced on Insect Cell are Safe and Immunogenic in Human Adults **Qiaoling Yan,** *CanSino Biologics Inc., China* *(16:50-17:05)*	An Improved Theileria Parva Sporozoite Seroneutralization Assay to Evaluate Vaccine Candidates for East Coast Fever **Hannah Chege,** *University of Nairobi, Kenya* *(16:50-17:05)*
16:55-17:10	Rational Immunogen Design for a Pan-Betacoronavirus Vaccine **Mihai Azoitei,** *Duke Human Vaccine Institute, USA*	Immunogenetic and Molecular Epidemiological Study of Small Ruminant Lentiviruses in Mongolia **Davaasuren Nergui,** *Mongolian University of Life Sciences, Mongolia* *(17:05-17:20)*	Two-year Antibody Persistence and Safety of a Single-Dose Live-Attenuated Chikungunya Virus Vaccine (VLA1553) in Adults Aged 18 Years and Above **Susanne Eder-Lingelbach,** *Valneva Austria GmbH* *(17:05-17:20)*
17:10-17:25	Safety and Efficacy Tests of Brucella Abortus Strain 104M in Human Volunteers **Huimin Wang,** *China Agricultural University, China*	Pilot-Scale Production of Inactivated Monoglycosylated Split H1N1 Influenza Virus Vaccine Provides Cross-Strain Protection Against Influenza Viruses **JR Chen**, *RuenHuei biopharma, Taiwan* *(17:20-17:35)*	
17:30-20:00	**POSTER SESSION 1**		**(Shilla 1-5)**
18:00-18:20	**ISV CONGRESS AWARDS CEREMONY** **Nina Russell,** *Gates Foundation, USA* **Linda Klavinskis,** *ISV President, King's College London, UK*		**(Shilla 1-5)**
18:00-20:00	**WELCOME RECEPTION** ***Sponsored by Epivax, Inc.***		**(Shilla 1-5/Hanra/Shilla Foyers/Hanra 1)**

TUESDAY 22 OCTOBER 2024

08:00-08:30	**MORNING COFFEE** ***Sponsored by SK bioscience*** **(Hanra Foyer)**		
08:30-08:55	**MORNING SESSION:** **(Hanra 1 & 2)** **Session Chair: Nina Russell,** *Gates Foundation, USA* **KEYNOTE SPEAKER:** **Targeting Airway Immunity with Novel Vaccine Strategies** **Peter Lawaetz Andersen,** *Novo Nordisk Foundation, Denmark*		
08:55-10:15	**PLENARY SESSION 3: AI AND MACHINE LEARNING FOR VACCINE R&D** **(Hanra 1 & 2)** **Session Chairs: Xavier Saelens,** *VIB-Ghent University, Belgium;* **Jason McLellan,** *The University of Texas at Austin, USA*		
08:55-09:20	AI-Immunology™ – A New Era in Vaccine Development **Andreas Holm Mattsson,** *Evaxion Biotech, Denmark*		
09:20-09:45	Digital Innovations in the Development of Next-Generation Influenza Vaccines **Danilo Casimiro,** *Sanofi Vaccines R&D, USA*		
09:45-10:00	VIOLIN in the Era of AI: An Integrative Vaccine Knowledgebase and Analysis System **Junguk Hur**, *University of North Dakota, USA*		
10:00:10:15	Artificial and Human Intelligences Combined: Removal of Inhibitory Sequences Improves Vaccine Immunogenicity and Efficacy **Guilhem Richard**, *EpiVax, Inc., USA*		
10:15-10:45	**COFFEE BREAK** ***Sponsored by GPN Vaccines*** **(Hanra Foyer)**		
10:45-12:25	**Concurrent Session: Bright Sparks in Vaccinology: Early Career Researchers** **Location: Rendezvous Room 2nd Floor** **Session Chairs:** **Linda Klavinskis,** *King's College London, UK* **Frédéric Tangy** *Oncovita - Institut Pasteur, France* **(See pages following program for details)**		
10:45-12:30	**CONCURRENT SESSION 4** **(Hanra 1)** **MUCOSAL VACCINES** **Session Chairs:** **Bin Wang,** Advaccine *Biopharmaceuticals Suzhou Co., Ltd., China* **Yoshimasa Takahashi,** *National Institute of Infectious Diseases, Japan*	**CONCURRENT SESSION 5** **(Hanra 2)** **THE MYSTERY OF MERS: VACCINES & IMMUNOLOGY** ***Co-Organized with IVI*** **Session Chairs:** **Baik Lin Seong** *Vaccine Innovative Technology ALliance Korea (VITAL-Korea), South Korea* **Jerome Kim,** *International Vaccine Institute (IVI), South Korea*	**CONCURRENT SESSION 6** **(Hanra 3)** **ROUNDTABLE: REGULATORY ISSUES FOR VACCINE DEVELOPMENT** **Session Chairs:** **Neil Almond,** *Medicines and Healthcare products Regulatory Agency (MHRA), UK* **Shan Lu,** *UMASS Chan Medical School, USA*
10:45-11:10	Inhaled SARS-CoV-2 Vaccine for Single-Dose Dry Powder Aerosol Immunization **Guanghui Ma,** *Chinese Academy of Sciences, China*	The International Vaccine Institute (IVI) and the Middle East Respiratory Syndrome in Korea **Jerome Kim,** *International Vaccine Institute (IVI), South Korea* *(10:45-10:55)*	**PANEL MEMBERS:** **Corey Casper,** *University of Washington, USA*

11:10-11:35	A Hitchhiker's Guide to Mucosal Immunity: Harnessing Albumin Hitchhiking for Enhanced Intranasal Vaccine Uptake and Efficacy **Brittany Hartwell,** *University of Minnesota, USA*	Development of the ChAdOx1 MERS Vaccine **Sarah Gilbert,** *University of Oxford, UK* *(10:55-11:20)*	**SungHee Hong,** *SK bioscience, South Korea* **Tao Zhu,** *CanSinoBIO, China* *(10:45-11:45)*
11:35-11:50	Bacteriophage T4 as a Protein-Based, Adjuvant- and Needle-Free, Mucosal Pandemic Vaccine Design Platform **Venigalla Rao** *The Catholic University of America, USA*	Rise in Broadly Cross-Reactive Adaptive Immunity Against Human β-Coronaviruses in MERS-Recovered Patients During the COVID-19 Pandemic **Nam-Hyuk Cho,** *Seoul National University College of Medicine, South Korea* *(11:20-11:45)*	**LATE BREAKER ABSTRACT SESSION**
11:50-12:05	Harnessing Innate Immune Memory for Enhancing Vaccine Efficacy: New Molecular Mechanisms Controlling Memory Establishment and Persistence **Diana Boraschi** *SUAT, China*	Development of MERS-CoV Vaccine Using an Attenuated and Highly Effective Recombinant Vesicular Stomatitis Virus (rVSV) System **Seung Ho Choo** *CREO SG Vaccine Institute, South Korea* *(11:45-12:05)*	Lipid Formulated Plasmid DNA Drives Robust Innate Immune Activation to Promote Adaptive Immunity **David Weiner,** *The Wistar Institute, USA* *(11:45-12:00)*
12:05-12:20	Heterologous Prime/Boost Immunization with Newcastle Disease Virus and Modified Vaccinia Virus Ankara Vectors as an Improved and Effective Strategy Against SARS-CoV-2 Infection **Juan Garcia-Arriaza** *Centro Nacional de Biotecnologia, Spain*	Purification and Characterization of Bivalent Vaccine Candidate Against SARS-CoV-1 and MERS-CoV Expressed as Inclusion Bodies in *E. coli* **Rahul Ahuja,** *Translational Health Science and Technology Institute (THSTI), India* *(12:05-12:20)*	An Intranasal Newcastle Disease Virus (NDV)-Based SARS-CoV-2 Omicron Vaccine Elicits Protective Immune Responses in Mice and Hamsters **Stefan Slamanig,** *Icahn School of Medicine at Mount Sinai, USA* *(12:00-12:15)*
		Protein Nanoparticle Vaccines Induce Potent Neutralizing Antibody Responses Against MERS-CoV **Cara Chao,** *University of Washington, USA* *(12:20-12:35)*	Safety and Immunogenicity of a SARS-CoV-2 mRNA Virus-like Particle Vaccine in Adults 18 years of Age and Older in a Phase 1 Randomized Clinical Trial **Lee-Jah Chang,** *AstraZeneca, USA* *(12:15-12:30)*
12:30-14:00	**LUNCH *Sponsored by Vaxxas***		**(Hanra 1 & 2)**

12:45-14:00	**Current Status and Future Prospects of New Vaccine Development Workshop** **(Hanra 3)** ***Organized by Global Vaccine Leading Technology Center (GVLTC)*** **Workshop Chair: Jeong-Taek Woo,** *GVLTC* **-** Introduction to the GVLTC (12:45-12:50) **Kee-Jong Hong,** *Gachon University* - Global Pandemic Preparedness and Vaccine R & D in Korea (12:50-13:15) **Jae-Chul Pyun,** *Yonsei University* - Rapid Screening of Target Antigenic Sites for SARS-CoV-2 Vaccine Development Using Fv-Antibody Library (13:15-13:40) **Myung-shin Lee,** *Eulji University* **– Dengue Vaccine Development: Codon-Pair Deoptimization and IFNAR2 KO Pig Model** (13:40-14:00)
13:30-15:00	**POSTER SESSION 2** **(Shilla 1-5)**
14:00-15:00	**ISV ANNUAL GENERAL MEETING** **(Hanra 1)** **Meeting Chair: Linda Klavinskis,** *King's College London, UK*
15:00-15:30	**COFFEE BREAK *Sponsored by BioNTech*** **(Hanra Foyer)**
15:30-17:35	**PLENARY SESSION 4: DELIVERY & NEW ADJUVANTS** **(Hanra 1 & 2)** **Session Chairs: Lakshmi Krishnan,** *National Research Council Canada (NRC);* **Sarah Gilbert,** *University of Oxford, UK*
15:30-15:55	Vaccines for Older Adults: The Role of Adjuvants **Birgit Weinberger,** University *of Innsbruck, Austria*
15:55-16:20	A Gaps-and-Needs Analysis of Vaccine R&D in Africa: Recommendations to Improve the Research Infrastructure (RECORDING) **Nicaise Ndembi,** *Africa Centres for Disease Control and Prevention (Africa CDC), Ethiopia*
16:20-16:35	Clinical Assessment of Adjuvant Immunotherapy, INO-3107, in Adult Patients with Recurrent Respiratory Papillomatosis (RRP) **Michael Sumner**, *Inovio Pharmaceuticals, USA*
16:35-16:50	Effect of Adjuvants on the Efficacy of an Izumo1-based Immunocontraceptive Vaccine in Mice **Harm Hogenesch**, *Purdue University, USA*
16:50-17:05	Combination Adjuvants Targeting Nucleic Acid Sensors for Cancer Immunotherapy **Burcu Temizoz**, *The Institute of Medical Science, The University of Tokyo (IMSUT), Japan*
17:05-17:20	Novel Fully Synthetic Saponin-Based Vaccine Adjuvant for Protein-based Vaccines **ChunKai Chang**, *ImmunAdd, Taiwan*
17:20-17:35	Heroin and Fentanyl Vaccines Adjuvanted with Army Liposome Formulation **Essie Komla**, *Henry M. Jackson Foundation, USA*
18:00	**PICK UP FOR GALA DINNER (TICKETS REQUIRED)**

WEDNESDAY 23 OCTOBER 2024

08:00-08:30	**MORNING COFFEE** ***Sponsored by CanSinoBIO*** **(Hanra Foyer)**		
08:30-08:55	**MORNING SESSION:** **(Hanra 1 & 2)** **Session Chair: Manon Cox,** *NextWaveBio, USA* **KEYNOTE SPEAKER:** **Vaccines for Emerging Viruses** **Albert Osterhaus,** *University of Veterinary Medicine Hannover (TiHo), Germany*		
08:55-10:00	**PLENARY SESSION 5: THERAPEUTIC VACCINES AGAINST CANCER** **(Hanra 1 & 2)** **Session Chairs: David Weiner,** *The Wistar Institute, USA*; **Anne De Groot**, *EpiVax Inc., USA*		
08:55-09:20	A Synthetic Booster Vaccine for Chimeric Antigen Receptor T cells **Leyuan Ma,** *University of Pennsylvania, USA*		
09:20-09:45	mRNA-4157/V940, Individualized Neoantigen Therapy: mRNA Therapeutics Coming of Age in Cancer **Kaku Saito,** *Moderna, Japan*		
09:45-10:00	Recent Developments of an Improved Measles Vaccine Vector for Cancer Immunotherapy and New Prophylactic Vaccines **Frederic Tangy**, *Oncovita - Institut Pasteur, France*		
10:00-10:30	**COFFEE BREAK** ***Sponsored by EuBiologics*** **(Hanra Foyer)**		
10:30-12:30	**CONCURRENT SESSION 7** **(Hanra 1)** **VACCINE PRODUCTION AND EVALUATION** **Session Chair:** **Annette Vogel** *BioNTech, Germany* **Shan Lu,** *UMASS Chan Medical School, USA*	**CONCURRENT SESSION 8** **(Hanra 2)** **NEW VACCINES AGAINST OLD BUGS** **Session Chair:** **Michael McCluskie,** *National Research Council Canada (NRC), Canada* **Michael Schotsaert,** *Icahn School of Medicine at Mount Sinai, USA*	**CONCURRENT SESSION 9** **(Hanra 3)** **INNOVATIVE RNA VACCINE TECHNOLOGY** ***Co-Organized with IBS Korea Virus Research Institute*** **Session Chairs:** **Alexander Bukreyev,** *University of Texas Medical Branch (UTMB), USA* **Edward Rybicki,** *University of Cape Town, South Africa*
10:40-11:05	Blood on Chip: an in vitro Innate immune response model for Vaccine Development and Evaluation **Cyril Guyard** *BIOASTER, France*	New Technology, Vaccine, and Knowledge from Related Pneumococcal Serotypes **Moon Nahm** *University of Alabama at Birmigham, USA*	DegradaBALL-mRNA Vaccine to Advance Vaccine Delivery Against Future Pandemic: The 100 Days Mission **Dal-Hee Min** *Seoul National University, South Korea*
11:05-11:20	Development of a Thermostable, Immunogenic ACM Tunable Platform (ATP) for mRNA Delivery Using Amphiphilic Block Co-polymers **Jian Hang Lam,** *ACM Biolabs, China*	The Comparison of Plant Virus Nanoparticles in the Presentation of a Conserved Influenza Epitope to Develop a Universal Influenza Vaccine Candidate in Nicotiana Benthamiana **Kirti Daya,** *Biopharming Research Unit, University of Cape Town, South Africa*	SARS-CoV-2 Plasma Cells are Largely Excluded from the Bone Marrow Long-Lived Compartment 33 Months after mRNA Vaccination **Doan Nguyen,** *Emory University, USA*
11:20-11:35	Long-Term Immunogenicity of Typhoid Conjugate Vaccine Among Healthy Filipino Adults and Children **Rejwana Haque Pial,** *International Vaccine Institute, South Korea*	The Next Generation Influenza Vaccine: mRNA or Recombinant Protein? **João Paulo Portela Catani,** *VIB-UGent Center for Medical Biotechnology, Belgium*	A Novel Production Platform for mRNA Vaccines: Encapsidation in a Virus Capsid Protein in Plants **Edward Rybicki,** *University of Cape Town, South Africa*

11:35-11:50	Optimization and Scale Up of Suspension Vero Cell Culture Technology Towards Industrial Applications in Cost-Effective Production of Viral Vaccines **Lakshmi Krishnan,** *National Research Council Canada, Canada*	Passive Immune Protection Against A(H1N1) pdm2009 Virus Infection with In Vivo-delivered DNA-encoded Influenza H1HA-head and pan-NA Directed Monoclonal Antibodies in a Murine Challenge Model **Ami Patel,** *The Wistar Institute, USA*	A Quadrivalent mRNA Vaccine Against HSV-2 Showed the Enhanced Immunogenicity and Protection Against Primary and Latent Infections **Youngran Cho,** *The Catholic University of Korea, South Korea*
11:50-12:05	Army Liposome Formulation Containing QS-21 Modulates Proinflammatory Milieu and Innate Anti-viral Factors Rendering Human Monocyte-derived Macrophages Less Permissive to HIV-1 Infection **Mangala Rao** *US Military HIV Research Program, USA*	Pan-influenza B Virus Control with Single-Domain Antibodies Directed Against Hemagglutinin and Neuraminidase **Xavier Saelens,** *Ghent University and VIB, Belgium*	Novel One-component Ionizable Amphiphilic Janus Dendrimers (IAJD) as a Delivery Platform for Efficient mRNA Vaccine Development **Wook-Jin Park,** *University of Pennsylvania, USA*
12:05-12:20	Characterisation of Immune Responses to the rVSVΔG-LASV-GPC Vaccine Candidate in Healthy Adults **Marija Zaric,** *IAVI, Imperial College London, United Kingdom*	Novel Rabies Vaccine Offers Potential for Population Wide Pre-exposure Prophylaxis in Rabies Endemic Areas **Alexander Douglas,** *University of Oxford, United Kingdom*	mRNA Engineered Antibodies as Immune Therapeutics for Herpes Simplex Virus Associated Diseases **Sita Awasthi** *Perelman School of Medicine, USA*
12:30-14:00	**LUNCH *Sponsored by Valneva Austria GmbH*** **(Hanra 1 & 2)**		
12:45-13:45	**Canadian Government Workshop: Health Emergency Readiness Canada; Life Sciences and Biomanufacturing Capacity Building and Opportunity for Global Cooperation in Vaccine Development.** **(Hanra 3)** **Session Chair: Lakshmi Krishnan,** *Vice-President, National Research Council Canada* **Plenary Speaker: Ritu Banerjee,** *Assistant Deputy Minister, Industry Science Economic Development, Government of Canada* **Panel Discussion: International Experts**		
14:00-14:30	**ISV AWARDS CEREMONY** **(Hanra 1 & 2)**		
14:30–14:55	**PAPER OF THE YEAR PRESENTATION** **(Hanra 1 & 2)** **Session Chair: Linda Klavinskis,** *King's College London, UK* **HIV Vaccines Induce CD8+ T Cells with Low Antigen Receptor Sensitivity** **Mark Connors,** *NIH/NIAID, USA*		
14:55-15:45	**PLENARY SESSION 6: VACCINES FOR ONE HEALTH AND PANDEMIC PREPAREDNESS** **(Hanra 1 & 2)** **Session Chairs: Barbara Felber**, *National Cancer Institute, USA* **Dong Yu,** *Dynavax Technologies, USA*		
14:55-15:20	Jumping Around: Cross-Species Transmission of H5N1 **Angie Rasmussen,** *University of Saskatchewan, Canada*		
15:20-15:45	Bridging Veterinary and Human Vaccinology: Correlates of Protection and Post-Vaccination Monitoring for Enhanced Immunization Strategies **Alejandra Capozzo,** *UAI, Argentina*		
15:45-15:55	**CLOSING SESSION** **(Hanra 1 & 2)** **Joon Haeng Rhee,** *Chonnam National University, South Korea*; **Margaret Liu,** *ProTherImmune & Karolinska Institutet, USA & Sweden* **Shan Lu,** *UMass Chan Medical School, USA*		
15:55–16:00	**INTRODUCTION TO 2025 ISV ANNUAL CONGRESS** **(Hanra 1 & 2)** **Ed Rybicki,** *University of Cape Town, South Africa*		

ISV EDUCATION & TRAINING ACTIVITIES
All will be held in Rendezvous Room - Second Floor

BRIGHT SPARKS SESSIONS

MONDAY 21 OCTOBER 2024		TUESDAY 22 OCTOBER 2024	
15:30-17:20	**BRIGHT SPARKS IN VACCINOLOGY: PhD STUDENTS** **Session Chairs:** **Linda Klavinskis,** *King's College London, UK* **Jean Boyer,** *Agenta Therapeutics, USA*	**10:45-12:25**	**BRIGHT SPARKS IN VACCINOLOGY: EARLY CAREER RESEARCHERS** **Session Chairs:** **Linda Klavinskis,** *King's College London, UK* **Frédéric Tangy** *Oncovita - Institut Pasteur, France*
15:30-15:40	Evaluation of an Adjuvanted DNA Vaccine for the Control of Virulent Strains of Newcastle Disease Virus **Charlie Amoia** *Sokoine University of Agriculture, Tanzania*	**10:45-10:55**	Generation and Evaluation of an African Swine Fever Virus Mutant with Deletion of the CD2v and UK Genes **Teshale Araya** *Tigray Agricultural Research Institute, Ethiopia*
15:40-15:50	Intention to Receive COVID-19 and Influenza Vaccines During Pregnancy: A Prospective Cross-sectional Study Among Pregnant Women Attending Antenatal Care in Cape Town **Imen Ayouni Ep Labidi** *University of Cape Town, South Africa*	**10:55-11:05**	Understanding the Enhanced Immune Responses to High-Density Microarray Patch Vaccination through Spatial Transcriptomics and Antibody Repertoire Analysis **Jovin Choo,** *University of Queensland, Australia*
15:50-16:00	Efficient HBV Immunization Using a Self-Powered Microfluidic Chip for Reconstitution and Intradermal Delivery of CpG-adjuvanted HBs Vaccine **Elias Broeckhoven** *KU Leuven, Belgium*	**11:05-11:15**	Fc-modification of Anti-PcrV Gene-encoded Antibodies Modulates Complement-Mediated Killing of Pseudomonas aeruginosa **Jillian Eisenhauer,** *University of Pennsylvania/The Wistar Institute, USA*
16:00-16:10	Development of a Dual Vaccine Against Bovine Coronavirus and Lumpy Skin Disease Virus **Nicole Chineka** *University of Cape Town, South Africa*	**11:15-11:25**	A Phase III Randomized Controlled Multi-Centre Trial to Evaluate the Efficacy of the R21/Matrix-M Vaccine in African Children Against Clinical Malaria **Angela Gwakisa,** *Ifakara Health Institute, Tanzania*
16:10-16:20	Cinnamon and Spice as Adjuvants are Nice: Targeting TRP Channels to Boost Mucosal Immunization **Madison Davis,** *The University of Texas at Austin, USA*	**11:25-11:35**	Structural Basis of Broad Protection Against Influenza Virus by a Human Antibody Targeting the Neuraminidase Active Site Through a Recurring Motif in CDR-H3 **Gyunghee Jo,** *The Scripps Research Institute, USA*
16:20-16:30	High Throughput Epitope Mapping Using Charge Scanning Mutagenesis **Kawkab Kanjo,** *Indian Institution of Science, India*	**11:35-11:45**	YF17D-vectored COVID-19 Vaccine Protects from SARS-CoV-2-induced Adverse Pregnancy Outcomes in a Hamster Model of COVID-19 **Yana Kumpanenko,** *KU Leuven, Belgium*

16:30-16:40	A Two-Component Cocktail of Engineered E Domain III Nanoparticles Elicits Broadly Neutralizing Antibody Responses against Dengue virus in Mice **Margaret Mariano,** *Albert Einstein College of Medicine, USA*	**11:45-11:55**	Targeted Delivery of Immunotherapeutics to the Lower Regions of the Lung: Using One-component Ionizable Amphiphilic Janus Dendrimers to Deliver TGF-β mRNA to the Lung Parenchyma **Jaclynn Meshanni,** *University of Pennsylvania, USA*
16:40-16:50	Engineering, Structure, and immunogenicity of a Crimean-Congo Hemorrhagic Fever Virus Pre-fusion Heterotrimeric Glycoprotein Complex **Elizabeth McFadden,** *University of Texas at Austin, USA*	**11:55-12:05**	A Built-in Flagellin Adjuvanted Ferritin Nanocage Mucosal Vaccine Platform Induces High-quality Protective Immune Responses Against Respiratory Infections **Tien Duc Nguyen,** *Chonnam National University, South Korea*
16:50-17:00	Novel Adenoviral Vaccine Candidate Against a Century-old Disease: The Ongoing Search for an Efficient Immune-mediated Control of Chagas Disease **Sebastian Trinitario,** *IMPaM (UBA-CONICET), Argentina*	**12:05-12:15**	Improving Humoral Immunogenicity of Adenoviral Vector Vaccines by Capsid Display **Alexander Sampson,** *University of Oxford, United Kingdom*
17:00-17:10	Preparation and Immunogenicity Study of Novel Hepatitis B Virus-like Particles **Weixiao Wang,** *Nanjing Medical University, China*	**12:15-12:25**	Mapping the Serological Response to Chikungunya Infection and Vaccination **Daniel Yara,** *MHRA, United Kingdom*
17:10-17:20	A Novel Bovine TB Vaccine Borne Unexpectedly Out of Basic Mycobacterium Tuberculosis-Complex Virulence Research **Slim Zriba,** *University of Saskatchewan VIDO, Canada*		

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MENTORSHIP PROGRAM

TUESDAY 22 OCTOBER 2024

12:45-13:30	**MENTORSHIP PROGRAM: LEARN ABOUT THE ISV'S NEW PROGRAM** **PRESENTERS: Jean Boyer,** *Agenta Therapeutics, USA;* **Linda Lua,** *The Growth Impact Party Ltd, Australia*

CAREER DEVELOPMENT

WEDNESDAY 23 OCTOBER 2024

12:45-13:45	**CAREER DEVELOPMENT: HAVE YOUR QUESTIONS ANSWERED ABOUT DIFFERENT CAREER PATHS** **Session Chair:** *Michael Schotsaert, Ichan School of Medicine at Mount Sinai, USA* **PANEL:** **Barbara Felber,** *Head Human Retrovirus Pathogenesis Section, Center for Cancer Research, NCI, Vaccine Branch, USA* **Neil Almond,** *Head of the Blood and Tissue Pathogens, Adventitious Agents and Diagnostics group, Division of Virology, NIBSC, UK* **Lars Frelin,** *Associate Professor, Director of Education (grundutbildningsansvarig, GUA), Facility Manager at Karolinska Institutet, Sweden* **Alptekin Guler**, *Senior Scientist Infectious Disease Vaccines, BioNTech, Germany* **Stefan Jungbluth,** *Head of Business Development, UniversitätsKlinikum Heidelberg, Germany*

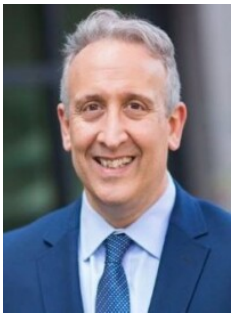
INVITED SPEAKERS

Peter Lawaetz Andersen
Novo Nordisk Foundation, Denmark

James Baber
Pfizer Vaccine Research and Development, Australia

Alejandra Capozzo
Universidad Abierta Interamericana (UAI), Argentina

Danilo Casimiro
Sanofi Vaccines R&D, USA



Corey Casper
University of Washington, USA

Nam-Hyuk Cho
Seoul National University College of Medicine, South Korea

Seung Ho Choo
CREO SG Vaccine Institute, South Korea

Mark Connors
NIAID, HIV-Specific Immunity Section, USA

Simon Draper
University of Oxford, United Kingdom

Sarah Gilbert
University of Oxford, United Kingdom

Cyril Guyard
BIOASTER, France

Brittany Hartwell
University of Minnesota, USA

SungHee Hong
SK bioscience Co., Ltd., South Korea

Joseph Jardine
Scripps Research Institute, USA

Hong Jin
Blue Lake Biotechnology, USA

Jerome Kim
International Vaccine Institute (IVI), South Korea

Shee Eun Lee
Chonnam National University, South Korea

Guanghui Ma
Chinese Academy of Sciences, China

Leyuan Ma
University of Pennsylvania, USA

Andreas Holm Mattsson
Evaxion Biotech, Denmark

INVITED SPEAKERS

Dal-Hee Min
Lemonex Inc/Seoul National University, South Korea

Moon Nahm
University of Alabama at Birmingham, USA

Nicaise Ndembi
Africa Centres for Disease Control and Prevention (Africa CDC), Ethiopia
(Recording)

Albert Osterhaus
University of Veterinary Medicine Hannover (TiHo), Germany

Sallie Permar
Weill Cornell Medicine, USA

Angie Rasmussen
University of Saskatchewan, Canada

Nina Russell
Gates Foundation, USA

Kaku Saito
Moderna, Japan

Yoshimasa Takahashi
National Institute of Infectious Diseases, Japan

Axel Timmermann
Pusan University, South Korea

Birgit Weinberger
University of Innsbruck, Austria

Tao Zhu
CanSino Biologics, China

CAREER DEVELOPMENT PANEL

Barbara Felber

Head Human Retrovirus Pathogenesis Section, Center for Cancer Research, NCI, Vaccine Branch, USA

Neil Almond

Head of the Blood and Tissue Pathogens, Adventitious Agents and Diagnostics group, Division of Virology, NIBSC, UK

Lars Frelin

Associate Professor, Director of Education (grundutbildningsansvarig, GUA), Facility Manager at Karolinska Institutet, Sweden

Alptekin Guler

Infectious Disease Vaccines, BioNTech, Germany

Stefan Jungbluth

Head of Business Development UniversitätsKlinikum Heidelberg, Germany

INVITED SPEAKER BIOGRAPHIES & ABSTRACTS

(Alphabetical Order)

Peter Lawætz Andersen

Professor Peter Lawætz Andersen is the Senior Vice President of the Novo Nordisk Foundation's Infectious Diseases department, which focuses on vaccines, immunity, antimicrobial resistance and anti-viral drug discovery. Peter has held this position since 2021.

Between 1991 and 2021, Peter held various positions at Statens Serum Institut, including Executive Vice President at the Center for Vaccine Research, Head of the Department of Infectious Diseases Immunology, and Research Director for the Tuberculosis Research Unit.

Peter is renowned for his research within the field of the development of new vaccines and diagnostic methods and has an extensive scientific production of more than 400 papers (H-index 119). He was the most cited researcher in Denmark within the field of immunology (1990 to 2005) and one of the most cited researchers in the world within the diverse field of Tuberculosis (2009). He has received several awards for his pioneering research, including the Novo Nordisk Prize in 2011.

Peter holds a doctor degree in Veterinary Medicine from the Royal Veterinary and Agricultural University (1988) and a DMSc from Copenhagen University (1996). He is also a professor at Copenhagen University.

Abstract

The accelerated development of vaccines against SARS Cov-2 is a great success story that has saved up to 20 million lives. However, vaccines against airway pathogens such as Corona and influenza still suffer from serious limitations. While the vaccines protect against severe disease they do not prevent transmission due to an insufficient level of mucosal immunity in the upper airways. Furthermore, immunological memory generated by the vaccines is insufficient which together with pathogen genetic drift necessitates frequent boosting to maintain the necessary level of immunity. A key challenge is how to maintain local immunity in the airways and the fundamental question is if this is even possible or if the expression of local immunity is downregulated by homeostatic mechanisms to prevent excessive lung damage? Of relevance for this discussion, the classical live attenuated vaccines against Measles and Rubella do maintain lifelong immunity. What are the characteristics of these infections and vaccines that differ so dramatically from the short-lived immunity found both after vaccination and natural infection with a number of upper airway viruses such Influenza, Corona, Rhinovirus and RSV.

The Novo Nordisk initiative for Vaccines and Immunity (NIVI) has recently been launched to address some of these scientific questions and develop vaccine technologies that promote a stable mucosal immune response that prevent both new infections and maintain control with already established chronic infections in the airways.

James Baber

Dr James Baber is a Senior Director for Pfizer Vaccine Clinical Research and Development based in Sydney, Australia. He completed his medical degree (MBChB) from the Auckland School of Medicine in New Zealand, and MPH (specializing in infectious diseases epidemiology and control) from the University of

New South Wales, Sydney, Australia. He is a registered medical practitioner in Australia.
Since joining Pfizer in 2008, James has worked as a Lead Clinician for multiple investigational vaccine programs including the Neisseria meningitidis serogroup B vaccine, Staphylococcus aureus vaccine, RSV older adult and maternal vaccines, COVID-19 vaccine, and mRNA Influenza vaccine, supporting global studies in the US, Europe, and Asia Pacific. James is currently the Asia Pacific Program lead, advancing development of Pfizer's innovative vaccines in the region.

Abstract
Lyme disease is the most common vector borne illness in Northern latitudes, with climate change contributing to the expanded range and activity of the Ixodes tick resulting in an increasing incidence of disease in humans. To address the urgent public health need for a protective vaccine, a Lyme disease vaccine (VLA15) is currently in clinical development. This 6-valent OspA based vaccine offers coverage for the dominant Borrelia genospecies endemic across North America and Europe. Preclinical studies have documented that active vaccination or passive transfer of VLA15 immune sera in mice confers protection in the murine tick challenge model. Moreover, passive transfer of human immune sera from clinical trial participants similarly protects mice against tick challenge, indicating that functional antibodies are generated after vaccination in people. Clinical data from the Phase 1/2 studies conducted to date have demonstrated that VLA15 is safe, well tolerated, and highly immunogenic in healthy children and adults 5 to <65 years of age. VLA15 is currently being assessed in a Phase 3 clinical study to determine the safety, immunogenicity, lot consistency, and efficacy in participants 5 years of age and older living in Lyme endemic areas.

Alejandra Victoria Capozzo

Dr. Alejandra Capozzo has an MD in Biology from the University of Buenos Aires (UBA), Argentina. She is a Doctor in Biotechnolgy also from the UBA. Her PhD thesis focused on alternative vaccines against foot-and-mouth disease directed by Dr José La Torre. She did postdoctoral studies in neonatal applied immunology at the Center for Vaccine Development (CVD) at University of Maryland (Baltimore, USA), where she worked on the development of new vaccines for neonates in the presence of maternal immunity. She has intensified her training in immunology at the National Academy of Medicine in Buenos Aires, focused on vaccines against Uremic hemolytic syndrome and animal models.
Dr Capozzo worked as Market Development Manager for Latin America at Prionics (a Swiss company); and as leader of research and development in Biogenesis-Bagó, an international veterinary vaccine producer. She is also trained in sales management.
From 2008 to 2023 she was the head of the applied veterinary immunology laboratory at the Institute of Virology and Technological Innovations, a CONICET-INTA. She is currently Principal Researcher of the Argentinean national research council (CONICET), the CEO of the Global Foot and Mouth Disease Research Alliance (GFRA), President of the Argentine Association of Veterinary Immunology, coordinator of the Latin American Veterinary Immunology Network, and the Chair of the Veterinary Immunology Committee of the International Union of Immunological societies (VIC-IUIS). Dr Capozzo participates in several transboundary disease groups in FAO-WOAH, as the co-chair of the Global Coordination Committee on Foot and Mouth Disease (GCC-FMD) and as a member of the Partnership and Financial panel (PFP).
Dr Capozzo has been a professor of immunology at the School of Veterinary Medicine of the University of

Buenos Aires for many years and directed 14 PhD theses. She is the Responsible Researcher of numerous national and international projects and has developed several products related to applied immunology that were transferred to Argentine and international companies. She is currently the Director of a Center focused on One health, located at the Interamerican University in Buenos Aires, since February 2024.

Abstract

Advances in veterinary vaccinology offers opportunitiesk for improving human vaccination strategies. Knowledge gained from developing, using, deploying, and assessing vaccine immunity in production animals in the field offers valuable insights for human immunization, particularly in post-vaccination monitoring, cross-protection, and vaccine selection. Insights from veterinary practices, including cost-effective monitoring techniques such as high-throughput serological assays, can assist in developing affordable post-vaccination monitoring assays for low- and middle-income countries.

Addressing cross-protection and vaccine selection remains a critical challenge. The selection of vaccines in production animals often involves evaluating antigenic diversity and potential for cross-protection. These principles are directly applicable to human vaccines, where antigenic variation in pathogens necessitates continual updates to vaccine formulations. Identifying correlates of protection is crucial for both veterinary and human vaccines. Studies in production animals have identified measurable indicators like antibody subclass quality and avidity, guiding vaccine efficacy evaluations and formulation updates to address pathogen antigenic diversity.

Success stories in controlling diseases like foot-and-mouth disease in South America highlight the importance of vaccination coupled with robust post-vaccination monitoring systems, emphasizing the need for vaccine banks and rapid response mechanisms for outbreak containment.

By integrating insights from veterinary vaccinology, particularly regarding correlates of protection and post-vaccination monitoring strategies, human vaccination efforts can be strengthened, contributing to improved disease control and prevention worldwide.

Danilo Casimiro

As Chief Science Officer and Global Head, External Scientific Affairs for Sanofi Vaccines, Dr. Casimiro is responsible for several external-facing functions of the Vaccines R&D unit, including teams for search-and-evaluation of vaccine candidates and vaccine innovations, scientific network development & partnerships, and external financing. More recently, he contributed to several business development projects including the recent acquisition of Translate Bio/USA and ORIGIMM/Austria by Sanofi. He has over 25 years of experience in research and development of vaccines and biologics in both pharmaceutical and non-profit sectors. Prior to joining Sanofi in November 2017, he was the Chief Scientific Officer at Aeras, a non-profit vaccine R&D organization funded by the Bill and Melinda Gates Foundation. During his 19 years at the Merck Research Laboratories, Danilo contributed to the licensure of Merck's human papillomavirus (HPV) vaccines, and the development of novel vaccine candidates and antibodies against multiple viral pathogens and novel immunotherapeutic approaches against cancer and neurodegenerative diseases. He also currently serves on several advisory committees such as BMGF-NIH Clinical AIDS Vaccine Development Program, USAID Malaria Vaccine Development Program, and the WHO/MPP mRNA Scientific Advisory Board. He received his B.S. in chemistry from the University of the Philippines, and his Ph.D. degree in chemistry/biochemistry and post-doctoral training from the California Institute of

Technology and the Scripps Research Institute-La Jolla, respectively.

Abstract

The emergence of Machine Learning (ML) tools has impacted the ways by which drugs and vaccines are being discovered and developed in the biopharmaceutical industry. Their applications range from designing the next generation of molecules, disease modeling, designing and managing clinical trials to manufacturing process optimization and automation. Sanofi is currently developing the next generation of influenza vaccines and has embraced the potential of ML tools to accelerate the pace of R&D in areas, such as (a) developing novel strain selection algorithms that enable consistent year-to-year protection against disease and (b) optimizing the performance of the mRNA platform. There are multiple strategies to improve efficacy of influenza vaccines year-after-year, including the inclusion of potent and safe adjuvants, addition of other influenza antigens such as neuraminidase and T-cell-inducing antigens. Hemagglutinin is the major mediator of immune protection against flu and in here, we describe the development of "virtual ferret model" to select strains with improved coverage breadth over the WHO selection. Additionally, the combined use of ML tools and high through-put mRNA screening has facilitated our ability to dissect the salient set of parameters that dictate the translation efficiency and/or stability of mRNA drug substance. As we continue to apply ML tools more broadly across the vaccine design space, the ambition to deliver transformative influenza vaccines can be realized.

Corey Casper

(Panel Speaker / Bio Only)

Dr. Casper is an executive leader and physician-scientist specializing in the development of vaccines and immunotherapies for infectious diseases, cancer, and immunology. He served as the Founding CEO of the Access to Advanced Health Institute (AAHI), a non-profit biotech organization dedicated to the advancement of vaccines and immunotherapeutics for global health in collaboration with academic, governmental, and pharmaceutical partners. With over two decades of experience, Dr. Casper has led the development of more than two dozen products, including vaccines that have progressed from preclinical stages to clinical trials and licensure.

His research and product development expertise include working on vaccines against diseases such as Chikungunya, Zika, Yellow Fever, and COVID-19. Dr. Casper has led the development of several vaccine adjuvants, RNA vaccines, and immunotherapies. Additionally, he has served as the principal investigator on over $100 million in grants, authored more than 130 peer-reviewed papers, and regularly presents at international conferences. Dr. Casper currently serves as a Clinical Professor of Medicine and Global Health at the University of Washington and an Affiliate Professor in the Vaccine and Infectious Disease Division of the Fred Hutch Cancer Center. He sees patients with cancer and infectious diseases at both institutions, and is actively involved in mentoring and capacity-building. He has played pivotal roles in large-scale research projects and collaborations with the U.S. government and pharmaceutical industry to address global health challenges.

Dr. Casper's achievements in product lifecycle management, strategic leadership, and scientific communication have earned him recognition as a leader in the field. His work has significantly impacted public health and vaccine accessibility, particularly in regions with limited healthcare infrastructure.

Nam-Hyuk Cho

Dr. Nam-Hyuk Cho has a longstanding interest in host-pathogen interactions, particularly in emerging human pathogens. He is currently a professor in the Department of Microbiology and Immunology at Seoul National University College of Medicine, Seoul, South Korea. Dr. Cho began studying immune responses and immunopathogenesis during the infection of Orientia tsutsugamushi, the causative agent of scrub typhus, during his Ph.D. training at Seoul National University. He expanded his research areas to virology while undergoing postdoctoral training at Harvard Medical School. Dr. Cho has a broad background in cellular immunology, molecular biology, microbiology, and virology. He has collaborated with clinicians in several Korean hospitals to study the immunological pathogenesis of several endemic and new emerging infectious diseases, including scrub typhus, severe fever with thrombocytopenia syndrome (SFTS), and emerging coronavirus infections.

Dr. Cho's group has been searching for protective antigens for vaccine development based on animal model studies and clinical research on scrub typhus. Additionally, they have been studying the virus-host cell interactions, focusing on new emerging viral pathogens such as SFTSV, MERS-CoV, and SARS-CoV-2. Understanding the fundamental mechanisms exploited by emerging human pathogens may not only contribute to developing effective measures against devastating infections but also provide valuable insights into the evolutionary pathways of our immune system.

Abstract

To develop a universal coronavirus (CoV) vaccine, long-term immunity against multiple CoVs, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, Middle East respiratory syndrome (MERS)-CoV, and future CoV strains, is crucial. Following the 2015 Korean MERS outbreak, we conducted a long-term follow-up study and found that although neutralizing antibodies and memory T cells against MERS-CoV declined over 5 years, some recovered patients exhibited increased antibody levels during the COVID-19 pandemic. This likely resulted from cross-reactive immunity induced by SARS-CoV-2 vaccines or infections. A significant correlation in antibody responses across various CoVs indicates shared immunogenic epitopes. Two epitopes-the spike protein's stem helix and intracellular domain-were highly immunogenic after MERS-CoV infection and after SARS-CoV-2 vaccination or infection. In addition, memory T cell responses, especially polyfunctional CD4+ T cells, were enhanced during the pandemic, correlating significantly with MERS-CoV spike-specific antibodies and neutralizing activity. Therefore, incorporating these cross-reactive and immunogenic epitopes into pan-CoV vaccine formulations may facilitate effective vaccine development.

Seung Ho Choo

Sixteen years of experience in CREOSG inc in Korea and Canada - Director of CREOSG vaccine institute - Manufacturing of inactivated HIV/AIDS vaccine and filing the IND to the US FDA, and Completion of the phase I study for HIV/AIDS vaccine - Completed the manufacturing process development for inactivated HIV/AIDS vaccine - Research & development of rVSV based vectored vaccine: Zika virus vaccine, COVID-19 vaccine, MERS vaccine, Crimean Congo virus vaccine, severe fever thrombocytopenia syndrome (SFTS) virus vaccine, hemorrhagic fever with renal syndrome (HFRS) vaccine - Process development for rVSV

vectored vaccines and cGMP manufacturing - Research and development of oncolytic virus for anti-cancer vaccine

Fourteen years of experience with LG Life Science in Korea - Five years as a research associate working on molecular biology for the recombinant protein expression, - Three years as a research scientist working on hepatitis B and C virus and HIV research project, - Two years as senior research scientist working on gene expression profile using Affymatrixgene chip - Four years as senior research scientist working on EMEA and FDA filing for bio-generic drugs.

Two years of experience in Enzynomics as a director working on development of reagents (Enzymes) for laboratory uses.

Abstract

The MERS coronavirus infected 2,562 people and caused 881 deaths in 2020, resulting in a mortality rate of 34.4%. No vaccine is currently available, and there is an urgent need to develop one to prepare for potential future pandemics. The spike protein, which binds to the DPP4 receptor and induces an immune response, is the primary target for a MERS vaccine. A vaccine candidate, rVSV MERS-mspS Gtc, was developed by replacing the spike protein gene (S) signal peptide with that of the melittin gene (msp) and its transmembrane and cytosolic domains (Gtc) with those of the VSV G gene. The modified S gene was inserted into an attenuated rVSV vector platform. In hDPP4 transgenic mice, rVSV with chimeric MERS S protein derivatives induced strong neutralizing antibodies and T cell responses. All vaccinated animals were protected from a heterologous MERS-CoV challenge, with no virus detected in lung samples. These findings suggest that the attenuated rVSV-based MERS vaccine is effective and safe against MERS-CoV.

Mark Connors

For the past 35 years Dr. Connors has been studying virus-specific immunity in animal models and humans. These studies include the immune response to HIV, RSV, Influenza virus, and SARS-CoV-2. He did his fellowship training under Robert Chanock and Brian Murphy at NIAID examining the immune response to respiratory virus vaccines. As Chief of the HIV-Specific Immunity Section of the Laboratory of Immunoregulation, NIAID, he has led research in understanding the mechanistic basis of an effective humoral and cellular response to HIV. His laboratory seeks to take the best available examples of immunologic control of HIV or antibody breadth in nature and systematically dissect the underlying mechanisms of these responses. His work on the cellular and humoral immune response to HIV has had a major impact on our current understanding of the basis of an effective immune response to HIV and other viruses and has suggested possible routes to use that information in strategies for immunization or immunotherapy. More recently he has used this information to examine the components (replication, route, valency, adjuvants, innate immunity response) of vaccines that contribute to an effective immune response to HIV, influenza virus, or SARS-CoV-2. This work includes basic immunology in humans and experimental animals, and the completion of 4 clinical trials of Ad4 recombinant vaccines for HIV and Influenza virus. His paper that was voted ISV paper of the year published in Science shows that prior HIV vaccines targeting the CD8+ T cell response induce cells that are not sufficiently sensitive to kill HIV infected cells. The work provides an explanation for the failure of these vaccines and a path forward to stimulating an effective response with CD8+ T cell mediated killing as the benchmark.

Abstract
Current HIV vaccines designed to stimulate CD8+ T cells have failed to induce immunologic control upon infection. The functions of vaccine-induced HIV-specific CD8+ T cells were investigated here in detail. Cytotoxic capacity was significantly lower than in HIV controllers and was not a consequence of low frequency or unaccumulated functional cytotoxic proteins. Low cytotoxic capacity was attributable to impaired degranulation in response to the low antigen levels present on HIV-infected targets. The vaccine-induced T cell receptor (TCR) repertoire was polyclonal and transduction of these TCRs conferred the same reduced functions. These results define a mechanism accounting for poor antiviral activity induced by these vaccines and suggest that an effective CD8+ T cell response may require a vaccination strategy that drives further TCR clonal selection.

Simon Draper

Simon Draper is Professor of Vaccinology and Translational Medicine at the University of Oxford. His lab is based in the Department of Biochemistry and Kavli Institute for Nanoscience Discovery. The group's clinical team are based at the University's Centre for Clinical Vaccinology and Tropical Medicine.
The Draper Lab study vaccine-induced immunity, with a particular focus on antibody immunology and human malaria infection. A critical strength of the group is a strong dual focus on preclinical vaccine development in parallel with early-phase clinical vaccine testing and experimental medicine studies. In particular, the group's research interests span: strategies for improved vaccine antigen identification; development of improved vaccine delivery strategies; assessment of quantitative antibody correlates of protective immunity; and assessment of human vaccine-induced antibody responses to guide immunogen design and to better understand protective mechanisms of immunity.
To date the group has undertaken 22 proof-of-concept Phase 1/2 clinical trials assessing novel vaccine delivery platforms and immunisation regimens; developing controlled human malaria infection (CHMI) models for Plasmodium falciparum and P. vivax; and testing novel blood-stage malaria vaccine antigens (PfRH5 for P. falciparum and PvDBP_RII for P. vivax). The PfRH5 clinical vaccine development programme now spans multiple partnerships across East and West Africa. The group has a strong track record of partnering with biotech and pharma, and participation in numerous collaborative programmes with academic and industrial partners, seeking to develop improved vaccines or antibody-based therapeutics.

Abstract
Plasmodium falciparum malaria affects 200-300 million people annually, resulting in the death of ~0.6 million individuals. Thus, despite increasing implementation of control measures, the burden of malarial death and disease remains far too high.
Two subunit vaccines are now approved for use against clinical P. falciparum malaria in young African children. These vaccines, called RTS,S/AS01 and R21/Matrix-M, are very similar in design and induce high level antibody responses that block infection by the liver-invasive sporozoite. These vaccines show moderate efficacy against clinical disease in young children, but efficacy wanes over time. Moreover, with every single sporozoite that slips through the net at the liver, a new blood-stage infection is established that brings risk of clinical disease. An effective subunit vaccine against the parasite's asexual blood-stage would thus be highly complementary to the approved anti-sporozoite vaccines, and provide a vital second line of defence in the blood; reduce mortality, morbidity and transmission of malaria; and offer the

prospect for a multi-stage vaccine approach. However, an effective blood-stage vaccine has proved elusive. Over recent years we have clinically developed vaccines targeting the P. falciparum reticulocyte-binding protein homologue 5 (RH5) and its wider invasion complex, which mediate a highly conserved and essential invasion pathway into the human red blood cell. Rational design and delivery of these new vaccines has built on our understanding of how vaccine-induced anti-RH5 human antibody responses can inhibit parasite growth, coupled with learnings from human experimental medicine studies. This talk will describe our on-going work to understand human anti-malarial antibodies and present safety, immunogenicity and efficacy data from our most recent Phase 1/2 clinical trials of RH5-based blood-stage vaccines undertaken in the UK and across East and West Africa.

Sarah Gilbert

Sarah Gilbert is a Professor of Vaccinology in the Pandemic Sciences Institute at Oxford University. She works on viral vectored vaccine development, with projects on influenza, Nipah, MERS, Lassa. Working with colleagues on the Old Road Campus in Oxford, she is able to take novel vaccines from design through GMP manufacturing to clinical development, with a particular interest in the rapid transfer of vaccines into GMP manufacturing and first in human trials. She was the Oxford Project Leader for ChAdOx1 nCoV-19, also known as Vaxevria/Covishield, which was estimated to have save 6.3 million lives in its first year of use.

Abstract

The Middle East respiratory syndrome coronavirus (MERS-CoV) causes a viral respiratory disease that was first described in 2012 and is now endemic in camels in Saudi Arabia. In 2015, a single traveller resulted in the largest outbreak of MERS outside the Middle East, resulting in 186 confirmed cases, and 38 deaths in South Korea. Public Health measures to contain and end the outbreak resulted in quarantine of almost 17000 individuals and multi-billion dollar economic losses.

The ChAdOx1 MERS vaccine has been tested for protective efficacy in hDPP4 transgenic mice and non-human primates, with protection demonstrated after a single dose. Two clinical studies have been conducted, in the UK and Saudi Arabia, demonstrating the induction of neutralising antibodies. These studies supported the development of the ChAdOx1 nCoV-19 vaccine in 2020.

A third, post-pandemic study of ChAdOx1 MERS in older adults is now in progress, examining the effect of prior vaccination against SARS-CoV-2 with either mRNA or ChAdOx1 vectored vaccines. Plans for further clinical development towards vaccine licensure will be presented.

Cyril Guyard

Doctor Cyril Guyard obtained his B.Sc. in Biochemistry with honors (1994) from University of Bourgogne, France and his M.Sc. in Molecular and Cellular Biology with honors (1996) from Louis Pasteur University of Strasbourg, France. He continued his training in Biology and Health Sciences at the Pasteur Institute of Lille, France and he earned his Ph.D. in 2001 at the University of Lille/Pasteur Institute of Lille, France. In 2002, Dr. Cyril Guyard joined the Laboratory of Pathogenesis of Infectious diseases of the Pasteur Institute of Lille/Inserm, France as a Post-doctoral fellow. In 2003, he obtained a Fellowship from the John E. Fogarty International Center and joined the Laboratory of Human Bacterial Pathogenesis from National

Institutes of Health, USA. In 2006, Dr. Cyril Guyard joined Public Health Ontario as a Principal Investigator. In 2007,
he was also appointed Assistant Professor in the Department of Laboratory Medicine and Pathobiology, Faculty of Medicine at University of Toronto. In 2008, in addition to his previous appointments, Dr. Guyard was cross-appointed as scientist in the Department of Microbiology of the Mount Sinai Hospital in Toronto. In 2013, Dr. Guyard joined Bioaster as Head of Technology Innovation Center. He is now Chief Scientific Officer.

Abstract
A significant challenge in the vaccine development process is the poor translatability between assays in model organisms and the human immune system. Animal models have often failed to accurately predict vaccine reactogenicity and effectiveness in humans, raising both ethical concerns over their use and questions about the balance of harm versus benefit. Consequently, there is a strong interest in reducing reliance on animal studies by developing advanced in vitro models.
Although organ-on-chip technology has achieved notable success in drug toxicity and screening applications, it remains underutilized in adjuvant and vaccine formulation research. This underuse may be due to the difficulty of creating physiologically relevant models that replicate innate immunity at the vaccine delivery site. Previous devices used in vaccine testing were often static systems with simplified cellular models, limiting their effectiveness for pre-clinical evaluation of adjuvants and vaccines.
In response to these needs, we created a microfluidic in vitro Organ-on-Chip platform prototype designed to emulate the site of intramuscular vaccine injection and allow for the characterization of local innate immune responses, which initiate subsequent adaptive immune responses. Muscle tissue, the preferred site for most clinical vaccine injections consists of a complex arrangement of muscle fibers, endothelial cells, and immune cells. To effectively replicate this complexity in our technology, we incorporated (1) a human skeletal muscle model alongside standard endothelial and immune cells, (2) a dynamic circulatory system that applies unidirectional physiological shear stress to endothelial cells and allows for recirculation of immune cells, and (3) the addition of neutrophils to the traditionally included human PBMCs. By applying shear stress, our prototype mimics the physiological behaviors of endothelial cells.
Our platform supports various longitudinal and end-point readouts, including classical immunology assays, RNaseq transcriptomic analyses, and high-resolution/live microscopy. These tools enable the evaluation and comparison of molecular reactogenicity signatures among different adjuvant and vaccine formulations.

Brittany Hartwell

Dr. Brittany Hartwell is an Assistant Professor of Biomedical Engineering at the University of Minnesota. Her lab's research in immunoengineering combines perspectives from biomolecular engineering, drug delivery, and immunology to develop molecular platforms that can target specific cells and tissues of the immune system to direct the immune response, with a particular focus on targeting and 'tuning' the mucosa. This work has broad applications ranging from the development of antigen-specific immunotherapies that induce immune tolerance against autoimmune and chronic inflammatory diseases, to development of targeted vaccines that activate immune protection against cancer and infectious diseases. For this work she was recently selected as one of four researchers worldwide to receive a 2022

Michelson Prize, awarded to early career investigators in human immunology and vaccine research. Prior to starting her faculty position at the University of Minnesota in fall 2021, she completed postdoctoral training with Dr. Darrell Irvine at Massachusetts Institute of Technology (2021) in immunoengineering, where she worked on developing mucosal vaccines. She received her PhD in biomolecular engineering with Dr. Cory Berkland from the University of Kansas (2016), where she worked on developing multivalent antigen-specific immunotherapy platforms for autoimmune diseases like multiple sclerosis. She received her B.S. in chemical and biological engineering from Iowa State University (2011).

Abstract

To combat the global HIV epidemic and persisting threats ranging from SARS-CoV-2 to influenza to tuberculosis, immunization strategies are needed that elicit protection at mucosal portals of pathogen entry. Immunization directly through the airway surfaces is effective in driving mucosal immunity, but poor vaccine uptake across the mucus and epithelial lining is a major limitation. The major blood protein albumin is constitutively transcytosed bidirectionally across the airway epithelium via interactions with the neonatal Fc receptor (FcRn). Exploiting this biology, here we demonstrate a strategy of 'albumin hitchhiking' to promote mucosal immunity using an intranasal (i.n.) vaccine consisting of protein immunogens modified with an amphiphilic albumin-binding polymer-lipid tail (forming amph-proteins). Amph-proteins persisted in the nasal passage and exhibited increased uptake into the mucosal tissue in an FcRn-dependent manner, leading to significantly enhanced uptake in key antigen-presenting cells and robust germinal center (GC) responses in the nasal-associated lymphoid tissue (NALT). I.n. immunization with amph-conjugated HIV Env gp120 or SARS-CoV-2 RBD proteins elicited robust antigen-specific IgG and IgA titers (100-1000-fold higher than unmodified protein) in the serum, upper and lower respiratory mucosa, and distal genitourinary mucosae of mice. Amph-RBD immunization induced high titers of SARS-CoV-2 neutralizing antibodies in serum, nasal washes, and bronchoalveolar lavage. Intranasal amph-protein immunization in rhesus macaques elicited ~10-fold higher antigen-specific IgG and IgA responses in the serum and nasal mucosa compared to unmodified protein, supporting the translational potential of this approach. These results suggest that employing amphiphile-protein vaccines to deliver antigen across the mucosal epithelium presents a promising and simple strategy to promote mucosal immunity against HIV, SARS-CoV-2, and other infectious diseases.

SungHee Hong

(Panel Speaker / Bio Only)

I am a regulatory affairs team leader at SK bioscience Co., Ltd. I have over 12 years of experience in the regulatory affairs of pharmaceuticals including vaccines. I have worked in QA department for 4 years and moved to regulatory affairs at Hanmi Pharmaceuticals, Co., Ltd. in Korea, before joining SK bioscience in 2016. I have a Bachelor's degree in Life science/Biology from the University of Toronto, Canada.

Joseph Jardine

Joseph Jardine is an Assistant Professor of Immunology and Microbiology at Scripps Research. He obtained his BS in Biochemistry from the University of Washington and completed his PhD at Scripps Research under the mentorship of William Schief, focusing on rational vaccine design. Following his doctoral studies,

Joseph was awarded the HHMI/Helen Hay Whitney postdoctoral fellowship, working with Dennis Burton to analyze vaccine antibody responses and engineer antibodies. In 2017, Joseph moved to Boston to help establish the Institute for Protein Innovation, a nonprofit organization focused on advancing protein and antibody engineering. In 2019, he returned to IAVI/Scripps, where he established a research group that integrates immunology and protein engineering.

Abstract

HIV antigenic diversity presents a critical challenge for antibody-based therapies. Broadly neutralizing antibodies (bnAbs) that target conserved epitopes on the HIV envelope glycoprotein (Env) have been isolated from HIV-infected donors, but these bnAbs exhibit variable potencies across different viral strains. Achieving both broad neutralization and high potency is critical for effective therapeutic interventions, as bnAb monotherapy often leads to viral escape. To overcome this, two primary strategies are employed: using cocktails of bnAbs as well as discovering new bnAbs with enhanced breadth and potency.

We are employing a multistate affinity maturation approach to generate engineered bnAbs (ebnAbs) with enhanced breadth and potency. Using yeast surface display and saturated mutagenesis libraries, we create bnAb binding "fingerprints" across diverse collections of HIV Env, allowing us to assess the effects of all single mutations on Env binding. These mutational datasets, combined with structure-based modeling and developability analysis, inform the design of combinatorial bnAb libraries containing multiple mutations to improve function. The combinatorial libraries are then screened to enrich for variants with improved binding across a diverse panel of Envs. After selections, enriched clones are deep sequenced, and variants that emerge across multiple datasets—indicating improved binding to diverse Envs—are selected for further characterization.

This approach has been successfully applied to three best-in-class bnAbs—PGT121, PGDM1400, and N49P7—that target non-overlapping epitopes on Env. The resulting ebnAbs exhibit significantly higher binding affinity, which has generally translated into increased breadth and potency across a diverse panel of HIV isolates in vitro. We are currently investigating how these enhancements impact protective efficacy and exploring strategies to incorporate these ebnAbs into a single trispecific molecule. This approach represents a broadly applicable strategy to enhance the efficacy of antiviral antibodies.

Hong Jin

Dr. Hong Jin is the Chief Scientific Officer at CyanVac LLC. She has led the efforts to progress PIV5-vectored Covid-19 and RSV vaccines from preclinical studies to phase 1 and 2 clinical trials. Prior to joining CyanVac, Dr. Jin was Sr. Director/Fellow at MedImmune and AstraZeneca responsible for viral vaccine development. She pioneered reverse genetic systems for influenza virus, RSV and Newcastle disease virus (NDV) and played critical roles in advancing candidate vaccines towards clinical trials and commercialization. She was instrumental in developing the strain selection process for annual commercial intranasal live attenuated influenza vaccine (FluMist) and clinical evaluation of pandemic influenza vaccines. She has authored more than 100 publications during her scientific career. Dr. Jin was nominated as a 2023 PharmaVoice100 to recognize her contributions to infectious disease vaccine development.

Abstract

Parainfluenza virus 5 (PIV5) is a negative-sense RNA virus that has been used for decades as a live

component of intranasal kennel cough vaccines for dogs. Despite human exposure to PIV5 through vaccinated dogs, it has never been shown to cause disease in humans. Two PIV5-vectored intranasal vaccines were constructed: BLB201 for respiratory syncytial virus (RSV) and CVXGA for COVID-19. These vaccines were created by inserting the RSV fusion (F) protein gene or the SARS-CoV-2 spike (S) protein gene into the PIV5 genome as a separate transcriptional unit. Both vaccine viruses replicate efficiently in serum-free Vero cells, are immunogenic, and provide protection against viral challenge infection in animal models. BLB201, the RSV vaccine, has been evaluated in a Phase 1 clinical trial of 30 adults at 107.5 PFU/dose, and in an ongoing Phase 1/2a trial of RSV-seropositive and seronegative children ages 6–59 months (63 enrolled to date) at 106.0 and 107.0 PFU/dose. BLB201 has demonstrated safety and immunogenicity, inducing systemic and mucosal antibody responses as well as RSV F-specific CD4+ and CD8+ T cell responses in adults and children. CVXGA, the COVID-19 vaccine, has been evaluated in a Phase 1 trial of 72 participants (WA1 strain) and in a Phase 2a trial of 227 participants (XBB1.5 strain) at up to 107.0 PFU/dose. The vaccine has been well tolerated, generating S-specific systematic and mucosal antibodies, and CD4+/CD8+ T cell immune responses. Protective efficacy of CVXGA will be assessed once the Phase 2a study is unblinded. CVXGA50 (KP2 variant) will be compared to mRNA vaccine in a Phase 2b study involving 10,000 participants as part of Project NextGen, a COVID-19 vaccine initiative funded by the Biomedical Advanced Research and Development Authority (BARDA).
Both preclinical and clinical data strongly support PIV5 as a promising vaccine vector for vaccine development.

Jerome Kim

Jerome H. Kim, M.D. is the Director General of the International Vaccine Institute (IVI) and an internationally recognized expert in vaccine development. Under his leadership, IVI has developed and distributed key vaccines, including an oral cholera vaccine and a typhoid conjugate vaccine (TCV), which achieved WHO prequalification in 2024. He holds professorships at multiple universities, including Seoul National University and Yonsei University. Dr. Kim earned his M.D. from Yale and has published over 350 papers.

Abstract #1 (Stanley Plotkin Lecture)

Regional vaccine security has been a major feature of the post-COVID-19 learning agenda, and nearly $5 billion USD have been pledged to support the development of vaccine manufacturing in Africa. The Africa CDC has set a target of 60% self-sufficiency in vaccines in Africa by 2040, a significant increase from the <1% self-sufficiency currently. However a limited focus on manufacturing itself may critically miss a aspect of sustainable manufacturing. If Africa is to do more than fill and finish (which does not mitigate the impact of pandemics of the supply of drug substance (ie, the vaccine before fill and finish). Unless Africa has the capacity to support all aspects of the vaccine value chain (spanning from disease burden, through discovery, development, delivery, manufacturing, regulatory approval, procurement, and implementation) then sustainable manufacturing will not be possible, and the newly built factories will not be able to support vaccine security during pandemics. AVEC Africa hopes to use end-to-end product development projects to train individuals and teams in the different elements of the vaccine ecosystem. IVI commits to help move projects, execute vaccine development, train personnel, and execute technology transfer using this model in Africa. The creation of the Africa Regional Office in Kigali, Rwanda, and the

establishment of a Kenya-based AVEC Africa office are the first steps, and projects and training have started to develop the AVEC Africa portfolio.

Abstract # 2 (MERS)

S. Korea experienced the largest outbreak of MERS outside of the Middle East in 2015. While not of the scale of the future COVID-19 pandemic, a number of lessons learned during that outbreak would prove to be highly effective in the subsequent coronavirus-related event, 2020-2023. IVI was the recipient of a ~34M USD award for MERS vaccine development. Some of the award was used to support the testing of the GeneOne/Inovio DNA MERS vaccine. In addition, IVI received a multicenter award from the Korean government for the development and testing of MERS vaccine evaluation system (in collaboration with SNU-Med, Yonsei University, and Atgen. IVI was the grant coordinator and the led the development of a pseudovirus-based neutralization assay. Finally, IVI was funded by the Coalition for Epidemic Preparedness Innovations (CEPI) to work with the National Institute for Biological Standards and Controls (NIBSC, UK) to obtain and characterize high-titer post-MERS infection serum for use as a laboratory standard. The techniques and experience developed during work on MERS were important for IVI's future work on COVID-19 vaccines (from site development through preclinical studies, assay development, and clinical trials).

Shee Eun Lee

Professor Shee Eun Lee has been dedicated to researching the development of adjuvants, which are considered critical components in vaccine and immunotherapy development, since joining Chonnam National University in South Korea in 2003. She reported a pioneering paper verifying flagellin's efficacy as a mucosal immune adjuvant, marking a significant advancement in this field. Since then, she has secured the original technology for flagellin, a universal adjuvant, and has continuously advanced her research to upgrade the flagellin-based adjuvant platform. Her work aims to apply this technology to infectious diseases and various immune disorders, including cancer. Through her ongoing research, she is contributing to the establishment of vaccine sovereignty and the development of next-generation immunotherapeutics.

Abstract

Alzheimer's disease (AD) and related tauopathies involve pathological tau protein aggregation, leading to neurofibrillary degeneration and dementia. Targeted immunotherapy to eliminate pathological tau aggregates can improve cognitive deficits in AD animal models. Effective immunotherapy should selectively target pathological tau while preserving normal tau function. The tau repeat domain (TauRD) is critical for tau-microtubule interactions and aggregation of hyperphosphorylated tau. Given that TauRD forms the structural core of tau aggregates, immunotherapies targeting TauRD-induced aggregates hold promise for treating tauopathies. We generated recombinant TauRD polypeptides that form neurofibrillary tangle-like structures and evaluated TauRD-specific immune responses following intranasal immunization with the mucosal adjuvant FlaB in BALB/C mice. Repeated immunizations at one-week intervals induced robust, TLR5-dependent TauRD-specific antibody responses. The resulting antiserum recognized only the aggregated form of TauRD, inhibiting filament formation and promoting the phagocytic degradation of TauRD aggregate fragments by microglia. The antiserum also specifically

recognized pathological tau conformers in the human AD brain. Based on these findings, we engineered a built-in flagellin-adjuvanted TauRD (FlaB-TauRD) vaccine and tested its efficacy in a P301S transgenic mouse model. Mucosal immunization with FlaB-TauRD improved the quality of life, ameliorating memory deficits and alleviating tauopathy progression. Notably, the survival of the vaccinated mice was dramatically extended. Our study demonstrates the efficacious induction of antibody responses specifically targeting pathological tau conformers and highlights the therapeutic potential of TauRD PHF conformer-targeting active immunization via the intranasal route. In conclusion, we developed a mucosal vaccine that exclusively targets pathological tau conformers and prevents disease progression, representing a promising approach for the treatment of tauopathies.

Guanghui Ma

Guanghui Ma is a professor of Institute of Process Engineering (IPE), CAS. She is an academician of Chinese of Academy Sciences, and TWAS member and AIMBE fellow. She is serving as Director of the State Key Laboratory of Biochemical Engineering. She received Bachelor degree from Gunma University, Master and PhD degrees from Tokyo Institute of Technology, respectively. She joined SKLBCE as a professor in 2001 and was promoted to the director in 2012. Her research interests focus on the preparation of uniform microspheres and microcapsules and their applications in biochemical engineering and biomedicine engineering, such as biochemical separation media, drug carriers, vaccine adjuvants (vaccine delivery systems), microcarriers for cell culture, and enzyme immobilization carriers. She has published over 500 papers, including *Nature, Nat. Mater., Nat. Nanotechnol. Nat. Biomed. Eng., Nat. Commun., Sci. Adv., JACS, Adv. Mater., etc*. She has more than 90 patents authorized, the technology and products have been commercialized in companies, and have been used in more than 500 affiliations in the world. She has received the State National Invention Award (2nd Class; 2009), the Beijing Science and Technology Award (1st Class; 2005), the Basic Research Achievement Award (1st Class prise of Science and Technology Award; 2020) of the Chemical Industry and Engineering Society of China, and Natural Science Award (1st Class; 2020) of the Chinese Society of Particuology.

Abstract

The coronavirus disease pandemic has fostered major advances in vaccination technologies; however, there are urgent needs of mucosal immune responses and single-dose, non-invasive administration. We developed a SARS-CoV-2 vaccine for single-dose, dry-powder aerosol inhalation that induces potent systemic and mucosal immune responses. Our vaccine encapsulates proteinaceous cholera toxin B subunit-assembled nanoparticles displaying the SARS-CoV-2 RBD antigen (R-CNP) within PLGA microcapsules of optimal aerodynamic size, and such unique nano-micro coupled structure supports efficient alveoli delivery, sustained R-CNP release, and antigen presenting cell uptake, which are favourable for invocation of immune responses. Porous PLGA micro-sized particle with uniform size was prepared firstly, then it was immersed in nano vaccine (R-CNP) aqueous solution, R-CNP diffused into the inside of PLGA microcapsule, the surface of microcapsule was self-healed just by increasing temperature to 42°C. Moreover, our vaccine successfully induces robust serological IgG and secretory IgA production, collectively conferring effective protection from SARS-CoV-2 challenge (including pseudovirus and the authentic virus) in mice, hamsters, and non-human primates. Finally, we also demonstrate a "mosaic iteration" of our vaccine that co-displays ancestral and Omicron's antigens, thus extending the breadth of antibody response against co-circulating strains and transmission of Omicron variant. These findings

support our inhalable vaccine as a promising candidate to prevent SARS-CoV-2 infection, disease, and transmission.

Leyuan Ma

Dr. Ma obtained his PhD degree in biomedical sciences from Dr. Michael Green's lab at the University of Massachusetts Medical School in 2016. Following graduation, Dr. Ma continued his postdoctoral fellowship in Immunotherapy and Immune Engineering at Massachusetts Institute of Technology and Howard Hughes Medical Institute under the guidance of Dr. Darrell Irvine. During his fellowship, Dr. Ma developed a synthetic booster vaccine to enhance the Chimeric Antigen Receptor T cell therapy for solid tumors, and he was supported by an American Cancer Society postdoctoral fellowship from 2019-2021. In 2022, Dr. Ma was appointed as an assistant professor in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania. Dr. Ma is also a member of the Raymond G. Perelman Center for Cellular and Molecular Therapeutics (CCMT) at the Children's Hospital of Philadelphia. Dr. Ma was awarded the NIAID new innovators award (DP2), the MRA Young Investigator Award, the Sontag Foundation Distinguished Scientist Award.

Abstract

Chimeric Antigen Receptor T cells (CAR T) are effective in hematologic malignancies, but strategies to augment their therapeutic impact especially in solid tumors are still needed. Here we demonstrate an approach to enhance CAR T function by vaccine-boosting donor cells through their chimeric receptor directly in vivo. Amphiphile CAR T ligand vaccine (amph-vax) were designed, which on injection trafficked to lymph nodes, decorated the surfaces of antigen presenting cells, and primed CAR T cells in the native lymph node microenvironment. Amph-vax boosting triggered massive CAR T expansion, increased donor cell polyfunctionality, and enhanced anti-tumor efficacy in multiple immunocompetent tumor models. Unexpectedly, in vivo vaccine boosting of CAR T cells triggered engagement of the endogenous immune system to circumvent antigen-negative tumor escape and more effectively treat established tumors with pre-existing antigenic heterogeneity. This process was accompanied by shifts in CAR T metabolism toward oxidative phosphorylation in CAR T cells and was critically dependent on CAR T-derived IFN-γ. We will also present a novel direct evolution-based ligand discovery approach for developing a customized booster vaccine for FDA-approved CD19 CAR T. In sum, vaccine boosting provides a clinically translatable strategy to enhance CAR T cell therapy against cancer.

Andreas Holm Mattsson

Andreas Holm Mattsson serves as Chief AI Officer at Evaxion Biotech, where he's been at the forefront in silico-based vaccine target discovery. He has played a key role in developing Evaxion's innovative AI-immunologyTM platform, a proprietary AI technology for identifying novel vaccine targets for cancer and infectious diseases. Andreas brings a strong educational background in bioinformatics from the Technical University of Denmark and has previously worked at Novo Nordisk. Since founding Evaxion in 2008, he has been an essential part of the company's growth, serving in various executive roles. His journey in the biotech industry reflects his dedication to advancing science and improving healthcare through innovative solutions.

Abstract

The growing challenge of antimicrobial resistance and the rapid emergence of new infectious pathogens highlight the critical need for innovative vaccine development strategies. Artificial intelligence (AI) and machine learning (ML) can significantly enhance the speed, efficiency, and precision of this process, aiding in preventing infectious diseases globally.

Evaxion, a pioneering TechBio company, has developed a clinically validated platform, AI-Immunology™, for rapid vaccine target discovery, design, and development. The platform consists of a collection of unique in-house developed AI building blocks that can be intelligently combined to generate tailored AI prediction models addressing complex immune-related healthcare issues.

AI-Immunology™ quickly identifies antigens that trigger robust and protective immune responses against pathogens. It leverages proteomic data to identify novel B-cell antigens, validated in preclinical models for several bacterial pathogens (S. aureus, N. gonorrhoeae, A. baumannii, K. pneumoniae, P. aeruginosa, M. catarrhalis, and non-typeable H. influenzae). Furthermore, it selects protective T-cell epitopes from any bacterial or viral target using genomic and proteomic data. In preclinical studies, an AI-Immunology™ designed vaccine induced a strong T-cell response and protected against lethal disease upon live viral challenge with SARS-CoV-2.

The validation of AI-Immunology™ demonstrates its ability to link predictions with preclinical and clinical outcomes, a groundbreaking achievement in vaccine research that forms the foundation of Evaxion's vaccine product candidates.

Unlike traditional reverse vaccinology approaches that heavily rely on previously tested antigens and existing immunological readouts, AI-Immunology™ is trained to identify underlying feature patterns, enabling rapid discovery of novel vaccine targets within hours or days instead of years. This significantly shortens the overall development timeline, offering a promising approach to accelerating the development of effective vaccines to combat the urgent challenges posed by antimicrobial resistance and emerging pathogens.

Dal-hee Min

Dr. Dal-Hee Min is currently a Professor at Seoul National University and co-founder of Lemonex Inc.

She received her Ph.D in Chemistry from the University of Chicago. After post-doctoral research at MIT, she started her academic career at KAIST (Korea) as an Assistant Professor in 2007 and moved to Seoul National University as an Associate Professor in 2011.

Her research focuses on drug delivery systems with a collective understanding of nano-surface chemistry and diverse biomedical applications of nanomaterials, including mRNA vaccines and gene therapies towards safe, effective, and thermostable biomedicines.

She received various prestigious awards, including 'The KCS-Wiley Young Chemist Award', 'The Korea L'Oreal UNESCO Fellowship Award for Women in Science' and 'The Order of Science and Technology Merit (Do-Yak Medal)' from the Korean Government.

She is actively involved in many global activities. For highlighted activities, she gave two invited talks at the World Economic Forum in 2018 where she introduced DDS technology-'Miniaturizing Biotechnology' in sessions 'Bio-Inspired Drug Delivery' and 'Harnessing Nature for Technology '. She also gave invited talks at the mRNA health conferences, PODD, JP Morgan, and BIO USA.

Abstract

Recently, there have been significant advances in RNA-based medicine, such as COVID-19 mRNA vaccines that employed lipid nanoparticles (LNPs). However, the need for next-generation mRNA delivery systems is strongly emerging due to 1) Stability: ultra-cold chain issues in storage and distribution due to the instability of LNPs, 2) Safety: side effects due to allergic reactions and systemic distribution due to its components, and 3) Speed: the difficulty of rapid mass production.

Lemonex develops safe and effective RNA medicine and cancer immunotherapy based on innovative non-viral, non-LNP, thermostable drug delivery platform technology. The core drug delivery system (DDS), 'DegradaBALL®', is a novel porous inorganic nanoparticle-based global first-in-class DDS that maximizes therapeutic efficacy and minimizes systemic side effects. DegradaBALL can solve cold-chain issues of current LNPs and maintain its stability for more than 2 yrs at room temperature. Also, DegradaBALL is compatible with various APIs including mRNA, siRNA and protein, enabling non-LNP, non-viral, extra-hepatic delivery. The advantages of DegradaBALL make it suitable for the '100 days mission', of which the aim is for the world to be able to respond to the next Disease X with a new vaccine in just 100 days.

We completed the phase I clinical trial of the siRNA-DegradaBALL pipeline (LEM-S401) and confirmed the safety and tolerability of DegradaBALL in healthy humans. We also obtained IND approval for another pipeline, LEM-mR203, COVID-19 mRNA-DegradaBALL vaccine. Recently, Lemonex signed a strategic partnership with CEPI (Coalition for Epidemic Preparedness Innovations) to develop a new "DegraderBALL-Reducerna" mRNA vaccine platform to advance vaccine delivery against future pandemics.

In this talk, I will introduce the development of DegradaBALL-based medicines, including next-generation prophylactic mRNA vaccines. We look forward to active discussions for partnership opportunities to develop safe and effective DegradaBALL-based mRNA vaccines and therapies.

Moon Nahm

Moon H. Nahm, Professor of Department of Medicine, with secondary appointment in Microbiology, obtained both his BA degree (in 1970) and MD degree (in 1974) from Washington University in St. Louis MO. In 1980, he completed both Internal Medicine and Laboratory Medicine residency training in Pathology Department, as well as completing post-doctoral research training in Microbiology Department at Washington University in St. Louis MO. He was a faculty member at Washington University in St. Louis and University of Rochester before he joined UAB. He was the director of the Clinical Immunology Laboratory for UAB hospitals. He has been the director of a WHO Pneumococcal Serology Reference Laboratory since 2001. He is currently an Endowed Professor Emeritus of Lung Health in the Department of Medicine at UAB.

Abstract

The bacterium Streptococcus pneumoniae, or pneumococcus, is a major human pathogen that possesses a variable polysaccharide capsule on its surface. Since the capsule serves as a key target for protective antibodies, pneumococcal vaccines are designed to include multiple capsule types for broad protection. However, certain capsule types, like 19A and 19F, share structural similarities, leading to situations where antibodies against 19F in the vaccine can cross-react with 19A capsules without effectively opsonizing

(marking for immune destruction) pneumococci. Recognizing this limitation, our laboratory developed a high-throughput opsonophagocytosis assay (OPA) using HL-60 cell lines, allowing for more accurate evaluation of vaccine efficacy against different pneumococcal strains. The OPA technology simplified the process of licensing vaccines and facilitated the development of adult-specific pneumococcal vaccines. Furthermore, research into the 19A and 19F capsule synthesis mechanisms revealed the 'wzy' gene encodes the capsule polymerase and showed molecular steps involved in the polymerase action.

Nicaise Ndembi

Professor Nicaise Ndembi is a Senior Advisor to the Africa CDC's Director General and currently Associate Professor, Division of Epidemiology and Prevention at the Institute of Human Virology (IHV), University of Maryland School of Medicine, Baltimore, USA. Dr. Ndembi is a graduate of Kanazawa University School of Medicine, Department of Viral Infection and International Public Health, Japan and a Research Professor within the same Institution. He is a Principal Investigator on numerous grants including US National Health Institute/NIAID. He is the Editor-in-Chief of the Journal of Public Health in Africa, AIDS Research and Therapy, and serves on various World Health Organization and US National Institute of Health study sections. Through his leadership, a framework for Africa vaccine manufacturing was established. He has authored or co-authored over 200 peer-reviewed papers and book chapters in professional journals.

Abstract

Sustained capacity-building efforts facilitated by a consortium of donors and partners, including EDCTP, the French National Agency for Research on AIDS and Viral Hepatitis (ANRS), the U.S. National Institutes of Health (NIH), the Welcome Trust, and the Bill & Melinda Gates Foundation (BMGF), can strengthen clinical trial capacity for improved pandemic preparedness, prevention, and response in Africa. This collaborative approach underscores the importance of international cooperation and investment in developing a resilient healthcare infrastructure capable of conducting clinical research to inform the response to future health crises. It also highlights the need for indigenous funding by African philanthropists and governments that signed the Abuja declaration two decades ago, committing to a minimum of 15% of their annual budget for the health sector, including research. This will contribute to the sustainability of the African clinical trial consortium and decolonizing Global Health. However, the implementation of this commitment by governments has not reached the desired level.

Africa's diverse genetic and epidemiological landscape presents a unique opportunity for conducting clinical trials that can offer insights into disease mechanisms and treatment responses in Africa that are globally relevant. The H3Africa initiative is a continental asset in this respect. The establishment of biobanks is a step towards harnessing this genetic diversity, providing valuable resources for research into genetics, infectious diseases, and non-communicable diseases. Leveraging Africa's growing biobanking infrastructure can also enhance the continent's readiness to participate in vaccine development and other diagnostic and therapeutic research critical for pandemic response.

Albert Osterhaus

Professor A.D.M.E. (Ab) Osterhaus, trained as a veterinarian with a PhD in Virology (Utrecht University), was head of the Department of Viroscience at Erasmus MC until 2014 and is currently Founding Director

of the Center of Infection Medicine and Zoonosis Research at the University of Veterinary Medicine Hannover. During almost 40 years as a scientific researcher and PI of numerous scientific projects, more than 80 human and animal viruses were discovered (e.g. human metapneumo-, human corona- and influenza viruses), their pathogenesis elucidated, and innovative intervention strategies developed. He helped authorities like WHO, to combat emerging infections like SARS, MERS and avian influenza. He mentored more than 85 PhD students, holds several key patents, and is author of more than 1350 scientific papers (H index >130). Ab Osterhaus firmly believes that scientists should translate their knowledge for the benefit and protection of society.

Abstract

To be better prepared for future emerging epidemics and pandemics, lessons should be learnt from intervention strategies practised during the most recent Influenza and COVID-19 pandemics. The exceptionally fast development and large-scale production of safe and effective vaccines against SARS-CoV-2, provided a crucial tool to mitigate morbidity and mortality levels during the emerging COVID-19 pandemic. Virtually all classical and novel vaccine development platforms were explored, which eventually led to more than 150 clinically tested COVID-19 vaccine candidates and more than two dozen of authorized or approved human vaccines. Live attenuated, inactivated and recombinant subunit vaccines were gradually outcompeted by recombinant viral vectored and eventually mRNA-based vaccines expressing the viral S protein. Safety, immunogenicity and protective efficacy were the most important selection criteria, that were addressed in a record time. However, decreasing protection against newly emerging SARS-CoV2 variants of concern, manufacturing complexity, production costs, and cold-chain requirements, collectively limited the applicability of some of the most successful vaccines, especially in low- and middle-income countries. For the choice of vaccine platform it is important to also consider correlates of antibody or T cell mediated protection, induced by natural infection or vaccination. We have addressed immune mediated correlates of protection against infections with emerging coronaviruses (SARS-CoV-2), influenza viruses (HPAI H5N1), flaviviruses (TBEV) and bunyaviruses (RVFV), as well as their relevance for vaccine development and production. Finally, our studies on properties and advantage of new-generation recombinant vaccine candidates and monoclonal antibodies produced in the fungal expression system Thermothelomyces heterothallica C1, will be presented.

Collectively, from the unprecedented and rapid response to the COVID-19 pandemic it may be concluded that continuously increasing knowledge of protective mechanisms as well as technological advances, will enable us to more efficiently tackle future emerging virus infections.

Sallie Permar

Dr. Sallie Permar is the Nancy C. Paduano Professor and Chair of Pediatrics at Weill Cornell Medicine and Pediatrician-in-Chief at NewYork-Presbyterian/Weill Cornell Medical Center. She is also Professor of Immunology and Microbial Pathogenesis at the Weill Cornell Graduate School of Medical Sciences. She received her M.D. from Harvard Medical School, a Ph.D. in Microbiology/Immunology from Johns Hopkins Bloomberg School of Public Health, and a Fellowship in Pediatric Infectious Diseases at Children's Hospital in Boston. After serving as an Assistant Professor of Pediatrics at Harvard Medical School, she joined the Duke University School of Medicine faculty where she was named the Wilburt C Davison Distinguished Professor of Pediatrics. With more than 15 years of experience in her field, she is a physician scientist

focused on prevention and treatment of neonatal viral infections and leads a laboratory investigating immune protection against vertically-transmitted viral pathogens, including HIV and cytomegalovirus (CMV).

Abstract

The pursuit of a vaccine for cytomegalovirus (CMV), the leading global infectious cause of birth defects and brain damage, has been ongoing for nearly 50 years. Yet, there are gaps in the knowledge of which immune responses are most important for a vaccine to block placental CMV transmission that are impeding rational vaccine development. We have used both studies of immune correlates of congenital CMV transmission in human cohorts and mechanistic models of congenital CMV infection in nonhuman primates to define the immunologic and virologic determinants of placental CMV transmission. This work has revealed that Fc-mediated effector antibody functions, but not neutralizing antibodies, are implicated to have a role in protection against congenital CMV infection. Moreover, the most successful CMV vaccines tested to date mediated partial immunity in the setting of limited neutralizing antibodies, yet induction of conformationally-dependent anti-viral antibodies and non-neutralizing antibody functions. Thus, we have developed and assessed the immunogenicity of CMV vaccination strategies to enhance these non-neutralizing effector antibody functions via impeding the viral immune evasion strategies. Enhancing antiviral immunity that is implicated in protection against placental CMV transmission through rational vaccine development may be key to reducing the impact of this common congenital virus infection and cause of long term disabilities.

Angie Rasmussen

Dr. Angela (Angie) Rasmussen, PhD is a virologist at the Vaccine and Infectious Disease Organization (VIDO) at the University of Saskatchewan. Her research focuses on the role of the host in virus susceptibility and pathogenesis, with a particular interest in emerging viruses that are or have the potential to be major threats to global health, such as avian influenza virus, dengue virus, Ebola virus, mpox (monkeypox) virus, MERS-CoV, and SARS-CoV-2. Her work combines classical experimental virology and animal models with systems biology approaches to study the global response to infection and how that contributes to pathogenesis or protection from emerging pathogens.

Dr. Rasmussen graduated from Smith College with a BA in Biological Sciences (2000) and received a MA (2005), MPhil (2006), and PhD (2009) in Microbiology and Immunology from Columbia University. She did her postdoctoral fellowship at the University of Washington and previously held faculty positions at the University of Washington and the Columbia Mailman School of Public Health, as well as an affiliation with the Georgetown Center for Global Health Science and Security. In addition to her primary appointment at VIDO, Angie is also an adjunct professor in the Department of Biochemistry, Microbiology, and Immunology at the University of Saskatchewan and an adjunct professor in the Department of Ecology and Evolution at Stony Brook University. She is the co-lead of the Coronavirus Variants Rapid Response Network (CoVaRR-Net) Host-Virus Interactions pillar. She is also a member of the WHO Ad Hoc Expert Committee for Preclinical Models of COVID-19 and sits on the Editorial Boards at Vaccine, mSphere, and Cell Reports.

In addition to her research, Dr. Rasmussen is a prolific science communicator on both social media and in the mainstream press, as well as a writer for numerous publications including Forbes, Leaps.org, Slate,

Foreign Affairs, the Washington Post, and the New York Times. She is passionate about advocating for equity in biomedical research and public health, and is a member of the US NIH Advisory Committee to the Director Working Group on Changing the Culture to End Sexual Harassment, as well as a faculty mentor for the volunteer science education group Wearing is Caring. She believes strongly that biosecurity and global public health must be collaborative international efforts and is eager to extend this outreach work in Canada and abroad.

Abstract

Cross-species transmission of highly pathogenic avian H5N1 influenza A virus (H5N1) has occurred multiple times since it emerged in 1997, both into humans and into other animals. In the current panzootic, there have been multiple instances of transmission from birds into mammals, including outbreaks at fur farms, marine mammal die-offs, and a large uncontrolled outbreak among dairy cows in the United States. Phylogenetic analysis demonstrates that the US dairy cattle outbreak began with a single independent spillover from birds in late 2023 and was undetected for nearly four months, allowing for broad spread across the country. Furthermore, sequence analysis reveals that viruses have spilled back from infected cows into birds, domestic cats, wild mammals, and humans. The ability of H5N1 to infect a broad variety of both avian and mammalian hosts presents significant barriers to control and reduce risks to both animals and humans. Adaptation to novel hosts can produce unpredictable outcomes and may increase the risk of reassortment and the emergence of more pathogenic or transmissible strains, including potential pandemic strains. Given that current approaches to H5N1 surveillance and containment have not been successful at stopping or reducing spillover to new species, a new strategy is warranted. H5N1 risk reduction should include research to assess potential susceptible hosts and approaches to veterinary and human vaccine development in addition to expanded surveillance and testing efforts.

Nina Russell

Dr. Nina Russell oversees the foundation's investments in vaccine and drug research and development to prevent and treat tuberculosis (TB) and HIV. These include vaccines, long-acting drugs, and biologics for HIV prevention, as well as TB vaccine and drug products that the foundation is advancing in close collaboration with the Bill & Melinda Gates Medical Research Institute and other partners. Nina also works in collaboration with the foundation diagnostics team to develop point-of-care TB diagnostics.

Nina has been involved with translational HIV vaccine research for over 20 years and, after joining the foundation in 2005, co-created the Collaboration for AIDS Vaccine Discovery, a foundation funding model that established a highly collaborative community of leading HIV scientists with a diverse portfolio of early- to late-stage active and passive immunization projects. This model has since been used to create the Collaboration for TB Vaccine Discovery, a foundation-supported international network of scientists and experts focused on TB vaccine discovery and translational research.

Previously, Nina worked at the Fred Hutchinson Cancer Research Center, where she managed a pipeline of Phase I and Phase II HIV vaccine clinical trials for the HIV Vaccine Trials Network, working in close collaboration with academic, biotech, and industry partners to advance novel vaccine candidates into clinical testing.

Nina serves on the Vaccine Research Center Scientific Advisory Working Group at the National Institutes

of Health (NIH) and the NIH's AIDS Vaccine Research Subcommittee. She completed a residency in internal medicine at the New York Hospital-Cornell Medical Center and a clinical and research fellowship in infectious diseases at the Montefiore Medical Center – Albert Einstein College of Medicine.
Nina received her M.D. from the Case Western Reserve University School of Medicine and a B.A. from Yale University.

Abstract
Dr. Nina Russell, Director for TB/HIV Research and Development at the Bill & Melinda Gates Foundation, will present an overview of the current vaccine development pipeline, emphasizing the crucial challenges and access priorities for TB and HIV vaccines. As global efforts intensify to combat the dual burden of these infectious diseases, Dr. Russell will provide a detailed analysis of the most promising candidates in development, including novel TB and HIV vaccine platforms designed to enhance efficacy and durability. Dr. Russell will outline the Gates Foundation's strategy for accelerating vaccine research and development, emphasizing public-private partnerships, and innovative funding models. The talk will underscore the foundation's commitment to achieving global health equity by ensuring that life-saving vaccines for TB and HIV are not only developed but made accessible to those who need them most.

Kaku Saito

Kaku Saito is the Senior Director and Head of Clinical Development (Oncology) for APAC at Moderna Japan, a role he has held since March 2023. He previously held leadership positions at Daiichi Sankyo, both in Japan and the U.S., where he played a pivotal role in the global clinical development of the antibody-drug conjugates. Dr. Saito holds a Ph.D. in Cancer Biology from Tohoku University and an Executive MBA from Rutgers Business School. His expertise spans oncology therapeutics, clinical trial management, and drug development, with numerous publications in leading medical journals.

Abstract
Background: mRNA-4157 is a novel, mRNA-based individualized neoantigen therapy designed to increase endogenous antitumor T-cell responses by targeting unique tumor mutations. In the phase 2 KEYNOTE-942 trial (mRNA-4157-P201), patients with resected high-risk stage IIIB–IV cutaneous melanoma receiving mRNA-4157 + pembrolizumab (pembro; combo) had prolonged recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) vs pembro alone (Weber JS, et al. *Lancet.* 2024).
Methods: Patients were assigned 2:1 to mRNA-4157 (1 mg IM, max 9 doses) + pembro (200 mg IV, max 18 cycles) or pembro alone. The primary endpoint was investigator-assessed RFS; secondary endpoints included DMFS and safety.
Results: With an additional year follow-up (data cutoff, 03 Nov 2023; median [range], 34.9 [25.1–51.0] mo) after the primary analysis, RFS benefit in the combo arm was maintained with 49% risk reduction in recurrence and/or death (HR [95% CI], 0.510 [0.288–0.906]; 2-sided nominal p-value 0.019). The 2.5-yr RFS rate of combo treatment (tx) vs pembro alone was 74.8% vs 55.6%. Combo tx also produced clinically meaningful, sustained improvement in DMFS vs pembro alone (HR [95% CI], 0.384 [0.172–0.858], 2-sided nominal p-value 0.0154). RFS benefit of combo vs pembro was consistently observed across key subgroups. mRNA-4157 was well tolerated and combo tx had a safety profile consistent with previous

analysis with no potentiation of immune-related AEs.
Conclusions: This 3-year analysis demonstrated durable clinical benefit with mRNA-4157 + pembro versus pembro alone, suggesting that this combination may provide significant advantages for a broad patient population. This session will review these results and further discuss the clinical development of mRNA-4157 for cancer patients. Clinical trial information: NCT03897881.

Yoshimasa Takahashi

Yoshimasa Takahashi, PhD, graduated from University of Tokyo. He received his postdoctoral training at the University of Maryland at Baltimore, where he worked on understanding the basic mechanisms for humoral immune memory and antibody responses. He joined the National Institute of Infectious Diseases (NIID) in Japan, and became Director at the Department of Immunology. He was appointed to Director of the Research Center for Drug and Vaccine Development, NIID in 2021. He also holds the position of Guest Professor at seven universities (Univ. of Tokyo, etc.). In this role, he trains graduate students in Immunology and Vaccinology.
Dr. Takahashi's research focuses on comprehending lymphocyte biology to unravel the humoral and cellular immune responses that underly vaccine effectiveness. By implementing high-throughput approach for human antibody analysis and isolation, he has identified novel classes of broadly protective antibodies against influenza, SARS-CoV-2, and other viruses. These findings provided the basis not only for antibody therapeutics but also for the rational design of next generation vaccines. Multiple vaccines and antibody therapeutics are under development by implementing computational approach.

Abstract
In-depth antibody repertoire and functional analysis against viral antigens have revealed several new signatures in the convergence and divergence of antibody responses that play important roles in adapting to viral antigens for conferring protection. Although the variable nature of immunodominant epitopes permits viral evasion from antibody responses, viral antigens possess epitopes that are crucial for viral fitness and are therefore conserved among variants and related viruses. The ability to recognize antigenically distinct viruses, defined as antibody breadth, is primarily achieved in B-cell populations by affinity-driven somatic evolution in germinal centers, sometimes referred to as antibody evolution. Our group has profiled antibody responses in humans and animal models against conserved epitopes from influenza, SARS-CoV-2, and other viruses. Studies from our group and others have unveiled the adaptive strategies of humoral immune responses to viral antigenic variations. Combined with the antibody-profiling data, computational approaches increase the feasibility of designing vaccine antigens and antibody therapeutics that target conserved epitopes for broad protection against antigenically divergent viruses. I will discuss the strategies to control antibody breadth for better vaccines and antibody therapeutics.

Axel Timmermann

Axel Timmermann conducted his PhD research at the Max Planck Institute of Meteorology in Hamburg, Germany and received his PhD in Meteorology in 1999 from the University of Hamburg. After 2 years as a postdoc in the Netherlands and 3 years as research team leader at the IfM-GEOMAR/University of Kiel,

Germany he moved to the University of Hawaii to work first as an associate professor and then from 2009-2016 as a full tenured professor at the International Pacific Research Center and the Department of Oceanography. In January 2017 Dr. Timmermann became the Director of the new IBS Center for Climate Physics (ICCP) at Pusan National University, where he also holds a Distinguished Professorship. In 2008 Axel Timmermann received the prestigious Rosenstiel Award in Oceanographic Science for his fundamental contributions to ocean science. In 2015 he was awarded the University of Hawai'i Regents' Medal for Research Excellence and in the same year he also became a Fellow of the American Geophysical Union. In April 2017 Prof. Timmermann received the Milankovic Medal from the European Geosciences Union in 2017 for his contributions to paleoclimate research. He has published over 228 peer-reviewed articles on subjects ranging from Quark-Gluon Plasma, relativistic hydrodynamics, the El Niño-Southern Oscillation, glacial cycles, abrupt climate change, climate prediction, human migration, bio-optics and dynamical systems' theory. Axel was listed in 2018~2023 as a Highly Cited Researcher by Clarivate Analytics. For his contributions to communicate climate research to the general public, Prof. Timmermann was awarded the "Scientist of the Year" award by the Korean Science Journalist Association in 2018.

Abstract

I will introduce some of the climate and disease modelling activities conducted at the IBS Center for Climate Physics (ICCP) at Pusan National University, South Korea and discuss how our existing model portfolio can be used in combination with biogeographic tools, epidemiological and agent-based models to determine the impact of past, present and future climate change on outbreak risks of diseases such as Malaria, Dengue Fever, Chikungunya, Zika, Yellow Fever.

1) The ICCP recently conducted a large-ensemble simulation with the Community Earth System model, version 2 (CESM2) with 1 degree global horizontal resolution. It comprises 100 climate model simulations, which cover the time range from 1850-2100 CE using the SSP 3-7.0 greenhouse gas emission scenario. The model simulations have been used to force the VECTRI epidemiological model in order to determine the future spread of Malaria and the time, when global warming-induced trends in Malaria transmission density exceed the level of natural variability.

2) We recently completed one of the highest-resolution global warming simulations to date, using the OpenIFS/FESOM climate model at 9 km global resolution. This unprecedented model simulation will provide more realistic regional climate information (including extreme events) that could be used for improved projections of future disease outbreaks.

3) We developed a new numerical computer model that simulates the spatio-temporal distribution of 2233 terrestrial mammal species on our planet and their response to future climate change and land use. The model is a unique tool to identify potential future hotspots for zoonotic infectious diseases.

4) Our center is developing a new generic modelling tool to simulate the spread of mosquito- and tick-borne diseases and their spread into new areas in response to future climate change.

I hope that my presentation will initiate a dialogue with conference participants, on how climate model simulations can be used to further determine risks of infectious disease outbreaks and increase overall preparedness.

Birgit Weinberger

Dr. Weinberger is a Full Professor of Immunology and the Head of the internationally renowned Institute for Biomedical Aging Research at the Universität Innsbruck, Austria, where aging processes are studied at the cellular and molecular level. Dr. Weinberger leads the "Immunosenescence and Vaccination" group.
Her research focuses on immunosenescence, particularly within the T cell compartment. Besides these basic research topics, the question how vaccinations can be optimized for the elderly is a central interest addressed in research projects analyzing immune responses to vaccination in older adults. Professional and public outreach to promote life-long vaccination concepts is an important part of her work. In addition, she is teaching immunology and aging-related topics at the Universität Innsbruck and is the Dean of Studies for Biology.
Dr. Weinberger studied biology in Regensburg, Germany and Boulder, CO, USA focussing on Genetics, Developmental Biology and Medical Microbiology. She holds a PhD from the Institute for Medical Microbiology and Hygiene of the University of Regensburg, where she worked on the role of Epstein-Barr Virus in transplant recipients.

Abstract
As people age, their immune system undergoes characteristic changes, often called immunosenescence. Changes in the function and composition of various immune cells, altered signal transduction, metabolic functions, and cytokine profiles contribute to this complex phenotype. Many vaccines are less immunogenic and effective in older adults, and several strategies have been followed to overcome these limitations.
Adjuvants can improve the efficacy of vaccines in older adults by enhancing the immune response on different levels. They work as delivery systems and/or immunostimulants, and several adjuvants are utilized in licensed vaccines specifically designed for older adults. Adjuvants often exert their effects at the injection site, where they can enhance antigen uptake and presentation, recruit immune cells, and improve or polarize cytokine production.
These outcomes are extensively investigated to elucidate the various modes of action. However, antigen-specific immune responses, namely antibodies and specific T cells, and ultimately clinical efficacy are the relevant read-out parameters in the clinical setting. Several adjuvants have been demonstrated to induce higher antibody and T-cell responses than the unadjuvanted antigen in older adults. Adjuvants can provide additional benefits by inducing a broader range of antibody specificities or targeting the antibody response against specific regions of the antigen. Direct comparisons of clinical efficacy or effectiveness are much rarer. We should also raise the question of whether immune responses induced by adjuvanted vaccines might be more durable and, therefore, provide longer-term protection.
Tremendous progress has been made in improving vaccines through the use of ever-more complex and sophisticated adjuvant systems, but we have also learned that not one perfect adjuvant fits all antigens, diseases, and target populations.

Tao Zhu

(Panel Speaker / Bio Only)
Tao ZHU, co-founder, Chief Scientific Officer (CSO) of CanSino Biologics. He has more than 20 years of

innovative vaccines R&D experience, including preclinical research, clinical research, and product registration. Zhu Tao obtained his Ph.D. in Chemical Engineering from the University of Pittsburgh in 2003. He established five leading technology platforms, including viral vector-based technology, synthetic vaccine technology, protein structure design and recombinant VLP technology, mRNA vaccine technology as well as formulation and delivery technology. He also led the research and development of more than 10 innovative vaccine products, including the world's first inhalation COVID-19 vaccine Convidecia Air, the WHO recommended adenovirus vector COVID-19 vaccine Convidecia, the only available recombinant Ebola vaccine, and the China's first tetravalent meningococcal conjugate vaccine. He has obtained 29 patent authorizations, and has published 61 scientific research papers in well-known domestic and foreign journals such as the Lancet.

ORAL PRESENTER ABSTRACTS

(Alphabetical Order by Presenting Author)

(1) Purification and characterization of bivalent vaccine candidate against SARS-CoV-1 and MERS-CoV expressed as inclusion bodies in E. coli

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Abstract: In the past 20 years, three beta coronaviruses—SARS-CoV, MERS-CoV, and SARS-CoV-2—have infected humans. There are no FDA-licenced vaccinations against MERS-CoV or SARS-CoV-1. Further, the development of vaccine that can accommodate multiple strains is urgently needed. In this study, the conserved epitopes of CoV1 RBD and MERS RBD were stitched on either side of novel nanoparticle scaffold without any tag. The codon optimized sequences were cloned into the pET28b (+) vector and transformed to the E. coli BL-21 host for expression. Following IPTG induction, the candidate namely, N9, expressed in E. coli cells and aggregated intracellularly as inclusion bodies. Inclusion bodies conventionally thought of as junk protein offer the advantage of cost effective and high yield purification without multiple chromatographic steps. The inclusion bodies (IBs) were recovered via exhaustive washing with ionic and non-ionic detergent to remove the contaminating proteins. The IBs were then solubilized using low amounts of urea as opposed to conventional harsh treatments like 8M Urea or 6 M GdnHCl which completely denature the protein. It was then followed by refolding in presence of sucrose as a stabilising agent. In SDS-PAGE analysis, the protein resolved as a ~69 kDa band indicating >95% purity. Size
exclusion chromatography indicated the formation of a multimeric structure. Dynamic light scattering based size measurement showed an average size of 26 nm whereas transmission electron microscopy results showed a size of 20–30 nm. There are 36 Tyr, 34 Phe, and 6 Trp residues in N9 which are sensitive to non-covalent interactions, polarity in the protein's milieu, and hydrogen bonding. Tryptophan fluorescence spectroscopy gave maxima at 343 nm. Additionally, the protein resisted any major changes in tertiary structure up till a temperature of 450C and was stable at 4 degrees Celsius for 21 days. The western blotting indicated reactivity with the stitched epitopes. The recovery yield for candidate N9 was ~85 mg/L which could be scaled to the yield up to 1g/L in a bioreactor. Further, immunological evaluation in BALB/c mice is ongoing with adjuvants Alum and AddaVax. Funding: The work was supported by the grant from the Coalition for Epidemic Preparedness Innovations ("CEPI") towards a Consortium involving THSTI and Panacea Biotec ltd.,to develop a Multi-epitope, Nanoparticle based broadly protective Beta coronavirus candidate vaccine ("Project").
Keywords: Bivalent nanoparticle vaccine, SARS, MERS, inclusion body, E. coli. **Abbreviations:** SARS: Severe acute respiratory syndrome, MERS: Middle East respiratory syndrome, RBD: Receptor binding domain, GdnHCl: guanidine hydrochloride, IBs: inclusion bod.

(2) A first-in-man placebo controlled, randomized, double-blind, phase I clinical trial of a multi antigen SARS-CoV DNA vaccine delivered by in vivo electroporation as a booster dose, following three doses of spike-based mRNA vaccines

Soo Aleman, Gustaf Ahlen, Jingyi Yan, Peter Bergman, Per Ljungman, Christian Bin Ahn Nordtoft, Sofia Appelberg, Matteo Cadossi, Simona Salati, Katja Tobin, Ola Tufvesson, Eva-Karin Gidlund, Friedeman Weber, Olivia Larsson, Urban Höglund, Lars Frelin, Ali Mirazimi, and Matti Sällberg

The COVID-19 pandemic has largely been controlled by active vaccination and adaptation of the SARS-CoV-2 virus to humans resulting in a milder disease. However, the constant evolution of the virus, and in particular in the receptor-binding domain (RBD) of the Spike (S) protein, has highlighted the need for vaccines targeting more stable domains of the virus. We developed a new vaccine, OC-007, based on the combination of three viral antigens, RBD-loops corresponding to the WH1, Alpha, and Beta variants, and the highly conserved membrane (M; WH1) and nucleoproteins (N;WH1). We evaluated the OC-007 DNA vaccine as a single booster dose (NaCl or 0.5 mg, 1.0 mg, or 2 mg OC-007 DNA) in 16 healthy volunteers following three doses of mRNA vaccines >3 months before inclusion. The study was designed as a first-in-man placebo controlled, randomized, double-blinded, dose escalation phase I clinical trial of the OC-007 DNA vaccine delivered by in vivo electroporation (EP). All subjects (38±13 age, and 62% men) were followed for three months after study drug injection and analyzed with respect to safety, tolerability, and SARS-CoV-specific immune responses. All subjects performed a weekly self-test for COVID-19 using a salivary rapid test. Overall, the OC-007 vaccine was deemed safe and

tolerable. No severe adverse events were recorded, except one adverse event of severe intensity was recorded in the 0.5 mg group with an increase in CPK levels that resolved spontaneously, possibly related to the study treatment or to intensive exercise. The most common side effect was transient pain during in vivo EP, with an average score of around 5 (visual analogue scale range 0-10), which returned to mean level of <3 in five minutes, < 2 in 15 minutes. We recorded a 5-fold increase in mean antibody levels to the S Beta variant and 20-fold to the N protein in the 2.0 mg dose group. A 2-fold increase was seen in mean neutralizing antibody levels to SARS-CoV-2 Beta (1.0 and 2.0 mg groups), and Omicron XBB1.5 variants (2.0 mg group). The overall strength of T cell responses, and in particular those to N and M (WH1), and N (Bat), significantly increased from baseline in the 0.5 mg group at day 14 and in the 2.0 mg group at day 84 ($p<0.01$, respectively, Fishers exact test). Two subjects in the 2.0 mg dose group, COVID-19 positive at day 21 and 28, respectively, had increasing humoral and T cell responses at day 14, and showed very strong recall responses at days 28 and 84. One in the placebo group was found COVID-19 positive at the time of vaccination. Taken together, although the study was small, a booster dose of the OC-007 DNA vaccine delivered by in vivo EP was safe and tolerable and seemed to induce immune responses comparable to other spike-based vaccines given as a 4th or 5th dose. Importantly, the OC-007 DNA vaccine improved unique broadly cross-reactive T cell responses to the highly conserved M and N proteins, a key feature of the vaccine design strategy.

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(3) mRNA engineered antibodies as immune therapeutics for herpes simplex virus associated disease.

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Herpes simplex virus-1 and 2 (HSV-1 and HSV-2) may cause life threatening infections such as neonatal herpes, herpes encephalitis, and disseminated infections in immunocompromised hosts. Antiviral therapy with acyclovir helps some individuals recover from the serious infection while others are left with serious sequelae. Antibody based treatment has been successfully used to treat cancers, immune disorders and many infections. While a few HSV mAbs are in early phase clinical trials, efficacy has yet to be proven. High production costs can further limit the accessibility and widespread use of such treatments. In this study, we investigated use of mRNA engineered antibodies for the treatment of severe HSV infection in the mouse genital infection model. We used an mRNA-based platform for expression of mouse specific mAb (IgG), single chain (sc Fv-Fc) and a bispecific (BsAb) antibody against two essential entry glycoproteins, gD and gB. The antibody heavy and light chains were expressed from a single bicistronic mRNA. Electrostatic steering mutations were incorporated to favor bispecific antibody formation. In vitro and in vivo administration of mRNA constructs for gD2 IgG, gB sc-Fv, and gD2-gB BsAb resulted in proper expression of each individual antibody and the bispecific antibody. These antibodies were formulated in lipid nanoparticles (LNP) individually or co-formulated in the same LNP and administered intravenously in mice to assess in vivo kinetics of mAb and BsAb expression. Serum IgG binding antibody kinetics measured by ELISA over 28 days revealed high-level expression of both gD2 IgG and gB sc-FV peaking on day 2 and still detectable on days 21 and 28 days, respectively. Peak binding antibody endpoint titers on day 2 for gD2 IgG, gB sc-Fv mAbs, and gD2-gB BsAb were 5 to 6 log10. Peak neutralizing antibody titers against HSV-2 were 4-8-fold higher when two mAbs were co-formulated or presented as bispecific Ab compared to when administered each mAb alone. Intravenous inoculation with mAbs and bispecific antibody encoding mRNA-LNP completely protected mice from HSV-2 genital herpes disease, subclinical and latent infection. mRNA engineered mAbs and bispecific antibodies provide a great promise to mitigate severe HSV disease and warrant further evaluation in therapeutic settings.

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(4) Rational Immunogen Design for a Pan-Betacoronavirus Vaccine

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Immune responses to SARS-CoV-2 primarily target the receptor binding domain of spike, which can readily mutate to escape acquired immunity. Other regions in the spike S2 subunit, such as the fusion peptide and the stem helix, are highly conserved across sarbecoviruses. However, these epitopes are partially occluded on the prefusion spike and subdominant, with only a small fraction of the humoral responses induced by vaccination or infection targeting them. With the goal of developing a next-generation pan-betacoronavirus vaccine, we recently reported the design of “epitope scaffolds” protein immunogens that elicited broadly cross-reactive antibodies against the fusion peptide and stem helix domains of coronavirus spikes. These immunogens display

the antibody-bound conformation of target epitopes onto the surface of engineered proteins for stabilization and unobstructed immune access. Epitope presentation and immunogen stability were optimized by integrating recently described AI-based protein engineering design and prediction methods into our computational platform. Engineered immunogens bound both mature and germline versions of multiple broad and protective human antibodies with high affinity as confirmed biochemically and structurally. Human antibodies isolated with epitope scaffolds as selection probes bound to multiple coronavirus spikes and protected against live MERS and SARS-CoV-2 virus challenges in mice, illustrating the potential of these immunogens to engage and amplify broad pre-existing humoral responses. In vaccinated mice, epitope scaffolds elicited sera that cross-reacted with diverse coronavirus spikes, including all human betacoronoviruses and animal viruses with pre-pandemic potential, and these responses protected against viral challenges. More recently, we found that these immunogens also induced broad responses in nonhuman primates. Antibodies that target the stem helix and have exceptional breadth within both 2b and 2c coronaviruses were isolated from vaccinated nonhuman primates. Importantly, the combination of mRNA spike with epitope scaffolds elicited sera with significant breadth against 2c coronaviruses, compared to mRNA spike or epitope scaffolds alone, thus providing a way to incorporate the immunogens engineered here into existing vaccination regiment to expand the breadth of the immune responses in the future. Taken together, our studies validate new pan-betacoranavirus vaccine candidates that preferentially elicit broad antibody responses against conserved coronavirus regions poorly targeted by current vaccines or natural immunity.

(5) Harnessing innate immune memory for enhancing vaccine efficacy: new molecular mechanisms controlling memory establishment and persistence

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Innate immune memory entails the capacity of innate immune cells to mount a more protective response to a new challenge. Innate immune memory can be generated in resident macrophages and tissue-infiltrating monocytes by previous exposure to an inflammatory event and is mostly based on epigenetic changes, resulting in a more protective reaction to a new challenge, which can result either in a potentiated secondary response or in tolerance. In mammals, including human beings, germline immune memory is generally non-specific, but it displays some degree of organ specificity, implying a role for the organ microenvironment in memory generation. We aim at exploiting the capacity of macrophages to generate non-specific defensive memory as a non-disrupting adjuvant strategy, for instance in the case of mucosal vaccines. We have used in vitro models of human primary cells (blood monocytes and gut-like monocyte-derived macrophages) to assess the generation of innate immune memory to different types of engineered and natural particulate challenges and known TLR agonists. Notably, memory generated in monocytes in much more potent than that inducible in resident macrophages, suggesting that memory induction requires an active local inflammatory event and the recruitment of monocytes from blood. Also, memory generated in mucosal and submucosal mast cells differs substantially from that observed in monocytes and macrophages and is also different between the two mast cell types. Memory generation, in particular the LPS-induced tolerance, seems to depend on chromatin/RNA modulation by G quadruplexes (G4). G4 are guanine-rich 4-stranded helical structures, which transiently form on nucleic acids around cations through Hoogsten hydrogen bonds and can interfere with various chromatin/RNA functions, including epigenetic modifications, by both enhancing and blocking them. We explored the role of G4 in LPS-induced tolerance in human monocytes with the use of the G4 ligand/stabilizer RHPS4 and identified a clear role of G4 in the development of innate memory towards a more inflammatory profile. Thus, a thorough analysis of the G4-dependent molecular mechanisms of innate memory could help us understanding how to modulate innate memory towards improved protection. Eventually, since the "immunobiography" of individual human beings is expected to differentially shape their innate immune memory, we suggest the need of an individual immune profiling as the basis for a tailored adjuvanticity strategy.
Work supported by the BMGF grant INV-059115, the ANSO grant ANSO-CR-KP-2022-01 and the China-Italy bilateral cooperation grant NSFC 82261138630.

(6) Novel Fully Synthetic Saponin-Based Vaccine Adjuvant for Protein-based Vaccines

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Adjuvants play a critical role in enhancing the immune response triggered by vaccine antigens, improving both its magnitude and duration. However, only a limited number of adjuvants have been approved for human vaccines, underscoring the urgent need for innovative adjuvant systems in global public health. QS-21, a glycoside extracted from Quillaja saponaria, is included in the licensed adjuvant AS01 used in vaccines for herpes zoster (Shingrix) and RSV (Arexvy). Yet, its widespread use is hindered by structural instability and low purification yield. Addressing these challenges, ImmunAdd has developed IA-05, a next-generation saponin adjuvant.. IA-05 is distinctive as it is fully synthetic and serves as a novel analog of QS-21. In preclinical studies of the adjuvanted flu vaccine, direct comparison between IA-05 and QS-21 demonstrated that IA-05 induces superior humoral and cellular-mediated immunity. It can be administered through various routes, including intranasal, intramuscular, and subcutaneous delivery. Mice receiving the IA-05-adjuvanted flu vaccine did not experience any side effects, and 4/7 mice vaccinated intranasally with IA-05-adjuvanted flu completely cleared heterologous viruses after challenge. In cancer immunotherapy studies, IA-05 has proven its ability to enhance vaccine efficacy by boosting antigen-specific CD8+ T-cell-mediated immunity when combined with anti-cancer vaccines. The IA-05 group showed enhanced tumor suppression effects, achieving tumor-free outcomes. The safety study showed that unlike QS-21, which induced a hemolysis effect of over 60% at a dose of 200 mcg/mL, IA-05 did not cause any hemolytic effect. This finding also correlated with the injection site reactions; IA-05 only caused slight edema and inflammation at a relatively high dose of 1000 mcg. The NOEAL (No Observed Effect Adverse Level) for IA-05 was determined to be over 5000 mcg in rats. Overall, IA-05 is a carefully engineered analog of QS-21 with enhanced stability, safety, scalability, and featuring a simplified formulation. It can be administered through various routes and demonstrates potent adjuvanticity in both prophylactic and therapeutic vaccine approaches.

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(7) Safety and immunogenicity of a SARS-CoV-2 mRNA virus-like particle vaccine in adults 18 years of age and older in a Phase 1 randomized clinical trial

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Background: Despite the rollout of effective vaccines against coronavirus disease 2019 (COVID-19), there remains an ongoing need for COVID-19 vaccines with improved potency, lower reactogenicity, broader coverage against emergent variants of SARS-CoV-2, and longer duration of protection. This study examined the safety and immunogenicity of two SARS-CoV-2 mRNA virus-like particle (VLP) vaccines. **Methods:** This is an ongoing, Phase I, open-label, randomized, active-controlled study assessing 2 dosages of AZD9838 (BA.4/5 variant) and AZD6563 (XBB.1.5 variant). Participants had previous natural immunity via either prior infection or primary series vaccination and were randomized to receive a single intramuscular injection of AZD9838 (Groups 1 and 2), AZD6563 (Groups 3 and 4), or 30 μg BNT162b2, a licensed SARS-CoV-2 mRNA vaccine (XBB1.5 variant). SARS-CoV-2 neutralizing antibody (nAb) titers against the ancestral, Omicron BA.4/5, Omicron XBB.1.5, and Omicron JN.1 variants were measured at baseline and Day 29. Solicited adverse reactions (ARs) were collected for 7 days post-vaccination and unsolicited adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs) were collected for 29 days post-vaccination. All comparisons were descriptive. **Results:** Overall, 166 healthy adults 18 to 64 years of age and 76 healthy adults ≥65 years of age were vaccinated. nAb geometric mean titers (GMTs) numerically increased from baseline and with increasing dosage of AZD9838 and AZD6563 in all groups. In participants 18 to 64 years of age, vaccination with dosage 2 of AZD6563 resulted in nAb GMTs similar to those observed with BNT162b2, while in adults ≥65 years of age, dosage 2 of AZD6563 generated a nAb GMT ratio of 1.92 (95% confidence interval 0.77, 4.75) for Omicron XBB.1.5 versus BNT162b2 at Day 29. Both AZD9838 and AZD6563 were well-tolerated at both dosages, with a numerically lower proportion of injection site pain and muscle aches reported among AZD6563 recipients compared with BNT162b2 recipients. Unsolicited AEs were numerically similar between groups; no related SAEs or AESIs were reported up to Day 29. **Conclusion:** This study showed that immunogenicity to a SARS-CoV-2 mRNA VLP vaccine was similar to that

of BNT162b2. Furthermore, the SARS-CoV-2 mRNA VLP vaccine was well tolerated, with fewer ARs reported compared with BNT162b2. **Funding:** This study was funded by AstraZeneca

(8) Protein nanoparticle vaccines induce potent neutralizing antibody responses against MERS-CoV

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Abstract: Middle East respiratory syndrome coronavirus (MERS-CoV) is a zoonotic betacoronavirus that causes severe and often lethal respiratory illness in humans. The MERS-CoV spike (S) protein is the viral fusogen and the target of neutralizing antibodies, and has therefore been the focus of vaccine design efforts. Currently there are no licensed vaccines against MERS-CoV and only a few candidates have advanced to Phase I clinical trials. Here we developed MERS-CoV vaccines utilizing a computationally designed protein nanoparticle platform that has generated safe and immunogenic vaccines against various enveloped viruses, including a licensed vaccine for SARS-CoV-2. Two-component protein nanoparticles displaying MERS-CoV S-derived antigens induced robust neutralizing antibody responses and protected mice against challenge with mouse-adapted MERS-CoV. Electron microscopy polyclonal epitope mapping and serum competition assays revealed the specificities of the dominant antibody responses elicited by immunogens displaying the prefusion-stabilized S-2P trimer, receptor binding domain (RBD), or N-terminal domain (NTD). An RBD nanoparticle vaccine elicited antibodies targeting multiple non-overlapping epitopes in the RBD, whereas anti-NTD antibodies elicited by the S-2P- and NTD-based immunogens converged on a single antigenic site. Our findings demonstrate the potential of two-component nanoparticle vaccine candidates for MERS-CoV and suggest that this platform technology could be broadly applicable to betacoronavirus vaccine development.

(9) An improved Theileria parva sporozoite seroneutralization assay to evaluate vaccine candidates for East Coast fever

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Immune correlates of protection are ideal tools to predict treatment or vaccine efficacy. However, the accuracy of the immune correlate and the capability to predict robustly the outcome of a vaccine candidate is determined by the performance of the in vitro immunoassay used. Several Theileria parva sporozoite seroneutralization assays have been previously used to assess antibody functional activities; however, a common limitation was the need for fresh material, target cells and sporozoites, and an operator-to-operator bias. An improved assay represents a positive step towards overcoming challenges associated with variability and it might provide a more reliable means of stablishing an immune correlate with protection after sub-unit vaccine administration. Here we describe several improvements, among them (1) the use of frozen parasites and target cells to avoid batch-to-batch variations and (2) the development of a new assay read-out based on the detection of infected cells by flow cytometry, instead of the use of Giemsa staining and microscopic evaluation, in order to increase reproducibility of results. The improved seroneutralization assay is not only able to detect the individual neutralizing capacity of antibodies; it also detects the additive effect of antibody combinations. This effect is described for the first time in Theileria parva and is of great interest for new antigen discovery and/or epitope discovery of already known antigens like p67, opening the avenue to in vitro down-selection of new Theileria parva vaccine candidates, thereby contributing to reducing the use of animals in challenge experiments.

(10) Pilot-scale production of inactivated monoglycosylated split H1N1 influenza virus vaccine provides crossstrain protection against influenza viruses

JR Chen, RH Biopharma

Influenza epidemics and pandemics caused by newly emerging virus strains highlight an urgent need to develop a universal vaccine against viruses. Previously, a monoglycosylated X-181mg vaccine demonstrated that the HA possessing a single N-acetylglucosamine at each N-glycosylation site is superior to confer broader protection in mice than conventional vaccines. However, the greatest challenge in conducting clinical trials is the need to develop robust manufacturing processes capable of producing vaccines at the pilot scale with the

desired stability, potency, and efficacy. Whether the monoglycosylated virus vaccine platform can be applied to the new vaccine strain in a timely manner and whether the mass-produced vaccine has the proper immunogenicity to induce cross-protective immunity remains unclear. Here, we show that a pilot-scale manufacturing process produced a monoglycosylated A/Brisbane/02/2018(H1N1) virus vaccine (IVR-190mg) with a single glycan at each glycosylation site of HA and NA. Compared with the fully glycosylated virus vaccine (IVR-190fg), the IVR- 190mg provided broader cross-protection in mice against a wide range of H1N1 variants. The enhanced antibody responses induced by IVR-190mg immunization include higher hemagglutination-inhibition titers, higher neutralization activity, more anti-HA head domain, more antiHA stem antibodies, higher neuraminidase activity inhibition titers, and notably, higher antibody-dependent cellular cytotoxicity. Additionally, the IVR-190mg also induced a more balanced Th1/Th2 response and elicited broader splenic CD4+ and CD8+ T-cell responses than IVR-190fg. This study demonstrated that IVR-190mg produced using a pilotscale manufacturing process elicits comprehensive cross-strain immune responses that have great potential to substantially mitigate the need for yearly reformulation of strain-specific inactivated vaccines.

(11) A Quadrivalent mRNA Vaccine Against HSV-2 Showed the Enhanced Immunogenicity and Protection Against Primary and Latent Infections

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Herpes Simplex Virus 2 (HSV-2) remains a significant global health concern, causing severe genital disease and establishing latent infections leading to recurrent outbreaks. Despite extensive research, no approved vaccine for genital herpes exists. This study presents the development and evaluation of a novel quadrivalent HSV-2 mRNA vaccine targeting envelope glycoproteins gB2, gC2, gD2, and gE2. We compared the quadrivalent vaccine to a single-antigen gD2 vaccine for immunogenic efficacy. Additionally, we assessed different lipid nanoparticle (LNP) formulation methods for the multivalent mRNA vaccine and evaluated full-length versus C-terminal truncated forms of the gD2 glycoprotein mRNA. The quadrivalent vaccine demonstrated significantly higher HSV-2 IgG titers (7 days post-immunization [dpi]: $p=0.0005$, 14 dpi: $p=0.0074$) and 50% neutralization titers (7 dpi: $p<0.0001$) compared to the single-antigen gD2 vaccine. LNP formulation methods did not significantly affect IgG or neutralization titers for the quadrivalent vaccine. The full-length gD2 vaccine showed superior neutralization compared to its truncated counterpart (14 dpi: $p<0.0001$). All vaccinated groups achieved 100% survival and effectively prevented dorsal root ganglia (DRG) latency following the HSV-2 challenge. Notably, the quadrivalent vaccine-induced effector memory CD8+ T cells after two vaccinations and the HSV-2 challenge provided enhanced protection of vaginal tissue compared to the gD2 vaccine. These findings suggest that the quadrivalent mRNA vaccine containing gB2, gC2, gD2, and gE2 offers a promising approach for preventing primary and latent HSV-2 infections. This study contributes valuable insights to the development of effective mRNA-based vaccines against HSV-2, potentially addressing a critical gap in genital herpes prevention.

(12) The comparison of plant virus nanoparticles in the presentation of a conserved influenza epitope to develop a universal influenza vaccine candidate in Nicotiana benthamiana

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The current global influenza vaccination rate (IVR) varies from >5% to ≤50%, with global IVRs skewing to a lower percentage of the general population. New flu vaccines are made annually which take an average of 5 months to produce, however, these vaccines are ineffective by the next winter season. This is owing to the current vaccine approach which focuses on the virus's surface glycoproteins; the epitopes of which are constantly mutating and reassorting resulting in antigenic drift and shift respectively, thus causing influenza

vaccines to often lose compatibility and/or specificity with circulating strains. Yearly vaccines are unpragmatic due to healthcare infrastructure and economic status in Sub-Saharan Africa, and so, a more relevant influenza vaccine approach is necessary. To address the need for a more affordable universal influenza vaccine, we made use of two approaches. Namely, the influenza ectodomain matrix protein (M2e), a highly conserved region with the potential of being a universal vaccine candidate, and secondly, the use of a plant expression system to ensure affordable, quick, and safe vaccine production. The M2e antigen is poorly immunogenic therefore the SpyTag/SpyCatcher conjugation system is used to display M2e on the surface of plant virus-like nanoparticles (VNPs). Five M2e peptide sequences of different origins fused with SpyCatcher (5xM2e-SC) and nanoparticles fused to SpyTag were synthesised and subsequently cloned into different plant expression vectors. Recombinant Agrobacterium harbouring genes were agroinfiltrated into Nicotiana benthamiana plants and expression time trials were performed to determine the optimal optical density (OD600) of Agrobacterium for infiltration and optimal protein accumulation days post-infiltration. Western blot analysis showed optimal expression of 5xM2e-SC and nanoparticles at 5 days post-infiltration using an infiltration OD600 of 0.5 and 0.25 respectively. The recombinant plasmids were successfully co-expressed in planta. The SpyTag/SpyCatcher conjugation was successfully confirmed by western blot analysis and transmission electron microscopy. The chimeric particles were successfully purified by use of polyethylene glycol precipitation and density gradient ultracentrifugation. The expected outcome is an influenza particulate candidate vaccine with the potential to confer broad protection against seasonal and new emerging pre-epidemic viral strains. The use of a plant-based expression system is more affordable than the traditional production system and the approach is fast thus enabling quick response to yearly influenza outbreaks.

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(13) Novel rabies vaccine offers potential for population wide pre-exposure prophylaxis in rabies endemic areas

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Despite the existence of effective vaccines, rabies causes 60,000 deaths annually. Current vaccines are mostly used for post-exposure prophylaxis (PEP) but are often not available when needed. Vaccines are recommended for pre-exposure prophylaxis (PrEP) for high-income travellers entering rabies-endemic countries, but are not available to those most at risk; children who reside in such countries. The use of rabies vaccines as PrEP for those who can afford it underlines its benefits, and the lack of access to those most at risk remains a striking health inequality. The relatively high costs of current rabies vaccines and the need for multiple doses means delivery of rabies PrEP programmes is considered too expensive for cost-effective use on a population level. RAB002 is a phase Ib/II clinical trial of a new rabies vaccine, ChAdOx2 RabG, including Tanzanian adults and children aged 2-6 years old. In both age groups, we compared participants receiving a single dose of ChAdOx2 RabG to those receiving a single dose of Verorab, a currently licenced rabies vaccine. In the paediatric age group, we also compare those receiving a single dose of ChAdOx2 RabG to those receiving two doses of Verorab according to a currently WHO-recommended PrEP schedule deployed locally. ChAdOx2 RabG was found to be well tolerated and highly immunogenic in both age groups. Using the accepted correlate of protection for rabies, virus neutralising antibody (VNA) levels, this new vaccine was found to be superior to the administration of a single dose of a currently licensed vaccine. In children, a single dose of ChAdOx2 RabG trended to superiority compared to a currently approved PrEP schedule requiring two doses of Verorab. A single-dose PrEP regime against rabies has the potential to address health inequality and prevent tens of thousands of rabies deaths each year. When coupled with the lower costs of manufacturing this vaccine, ChAdOx2 RabG performing at least as well as the currently approved PrEP schedule means single dose PrEP to control rabies is now within reach.

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(14) Two-year antibody persistence and safety of a single-dose live-attenuated chikungunya virus vaccine (VLA1553) in adults aged 18 years and above

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Background: VLA1553 is a live-attenuated chikungunya virus vaccine designed for active immunization as a prophylactic measure for individuals travelling to or living in endemic areas. Due to the sporadic epidemic occurrence of chikungunya, an immunological surrogate to assess clinical efficacy was accepted by regulators (FDA and EMA).

Methods: This phase 3 open-label, single arm long term antibody persistence and safety trial follows a subset (N=363) of VLA1553 vaccinees from a pivotal phase 3 trial (Schneider et al, 2023) where 4,115 adult participants received VLA1553 or placebo. The main study objective is to assess the proportion of participants with seroresponse (defined as μPRNT50 ≥150) annually, from 1 until 5 years after single immunization. Additionally, serious adverse events (SAE) were monitored from Month 6 until Year 2 post-vaccination. This presentation outlines immunogenicity and safety data collected until Year 2.

Results: The seroresponse rate was 97% (306/316, 95% CI 94.3% to 98.5%) at Year 2. The Day 29 GMT for the long-term follow-up cohort was 3,542, and GMT remained high with 785 at Year 2, considerably exceeding the seroresponse threshold of 150. In adults aged ≥65 years, antibody persistence was similar to younger adults throughout the follow-up. Ten SAEs were reported, all assessed as unrelated to VLA1553 by the investigators. Furthermore, no persistent adverse event of special interest was identified, indicating that no safety concern was identified in VLA1553-303 until Year 2.

Conclusions: These results suggest that our live-attenuated vaccine induces a robust and long-lasting immunity after a single dose.

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(15) Peripheral co-delivery of plasmid-encoded mucosal chemokine CCL27 enhances mucosal immunity and supports protection from heterologous SARS-CoV-2 and H5N1 influenza challenges in vivo

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Abstract: Mucosal surfaces are the primary entry sites for numerous pathogens. While peripheral vaccination can support robust antigen-specific cellular and humoral immunity, it requires active infection to pull antigen-specific memory cells to the mucosa and relies on passive transudation of antibodies for protection at mucosal surfaces. We reported that co-delivery of the mucosal homing chemokine CCL27 (CTACK) with a DNA plasmid encoding parental SARS-CoV-2 spike (pS) generates antigen-specific IgA in the lung, antigen-specific CD8+ T cells at mucosal surfaces and was 100% protective in a heterologous Delta VOC challenge model. This is the first report of a parentally delivered original SARS-CoV-2 spike antigen engendering complete heterologous protection. Here, we extend this work and demonstrate that co-delivery of plasmid-encoded CTACK (+pCTACK) with pS supports protection from heterologous challenges with SARS-CoV-Omicron variants. pCTACK co-delivery significantly lowered viral loads when mice were challenged with SARS-CoV-2 Omicron variants (BA.2 and XBB.1). Generating robust mucosal immunity with vaccination will be particularly important in the context of rapidly emerging respiratory viruses. We developed seasonal H1N1 influenza, and highly pathogenic avian influenza (HPAIs) H5N1 hemagglutinin (HA) DNA antigens. When delivered alone, these immunogens induced robust peripheral humoral and cellular responses in mice. However, co-delivery with pCTACK increased HA-specific antibodies in bronchoalveolar lavage, increased antigen-specific CD8+T cells in the lung mucosa, and enhanced survival following heterologous lethal intranasal H5N1 influenza challenge and homologous H1N1 challenge. These data have broad implications for the generation of mucosal immunity with parenteral vaccination, important implications for the development of medical countermeasures targeting emerging H5N1 influenza viruses, and demonstrate the feasibility of using mucosal adjuvants to augment parenteral vaccine-induced immunity at mucosal surfaces supporting improved outcomes following respiratory virus infection.

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(16) Heterologous prime/boost immunization with Newcastle disease virus and modified vaccinia virus Ankara vectors as an improved and effective strategy against SARS-CoV-2 infection

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Effective vaccination strategies quickly adapted to new emerging viruses and capable of inducing robust, broad and durable antigen-specific protective immune responses are necessary. In particular, viral vectors are powerful vaccine platforms against emerging viruses like severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this study, we studied the immunogenicity and efficacy against SARS-CoV-2 infection triggered in transgenic K18-hACE2 mice by different prime/boost vaccination regimens (mucosal and systemic) comprising two vaccine candidates based on Newcastle disease virus (NDV) and Modified vaccinia virus Ankara (MVA) vectors expressing a prefusion-stabilized SARS-CoV-2 spike (S) protein (NDV-HXP-S and MVA-S(3P), respectively). The results showed that the vaccine regimens fully protected K18-hACE2 mice from morbidity and mortality caused by SARS-CoV-2 infection, with the sequential intranasal administration of NDV-HXP-S followed by an intramuscular inoculation of MVA-S(3P) resulting in no detectable viral replication (mRNA and infectious virus) in respiratory tissues, only mild and occasional lung histopathological lesions, and reduced levels of pro-inflammatory cytokines in the lungs. High titers of binding anti-S IgG antibodies, with a Th1 bias, and neutralizing antibodies against the ancestral Wuhan strain of SARS-CoV-2 and different variants of concern were detected in all vaccinated animals. Moreover, antigen-specific CD4+ and CD8+ T-cellular immune responses were induced, with the NDV-HXP-S/MVA-S(3P) combination favoring higher magnitude of S-specific CD8+ T cells. This research demonstrates the potential of heterologous NDV/MVA prime/boost vaccine strategies for the generation of potent and broad SARS-CoV-2-specific humoral and T-cellular immune responses, capable of preventing SARS-CoV-2 infection and disease. The use of such combined prime/boost vaccination regimen should be explored for durability and against other emerging or re-emerging viruses for which effective vaccines are not available.

(17) Effect of adjuvants on the efficacy of an Izumo1-based immunocontraceptive vaccine in mice

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Reduction and fragmentation of habitat, loss of natural predators, and climate change has led to local overpopulations of wild animals which necessitates population control measures to avoid negative effects on the environment and other animal species. Immunocontraception is a nonlethal control method that is generally safe for humans and animals. Currently, immunocontraceptive vaccines are based on inducing immune responses in female animals against gonadotropin-releasing hormone and against zona pellucida proteins. These vaccines require strong adjuvants (typically modified Freund's adjuvants) to overcome immune tolerance and are modestly effective. An alternative strategy is to immunize female animals against sperm proteins. Izumo1 is a conserved sperm protein that is expressed on the surface of sperm cells following the acrosome reaction. It binds to a receptor called Juno on oocytes and plays a critical role in the adhesion of sperm cells to oocytes. Izumo1-deficient mice are infertile. We expressed the extracellular N-terminal Izumo domain and immunoglobulin domain of mouse Izumo1 in Chinese Hamster Ovary cells. Vaccines were formulated with the oil-in-water emulsion AddaSO3, with a combination adjuvant (NanoST) composed of plant-derived nanoparticles and the STING agonist ADU-S100, or with NanoST mixed with AddaSO3. Female mice were immunized twice with the vaccine and then blood samples were collected and the mice were mated. Immunization with all three vaccine formulations induced a robust anti-Izumo1 immune response. However, mice that received the vaccine formulated with NanoST alone or NanoST mixed with AddaSO3 had a greater (up to 66%) reduction of fertility. These data support the further development of an immunocontraceptive vaccine based on Izumo1 for wildlife population control.

(18) VIOLIN in the Era of AI: An Integrative Vaccine Knowledgebase and Analysis System

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Abstract: As illustrated by the role of vaccination against the COVID-19 pandemic, vaccination is one of the most significant inventions in modern medicine. The VIOLIN vaccine knowledgebase (https://violinet.org) is the first and most comprehensive vaccine knowledge database and analysis system covering the complete vaccine life cycle. VIOLIN offers in-depth information on over 4,700 vaccines targeting 217 pathogens or non-infectious diseases, such as cancers and allergies. The vaccines annotated in VIOLIN include licensed vaccines, vaccines being tested in clinical trials, and vaccines experimentally verified effective in at least one laboratory animal model. VIOLIN is an invaluable resource for understanding various aspects of vaccines, including vaccine antigens, host responses, adverse events, and formulation strategies. It also includes multiple specialized sub-databases: (i) the Protegen database with over 1,600 protective vaccine antigens, (ii) the Vaxjo database containing over 120 vaccine adjuvants, (iii) the Vaxvec database containing over 60 vaccine vectors, (iv) the VaximmutorDB with over 1,700 immune factors across 13 host types, and (v) the Cov19VaxKB, dedicated to COVID-19 vaccine knowledge. In addition to these resources, VIOLIN also includes Vaxign, the pioneering web-based vaccine design pipeline, and Vaxign-ML, a machine learning tool for rational vaccine design. These vaccine design tools have been instrumental in predicting vaccine candidates for various infectious diseases such as COVID-19 and brucellosis. Additionally, we have been continuously collecting and annotating protective antigens and storing them in the Protegen database, which has been widely used as the gold standard for different vaccine design tool development. Furthermore, we have applied large language models (LLMs)-based approaches to support our vaccine research. For example, we have developed LLM-based natural language processing methods to mine gene-gene or proteinprotein interactions and extract useful vaccine information from clinical vaccine trial studies. To support standardized representation and data integration, we have established several community-based ontologies, including the Vaccine Ontology and the Ontology of Adverse Events. These ontologies facilitate advanced data analysis and natural language processing applications. Collectively, VIOLIN stands at the forefront of vaccine informatics and AI research as a comprehensive and dynamic platform. To further enhance open vaccine research, we are initiating a community-driven effort in vaccine informatics, with the goal of developing a minimal information standard for vaccine investigations, ontology modeling, and advanced vaccine data integration and analysis.

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(19) Development of parenteral vaccines for global control of rotavirus diarrhea in children: progress and update

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Background: Rotavirus remains the most important cause of severe diarrhea and kills ~200,000 children each year mostly in low- and middle-income settings despite the introduction of four live oral rotavirus vaccines in more than 120 countries. To overcome low efficacy and more effectively control rotavirus disease and deaths, we have advanced the human rotavirus strain CDC-9 as a candidate vaccine for intramuscular (IM) or intradermal (ID) administration using a microneedle patch (MNP). While the proof of concept for parenteral vaccination with inactivated rotavirus vaccine (IRV) has been established in pre-clinical studies, no such studies have been done with live rotavirus vaccine because of lack of understanding of rotavirus attenuation and concerns about its safety. **Methods:** We conducted GLP toxicology studies of IM IRV in guinea pigs and Wistar rats and MNP IRV in Wistar rats, both given four times at a dose of ≥ 7.5 μg with a 28 day interval.. We are conducting phase 1 clinical trials to evaluate the safety and immunogenicity of IM IRV (adjuvanted) and MNP IRV in Healthy Adults in accordance with the United States and International Conference on Harmonization regulations. We utilized reverse genetics technology to identify molecular signatures that mediate rotavirus adaptation in cell culture and attenuation in neonatal rats and conducted a feasibility study of the live attenuated rotavirus vaccine (LARV) for IM administration in gnotobiotic piglets. **Results:** We demonstrated that repeat administrations of IRV (≥ 7.5 μg/dose) by IM or MNP inoculation did not induce any adverse local or systemic effects in Wistar rats or guinea pigs. Currently we are evaluating the safety and immunogenicity of both IRV presentations at high (7.5 μg) and low (3.75) doses in phase 1 clinical trial in healthy adults. We demonstrated that the CDC-9 strain while serially passaged in Vero cells underwent several key amino acid mutations mainly in VP4, resulting in spike protein structural changes, virus adaptation and enhanced growth in cell culture. We generated various recombinant CDC-9 viruses expressing single mutations or combinations of two, three or four mutations and identified a couple of key amino acid changes in VP5 that rendered the virus attenuated in neonatal rats. We found that IM-administered LARV caused neither rotavirus infection nor pathological changes in the intestine, mesenteric lymph nodes and spleen of piglets at day 3 of

post-dose 1 vaccination. We demonstrated that three doses of LARV (105.6 ffu/dose) by IM injection induced significantly higher geometric mean titers (GMT) of antibodies than three doses of an orally administered vaccine (IgA 3,901 vs. 53, IgG 4,564 vs. 94, neutralizing antibody 320 vs. 37), and superior protection against oral challenge with a virulent human rotavirus (rotavirus shedding score 1.47 vs. 4.22). **Conclusion:** IM-administered LARV CDC-9 appeared safe and highly immunogenic in animal studies. Parenterally administered IRV and LARV have potential to effectively prevent severe rotavirus diarrhea and death among children in the world.

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(20) Broad filovirus protection via NK cell activation and neutrophil phagocytosis in mice induced by a YF17D-vectored Sudan virus vaccine

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Filoviruses, with prototype Ebola virus and related Sudan virus causing fatal systemic multi-organ disease, are a threat to global public health, with recurring outbreaks resulting in large epidemics over the last decennia. While substantial efforts have been undertaken to develop an Ebola virus vaccine, no vaccine nor countermeasure are available for Sudan virus. We developed a recombinant yellow fever 17D-based vaccine candidate expressing Sudan virus-glycoprotein as protective antigen. The vaccine is immunogenic in mice with robust cell-mediated and strong humoral immune responses for both Sudan and yellow fever virus. More specifically, humoral immune responses for SUDV are associated with natural killer cell activation and antibody mediated neutrophil phagocytosis, whereas SUDV specific cellular immunity was identified as CD4+IFNγ and CD4+TNFa secreting T cells. YFV immunity is conferred through CD8+IFNγ T cells and neutralizing antibodies. Lastly, this vaccine candidate also confers broad protection against surrogate filovirus challenge, which makes it an ideal candidate for broad protection across orthologues within the Ebolavirus genus such as Ebola virus and Bundibugyo virus.

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(21) Heroin And Fentanyl Vaccines Adjuvanted with Army Liposome Formulation

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Opioid use disorder (OUD) and fatal overdose due to consumption of fentanyl-laced drugs are global concerns. Data from the US Centers for Disease Control and Prevention indicate that fatal overdose cases were 107,543 over the last year with 74,704 due to synthetic opioids, predominantly fentanyl and fentanyl derivatives. Currently, 902,000 Americans are using heroin, which in now is laced with fentanyl. The major barrier towards mitigation of opioid use disorder, particularly in the case of fentanyl-laced heroin, remains the unavailability of effective treatment modalities. There are only 3 pharmacotherapies approved to treat OUD including methadone, buprenorphine, and naltrexone or their combinations. Their efficacies are diminished by the availability of more potent fentanyl analogues. This is particularly true with overdose rescue antagonist, naloxone. Current efforts are focused on active immunizations using opioid conjugate vaccines as alternatives or complementary treatment strategies to currently available drugs against OUD. The architecture of conjugate vaccines consists of a hapten, which is a structural analogue of the target drug conjugated to an immunogenic carrier protein, mixed with a potent adjuvant. Our laboratory developed 6-AmHap as a hapten for a heroin vaccine and para-FenHap as a hapten for fentanyl vaccine. The haptens were conjugated to tetanus toxoid (TT) using SM-(PEG)2 linker. Army Liposome Formulation (ALF) containing monophosphoryl lipid A mixed with aluminum hydroxide were used as the adjuvants for mouse and rat studies. The heroin vaccine protected mice and rats from both subcutaneous and intravenous heroin challenge and induced antibodies that cross-reacted with heroin, morphine, and other opioids, but not the therapeutics for OUD. The heroin vaccine had a good safety profile in a GLP rabbit pharmacology-toxicology study and induced antibody endpoint titers ≥1 million. An Investigation New Drug application has been submitted to the FDA in preparation for a phase 1 clinical trial of the heroin vaccine. The fentanyl vaccine protected mice from fentanyl challenge and induced antibodies that

cross-reacted with other fentanyl analogs commonly found in confiscated substances of abuse, but not the therapeutics for substance abuse. When combined to form a bivalent vaccine, both heroin's and fentanyl's effects were attenuated in mice models. The binding affinities (Kd) of induced antibodies to heroin and fentanyl from the bivalent vaccine were less than 0.5 nM, demonstrating high affinity antibody production.

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(22) Optimization And Scale Up Of Suspension Vero Cell Culture Technology Towards Industrial Applications In Cost-Effective Production Of Viral Vaccines

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Vero cells are widely accepted, continuous cell line by the regulatory authorities (such as WHO) for the manufacture of viral vaccines. The continuous Vero cell line has been commercially used, after propagation on microcarriers, for the production of rabies, polio, enterovirus 71 and COVID19 vaccines. The growth of Vero cells is anchorage-dependent, and cells need to be dissociated enzymatically or mechanically for the process of sub-cultivation. This process is labor intensive and complicated in process scale-up. Adaptation of Vero cells to grow in suspension significantly simplifies scale-up and manufacturing processes, and can significantly reduce production cost. We previously reported a successful adaptation of adherent Vero cells originated from ATCC CCL-81 to grow in suspension in serum-free and animal component-free media developed in-house. The suspension adapted cells were found to retain their genetic stability and to be non-tumorigenic. Present work continues the development and optimization of cell culture process and feeding strategy to improve the growth of suspension Vero cell and conduct production case studies of vesicular stomatitis virus (VSV), herpes simplex virus-1 (HSV-1) and yellow fever virus (YFV). Data from our study showed the suspension adapted Vero cells retained similar or showed better productivity for VSV, HSV-1 and YFV to that obtained in adherent batch culture. The volumetric productivity of VSV increased with the increasing cell density at infection in batch culture. The VSV productivity increased up to one log, at 1.1E10 TCID50/mL, when a 3L perfusion culture was infected at a cell density of 7.0E6 cells/m. In contrast, high titer production of HSV-1 in the Vero culture was limited by the maximum cell density in batch culture and the virus infection process was also inhibited by metabolites secreted in the culture even at low cell density such as 1x106 cells/mL. However, with a much higher multiplicity of infection we could achieve high HSV-1 production in batch culture. Perfusion culture improved nutrient supply, removes inhibitory metabolites and therefore provides a favorable condition for virus infection at higher cell density. A HSV-1 titer of 1.1E9 TCID50/mL was achieved in a perfusion culture infected at 5.0E6 cells/mL when comparing to a titer of 2.6E8 TCID50/mL obtained in a batch culture infected at 1.4E6 cells/mL.These titers are significantly higher than the best titers achieved in respective adherent Vero culture process. The production of HSV-1 was successfully scaled up to 60L pilot-scale bioreactor for demonstration of large-scale manufacturing of viral vaccines. Lastly, Yellow fever virus vaccine strain 17D was also successfully produced in suspension Vero cell bioreactor culture at a titer of >1E8 pfu/mL through optimization of culture condition. This study demonstrates that batch or perfusion suspension Vero culture is a much-simplified process than current adherent culture technology for manufacturing of viral vaccines, and offers great potentials in reducing the cost of goods. To the best of our knowledge, NRC is the only organization that has successfully developed industrial grade suspension Vero cell culture and scaled up the cell culture process to pilot-scale bioreactor demonstrating feasibility for the large-scale manufacturing. **Key Words:** Vero cell culture, viral vaccine, therapeutic virus, herpes simplex virus-1.

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(23) Development of a thermostable, immunogenic ACM Tunable Platform (ATP) for mRNA delivery using amphiphilic block co-polymers

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Lipid nanoparticles (LNPs) are considered the best-in-class for mRNA delivery, but their thermal instability restricts their duration of use after thawing and their distribution to regions with cold chain infrastructure. Lyophilization is extensively used in the pharmaceutical industry to improve stability and shelf life of many medications but its application to LNPs is not trivial given the need for careful selection of multiple processes and parameters. An alternative approach is the incorporation of specialized ionizable lipids that impart

increased stability. Here, we show that replacement of DMG-PEG2000 with the block co-polymer PBD-b-PEO results in a highly stable ACM Tunable Platform (ATP) formulation that can undergo prolonged storage in liquid format at 4oC with no detriment to its structure and function. Dynamic light scattering (DLS) measurements of mRNA-ATP revealed a stable size distribution profile for 24 weeks at 4oC whereas mRNA-LNPs became unstable after four weeks. Furthermore, mRNA integrity and in vitro HEK293 transfection did not show evidence of deterioration. Characterization of tissue distribution by IVIS® imaging after intravenous (IV) or intramuscular (IM) administration of luciferase mRNA-ATP revealed a substantial reduction in liver affinity concomitant with increased deposition in secondary lymphoid organs. Cellular level analysis by flow cytometry showed efficient ATP uptake by macrophages and different subsets of dendritic cells (cDC1, cDC2 and pDCs). Based on these attributes, we evaluated ATP as a carrier for an mRNA vaccine. Mice given two IM injections of mRNA-ATP exhibited mild, transient weight loss two days after each dose but did not present with evidence of systemic toxicity (i.e.: normal serum ALT, CRP and creatinine), indicating good tolerability. Vaccinating with freshly fabricated ovalbumin (OVA) mRNA-ATP generated robust and durable OVA-specific IgG titers and H-2kb/SIINFEKL pentamer+ CD8+ T cells. Notably, SIINFEKL-specific, IFNγ-producing CD8+ T cells were detected in the spleens of ATP-vaccinated mice at twice the frequency as LNP-vaccinated mice, 154 days after study start. Despite its immunogenicity, repeated IV administrations of ATP did not boost anti-PEG antibodies, unlike LNPs which efficiently boosted such antibodies with consecutive doses. Immunogenicity of OVA mRNA-ATP remained intact after prolonged storage at 4oC. Similar frequencies of circulating effector memory, central memory or Pent+ CD8+ T cells were induced by one dose of fresh or aged ATP. Moreover, aged ATP was more immunogenic than freshly fabricated LNPs, based on the significantly higher frequencies of Pent+ CD8+ T cells at multiple time points after one or two doses. Although the OVA-specific IgG titer induced by aged ATP trended lower than fresh ATP, the response was vigorously boosted by the second dose of aged ATP. The potential for clinical translation was determined by vaccinating Golden Syrian hamsters with ATP encapsulating ancestral SARS-CoV-2 spike mRNA. Hamsters developed high levels of spike-specific IgG similar to those generated by the LNP comparator and were strongly protected against weight loss induced by live virus challenge. Cumulatively, we have demonstrated mRNA-ATP to be highly stable, immunogenic and possesses potential for clinical translation.

(24) Immunogenetic and Molecular Epidemiological Study of Small Ruminant Lentiviruses in Mongolia

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Maedi-visna (MV) is caused by Small Ruminant Lentiviruses (SRLV) and prevalent in sheep and goats worldwide including Mongolia. The viral strains circulating in native Mongolian sheep infected with these SRRVs were unknown which aims the main part of the study. Over ten novel viral sequences for SRLV determined by Sanger sequencing. All Mongolian SRLV sequences clustered within the divergent subtype A22, which was previously found only in Fertile Crescent regions, including Lebanon, Jordan, and Iran, where the first sheep-domestication (Ovis aries) occurred. According to the phylogenetic analysis, genotype A has two ancestors from the ancient Fertile Crescent: (1) Turkish strains and (2) Iranian, Jordanian, and Lebanese strains. The first ancestor spread westward, whereas the second spread eastward, ultimately reaching Mongolia. The exon 2 of alleles Ovar-DRB1 gene (ovine major histocompatibility complex class II gene) is highly polymorphic and contributed to the host immune response. Some foreign sheep breed with certain alleles of Ovar-DRB1 and TMEM154 (transmembrane protein) genes known to correlated with SRRV susceptibility/resistance. The dominant native sheep breed Mongol with population size of thirty millons in Mongolia is never studied for immunogenetic polymorphism in context with disease susceptibility/resistance. The improved sheep breed Sumber is a crossbreed of Mongol sheep with Karakul sheep, which known susceptible for SRLV. Some known and novel alleles of Ovar-DRB1 haplotype found in native Mongol sheep breed by restrition fragment length polymorphism (RFLP) and Sanger sequencing. The unknown Ovar-DRB1 haplotypes in Mongol sheep shared 2-3 bp deletion with Turkish and African native sheep breeds with increased SRLV susceptibility. The known SRLV-susceptible allele (E35) of TMEM154 gene were determined in native Mongolian sheep breed and improved sheep breed Sumber. No protective allele (s) K was found in native sheep breed but in low frequency in Sumber breed. The immunogenetic studies of Ovar-DRB1 exon 2 genes indicate it's correlation with SRLV seropositivity. This is consistent with previous studies - SRLV prevalence in almost all twenty one provinces of Mongolia. But the SRLV resistant allele K35 of TMEM154 gene is not correlated with current virus genotype and native Mongolian sheep breed. The development of animal breeding strategy, specially in retroviral infections and/or discovery of retroviral vaccines needs further studies in immunogenetics for animal breed, polymorphism of immune genes as MHC and other immunoreceptors.

Key words: retrovirus, immunogenetic, major histocompatibility complex, immunoreceptor, viral immunology.

(25) SARS-CoV-2 Plasma Cells are Largely Excluded from the Bone Marrow Long-Lived Compartment 33 Months after mRNA Vaccination

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The goal of any vaccine is to induce long-lived plasma cells (LLPC) to provide life-long protection. Natural infection by influenza, measles, or mumps viruses generates bone marrow (BM) LLPC similar to tetanus vaccination which affords safeguards for decades. Although the SARS-CoV-2 mRNA vaccines protect from severe disease, the serologic half-life is short-lived even though SARS-CoV-2-specific plasma cells can be found in the BM. To better understand this paradox, we enrolled 19 healthy adults at 2.5-33 months after SARS-CoV-2 mRNA vaccine and measured influenza-, tetanus-, or SARS-CoV-2-specific antibody-secreting cells (ASC) in LLPC (CD19-) and Non-LLPC (CD19+) subsets within the BM. All individuals had IgG ASC specific for influenza, tetanus, and SARS-CoV-2 in at least one BM ASC compartment. However, only influenza- and tetanus-specific ASC were readily detected in the LLPC whereas SARS-CoV-2 specificities were mostly excluded. The ratios of Non-LLPC:LLPC for influenza, tetanus, and SARS-CoV-2 were 0.61, 0.44, and 29.07, respectively. Even in five patients with known PCR-proven history of infection and vaccination, SARS-CoV-2-specific ASC were mostly excluded from the LLPC. These specificities were further validated by using multiplex bead binding assays of secreted antibodies in the supernatants of cultured ASC. Similarly, the IgG ratios of Non-LLPC:LLPC for influenza, tetanus, and SARS-CoV-2 were 0.66, 0.44, and 23.26, respectively. While serum IgG titers specific for influenza and tetanus correlated with IgG LLPC, serum IgG levels for SARS-CoV-2, which waned within 3-6 months after the vaccine, were associated with IgG Non-LLPC. In all, our studies demonstrate that rapid waning of serum antibodies is accounted for by the inability of mRNA vaccines to induce BM LLPC. Funding Information: This work was supported by the following grants: NIH/NIAID R01AI172254, R01AI121252, 1P01AI125180, U01AI141993, U54CA260563, and the Bill & Melinda Gates Foundation Grant INV-002351.

(27) Passive immune protection against A(H1N1)pdm2009 virus infection with in vivo-delivered DNA-encoded influenza H1HA-head and pan-NA directed monoclonal antibodies in a murine challenge model

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There are 1 billion cases of seasonal influenza each year. Annual immunization is recommended, however additional strategies for pre-exposure prophylaxis such as monoclonal antibodies (mAbs) would afford tremendous benefit to at-risk populations who respond poorly to conventional inactivated and live-attenuated vaccines. Nirsevimab (Beyfortus™), an updated anti-respiratory syncytial virus (RSV) mAb, was approved by multiple regulatory agencies including the U.S. FDA, European Union EMA, Health Canada, Japan PMDA and the UK MHRA. The CDC has since included nirsevimab on its vaccine schedule for infants <8 months of age, opening new possibilities for mAb delivery against seasonal infections like influenza. We previously described engineering synthetic DNA-encoded antibodies (DMAbs) as a strategy to improve mAb biologic dosing, stability and accessibility for global population coverage, especially in low-/middle-income countries and resource-limited settings. Building on this, we engineered DMAbs encoding the heavy and light chain genes from anti-A/H1N1 influenza A virus (IAV) hemagglutinin (HA) or pan-neuraminidase (NA) mAbs. HA-DMAbs were designed to target the HA globular head and NA-DMAbs engineered to target active site epitopes. DMAbs were sequence optimized and tested for their ability to express in vitro and bind to target HA or NA antigen. Subsequently, in vivo expression was evaluated in BALB/c mice (n=5/group), achieving Cmax serum >20ug/mL. Two each of the HA and NA DMAb candidates were selected for further evaluation, demonstrating serum binding and neutralization activity against A(H1N1)pdm2009 lineage viruses. These candidates were administered to DBA/2 mice (n=15 mice/group) alone and in combinations, followed by intranasal challenge on day 6 post-administration with A/H1N1 A/California/07/2009 X179A. Lung histopathological analysis indicated dose-dependent interstitial pneumonia and positive staining to influenza NP antigen. Lesions and positive staining were observed in negative control groups and low dose DMAb groups. Groups receiving higher doses of DMAb did not display lesions. Transcriptomic analyses highlight distinct differences between DMAb protected groups versus uninfected and infected controls. Taken together, these data demonstrate that synthetic DMAbs targeting HA or NA are functional and afford protection in mice against lethal A(H1N1) pdm2009 virus infection, even at very low doses, supporting evaluation in larger animal models with potential for translational development. Synthetic DNA-encoded antibody delivery offers important advantages for significant world populations, with potential for providing standalone influenza prophylaxis or adjunct to vaccination.

(28) Long-Term Immunogenicity of Typhoid Conjugate Vaccine among Healthy Filipino Adults and Children

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Background: Typhoid Conjugate Vaccine (TCV) has a proven record of providing good immune response among adults and children. However, data on long-term immunogenicity delivered is sparse. We present the results of long-term immunogenicity investigated over consecutively 3 years after a typhoid conjugate vaccine composed of Vi polysaccharide conjugated to diphtheria toxoid (Vi-DT) was introduced to the healthy population aged 2-45 years in the Philippines. **Methods:** In this observational study, we followed up the participants who were vaccinated by either the Vi-DT vaccine or comparator vaccine, the Vi-polysaccharide vaccine, till five years after the enrollment of the phase I study, where we assessed the safety and immunogenicity of the Vi-DT vaccine among healthy Filipino adults and children, aged 2-45 years. Participants who had received at least one dose of either Vi-DT or Vi-Polysaccharide vaccine and agreed to provide at least one blood sample were enrolled in the study. Blood samples were collected to assess the long-term immunogenicity using Anti-Vi IgG and Serum Bactericidal Antibody (SBA) at three different time points: 3 years, 4 years, and 5 years after vaccination. **Findings:** Between 30 October 2019 and 13 January 2022, efforts were made to enroll and collect blood samples from 137 participants who received at least one Vi-DT or Vi-Polysaccharide vaccine after 3 years post-vaccination. Anti-Vi IgG seroconversion was higher than the comparator vaccine in all age strata, 98.44% (95%CI:91.67,99.72) at year 3, 100% (95% CI: 94.08.100.00) at year 4 and 98.41% (95%CI: 91.54,99.72). Anti-Vi IgG GMT was higher in the test group of the vaccine among all age strata as well. Seroconversion by SBA analysis was higher in the 18-45 group of adults by 75% (95% CI: 50.50,89.82), 86.67% (62.12,96.26), and 60% (35.75,80.18) at 95% CI at 3rd, 4th and 5th year respectively. **Interpretation: A** single dose of Vi-DT vaccine is capable of providing long-term persistence of immunogenicity for at least five years after vaccination. The results will support the WHO guideline for the necessity of booster doses in endemic areas.

(29) The next generation influenza vaccine: mRNA or recombinant protein?

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Most of the commercialized flu shots are split virions produced in embryonated chicken eggs, an almost one centenary old technique to propagate influenza viruses. Different types of influenza vaccines have been recently approved, such as live-attenuated influenza viruses, mammalian cell culture-based inactivated and split virions, or recombinant protein. The quest for the next generation of influenza vaccines aims to deliver a candidate with broader strain coverage and higher efficacy compared to currently approved vaccines. The success of mRNA vaccines in preventing severe disease due to SARS-CoV-2 infection has prompted the exploration of this platform for other vaccine-preventable diseases, including influenza. Here, we compared the immunogenicity and protective potential of recombinant hemagglutinin (HA) and neuraminidase (NA) proteins with mRNA vaccines encoding the same influenza antigens in a mouse model. We used HA and NA from strains that were recommended for the 2018/19 season (H1N1 A/Michigan/45/2015, H3N2 A/Singapore/INFIMH-16-0019/2016, Victoria B/Colorado/06/2017, and Yamagata B/Phuket/3073/2013) to compare the performance of AF03-adjuvanted recombinant proteins versus mRNA-lipid nanoparticles (LNPs) vaccines. BALB/c mice were immunized with 1, 0.2, or 0.04μg (per component) of octavalent protein or mRNA-LNP vaccines in a prime/boost regimen. mRNA immunization induced similar responses as the adjuvanted protein against HA components as determined by ELISA. Interestingly, mRNA induced higher antibody and inhibition titers against the NA components than protein-based immunization. Mice that were immunized with 0.2μg of octavalent protein or mRNA were challenged with A/Belgium/45-ma/2009 or A/Wisconsin/588/2019 (both H1N1) or B/Phuket/3073/2013, B/Colorado/06/2017, or B/Washington/02/2019. Mice that had been immunized with octavalent protein or mRNA-LNP were equally protected against those challenge strains. Interestingly, when mice were challenged with historical H3N2 influenza virus strains X31, X47, or X79, the mRNA-LNP immunization conferred protection while protein-based immunization did not. mRNA-LNP immunization

induced increased serum IgG antibodies against X47 HA and NA, although hemagglutination or NA inhibition titers against X47 were not detectable. In summary, in this preclinical model, mRNA immunization induced higher serum antibody responses against NA components than the protein-based immunization, while the response against HA was similar. Both mRNA and protein-based immunizations were able to protect mice against challenge with recent H1N1 and IBV strains. Strikingly, only mRNA-based immunization was able to protect mice against historical H3N2 challenges and induced higher titers of cross-reactive antibodies against both HA and NA. This study was funded by Sanofi. TUV is a Sanofi employee and may hold stock options in the company.

(30) Army liposome formulation containing QS-21 modulates proinflammatory milieu and innate anti-viral factors rendering human monocyte-derived macrophages less permissive to HIV-1 infection

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Adjuvants are critical components of many vaccine formulations. We have created a family of adjuvants known as Army Liposomal Formulations (ALF) consisting of saturated phospholipids, synthetic monophosphoryl lipid A and either 43 mol% or 55 mol% (ALF55) cholesterol. An additional immunostimulant the saponin QS21 is incorporated into ALF55 to generate ALFQ, a highly promising adjuvant that has been utilized in three completed Phase 1 human clinical trials, four ongoing trials, and with nine trials in the pipeline. ALFQ has profound immune-stimulatory responses in human monocyte-derived macrophages (MDM). ALF55 comprises small unilamellar vesicles (SUVs, 50nm), while ALFQ is polydisperse with mainly large-giant unilamellar vesicles (GUVs, 50nm to ≥ 30,000nm in diameter). The uptake of GUVs by MDM was time-dependent and could be observed using fluorescent-labeled lipids. Uptake was seen as early as 1 hour and by 18-24h, MDMs were loaded with GUVs. MDMs are highly permissive to HIV-1 infection, potentially due to the downregulation of innate factors during the differentiation process. We evaluated whether exposure of MDM differentiated from PBMCs of HIV-1 seronegative donors (RV229B, WRAIR Protocol #1386) to ALFQ could restrict HIV-1 infection. Primary human monocytes were differentiated into MDM following in-vitro culture in media supplemented with M-CSF. The MDMs were infected with purified primary HIV-1 and subsequently exposed to ALFQ or alternatively, MDMs were exposed to ALFQ and then infected with HIV-1. HIV-1 infection was determined by flow cytometry. Pre- and post-treatment of MDMs with ALFQ resulted in a significant decrease in HIV-1 infection and this was dependent on the time of exposure of MDMs to ALFQ. ALFQ upregulated MHC Class II and CD86 molecules on the surface of MDM and downregulated CD163, CD206, and CD14. In addition, MDMs cultured with ALFQ induced higher levels of proinflammatory cytokines, notably IFN-gamma and IL-1beta, compared to MDMs cultured with ALF55. ALFQ and not ALF55 upregulated innate anti-viral factors notably APOBEC3A and IFI16, leading to decreased HIV-1 permissivity. This effect was lost by knockdown with APOBEC3A siRNA. Our findings highlight a relationship between innate immune activation, proinflammatory milieu, and upregulation of anti-HIV proteins. Induction of these responses can switch the HIV-1 permissive MDM into a more refractory phenotype. Thus, ALFQ serves not only as a robust and potent adjuvant when present in vaccines but could also serve as a potential therapeutic agent against HIV-1.

(31) Bacteriophage T4 as a Protein-Based, Adjuvant- and Needle-Free, Mucosal Pandemic Vaccine Design Platform

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We present here a novel protein-based, bacteriophage T4 platform for rapid design of efficacious vaccines against bacterial and viral pathogens. Bacteriophage T4 infects Escherichia coli bacterium. It is one of the most stable and structurally and genetically well-characterized viruses. The phage has a large 120 x 86 nm prolate icosahedral capsid (head) containing ~171kb packaged double-stranded linear genome. Its exterior is coated with two nonessential outer capsid proteins, Soc (small outer capsid protein) (9.1 kDa; 870 copies per capsid) and Hoc (highly antigenic outer capsid protein) (40.4 kDa; 155 copies per capsid). Soc binds as a trimer at the quasi-three-fold-axes by clamping two adjacent capsomers and provides additional stability to an already very

stable capsid. Hoc is a 18nm-long fiber and acts as an adhesin allowing phage to bind to bacterial and mammalian cell surfaces. Both have nanomolar affinity and exquisite specificity to T4 capsid and can be used as adapters for high density display of pathogen antigens on the surface through in vitro or in vivo assembly. Using T4 phage as a surface display platform, we have designed a series of nanoparticle vaccines against deadly infectious agents including Bacillus anthracis (anthrax), Yersinia pestis (plague), HIV, SARS-Co-V2 (COVID-19), influenza-A (Flu), and dengue virus. The T4 vaccines are stable at room temperature, do not need an adjuvant, and are effective as needle-free intranasal vaccines. In animal models including mice, rabbits, and macaques, complete protection was observed against lethal challenges with the respective infectious agents (except HIV). Intranasal or intramuscular administration of two doses of T4 vaccines induced robust systemic humoral and cellular immune responses that include neutralizing antibodies, CD4 and CD8 T cell immunity, and Th1-biased cytokine responses. Additionally, intranasal immunizations elicited mucosal immunity including high secretory IgA titers in sera and bronchoalveolar lavage fluids, and effector (TEM), central (TCM), and tissue-resident memory CD4+ T cells (TRM) at mucosal sites in the case of the T4-Flu vaccine. The nasal vaccines conferred complete protection and also sterilizing immunity against multiple SARS-CoV2 variants. The modular, temperature-stable, needle- and adjuvant-free, phage T4 nanovaccine platform might be a good candidate for global vaccine development for low and middle income countries, and as a complementary platform for emergency preparedness against epidemic and pandemic pathogens. References: Tao et al (2018) Bacteriophage T4 nanoparticles for vaccine delivery against infectious diseases. Adv. Drug Delivery Rev. 18: 30164-79. Zhu et al., (2024) Bacteriophage T4 as a Protein-Based, Adjuvant- and Needle-Free, Mucosal Pandemic Vaccine Design Platform. Ann. Rev. Virology (in press) https://doi.org/10.1146/annurev-virology-111821-111145.

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(32) Artificial and Human Intelligences Combined: Removal of Inhibitory Sequences Improves Vaccine Immunogenicity and Efficacy

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Computational vaccinology has enabled the rapid development of new vaccines, with applications in both infectious disease and oncology. Most approaches use in silico tools predicting HLA Class I and/or HLA Class II restricted epitopes to identify highly immunogenic candidate antigens from the genome of pathogens, or to develop epitope-based immunotherapies such as personalized cancer vaccines. T cell epitope prediction tools mainly focus on modeling the interaction between putative epitopes and HLA molecules but lack the ability to assess how the peptide-MHC (pMHC) complex interacts with T cell receptors (TCR) and whether these epitopes are likely recognized by effector T cells (Teff) or regulatory T cells (Treg). Our group recently discovered that the prediction of epitopes for vaccines is improved when removing T cell epitopes homologous to self-epitopes at the TCR interface, as T cells that recognize these cross-conserved "self-like" epitopes may be tolerant to them or actively tolerogenic. Preclinical studies have shown identifying these self-like epitopes is an important step for the development of vaccines against infectious agents and cancer. We have developed the JanusMatrix tool to assess pMHC cross-conservation with self-sequences, allowing for the in silico discrimination of immune activating (Teff) and immune dampening (Treg) T cell epitopes. JanusMatrix was employed to identify putative Treg epitopes from influenza (H7N9 HA) and self-antigens (Factor V). These epitopes were subsequently confirmed to suppress Teff responses and activate Tregs when tested in vitro with healthy donor PBMCs. Immune engineering experiments with H7N9 HA showcased that disruption of the validated Treg epitope improved antigen immunogenicity over the wild-type antigen, and enhanced vaccine efficacy in an H7N9 lethal challenge study. In addition, our group demonstrated that inhibitory (suppressor) neoantigen sequences identified in a mouse cancer cell line (CT26) dampened the immune response to a neoantigen-based vaccine by 5-fold and that they should therefore be identified and excluded from cancer vaccine designs. To further exemplify the benefit of JanusMatrix in oncology, we performed retrospective studies of cancer mutanomes highlighting improved prediction of survival when removing putative Treg neoepitopes from neoepitope burden calculations. Ongoing efforts in pandemic preparedness and precision medicine has highlighted the need for rapid design and manufacturing of novel vaccines. Immunoinformatic pipelines that can rapidly scan the genome of pathogens or cancer cells and identify the “best" antigens are in high demand. We have developed web-based vaccine design platforms for infectious disease and cancer immunotherapy that enable the identification of highly immunogenic antigens and the removal of deleterious sequences that may curtail vaccine efficacy. We showed in in vitro and in vivo studies that screening, removing, and modifying suppressor epitopes improves vaccine immunogenicity and efficacy. Usage of these platforms for vaccine development will enable the

generation of better and safer vaccines.

(33) A Novel Production Platform for mRNA Vaccines: Encapsidation in a Virus Capsid Protein in Plants

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While the feasibility and effectiveness of using mRNA molecules to express vaccine antigens has been amply proven during the SARS-CoV-2 pandemic, the acceptability of the adverse events associated with the lipid nanoparticles (LNPs) – which include pain, swelling, fever, and systemic inflammatory responses – bring their general acceptability for routine vaccination into question1. The requirement for a cold chain for transport and a relatively short usable life for the vaccines are also problematic. Moreover, their production by in vitro transcription and the subsequent formulation are expensive processes: this could limit their more widespread use, especially for LMICs and poorer populations everywhere, without state intervention. The use of such vaccines for mass vaccination of farmed animals is also unlikely, given their cost. Accordingly, our group has explored the production of mRNA vaccines for animals by transient expression in plants, with in planta encapsidation of the specific antigen-encoding mRNAs by co-expressed tobacco mosaic virus coat protein (TMV CP). This allows the selection of full or near-full length mRNAs by specific binding of the TMV CP to mRNAs containing the TMV origin of assembly stem-loop sequence (OAS), and their subsequent stabilisation by complete encapsidation. The platform lends itself to encapsidation of a very wide range of mRNAs, as the length of the helical rodlike pseudovirions (PsVs) that form is proportional to the length of the mRNA. The stability of the PsVs is also impressive: native TMV virions can be stored indefinitely at 4oC and have a half-life at 80oC of 30 minutes; the PsVs have identical properties2. This encapsidation could serve two purposes: first, it would be a means of very quickly stabilising conventional synthetic mRNAs for later purification and reformulation with a cheap and very readily produced reagent (TMV CP); second, the mRNA is specifically encapsidated, which serves as a means of primary purification away from reaction by-products such as shorter RNAs, nucleotides and enzymes. Stabilisation of mRNAs would enable their simple and inexpensive purification as PsVs, after which they could either be used as vaccines themselves, or used for stable storage under ordinary refrigerator conditions or as lyophilisates before final purification of RNA and reformulation for use. We will present results of experiments using the platform for production of TMV CP encapsidated mRNAs encoding the VP2 capsid protein of African horse sickness virus, the CP of beak and feather disease virus of psittacines, and the RBD domain of SARS-CoV-2 S protein. These include proof of expression of the encapsidated mRNAs in mammalian cells in culture, as well as proof of immunogenicity of encapsidated mRNA in mice (AHSV VP2 and SARS-CoV-2 RBD), and parrots (BFDV CP). The potential use of purified TMV CP to encapsidate mRNAs made by cell-free transcription will also be explored.

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(34) Pan-influenza B virus control with single-domain antibodies directed against hemagglutinin and neuraminidase

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Influenza B viruses are antigenically diverse and contribute significantly to the annual influenza burden. Here we report the isolation and characterization of influenza B neutralizing single-domain antibodies that target highly conserved regions of the influenza B hemagglutinin and neuraminidase. One of these single-domain antibodies prevents the conformational transition from the pre- to the post-fusion state of hemagglutinin by targeting a unique quaternary epitope spanning two protomers in the hemagglutinin stem region. A second single-domain antibody broadly inhibits influenza B neuraminidase activity, including an oseltamivir-resistant influenza B neuraminidase, by binding to catalytic residues in the active site of the enzyme. Head-to-tail fusions of these single-domain antibodies were generated to create bispecific binders that further improve the neutralization breadth and potency against influenza B. Furthermore, these single-domain antibodies, fused to a human IgG1-Fc domain, fully protect mice against an otherwise lethal influenza B virus challenge. Our findings

underscore the potential of engineering single-domain antibodies as broad-spectrum prophylactics with heightened efficacy against influenza B virus infections.

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(35) Lung eosinophil recruitment and type 2 host immune responses in vaccinated mice is non-pathological and correlates with protection during influenza infection in mice with infection-permissive or sterilizing immunity.

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Type 2 host immune responses to virus infection are characterized by a typical IL4/5/13 cytokine response and granulocytes like eosinophils. These immune features are typically driven by Th2 cells during host immune responses to infection and homeostasis. Lung eosinophilia after respiratory viral infection has been linked to aberrant Th2 responses like vaccine-associated enhanced respiratory disease, but has been decoupled from pathology in some models of respiratory viral infection, with or without prior vaccination. We characterized mouse lung eosinophils after a sublethal, vaccine-matched influenza challenge (breakthrough infection). Post-challenge, we observed CD101+ Siglec-Fhi lung eosinophils in mice that received trivalent inactivated influenza vaccine. This group did not have strong inflammatory cytokine expression, detectable viral titers, allergic levels of total IgE, severe lung pathology, goblet cell hyperplasia, or enhanced morbidity. In contrast, unvaccinated mice exhibited no eosinophilia, despite high viral titers, strong pro-inflammatory cytokine profiles, and significant pathology with infiltrating immune cells like inflammatory monocytes and neutrophils. Longitudinal analyses at days 1, 3, 7, 10, and 28 post-challenge revealed no overt Th2 cytokine signal in the lungs of breakthrough infection mice, suggesting that non-canonical mechanisms and cell circuits promoted lung eosinophilia in this model. Furthermore, lung eosinophils correlated with protection and not pathology in breakthrough influenza infection of mice. In a similar type 2 fashion, but without the eosinophil influx, lungs of AddaVax-adjuvanted influenza vaccinated mice with sterilizing immunity show strong IL4/5/13 cytokine profiles upon infection. Again, this type 2 response correlates with full protection. The outcome of these studies suggests that the host immune response to infection is skewed by vaccination and leans towards type 2 host immune responses that correlate with infection rather than pathology.

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(36) Vaccine Development against Multidrug Resistant A. baumannii Infection

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The rise of multidrug-resistant Acinetobacter baumannii has posed significant challenges to global healthcare, necessitating the urgent development of effective vaccines. A. baumannii is a formidable pathogen responsible for a range of severe infections, particularly in immunocompromised individuals and those in intensive care units. The intrinsic and acquired resistance mechanisms of this pathogen render many traditional antibiotics ineffective, leading to increased morbidity and mortality rates. Vaccine development offers a promising solution to address this critical healthcare challenge. There are many challenges in developing A. baumannii vaccines. This pathogen can infect multiple organs and cause various diseases, with pathogenic mechanisms and protective antigens potentially differing depending on the disease. Elderly or immunocompromised patients are at high risk for infection and their compromised immune response poses additional hurdles for vaccine development. Furthermore, these populations represent the potential target groups for vaccine against A. baumannii infections. For hospitalized patients, the window for vaccine-induced immunization to be effect is very short. Therefore, rapid efficacy induced by vaccination is vital for vaccine development against A. baumannii. Our work focuses on the vaccine development against A. baumannii aiming to address these challenges. We have employed reverse vaccinology to screen for potential recombinant protein vaccine candidates. This innovative approach has allowed us to identify several antigens that exhibit strong immunogenicity and potential for inclusion in a vaccine formulation. Additionally, we have developed an

inactivated vaccine based on trained immunity principles, which has demonstrated rapid immune protection in preliminary studies. Our research also delves into the mechanisms underlying this quick immune response, providing a deeper understanding of how trained immunity can be harnessed for effective vaccine development. A successful vaccine against A. baumannii will help us control its infection and overcome the development of multidrug resistance. **Keywords: Acinetobacter** baumannii, multidrug resistance, reverse vaccinology, recombinant protein vaccine, trained immunity, inactivated vaccine.

(37) An intranasal Newcastle disease virus (NDV)-based SARS-CoV-2 Omicron vaccine elicits protective immune responses in mice and hamsters

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Many lives have been saved thanks to the rapid development of coronavirus disease 2019 (COVID-19) vaccines during the early phases of the pandemic. The majority of COVID-19 vaccines currently in use are delivered intramuscularly. While intramuscular administration typically induces high levels of serum antibodies preventing severe disease, failing to induce immunity in the respiratory tract may lower the efficacy against asymptomatic COVID-19 infections and transmission. A next-generation of mucosal vaccines is necessary to protect the – often neglected – more vulnerable and immunocompromised segments of the population. Here, we developed an intranasal Newcastle disease virus (NDV)-based vaccine expressing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike stabilized in its pre-fusion conformation (NDV-HXP-S). As new variants of concern (VOCs) with increased immune escape emerged, we updated the NDV-HXP-S vaccine to target the Omicron variants BA.1 and XBB.1.5. We demonstrated, that the immune responses from intramuscular vaccination with mRNA-LNPs is enhanced by the intranasal NDV-HXP-S boosting, resulting in improvement of serum neutralization titers and induction of mucosal immunity in mice. Furthermore, one or two intranasal immunizations with NDV-HXP-S expressing the XBB.1.5 spike induced protective immunity in naïve mice. In addition, intranasal vaccination with NDV-HXP-S XBB.1.5 protected hamsters from variant matched infection. We found significantly reduced virus shedding in vaccinated hamsters, providing complete protection to naïve co-housed animals in a direct contact transmission study. Taken together, this data demonstrates that intranasal vaccination or boosting with variant adapted NDV-HXP-S induces protective mucosal immunity and mitigates viral spread in pre-clinical animal models.

(38) Clinical Assessment of Adjuvant Immunotherapy, INO-3107, in Adult Patients with Recurrent respiratory papillomatosis (RRP)

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Objective(s): To evaluate the safety, immunogenicity, and efficacy of INO-3107, a DNA vaccine designed to elicit targeted T-cell responses against HPV-6 and HPV-11, in adult patients with recurrent respiratory papillomatosis (RRP; NCT04398433) Methods: Eligible patients required ≥2 surgical interventions for RRP in the year preceding dosing (median 4 surgeries/preceding year). INO-3107 was administered by intramuscular (IM) injection via a device on Weeks 0, 3, 6, and 9. Patients underwent surgical debulking within 14 days of the first dose, and office laryngoscopy with staging at screening and Weeks 6, 11, 26, and 52. The primary endpoint was safety and tolerability assessed by treatment-emergent adverse events (TEAEs). Secondary endpoints included the frequency of surgical interventions post INO-3107 and cellular immune responses. Results: Of the 32 adult RRP patients enrolled in the study 13 (41%) reported a treatment-related AE (41%) The most frequent treatment-related AE's reported were Injection site pain (31%) and fatigue (9%). One TEAE (pain) was Grade 2 severity. All other TEAE reports were Grade 1. No treatment-related adverse events greater than grade 2 severity

were reported. Modified Derkay-Pransky severity scores improved from baseline to Week 52. INO-3107 induced durable cellular responses and was able to generate T-cells against HPV-6 and HPV-11. Reduction of surgeries compared to baseline was demonstrated in 26 patients (81.3%). Conclusion: INO-3107 is tolerable and immunogenic. The evidence demonstrates a clinical benefit as the majority of adult RRP patients who received therapy required fewer surgical procedures compared to baseline.

(39) Recent developments of an improved measles vaccine vector for cancer immunotherapy and new prophylactic vaccines

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The measles vector (MV) platform has been developed from the live attenuated measles vaccine, one of the safest and most efficacious vaccines available. For many years at Institut Pasteur, we have been working on several recombinant vaccines using this platform, such as HIV, West Nile virus, chikungunya virus, Lassa fever virus and SARS-CoV-2. In preclinical and clinical studies, this platform has demonstrated its capacity to provide efficient protection against various pathogens. In clinical trials, MV platform was demonstrated safe and immunogenic in the presence of preexisting measles immunity. Its well-established manufacturing process allows to rapidly scale-up vaccine production at low cost. From this experience, Oncovita emerged as an Institut Pasteur spin-off biotech company with the aim of clinically developing both anticancer immunotherapy and preventive vaccines using the measles Schwarz vaccine platform. The primary objective is to develop an immuno-oncolytic anti-cancer vaccine. We have generated a highly improved immuno-oncolytic virus by deleting the viral protein C from measles vaccine and demonstrated its great capacity to eliminate grafted mouse tumors in immunocompetent mice or grafted human patient-derived tumors in immunodeficient mice. We have demonstrated the immune mechanism of action of this virus through the induction of CD8 and NK cells and the role of defective interfering RNA molecules that are produced at a very high level by this modified virus. A clinical phase I/II trial is in preparation to evaluate the intra-tumoral administration of this virus in solid tumors and metastasis. Oncovita is also developing new preventive vaccines against endemic pathogens listed in the high priority list of WHO. The cloning capacity and speed of recombinant vaccines rescue allow this platform to deliver new vaccine candidates in the 100 days requested by health organizations. All these new developments and preclinical results will be presented.

(40) Combination adjuvants targeting nucleic acid sensors for cancer immunotherapy

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Innate immune sensing of nucleic acids derived from invading pathogens or tumor cells via pattern recognition receptors is crucial for mounting protective immune responses against infectious disease and cancer. Recently, discovery of tremendous amounts of nucleic acid sensors as well as identification of natural and synthetic ligands for these receptors revealed the potential of adjuvants targeting nucleic acid sensing pathways for designing efficacious vaccines. Especially, current data indicated that unique adjuvants targeting TLR9 and stimulator of interferon genes (STING)-dependent cytosolic nucleic acid sensing pathways along with the combinations of already existing adjuvants are promising candidates for this purpose. Agonists for TLR9 and stimulator of IFN genes (STING) offer therapeutic applications as both anti-tumor agents and vaccine adjuvants, though their clinical applications are limited; the clinically available TLR9 agonist is a weak IFN inducer and STING agonists induce undesired type 2 immunity. Yet, combining TLR9 and STING agonists overcame these limitations by

synergistically inducing innate and adaptive IFNγ to become an advantageous type 1 adjuvant, suppressing type 2 immunity, in addition to exerting robust anti-tumor activities when used as a monotherapeutic agent for cancer immunotherapy. Here, we show that combination of TLR9 and STING agonists synergistically induce IL-12 and type I IFN production from murine APCs. Synergistic effect of the TLR9 and STING agonists on IL-12p40 are observed on protein, mRNA and promoter activation levels and transcriptional regulation is mediated by a 200 bp region situated at 983 bp upstream of IL-12p40 transcription initiation site. Moreover, local combination treatment promoted strong anti-tumor immunity in Pan02 peritoneal dissemination model via the mechanisms involving both CD4 and CD8 T cells, as well as co-operative action of IL-12 and type I IFNs. Furthermore, rechallenge studies in the long-term survivors suggested the elicitation of Pan02-specific memory responses that provide protection against secondary tumor challenge. Nevertheless, combination-adjuvanted peptide vaccine could induce potent Ag-specific Th1-type and CD8 T cell immune responses against synthetic long peptides and neopeptide pools derived from melanoma and mesothelioma tumors. Importantly, combination-adjuvated peptide vaccine exhibited robust anti-tumor effect that was synergistically enhanced by anti-PD-1 treatment in the immune checkpoint blockade-resistant melanoma model B16-F10-OVA. Therefore, combination of TLR9 and STING agonists may have clinical applications as potent anti-tumor agents, and elicitation of the mechanisms mediating the synergism between TLR9 and STING agonists may hold a key in successful cancer immunotherapy and provide further insights into dual agonism of innate immune sensors during host homeostasis and diseases.

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(41) K3-SPG-mediated long-term protection against viral infection

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In the face of recurrent global pandemics, rapid and effective vaccine development remains key for saving lives and controlling societal impacts. While effective, conventional approaches to vaccine development are often time-consuming, hindering our ability to respond swiftly to emerging pathogens. In the fight against SARS-CoV-2, the mRNA vaccine development took only approximately 1 year, however, the estimated total number of deaths were at least 3 million by 31 December 2020 (World Health Organization). Furthermore, from the time of the vaccine launch to the completion of the first immunization, additional millions of lives were lost. Moving forward, researchers across the globe are cooperating to achieve the 100-day mission as we prepare for the next pandemic. The missions' primary objective is to produce a vaccine in 100 days upon the emergence of a new pathogen, while also putting in efforts to develop an emergency treatment to further mitigate infection and mortality rates until vaccines become available. A component that has attracted the attention of current research is vaccine adjuvants, such as Toll-like receptor (TLR) 9 agonists CpG deoxynucleotides (CpG ODNs), which has been extensively reported to be immunogenic and has the capability to confer innate immune memory targeting various pathogens. By itself, CpG ODNs have demonstrated significant protection against bacteria, viruses, and parasites, however, their effectiveness against influenza viruses remain limited. To address this gap, our study focuses on the development of K3-SPG, a novel CpG-ODN complex as an emergency treatment in future pandemics. Here, we report that intranasal administration of K3-SPG alone confers full protection against influenza virus (H1N1) in mice, with potent antiviral effects sustained for at least 80 days. Interestingly, protection against influenza virus requires only 3 days of pre-exposure to K3-SPG with no discernible adverse effects. Moreover, desired effect was enhanced by local administration, suggesting the importance of the route of adminstration depending on the type of pathogen. Using various approaches to investigate underlying mechanisms, we identified rapid changes in immune cell subsets as early as 24 hours after administration, along with correlations between different cell subsets. Collectively, our findings suggest that K3-SPG is a promising candidate for emergency treatment in pandemic responses, effective not only against influenza viruses, but also with potential efficacy against other respiratory viruses.

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(42) Increased potency and breadth of protection conferred by a next-generation pre-emptive SARS-CoV-2 vaccine targeting both B and T cell responses

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The current spike alone-based SARS-CoV-2 vaccines are not a long-term solution to the ongoing pandemic or to prevent future outbreaks. Our concept is to target conserved T cell antigens to provide an added benefit, on top of neutralizing antibodies against Spike, leading to a superior B and T cell-based next-generation Coronavirus (CoV) vaccine capable of conferring durable, cross-strain protection obviating the need for frequent boosters and for updating the vaccine to match the circulating virus strains. To that end, we identified a subset of CoV antigens for evaluation as vaccine candidates based on: (1) conservation amongst millions of animal and human CoV, (2) recognition by the immune systems of SARS-CoV-2 exposed individuals, (3) correlation with protection against disease in COVID-19 patients, and (4) safety, immunogenicity and protective efficacy in animal models of COVID-19 disease. Several prototype mRNA vaccines based on these antigens have demonstrated the strong T-cell dependent protective efficacy leading to the selection of three lead candidate antigens. In addition, when combined with Spike, protection induced by these T cell antigens was superior against challenge with multiple variants of concern versus the spike-only vaccine benchmark. Furthermore, the inclusion of these T cell antigens enhanced protection against infection with the Delta variant and subsequent reinfection with the Omicron variant by significantly preventing morbidity (weight loss) and substantially reducing virus replication. This suggests the possibility of protecting individuals from disease as well as a population benefit of reducing virus transmission from person to person. In contrast, while the Spike alone-based vaccine protected against Delta infection, it was not protective against reinfection with Omicron, as measured both by weight loss and virus replication. The critical role of T cells was shown by 1) the presence of high levels of antigen-specific CD4 and CD8 T cells in the lungs of protected, but not protected, animals, and 2) T cell depletion studies, where both CD4+ and CD8+ T cells were demonstrated to be effector cells for protection. Taken together, these data strongly support the hypothesis that a next-generation multi-antigen CoV vaccine eliciting both antibodies and T-cell responses will increase the breadth of protective immunity compared to current Spike alone-based vaccines. If successful, such a multi-antigen CoV vaccine has the potential to protect against not only past and current CoV strains and variants but also against potential future outbreaks that may be caused by the zoonotic transmission of yet another animal-derived SARS-like CoV.

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(43) Analysis of Adverse Events in Immunocompromised Individuals Following Moderna COVID-19 Vaccination: Insights From 701,070 Reported Cases (December 2020 to June 2023)

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Background: About 3% of US adults have compromised immune systems, heightening their vulnerability to infections such as COVID-19. This group includes elderly individuals and those with conditions such as cancer (hematologic cancer), HIV, chronic kidney diseases, and transplant recipients. Immunocompromised (IC) individuals are a priority for COVID-19 vaccinations, despite concerns about vaccine safety due to their health conditions. In response to these concerns, a descriptive analysis was conducted to assess the safety of Moderna SARS-CoV-2 vaccines among IC individuals. **Objectives:** This study aimed to assess the risk and safety outcomes in IC individuals following the administration of Moderna COVID-19 vaccines. The focus includes specific risks following vaccination, overall safety, and adverse events (AEs), of special interest (AESIs) across key IC subgroups, including cancer patients, those with chronic kidney disease, transplant recipients, and individuals with hematologic malignancies. **Methods:** We retrieved spontaneous AE case reports from IC individuals after receiving a Moderna vaccine targeting SARS-CoV-2 from the Moderna Global Safety Database (GSDB) between

December 18, 2020, and June 17, 2023. IC individuals were identified based on reported immunodeficiency disorders, including acquired and primary types, transplant-related immune conditions like transplant rejections and post-transplant complications, hematologic conditions, and the use of concomitant immunosuppressants. Severe IC conditions were identified to form a subgroup for further analysis, focusing on their AEs. Analyses were conducted based on region, patient demographics, the most frequently reported preferred terms, and comorbidities. We also examined reactogenicity, non-reactogenicity events, and overall safety outcomes. **Results:** From approximately 1 billion doses of Moderna vaccines targeting SARS-CoV-2 administered globally, 701,070 cases reported AEs in the Moderna GSDB. Most of these reports came from the EU (52%) and North America (39%) and were commonly reported in adult and senior age groups. Of these cases, 1.3% (9,072 cases) were in IC individuals with nearly all were from EU and North America and the split was similar. The general age group for IC reported cases spanned adults to seniors, with 61.8% of cases in those aged ≥50 years. Within the IC group, the most severe subgroups were those with cancer (23%), HIV (13%), renal disease (6%), and those who had undergone transplants (5%). Although all reported cases were commonly reported in women, the IC severe subgroups showed an equal gender reporting distribution. Commonly reported symptoms were associated with vaccine reactogenicity, such as headache, fever, fatigue, chills, muscle pain, nausea, general discomfort, pain at the injection site, and joint pain. Non-reactogenic terms such as dyspnea, dizziness, diarrhea, cough, pruritus, rash, and lymphadenopathy were observed in IC subgroups. The most common comorbidities in IC cases were hypersensitivity, respiratory issues, cardiovascular conditions, and diabetes. **Conclusions:** The safety profile of Moderna vaccines targeting SARS-CoV-2 in IC individuals appeared similar to that in the general population. Despite these encouraging findings, vigilant monitoring of reported AEs in the IC population will continue. Further research is crucial to understand the effects of immunosuppressants on vaccinated IC individuals.

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(44) Long-Term Impact of Rotavirus Vaccination on All-Cause and Rotavirus-Specific Gastroenteritis and Strain Distribution in Central Kenya: An 11-Year Interrupted Time-Series Analysis

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Background: Kenya introduced a monovalent rotavirus vaccine into her National Immunization Program in July 2014. The study evaluated the long-term impact of the vaccine on all-cause and rotavirus-specific acute gastroenteritis (AGE) and strain epidemiology in Kenya. **Methods:** Data on all-cause and rotavirus-specific AGE and strain distribution were derived from an eleven-year hospital-based surveillance of AGE among children aged <5 years at Kiambu County Teaching and Referral Hospital (KCTRH) in Central Kenya between 2009 and 2020. Fecal samples were screened for rotavirus using ELISA and genotyped using multiplex semi-nested RT-PCR. Trends in all-cause and rotavirus-related AGE and strain distribution were compared between the pre-vaccine (July 2009-June 2014), early post-vaccine (July 2014-June 2016) and late post-vaccine (February 2019-October 2020) periods. **Results:** Rotavirus-specific AGE was detected at 27.5% (429/1546, 95% CI: 25.5-30.1%) in the pre-vaccine period; 13.8% (91/658, 95% CI: 11.3-16.6%) in the early post-vaccine period; and 12.0% (229/1916, 95% CI: 10.6-13.5%) in the late post-vaccine period. This amounted to a decline of 49.8% (95% CI: 34.6%-63.7%) in rotavirus-specific AGE in the early post-vaccine period and 53.4% (95% CI: 41.5-70.3%) in the late post-vaccine period. All-cause AGE hospitalizations declined by 40.2% (95% CI: 30.8%-50.2%) and 75.3% (95% CI: 65.9-83.1%) in the early post-vaccine and late post-vaccine periods, respectively. G3P[8] was the predominant strain in the late post-vaccine period, replacing G1P[8] which had predominated in the pre-vaccine and early post-vaccine periods. Additionally, there was increased detection of uncommon strains G3P[6] (4.8%) and G12P[6] (3.5%) in the post-vaccine era. **Conclusion:** Rotavirus vaccination has resulted in a significant decline in all-cause and rotavirus-specific AGE, and thus, provides strong evidence for public health policy makers in Kenya to support the sustained use of the rotavirus vaccine in routine immunization. However, the

shift in strain dominance and age distribution of rotavirus AGE underscores the need for continued surveillance to assess whether any such changes could diminish the vaccine effectiveness. **Keywords:** Rotavirus; gastroenteritis; coverage; strains; vaccine impact; Kenya.

(45) Safety and efficacy tests of Brucella abortus strain 104M in human volunteers

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Human brucellosis is caused by direct contact with infected cattle(Brucella abortus), sheep, goats(Brucella melitiness), pigs(Brucella suis), and dogs(Brucella canis) or consumption of the contaminated animal products or inhaling airborne agents. In China, human brucellosis is an emerging disease and expanding from northwestern to southwestern China, from Inner Mongolia, Xinjiang, Qinghai, Ningxia, Shandong, Hebei to Yunnan provinces. This increasing incidence attributes to expansion of livestock industries, poor animal vaccination program and uncontrolled animal trade. Brucella abortus strain 104M, a spontaneously attenuated strain has been approved as a live vaccine against human brucellosis for 6 decades in China. Nevertheless, the underlying mechanism of immune responses remains elusive. In the present study, 13 volunteers aged 25-55 received 104M strain by skin scratch while 10 young students were treated with physiological saline as the control group. The safety test was assessed by monitoring body temperature and scratch inflammation for 2 weeks while the efficacy was determined by antibody levels, T cell activations and cytokines for 6 months. Results showed that no adverse effects were observed in the inoculated group except for 1 person with transient bung up and the strain104M induced 50% positive IgG antibodies on day 30, amounted to 100% positivity after 60 days and maintained for 6 months. Meanwhile, IgG antibodies was amounted to maximal level compared to slow increasing IgA levels on day 180 post immunization. However, IgM antibodies level reached its peak on day 90, and then decreased gradually on day 180.Compared to the control group, significantly increasing cytokines (IL-2, TNF-α, and IFN-γ) were found in the supernatants of peripheral bloods stimulated with 104M strain on day 90 while Th1 cytokines(IL-2, TNF-α and IFN-γ) and IL-17A decreased gradually on day 180 in the vaccinated group. However, 104M strain-elicited TNF-α maintained significantly higher levels compared to that of the control group. No significant difference of CD3+ ratio was found between the vaccinated group and control group during the observation. Regarding 104M clearance in the bloods, all samples were positive on day 90 and converted to be negative by fluorescence quantitative PCR assay. Based on above evidences, skin scratch delivery is a safe and effective immunization route in all the volunteers. Both humoral response and cellular immunity stimulated by Brucella abortus 104M vaccine are promising approach combating human brucellosis in the preliminary study. Key words: Brucella abortus 104M; safety test; efficacy test; human brucellosis.

(46) TRANSFECTION OF THE APICOMPLEXAN PARASITE THEILERIA PARVA SPOROZOITES: TOWARDS CRISPR/CAS GENE EDITING FOR VACCINE DEVELOPMENT.

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East Coast fever (ECF), caused by Theileria parva, is a deadly disease affecting cattle in sub-Saharan Africa. Theileria parva invades the host cells, causing cancer-like symptoms, leading to death within three weeks of infection by a build-up of fluid in the lungs, causing the animals to suffocate. Currently, the only available vaccine for ECF is the infection and treatment method (ITM), where live sporozoites are injected into cattle. ITM needs the co-administration of long-acting tetracycline. To offer an alternative to the existing vaccine and circumvent the reliance on antibiotics, we endeavored to use CRISPR/Cas9 gene-editing technology to modify the T. parva parasite genome to generate a live-attenuated vaccine. To achieve this, an efficient transfection system for T. parva is required. We report on a transfection system of T. parva sporozoites using electroporation technology. A plasmid containing a T. parva elongation factor-1 alpha (ef-1α) promoter and an Azami Green reporter was electroporated into Theileria parva Muguga sporozoites. The sporozoites were then incubated at 30°C with 5% CO2 in RPMI media. Counterstaining with a monoclonal antibody against p67, a major sporozoite surface antigen, was performed to confirm possible transfection events. Transfected sporozoites were stained at 4-time points with an anti-p67 primary antibody and APC anti-mouse IgG as the secondary antibody. The first

transfection events were seen 18h post-transfection on a cytospin slide using an LSM 900 confocal microscope. The fluorescence of sporozoites under the GFP filter (Azami green) corresponded with the p67 staining under the APC filter, confirming that the green fluorescence observed was from transfected sporozoites. Flow cytometry also confirmed successful transfection, putting the efficiency at 1.32%. This established electroporation protocol is a crucial delivery tool for the CRISPR/Cas9 components, facilitating targeted genome editing. Through bioinformatics analysis, we have identified candidate genes for attenuation, paving the way for developing an effective vaccine against ECF. In summary, our research represents a significant step towards combatting ECF and addressing the challenges of current vaccination strategies. By harnessing the power of CRISPR/Cas9 technology, we aim to contribute to developing sustainable solutions for livestock health and welfare in sub-Saharan Africa.

(47) Lipid formulated plasmid DNA drives robust innate immune activation to promote adaptive immunity

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Gene-vectored vaccines have grown in importance over the past several years, exemplified by exemplified by the approvals of lipid nanoparticle-formulated mRNA (mRNA-LNPs), viral-vectored vaccines, and a jet-delivered DNA vaccine for SARS-CoV-2. However, understanding the differences between lipid-based formulations for delivering DNA and mRNA-LNPs in particular has not been studied, and characterization of lipid-formulated DNA could build upon current genetic delivery approaches. Here, we study a lipid-based plasmid DNA vaccine formulation which we demonstrate induces potent innate and adaptive immunity at low doses with similar potency to mRNA-LNPs and adjuvanted protein. Using an influenza virus hemagglutinin-encoding construct (HA), we show that lipid-formulated plasmid DNA drives potent inflammation dependent on the cGAS-STING-TBK1 pathway but independent of TLR9. Priming with a HA-expressing lipid-formulated DNA construct demonstrated robust activation in migratory DC (mDC) subpopulations and significant upregulation of mDCs and neutrophils. Transcriptomics elucidated activation and upregulation of pro-migration factors among multiple innate immune populations after priming with lipid-formulated DNA. HA-expressing lipid-formulated DNA uniquely induced superior HA-specific CD8+ T cell responses relative to other platforms. HA-expressing lipid-formulated DNA additionally induced robust germinal center responses attenuated in frequency to mRNA-LNPs and adjuvanted protein, but with humoral immune responses equivalent in titer, durability, and function. Extending these findings to an additional pathogen antigen, a SARS-CoV-2 spike-encoding lipid-formulated DNA construct elicited protective efficacy comparable to spike mRNA-LNPs. Thus, this study identifies priming mechanisms and characterizes immune phenotypes after lipid-formulated DNA immunization, suggesting additional avenues for vaccine development.

(48) A VLP-like Polio Vaccine Candidate produced on insect cell are safe and immunogenic in human adults

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Abstract: Currently used two polio vaccines, inactivated poliovirus vaccine (IPV) and live attenuated oral poliovirus vaccine (OPV), manufactured from live virus represent a risk of vaccine associated paralytic poliomyelitis (VAPP), circulating vaccine derived polioviruses (cVDPV) and unintentional release of the virus. nOPV2 is a genetically modified version of mOPV2 designed to improve the genetic stability of the vaccine virus, thereby reducing the chance of reverting to a neurovirulent phenotype. Field data demonstrate that nOPV2

retains its enhanced genetic stability with a substantially lower rate of reversion and risk of cVDPV2 emergence compared to Sabin OPV2. Recombinant VLP-like Polio vaccines, assembled from the structural proteins of polioviruses and containing no genetic material, can eliminate all of these risks posed by OPV, IPV and nOPV, and represent a novel weapon necessary to achieve and maintain global Polio eradication. We have developed a polio VLP vaccine (VLP-Polio) candidate based on insect cell-baculovirus platform, which contain three types of VLPs formulated with aluminum Adjuvant. 10L scale production process and related analytical methods have been developed for three types of VLPs. The characterization results indicate that three purified VLP bulk were overall pure, homogenous and relatively thermos-stable empty nanoparticles with 30-40nm in diameter. The non-clinical study results demonstrate that the VLP-Polio vaccine is safe and immunogenic and it can stimulate neutralizing antibodies against three type polioviruses in tested animal models, and is noninferior to sIPV/cIPV. A First-in-human Trial (FIH) has already been initiated in Australia to primarily access safety and tolerability of low adjuvant dose, medium dose and high dose of VLP-Polio in adults, comparing to the marketed inactivated poliomyelitis vaccine IPOL® as the positive control. This is a randomized, observer blind, positive controlled Phase 1 clinical trial, enrolling 72 healthy adults aged between 18 and 54 years. The obtained interim results showing a good safety profile with no grade 3 and above AE, or SAE observed. The immunogenicity data indicate that the VLP-Polio candidate vaccine in all three different formulations successfully triggers immune responses against Poliovirus types 1, 2, and 3. Additionally, with a seraprotection rate defined as 1:8, the rate increased from 77.8%-94.4% to 100% in all participants after vaccination. These results suggest that the VLP-Polio candidate vaccine is safe, tolerable and immunogenic in health adults when administrated via intramuscular injection. The FIH trial in AUS is funded by Bill & Melinda Gates Foundation.

(49) Characterisation of Immune Responses to the rVSVΔG-LASV-GPC Vaccine Candidate in Healthy Adults

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Abstract: Lassa Fever is an acute viral haemorrhagic disease caused by Lassa Virus (LASV) and is endemic to several parts of West Africa. A 2023 outbreak in Nigeria involved 4702 suspected cases and 152 deaths. A safe and effective vaccine against LASV could prevent or control outbreaks. We report on a dose-escalation phase I study in 114 healthy adult volunteers conducted at sites in US and Liberia, investigating safety and immunogenicity of a replication-competent recombinant vesicular stomatitis viral vector vaccine encoding LASV glycoprotein (rVSVΔG-LASV-GPC). Vaccine was administered intra-muscularly as a single injection or in a homologous prime-boost regimen using a 6-20-week interval and was well tolerated. We present in detail analyses of the immune responses up to 12 months after vaccination, demonstrating the induction of serum IgM and IgG antibodies recognizing homologous and heterologous LASV GPC. In addition, we detected neutralizing antibody titers in sera collected at various time points post vaccination that were also able to neutralize LASV of heterologous lineages. Furthermore, rVSVΔG-LASV-GPC vaccination induced Th1-biased CD4+ T cell responses characterized by interferon-γ, IL-2 and tumour necrosis factor-α secretion and CD8+ T cells of monofunctional, polyfunctional and cytotoxic phenotypes. Additionally, we used a systems vaccinology approach to identify early biomarkers and immune signatures associated with rVSVΔ-LASV-GPC vaccination in humans. We identified a signature of early innate markers correlating with anti-LASV-GPC IgM and IgG binding and neutralizing antibody levels on day 28 and beyond. Consistently, we also found an early cytokine signature linked to anti-vector antibodies and LASC GPC-specific T cell responses. Overall, our results show replication-competent rVSV-vector induces a milieu of innate antiviral responses that can orchestrate rapid development of durable adaptive immunity against LASV GPC. Taken together, these results suggest a favourable immune profile induced by rVSVΔG-LASV-GPC vaccine, supporting the progression of this vaccine candidate to phase 2 trials.

(50) Safety and immunogenicity of Ad5-nCoV given as the second booster following three doses of CoronaVac: a multicentre, open-label, phase 4, randomised trial

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Background: Protection against symptomatic disease diminishes rapidly following the third booster dose of CoronaVac, prompting the recommendation of a fourth booster in multiple countries. This study aimed to assess the safety and immunogenicity of the second booster immunization involving nebulised inhaled Ad5-nCoV, intramuscular injection of Ad5-nCoV, and CoronaVac. **Methods:** This study was an open, randomised, parallel-controlled Phase 4 clinical trial in which healthy adults 18 years of age or older who were eligible to have completed two doses of CoronaVac primary immunisation and one dose of CoronaVac booster immunisation at least 6 months previously were randomised (1:1:1) to receive a fourth dose of nebulised inhalation of Ad5-nCoV (0.1 mL), intramuscular Ad5-nCoV (0.5mL) and CoronaVac (0.5mL). The primary endpoints were safety and immunogenicity (GMT of serum neutralising antibodies against prototype live SARS-CoV-2 virus 28 days after the second dose of immunisation). **Results:** The study enrolled a total of 365 subjects, with 117 receiving nebulised inhalation of Ad5-nCoV, 120 receiving intramuscular injection of Ad5-nCoV, and 119 inoculated with CoronaVac. Within 28 days after immunisation, the intramuscular Ad5-nCoV group had a higher incidence of adverse reactions compared to the nebulised inhalation and CoronaVac groups ($P<0.001$), with rates of 30%, 9%, and 14%, respectively. No serious adverse events related to vaccination were reported. Before booster immunisation, neutralising antibody levels against the SARS-CoV-2 wild strain were similarly low in all three groups, with geometric mean titers (GMTs) ranging from 11.0 to 15.5. Heterologous boosting with aerosolised Ad5-nCoV resulted in a GMT of 672.4 (95% CI 539.7–837.7), while intramuscular Ad5-nCoV led to a serum neutralising antibody GMT of 582.6 (505.0–672.2) 28 days after the booster dose, both significantly higher than the CoronaVac group (58.5 [48.0–71.4]; $p<0.0001$). Additionally, 28 days after booster immunisation, the GMTs of pseudovirus-neutralising antibodies induced by nebulised inhalation of Ad5-nCoV and intramuscular injection of Ad5-nCoV against the Omicron (BA.4/5) variant were 108.2 [84.3-138.9] and 79.9 [65.4-97.6], respectively, significantly higher than CoronaVac at 18.7 [17.1-20.5], $P<0.0001$. On day 14 after booster immunisation, nebulised inhaled Ad5-nCoV induced significant cellular immune responses with median IFN-γ counts of 117 (IQR 3-437) and IL-2 of 83 (20-393). Both intramuscular injections of Ad5-nCoV and CoronaVac exhibited lower cellular immune responses relative to the nebulised inhaled Ad5-nCoV group, and there was no significant increase in TNF-α after immunisation in either group. **Conclusions:** The booster immunisation with inhaled Ad5-nCoV or intramuscular Ad5-nCoV as the fourth injection was safe and highly immunogenic, with significant immune responses against the Omicron (BA.4/5) variant despite reduced antibody levels. This study increase confidence in heterologous sequential booster immunisation with inhaled Ad5-nCoV or intramuscular Ad5-nCoV and support the accelerated expansion of this immunisation strategy.

BRIGHT SPARKS PHD STUDENTS
PRESENTER ABSTRACTS
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Evaluation of an adjuvanted DNA vaccine for the control of virulent strains of Newcastle disease virus

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Background: Newcastle disease virus (NDV) is a significant avian pathogen that causes substantial economic losses globally. Vaccination is the most effective way to control Newcastle disease (ND); however, existing commercial vaccines do not protect against many of the concerning, highly virulent strains circulating around the globe. Thus, new vaccines are needed to protect food security worldwide, including in Africa where ND causes significant impacts. This study aims to create a genotype-matched DNA vaccine that is more immunogenic for genotype VII and more stable than live-attenuated vaccines (LAVs). It is hypothesized that a genotype-matched vaccine will be more immunogenic than the currently available genotypes I and II vaccines and will provide better protection against virulent NDV. Methods: A DNA vaccine for NDV was developed using the F and HN genes of genotype VII, adjuvanted with interferon lambda (IL-28b). The efficacy of our vaccine was compared to that of the LaSota vaccine (positive control) by vaccinating different groups of chickens and confirming protective antibody titer using the indirect haemagglutination assay (IHA). The NDV strain ON148423 isolated from an outbreak of ND in chickens in Tanzania and identified as velogenic was used for the challenge phase. Results: The antibody response elicited by the candidate vaccine and the results of the viral challenge study suggest that it could be a suitable vaccine for combating the disease. Our new vaccine yields the best results, particularly when administered via intramuscular injection. Following the virus challenge, our new vaccine adjuvanted with IL-28b provided 80% protection, compared to the 60% protection provided by LaSota-immunized chickens against genotype VII NDV. These results indicate that our new vaccine is promising. Conclusions: NDV is a significant pathogen in the veterinary world and also has the potential to emerge in humans. It is worth noting that before the early 2000s, people believed that CoVs were not significant human pathogens, but only posed a threat to animals. However, we now know that this can change rapidly. Developing vaccines against ND would not only benefit farmers and food security but could also prevent a potential pandemic in humans.

Intention to receive COVID-19 and Influenza vaccines during pregnancy: a prospective cross-sectional study among pregnant women attending antenatal care in Cape Town.

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Background: Vaccination in pregnancy protects the expectant mother, their fetuses, and their infants from infection during the first few months of life. This study aims to assess and identify factors associated with the willingness of pregnant women to receive Influenza and COVID-19 vaccines during pregnancy. **Methods:** A multi-methods cross-sectional study was conducted at Mowbray Maternity, New Somerset, and Groote Schuur hospitals in Cape Town among pregnant women attending antenatal clinics. Participants were asked to complete a self-administered questionnaire about their attitudes towards vaccination against Influenza and COVID-19 vaccines in pregnancy. Descriptive statistics and logistic regression were performed to assess factors associated with vaccine acceptance. Seven participants who did not participate in the quantitative component were interviewed. **Results:** 500 pregnant women completed the questionnaire of whom 47,6% were vaccinated against COVID-19 before pregnancy. There were 258 (51,6%) participants who reported trusting COVID-19 vaccines, compared to 353 (70,6%) who reported trusting Influenza vaccines ($p<0.001$). Similarly, 245 (49%) of the pregnant women were willing to receive the Influenza vaccine during pregnancy as opposed to 18 (4%)

willing to accept the COVID-19 vaccine while pregnant (p<0.001). Factors associated with the acceptance of the Influenza vaccine in pregnancy included the belief that the vaccine protects pregnant women against Influenza (OR 2.2 95%CI [1.36-3.57]) and that it is safe to receive the vaccine during pregnancy (OR 7.77 95%CI [4.85-12.69]). Being concerned about getting COVID-19 during pregnancy (OR 4.65, 95%CI [1.16-17.9]) and the belief that the COVID-19 vaccine is safe (OR 8.54 95%CI [3.67-19.96]), and important (OR 10.13 95%CI [2.27- 45.3]) during pregnancy were significantly associated with vaccine acceptance. **Discussion:** Acceptance of vaccines against COVID-19 and Influenza was driven by women's belief in their safety and protective effect during pregnancy. Vaccines will only be effective if pregnant women choose to get vaccinated and present their children for vaccination. Therefore, addressing determinants of vaccine acceptance and uptake, such as maternal knowledge, attitudes, and beliefs about recommended vaccines in pregnancy and childhood, should be prioritized.

Efficient HBV immunization using a self-powered microfluidic chip for reconstitution and intradermal delivery of CpG-adjuvanted HBs vaccine

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Population-wide vaccination is essential to fight hepatitis B virus (HBV) infection and liver cancer. Current HBV vaccines consist of recombinant HBs antigen adjuvanted with alum, administered over three doses by intramuscular injection. Novel formulations such as Heplisav-B® using CpG1018 as adjuvant may increase seroconversion rates and anti-HBs antibody responses while reducing the number of doses required for immunization. Here we introduce a novel self-powered ID vaccine applicator and explore intradermal (ID) vaccination to further enhance HBs immunogenicity with dose-sparing potential by fractional dosing. For that purpose we developed a compact and easy-to-use microfluidic device (iSIMPLE vaccine chip) that integrates (i) on-device storage of lyophilized antigen and adjuvant, (ii) controlled vaccine reconstitution and (iii) subsequent ID injection, potentially by self-administration. The iSIMPLE device, made from inexpensive materials like double-sided tape, filter paper and plastic, is easy to fabricate while liquid handling and pressure generation is fully self-powered (Dal Dosso et al. Biomed. Microdevices, 2018). For proof of concept, Sprague-Dawley rats that had been primed with a fractional (1/50) ID dose of Heplisav-B® were used to mimic baseline HBV immunization as would be conferred by current heptavalent childhood vaccines. These animals were then ID vaccinated using our iSIMPLE microfluidic device whereby HBs and CpG (equivalent to 1/50 dose of Heplisav-B®) had been stored in separated chambers on the device itself, to be reconstituted in dedicated micro-mixing chambers on-chip prior to overpressure creation for ID injection. Animals that got HBsAg premixed with CpG, administered using a syringe and the Mantoux technique, served as controls. Humoral immune responses were measure by ELISA and anti-HBs antibodies levels exceeding 10 mIU/mL considered as seroprotective. ID immunization by iSIMPLE reached 100% efficacy which is similar, if not superior, to immunization by the Mantoux technique (80% seroprotection) in the same rat model. Moreover, both seroconversion rates as well as antibody levels were significantly and consistently higher compared prime-only baseline controls (10% seroconversion with anti-HBs hardly reaching the seroprotective threshold). In conclusion, ID vaccination using our integrated iSIMPLE vaccine chip allows for convenient ID immunization against HBV and beyond, using established antigens and adjuvants, yet stored in a compact liquid or lyophilized thermostable form that facilitates logistics and administration for global vaccine access.

Development of a dual vaccine against bovine coronavirus and lumpy skin disease virus.

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Bovine coronavirus (BCoV) is a pneumo-enteric virus that causes significant respiratory and intestinal infections in cattle and other ruminants. Lumpy skin disease virus (LSDV) is the causative agent of lumpy skin

disease (LSD), another important cattle disease, that is endemic in Africa and rapidly advancing to other areas. These viruses have large health and economic consequences for the cattle farming industry and prophylactics which are safe and effective against these pathogens are needed. In this study, a recombinant LSDV expressing nucleocapsid and spike proteins of BCoV was constructed (LSDV-BCoV-K1L). The BCoV spike and nucleocapsid antigens used in the vaccine were based on the consensus sequences of 38 spike and 24 nucleocapsid amino acid sequences that included viruses from multiple genotypes of BCoV. The following modifications were made to the spike protein to improve the stability, localisation and expression: the native leader sequence of the spike protein was replaced with the tissue plasminogen activator leader sequence, the cleavage site was replaced with a flexible linker sequence and two stabilising proline mutations were introduced. Insertion of the foreign gene cassette between LSDV open reading frames 49 and 50 was confirmed by polymerase chain reaction and DNA sequencing. In addition, expression of the BCoV spike and nucleocapsid proteins in cells infected with LSDV-BCoV-K1L was confirmed by Western blot analysis. The immunogenicity of LSDV-BCoV-K1L was compared to the parent virus, nLSDVSODis-UCT, in mice. Mice immunised with LSDV-BCoV-K1L developed high titres of spike specific antibodies and low titres of antibodies to the nucleocapsid. This dual vaccine against lumpy skin disease and BCoV warrants further assessment in cattle.

Cinnamon and Spice as Adjuvants are Nice: Targeting TRP Channels to Boost Mucosal Immunization

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The COVID-19, Ebola, and influenza pandemics over the last two decades have heightened the need for vaccines that are easy to transport, and which can be administrated in a needle-free manner. The oral mucosa is a notable target due to its large surface area and access to the systemic circulation while bypassing the harsh environment of the gastrointestinal tract, however, the immune response generated through the sublingual and buccal mucosa are not as potent as those given by injection. We aim to address this issue through the use of film-based formulations and transient receptor potential channel (TRP) agonists to improve vaccine potency. TRPs are cellular sensors that respond to a wide spectrum of endogenous and exogenous chemical and physical stimuli. TRPs, present on taste buds, sensory ganglion neurons, the epithelial lining of the oronasal cavity, T cells and antigen presenting cells mediate localized, transient proinflammatory response. We found that TRPs can be stimulated by components associated with taste and sensation of food such as capsaicin, vanillin and cinnamaldehyde in an in vitro model of the human oral mucosa as shown by the release of IL-6 (>2000 pg/mL), TNF-α (20-40pg/mL) and GM-CSF (17-28pg/mL) 24 hours after treatment. Use of cinnamaldehyde (74%, $p=0.006$) and bisandrographolide A (76%, $p<0.001$, a component of King of Bitters) significantly improved deposition of a recombinant adenovirus in human buccal explants. Mice immunized by the buccal route with films containing influenza A and cinnamaldehyde had the highest rate of survival post-challenge (67% vs 20% no formulation) and exhibited a significant reduction in viral load compared to unvaccinated mice ($p<0.001$). These studies suggest that TRP channels in the oral mucosa can be targeted with known agonists like capsaicin, cinnamaldehyde, or vanillin to enhance the immune response to vaccines. Much like an adjuvant, these flavoring components can trigger a proinflammatory cytokine response, do not hinder vaccine uptake, and amplify the protective immunity of a vaccine.

High throughput epitopemapping using charge scanning mutagenesis

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Knowledge of neutralizing epitopes is important for developing vaccines and inhibitors against viral pathogens. We describe a rapid and efficient method for epitope mapping, employing barcoded charged scanning mutagenesis libraries displayed on the yeast surface, and screened using flow cytometry coupled to deep sequencing. Charged residues are well tolerated at surface positions, yet such substitutions at epitope residues strongly perturb binding to a cognate partner. We therefore constructed a charged scanning library of the SARS-CoV-2 Receptor Binding Domain at exposed residues, linking every mutation in the library to a

defined, unique barcode introduced by PCR for each position. In contrast to deep mutational scans, charged scanning mutagenesis with the introduced barcoding strategy employs libraries with ~30-fold lower diversity, facilitating library construction, screening, and downstream analysis, and also allowing for further multiplexing of samples, thus accelerating interaction site identification, as well as vaccine and inhibitor development. The scanning library and the deep sequencing read analysis approach were first validated by mapping the known RBD interacting residues with the ACE2 receptor. Aspartate mutations had minimal to no effect on protein expression. The ACE2 epitope could be mapped by sorting and sequencing populations with abolished binding with precision and recall values of 93% and 65%, respectively. The approach was further used to map epitopes targeted in polyclonal sera of mice immunized with different SARSCoV-2 immunogens, and in sera of human patients in India, who suffered a breakthrough infection during the period November 2021 - January 2022 , after receiving two doses of the ChAdOx1 nCoV- 19 adenoviral vector vaccine. Sera were collected 4-6 weeks post infection. An enrichment of antibodies targeting class-I and recently discovered, rare, cryptic class-V epitopes was detected in the human sera. The class-V epitope is highly conserved across all SARS-CoV-2 variants, including the recent XBB.1.5 variant. Serum neutralization assays against Omicron BA.1, BA.5, and XBB.1.5 variants confirmed the epitope mapping results. The sera analyzed in the present work are from a highly exposed population that lacked access to updated vaccines. These results contrast with those from high-income countries, where many were vaccinated multiple times with updated mRNA vaccines. However, in the absence of XBB exposure or vaccination, the resulting sera poorly neutralized XBB variant viruses.

A Two-Component Cocktail of Engineered E Domain III Nanoparticles Elicits Broadly Neutralizing Antibody Responses against Dengue virus in Mice

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Dengue virus (DENV) is a positive-strand RNA virus that is part of the Flaviviridae family transmitted by mosquitoes in tropical countries along the equator, where 42% of the global population reside. There are 4 serotypes of DENV (DENV1-4) that cocirculate in endemic regions and infects up to 400 million people per year. Primary infection by a single serotype causes self-limiting febrile illness, but secondary infection by a heterologous serotype can lead to Severe Dengue, characterized by shock, hemorrhagic disease, and even death. Neutralizing antibodies are key mediators of long-term protection; however cross-reactive, but non-neutralizing antibodies can cause antibody dependent enhancement (ADE) of disease, which is thought to contribute to Severe Dengue. Therefore, eliciting a potent, broadly neutralizing antibody (bNAb) response against all four DENV serotypes is critical for effective vaccine design. As a vaccine target, we focus on the DENV envelope glycoprotein E, which forms the scaffold for the virus particle and mediates cell attachment and viral entry. The E DIII domain specifically plays a role in host receptor binding and is conserved among all four serotypes. Although E DIII is highly immunogenic and is the target of bnAbs, certain epitopes are not broadly neutralizing and elicitation of Abs against these epitopes is undesirable. Here, we developed nanoparticle vaccines bearing engineered DIII variants in which epitopes targeted by non-neutralizing antibodies were mutated via structure-guided design and phage display. We then assessed their capacity to elicit neutralizing and protective responses and found that presentation, formulation, and administration of these DIII variants is critical to a potent in vivo response. Finally, we showed a two-component cocktail of these DIII variants elicited a broadly neutralizing DENV1-4 response in mice and passive transfer of sera from animals immunized with a two-component cocktail reduced viral replication in vivo. Taken together, these results suggest immunization with DIII variants offer a more targeted immune response as a subunit vaccine and may also offer lower risk of ADE by immunofocusing the response to critical epitopes that elicit broadly neutralizing antibodies. These findings provide insights into more effective DENV vaccine design that elicits a broadly protective response against all four DENV serotypes.

Engineering, structure, and immunogenicity of a Crimean–Congo hemorrhagic fever virus pre-fusion heterotrimeric glycoprotein complex

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Crimean–Congo hemorrhagic fever virus (CCHFV) is a widespread tick-borne virus that can cause severe viremia and hemorrhagic fever in humans with case fatality rates (CFR) of up to 40%. The virus is primarily spread by ticks of the Hyalomma genus, which are distributed widely throughout parts of Europe, Africa, and Asia, but CCHFV has a broad host range and can infect a diverse species of wild animals. The viral genome M segment encodes for a glycoprotein precursor complex (GPC), which undergoes proteolytic processing events to generate mature proteins found on the viral envelope. In addition to a highly glycosylated mucin-like domain (MLD) at the N-terminus, the GPC comprises three glycoproteins (GP38, Gn, and Gc) and an incompletely understood accessory protein (NSm). The organization of the CCHFV M segment is more complex than other bunyaviruses, such as hantaviruses, where the M segment encodes for only Gn and Gc. Due to the complex organization of the CCHFV M segment, protein expression and stability have been obstacles to conducting structural studies, protein subunit vaccination studies, and antibody isolation studies. The glycoproteins are major targets for vaccine and antibody therapeutic development, yet little is known about their structural organization and function in the viral life cycle. Gc mediates membrane fusion and is presumed to form a complex with Gn on the viral surface, whereas GP38, a protein unique to nairoviruses, is thought to be a secreted protein with unknown function. However, GP38 has recently been detected on the viral surface, raising questions about whether it functions with Gn or Gc in the fusion process. To date, structures of Gn, Gc in its pre-fusion conformation, and pre-fusion CCHFV glycoprotein complexes have not been reported, which are vital for understanding the fusion process and the development of effective medical interventions. We designed and characterized a stable GP38-Gn heterodimer, featuring an engineered disulfide bond between GP38 and Gn that increases expression and thermostability. We leveraged this design to obtain a cryo-EM structure of GP38-$Gn^{H\text{-}DS}$ in complex with Gc. The complex reveals a GP38-Gn-Gc heterotrimer which is fortified by polar contacts between Gn and Gc, GP38 and Gn, and a contact between GP38 and Gc. The structure of GP38-GnH-DS-Gc rationalizes GP38's association with the virion and defines the pre-fusion conformation of the CCHFV Gc fusion loops. We also assess the immunogenicity of GP38-GnH-DS-Gc and its ability to protect mice from a lethal CCHFV-IbAr10200 challenge and find that the heterotrimer elicits neutralizing antibodies, a strong GP38-specific antibody titer, and protects 40% of mice from lethal viral challenge.

Novel adenoviral vaccine candidate against a century-old disease: the ongoing search for an efficient immune-mediated control of chagas disease

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3 IBIMOL (UBA-CONICET)

Chagas disease is a neglected tropical disease caused by the protozoan parasite Trypanosoma cruzi (T. cruzi). This potentially life-threatening illness is endemic in 21 Latin American countries. Despite initially being confined to rural areas of these countries, increased population mobility has shifted the problem to urban areas and led to a rise in the number of infected people in developed countries such as United States of America, Canada, Japan, Australia, and most parts of Europe. There is no vaccine approved for preventing or treating Chagas disease. However, it is not due to lack of interest and involvement of scientific community, which has been studying T. cruzi immune-mediated control since 1912, few years later of Carlos Chagas´ first description of the disease. There are many reasons why no vaccine has reached clinical development stage yet, among them: The parasite presents multiple evasion mechanisms such as rapid and stealth invasion avoiding trigger host pattern recognition receptors, complex and relatively slow life cycle with extracellular and intracellular life stages, proliferative and dormant states, antioxidant mechanisms, complement inactivation, unspecific polyclonal B-cell activation, "distracting immunodominance" without full protection and large antigen repertoire encoded by highly polymorphic gene superfamilies that acts as a smoke screen. Despite these obstacles, the cost-effectiveness of vaccination highlights the need for including either prophylactic or therapeutic vaccines together with improvement in diagnosis, vector control plans and

chemotherapy in the overall long-term strategy to tackle Chagas disease. Our group has developed Traspain (Trasp), a novel chimeric antigen that displays key domains for humoral and cytotoxic anti-parasite protective immunity. Previous results indicate outstanding prophylactic performance when combined with c-di-AMP (CDA) as subunit vaccine strategy. In order to improve antigen-specific T cell response, we designed a replication-incompetent adenoviral vector (Ad48) for Traspain gene delivery (Ad48-trasp) as vaccine candidate. After detecting antigen expression in-vitro by indirect immunofluorescence and Western blot, immune response and prophylactic efficacy were analyzed in homologous and heterologous prime-boost schemes. Groups of C3H mice were vaccinated twice with: I) 109 PFU of Ad48-trasp, II) Trasp-CDA (10 ug - 50 ug), III) Ad48-trasp + Trasp-CDA or IV) PBS. For immune response analysis, epitope-specific circulating cytotoxic T lymphocytes (CTLs) and their memory phenotype were evaluated using dextramer staining. Moreover, activation markers (AIM) and cytokine production (ICS) in splenocytes after antigen recall were studied by flow cytometry. Regarding prophylactic efficacy, vaccinated mice were subsequently challenged with blood trypomastigotes from T. cruzi K98 clone. During the acute phase of the infection parasitemia, enzymes in blood as tissue damage indicators and electrocardiograms were evaluated. Once parasites in blood become undetectable, the chronic phase begins. Skeletal and cardiac muscular damage was then analyzed again by measuring enzymes in blood and performing electrocardiograms, and later mice were euthanized to study inflammatory infiltration and fibrosis through histology and to assess tissue parasite burden using qPCR. Groups I) and III) showed a remarkably strong antigen-specific CTL response (% CD8+ CD44high TEWETGQI+ 13.24%* and 11.48%* respectively) compared to PBS. Phenotypic analysis revealed above 40% of short-lived effector cells among them (CD127low, KLRG1high). A marked increase of IFNγ and TNFα productor cells was observed in T CD8+ subset among groups I and III. This increase was also observed in T CD4+ subset for group III. Regarding prophylactic efficacy, groups vaccinated with Ad48-trasp showed a significant decrease ($p<0,005$) in parasitemia and tissue damage indicators levels. Cardiac function was conserved in both phases as indicated by the p-wave and cQT interval values. Inflammatory infiltrate as well as fibrosis were reduced when compared with control group and tissue parasitism study showed a great reduction for the group vaccinated with the homologous prime-boost scheme. Considering these results, Ad48-trasp appears as a high potential approach for improving the current strategies of vaccine-mediated control of T. cruzi. Currently, therapeutics schemes are also being assayed. In both cases, our aim is to reach the clinical trial stage to successfully transition from vaccines to vaccination and ultimately put science at the service of society.

Preparation and Immunogenicity Study of Novel Hepatitis B Virus-like Particles

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Background: Traditional S protein-based hepatitis B vaccines have a 5%-10% non-response or low-response rate in certain individuals due to genetic factors. The preS1 and preS2 regions of the hepatitis B virus, containing viral neutralizing epitopes, enhance immune response and can effectively induce protective antibodies in this subset. This study examines a novel hepatitis B virus-like particles (VLPs) vaccine with truncated L protein, M protein, and S protein, showing excellent immunogenicity in animal models. **Objective:** To analyze the physicochemical properties of the L protein, construct expression plasmids for truncated L (NL) and M proteins, express NL and M proteins to form S protein VLPs, and evaluate their immunogenicity in vivo, thus laying a foundation for developing a new generation of recombinant hepatitis B vaccines.
Methods: Bioinformatics tools analyzed the physicochemical properties of the L protein. Expression frames and resistance markers of the pCHO1.0 plasmid were modified to create pCHO1.0-1-NL and pCHO1.0new-1-M plasmids. These were co-transfected into CHO-S cells, and stable high-expression cell lines were selected via dual-stage pressure screening with puromycin, MTX, and G418. High-expression culture media were screened, and target protein expression levels were detected by ELISA. Proteins were purified using ion-exchange chromatography, with purity and activity confirmed by SDS-PAGE, Western Blot, and ELISA. VLP formation was observed via transmission electron microscopy. The NLMS vaccine was formulated with an aluminum hydroxide adjuvant and immunized in BALB/c mice, using a commercial recombinant hepatitis B vaccine as a reference. Antibody titers against preS1, preS2, and S were measured, and the half-effective dose (ED50) was calculated. Cytokine levels of IFN-γ, IL-2, and IL-6 produced by mouse spleen cells upon antigen stimulation were quantified by ELISA. **Results:** Bioinformatics analysis revealed amino acids 2-19 of the preS1 region are hydrophobic, affecting target protein secretion. Truncated L protein (NL) and M protein VLPs were successfully generated, with transmission electron microscopy confirming 22 nm VLPs. Mice immunized with 0.5 μg/mL NLMS vaccine had antibody titers of 1:4096, compared to 1:1024 for mice immunized with 20 μg/mL

commercial vaccine. The ED50 for the NLMS vaccine was 0.078 μg/mL, versus 2.190 μg/mL for the reference vaccine. The NLMS vaccine stimulated over six times the concentration of IFN-γ, IL-2, and IL-6 compared to the PBS control group. **Conclusion:** HBV VLPs containing NL, M, and S proteins were successfully constructed and expressed. Animal studies showed the NLMS vaccine has superior immunogenicity compared to the commercial S protein hepatitis B vaccine, providing a basis for the development of a new recombinant hepatitis B vaccine.

A novel bovine TB vaccine borne unexpectedly out of basic Mycobacterium tuberculosis-complex virulence research.

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Mycobacterium tuberculosis (M. tb) uses its type-7 secretion system ESX-1 to export virulence effector proteins that are also highly immunogenic. In this study, we introduced into the genetically tractable, fast-growing and non-pathogenic model mycobacteria, Mycobacterium smegmatis, genes encoding proteins of the multi-component M. tb ESX-1 to see if we can express and reconstitute a fully functional secretion system. Specifically, M. smegmatis was transformed with either only a DNA fragment containing the M. tb esx-1 locus, only a DNA fragment containing the M. tb espACD operon or both fragments. We found that while M. smegmatis with the M. tb esx-1 locus alone can produce a functional ESX-1 system, both the esx-1 locus and espACD operon were needed to produce a strongly expressed, stable and optimally functioning protein secretion system. Although the ESX-1 system is critical for the virulence of M. tb, we found its reconstitution in M. smegmatis did not make it pathogenic. Strikingly, we found M. smegmatis with both the esx-1 locus and espACD operon – which we have named MSX-1 – performed just as well as the live attenuated M. bovis BCG vaccine in protecting mice against the TB bacillus without sensitizing them to purified protein derivative (PPD). Our study confirms the notion that the minimal functioning unit of ESX-1 is encoded by both the esx-1 locus and espACD operon but more notably, our work also offers a novel TB vaccine candidate for use in livestock and wildlife that will not render useless the existing PPD skin test used for bovine TB diagnoses.

BRIGHT SPARKS EARLY CAREER RESEARCHERS
PRESENTER ABSTRACTS
(Alphabetical Order by Presenting Author)

Generation and Evaluation of an African Swine Fever Virus Mutant with Deletion of the CD2v and UK Genes

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African swine fever (ASF) is a highly contagious and often lethal disease caused by African swine fever virus (ASFV). ASF emerged in China in August 2018 and has since rapidly spread into many areas of the country. The disease has caused a significant impact on China's pig and related industries. A safe and effective vaccine is needed to prevent and control the disease. Several gene- deleted ASFVs have been reported; however, none of them is safe enough and commercially available. In this study, we report the generation of a double gene-deleted ASFV mutant, ASFV- SY18-ΔCD2v/UK, from a highly virulent field strain ASFV-SY18 isolated in China. The results showed that ASFV-SY18-ΔCD2v/UK lost hemadsorption properties, and the simultaneous deletion of the two genes did not significantly affect the in vitro replication of the virus in primary porcine alveolar macrophages. Furthermore, ASFV-SY18-ΔCD2v/UK was attenuated in pigs. All the ASFV-SY18-ΔCD2v/UK-inoculated pigs remained healthy, and none of them developed ASF-associated clinical signs. Additionally, the ASFV-SY18-ΔCD2v/UK-infected pigs developed ASFV-specific antibodies, and no virus genome was detected in blood and nasal discharges at 21 and 28 days post-inoculation. More importantly, we found that all the pigs inoculated with 104 TCID50 of ASFV-SY18-ΔCD2v/UK were protected against the challenge with the parental ASFV-SY18. However, low-level ASFV DNA was detected in blood, nasal swabs, and lymphoid tissue after the challenge. The results demonstrate that ASFV-SY18-ΔCD2v/UK is safe and able to elicit protective immune response in pigs and can be a potential vaccine candidate to control ASF. **Keywords:** African swine fever; live attenuated virus; safety; protective efficacy; pig.

Understanding the Enhanced Immune Responses to High-Density Microarray Patch Vaccination through Spatial Transcriptomics and Antibody Repertoire Analysis

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The ongoing COVID-19 pandemic has highlighted the importance of vaccination as a critical public health tool against current and emerging pathogens. While vaccines have traditionally been delivered via needle-and-syringe injection, much work into alternative delivery systems has been conducted. The immunologically active microenvironment and the high density of antigen-presentingcells make the skin an attractive target for vaccination. The use of microarray patches to deliver vaccines directly these layers of the skin present a promising alternative to traditional vaccine delivery mechanisms. One such microarray patch is the Vaxxas High-Density Microarray patch (HD-MAP). Delivery of vaccines via the HD-MAP has shown dramatic improvements in immunogenicityin terms of magnitude, breadth and quality of the immune response. Here, we aim to further understand these immune responses using novel transcriptomic techniques. We used newly available spatial transcriptomics tools (10x Genomics Visium and Xenium) on skin biopsies from the HD-MAP application site to examine the immunological mechanisms underpinning the immune enhancement phenomena associated with HD-MAP vaccine delivery. We also used single-cell sequencing ofB cells from mice vaccinated with a SARS-CoV-2 spike protein vaccine via the intradermal or HD-MAP routes to further understand the functional immune outcomes. Spatial transcriptomicanalysisof the HD-MAP application site revealed rapid triggering of a localized enhanced inflammatory state in the skin, characterized by multiple inflammatory signaling pathways, resulting in rapid infiltration of multiple immune cells. The B-cell repertoire analysis showed that HD-MAP vaccination produces populations ofantibodies of greater diversity than intradermal injection.Analysis of recombinantly-expressedantibody clones revealed antibodies isolated from HD-MAP vaccinated animals showed enhanced neutralization capacity against multiple SARS-CoV-2 virus variants compared to those derived from intradermal vaccination. This work provides unprecedented detail into the precise transcriptional mechanisms and functional antibody responses following HD-MAP vaccination.

These findings have implications for future microarray patch-delivered vaccine development and design.

Fc-modification of anti-PcrV gene-encoded antibodies modulates complement-mediated killing of Pseudomonas aeruginosa

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Prior to the SARS-CoV-2 pandemic, growing antimicrobial resistance (AMR) was a critical global health concern due to a rise in broad-spectrum antibiotic usage. During the pandemic, majority of COVD-19 patients received one or more antibiotics at the time of hospital admission which has led to an increase in multi-drug resistant Pseudomonas aeruginosa. With a lack of new antibiotic therapeutics or successful vaccine candidates, monoclonal antibody (mAb) approaches are emerging as potential strategies to combat AMR pathogens. Synthetic DNA plasmid vectors can be engineered to encode immunoglobulin heavy and light chains, followed by direct delivery in vivo by IM injection and electroporation. DNA-encoded antibodies (DMAb) enable transient expression and secretion of mAb directly by skeletal muscles resulting in biologically relevant levels for months. Previously, we described both protection and long-term expression of anti-type IIII secretion system component PcrV DMAb-V2L2. It has been shown that control and clearance of P. aeruginosa depends on phagocyte recognition, engulfment, and degradation of bacteria. Here we extend this work to hypothesize that P. aeruginosa mAb-mediated protection in high-risk patients could benefit from enhanced recruitment of immune components that trigger the classical complement system to augment bacteria clearance. Building on previous work evaluating Fc-modified DMAbs in a vaginal Neisseria gonorrhoeae challenge, we designed 5 V2L2 DMAb variants encoding modifications in the human IgG1 heavy chain constant region with the goal of modulating binding to complement protein C1q and complement deposition. BALB/c mice (n=5/group) administered Fc-complement variant V2L2 DMAbs transiently express antibody for months post-administration. Mice (n=10/group) were either administered WT-fc or Fc-mod DMAb-V2L2 and infected after 28 days in an acute Pseudomonas aeruginosa PAO1 infection model. Here significantly lower bacterial load was detected in the lung and nasal washes in the mice administered complement enhanced Fc-DMAb compared with WT-Fc DMAb. Overall, we demonstrated that gene-encoded antibodies can be sequence modified to modulate complement engagement as a strategy to increase antibody potency as determined by bacterial clearance. To date, we have also expanded on this work to modulate the potency of DMAbs targeting both Streptococcus pneumoniae DMAbs and MRSA. Overall, we have demonstrated an advantage of plasmid engineering and sequencing optimization to improve downstream complement engagement for improved bacterial clearance. Together these studies show implications for gene-delivered antibody development as a potential strategy for the treatment or prevention of AMR infections in larger animals and humans.

A Phase III randomized controlled multi-centre trial to evaluate the efficacy of the R21/Matrix-M vaccine in African children against clinical malaria.

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Introduction: Malaria has long been the leading cause of morbidity and mortality worldwide. The R21/Matrix-M malaria vaccine has reached the WHO-specified goal of 75% protection in the target population of African children. This pre-erythrocytic malaria vaccine was developed at the University of Oxford (Oxford, UK) and is currently manufactured by the Serum Institute of India. Through booster vaccinations, the safety and

immunogenicity of R21 has shown significant promises in different parts of Africa where the trial is conducted. **Objectives:** The objectives of the present study were (i) to assess the protective efficacy of R21/Matrix-M against clinical malaria caused by Plasmodium falciparum, in 5-36 month old children living in a malaria endemic area, 12 months after completion of the primary course (standard vaccination regime) and (ii) to assess the safety and reactogenicity of R21/Matrix-M, in both vaccination regimes, of children living in a malaria endemic area, in the month following each vaccination, and 12 months after completion of the primary course. **Methodology:** This is a double-blinded phase III randomized controlled trial, where children aged 5–17 months were enrolled for the study. Eligible participants were randomly assigned to receive three vaccination doses with a booster dose after 12 months. Following an extension of two years; the study will assess safety, efficacy and immunogenicity of a second and third booster dose given 12 months apart. **Results:** A single booster dose of R21/Matrix-M restored high antibody concentrations after primary series of vaccinations. Administration of this booster dose led to sustained protective immunity over the second year when administering R21 with the higher adjuvant dose. Most malaria vaccines that target the P falciparum circumsporozoite protein have aimed to induce protective antibodies to the highly conserved NANP repeat sequence. In both the first and second year of follow-up, when assessing protection against the first or any malaria episode, analysis of the reverse cumulative distribution data suggests that a level of more than 6500 ELISA units per mL was associated with a 77% reduction in the risk of malaria. **Conclusion:** This study confirms that a booster dose of R21/Matrix-M at 1 year following the primary three-dose regimen maintained high efficacy against first and multiple episodes of clinical malaria AND induced antibody concentrations that correlated with vaccine efficacy'.

Structural basis of broad protection against influenza virus by a human antibody targeting the neuraminidase active site through a recurring motif in CDR-H3

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Influenza viruses remain a substantial global health concern, underscoring the urgent need for universal vaccines capable of conferring broad protection against diverse viral strains. Neuraminidase (NA), an essential surface glycoprotein of influenza virus, is crucial for influenza virus release and spread, making it a promising target for vaccine development. Here we describe the cryo-electron microscopy (cryo-EM) structures of a DA03E17, a broadly protective monoclonal antibody isolated from an H1N1-infected donor, in complex with N1, N2, and B NAs. DA03E17 displayed broad and potent inhibitory activity against influenza A and B virus NAs and provided in vitro neutralization and in vivo protection against infection with several types of influenza viruses. Our structural analysis revealed that DA03E17 utilizes its long CDR-H3 to target the NA active site epitopes that are highly conserved across influenza A and B virus NAs. Notably, the CDR-H3 contains a DR (Asp-Arg) motif which engages the catalytic site of NA, mimicking sialic acid interaction. This motif is identified as a recurring molecular feature of NA antibody responses present in several NA active site-targeting antibodies from different individuals, indicating a conserved mechanism of receptor mimicry. The identification of these recurring molecular features provides crucial insights for developing NA-based universal vaccines. Furthermore, the antibody employs a mechanistic strategy of glycan accommodation by inducing conformational changes in surrounding glycans at the NA active site, thereby inhibiting the NA of the recently circulating H3N2 viruses. Our data provide evidence for a conserved receptor mimicry mechanism of antibody CDR-H3 for broad inhibition of influenza A and B virus NAs and will guide the design of NA-based universal influenza vaccines.

YF17D-vectored COVID-19 vaccine protects from SARS-CoV-2-induced adverse pregnancy outcomes in a hamster model of COVID-19

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The COVID-19 pandemic has profoundly impacted global health, with varying consequences for different demographic groups. While healthy individuals of reproductive age typically experience mild or no symptoms, pregnant women are at a markedly higher risk of severe illness, hospitalization, and need for additional ventilation. Despite this, the effects of SARS-CoV-2 on maternal and neonatal health remain poorly understood. Notably, vaccine hesitancy among pregnant women has been reported to range from 26% to 57%, regardless of the reduction in maternal mortality and morbidity associated with vaccination. We thus aim to explore the potential of vaccination as a prophylactic measure to mitigate the risk of SARS-CoV-2 on poor pregnancy outcomes. Here we show that infection of pregnant Syrian hamsters with SARS-CoV-2 (B.1.1.7) significantly impacts maternal and perinatal health. Infected pregnant dams showed clear COVID-19-like pathology, yet without evidence of increased viral loads or exacerbated acute respiratory disease as compared to non-pregnant controls. Still, they experienced a transient yet marked drop in weight gain. Infectious virus was detected in the fully formed placentas of animals infected at a late gestational stage, but not in the respective pups. This suggests that a virus-induced cytokine storm and coagulation disorder may contribute to placental insufficiency, rather than vertical (transplacental) transmission of the virus; further confirmed by histopathological analysis of respective tissues at the feto-maternal interface. Importantly, pups born to females infected on day E4.5 (time of implantation) exhibited a markedly higher risk of intrauterine growth restriction (29 pups in the infected group; n=65; 4 pups in the uninfected controls, n=34; OR 6.05 [2.0-17.2], P = 0.0014). Prophylactic vaccination with a YF17D-vectored COVID-19 vaccine significantly improved outcomes in SARS-CoV-2-infected pregnant hamsters. Firstly, vaccination led to faster viral clearance in the upper airways and reduced lung damage in the dams, as measured by a cumulative lung pathology score. Moreover, pups born to infected but vaccinated dams were larger than those born to unvaccinated ones (P = 0.02), indicating maternal immunization's protective effect on fetal growth. In summary, we established a robust animal model to show to what extent SARS-CoV-2 infection may affect pregnancy outcomes, impacting both early and late embryonic development. As we demonstrate for proof-of-concept, vaccination offers a promising intervention to protect the health of both mothers and their babies, thus mitigating the risk of SARS-CoV-2 in pregnancy.

Targeted delivery of immunotherapeutics to the lower regions of the lung: using one-component Ionizable Amphiphilic Janus Dendrimers to deliver TGFβ mRNA to the lung parenchyma.

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Current strategies for delivery of immunotherapeutics to the lung are primarily targeted to the upper portions of the airways, an effective method for the treatment of large airway diseases such as asthma. However, targeted delivery of therapeutics to the lower regions of the lung is necessary for treatment of parenchymal lung injury and disease. Specific delivery of immunotherapeutics to the respiratory epithelium is challenging, which currently limits clinical usage. The current study focused on the development of an immunotherapeutic delivery system for lower lung. We utilized one-component Ionizable Amphiphilic Janus Dendrimers (IAJDs) as a vehicle to deliver mRNA immunotherapies. For this study, we focused the delivery of an anti-inflammatory cytokine mRNA, transforming growth factor-beta (TGF-β), to produce transient protein expression in the lower regions of the lung. TGF-β is of particular interest as it plays a major role in liming injury related immune responses. Various doses of TGF-β mRNA, formulated with IAJD, were administrated to mice via retro-orbital injections. Mice were euthanized 24 hours post-injections, and lung, liver, spleen, and kidney tissues were collected for further analysis. The collected tissues were stained with hematoxylin and eosin and evaluated for histopathological alterations. Lung tissue was also immunohistochemically stained for TGF-β or IgG control to confirm TGF-β protein expression. We demonstrated that delivering 10 μg/mouse of mRNA TGF-β showed diffuse TGF-β protein expression within the lung parenchyma. Additionally, we observed no toxicity in the liver, spleen, or kidney, with some non-significant increases in fibrin deposition in the lung at a high dose of 30 μg/mouse. Following toxicity testing and characterization, intratracheal (i.t.) bleomycin exposure was used as a model of acute lung injury to test TGF-β mRNA-IAJD efficacy. TGF-β mRNA-IAJD (10 μg/mouse) was delivered to i.t bleomycin (3U/kg) or vehicle (PBS) exposed mice and bronchoalveolar lavage fluid (BAL) and cells, CD45+ lung digest cells, and lung tissue were collected 3 days post exposure/treatment. TGF-β mRNA was found to

reduce bleomycin-induced changes in pulmonary cell phenotype 3 days post exposure when compared to PBS controls. Additionally, treatment with TGF-β mRNA mitigated bleomycin-induced increases in pro-inflammatory cytokines including IL-6 and CXCL-10. This study highlights IAJD's potential for precise, effective delivery of TGF-β mRNA to the lung parenchyma. This delivery system offers a promising approach for the targeting of immunotherapeutics to the lower regions of the lung, a strategy necessary to fill the current clinical gap in the treatment of parenchymal lung injury and disease.

A built-in flagellin adjuvanted ferritin nanocage mucosal vaccine platform induces high-quality protective immune responses against respiratory infections

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Protein nanocages have emerged as promising carriers in biomedicine, with ferritin nanocages gaining particular attention as a vaccine platform in both preclinical and clinical studies. Our research aims to develop a ferritin-based nanocage vaccine platform that incorporates protein adjuvants and antigens in a single formulation to combat bacterial and viral infection. Flagellin, an excellent mucosal protein adjuvant, activates TLR5 on the cell surface and the NAIP5/NLRC4 inflammasome in the cytosol. We used pneumococcal surface protein A (PspA) as a model antigen for the construction of built-in flagellin adjuvanted nanocage mucosal vaccine platform. Based on previous findings showing that a mucosal FlaB-tPspA (flagellin fused with truncated PspA antigen of S. pneumoniae; BP) vaccine-induced protective immune response, we developed a ferritin nanocage vaccine displaying both components (Ftn:tPspA:FlaB; FPB NC) using the SpyTag/SpyCatcher strategy for the multivalent presentation of both antigen and adjuvant on a nanocarrier. The ratio of antigen to adjuvant could be easily modulated. FPB NC translocated to draining lymph nodes with higher efficiency than BP. Compared with BP, intranasal immunization with the FPB NC vaccine significantly enhanced mucosal immune responses with more efficient B-cell memory generation and antibody maturation accompanying earlier and more robust germinal center reactions. The FPB NC vaccine induced more balanced (Th1/Th2) immune responses with significantly potentiated IFNγ production by T cells. Mice immunized with the FPB NC vaccine exhibited enhanced protection against lethal infection compared to BP. We extended this platform to develop a mucosal SARS-CoV-2 vaccine, creating a ferritin nanocage displaying both dimerized receptor-binding domain (RBD) and flagellin. This formulation stimulated robust neutralizing antibody generation in the systemic compartment higher than convalescent patients' sera and significantly enhanced mucosal secretory IgA antibody responses.

Improving humoral immunogenicity of adenoviral vector vaccines by capsid display

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Replication incompetent adenoviruses were rapidly deployed during the COVID-19 pandemic after a decade of development as a vaccine platform for emerging pathogens. Adenoviral vectors elicit potent T cell responses to encoded transgenes, but historically have elicited modest antibody responses in comparison to mRNA or Virus-Like Particle (VLP) platforms. In addition to encoding antigenic transgenes, adenoviral vectors can also be modified to display antigens on the virion surface – however, capsid modification sites are poorly characterised for adenoviruses other than human adenovirus 5, which is disadvantageous due to hepatotoxicity and pre-existing anti-vector immunity. Here, we identify sites in the major capsid protein (hexon) of chimpanzee adenoviruses ChAdOx1 and ChAdOx2 that tolerate insertion of antigenic sequences and show that inserted epitopes are accessible on the virion surface. Using the NANP linear epitope from Plasmodium falciparum, we demonstrate that modified vectors displaying this epitope elicit up to 65-fold greater total IgG responses to the NANP repeats than a vector encoding the full-length protein without impeding immunogenicity of an additional antigenic transgene. Furthermore, insertion of the DogTag peptide allowed coupling of native antigens via

protein superglue technology: decoration of the adenoviral capsid with the SARS-CoV-2 Receptor Binding Domain (RBD) led to >10-fold total IgG binding to the SARS-CoV-2 RBD and up to 17-fold greater neutralisation relative to a viral vector expressing the full-length spike. RBD decorated vectors retained infectivity and still elicited equivalent T cell responses to an encoded transgene as the wild-type viral vector. Capsid decoration also enabled partial escape from anti-vector immunity in an in vitro neutralisation assay. Overall, characterisation of these sites adds additional functionality to the chimpanzee adenoviral vector platform, enabling potent humoral responses to displayed antigens while retaining strong T cell responses to the encoded transgene. Capsid display is therefore an attractive strategy to enhance immunogenicity of adenoviral vectors, and represents a promising approach in the development of next-generation adenoviral vaccines against challenging pathogens.

Mapping the serological response to Chikungunya infection and vaccination

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It is estimated that more than 75% of the global population are at risk of infection with Chikungunya virus (CHIKV). Whilst infrequently lethal, a significant proportion of those infected with CHIKV suffer from chronic debilitating polyarthralgia. Despite the economic burden of chronic disease and increasing global prevalence of CHIKV, no vaccine has been licensed for use beyond the USA. It is well documented that the development of a specific anti-CHIKV serological response is critical in conferring immunity against future CHIKV disease. Previously, using the cynomolgus macaque model, we have demonstrated that specific convalesce plasma and vaccine immune serum pools confer different levels of protection against subsequent challenge with CHIKV ESCA strain LR2006 – OPY. These differences were associated with quantitative differences measured by binding assays. We are now interested to establish whether these differences in protection are associated with qualitative as well as quantitative differences in the antibody repertoire. Therefore, in this study we aim to determine the epitopes recognised by protective anti-CHIKV responses. Here, the epitope targets of convalescence plasma and vaccinated serum known to protect in vivo, were compared using microarrays displaying the proteome of an ESCA CHIKV isolate. To characterise the convalescence response in greater detail, two pools of convalescent plasma were examined: (i) the 1st International Standard for anti-CHIKV IgG (1502/19), material derived from an individual who contracted CHIKV in 2016 in Brazil, and (ii) candidate plasma material which was also examined during the establishment study for 1 st IS for anti-CHIKV IgG (1504/19), collected from 10 Puerto Ricans contracting CHIKV in 2014. Following this, similar analysis was carried out with pooled serum from clinical trial volunteers receiving either one- or two-doses of a candidate inactivated virus vaccine. Both convalescent materials contained antibodies which targeted CHIKV structural proteins such as E1 and E2, and non-structural proteins (NSPs) including NSP1. Interestingly, there were overlapping and non-overlapping target epitopes between the two convalescent materials. For the vaccinated serum pools, both vaccinated groups developed antibodies targeting the same epitopes for both structural proteins and NSPs. It was identified that all the examined materials produced an antibody fraction which targeted the same epitopes. To independently validate antigenic regions, the examined materials were incubated with either pseudotyped viruses containing a vesicular stomatitis virus core and expressing CHIKV E1/2 glycoproteins, or synthesised peptides composed of the amino acids anti-CHIKV antibodies targeted. Finally, since neutralisation assays of anti-CHIKV immunity are insufficiently sensitive to establish quantitative differences in seroreactivity associated with protection in vivo, we investigated whether modifications of these assays would produce a more sensitive assay that will establish a robust correlate of serological mediated protection. Our data shows that all materials successfully neutralised, yet with different potencies. These data indicate antibody response in vaccine serum recapitulates the response of convalescent patients and advances the development of assays that correlate protection in infected and immunised patients against CHIKV disease.

P1 Generation and Evaluation of an African Swine Fever Virus Mutant with Deletion of the CD2v and UK Genes

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African swine fever (ASF) is a highly contagious and often lethal disease caused by African swine fever virus (ASFV). ASF emerged in China in August 2018 and has since rapidly spread into many areas of the country. The disease has caused a significant impact on China's pig and related industries. A safe and effective vaccine is needed to prevent and control the disease. Several genedeleted ASFVs have been reported; however, none of them is safe enough and commercially available. In this study, we report the generation of a double gene-deleted ASFV mutant, ASFVSY18-ΔCD2v/UK, from a highly virulent field strain ASFV-SY18 isolated in China. The results showed that ASFV-SY18-ΔCD2v/UK lost hemadsorption properties, and the simultaneous deletion of the two genes did not significantly affect the in vitro replication of the virus in primary porcine alveolar macrophages. Furthermore, ASFV-SY18-ΔCD2v/UK was attenuated in pigs. All the ASFV-SY18-ΔCD2v/UK-inoculated pigs remained healthy, and none of them developed ASF-associated clinical signs. Additionally, the ASFV-SY18-ΔCD2v/UK-infected pigs developed ASFV-specific antibodies, and no virus genome was detected in blood and nasal discharges at 21 and 28 days post-inoculation. More importantly, we found that all the pigs inoculated with 104 TCID50 of ASFV-SY18-ΔCD2v/UK were protected against the challenge with the parental ASFV-SY18. However, low-level ASFV DNA was detected in blood, nasal swabs, and lymphoid tissue after the challenge. The results demonstrate that ASFV-SY18-ΔCD2v/UK is safe and able to elicit protective immune response in pigs and can be a potential vaccine candidate to control ASF.

P2 A Phase III randomized controlled multi-centre trial to evaluate the efficacy of the R21/Matrix-M vaccine in African children against clinical malaria.

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Introduction

Malaria has long been the leading cause of morbidity and mortality worldwide. The R21/Matrix-M malaria vaccine has reached the WHO-specified goal of 75% protection in the target population of African children. This pre-erythrocytic malaria vaccine was developed at the University of Oxford (Oxford, UK) and is currently manufactured by the Serum Institute of India. Through booster vaccinations, the safety and immunogenicity of R21 has shown significant promises in different parts of Africa where the trial is conducted.

Objectives

The objectives of the present study were (i) to assess the protective efficacy of R21/Matrix-M against clinical malaria caused by Plasmodium falciparum, in 5-36 month old children living in a malaria endemic area, 12 months after completion of the primary course (standard vaccination regime) and (ii) to assess the safety and reactogenicity of R21/Matrix-M, in both vaccination regimes, of children living in a malaria endemic area, in the month following each vaccination, and 12 months after completion of the primary course.

Methodology

This is a double-blinded phase III randomized controlled trial, where children aged 5–17 months were enrolled for the study. Eligible participants were randomly assigned to receive three vaccination doses with a booster dose after 12 months. Following an extension of two years; the study will assess safety, efficacy and immunogenicity of a second and third booster dose given 12 months apart.

Results

A single booster dose of R21/Matrix-M restored high antibody concentrations after primary series of vaccinations. Administration of this booster dose led to sustained protective immunity over the second year when administering R21 with the higher adjuvant dose. Most malaria vaccines that target the P falciparum circumsporozoite protein have aimed to induce protective antibodies to the highly conserved NANP repeat sequence. In both the first and second year of follow-up, when assessing protection against the first or any malaria episode, analysis of the reverse cumulative distribution data suggests that a level of more than 6500 ELISA units per mL was associated with a 77% reduction in the risk of malaria.

Conclusion

This study confirms that a booster dose of R21/Matrix-M at 1 year following the primary three-dose regimen maintained high efficacy against first and multiple episodes of clinical malaria AND induced antibody concentrations that correlated with vaccine efficacy'.

P3 Structural basis of broad protection against influenza virus by a human antibody targeting the neuraminidase active site through a recurring motif in CDR-H3

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Influenza viruses remain a substantial global health concern, underscoring the urgent need for universal vaccines capable of conferring broad protection against diverse viral strains. Neuraminidase (NA), an essential surface glycoprotein of influenza virus, is crucial for influenza virus release and spread, making it a promising target for vaccine development. Here we describe the cryo-electron microscopy (cryo-EM) structures of a DA03E17, a broadly protective monoclonal antibody isolated from an H1N1-infected donor, in complex with N1, N2, and B NAs. DA03E17 displayed broad and potent inhibitory activity against influenza A and B virus NAs and provided in vitro neutralization and in vivo protection against infection with several types of influenza viruses. Our structural analysis revealed that DA03E17 utilizes its long CDR-H3 to target the NA active site epitopes that are highly conserved across influenza A and B virus NAs. Notably, the CDR-H3 contains a DR (Asp-Arg) motif which engages the catalytic site of NA, mimicking sialic acid interaction. This motif is identified as a recurring molecular feature of NA antibody responses present in several NA active site-targeting antibodies from different individuals, indicating a conserved mechanism of receptor mimicry. The identification of these recurring molecular features provides crucial insights for developing NA-based universal vaccines. Furthermore, the antibody employs a mechanistic strategy of glycan accommodation by inducing conformational changes in surrounding glycans at the NA active site, thereby inhibiting the NA of the recently circulating H3N2 viruses. Our data provide evidence for a conserved receptor mimicry mechanism of antibody CDR-H3 for broad inhibition of influenza A and B virus NAs and will guide the design of NA-based universal influenza vaccines.

P4 A randomised, controlled, double-blind, parallel group, single center Phase Ib trial to assess safety, reactogenicity and immunogenicity of a candidate dual-stage malaria vaccine, SumayaVac-1 (MSP-1 with GLA-SE as adjuvant) in healthy malaria exposed adults of African origin aged 18-45 years

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INTRODUCTION

The Merozoite Surface Protein (MSP)-1 is one of the most abundant proteins on the merozoite surface and is essential for *P. falciparum* development. A number of follow-up immuno-epidemiological studies have strongly suggested that antibodies targeting the proteins expressed on the merozoite surface confer protective immunity against asexual blood stage parasites. Therefore, the idea of targeting the step of malaria parasite invasion of RBCs as an anti-malarial strategy has gained strong scientific support over many years. Based on a number of biological, functional, epidemiological and immunological studies investigating MSP-1, this protein is currently considered a prime candidate antigen for vaccine development against malaria.

METHODOLOGY.

This randomised, double-blinded, controlled study was designed to evaluate the safety, reactogenicity and immunogenicity of the candidate malaria vaccine, SumayaVac-1 (recombinant, fully length MSP-1 with GLA-SE as adjuvant). Forty participants (male and female) were enrolled, of which 20 participants were randomised to receive three monthly inoculations according to 0,1,2 month schedule with the SumayaVac-1 (composed of 150 µg MSP-1 drug product + 5 µg GLA-SE adjuvant) and 20 participants to receive the registered rabies vaccine (Verorab®) as controls. Safety data were collected throughout the study period with solicited adverse events (AEs) collected 7 days after each vaccination and unsolicited adverse events (AEs) collected throughout the study period. Samples for safety and immunological laboratory assessments were collected at different time points.

RESULTS

Safety data of participants including solicited adverse events and unsolicited adverse events as well as safety laboratory results throughout the study period will be presented.

CONCLUSION

We will conclude on the vaccine's safety based on the safety data obtained from vaccinated participants.

P5 Strategy to develop updated COVID-19 vaccines based on Ad5/35 platform for effective response to emerging variants

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron strain has evolved into highly divergent variants with multiple sub-lineages. These newly emerging variants threaten the efficacy of available coronavirus disease 2019 (COVID-19) vaccines. To mitigate the occurrence of breakthrough infections and re-infections, and more importantly, to reduce the disease burden, it is essential to develop a strategy for producing updated vaccines that can provide broad neutralization against both currently circulating and emerging variants. Using phylogenetic trees based on spike protein sequences and antigenic cartography based on neutralization, we selected variants that are antigenically distant from previously circulating variants and developed updated variant-specific vaccines using an Ad5/35 platform-based non-replicating recombinant adenoviral vector. We compared the immune responses elicited by the existing and updated vaccines in mice. We found that updated vaccines tailored by our strategy exhibited improved neutralization ability compared to existing vaccines. These results highlight the importance of vaccine development to keep pace with the evolution of SARS-CoV-2 variants and the need for updated vaccines.

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P6 Is the cessation of vaccination of small ruminants with Rev-1 responsible for the highly endemic situation of human brucellosis in Algeria?

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Introduction

Brucellosis caused by Brucella is one of the most common zoonosis in the world representing a serious threat to human health. The existence of brucellosis in Algeria dates to the beginning of the 19th century. In 2006, the Algerian authorities started the Rev-1 vaccination of sheep and goats; consequently, there was a significant improvement of small ruminant brucellosis sanitary status, and a reduction in cases of human brucellosis in the regions concerned.

Materiel and Methods

Our aim is to investigate the effects of stopping the Rev-1 conjunctival vaccination of small ruminants on the incidence of human brucellosis in Medea, Algeria. Data of brucellosis human cases were collected from 2011 to 2021 from the Directorate of Public Health (DSP) and the infectious department at Medea hospital.

Results and Discussion

The results showed that during these eleven years of study 795 cases were collected from the DSP and 141 patients were hospitalized at the infectious department of the wilaya of Medea. The results show a clear increase in cases of human brucellosis from 2017, the year in which vaccination of small ruminants against brucellosis by Rev1 was stopped. Human brucellosis affects all age groups with different percentages, but the rate was highest in the 20-44 age group, with a predominance of men, the majority of whom were of rural origin. The incidence of human brucellosis increased significantly after the vaccination campaign was stopped. It is widely accepted that in areas where brucellosis is endemic in small ruminants, vaccination is the only suitable method for disease's control. Vaccination of animals has a direct impact on the incidence of brucellosis in both animals and humans due to an increase in the number of immune animals, and a reduction in the number aborting and therefore excreting the organism.

P7 Evaluation of oral cholera vaccine (Euvichol-Plus) effectiveness against Vibrio cholerae in Bangladesh: An interim analysis

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Background

Millions of doses of inactivated oral cholera vaccine (OCV) have been deployed from the global OCV stockpile to control cholera in over 20 cholera-affected countries. However, information on the effectiveness of Euvichol-Plus, the only vaccine currently used in the stockpile, is scant. The use of this vaccine in a recent epidemic in Dhaka, Bangladesh, allowed an evaluation using a test-negative design.

Methods

A 2-dose regimen of Euvichol-Plus vaccine was delivered to persons aged >1 year in a total population of ca.900,000 in two rounds between June and August 2022, with prospective documentation of the identities of all subjects who received the vaccine. We undertook prospective, systematic surveillance for diarrhea in the two facilities constituting the major sources of care for the target population and enrolled patients with acute watery diarrhea who were aged ≥1 year on the first day of the vaccination campaign, who had resided in the study area from the campaign initiation and who presented for care between August 21, 2022, and August 20, 2023. Fecal culture test-positive cholera cases, up to four fecal cholera culture-negative controls, matched to each case by age and date of presentation, and health facility, were sought for each cholera-positive case. The vaccination status of all enrolled patients was ascertained from
documented sources in a manner blinded to their culture results. Conditional logistic regression models were used to estimate the odds ratio for the association between vaccination and cholera, and vaccine effectiveness (VE) of a two-dose regimen, the primary analysis, was calculated as [(1-odds ratio) ×100].

Findings

226 cases and 552 matched controls were included in this analysis. The VE of two doses of Euvichol-Plus vaccine against cholera was 66% (99.5% CI: 30 to 83) for all recipients. No protection (12%; 95% CI: -95 to 60) was observed for children aged <5 years at presentation, whereas protection was 79% (95% CI: 60 to 89) for who presented at ages ≥5 years. VE against cholera with moderate to severe dehydration was 69% (95% CI: 44 to 83) overall, but 6% (95% CI: -206 to 71) for children presenting at ages <5 years.

Interpretation

Significant protection of the Euvichol-Plus vaccine was observed against cholera of any severity as well as cholera with moderate to severe dehydration. However, the protection was observed only in older children and adults.

P8 YF17D-vectored COVID-19 vaccine protects from SARS-CoV-2-induced adverse pregnancy outcomes in a hamster model of COVID-19

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The COVID-19 pandemic has profoundly impacted global health, with varying consequences for different demographic groups. While healthy individuals of reproductive age typically experience mild or no symptoms, pregnant women are at a markedly higher risk of severe illness, hospitalization, and need for additional ventilation. Despite this, the effects of SARS-CoV-2 on maternal and neonatal health remain poorly understood. Notably, vaccine hesitancy among pregnant women has been reported to range from 26% to 57%, regardless of the reduction in maternal mortality and morbidity associated with vaccination. We thus aim to explore the potential of vaccination as a prophylactic measure to mitigate the risk of SARS-CoV-2 on poor pregnancy outcomes.

Here we show that infection of pregnant Syrian hamsters with SARS-CoV-2 (B.1.1.7) significantly impacts maternal and perinatal health. Infected pregnant dams showed clear COVID-19-like pathology, yet without evidence of increased viral loads or exacerbated acute respiratory disease as compared to non-pregnant controls. Still, they experienced a transient yet marked drop in weight gain. Infectious virus was detected in the fully formed placentas of animals infected at a late gestational stage, but not in the respective pups. This suggests that a virus-induced cytokine storm and coagulation disorder may contribute to placental insufficiency, rather than vertical (transplacental) transmission of the virus; further confirmed by histopathological analysis of respective tissues at the feto-maternal interface. Importantly, pups born to females infected on day E4.5 (time of implantation) exhibited a markedly higher risk of intrauterine growth restriction (29 pups in the infected group; n=65; 4 pups in the uninfected controls, n=34; OR 6.05 [2.0-17.2], P = 0.0014). Prophylactic vaccination with a YF17D-vectored COVID-19 vaccine significantly improved outcomes in SARS-CoV-2-infected pregnant hamsters. Firstly, vaccination led to faster viral clearance in the upper airways and reduced lung damage in the dams, as measured by a cumulative lung pathology score. Moreover, pups born to infected but vaccinated dams were larger than those born to unvaccinated ones (P = 0.02), indicating maternal immunization's protective effect on fetal growth.

In summary, we established a robust animal model to show to what extent SARS-CoV-2 infection may affect pregnancy outcomes, impacting both early and late embryonic development. As we demonstrate for proof-of-concept, vaccination offers a promising intervention to protect the health of both mothers and their babies, thus mitigating the risk of SARS-CoV-2 in pregnancy.

P9 Improving humoral immunogenicity of adenoviral vector vaccines by capsid display

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Replication incompetent adenoviruses were rapidly deployed during the COVID-19 pandemic after a decade of development as a vaccine platform for emerging pathogens. Adenoviral vectors elicit potent T cell responses to encoded transgenes, but historically have elicited modest antibody responses in comparison to mRNA or Virus-Like Particle (VLP) platforms. In addition to encoding antigenic transgenes, adenoviral vectors can also be modified to display antigens on the virion surface – however, capsid modification sites are poorly characterised for adenoviruses other than human adenovirus 5, which is disadvantageous due to hepatotoxicity and pre-existing anti-vector immunity.

Here, we identify sites in the major capsid protein (hexon) of chimpanzee adenoviruses ChAdOx1 and ChAdOx2 that tolerate insertion of antigenic sequences and show that inserted epitopes are accessible on the virion surface. Using the NANP linear epitope from Plasmodium falciparum, we demonstrate that modified vectors displaying this epitope elicit up to 65-fold greater total IgG responses to the NANP repeats than a vector encoding the full-length protein without impeding immunogenicity of an additional antigenic transgene. Furthermore, insertion of the DogTag peptide allowed coupling of native antigens via protein superglue technology: decoration of the adenoviral capsid with the SARS-CoV-2 Receptor Binding Domain (RBD) led to >10-fold total IgG binding to the SARS-CoV-2 RBD and up to 17-fold greater neutralisation relative to a viral vector expressing the full-length spike. RBD decorated vectors retained infectivity and still elicited equivalent T cell responses to an encoded transgene as the wild-type viral vector. Capsid decoration also enabled partial escape from anti-vector immunity in an in vitro neutralisation assay.

Overall, characterisation of these sites adds additional functionality to the chimpanzee adenoviral vector platform, enabling potent humoral responses to displayed antigens while retaining strong T cell responses to the encoded transgene. Capsid display is therefore an attractive strategy to enhance immunogenicity of adenoviral vectors, and represents a promising approach in the development of next-generation adenoviral vaccines against challenging pathogens.

P10 Dose-ranging study of a self-amplifying RNA and LNP-carrier vaccine in mice and pigs

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The pandemic of SARS-CoV2 led to the first-time authorization of messenger ribonucleic acid (mRNA) based vaccines that employ synthetic mRNA molecules. The mRNA platform carries several advantages over other vaccination strategies, including its flexibility by sequence engineering. Although the approved mRNA vaccines have proven their prophylactic efficacy, a regular booster vaccination is required due to modest longevity of neutralizing antibodies and T cell responses (1). Additionally, these vaccines have shown to elicit various side effects ranging from local reactogenicity to rare but serious disease (2). This has revealed a need for the development of vaccine platforms that not only provide the flexibility of mRNA technology, but are also able to balance vaccine immunogenicity and reactogenicity to provide a broad and enduring protection.

The self-amplifying RNA (saRNA) platform encodes an alpha-viral derived replicase complex and allows the incorporation of multiple antigens by insertion of multiple sub-genomic promoters. Upon cytoplasmic delivery, this replicase amplifies the original RNA-strand and generates multiple copies of sub-genomic RNA. This mechanism leads to a higher and more persistent antigen load inside the host cell at a lower vaccine dosage. This guarantees a better antigen expression timeframe and threshold required for the induction of a potent adaptive immune response. Altogether, these features provide the possibility to use lower dosages and/or less frequent administrations, which in turn provides an advantage in its production cost and risk for side effects.

In the work demonstrated here, we investigated how different doses of our proprietary in-house developed saRNA constructs affect the innate, humoral and cellular immune response in outbred mice and pigs. In mice, three different doses (0.5, 2 and 5 µg) of saRNA and conventional mRNA vaccines were compared in a prime-boost setup. Here, we observed a dose-dependent serum cytokine response for both vaccine setups. Similar observations were made for the humoral response, as quantified by serum antibody titers and antigen specific memory B cells. In contrast, T cells responses were generally maintained well for saRNA vaccinated mice, even at the lowest dose, especially for CD4 T cells. In pigs, we evaluated four different saRNA vaccine doses (1, 3, 10, and 30 µg) using a similar prime-boost regimen. For all doses, no distinct serum cytokine responses or increases in systemic temperature were detected post-vaccination. Additionally, there was little effect of the dosage on the elicited neutralizing antibody titer after boost. Even more, using ELISpot, pigs vaccinated with the lowest dose (1 µg) yielded the highest number of IFNγ producing cells within the PBMC population.

Altogether, these proof-of-concept data in mice and pigs confirm that our novel saRNA-based vaccines maintain their immunological potency at lower doses and even provide potential for further dose reduction. By continuing to optimize our saRNA vaccine platform, we aim to develop a new generation of vaccines able to balance immunogenicity and reactogenicity and as such helping us to be prepared for emerging pathogen outbreaks and potential future pandemics.

P11 Safety of the candidate rabies vaccine ChAdOx2 RabG in adult and pediatric populations from a rabies endemic region: A Phase Ib/II age de-escalation, dose escalation, open-label head-to-head, partially randomized clinical trial

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INTRODUCTION

In Africa, dog-mediated rabies causes an estimated 21,476 human deaths annually disproportionately in marginalized populations. This represents 36.4% of all deaths due to rabies globally and this could be underestimation. Of these deaths 40% occur among children under 15years. While rabies is 100% fatal once clinical symptoms appear, it is preventable by both pre- and post-exposure prophylaxis vaccines. The costs for both are too high, which coupled with the need for multiple visits means pre-exposure prophylaxis (PrEP) is too expensive for large-scale vaccination campaigns that have been used to combat other diseases like measles. Post-exposure prophylaxis (PEP) carries significant out of pocket expenses for many people, leading to it being unaffordable or causing financial stress. The PEP cost is estimated to be 5.8% of the average African's gross national income (GNP) or 51 days of wages, which most cannot afford. This prevents the full potential of rabies vaccines from being realized. It is therefore essential to explore vaccines that can have lower costs and require single dose immunization for mass vaccination in marginalized communities, not only in Africa but all LMICs. ChAdOx2 RabG has the potential to lower costs and make mass vaccination campaigns realistic. Chimpanzee adenovirus vaccines vectors have been administered to billions of people and show a good tolerability and safety profile. ChAdOx2 viral vectored vaccines have shown to be both safe and immunogenic in previous clinical trials against rabies (RAB001) and other diseases (HAV001). Single-dose immunisation with the ChAdOx2 RabG vaccine has been shown to elicit high levels of neutralising antibody in animal models and clinical trials.

METHODS

We conducted a study aiming to generate data on a safety, tolerability and immunogenicity of the candidate rabies vaccine ChAdOx2 RabG following vaccination in adult and pediatric populations from a rabies endemic region. This was an age de-escalation, dose-escalation, open label, head-to-head partially randomized trial with an inactivated rabies vaccine comparator. We enrolled Healthy adults (18-45 years) and young children (2-6 years) residing in Bagamoyo, Tanzania. Safety data was collected throughout the study period for both clinical and laboratory adverse events (AEs). Solicited adverse events (AEs) was collected for 7 days after vaccination and unsolicited AEs collected through day 28 post vaccination. Samples for safety and immunological laboratory assessments were collected at different time points.

RESULTS

Safety and tolerability data of participants including solicited adverse events and unsolicited adverse events as well as safety laboratory results throughout the study period will be presented.

CONCLUSION

There were no safety concerns during the trial, and ChAdOx2 RabG was found to be well tolerated by both adults and younger children in Tanzania. The study is currently in the follow-up period, with data on immunogenicity being generated.

P12 Single dose new generation heartwater vaccine for smallholder farmers

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Previously, a heartwater pLamp multi epitope DNA (ME-DNA) vaccine showed protective efficiency when administered three times at three-week intervals via the intradermal route (ID) route using the gene gun and the intramuscular (IM) route. However, gene gun immunisation is not practical for the smallholder farmers. Nanoparticles as delivery system for the DNA vaccine could offer a suitable alternative since the formulation can be given as a single dose via IM or subcutaneous (SC) route. In this study, ME-DNA was adsorbed onto Poly Lactic-co-Glycolic Acid (PLGA) biodegradable nanoparticles. In vitro release profile of ME-DNA vaccine from nanoparticles administered as one single vaccine was done. After 24h, a burst release of ME-DNA was detected in the supernatant, followed by an increased release at days 7-14. A subsequent low release of the remaining ME-DNA by 21-42 days was evident. Furthermore, cellular uptake of nanoparticles was studied where a plasmid DNA containing gene for green fluorescent protein (GFP) was adsorbed into polymers. This was used to transfect sheep peripheral blood mononuclear cells (PBMC). The transfected PBMC were analysed by ZOE™ Fluorescent Cell Imager at different time points. The gene expression could be detected within 24 hrs suggesting that the plasmid was taken up by the cells. Immune responses induced in vitro by the nanoparticle DNA vaccine were then evaluated using transcriptome sequencing. Heartwater immune sheep PBMC were stimulated with either the nanoparticles alone or with the DNAnano at different time points. Transcription of the plasmid was detected in all the DNAnano samples except at 0h and in none of the nano only samples, confirming that the CD4 and CD8 epitopes are transcribed in sheep cells. We are currently investigating the innate and adaptive immune responses induced by the vaccine in sheep and the efficacy compared to that evoked by a naked vaccine.

P13 Nanoparticle mapping and sorting to assess quality and bioactivity of particulate vaccines and viruses

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When evaluating vaccine efficacy against infectious diseases, biological samples from animal models and patients are used to measure virus levels, antibody and cytokine production, and induction of cellular immunity. On the other hand, these samples also contain extracellular particles with bioactive molecules such as nucleic acids, lipid and proteins. Especially, during influenza virus infection, host cell-derived vesicles and neutrophil extracellular traps as well as viral particles are released into the extracellular space and are involved in pathogenesis. Therefore, quantification of these extracellular particles may offer a new indicator for assessing pathogenesis and vaccine efficacy in infectious diseases. Despite this potential, an efficient method for quantifying extracellular particles at the single-particle level remains lacking. In addition, some vaccines and adjuvants, such as mRNA vaccines, also exist in particulate form. Thus, single-particle analysis holds promise for evaluating not only extracellular particles but also the vaccine formulation itself.
In this study, we attempted to quantify extracellular particles and vaccine formulations using a high-resolution flow cytometer. Our unique staining method, targeting all elements of the particles, combined with machine learning, allowed to characterize viral particles and host-derived extracellular particles in bronchoalveolar lavage fluid from influenza virus-infected mice. Furthermore, the isolation of these particles through flow cytometric sorting revealed the differing virulence of each viral particle. Finally, we applied this technology to assess mRNA vaccine formulation and identified their heterogeneity. Based on these results, this technology is expected to be a robust method for evaluating vaccine efficacy and checking the quality of nanoparticle vaccines and adjuvants.

P14 Analysis of Neutralizing Antibody Dynamics According to COVID-19 Vaccination Status: A Comparative Study of vaccine strain and circulating variant

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As the COVID-19 virus continues to produce variants, improved vaccines are being developed to enhance immunity. This study aims to understand the formation of neutralizing antibodies (nAbs) against variant viruses based on vaccination status and infection history and to track changes in nAb titers over time.
We conducted a longitudinal study involving 230 individuals, collecting serum samples in August and December 2022 to observe the changes in nAb titers over a four-month interval. Participants were categorized based on their vaccination status and infection history. nAb titers against the Wuhan strain and the Omicron subvariant XBB.1.9.1 were quantified. In April 2023, an additional cohort of 54 individuals who received the bivalent vaccine was analyzed for cross-neutralization against both the vaccine strains and the latest circulating strain, EG.5.1.
Over the four-month interval, nAb titers against the Wuhan strain and XBB.1.9.1 increased 2.5-fold and 2.1-fold, respectively. Peak nAb levels were observed one month post-vaccination or infection, followed by a gradual decline, though titers remained detectable at low levels. Booster vaccination elicited the highest nAb titers for both strains. Regarding infection history, in the uninfected and primary infection cohorts, the bivalent booster significantly elevated nAb titers compared to unvaccinated individuals. In contrast, in the reinfection group, titers increased for the Wuhan strain but showed no significant change for XBB.1.9.1. Age-stratified analysis revealed that elderly individuals initially exhibited higher nAb titers against the Wuhan strain compared to children and adolescents; however, this difference was not sustained by December 2022. No significant age-related differences in nAb titers were observed for XBB.1.9.1 at either time point. Cross-neutralization analyses indicated that bivalent vaccine recipients exhibited reduced nAb titers against circulating strains compared to the vaccine strains.
The nAb titers for COVID-19 are more influenced by vaccination and infection history than by age. Booster vaccination enhance nAb titers against circulating strains compared to unvaccinated individuals. These results advocate for targeted booster vaccination programs, particularly for high-risk populations, to ensure ongoing protection against SARS-CoV-2 variants. Continuous surveillance and rapid adaptation of vaccine formulations are crucial to managing the pandemic and preventing future outbreaks.

P15 Exploring regional disparities in measles vaccination coverage and influencing factors: an ecological study in Japan, FY 2022

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Background: The decline in measles vaccination coverage is a global concern. The World Health Organization reported a sustained decline in the coverage of the first dose of the measles vaccine, falling to 81% in 2021, which is the lowest level since 2008. In Japan, the coverage of the first dose of the measles vaccine, which had exceeded the target of 95.0% since fiscal year (FY) 2010, fell to 93.5% in FY 2021. In FY 2022, the coverage improved to 95.4%, but varied by municipality. Regional disparities in vaccination coverage contribute to health inequalities by affecting the morbidity, severity, and mortality rates of vaccine-preventable diseases. However, few studies have focused on regional disparities in measles vaccination coverage. This study aimed to clarify the regional disparities in measles vaccination coverage by municipality in Japan and identify the influencing factors.
Methods: In this ecological study, measles vaccination coverage in FY 2022, population density, the area deprivation index (ADI) (an indicator of socioeconomic status), the proportion of foreign nationals, single-father households, single-mother households, and mothers aged ≥30 years, and the number of medical facilities, pediatricians, and non-pediatric medical doctors in 1,698 municipalities were extracted from Japanese government statistics. Negative binomial regression was performed with the number of children vaccinated against measles as the dependent variable, the number of children eligible for measles vaccination as the offset term, and other factors as independent variables.
Results: The mean measles vaccination coverage by municipality was 91.2% (range: 0-100%, 50th percentile: 94.2%), and vaccination coverage was less than 95.0% in 54.3% of municipalities. Vaccination coverage was significantly positively associated with population density (incidence rate ratio [IRR]: 1.004, 95% confidence interval [CI]: 1.001-1.006) and the proportion of foreign nationals (IRR: 1.002, 95% CI: 1.000-1.005). Vaccination coverage was significantly negatively associated with the proportion of single-father households (IRR: 0.976, 95% CI: 0.954-0.999), mothers aged ≥30 years (IRR:0.999, 95%CI: 0.998-0.999), and the ADI (IRR: 0.970, 95% CI: 0.960-0.980).
Conclusion: This study demonstrated regional disparities in measles vaccination coverage in Japan. Single-father households, age of mothers, and socioeconomic status may be key factors when municipalities consider strategies to improve vaccination coverage.

P16 Peripheral co-delivery of plasmid-encoded mucosal chemokine CCL27 enhances mucosal immunity and supports protection from heterologous SARS-CoV-2 and H5N1 influenza challenges in vivo

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Abstract
Mucosal surfaces are the primary entry sites for numerous pathogens. While peripheral vaccination can support robust antigen-specific cellular and humoral immunity, it requires active infection to pull antigen-specific memory cells to the mucosa and relies on passive transudation of antibodies for protection at mucosal surfaces. We reported that co-delivery of the mucosal homing chemokine CCL27 (CTACK) with a DNA plasmid encoding parental SARS-CoV-2 spike (pS) generates antigen-specific IgA in the lung, antigen-specific CD8+ T cells at mucosal surfaces and was 100% protective in a heterologous Delta VOC challenge model. This is the first report of a parentally delivered original SARS-CoV-2 spike antigen engendering complete heterologous protection. Here, we extend this work and demonstrate that co-delivery of plasmid-encoded CTACK (+pCTACK) with pS supports protection from heterologous challenges with SARS-CoV-Omicron variants. pCTACK co-delivery significantly lowered viral loads when mice were challenged with SARS-CoV-2 Omicron variants (BA.2 and XBB.1). Generating robust mucosal immunity with vaccination will be particularly important in the context of rapidly emerging respiratory viruses. We developed seasonal H1N1 influenza, and highly pathogenic avian influenza (HPAIs) H5N1 hemagglutinin (HA) DNA antigens. When delivered alone, these immunogens induced robust peripheral humoral and cellular responses in mice. However, co-delivery with pCTACK increased HA-specific antibodies in bronchoalveolar lavage, increased antigen-specific CD8+T cells in the lung mucosa, and enhanced survival following heterologous lethal intranasal H5N1 influenza challenge and homologous H1N1 challenge. These data have broad implications for the generation of mucosal immunity with parenteral vaccination, important implications for the development of medical countermeasures targeting emerging H5N1 influenza viruses, and demonstrate the feasibility of using mucosal adjuvants to augment parenteral vaccine-induced immunity at mucosal surfaces supporting improved outcomes following respiratory virus infection

P17 Targeted delivery of immunotherapeutics to the lower regions of the lung: using one-component Ionizable Amphiphilic Janus Dendrimers to deliver TGFÎ² mRNA to the lung parenchyma.

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Current strategies for delivery of immunotherapeutics to the lung are primarily targeted to the upper portions of the airways, an effective method for the treatment of large airway diseases such as asthma. However, targeted delivery of therapeutics to the lower regions of the lung is necessary for treatment of parenchymal lung injury and disease. Specific delivery of immunotherapeutics to the respiratory epithelium is challenging, which currently limits clinical usage. The current study focused on the development of an immunotherapeutic delivery system for lower lung. We utilized one-component Ionizable Amphiphilic Janus Dendrimers (IAJDs) as a vehicle to deliver mRNA immunotherapies. For this study, we focused the delivery of an anti-inflammatory cytokine mRNA, transforming growth factor-beta (TGF-β), to produce transient protein expression in the lower regions of the lung. TGF-β is of particular interest as it plays a major role in liming injury related immune responses. Various doses of TGF-β mRNA, formulated with IAJD, were administrated to mice via retro-orbital injections. Mice were euthanized 24 hours post-injections, and lung, liver, spleen, and kidney tissues were collected for further analysis. The collected tissues were stained with hematoxylin and eosin and evaluated for histopathological alterations. Lung tissue was also immunohistochemically stained for TGF-β or IgG control to confirm TGF-β protein expression. We demonstrated that delivering 10 µg/mouse of mRNA TGF-β showed diffuse TGF-β protein expression within the lung parenchyma. Additionally, we observed no toxicity in the liver, spleen, or kidney, with some non-significant increases in fibrin deposition in the lung at a high dose of 30 µg/mouse. Following toxicity testing and characterization, intratracheal (i.t.) bleomycin exposure was used as a model of acute lung injury to test TGF-β mRNA-IAJD efficacy. TGF-β mRNA-IAJD (10 µg/mouse) was delivered to i.t bleomycin (3U/kg) or vehicle (PBS) exposed mice and bronchoalveolar lavage fluid (BAL) and cells, CD45+ lung digest cells, and lung tissue were collected 3 days post exposure/treatment. TGF-β mRNA was found to reduce bleomycin-induced changes in pulmonary cell phenotype 3 days post exposure when compared to PBS controls. Additionally, treatment with TGF-β mRNA mitigated bleomycin-induced increases in pro-inflammatory cytokines including IL-6 and CXCL-10. This study highlights IAJD's potential for precise, effective delivery of TGF-β mRNA to the lung parenchyma. This delivery system offers a promising approach for the targeting of immunotherapeutics to the lower regions of the lung, a strategy necessary to fill the current clinical gap in the treatment of parenchymal lung injury and disease.

P18 A built-in flagellin adjuvanted ferritin nanocage mucosal vaccine platform induces high-quality protective immune responses against respiratory infections

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Protein nanocages have emerged as promising carriers in biomedicine, with ferritin nanocages gaining particular attention as a vaccine platform in both preclinical and clinical studies. Our research aims to develop a ferritin-based nanocage vaccine platform that incorporates protein adjuvants and antigens in a single formulation to combat bacterial and viral infection. Flagellin, an excellent mucosal protein adjuvant, activates TLR5 on the cell surface and the NAIP5/NLRC4 inflammasome in the cytosol. We used pneumococcal surface protein A (PspA) as a model antigen for the construction of built-in flagellin adjuvanted nanocage mucosal vaccine platform. Based on previous findings showing that a mucosal FlaB-tPspA (flagellin fused with truncated PspA antigen of S. pneumoniae; BP) vaccine-induced protective immune response, we developed a ferritin nanocage vaccine displaying both components (Ftn:tPspA:FlaB; FPB NC) using the SpyTag/SpyCatcher strategy for the multivalent presentation of both antigen and adjuvant on a nanocarrier. The ratio of antigen to adjuvant could be easily modulated. FPB NC translocated to draining lymph nodes with higher efficiency than BP. Compared with BP, intranasal immunization with the FPB NC vaccine significantly enhanced mucosal immune responses with more efficient B-cell memory generation and antibody maturation accompanying earlier and more robust germinal center reactions. The FPB NC vaccine induced more balanced (Th1/Th2) immune responses with significantly potentiated IFNγ production by T cells. Mice immunized with the FPB NC vaccine exhibited enhanced protection against lethal infection compared to BP. We extended this platform to develop a mucosal SARS-CoV-2 vaccine, creating a ferritin nanocage displaying both dimerized receptor-binding domain (RBD) and flagellin. This formulation stimulated robust neutralizing antibody generation in the systemic compartment higher than convalescent patients' sera and significantly enhanced mucosal secretory IgA antibody responses

P19 Long term immune responses study of Influenza B derived recombinant trimeric soluble Hemagglutinin (HA) antigen in mice

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Among the four Influenza (Flu) subtypes, type A has been widely studied owing to its large host reservoir range, higher pathogenicity and pandemic potential. Influenza type B virus is lesser explored as it circulated mainly in humans with some recent reports suggesting its prevalence in seals and pigs also. However, recent findings have shown association of high mortality, severe disease conditions and hospitalisations influenced by Influenza B subtype infection. These sets of data surely indicate that Influenza B is no longer a mild version of Flu. For sub-unit vaccines of Influenza, HA (Hemagglutinin) is the most studied antigen as it is most abundant surface antigen giving vast coverage of neutralizing protective response. In this context, we have investigated the immunogenicity potential of a soluble Hemagglutinin (HA) trimeric protein derived from Influenza B/Washington/02/2019 (B/Victoria lineage)-like virus (2021-22 WHO recommended circulating strain) by expression in Expi293F mammalian cell system. We generated the recombinant ectodomain of HA protein (named HA-BWtrimer) in its native like-form by stapling trimerization Foldon domain at C-terminal. This protein was found to be thermostable and capable of forming antiparallel beta sheets with some proportion of alpha-helices. This antigen was assessed for its immunogenic potential in BALB/c mice with two doses (prime-boost) via intramuscular immunization and the immune responses were measured for over a period of up to 12 months. The HA-BWtrimer antigen was able to elicit memory B cell responses uptil 6 months and beyond as measured via in vitro stimulation of immunized mice splenocytes by ELISpot. The measurement of HI and MNT titres of immunized mice sera is ongoing. Nonetheless, this work shows the potential for long-term immunological memory established by a soluble recombinant trimer HA Influenza B specific immunogen, which will further contribute to a better understanding of human Influenza vaccine immunobiology.

P20 Removed

P21 Mosaic sarbecovirus nanoparticles elicit cross-reactive responses in pre-vaccinated animals

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Immunization with mosaic-8b [60-mer nanoparticles presenting 8 SARS-like betacoronavirus (sarbecovirus) receptor-binding domains (RBDs)] elicits more broadly cross-reactive antibodies than homotypic SARS-CoV-2 RBD-only nanoparticles and protects against sarbecoviruses. To investigate original antigenic sin (OAS) effects on mosaic-8b efficacy, we evaluated effects of prior COVID-19 vaccinations in non-human primates and mice on anti-sarbecovirus responses elicited by mosaic-8b, admix-8b (8 homotypics), or homotypic SARS-CoV-2 immunizations, finding greatest cross-reactivity for mosaic-8b. As demonstrated by molecular fate-mapping in which antibodies from specific cohorts of B cells are differentially detected, B cells primed by WA1 spike mRNA-LNP dominated antibody responses after RBD-nanoparticle boosting. While mosaic-8b- and homotypic-nanoparticles boosted cross-reactive antibodies, de novo antibodies were predominantly induced by mosaic-8b, and these were specific for variant RBDs with increased identity to RBDs on mosaic-8b. These results inform OAS mechanisms and support using mosaic-8b to protect COVID-19 vaccinated/infected humans against as-yet-unknown SARS-CoV-2 variants and animal sarbecoviruses with human spillover potential. In addition, we will discuss other mosaic vaccination strategies that have resulted in improved breadth and neutralization potency in both naïve and previously vaccinated animals. These include a mosaic nanoparticle with RBDs that are computationally selected to elicit responses to conserved RBD epitopes, as well as a prolonged release vaccination strategy using atomic layer deposition (ALD) of mosaic-8b. Both strategies show continued promise with the development of mosaic nanoparticles as broadly protective vaccines.

P22 Mapping the serological response to Chikungunya infection and vaccination

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It is estimated that more than 75% of the global population are at risk of infection with Chikungunya virus (CHIKV).Whilst infrequently lethal, a significant proportion of those infected with CHIKV suffer from chronic debilitating polyarthralgia. Despite the economic burden of chronic disease and increasing global prevalence of CHIKV, no vaccine has been licensed for use beyond the USA.
It is well documented that the development of a specific anti-CHIKV serological response is critical in conferring
immunity against future CHIKV disease. Previously, using the cynomolgus macaque model, we have demonstrated that specific convalesce plasma and vaccine immune serum pools confer different levels of protection against subsequent challenge with CHIKV ESCA strain LR2006 – OPY. These differences were associated with quantitative differences measured by binding assays. We are now interested to establish whether these differences in protection are associated with qualitative as well as quantitative differences in the antibody repertoire. Therefore, in this study we aim to determine the epitopes recognised by protective anti-CHIKV responses.
Here, the epitope targets of convalescence plasma and vaccinated serum known to protect in vivo, were compared using microarrays displaying the proteome of an ESCA CHIKV isolate. To characterise the convalescence response in greater detail, two pools of convalescent plasma were examined: (i) the 1st International Standard for anti-CHIKV IgG (1502/19), material derived from an individual who contracted CHIKV in 2016 in Brazil, and (ii) candidate plasma material which was also examined during the establishment study for 1st IS for anti-CHIKV IgG (1504/19), collected from 10 Puerto Ricans contracting CHIKV in 2014. Following this, similar analysis was carried out with pooled serum from clinical trial volunteers receiving either one- or two-doses of a candidate inactivated virus vaccine.
Both convalescent materials contained antibodies which targeted CHIKV structural proteins such as E1 and E2, and non-structural proteins (NSPs) including NSP1. Interestingly, there were overlapping and non-overlapping target epitopes between the two convalescent materials. For the vaccinated serum pools, both vaccinated groups developed antibodies targeting the same epitopes for both structural proteins and NSPs. It was identified that all the examined materials produced an antibody fraction which targeted the same epitopes. To independently validate antigenic regions, the examined materials were incubated with either pseudotyped viruses containing a vesicular stomatitis virus core and expressing CHIKV E1/2 glycoproteins, or synthesised peptides composed of the amino acids anti-CHIKV antibodies targeted.
Finally, since neutralisation assays of anti-CHIKV immunity are insufficiently sensitive to establish quantitative differences in seroreactivity associated with protection in vivo, we investigated whether modifications of these assays would produce a more sensitive assay that will establish a robust correlate of serological mediated protection. Our data shows that all materials successfully neutralised, yet with different potencies. These data indicate antibody response in vaccine serum recapitulates the response of convalescent patients and advances the development of assays that correlate protection in infected and immunised patients against CHIKV disease.

P23 Protein nanoparticle vaccines induce potent neutralizing antibody responses against MERS-CoV

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Middle East respiratory syndrome coronavirus (MERS-CoV) is a zoonotic betacoronavirus that causes severe and often lethal respiratory illness in humans. The MERS-CoV spike (S) protein is the viral fusogen and the target of neutralizing antibodies, and has therefore been the focus of vaccine design efforts. Currently there are no licensed vaccines against MERS-CoV and only a few candidates have advanced to Phase I clinical trials. Here we developed MERS-CoV vaccines utilizing a computationally designed protein nanoparticle platform that has generated safe and immunogenic vaccines against various enveloped viruses, including a licensed vaccine for SARS-CoV-2. Two-component protein nanoparticles displaying MERS-CoV S-derived antigens induced robust neutralizing antibody responses and protected mice against challenge with mouse-adapted MERS-CoV. Electron microscopy polyclonal epitope mapping and serum competition assays revealed the specificities of the dominant antibody responses elicited by immunogens displaying the prefusion-stabilized S-2P trimer, receptor binding domain (RBD), or N-terminal domain (NTD). An RBD nanoparticle vaccine elicited antibodies targeting multiple non-overlapping epitopes in the RBD, whereas anti-NTD antibodies elicited by the S-2P- and NTD-based immunogens converged on a single antigenic site. Our findings demonstrate the potential of two-component nanoparticle vaccine candidates for MERS-CoV and suggest that this platform technology could be broadly applicable to betacoronavirus vaccine development

P24 Leveraging non-spike antigens for broad immune protection against SARS-CoV-2 Variants

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Emergence of SARS-CoV-2 variants and waning of vaccine-induced immunity results in reduced vaccine efficacy and reinfection. Licenced COVID-19 vaccines are directed against the viral spike protein, but the selection of spike as the sole antigen results in limited and narrow responses that are not reflective of T cell responses observed after mild COVID-19. There still exists an unmet need for 'next generation' COVID19 vaccines that induce durable immunity, prevent breakthrough infections and potentially block transmission.
We developed mRNA vaccines that encode the receptor binding domain (RBD) of the spike protein fused to an oligomerisation domain that acts as a self-adjuvant, the nucleocapsid (N) protein, and a truncated version of non-structural protein 3 (tNSP3). Unlike the spike, N and tNSP3 proteins are highly conserved, and present major targets for T cell responses. Importantly, our analysis of SARS-CoV-2 N and tNSP3 specific T cells in COVID19 convalescents showed that N and tNSP3 induced strong and durable CD4+ and C8+ T cell responses. Hence, the inclusion of N and tNSP3 proteins in a multi-valent COVID19 vaccine can increase the breath of T cell and antibody responses, potentially providing enhanced protection against current and emerging variants.
In this study, mice were immunised twice with the mRNA vaccines at three weeks intervals. RBD and N- specific antibody responses were analysed by enzyme-linked immunoassay (ELISA), while the magnitude and polyfunctionality of RBD, N and tNSP3-specific T-cell responses were analysed by IFN-γ enzyme-linked immunosorbent spot (ELISpot) and intracellular cytokine staining (ICS) assays. Results show that the RBD and N vaccines induced strong antibody and T cell responses, while the tNSP3 vaccinated mice had strong T cell responses. Hence, all three vaccines were individually immunogenic. Evaluation of immunogenicity and efficacy of cocktail vaccination is currently underway.

P25 Evaluation of an adjuvanted DNA vaccine for the control of virulent strains of Newcastle disease virus

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Background:
Newcastle disease virus (NDV) is a significant avian pathogen that causes substantial economic losses globally. Vaccination is the most effective way to control Newcastle disease (ND); however, existing commercial vaccines do not protect against many of the concerning, highly virulent strains circulating around the globe. Thus, new vaccines are needed to protect food security worldwide, including in Africa where ND causes significant impacts. This study aims to create a genotype-matched DNA vaccine that is more immunogenic for genotype VII and more stable than live-attenuated vaccines (LAVs). It is hypothesized that a genotype-matched vaccine will be more immunogenic than the currently available genotypes I and II vaccines and will provide better protection against virulent NDV.
Methods:
A DNA vaccine for NDV was developed using the F and HN genes of genotype VII, adjuvanted with interferon lambda (IL-28b). The efficacy of our vaccine was compared to that of the LaSota vaccine (positive control) by vaccinating different groups of chickens and confirming protective antibody titer using the indirect haemagglutination assay (IHA). The NDV strain ON148423 isolated from an outbreak of ND in chickens in Tanzania and identified as velogenic was used for the challenge phase.
Results:
The antibody response elicited by the candidate vaccine and the results of the viral challenge study suggest that it could be a suitable vaccine for combating the disease. Our new vaccine yields the best results, particularly when administered via intramuscular injection. Following the virus challenge, our new vaccine adjuvanted with IL-28b provided 80% protection, compared to the 60% protection provided by LaSota-immunized chickens against genotype VII NDV. These results indicate that our new vaccine is promising.
Conclusions:
NDV is a significant pathogen in the veterinary world and also has the potential to emerge in humans. It is worth noting that before the early 2000s, people believed that CoVs were not significant human pathogens, but only posed a threat to animals. However, we now know that this can change rapidly. Developing vaccines against ND would not only benefit farmers and food security but could also prevent a potential pandemic in humans.

P26 Intention to receive COVID-19 and Influenza vaccines during pregnancy: a prospective cross-sectional study among pregnant women attending antenatal care in Cape Town.

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Background: Vaccination in pregnancy protects the expectant mother, their fetuses, and their infants from infection during the first few months of life. This study aims to assess and identify factors associated with the willingness of pregnant women to receive Influenza and COVID-19 vaccines during pregnancy.
Methods: A multi-methods cross-sectional study was conducted at Mowbray Maternity, New Somerset, and Groote Schuur hospitals in Cape Town among pregnant women attending antenatal clinics. Participants were asked to complete a self-administered questionnaire about their attitudes towards vaccination against Influenza and COVID-19 vaccines in pregnancy. Descriptive statistics and logistic regression were performed to assess factors associated with vaccine acceptance. Seven participants who did not participate in the quantitative component were interviewed.
Results: 500 pregnant women completed the questionnaire of whom 47,6% were vaccinated against COVID-19 before pregnancy. There were 258 (51,6%) participants who reported trusting COVID-19 vaccines, compared to 353 (70,6%) who reported trusting Influenza vaccines ($p<0.001$). Similarly, 245 (49%) of the pregnant women were willing to receive the Influenza vaccine during pregnancy as opposed to 18 (4%) willing to accept the COVID-19 vaccine while pregnant ($p<0.001$). Factors associated with the acceptance of the Influenza vaccine in pregnancy included the belief that the vaccine protects pregnant women against Influenza (OR 2.2 95%CI [1.36-3.57]) and that it is safe to receive the vaccine during pregnancy (OR 7.77 95%CI [4.85-12.69]). Being concerned about getting COVID-19 during pregnancy (OR 4.65, 95%CI [1.16-17.9]) and the belief that the COVID-19 vaccine is safe (OR 8.54 95%CI [3.67-19.96]), and important (OR 10.13 95%CI [2.27- 45.3]) during pregnancy were significantly associated with vaccine acceptance.
Discussion: Acceptance of vaccines against COVID-19 and Influenza was driven by women's belief in their safety and protective effect during pregnancy. Vaccines will only be effective if pregnant women choose to get vaccinated and present their children for vaccination. Therefore, addressing determinants of vaccine acceptance and uptake, such as maternal knowledge, attitudes, and beliefs about recommended vaccines in pregnancy and childhood, should be prioritized.

P27 Efficient HBV immunization using a self-powered microfluidic chip for reconstitution and intradermal delivery of CpG-adjuvanted HBs vaccine

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Population-wide vaccination is essential to fight hepatitis B virus (HBV) infection and liver cancer. Current HBV vaccines consist of recombinant HBs antigen adjuvanted with alum, administered over three doses by intramuscular injection. Novel formulations such as Heplisav-B® using CpG1018 as adjuvant may increase seroconversion rates and anti-HBs antibody responses while reducing the number of doses required for immunization. Here we introduce a novel self-powered ID vaccine applicator and explore intradermal (ID) vaccination to further enhance HBs immunogenicity with dose-sparing potential by fractional dosing. For that purpose we developed a compact and easy-to-use microfluidic device (iSIMPLE vaccine chip) that integrates (i) on-device storage of lyophilized antigen and adjuvant, (ii) controlled vaccine reconstitution and (iii) subsequent ID injection, potentially by self-administration. The iSIMPLE device, made from inexpensive materials like double-sided tape, filter paper and plastic, is easy to fabricate while liquid handling and pressure generation is fully self-powered (Dal Dosso et al. Biomed. Microdevices, 2018).
For proof of concept, Sprague-Dawley rats that had been primed with a fractional (1/50) ID dose of Heplisav-B® were used to mimic baseline HBV immunization as would be conferred by current heptavalent childhood vaccines. These animals were then ID vaccinated using our iSIMPLE microfluidic device whereby HBs and CpG (equivalent to 1/50 dose of Heplisav-B®) had been stored in separated chambers on the device itself, to be reconstituted in dedicated micro-mixing chambers on-chip prior to overpressure creation for ID injection. Animals that got HBsAg premixed with CpG, administered using a syringe and the Mantoux technique, served as controls. Humoral immune responses were measure by ELISA and anti-HBs antibodies levels exceeding 10 mIU/mL considered as seroprotective.
ID immunization by iSIMPLE reached 100% efficacy which is similar, if not superior, to immunization by the Mantoux technique (80% seroprotection) in the same rat model. Moreover, both seroconversion rates as well as antibody levels were significantly and consistently higher compared prime-only baseline controls (10% seroconversion with anti-HBs hardly reaching the seroprotective threshold).
In conclusion, ID vaccination using our integrated iSIMPLE vaccine chip allows for convenient ID immunization against HBV and beyond, using established antigens and adjuvants, yet stored in a compact liquid or lyophilized thermostable form that facilitates logistics and administration for global vaccine access.

P28 Feasibility of Smart LNP Monitoring: Intelligent Screening Technologies for designing ionizable lipid and optimizing LNP

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Since the COVID-19 pandemic, mRNA vaccines have become a new mainstay in the field of vaccinology. To improve the delivery efficiency of mRNA therapeutics, lipid nanoparticles (LNPs) have also gained attention. However, the design of lipid nanoparticles has traditionally been based on human intuition. In this study, we used machine learning (ML) techniques to derive the chemical structure of cationic ionizable lipids and to develop a rational method for designing different LNP compositions to optimize them. We analyzed 213 LNPs to predict their in vivo mRNA expression efficiency using a Random Forest regression model trained with 314 features. The model, which predicted mRNA expression levels after administration to mice via intradermal injection, identified phenols present in the ionizable lipids as the main substructures affecting mRNA encapsulation and expression. The specific phospholipid combinations used as components of the LNPs, as well as the N/P ratio and mass ratio, were found to affect mRNA delivery efficacy. Structural analysis via Cryo-EM also confirmed that the carbon chain length of the ionizable lipids' tail correlates with the multicompartment ratio, which can affect the performance of the LNPs. This integrated approach provides a framework for advanced LNP design, holding promise for the development of more efficient and versatile mRNA therapeutics.

P29 Development Of A Dual Vaccine Against Bovine Coronavirus And Lumpy Skin Disease Virus

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Bovine coronavirus (BCoV) is a pneumo-enteric virus that causes significant respiratory and intestinal infections in cattle and other ruminants. Lumpy skin disease virus (LSDV) is the causative agent of lumpy skin disease (LSD), another important cattle disease, that is endemic in Africa and rapidly advancing to other areas. These viruses have large health and economic consequences for the cattle farming industry and prophylactics which are safe and effective against these pathogens are needed. In this study, a recombinant LSDV expressing nucleocapsid and spike proteins of BCoV was constructed (LSDV-BCoV-K1L). The BCoV spike and nucleocapsid antigens used in the vaccine were based on the consensus sequences of 38 spike and 24 nucleocapsid amino acid sequences that included viruses from multiple genotypes of BCoV. The following modifications were made to the spike protein to improve the stability, localisation and expression: the native leader sequence of the spike protein was replaced with the tissue plasminogen activator leader sequence, the cleavage site was replaced with a flexible linker sequence and two stabilising proline mutations were introduced. Insertion of the foreign gene cassette between LSDV open reading frames 49 and 50 was confirmed by polymerase chain reaction and DNA sequencing. In addition, expression of the BCoV spike and nucleocapsid proteins in cells infected with LSDV-BCoV-K1L was confirmed by Western blot analysis. The immunogenicity of LSDV-BCoV-K1L was compared to the parent virus, nLSDVSODis-UCT, in mice. Mice immunised with LSDV-BCoV-K1L developed high titres of spike specific antibodies and low titres of antibodies to the nucleocapsid. This dual vaccine against lumpy skin disease and BCoV warrants further assessment in cattle.

P30 Cinnamon and Spice as Adjuvants are Nice: Targeting TRP Channels to Boost Mucosal Immunization

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The COVID-19, Ebola, and influenza pandemics over the last two decades have heightened the need for vaccines that are easy to transport, and which can be administrated in a needle-free manner. The oral mucosa is a notable target due to its large surface area and access to the systemic circulation while bypassing the harsh environment of the gastrointestinal tract, however, the immune response generated through the sublingual and buccal mucosa are not as potent as those given by injection. We aim to address this issue through the use of film-based formulations and transient receptor potential channel (TRP) agonists to improve vaccine potency. TRPs are cellular sensors that respond to a wide spectrum of endogenous and exogenous chemical and physical stimuli. TRPs, present on taste buds, sensory ganglion neurons, the epithelial lining of the oronasal cavity, T cells and antigen presenting cells mediate localized, transient proinflammatory response. We found that TRPs can be stimulated by components associated with taste and sensation of food such as capsaicin, vanillin and cinnamaldehyde in an in vitro model of the human oral mucosa as shown by the release of IL-6 (>2000 pg/mL), TNF-α (20-40pg/mL) and GM-CSF (17-28pg/mL) 24 hours after treatment. Use of cinnamaldehyde (74%, $p=0.006$) and bisandrographolide A (76%, $p<0.001$, a component of King of Bitters) significantly improved deposition of a recombinant adenovirus in human buccal explants. Mice immunized by the buccal route with films containing influenza A and cinnamaldehyde had the highest rate of survival post-challenge (67% vs 20% no formulation) and exhibited a significant reduction in viral load compared to unvaccinated mice ($p<0.001$). These studies suggest that TRP channels in the oral mucosa can be targeted with known agonists like capsaicin, cinnamaldehyde, or vanillin to enhance the immune response to vaccines. Much like an adjuvant, these flavoring components can trigger a proinflammatory cytokine response, do not hinder vaccine uptake, and amplify the protective immunity of a vaccine.

P31 The comparison of plant virus nanoparticles in the presentation of a conserved influenza epitope to develop a universal influenza vaccine candidate in Nicotiana benthamiana

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The current global influenza vaccination rate (IVR) varies from >5% to ≤50%, with global IVRs skewing to a lower percentage of the general population. New flu vaccines are made annually which take an average of 5 months to produce, however, these vaccines are ineffective by the next winter season. This is owing to the current vaccine approach which focuses on the virus's surface glycoproteins; the epitopes of which are constantly mutating and reassorting resulting in antigenic drift and shift respectively, thus causing influenza vaccines to often lose compatibility and/or specificity with circulating strains. Yearly vaccines are unpragmatic due to healthcare
infrastructure and economic status in Sub-Saharan Africa, and so, a more relevant influenza vaccine approach is necessary.
To address the need for a more affordable universal influenza vaccine, we made use of two approaches. Namely, the influenza ectodomain matrix protein (M2e), a highly conserved region with the potential of being a universal vaccine candidate, and secondly, the use of a plant expression system to ensure affordable, quick, and safe vaccine production. The M2e antigen is poorly immunogenic therefore the SpyTag/SpyCatcher conjugation system is used to display M2e on the surface of plant virus-like nanoparticles (VNPs).
Five M2e peptide sequences of different origins fused with SpyCatcher (5xM2e-SC) and nanoparticles fused to SpyTag were synthesised and subsequently cloned into different plant expression vectors. Recombinant Agrobacterium harbouring genes were agroinfiltrated into *Nicotiana benthamiana* plants and expression time trials were performed to determine the optimal optical density (OD600) of Agrobacterium for infiltration and optimal protein accumulation days post-infiltration. Western blot analysis showed optimal expression of 5xM2e-SC and nanoparticles at 5 days post-infiltration using an infiltration OD600 of 0.5 and 0.25 respectively. The recombinant plasmids were successfully co-expressed in planta. The SpyTag/SpyCatcher conjugation was successfully confirmed by western blot analysis and transmission electron microscopy. The chimeric particles were successfully purified by use of polyethylene glycol precipitation and density gradient ultracentrifugation.
The expected outcome is an influenza particulate candidate vaccine with the potential to confer broad protection against seasonal and new emerging pre-epidemic viral strains. The use of a plant-based expression system is more affordable than the traditional production system and the approach is fast thus enabling quick response to yearly influenza outbreaks.

P32 High throughput epitope mapping using charge scanning mutagenesis

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Knowledge of neutralizing epitopes is important for developing vaccines and inhibitors against viral pathogens. We describe a rapid and efficient method for epitope mapping, employing barcoded charged scanning mutagenesis libraries displayed on the yeast surface, and screened using flow cytometry coupled to deep sequencing. Charged residues are well tolerated at surface positions, yet such substitutions at epitope residues strongly perturb binding to a cognate partner. We therefore constructed a charged scanning library of the SARS-CoV-2 Receptor Binding Domain at exposed residues, linking every mutation in the library to a defined, unique barcode introduced by PCR for each position. In contrast to deep mutational scans, charged scanning mutagenesis with the introduced barcoding strategy employs libraries with ~30-fold lower diversity, facilitating library construction, screening, and downstream analysis, and also allowing for further multiplexing of samples, thus accelerating interaction site identification, as well as vaccine and inhibitor development. The scanning library and the deep sequencing read analysis approach were first validated by mapping the known RBD interacting residues with the ACE2 receptor. Aspartate mutations had minimal to no effect on protein expression. The ACE2 epitope could be mapped by sorting and sequencing populations with abolished binding with precision and recall values of 93% and 65%, respectively. The approach was further used to map epitopes targeted in polyclonal sera of mice immunized with different SARSCoV-2 immunogens, and in sera of human patients in India, who suffered a breakthrough infection during the period November 2021 - January 2022, after receiving two doses of the ChAdOx1 nCoV- 19 adenoviral vector vaccine. Sera were collected 4-6 weeks post infection. An enrichment of antibodies targeting class-I and recently discovered, rare, cryptic class-V epitopes was detected in the human sera. The class-V epitope is highly conserved across all SARS-CoV-2 variants, including the recent XBB.1.5 variant. Serum neutralization assays against Omicron BA.1, BA.5, and XBB.1.5 variants confirmed the epitope mapping results. The sera analyzed in the present work are from a highly exposed population that lacked access to updated vaccines. These results contrast with those from high-income countries, where many were vaccinated multiple times with updated mRNA vaccines. However, in the absence of XBB exposure or vaccination, the resulting sera poorly neutralized XBB variant viruses.

P33 Broad filovirus protection via NK cell activation and neutrophil phagocytosis in mice induced by a YF17D-vectored Sudan virus vaccine

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Filoviruses, with prototype Ebola virus and related Sudan virus causing fatal systemic multi-organ disease, are a threat to global public health, with recurring outbreaks resulting in large epidemics over the last decennia. While substantial efforts have been undertaken to develop an Ebola virus vaccine, no vaccine nor countermeasure are available for Sudan virus. We developed a recombinant yellow fever 17D-based vaccine candidate expressing Sudan virus-glycoprotein as protective antigen. The vaccine is immunogenic in mice with robust cell-mediated and strong humoral immune responses for both Sudan and yellow fever virus. More specifically, humoral immune responses for SUDV are associated with natural killer cell activation and antibody mediated neutrophil phagocytosis, whereas SUDV specific cellular immunity was identified as CD4+IFNγ and CD4+TNFa secreting T cells. YFV immunity is conferred through CD8+IFNγ T cells and neutralizing antibodies. Lastly, this vaccine candidate also confers broad protection against surrogate filovirus challenge, which makes it an ideal candidate for broad protection across orthologues within the Ebolavirus genus such as Ebola virus and Bundibugyo virus.

P34 mRNA-based personalized cancer vaccines in colorectal cancer in mouse model: Early vaccination as a strategic treatment

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Colorectal cancer (CRC) remains a leading cause of cancer-related deaths worldwide, with increasing incidence rates emphasizing the need for effective treatments. While early-stage CRC can be managed surgically, recurrence and chemotherapeutic resistance remain significant challenges. Personalized cancer vaccines (PCVs) have emerged as a promising immunotherapeutic approach, potentially reducing tumor recurrence through memory T-cell responses targeting patient-specific neoantigens. This study employed a proprietary prediction process to identify MHC class I and II-restricted neoantigens and investigated their immunogenicity and anti-cancer efficacy using an mRNA-based cancer vaccine platform in a mouse CRC model. Of the 20 MHC class I-restricted neoantigen candidates, two demonstrated immunogenicity via IFN-γ ELISpot, while three of the 12 MHC-II candidates were immunogenic. Vaccination with MHC-II-restricted neoantigens exhibited strong anti-cancer efficacy, significantly inducing cell-mediated immune responses. Notably, early-stage vaccination produced a robust anti-cancer effect. The mRNA vaccine prevented CRC recurrence and sustained neoantigen-specific immune responses through memory T cells. Combining the mRNA vaccine with immune checkpoint inhibitors (anti-PD-1 and -Tim-3 antibodies) synergistically inhibited tumor growth. These findings highlight the therapeutic potential of PCVs in CRC treatment and underscore the importance of early vaccination to enhance anti-cancer efficacy.
This study contributes valuable insights into the development of mRNA-based personalized cancer vaccines for CRC, offering a promising strategy to address the challenges of recurrence and treatment resistance in this prevalent cancer type.

P35 A Quadrivalent mRNA Vaccine Against HSV-2 Showed the Enhanced Immunogenicity and Protection Against Primary and Latent Infections.

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Herpes Simplex Virus 2 (HSV-2) remains a significant global health concern, causing severe genital disease and establishing latent infections leading to recurrent outbreaks. Despite extensive research, no approved vaccine for genital herpes exists. This study presents the development and evaluation of a novel quadrivalent HSV-2 mRNA vaccine targeting envelope glycoproteins gB2, gC2, gD2, and gE2. We compared the quadrivalent vaccine to a single-antigen gD2 vaccine for immunogenic efficacy. Additionally, we assessed different lipid nanoparticle (LNP) formulation methods for the multivalent mRNA vaccine and evaluated full-length versus C-terminal truncated forms of the gD2 glycoprotein mRNA. The quadrivalent vaccine demonstrated significantly higher HSV-2 IgG titers (7 days post-immunization [dpi]: $p=0.0005$, 14 dpi: $p=0.0074$) and 50% neutralization titers (7 dpi: $p<0.0001$) compared to the single-antigen gD2 vaccine. LNP formulation methods did not significantly affect IgG or neutralization titers for the quadrivalent vaccine. The full-length gD2 vaccine showed superior neutralization compared to its truncated counterpart (14 dpi: $p<0.0001$). All vaccinated groups achieved 100% survival and effectively prevented dorsal root ganglia (DRG) latency following the HSV-2 challenge. Notably, the quadrivalent vaccine-induced effector memory CD8+ T cells after two vaccinations and the HSV-2 challenge provided enhanced protection of vaginal tissue compared to the gD2 vaccine. These findings suggest that the quadrivalent mRNA vaccine containing gB2, gC2, gD2, and gE2 offers a promising approach for preventing primary and latent HSV-2 infections. This study contributes valuable insights to the development of effective mRNA-based vaccines against HSV-2, potentially addressing a critical gap in genital herpes prevention.

P36 Rational Design And Experimental Validation Of Vaccine Candidates Against Sars-Cov-2 Based On T-Cell Epitopes

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The severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is the cause of coronavirus disease 2019 (COVID-19), which can present from asymptomatic to cause death (Dhama et al., 2020). Currently, there are vaccines against SARSCoV-2 approved for application in humans. All approved vaccines against this coronavirus focus on S protein and antibody immune response, but S protein is the one with the most mutations across the SARS-CoV-2 variants (Kurhade et al., 2023). An alternative broad-spectrum vaccine against variants of this virus are conserved regions throughout SARS-CoV-2 proteome with focus on the induction of T cell immune response. The main objective of this work is to develop new vaccine candidates against SARS-CoV-2 based on T-cell epitopes using in silico, in vitro and in vivo tools.
As a proof of concept, this work focused on developing of vaccines based on T epitopes for the most frequent alleles of human leukocyte antigens (HLA) in Mexico. An updated database of high-resolution HLA allele frequencies for Mexico was generated through Allele Frequency Net Database and bibliographic review. Allele frequencies were validated from random genotyping of individuals with Mexican ancestry. Conserved T epitopes were identified across the SARS-CoV-2 proteome using artificial intelligence tools and these were filtered. Four class I and four class II T epitopes were selected for in silico and in vitro validation. According to predictions, class I and class II epitopes are strong binders for HLA-C*03:04 and HLA-DRB1*04:07, respectively. For in silico validation, molecular dynamics between epitopes and HLAs are being performed. For in vitro validation, the eight epitopes were obtained by chemical synthesis and PBMCs were obtained from donors possessing the HLA-C*03:04 and HLA-DRB1*04:07 alleles. Currently, flow cytometry and ELISpot assays are being performed to evaluate the immune response of epitopes. To increase the immunogenicity of the epitopes, some of these were displayed in tubeshaped pseudoviral particles made from rotavirus VP6 protein through bioconjugation and genetic insertion. After, their induction of immune response will be evaluated by in vitro assays.
Later, the work contemplates the production of multi-epitope constructs using the mRNA vaccine platform and their *in vivo* evaluation in rodent models. During this work, a pipeline has been developed for the design of vaccine candidates based on T epitopes and in vitro and in vivo evaluations will allow the validation of this pipeline.

P37 Integration of TLR7/8 Agonists in Lipid Nanoparticle Delivery Systems Enhanced Modified mRNA Vaccine Efficacy for Cancer Immunotherapy

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Current mRNA cancer vaccines often utilize unmodified mRNA due to induce the innate immune response, such as TLR7/8 signaling, which is crucial for anti-cancer effects. However, N1-methyl-pseudouridine (m1Ψ) modified mRNA, while potentially safer, shows lower induction of innate immune response. This study aims to enhance m1Ψ-modified mRNA expression and improve both innate and adaptive immune responses by incorporating TLR7/8 agonists into lipid nanoparticle (LNP) delivery systems. Various TLR7/8 agonists were tested at different concentrations in LNPs, with mRNA expression efficiency evaluated using firefly luciferase (F/L) antigen. Distribution and expression were assessed via intradermal, intramuscular, and intravenous routes, leading to the selection of LNP formulations containing 0.5% agonist. Subsequent analysis using mRNA encoding HPV16 E7 and HPV18 E6 antigens revealed enhanced HPV-specific CD8+ T-cell and cytokine responses in the 0.5% TLR7/8 agonist group compared to conventional LNP formulations. Future studies will investigate anti-tumor effects in relevant models and assess T-cell responses in hTLR8-transgenic mice to account for potential species-specific differences in TLR8 signaling. This research aims to elucidate the impact of TLR7/8 agonists in LNPs on mRNA expression and immune responses, potentially advancing the development of more effective mRNA-based cancer immunotherapies.

P38 A Two-Component Cocktail of Engineered E Domain III Nanoparticles Elicits Broadly Neutralizing Antibody Responses against Dengue virus in Mic

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Dengue virus (DENV) is a positive-strand RNA virus that is part of the Flaviviridae family transmitted by mosquitoes in tropical countries along the equator, where 42% of the global population reside. There are 4 serotypes of DENV (DENV1-4) that cocirculate in endemic regions and infects up to 400 million people per year. Primary infection by a single serotype causes self-limiting febrile illness, but secondary infection by a heterologous serotype can lead to Severe Dengue, characterized by shock, hemorrhagic disease, and even death. Neutralizing antibodies are key mediators of long-term protection; however cross-reactive, but non-neutralizing antibodies can cause antibody dependent enhancement (ADE) of disease, which is thought to contribute to Severe Dengue. Therefore, eliciting a potent, broadly neutralizing antibody (bNAb) response against all four DENV serotypes is critical for effective vaccine design.

As a vaccine target, we focus on the DENV envelope glycoprotein E, which forms the scaffold for the virus particle and mediates cell attachment and viral entry. The E DIII domain specifically plays a role in host receptor binding and is conserved among all four serotypes. Although E DIII is highly immunogenic and is the target of bnAbs, certain epitopes are not broadly neutralizing and elicitation of Abs against these epitopes is undesirable.

Here, we developed nanoparticle vaccines bearing engineered DIII variants in which epitopes targeted by non-neutralizing antibodies were mutated via structure-guided design and phage display. We then assessed their capacity to elicit neutralizing and protective responses and found that presentation, formulation, and administration of these DIII variants is critical to a potent in vivo response. Finally, we showed a two-component cocktail of these DIII variants elicited a broadly neutralizing DENV1-4 response in mice and passive transfer of sera from animals immunized with a two-component cocktail reduced viral replication in vivo. Taken together, these results suggest immunization with DIII variants offer a more targeted immune response as a subunit vaccine and may also offer lower risk of ADE by immunofocusing the response to critical epitopes that elicit broadly neutralizing antibodies. These findings provide insights into more effective DENV vaccine design that elicits a broadly protective response against all four DENV serotypes.

P39 Novel Tuberculosis (TB) Oral Vaccine Candidate: Enhancing Mucosal Immunity with Recombinant Secretory IgA (SIgA) in Goat Milk

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Introduction:
The global prevalence of Tuberculosis (TB) is a significant health concern, with over 10 million new infections each year. Approximately 5% of these cases progress to active TB, while 95% develop latent TB infection (LTBI), affecting nearly a quarter of the global population with risk of reactivation within 2 to 5 years. Bacille Calmette-Guérin (BCG) vaccine, the only licensed TB vaccine, has variable and limited effectiveness in preventing pulmonary TB, particularly in adults. Recent research into mucosal vaccines for TB presents promising alternatives. Mucosal vaccines can induce robust immune responses directly at the respiratory mucosa and lungs, the primary sites of TB infection. This localized immune activation is more likely to provide effective protection against pulmonary TB compared to the systemic immune response elicited by parenteral BCG vaccination. Advances in this field include recombinant vaccines that enhance specific immunogenicity towards TB antigens through mucosal immunization routes. Our study explores using the mammary gland of non-transgenic goat to produce a novel recombinant vaccine candidate, combining secretory IgA (SIgA) with epitopes from active, latent, and reactivated TB. This approach aims to enhance mucosal immunity and provide comprehensive protection across different stages of TB infection.
Methods:
The vaccine candidate was developed by engineering recombinant epitopes including Antigen 85b (Ag85b) for active TB, alpha-crystallin (Acr) for latent TB, and resuscitation-promoting factor E (RpfE) for reactivated TB, combined with SIgA. We evaluated the immunological response by administering goat milk containing the recombinant protein directly as oral immunization, without any purification process. Additionally, we assessed the immune response to a prime-boost regime using the BCG vaccine. Five groups of Balb/C mice (n=5) were categorized as follows: recombinant milk (RM), normal milk (NM), BCG prime with RM boost (BCG-RM), BCG prime with NM boost (BCG-NM), and BCG alone (BCG). The RM and NM groups received daily oral immunizations with RM or NM for two weeks. The BCG-primed groups received booster doses of RM or NM daily for two weeks, one month after the initial BCG vaccination. Two weeks after the final immunization, the mice were sacrificed, and IgA levels in saliva and lung lavage were measured using enzyme-linked immunosorbent assay (ELISA).
Results:
Mice immunized with recombinant vaccine-containing milk, especially those primed with BCG, showed a significant increase in IgA levels in saliva and lung lavage compared to the normal milk and BCG-only groups. These results indicate that the recombinant vaccine-containing milk can effectively induce a strong mucosal immune response against TB.
Conclusion:
Our study demonstrates that recombinant vaccine-containing milk from the mammary gland of non-transgenic goat enhances mucosal immunity with oral immunization. The significant increase in IgA levels in mice, particularly in BCG-primed groups, highlights the potential of this vaccine as a booster candidate with BCG.

P40 Development of a cross-presentation enhancing flagellin-based adjuvant for cancer vaccines: the Flt3L-FlaB hybrid adjuvant

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Cancer vaccines synergize with other immunotherapeutic modalities such as cell therapies and immune check point inhibitors, and reaching to the mainstream of cancer therapeutics. Cancer vaccines should robustly induce tumor-specific cytotoxic T lymphocyte (CTL) responses. Significant efforts have been directed toward developing effective adjuvants to enhance efficacies of therapeutic cancer vaccines. For this end, adjuvants for cancer vaccines should preferentially activate cross presenting dendritic cells (DCs) to bolster CTL responses. Among the subsets of dendritic cells, type I conventional DCs (cDC1s) have gained attention for their ability to cross-present antigens to CD8+ T cells. Previous research underscores the significance of the Fms-like tyrosine kinase-3 ligand (Flt3l) in the cDC1 development. Administration of Flt3L has been shown to promote the expansion of endogenous CD103+ cDC1 cells within the lymph node and the tumor microenvironment. Our group is working on the engineering of flagellin for therapeutic cancer vaccines. We have shown that a flagellin (Vibrio vulnificus FlaB) enhances therapeutic efficacies of cancer vaccines by activating both cell surface TLR5 and cytosolic NLRC4 pathways in DCs. In this study, we have engineered a fusion protein, Flt3L-FlaB (FB), designed to boost cDC1-mediated antigen cross-presentation and subsequent CTL-mediated tumor suppression. Vaccination with E7 antigen in a mouse TC-1 cervical cancer model using FB adjuvant significantly suppressed tumor growth and enhances survival rates. In the mice vaccinated with E7-FB, marked induction of antigen-specific CTLs and enhanced IFN-γ responses were noted. The augmented CTL response could be attributed to the expansion of DCs. The DC expansion/activation was paralleled with the rise in the number of CD8+ T cells exhibiting stemness (Tscm) and precusor of exhaustion (Tpex) characteristics, which would underlie the significantly enhanced tumor suppression by the combination of anti-PD-1 antibody. The FB adjuvanted cancer vaccine conditioned “cold” tumor microenvironment to be keenly responsive to the immune checkpoint blockade. Overall, the Flt3L-FlaB hybrid adjuvant would serve an efficacious component of therapeutic cancer vaccines, expanding the foothold of vaccines in cancer immunotherapy.

P41 Eliminating the Risk of Antibody-Dependent Enhancement with Multivalent ZIKV DNA Vaccines

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Zika virus (ZIKV) is a significant public health concern due to its association with severe birth defects when infection occurs during pregnancy. There is currently no vaccine available to prevent ZIKV infection. The majority of ZIKV vaccines under development focus on the induction of neutralizing antibodies (NAbs) against the viral envelope (E). However, targeting the E antigen carries a risk of antibody-dependent enhancement (ADE) of infection which can lead to more severe disease outcomes. This risk underscores the need for alternative vaccine strategies that do not rely on E protein-induced NAbs.

Adaptive immune responses, particularly CD8+ T-cell responses, have shown a preferential targeting of highly conserved non-structural (NS) proteins (such as NS1, NS3, and NS4) during natural ZIKV infection. Importantly, NS proteins do not elicit NAbs, thereby mitigating the risk of ADE, making them attractive targets for vaccine development.

In this study, we focused on developing DNA vaccines targeting the NS proteins of ZIKV. We designed DNA vaccines encoding the NS3 and NS4 proteins (pNS3 and pNS4, respectively) and evaluated their immunogenicity in a BALB/c mice model. Using a fluorescent target array and IFN-γ Enzyme-Linked Immunospot (ELISpot) assays, both pNS3 and pNS4 vaccines were demonstrated to be highly immunogenic, eliciting strong antigen-specific T-cell responses. Building on these results, we developed a combined DNA vaccine encoding both NS3 and NS4 (pNS3/4) along with a DNA vaccine encoding the secreted NS1 protein (p-tpaNS1). The p-tpaNS1 vaccine has been extensively validated in our previous studies and is protective and highly immunogenic. BALB/c mice were vaccinated with a cocktail of pNS3/4 and p-tpaNS1, and the protective efficacy of this combination was evaluated using RT-qPCR following ZIKVPRVABC59 challenge.

Our results showed that the cocktail vaccination significantly reduced viral titres 24h after ZIKV challenge. Specifically, multivalent NS vaccination demonstrated superior reduction of ZIKV replication and compared to vaccination with only p-tpaNS1 vaccine. This indicates that the addition of NS3 and NS4 targets in the vaccine formulation enhances p-tpaNS1 protective efficacy.

In conclusion, our study presents a novel multivalent T-cell based vaccine strategy targeting NS proteins of ZIKV. This approach not only demonstrates high immunogenicity and enhanced protective efficacy but completely abrogates the risk of ADE, a significant concern in flavivirus vaccine development. Our findings have important implications for the development of a safe and effective ZIKV vaccine, providing a new direction for preventing the severe clinical outcomes associated with ZIKV infection.

P42 Novel Adenoviral Vaccine Candidate Against A Century-Old Disease: The Ongoing Search For An Efficient Immune-Mediated Control Of Chagas Disease

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Chagas disease is a neglected tropical disease caused by the protozoan parasite *Trypanosoma cruzi* (*T. cruzi*). This potentially life-threatening illness is endemic in 21 Latin American countries. Despite initially being confined to rural areas of these countries, increased population mobility has shifted the problem to urban areas and led to a rise in the number of infected people in developed countries such as United States of America, Canada, Japan, Australia, and most parts of Europe.

There is no vaccine approved for preventing or treating Chagas disease. However, it is not due to lack of interest and involvement of scientific community, which has been studying *T. cruzi* immune-mediated control since 1912, few years later of Carlos Chagas´ first description of the disease. There are many reasons why no vaccine has reached clinical development stage yet, among them: The parasite presents multiple evasion mechanisms such as rapid and stealth invasion avoiding trigger host pattern recognition receptors, complex and relatively slow life cycle with extracellular and intracellular life stages, proliferative and dormant states, antioxidant mechanisms, complement inactivation, unspecific polyclonal B-cell activation, "distracting immunodominance" without full protection and large antigen repertoire encoded by highly polymorphic gene superfamilies that acts as a smoke screen.

Despite these obstacles, the cost-effectiveness of vaccination highlights the need for including either prophylactic or therapeutic vaccines together with improvement in diagnosis, vector control plans and chemotherapy in the overall long-term strategy to tackle Chagas disease.

Our group has developed Traspain (Trasp), a novel chimeric antigen that displays key domains for humoral and cytotoxic anti-parasite protective immunity. Previous results indicate outstanding prophylactic performance when combined with c-di-AMP (CDA) as subunit vaccine strategy. In order to improve antigen-specific T cell response, we designed a replication-incompetent adenoviral vector (Ad48) for Traspain gene delivery (Ad48-*trasp*) as vaccine candidate.

After detecting antigen expression *in-vitro* by indirect immunofluorescence and Western blot, immune response and prophylactic efficacy were analyzed in homologous and heterologous *prime-boost* schemes. Groups of C3H mice were vaccinated twice with: I) 109 PFU of Ad48-*trasp*, II) Trasp-CDA (10 ug - 50 ug), III) Ad48-*trasp* + Trasp-CDA or IV) PBS. For immune response analysis, epitope-specific circulating cytotoxic T lymphocytes (CTLs) and their memory phenotype were evaluated using dextramer staining. Moreover, activation markers (AIM) and cytokine production (ICS) in splenocytes after antigen recall were studied by flow cytometry.

Regarding prophylactic efficacy, vaccinated mice were subsequently challenged with blood trypomastigotes from *T. cruzi* K98 clone. During the acute phase of the infection parasitemia, enzymes in blood as tissue damage indicators and electrocardiograms were evaluated. Once parasites in blood become undetectable, the chronic phase begins. Skeletal and cardiac muscular damage was then analyzed again by measuring enzymes in blood and performing electrocardiograms, and later mice were euthanized to study inflammatory infiltration and fibrosis through histology and to assess tissue parasite burden using qPCR.

Groups I) and III) showed a remarkably strong antigen-specific CTL response (%CD8+ CD44high TEWETGQI+ 13.24%* and 11.48%* respectively) compared to PBS. Phenotypic analysis revealed above 40% of short-lived effector cells among them (CD127low, KLRG1high). A marked increase of IFNγ and TNFα productor cells was observed in TCD8+ subset among groups I and III. This increase was also observed in T CD4+ subset for group III.

Regarding prophylactic efficacy, groups vaccinated with Ad48-trasp showed a significant decrease ($p<0.005$) in parasitemia and tissue damage indicators levels. Cardiac function was conserved in both phases as indicated by the p-wave and cQT interval values. Inflammatory infiltrate as well as fibrosis were reduced when compared with control group and tissue parasitism study showed a great reduction for the group vaccinated with the homologous *prime-boost* scheme.

Considering these results, Ad48-trasp appears as a high potential approach for improving the current strategies of vaccine-mediated control of T. cruzi. Currently, therapeutics schemes are also being assayed. In both cases, our aim is to reach the clinical trial stage to successfully transition from vaccines to vaccination and ultimately put science at the service of society.

P43 Design and In-Silico evaluation of a novel multiepitope-based recombinant DNA Vaccine Candidate against Lassa Hemorrhagic Fever

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Emerging and re-emerging infectious pathogens are major threats to global public health. With the continued rise in the number of annual reported cases in Nigeria, the genomic diversity of the virus, as well as the expanding geography and species distribution of its reservoir hosts, Lassa fever has become a foremost endemic neglected zoonosis in Nigeria, with no available vaccine for its prevention globally. The present study aimed to develop a cross protective, multiepitope-based recombinant DNA Vaccine against Lassa Virus strains circulating in Nigeria. Several Multiple humoral and cell-mediated epitopes were mapped from each consensus sequences of a total of 69 glycoprotein and 67 nucleoprotein sequences of the Lassa virus (LASV) strains across lineage I, II, III and VI circulating in Nigeria and characterized using high-throughput *in silico* bioinformatics tools to construct a putative LASV vaccine candidate, and the constructed candidate was evaluated in silico for its structural and physicochemical properties. A total of 4, 10 and 3 CTL, HTL and linear B-cell non-toxic, non-allergenic and highly antigenic epitopes were mapped and used for the construction of the vaccine candidate. The chimeric LASV vaccine had good expression levels in procaryotic and eucaryotic cells, was thermostable, hydrophobic, non-allergenic, non-toxigenic and highly antigenic. Also, the putative candidate elicited both humoral and cell-mediated immune response, in addition to its induction of interferon gamma after a prime and boost dose-regime. Furthermore, the putative vaccine candidate was able to adapt to the codon usage of *E. coli* and *Cavia porcellus* (Guinea Pig), and successfully cloned in pVAX1 vector. In conclusion, this study was able to design and construct a high quality LASV vaccine candidate from the circulating strains in Nigeria, preparatory to further downstream *in vitro* and *in vivo* validations and Proof of Concept experiments.

P44 Enhanced Sensitivity in Assessing mRNA-LNP Vaccine Reactogenicity Using IL-1ra Knockout Mice

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mRNA-LNP vaccines, a promising tool for immunotherapy, demand meticulous preclinical safety evaluation. This study introduces a novel approach, utilizing IL-1ra knockout mice, a unique model lacking the inhibitory factor against IL-1, exhibiting heightened immune response susceptibility compared to wild-type counterparts. We formulated HPV16/18 E6/E7 mRNA, encoded with n1-methyl pseudouridine, using two LNP types: Moderna's SM-102-based LNP (M-LNP) as a reference and a Developed LNP (D-LNP) as a positive control for toxicity evaluation. The physicochemical properties of the mRNA-LNP formulations were confirmed via dynamic light scattering. Both IL-1ra knockout and wild-type mice received intramuscular injections of the mRNA-LNP vaccine (50 μg/head) twice at a 7-day interval. In wild-type mice, M-LNP and D-LNP weights decreased and recovered at similar rates after vaccination, but in IL-1ra knockout mice, the D-LNP vaccine caused greater weight loss and slower recovery than the M-LNP vaccine. Necropsy was performed two days after the second injection to assess safety profiles. Vaccination groups showed increased spleen and lymph node weights, with IL-1ra knockout mice exhibiting significantly greater spleen weight increases compared to wild-type mice. Blood analysis revealed a statistically significant increase in leukocyte counts in the IL-1ra knockout vaccination group, indicating an enhanced inflammatory response. The immunological analysis demonstrated stronger antigen-specific immune responses in IL-1ra knockout mice compared to wild-type mice. Consistently, inflammatory factor levels in muscle tissues surrounding injection sites were higher in vaccinated IL-1ra knockout mice than in wild-type counterparts. This study showed no difference in the toxicity of the two types of LNPs in wild-type mice, whereas there was a difference in IL-1ra knockout mice, suggesting the need to utilize these KO mice for mRNA-LNP nonclinical toxicity studies.

P45 Exploring COVID-19 vaccine antigen design guidelines to improve the efficiency of broadly neutralizing antibody induction

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The development of SARS-CoV-2 Spike (S) protein with two proline substitutions (S-2P) has contributed not only to structural analysis, but also to vaccine development. However, considering the emerging potential of highly pathogenic variants and next novel coronaviruses, it is important to develop antigens exhibiting better immunogenicity and broadly neutralizing antibody inducibility. In this study, we attempted to improve the S protein and evaluated its protein characteristics, immunogenicity, neutralizing antibody inducibility and cross-reactivity.

Three S-protein antigens were prepared for the SARS-CoV-2 ancestral strain and BA.5, respectively: 1) S-2P, 2) S-6P with six proline substitutions, and 3) S-6PSS with four cysteine substitutions, forming disulfide bonds between the protomers, in the S-6P. First, antigens were evaluated by cryo-electron microscopy (EM) structural analysis, thermal stability assay and S-protein assembly evaluation. Next, these antigens were intramuscularly or intranasally vaccinated in BALB/c mice and collected serum and nasal wash which are used to measure S-specific IgG/IgA against the ancestral strain and BA.5, respectively. Finally, the neutralizing antibody titers were measured using pseudotyped viruses bearing the S proteins of SARS-CoV-2 major variants.

Cryo-EM structural analysis revealed that ancestral S-2P and S-6P exhibit mainly one-RBD-up structures, while others show only all RBD-down structure. Thermal stabilities of S-6P and S-6PSS were higher than that of S-2P, respectively. S-protein assembly state was best for S-6PSS. As the results of immunogenicity testing, intramuscularly vaccinated serum S-specific IgG and neutralizing antibody titers to the same strain as the vaccine antigen were induced to the equivalent levels for all antigens, whereas neutralizing antibody titers to heterologous variants were induced significantly higher for S-6PSS than those for S-2P and S-6P. In contrast, nasal antibody responses did not correlate with any of the factors, therefore other characteristics may be important for intranasal vaccines. These results suggest that antigens exhibiting all RBD-down and proper trimerization may induce more neutralizing antibodies in the less-mutation regions other than the receptor-binding motif, which may be an element towards universal vaccine-antigen design.

P46 High-Capacity Adenoviral Vectors as a Novel Platform for Multi-Pathogen Vaccines

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Neglected tropical diseases and emerging outbreak pathogens frequently co-localize geographically, posing substantial challenges to public health systems. Multi-pathogen vaccines represent a promising strategy to address this convergence by targeting multiple pathogens simultaneously within a single vaccine. This approach has the potential to enhance the efficiency, coverage, and cost-effectiveness of immunization programs. However, existing vaccine platforms struggle with the efficient accommodation of multiple antigens. Adenoviral vectors are a well-established vaccine platform, but their potential is limited by their restricted insert capacity. High-capacity adenoviral vectors, which are devoid of all viral coding sequences, offer a solution to this limitation. With up to 36 kbp of insert capacity, these vectors can facilitate the expression of multiple antigens within a single viral vector vaccine. Furthermore, existing data demonstrate that vaccination with high-capacity adenoviral vectors induces a multispecific T-cell response covering multiple CD8 epitopes, a stronger, longer-lasting humoral response, and reduced anti-vector immunity compared to first-generation adenoviral vectors. This makes high-capacity adenoviral vectors a promising platform for multi-pathogen vaccine development. Here, we detail the development, production, and immunogenicity assessment of high-capacity adenoviral vectors derived from the AdHu5, ChAd68, and ChAdY25 adenoviral serotypes. Our experiments are focused on evaluating antigen expression levels and the immunogenicity of these novel constructs. Long-term animal studies are currently ongoing, aiming to assess both humoral and cellular immune responses following homologous and heterologous prime-boost vaccination regimens. Concurrently, we are conducting experiments aimed at assessing the most feasible methods for scalable manufacturing of said vectors. These parallel efforts are crucial to ensure the feasibility of producing these vectors at the scale necessary for widespread immunization. Together, these endeavours mark a significant step toward the realisation of effective multi-pathogen vaccines, highlighting the potential of high-capacity adenoviral vectors to enhance the versatility and impact of future immunization strategies.

P47 Dose-Dependent Effects of dsRNA Contamination on mRNA Vaccine Expression and Immunogenicity: Implications for Optimization of mRNA Production and Purification

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Double-stranded RNA (dsRNA), a primary contaminant in in vitro transcription (IVT) mRNA production, can compromise the safety and efficacy of mRNA vaccines by inducing unintended immune responses. This study investigates the impact of dsRNA contamination on mRNA expression and immunogenicity to emphasize the importance of dsRNA purification in vaccine development. mRNA was synthesized via IVT using uridine and N1-methyl-pseudouridine nucleosides, followed by cellulose purification to assess residual dsRNA levels. To systematically evaluate the effects of dsRNA contamination, purified mRNA was supplemented with increasing concentrations of dsRNA. In vivo studies in mice revealed that higher dsRNA concentrations correlated with enhanced innate immune responses, characterized by elevated pro-inflammatory cytokine production and decreased mRNA expression, regardless of the nucleoside composition used in IVT mRNA synthesis. Dosing-dependent dsRNA gradients were incorporated into mRNA encoding influenza hemagglutinin (HA) antigen to distinguish between expression-related and specific immune responses. Results showed a decline in antibody titers and T cell-mediated immunity as dsRNA concentrations in HA mRNA increased, further highlighting the detrimental impact of dsRNA contamination on mRNA vaccine efficacy. This study underscores the critical importance of minimizing dsRNA impurities in IVT mRNA to ensure controlled immune responses and develop safer, more effective mRNA treatments. By systematically evaluating the dose-dependent effects of dsRNA contamination on mRNA expression and immune responses, this research provides valuable benchmarks for optimizing mRNA production and purification strategies, potentially advancing the field of mRNA vaccine development.

P48 Modification of PEG-lipids and phospholipids in mRNA-lipid nanoparticle vaccines reduce adverse reactions with sustained efficacy

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mRNA-based vaccines comprise mRNA encoding antigen proteins and lipid nanoparticles (LNPs), which encapsulate the mRNA and prevent its degradation. LNPs function as delivery carriers of antigen-encoding mRNA and are composed of four essential components: ionizable lipids, helper lipids (phospholipids), cholesterol, and polyethylene glycol (PEG) lipids. Among these, ionizable lipids have been studied and screened because they play important roles in mRNA packaging and endosomal escape, as well as in vaccine-related adverse reactions. However, the effect of other LNP lipid components on the mRNA-LNP vaccine response has not been sufficiently clarified. In this study, we evaluated the effects of PEG-lipid density and phospholipid structure on the mRNA/LNP vaccine efficacy and adverse reactions. Clinically approved mRNA-LNP vaccines utilize PEG2000-lipid as a PEG-lipid and distearoylphosphatidylcholine (DSPC) as a phospholipid in their formulation. Using this formulation as a control, the mRNA encoding the spike protein of SARS-CoV-2 was formulated in LNPs with various PEG densities. After vaccination, anti-spike IgG production and spike-specific T-cell activation were altered depending on PEG density. The levels of inflammatory cytokines in the blood, measured as an indicator of adverse reactions, were also altered depending on the PEG-lipid density. These results highlight the importance of setting a well-balanced PEG density that reduces adverse reactions while sustaining vaccine efficacy. Subsequently, mRNA-LNPs substituting DSPC with other phospholipids were prepared to evaluate the effect of phospholipid structures on vaccine responses. All formulations resulted in similar anti-spike IgG production and spike-specific T-cell responses. In contrast, the substitution of DSPC with phospholipids reduced inflammatory cytokine production compared to LNPs with DSPC. These results indicate that by altering phospholipids, the extent of mRNA/LNP vaccine-related adverse reactions can be reduced while maintaining vaccine efficacy. Although PEG-lipid and phospholipids have been underappreciated, our results suggest that by simply optimizing their content and structure, mRNA-LNPs with reduced inflammatory cytokine induction can be successfully constructed while maintaining vaccine efficacy. Thus, these findings support the development of safe mRNA vaccines for overcoming vaccine-related adverse reactions.

P49 Detection of Chimeric Secretory IgA: TB Multi-epitopes Protein in Milk samples and Protein purification in Development of Mucosal Vaccine Against Tuberculosis

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Introduction: Tuberculosis (TB), caused by Mycobacterium tuberculosis (M.tb), remains one of the leading infectious diseases worldwide. The Bacillus Calmette-Guérin (BCG) vaccine, the only currently available TB vaccine, offers limited protection against pulmonary TB in adults. Therefore, there is a critical need to develop new effective vaccines to prevent TB. Considering Mycobacterium tuberculosis (Mtb) primarily infects the lungs, it may be more effective to match the route of infection to the route of vaccination when developing TB vaccines. Mucosal vaccines are a promising strategy for TB prevention, as they can stimulate both systemic and mucosal immunity.
This study explores the development and evaluation of a novel mucosal TB vaccine utilizing TB multi-epitopes. However, the development of mucosal vaccines for TB has been challenging due to the complex nature of the mucosal immune system. Therefore, utilising immunophysiology of secretory IgA (sIgA), the primary specific element of defence at the mucosal level, there is potential to design experimental vaccines with high stability in the mucosal environment. One of the unique features of our approach is that the recombinant chimeric protein production was produced by the mammary gland of goat, resulting in a high reproducibility and fully functional protein. Our approach to in vivo mucosal immunization through intranasal administration is promising, with a particular focus on utilizing the stable properties of chimeric protein for effective nasal delivery of vaccines.

Methods: AAV vector carrying TB multi-epitopes and secretory IgA-J chain were co-transducted into the mammary gland of goat, and the milk was collected daily. The chimeric protein containing TB multi-epitopes antigen and secretory component in milk was detected by Western blot analysis against anti-Histag and anti-Ag85b antibody. The protein was then purified from the milk using a Akta Prime purification system. The fractions were then analyzed by SDS-PAGE and Western blot.

Results: In milk containing chimeric protein, band corresponding to murine secretory component (75 kDa) can be detected against anti-Histag monoclonal antibody analysed by Western blot. Band corresponding to multi-epitopes Antigen Fc-alpha (75 kDa) against anti-Ag85b polyclonal antibody can also be observed. After the chimeric protein was purified using Akta Prime Purification System, a purity of 95% of chimeric protein was obtained and detected by Western blot at 75 kDa.

P50 Enhanced immunogenicity of hetero-bivalent SARS-CoV-2 mRNA vaccine strategy

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A severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative pathogen of the coronavirus disease 2019 (COVID-19) first reported in 2019. A number of variants caused by genetic mutations have appeared even after the SARS-CoV-2 pandemic and the cases of COVID-19 have been steadily reported despite the high vaccination rate worldwide. Spike protein is the major antigen of SARS-CoV-2 vaccines and has a high immune-inducing ability. However, the variations of Spike protein have been continuously accumulated through vaccine immune pressure and evolution. There are many vaccines developed, but it is still necessary to find an advanced vaccine with improved efficacy and broad protective immunity against various SARS-CoV-2 strains. Therefore, we aimed to develop an improved bivalent vaccine candidate with more conserved antigen. The mutations of amino acid sequences of vaccine candidate were introduced to increase structural stability of antigen and the nucleotide sequences were modified to optimize the stability of mRNA and increase the protein expression through in-silico structure modeling based on rosetta energy score. We immunized vaccine candidates into Balb/c mice twice and collected the serum and splenocytes for evaluating humoral and cellular immune responses. As the results, the bivalent vaccine candidate of Spike and more conserved antigen induced highest level of neutralizing antibodies against SARS-CoV-2 variants even though it is half dose of spike antigen compared to a monovalent spike antigen. In particular, it was confirmed that the T-cell immune response such as interferon-gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) was significantly higher in the group immunized with the hetero-bivalent than the other groups through ELISpot and intracellular cytokine staining. In conclusion, the additional conserved antigen plays an important role in enhancing immunogenicity and can be a more efficient option as highly immunogenic vaccine candidate for preparing continuous emergence of SARS-CoV-2 variants.

P51 Systems serology-based comparison of humoral responses induced by liposome or alum adjuvanted SARS-CoV-2 spike protein

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Liposome-based adjuvants have been developed over the past two decades for vaccines against various diseases. Following the approval of liposome-based adjuvants, Matrix-M and lipid nanoparticles (LNP) have recently been developed in multiple SARS-CoV-2 vaccines. Despite these advancements, the precise immunological mechanisms underlying adjuvant activity remain poorly understood. To address this gap, we used systems serology approaches to explore the adjuvanticity of IVI Liposome-based Adjuvant (ILA) in depth and compare it with aluminum hydroxide (Alum). Our study focused on evaluating antigen-specific antibody responses to the SARS-CoV-2 spike (S) protein in mice immunized with ILA versus Alum. We found that ILA-immunized mice exhibited significantly higher levels of antigen-specific IgG2a, IgG2b, and IgG3 antibodies targeting various antigenic domains compared to those immunized with S alone or Alum. While it was challenging to differentiate in immune responses between the adjuvants based on antigen-specific antibodies and neutralizing antibody titers, which are traditional comparison assays, the antibodies of ILA groups demonstrated a high binding ability to FcγR1, FcγR3, and FcγR4 through the systems serology. Beyond antibody profiles, our analysis also identified distinct Fc effector functions between ILA and Alum groups. ILA-adjuvanted group demonstrated increased antibody-mediated monocyte and neutrophil phagocytosis, as well as enhanced complement deposition, suggesting a potentially stronger immune response modulation compared to Alum. These univariate and multivariate comparisons between adjuvants provide a deeper insight into which immune responses can influence the protection of vaccines. These findings underscore the utility of systems serology in unraveling the complexities of adjuvant-induced immunity, highlighting ILA as a promising adjuvant for enhancing vaccine efficacy against SARS-CoV-2 and potentially other pathogens.

P52 Potential of mRNA-Encoded Human Neutralizing Antibody Against SFTSV Gn

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Severe fever with thrombocytopenia syndrome (SFTS), first identified in China in 2009, has emerged as a significant health concern in East Asia, particularly in South Korea, China, and Japan. This tick-borne disease, caused by SFTS virus (SFTSV), induces severe symptoms, including fever, muscle pain, and thrombocytopenia, often resulting in high mortality rates. Despite its severity, no approved vaccines or treatments currently exist. This study explores the therapeutic potential of mRNA-encoded neutralizing antibodies (Ab10) targeting the SFTSV Gn protein, which was previously published. We successfully expressed Ab10 using mRNA technology, confirming its efficacy both in vitro and in vivo. The mRNA-expressed antibodies effectively bind to SFTSV Gn, with dose-dependent expression and neutralizing activity confirmed through in vivo studies and focus reduction neutralization tests (FRNT). mRNA-Ab10, delivered via lipid nanoparticles and administered intravenously to mice, showed sustained antibody expression for over seven days. In a challenge study using IFNAR-/- mice infected with SFTSV, mRNA-Ab10 treatment significantly improved survival rates compared to the control group. Treated mice exhibited initial weight loss followed by recovery, indicating the therapeutic effect of mRNA-Ab10. Furthermore, the treatment showed a protective effect on the spleen, a primary target of SFTSV, and reduced viral titers compared to the control group. The findings suggest that mRNA-Ab10 holds significant potential as an effective treatment for SFTS, offering a novel therapeutic approach for this life-threatening disease.

P53 Comparative Analysis of Expression Dynamics, Immunogenicity, and Safety Profiles for Linear and Circular mRNA Vaccine Platforms

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mRNA vaccines have revolutionized vaccine development, as evidenced during the COVID-19 pandemic, and continue to advance in research and clinical applications. While linear mRNA platforms are well-established, emerging technologies such as circular RNA offer promising alternatives. This study comprehensively compares linear and circular mRNA vaccine platforms, focusing on their expression dynamics, immune responses, and safety profiles through in vitro and in vivo experiments. Key findings demonstrate that circular RNA maintains prolonged-expression compared to linear mRNA. For the next step, immunogenicity was evaluated using influenza HA as a model antigen. Both linear and circular RNA vaccines elicited similar neutralizing antibody titers against the virus. In T-cell responses, linear RNA induced slightly higher cytokine levels compared to circular RNA. Safety evaluations revealed transient adverse effects resolving within 14 days post-vaccination for both platforms. However, high-dose intramuscular administration in mice showed platform-specific differences in potential toxicity. Modified and circular mRNA platforms exhibited increased susceptibility to bone marrow toxicity, while wild-type mRNA elicited stronger lymph node responses. Understanding these platform-specific characteristics is crucial for optimizing mRNA vaccine selection based on specific therapeutic or prophylactic needs. Taken together, these findings provide valuable insights to guide future advancements in mRNA-based immunotherapy, emphasizing the importance of tailored platform selection for diverse applications in vaccine development.

P54 Dose-Dependent Serological Profiling of AdCLD-CoV19-1 Vaccine in Adults

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AdCLD-CoV19-1, a chimeric adenovirus-based SARS-CoV-2 vaccine, has demonstrated robust antibody responses in preclinical models, including mice and non-human primates, following a single dose. In this study, we extended these findings to human subjects through a comprehensive systems serology analysis to evaluate the clinical humoral immune responses elicited by different doses of AdCLD-CoV19-1. Serum samples were collected from participants aged 19 to 64 years who were administered either a low dose (5.0 × 10^10 viral particles) or a high dose (1.0 × 10^11 viral particles) of the vaccine. The antibody responses were assessed against various domains of the SARS-CoV-2 Spike (S) protein, including full-length S, S1, S2, and the receptor binding domain (RBD). Our findings indicate significant improvements in humoral immune responses in both dose groups post-vaccination. Notably, the high-dose group exhibited a more pronounced increase in several antibody features compared to the low-dose group. Specifically, IgG, IgG1, IgG2, and IgM levels were significantly higher in the high-dose group for the full-length S and S2 antigens. Fc receptor profiling further revealed elevated levels of FcγRIIA, FcγRIIB, and FcγRIIIB in the high-dose group, correlating with enhanced antibody-dependent neutrophil phagocytosis (ADNP). Moreover, computational analyses including multivariate approach identified key antibody and Fc receptor features that distinguished the high-dose group from the low-dose group, emphasizing the roles of Fc γ RIIA for the full-length S antigen and IgG for the S2 antigen. These insights highlight the importance of diverse humoral immune responses in evaluating vaccine efficacy. The study suggests that higher doses of adenovirus vector-based SARS-CoV-2 vaccines may offer improved immunogenicity, providing valuable guidance for optimizing vaccine dosing regimens in clinical settings. Future research should focus on longitudinal immune response tracking and the impact of booster vaccinations to further refine vaccine strategies against SARS-CoV-2 and emerging variants. This approach will be crucial for advancing our understanding of vaccine-induced immunity and enhancing global pandemic preparedness.

P55 The research and development of a human cytomegalovirus vaccine

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Human cytomegalovirus (HCMV) is the predominant congenital infection worldwide, leading to severe health complications like microcephaly, sensorineural hearing loss, and cognitive impairment in newborns. Each year, almost one million infants, which accounts for 1 out of every 150 live births, are born with congenital human cytomegalovirus infection. The US National Institute of Medicine has given high priority to the development of a CMV vaccine due to the significant burden of disease caused by congenital CMV (cCMV) infection. However, there is presently no approved vaccine for CMV. Our HCMV vaccine, which uses recombinant protein and a new adjuvant, is projected to fill a gap in the domestic and international HCMV vaccine markets and has significant social and economic value.
Recent research has discovered that PC Pentamer is the primary target of neutralizing antibody responses against HCMV. Vaccines based on Pentamer may induce powerful and extensive neutralizing responses that are 100 to 1,000 times more than gB in infections of epithelial and endothelial cells in various animal models. In this investigation, we created the vaccine by utilizing the recombinant protein PC pentamer and gB, which were designed based on the structural characteristics of the pre-fusion or a nanoparticle conformation, to serve as vaccine antigens. Using the BFA01 adjuvant, our team induces both a high-level persistent antibody response and a Th1 type immune response.
There is a 60% prevalence of HCMV seropositivity in developed countries, while 90% is common in developing countries. Research and development of HCMV vaccines in developed countries in Europe and the United States emphasizes the protection of uninfected people (at least 30-40%), since a significant proportion of people in those areas haven't been infected. HCMV virus is already present in more than 95% of the domestic Chinese population, according to a survey conducted among Chinese people. Therefore, by preventing the reinfection of a new type of HCMV or reactivation of the latent virus, our HCMV vaccine is expected to extend protection to previously infected populations.

P56 Engineering, structure, and immunogenicity of a Crimean–Congo hemorrhagic fever virus pre-fusion heterotrimeric glycoprotein complex

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Crimean–Congo hemorrhagic fever virus (CCHFV) is a widespread tick-borne virus that can cause severe viremia and hemorrhagic fever in humans with case fatality rates (CFR) of up to 40%. The virus is primarily spread by ticks of the Hyalomma genus, which are distributed widely throughout parts of Europe, Africa, and Asia, but CCHFV has a broad host range and can infect a diverse species of wild animals. The viral genome M segment encodes for a glycoprotein precursor complex (GPC), which undergoes proteolytic processing events to generate mature proteins found on the viral envelope. In addition to a highly glycosylated mucin-like domain (MLD) at the N-terminus, the GPC comprises three glycoproteins (GP38, Gn, and Gc) and an incompletely understood accessory protein (NSm). The organization of the CCHFV M segment is more complex than other bunyaviruses, such as hantaviruses, where the M segment encodes for only Gn and Gc. Due to the complex organization of the CCHFV M segment, protein expression and stability have been obstacles to conducting structural studies, protein subunit vaccination studies, and antibody isolation studies.
The glycoproteins are major targets for vaccine and antibody therapeutic development, yet little is known about their structural organization and function in the viral life cycle. Gc mediates membrane fusion and is presumed to form a complex with Gn on the viral surface, whereas GP38, a protein unique to nairoviruses, is thought to be a secreted protein with unknown function. However, GP38 has recently been detected on the viral surface, raising questions about whether it functions with Gn or Gc in the fusion process. To date, structures of Gn, Gc in its pre-fusion conformation, and pre-fusion CCHFV glycoprotein complexes have not been reported, which are vital for understanding the fusion process and the development of effective medical interventions. We designed and characterized a stable GP38-Gn heterodimer, featuring an engineered disulfide bond between GP38 and Gn that increases expression and thermostability. We leveraged this design to obtain a cryo-EM structure of GP38-GnH-DS in complex with Gc. The complex reveals a GP38-Gn-Gc heterotrimer which is fortified by polar contacts between Gn and Gc, GP38 and Gn, and a contact between GP38 and Gc. The structure of GP38-GnH-DS-Gc rationalizes GP38's association with the virion and defines the pre-fusion conformation of the CCHFV Gc fusion loops. We also assess the immunogenicity of GP38-GnH-DS-Gc and its ability to protect mice from a lethal CCHFV-IbAr10200 challenge and find that the heterotrimer elicits neutralizing antibodies, a strong GP38-specific antibody titer, and protects 40% of mice from lethal viral challenge.

P57 Evaluating Stability, Toxicity, and Immunogenicity of Inactivated Rotavirus Vaccine using a Dissolving Microneedle Patch

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Background
Rotavirus (RV) remains a leading cause of severe diarrheal disease in young children, with suboptimal effectiveness of oral RV vaccines in low and middle-income countries. We are developing an inactivated rotavirus vaccine (IRV) formulated into dissolving microneedle patches (dMNPs) as an alternative delivery platform to potentially improve immunogenicity and circumvent challenges with oral vaccines.

Methods
Three separate batches of IRV dMNPs were manufactured targeting 6.5 ± 1.5 µg IRV per patch, determined by a qualified Bradford assay. Accelerated and long-term stability studies were evaluated for IRV dMNPs stored at 5 °C and 25 °C/60% RH over 12 months. Preclinical toxicity and immunogenicity were evaluated in Wistar rats that received 4 intradermal doses (n+1) of at least 7.5 µg IRV dMNP at 2-week intervals. Neutralizing antibody titers in sera were measured by a microneutralization assay. Safety assessments included clinical observations, body weights, temperatures, hematology, clinical chemistry and histopathology in rats.

Results
We manufactured three nonGMP dMNP batches and demonstrated consistent IRV potency of an average 7.2 µg protein per patch (1.4% CV) by Bradford assay. IRV dMNPs maintained stable protein content and potency for at least 12 months under both storage conditions (5°C and 25 °C/60% RH). Following three intradermal administrations in rats, robust virus-neutralizing antibody responses were induced, with mean peak titers of 1,280 representing 64-fold increases over baseline. No adverse clinical signs were observed in rats that received four doses of IRV dMNP. Hematological changes included transient increases in white blood cells, lymphocytes, eosinophils, monocytes and select clinical chemistries. Histological findings were limited to minimal-to-moderate, reversible inflammation and ulceration confined to the application sites.

Conclusion
The IRV dMNP platform demonstrated consistent manufacturing, with low batch variability and maintained antigen stability for at least 12 months at 5°C and 25°C/60% RH. Intradermal administration in rats induced potent functional antibody responses against rotavirus without significant systemic toxicity in a GLP toxicology study. Phase 1 clinical trial of the IRV dMNP is under way to test the safety and immunogenicity in healthy adults. The microneedle patch represents a viable platform to help address the persistent global burden of rotavirus diarrheal disease particularly in resource-limited settings facing challenges with oral vaccines.

P58 Attitudes towards vaccination against COVID-19 during pregnancy and its determinants among people of reproductive age

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Background: Vaccine hesitancy toward COVID-19 vaccination remains a global challenge, while previous studies overlook the attitudes of reproductive-age individuals, which is closely related to vaccine acceptance during pregnancy. In this study, we aimed to explore the attitudes toward COVID-19 vaccines during pregnancy and the determinants among the Chinese reproductive-age population.
Methods: We conducted an anonymous cross-sectional study in China from July 4 to August 11, 2023. Structured questionnaires on vaccine hesitancy during pregnancy, socio-demographic characteristics, behavior characteristics, health-related factors, and mental health status were sent online to reproductive-age individuals (both males and females). Logistic regression models were performed to explore the potential determinants of their attitudes toward the COVID-19 vaccination during pregnancy, presented by crude odds ratios (cORs) and adjusted odds ratios (aORs) with 95% confidence intervals (CIs).
Results: Among 2996 participants of reproductive age, 86.9% exhibited significant hesitancy towards receiving the COVID-19 vaccine during pregnancy. Participants of older age (aOR=1.36, 95% CI: 1.04-1.78), nonsmokers (aOR=1.43, 95% CI: 1.08-1.89), with a longer duration since their last COVID-19 vaccination (≥24 months: aOR=2.38, 95% CI: 1.21-4.70), and exhibiting marked pandemic fatigue (moderate: aOR=2.01, 95% CI: 1.58-2.55; high: aOR=3.51, 95% CI: 2.42-5.07) were prone to refuse COVID-19 vaccines during pregnancy. The presence of generalized anxiety disorder may push the vaccination behavior (aOR=0.74, 95% CI: 0.56-0.97). The factors influencing the attitudes of female participants were similar to the above results but more noteworthy. The top three reasons for hesitation were concerns about the adverse health effects of vaccines on pregnant women (77.72%), fetuses (72.13%), and newborns/infants (58.77%), respectively.
Conclusion: The Chinese reproductive-age population showed a very high level of hesitation to receive the COVID-19 vaccines during pregnancy. Age, smoking habits, time of the most recent vaccination, generalized anxiety disorder, and apparent pandemic fatigue were the potential determinants that affected vaccine hesitancy to varying degrees. Under the context of the existing circumstances and the WHO's encouragement, this study provides data support for possible future policy changes and emphasizes the importance of public health strategies to promote vaccination in this population.

P59 Evaluation of Immunogenicity and Safety of the COVID-19 DNA Vaccine INO-4800 in China

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Background: INO-4800 is a DNA-based vaccine encoding the spike protein of SARS-CoV-2. This phase 2 trial was conducted to evaluate the immunogenicity and safety of INO-4800 as primary series in adults. Methods: We did a randomized, observer-blind, placebo-controlled phase 2 trial of intradermal injection of INO-4800 in healthy adults and elderly aged 18-85 years. Eligible participants from each age group were recruited and randomly assigned in a 3:3:2 ratio to receive two doses of INO-4800 (1.0 mg or 2.0 mg) or placebo followed by electroporationat day 0, and day 28. The primary endpoints for immunogenicity were the geometric mean titres (GMTs) of ELISA spike-binding antibodies and live SARS-CoV-2 neutralizing antibody at day 30 after the second dose. The primary endpoint for safety was the occurrence of adverse events within 30 days after vaccination. Findings: A total of 781 volunteers were recruited and screened for eligibility. Of them, 320 eligible young adult (≥18 to <60 years old) and 320 elderly (≥60 to ≤85 years old) were randomly assigned to receive the low-dose (1.0 mg, n=120) or high-dose (2.0 mg, n=120) INO-4800, or placebo (n=80), respectively. Significant increases of spike-binding antibodies at day 30 after the second dose were noted in both the low-dose and high-dose groups, with GMTs of 1609.3 (95% CI: 1385.5-1869.3) and 3016.7 (95% CI: 2577.4-3530.8), respectively. Additionally, both dose groups induced neutralizing antibodies against live SARS-CoV-2, with GMTs of 4.7 (95% CI: 4.2-5.3) and 6.6 (95% CI: 5.9-7.4) at day 30 after the second dose. The incidence of adverse events within 30 days after vaccination was slightly higher in the high-dose group (115 [47.9%]) than that in the low-dose group (105 [43.8%]) (p=0.0060). All adverse reactions were grade 1 or grade 2, primarily occurring within 14 days after vaccination. No vaccine related serious adverse events were reported. Interpretation: The COVID-19 DNA vaccine INO-4800 at two doses (1.0 mg or 2.0 mg) showed acceptable safety profile, and modest immuogenictiy, with the high-dose silightly more immunogic than the low-dose. Keywords: COVID-19; DNA vaccine; Immunogenicity; Safety; Primary immunization

P60 Immunogenicity and protective efficacy study of pentameric M2e-based subunit immunogen expressed in mammalian cells

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The yearly outbreaks and intermittent pandemics have elevated the management of influenza to a top public health priority. The path toward creating a next generation universal influenza vaccine is both exciting and challenging. The Matrix-2 ectodomain (M2e) glycoprotein is a desirable target for the development of universal influenza vaccine, because of the presence of conserved residues. This study was based on previously produced M2e protein, stapled thrice (M2e-3x) along with tetramerizing domain tGCN4. M2e-5x immunogen was designed by linking conserved matrix ectodomain peptides to the tetramerizing domain and a His6 tag at the C-terminus, and was expressed in Expi293F cells. In the blue native-PAGE M2e-5x proteins showed formation of high molecular mass oligomers at an apparent molecular weight of 650 kDa and the SEM analysis confirmed the well-dispersed spherical particles with size ranging between 300 to 450 nm. Although M2e-5x upon intramuscular administration with AddavaxTM adjuvant induced a strong immunogenicity in one prime and two booster dose regimen, however it failed to protect upon challenge with high lethal doses (10 and 5 MLD50) of Inf/A/PR/8/34 (PR8) and Inf/A/X31 (H3N2) viruses. Although, the vaccinated mice challenged with 5 MLD50 dose, showed a significant reduction in the virus titres and low histopathological damage in the lungs as compared to the mice challenged with higher dose of 10 MLD50. Further studies are ongoing to evaluate the protective efficacy of M2e-5x in combination with subunit trimeric HA soluble immunogen. Nevertheless, our data suggests that the conserved M2e-based immunogens might not be a promising approach for the development of a stand-alone vaccine candidate, but rather could be used in combination for the development of multivalent or cocktail vaccine candidates where it could enhance the virus clearance and is a better supplement to stimulate the T cell immune arm.

P61 High-throughput mutation escape profiling accelerates antibody evaluation and vaccine design

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Predicting viral evolution is crucial for developing effective countermeasures against rapidly mutating viruses. However, comprehensive profiling of viral evolution remains a significant challenge. SARS-CoV-2, which has circulated within the human population for four years since its emergence in late 2019, exemplifies this issue by continuously evolving into new variants. Despite the development of various neutralizing antibodies and vaccines, the pace of drug development lags behind the rate of viral mutation, leading to the emergence of variants that evade these countermeasures. Therefore, there is an urgent need for rational prediction of viral mutation trajectories and timely adjustment of development strategies for neutralizing antibodies and vaccines to prepare for potential large-scale outbreaks of emergent viruses.
In 2020, a virus mutation escape profiling technique based on deep mutation scanning and yeast surface display showed potential in predicting the mutation direction of SARS-CoV-2. However, due to low experimental throughput and high costs, accurately predicting viral mutations on a large scale and within a short timeframe remains challenging.
We have improved this technique, enhancing experimental throughput by two orders of magnitude and establishing a high-throughput viral mutation escape profiling platform. Utilizing this platform, we conducted large-scale mutation escape mapping of antibodies targeting SARS-CoV-2 from diverse immune backgrounds. These antibodies were then subjected to unsupervised clustering based on their corresponding mutation escape profiles, enabling comprehensive exploration of the binding epitopes of various antibody groups. Additionally, we analyzed the differences in humoral immune responses across different immune backgrounds by examining the proportions of various antibody groups present. Our findings indicate that breakthrough infections of Omicron variants primarily recall the immune response stimulated by vaccination with ancestral SARS-CoV-2, with over half of the resulting antibodies demonstrating inferior neutralizing abilities and lacking broad-spectrum protective effects against subsequent Omicron subvariants. However, exposure to Omicron variants twice effectively mitigated this immune imprinting phenomenon, providing significant insights for vaccination strategies.
Furthermore, we established a predictive model for SARS-CoV-2 mutation direction based on extensive data gathered from antibody mutation escape mappings. The feasibility of this model's predictions was preliminarily validated through a retrospective study of ancestral SARS-CoV-2 evolution and successfully predicted the evolutionary trends of Omicron subvariants. Integrating these predicted mutations into future vaccine designs could elicit broad-spectrum immune responses and provide long-term protection.
In summary, we have developed a high-throughput platform for mapping viral mutation escape, demonstrating its substantial potential to expedite the evaluation of antibodies and the design of vaccines within the context of SARS-CoV-2 research. We are confident that our platform will offer significant and valuable guidance for the screening of antibodies and the design of vaccines against future viral threats.

P62 Immune responses and transcription landscape of adults with the third dose of homologous and heterologous booster vaccines of COVID-19

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Background: Heterologous booster vaccines are more effective than homologous booster vaccines in combating the coronavirus disease 2019 (COVID-19) outbreak triggered by SARS-CoV-2 in the context of decaying vaccine protection and the prevalence of emerging associated variants (VOCs) and immune escape. However, our understanding of homologous and heterologous booster vaccines for COVID-19 remains limited.
Methods: We recruited 36 healthy participants from two cohorts who were primed with two-dose inactivated COVID-19 vaccine before, vaccinated with COVID-19 inactivated vaccine and adenovirus-vectored vaccine (intramuscular and aerosol inhalation of Ad5-nCoV) as a third booster dose. We assessed the immune responses of participants before and 14 days after vaccination, including levels of neutralizing antibodies, IgG, and cytokines, and quantified the transcriptional profile of peripheral blood mononuclear cells (PBMCs).
Results: In both cohorts, the Ad5-nCoV group showed a significantly higher neutralizing antibody geometric mean titre (GMT) compared to the ICV group after 14 days of heterologous boosting. The intramuscular Ad5-nCoV group had a GMT of 191.8 (95% CI 129.0, 285.1) compared to 38.1 (95% CI 23.1, 62.8) in the ICV1 group ($p<0.0001$). The aerosolized Ad5-nCoV group had a GMT of 738.4 (95% CI 250.9-2173.0) compared to 244.0 (95% CI 135.0, 441.2) in the ICV2 group ($p=0.0434$). Participants in the aerosolized Ad5-nCoV group had median IFN-γ+ spot counts of 36.5 (IQR 15.3-58.8) per 106 PBMCs, whereas, both intramuscular Ad5-nCoV and CoronaVac immunization as the third dose showed lower responses. This suggests that a third dose of booster Ad5-nCoV vaccine (especially aerosolized inhalation) as a heterologous vaccine booster induces stronger humoral and cellular immune responses, which may be more potent against VOCs than the use of inactivated vaccine homologs. In transcriptomic analyses, both aerosolized inhalation/intramuscular injection of the Ad5-nCoV vaccine and inactivated vaccine induced a large number of differentially expressed genes that were significantly associated with several important innate immune pathways including inflammatory responses, regulation of the defense response, and regulation of cytokine production. In addition, we identified crucial molecular modules of protective immunity that are significantly correlated with vaccine type and neutralising antibodies level.
Conclusion: The aerosolized inhalation/intramuscular injection of the Ad5-nCoV vaccine-mediated stronger humoral and cellular immune responses compared with the inactivated vaccine, and correlated significantly with innate immune function modules, supporting a heterologous booster immunization strategy.

P63 Lyophilized PLGA hollow microcapsules promote broad antibody and T-cell responses by enhancing antigen presentation

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The COVID-19 pandemic has heightened interest in potent and thermostable vaccines. Although lyophilization is a well-established technology for increasing thermostability, conventional aluminum adjuvants will lose effectiveness after lyophilization. Here, we describe a lyophilizable capsule (LyoCap) adjuvant made of pure poly(lactic-co-glycolic) acid, which induces a robust and balanced immune response. With antigen post-encapsulated inside LyoCap, the lyophilized vaccine remains stable for three months at room temperature and elicits fast dendritic cell recruitment and activation, as well as improving antigen cross-presentation and further enhancing the immune response in lymph nodes. Of note, LyoCap keeps a balance between the Th1 and Th2 responses and enhances humoral and cellar immunity simultaneously. This LyoCap-adjuvanted SARS-CoV-2 subunit vaccine successfully induces potent and broad neutralizing antibodies against multiple viral variants and elicits robust cellular responses against conserved peptides. Moreover, with a sequential immunization strategy in nonhuman primates, the LyoCap adjuvanted vaccine enhanced protection against new variants. Finally, the LyoCap adjuvanted influenza subunit vaccine also effectively protects mice against homologous and heterologous viral challenges. Overall, we describe a polymeric lyophilizable micro-capsule adjuvant to induce a robust and balanced immune response to viral antigens, with promising implications for clinical translation.

Key Words: COVID-19; lyophilizable vaccine; cellular immunity; nonhuman primates.

P64 Mycobacterial fusion protein eliciting anti-tumor activity through NK cells activation

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Mycobacterial components have been used as immunoadjuvants. Mycobacterium bovis BCG is a gold standard in the treatment of high-risk, non-muscle-invasive bladder cancer, and its cell wall skeletons have been applied to treat bladder cancer in animal models and several cancers in humans. Therefore, we have investigated whether the mycobacterial fusion proteins had anti-tumoral activity and could be used as a therapeutic tumor vaccine. The fusion protein with anti-tumor activity (MPAT) in vitro/in vivo was identified. MPTA enhanced the expansion of both CD4+ and CD8+ T cells, key components of adaptive immunity, via activation of dendritic cells and macrophages, and also induced activation of NK cells. These activated cells led to Lewis lung cancer cells (LLC) apoptosis in vitro. MPTA/DDA_MPL significantly reduced tumor growth by three times subcutaneous injection with a 10-day interval at 5 or 6 days after LLC injection into mouse skin, compared to the adjuvant control group. MPTA induced significant infiltration of the NK and T cells in both the spleen and tumor microenvironment. Now, we are investigating the detailed underlying mechanism and searching the chemotherapeutic agents or immunostimulants with synergic activity with MPTA. This study highlights the promise of MPTA as a therapeutic tumor vaccine.

P65 Salmonella Typhi Vi-specific serological profiling among children, adolescent, and adults after typhoid vaccination

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Background Typhoid fever is still a major public health concern in low and middle-income countries. Vi polysaccharide vaccines were developed to prevent and control typhoid fever in endemic region but showed poor immunogenicity in children under 2 years. To overcome the limitations and to generate a robust immune response against S. Typhi, typhoid conjugate vaccines (TCVs) have been developed and three TCVs (Typbar TCV®, TYPHBEV®, SKY Typhoid) have been pre-qualified by World Health Organization. Although anti-Vi IgG has been widely used for surrogate marker of protection against typhoid fever and primary endpoint of immunogenicity of TCV for licensure of vaccine, antibody-mediated protective mechanisms are not fully understood.
Methods Previously, in the phase 1 study of Vi-DT conjugate vaccine, a total 144 participants in three different age strata (2-5, 6-17, and 18-45 years) were recruited to assess safety and immunogenicity of Vi-DT TCV (SKY Typhoid). Participants were immunized with Vi-DT TCV twice at one-month interval or Vi polysaccharide vaccine with single injection. In this study, we are analyzing samples to seek distinct immune responses among children, adolescent, and adults after vaccination with Vi-DT TCV or Vi-PS vaccine using systems serology tool, which includes not only Vi-specific IgG but also antibody function including serum bactericidal antibody, antibody-dependent (AD) cell phagocytosis, AD complement deposition, AD NK cell activation, Fc receptor binding, etc.
Results Biophysical profiling of antibodies (isotypes, subclasses, and FcR) were statistically significant increased after Vi-DT vaccination compared to Vi-PS. Interestingly, anti-Vi total IgG was not statistically different between children and adult at one month after Vi-DT TCV vaccination. However, anti-Vi IgG1 and IgG3 were significantly higher in children compared to adults ($P<0.05$). Functional activities (ADCP, ADCD, ADNP) were increased after 2nd dose of TCV, especially in children although comparable anti-Vi IgG were observed post vaccination between first and second dose.
Conclusion Distinct biomarkers between children and adults would be helpful to understand immune responses and antibody-mediated protection against typhoid infection.

P66 Assessing the Efficacy of Modified Nucleoside mRNA Vaccine in Chronic Inflammation

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The advent of mRNA vaccines has been pivotal in mitigating the COVID-19 pandemic. However, several side effects, such as myocarditis and muscle disruption, have been reported post-mRNA vaccination. In the context of chronic inflammatory diseases, pro-inflammatory cytokines like IL-6 are continuously induced, potentially leading to a cytokine storm when combined with the immune responses triggered by mRNA immunization. Additionally, chronic inflammatory diseases can create an immunosuppressive environment by increasing M2 macrophages and regulatory T cells, which might downregulate the immune responses to mRNA vaccines. This study investigates the immune response to mRNA vaccines in the context of chronic inflammation using a lipopolysaccharide (LPS)-induced chronic inflammatory mouse model. To assess immune responses in a chronic inflammatory setting, C57BL/6 mice equipped with osmotic pumps delivering LPS were immunized twice over two weeks with mRNA vaccines. Two days after the final vaccination, hearts, splenocytes, and lymph nodes were analyzed using quantitative PCR (QT-PCR), flow cytometry, and ELISpot assays. Pro-inflammatory cytokines and inflammation were induced in the hearts of the LPS mice model, confirming the establishment of an adequate chronic inflammatory mouse model. Following mRNA vaccine administration to LPS-implanted mice, there was an increase in myocarditis markers such as Myh7, ANP, and pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6. Additionally, the inflammatory area in the hearts of the chronic inflammatory mouse model was amplified. Immune responses to the mRNA vaccine were significantly downregulated in chronic inflammatory mice, as evidenced by the reduced activation of antigen-presenting cells (macrophages, dendritic cells, B cells) and decreased pro-inflammatory cytokine secretion by T cells compared to controls. mRNA immunization in chronic inflammatory environments may result in myocarditis and diminished immune responses compared to normal conditions. During mRNA vaccine manufacturing, uridine triphosphate (UTP) is often replaced with modified UTP to suppress Toll-like receptor 7 (TLR7) activation and enhance expression. However, recent studies suggest that this modification might induce a suppressive immune environment, potentially leading to cancer or other issues, particularly in the context of chronic inflammation where immune responses to modified UTP could be highly detrimental.

P67 Impact of Poly(A) Tail Structures on Expression and Immune Responses in mRNA Vaccine Efficacy

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mRNA vaccine development has prompted extensive research into optimal mRNA sequence and structure design. The typical cap-dependent mRNA sequence consists of cap, 5'UTR, GOI (gene of interest), 3'UTR, and poly(A). This study investigates the impact of various poly(A) sequences on mRNA stability, translation efficiency, and subsequent immune responses. Four poly(A) constructs were examined: A50-Linker-A50-complement linker sequence (A50L50-loop), A50-Linker-A50 (A50L50), A30-linker-A70 (A30L70), and A120. The A50-linker-A50-complement linker sequence, forming a compact structure, was hypothesized to enhance mRNA stability and translation efficiency. In vitro studies using Firefly Luciferase(F/L)-coding mRNA-poly(A) constructs in cell transfections revealed time-dependent luminescence patterns. In vivo experiments in C57/BL mice, utilizing F/L-mRNA or human EPO-mRNA, demonstrated that the A50L50-loop structure sequence consistently exhibited the highest expression, followed by A30L70. To correlate expression levels with immune responses, mRNA-poly(A) constructs coding for HPV E6 and E7 antigens were administered to C57/BL mice. Flow cytometry analysis of splenocytes showed minimal but noticeable differences in T-cell activation and cytokine markers, generally aligning with expression level trends. Changing the antigen to influenza HA and immunizing with mRNA-poly(A) coding for HA in Balb/c mice revealed that A30L70 was predominant, followed by A50L50-loopO, based on T-cell cytokine increase and antibody responses. These findings suggest that expression levels may influence immune responses, albeit to a lesser extent than anticipated. The discrepancy between expression levels and immune response magnitudes implies a potential upper limit to the expression level required for enhanced immune responses. This study highlights the complex relationship between poly(A) tail structures, mRNA expression, and immune responses in mRNA vaccine design. Further investigation is warranted to elucidate the multifaceted role of poly(A) sequences in enhancing immune responses beyond their impact on expression levels, potentially leading to more effective mRNA vaccine formulations.

P68 Immunogenicity of Recombinant Secretory Immunoglobulin A - Antigen 85B Chimeric Protein in Goat's Milk as a Potential Booster Vaccine against Tuberculosis in BCG-Primed Mice

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An improved vaccine against tuberculosis (TB) is urgently needed to enhance the impact of TB immunisation offered by BCG, the only licensed TB vaccine, which is currently unable to substantially reduce the number of TB cases globally. A large majority of new TB vaccine candidates use the parenteral and invasive route of immunisation without showing significant superiority to BCG. Wide-ranging vaccination strategies should be considered to improve the chances of finding an ideal TB vaccine. Here we explore the potential of a non-invasive immunisation route against TB, specifically looking at the oral route of vaccination as a potential strategy to develop a new TB vaccine, which is arguably the most preferred route of vaccination due to the ease of administration at a lower cost compared to injectable vaccines. The downstream hostile gut environment poses a major challenge to oral vaccine development. Several strategies to overcome that challenge have been studied such as using live-attenuated vectors and nanoparticles. Our group is at an early stage of developing an oral TB vaccine candidate based on a chimeric secretory IgA-Ag85B subunit vaccine constructed to withstand the gut environment and reach the mucosal immune cells to initiate immune responses. We are currently evaluating the immunogenicity of the vaccine candidate as a booster to BCG in a mouse model to further assess its potential. BALB/c mice primed with BCG were given the vaccine candidate orally, with subsequent collection of samples from euthanised mice 4 weeks post-booster to determine the T cell responses in the spleen using flow cytometry, and anti-Ag85B IgG levels in serum and anti-Ag85B IgA levels in bronchoalveolar lavage by using ELISA. The findings from this study would offer new knowledge regarding oral immunisation by using recombinant secretory IgA construct that could potentially become a candidate vaccine for future TB vaccine development.

P69 A novel bovine TB vaccine borne unexpectedly out of basic Mycobacterium tuberculosis-complex virulence research

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Mycobacterium tuberculosis (M. tb) uses its type-7 secretion system ESX-1 to export virulence effector proteins that are also highly immunogenic. In this study, we introduced into the genetically tractable, fast-growing and non-pathogenic model mycobacteria, Mycobacterium smegmatis, genes encoding proteins of the multi-component M. tb ESX-1 to see if we can express and reconstitute a fully functional secretion system. Specifically, M. smegmatis was transformed with either only a DNA fragment containing the M. tb esx-1 locus, only a DNA fragment containing the M. tb espACD operon or both fragments. We found that while M. smegmatis with the M. tb esx-1 locus alone can produce a functional ESX-1 system, both the esx-1 locus and espACD operon were needed to produce a strongly expressed, stable and optimally functioning protein secretion system. Although the ESX-1 system is critical for the virulence of M. tb, we found its reconstitution in M. smegmatis did not make it pathogenic. Strikingly, we found M. smegmatis with both the esx-1 locus and espACD operon – which we have named MSX-1 – performed just as well as the live attenuated M. bovis BCG vaccine in protecting mice against the TB bacillus without sensitizing them to purified protein derivative (PPD). Our study confirms the notion that the minimal functioning unit of ESX-1 is encoded by both the esx-1 locus and espACD operon but more notably, our work also offers a novel TB vaccine candidate for use in livestock and wildlife that will not render useless the existing PPD skin test used for bovine TB diagnoses.

P70 Preparation and Immunogenicity Study of Novel Hepatitis B Virus-like Particles

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Background: Traditional S protein-based hepatitis B vaccines have a 5%-10% non-response or low-response rate in certain individuals due to genetic factors. The preS1 and preS2 regions of the hepatitis B virus, containing viral neutralizing epitopes, enhance immune response and can effectively induce protective antibodies in this subset. This study examines a novel hepatitis B virus-like particles (VLPs) vaccine with truncated L protein, M protein, and S protein, showing excellent immunogenicity in animal models.
Objective: To analyze the physicochemical properties of the L protein, construct expression plasmids for truncated L (NL) and M proteins, express NL and M proteins to form S protein VLPs, and evaluate their immunogenicity in vivo, thus laying a foundation for developing a new generation of recombinant hepatitis B vaccines.
Methods: Bioinformatics tools analyzed the physicochemical properties of the L protein. Expression frames and resistance markers of the pCHO1.0 plasmid were modified to create pCHO1.0-1-NL and pCHO1.0new-1-M plasmids. These were co-transfected into CHO-S cells, and stable high-expression cell lines were selected via dual-stage pressure screening with puromycin, MTX, and G418. High-expression culture media were screened, and target protein expression levels were detected by ELISA. Proteins were purified using ion-exchange chromatography, with purity and activity confirmed by SDS-PAGE, Western Blot, and ELISA. VLP formation was observed via transmission electron microscopy. The NLMS vaccine was formulated with an aluminum hydroxide adjuvant and immunized in BALB/c mice, using a commercial recombinant hepatitis B vaccine as a reference. Antibody titers against preS1, preS2, and S were measured, and the half-effective dose (ED50) was calculated. Cytokine levels of IFN-γ, IL-2, and IL-6 produced by mouse spleen cells upon antigen stimulation were quantified by ELISA.
Results: Bioinformatics analysis revealed amino acids 2-19 of the preS1 region are hydrophobic, affecting target protein secretion. Truncated L protein (NL) and M protein VLPs were successfully generated, with transmission electron microscopy confirming 22 nm VLPs. Mice immunized with 0.5 μg/mL NLMS vaccine had antibody titers of 1:4096, compared to 1:1024 for mice immunized with 20 μg/mL commercial vaccine. The ED50 for the NLMS vaccine was 0.078 μg/mL, versus 2.190 μg/mL for the reference vaccine. The NLMS vaccine stimulated over six times the concentration of IFN-γ, IL-2, and IL-6 compared to the PBS control group.
Conclusion: HBV VLPs containing NL, M, and S proteins were successfully constructed and expressed. Animal studies showed the NLMS vaccine has superior immunogenicity compared to the commercial S protein hepatitis B vaccine, providing a basis for the development of a new recombinant hepatitis B vaccine.

P71 Activation of Innate Immunity by Aluminum Adjuvant Enhances 2'3'-cGAMP and Decitabine Delivery for Antitumor Therapy

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Despite the widespread use of aluminum adjuvants in human vaccinations, they are rarely applied in tumor treatment. It has been reported that alum induces cell death followed by the release of host cell double-stranded DNA (dsDNA). Cyclic GMP-AMPP (cGAMP) functions as an endogenous second messenger in metazoans and triggers interferon production in response to cytosolic DNA. cGAMP activates stimulator of interferon genes (STING), which activates a signaling cascade leading to the production of type I interferons and other immune mediators. Building on these findings, we easily prepared a mixed adjuvant of aluminum and cGAMP (AcG) and administered it with an antigen. We found that aluminum adjuvant significantly increased cellular uptake of cGAMP, inducing a robust anti-tumor immune response. It was effective in inducing tumor regression and extending survival in primary mouse models of lymphoma, breast cancer, and melanoma.

Specifically, AcG potentiated the activation of the cGAS-STING pathway, thereby promoting the activation and cross-presentation capabilities of dendritic cells (DCs), which subsequently enhanced the anti-tumor immune response of CD8+ T cells. Furthermore, the aluminum adjuvant component of AcG improved the interaction between DCs and CD4+ T cells, as well as the presentation of MHC-II antigens, thereby augmenting the tumoricidal activity of CD4+ T cells. Utilizing single-cell sequencing technology, we identified that Mono-MEFV within the tumor microenvironment (TME) increased the recruitment of NK cells via the secretion of chemokines, further amplifying the anti-tumor immune response.

Additionally, our data indicated that the combination of aluminum and cGAMP adjuvants enhanced the overall immune landscape within the TME. This included not only increased infiltration of NK cells but also a more favorable ratio of effector to regulatory T cells, which contributed to a sustained anti-tumor response. The dual activation of both innate and adaptive immune pathways by AcG underscores its potential as a versatile adjuvant for cancer immunotherapy. This coordinated activation of the immune system and modulation of the TME by AcG resulted in significant tumor inhibition and reduced postoperative tumor recurrence, supporting its potential application in personalized immunotherapy in conjunction with CAR-T therapy.

Overall, our findings suggest that AcG could serve as a powerful adjuvant in cancer immunotherapy, offering a novel strategy to enhance anti-tumor immunity and improve clinical outcomes.

P72 Plant-Produced Recombinant Influenza A Virus Candidate Vaccine Targeting the Conserved M2e Protein and Hemagglutinin Stalk Region

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Influenza, a highly contagious viral respiratory disease, poses significant global health and economic challenges. Current vaccines, which mainly target the variable hemagglutinin (HA) head, often exhibit reduced effectiveness as viral strains evolve through antigenic drift and shift, necessitating frequent updates. In response, the development of a universal influenza vaccine focusing on conserved regions of the virus, such as the extracellular domain of the matrix 2 protein (M2e) and the HA Stalk region, offers promise for broader and more durable protection.
This study aims to develop a universal influenza vaccine by targeting the conserved M2e protein region and displaying it on the self-assembling influenza A HA stalk, which is also highly conserved, utilizing a plant-based expression system. Expression of the 5xM2e-HAStalk fusion protein in Nicotiana benthamiana plants was validated through western blotting, with self-assembly confirmed via transmission electron microscopy (TEM) and particles of 80-120nm in diameter were observed. Purification of the fusion protein was achieved using iodixanol density gradient ultracentrifugation, and the purity and quantity of the chimeric Influenza virus-like particle were determined by gel densitometry, revealing a yield of approximately 400 mg/kg of fresh weight leaf (FWL).
The chimeric universal influenza vaccine candidate will be utilized for immunization studies in quails, and assessed for cross-reaction against other influenza strains. Following immunization, sera and egg yolk will be collected to assess the vaccine's effectiveness in eliciting both humoral and cellular immune responses. This approach holds promise for advancing our understanding and management of influenza outbreaks.

P73 Rational Vaccine Design to Target Conserved Regions of Rapidly Evolving Pathogens

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Rapidly evolving pathogens like HIV, influenza, and SARS-CoV-2 escape immune responses by accumulating mutations in their surface proteins without losing fitness. This has made the development of broadly protective vaccines against these viruses challenging. Currently, no effective vaccine exists against HIV, while approved vaccines against influenza and SARS-CoV-2 need to be regularly updated and offer variable protection depending on how well their composition matches circulating virus strains. Nevertheless, all these viruses contain highly conserved regions critical for receptor engagement and fusion with target cells. Antibodies against these epitopes have been isolated and typically show broad recognition of diverse virus variants, giving hope that the induction of such antibodies in high titers could eventually lead to the development of an HIV, universal influenza, or pancoronavirus vaccine. Broadly protective antibodies are rarely induced in high titers by natural infections with these pathogens or through vaccination with native viral proteins. Therefore, additional strategies are needed to develop broadly protective vaccines against HIV, influenza, or coronaviruses.

Here we will describe general vaccine design strategies to induce broadly protective antibodies against conserved epitopes on viral proteins by directing humoral responses from variable, immunodominant epitopes to conserved, subdominant regions. Different immunogen design approaches, such as epitope scaffolding to non-viral proteins and epitope masking by glycans or mutagenesis, were applied to elicit antibodies with broad reactivity against HIV, SARS-CoV-2, or influenza. For HIV vaccine design, we developed a new class of non-Env derived immunogens that preferentially engage B cell receptors with long CDR H3 loops. These immunogens robustly activate diverse precursors of the glycan-V3 broadly neutralizing antibody DH270.6 in stringent animal models that can generate DH270.6-like antibodies with diverse CDR H3 loops. A similar immunogen design approach is now being tested to elicit antibodies with long CDR H3 against influenza neuraminidase. For SARS-CoV-2, we recently reported the design of “epitope scaffolds” protein immunogens that elicited broadly cross-reactive antibodies against two highly conserved regions of coronavirus spike proteins which are partially occluded on the prefusion spike, the stem helix and a site adjacent to the fusion peptide. When used as immunogens multimerized on nanoparticles in mice, epitope scaffolds elicited sera responses that cross-reacted with spikes from multiple coronaviruses, including all human betacoronoviruses and animal viruses with pre-pandemic potential, and protected against live virus challenges. Results from ongoing studies describing the ability of epitope scaffolds to protect against coronavirus infection in nonhuman primates will be discussed. Epitope scaffolding, together with glycosylation and surface resurfacing were also used to design immunogens that focused immune responses to the conserved HA head trimer interface epitope on influenza hemagglutinin. Taken together, our studies will describe common vaccine design strategies to preferentially elicit broad antibody responses against conserved regions of pathogens that are poorly targeted by traditional vaccines or natural immunity.

P74 Preclinical Evaluation of MVdeltaC: An Oncolytic Virus Derived from Measles Schwarz Vaccine for Cancer Therapy

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ONCOVITA is a biotech company that emerged as a spin-off from Institut Pasteur. Our primary objective is to develop an immuno-oncolytic anti-cancer vaccine using the Measovir platform, a proprietary technology derived from the safe and highly immunogenic measles Schwarz vaccine virus. By abolishing the expression of the viral protein C, which controls viral replication in infected cells, we have generated the oncolytic MVdeltaC virus. MVdeltaC targets tumors by exploiting the overexpression of CD46 measles vaccine receptor on a wide array of human cancer cells. The anti-cancer efficacy of MVdeltaC was evaluated both in vitro and in vivo. In vitro, MVdeltaC exhibited robust oncolytic activity against diverse human cancer cell lines, including mesothelioma, lung adenocarcinoma, hepatocarcinoma, bladder, ovarian, and cervical cancers, with 70% of the cell lines responding to treatment. This enhanced activity compared to the Schwarz vaccine virus is attributed to MVdeltaC’s ability to generate 5’ copy-back RNA defective genomes, inducing a strong type I interferon response.

In vivo, MVdeltaC significantly inhibited tumor growth in patient-derived xenograft models in immunodeficient mice. In NOD/SCID mice grafted with human mesothelioma, a single intraperitoneal injection of a low dose of MVdeltaC significantly reduced tumor mass within two weeks. Weekly intratumoral injections in nude mice with mesothelioma or bladder cancer xenografts further confirmed its efficacy. In immunocompetent A/J mice bearing neuroblastoma tumors, five intratumoral injections of MVdeltaC resulted in complete tumor rejection in 90% of the animals. The efficacy of MVdeltaC relies on CD8 T and NK cells as their depletion abolishes efficacy of MVdeltaC. Moreover, mice previously immunized with measles vaccine reject their tumors upon MVdeltaC treatment more rapidly than naïve animals, suggesting that prior immunity to measles enhances the anti-tumor response.

These preclinical findings support the potential of MVdeltaC as an effective immuno-oncolytic virus. ONCOVITA is currently producing GMP batches of MVdeltaC and preparing for an initial clinical trial in patients with solid tumors.

P75 Efficacy of a ready-to-use porcine bivalent mycoplasma subunit vaccine against Mycoplasma hyorhinis and Mycoplasma hyopneumoniae challenge

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Mycoplasma hyopneumoniae (Mhp) is the causative agent of swine enzootic pneumonia (SEP) and a major contributor to respiratory diseases. SEP is closely related to retarded growth and low feed efficiency. Mycoplasma hyorhinis (Mhr) is a pathogen causing polyserositis and arthritis in afflicted pigs. It was previously shown that vaccination of piglets with a Mhr subunit vaccine significantly increased the survival rate in two suspected Mhr positive farms (90.6% vs 78.4% and 85.4% vs 77.3%, respectively). It was also found that piglets vaccinated with the Mhr subunit vaccine had fewer lesions in the lungs after Mhp challenge, suggesting that the Mhr vaccine may offer partial protection against Mhp infection in pigs. In the present study, the Mhp antigen was included in the Mhr subunit vaccine to generate a Mhr/Mhp bivalent subunit vaccine and the efficacy of this bivalent vaccine against Mhr and Mhp was evaluated in specific pathogen free (SPF)-pigs negative for porcine mycoplasma. After Mhr challenge, the clinical score of vaccination group was significantly lower than that of control group on day 11, 12 and 17 after challenge. The Mhr-specific antibody titer in serum in vaccinated pigs rose quickly and was sero-positive one week after challenge, possibly accounting for lower clinical scores in vaccination group. Pathological examination showed that the average lesion score for pleurisy and pericarditis was significantly lower in vaccinated pigs and the average lesion score (polyserositis and arthritis) in vaccinated pigs was also significantly lower than that in control pigs. The vaccinated pigs were positive for Mhp-specific antibody 2 weeks after vaccination and they stayed serum positive for Mhp antibody on the day of Mhp challenge. Pathological examination of the lungs after Mhp challenge showed that the vaccinated pigs had significantly lower lesion score in cardiac lobes, diaphramatic lobes, and intermediate lobes and the average lung lesion score (apical lobes, cardiac lobes, diaphramatic lobes, and intermediate lobes) was also lower in vaccinated pigs. These results demonstrated that vaccinating pigs with one dose of bivalent subunit Mhp/Mhr vaccine at 5 weeks old can obviously reduce clinical symptoms, polyserositis, arthritis, and lung lesions induced by Mhr and Mhp.

P76 Synergistic Effects of Codon Optimization and Wild-Type UTP for Enhancing mRNA Therapeutic Efficacy

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mRNA vaccines show great promise for personalized cancer immunotherapy due to their rapid development potential and ability to induce antigen-specific T-cell responses. While modRNA (with m1Ψ) has been widely used, its low immunostimulatory properties and potential for +1 ribosomal frameshifting may limit its efficacy in cancer vaccines. This study aimed to develop codon optimization strategies for unmodified mRNA (with wild-type UTP) vaccines to enhance innate immune responses while maintaining in vivo expression levels comparable to modRNA. Two antigens, HPV16 E7 and Ovalbumin, were subjected to sequence modifications based on four criteria derived from RNA sensing mechanisms. The resulting sequence alterations ranged from 6.5% to 16.2%, leading to significant changes in predicted RNA secondary structures. In vitro studies confirmed antigen protein expression from these codon-optimized mRNA sequences via Western blot analysis, with notable differences in IVT efficiency and protein expression among variants. C57BL/6 mice were immunized twice with LNP-formulated mRNA variants, and immune responses were analyzed one week post-final immunization. IFN-γ ELISpot and flow cytometry analyses revealed that codon sequence modifications based on criteria 1 and 3 induced increased IFN-γ-producing CD8+ T cells for both antigens, as well as enhanced TNF-α expression. These findings suggest that strategic codon optimization of antigen mRNA sequences can significantly improve unmodRNA vaccine efficacy. Future studies will further investigate the mechanisms underlying these immune response differences and evaluate the impact on anti-tumor efficacy. This approach holds promise for developing more effective, cost-efficient, and immunologically potent mRNA-based cancer vaccines, potentially advancing the field of personalized cancer immunotherapy.

P77 Two-year antibody persistence and safety of a single-dose live-attenuated chikungunya virus vaccine (VLA1553) in adults aged 18 years and above

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Background
VLA1553 is a live-attenuated chikungunya virus vaccine designed for active immunization as a prophylactic measure for individuals travelling to or living in endemic areas. Due to the sporadic epidemic occurrence of chikungunya, an immunological surrogate to assess clinical efficacy was accepted by regulators (FDA and EMA).

Methods
This phase 3 open-label, single arm long term antibody persistence and safety trial follows a subset (N=363) of VLA1553 vaccinees from a pivotal phase 3 trial (Schneider et al, 2023) where 4,115 adult participants received VLA1553 or placebo. The main study objective is to assess the proportion of participants with seroresponse (defined as µPRNT50 ≥150) annually, from 1 until 5 years after single immunization. Additionally, serious adverse events (SAE) were monitored from Month 6 until Year 2 post-vaccination. This presentation outlines immunogenicity and safety data collected until Year 2.

Results
The seroresponse rate was 97% (306/316, 95% CI 94.3% to 98.5%) at Year 2. The Day 29 GMT for the long-term follow-up cohort was 3,542, and GMT remained high with 785 at Year 2, considerably exceeding the seroresponse threshold of 150. In adults aged ≥65 years, antibody persistence was similar to younger adults throughout the follow-up. Ten SAEs were reported, all assessed as unrelated to VLA1553 by the investigators. Furthermore, no persistent adverse event of special interest was identified, indicating that no safety concern was identified in VLA1553-303 until Year 2.

Conclusions
These results suggest that our live-attenuated vaccine induces a robust and long-lasting immunity after a single dose.

P78 An Improved Measles Virus Vaccine Vector for Rescuing Recombinant Measles Expressing Large and Multiple Heterologous Antigens: Creating a Three-in-One Vaccine

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The measles vector (MV) platform has been developed from the live attenuated measles vaccine, one of the safest and most efficacious vaccines available. In preclinical and clinical studies, this platform has demonstrated its adaptability in stimulating immune responses and providing efficient protection against various pathogens. Moreover, its well-established manufacturing process offers a means to rapidly scale-up vaccine production at low cost for stockpiling purposes and as a rapid response to epidemic threats. To further enhance the MV vector, we developed an improved version using a bacterial artificial chromosome (BAC) plasmid. This improved MV vector can now stably accommodate and express over 7.5 kb of additional foreign genes within a single recombinant MV. Additionally, new transcription unit sites enable the insertion of multiple genes in tandem into the measles genome. Our proof-of-concept study successfully created a three-in-one combined MV vector that simultaneously expresses three protective antigens from Chikungunya virus (CHIKV), West Nile virus (WNV), and Zika virus (ZIKV). Immunization of mice with this multivalent, replication-competent vaccine elicited robust immune responses, both humoral and cell-mediated, and provided effective protection against challenges from all three viruses in a mouse model.

P79 Multigenic universal influenza DNA vaccine delivered via needle-free gene gun induces broad immunity against diverse influenza viruses in mice and nonhuman primates

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We developed a universal influenza (UFlu) DNA vaccine to address the need for improved protection from annual influenza and future variants with pandemic potential. UFlu encodes the HA Stem and matrix-2 protein ectodomain (M2e) consensus sequences from human, swine and avian strains to elicit broad protective antibody and nucleoprotein (NP) to induce protective T cells responses. To maximize immunogenicity and minimize the number of plasmids, the antigens and a genetic adjuvant (IL-12) were encoded into dual promoter plasmid cassettes. For these studies, we employed a needle-free gene gun (GG) that delivers DNA into the epidermis and induces protective levels of systemic and mucosal immune responses in large animals and humans using very low amounts of DNA (< 20 µg) per dose.

In mice, UFlu induced broad antibody and T cell responses and broad protection from representative influenza viruses, including superior protection against certain influenza strains when compared to a strain-matched inactivated vaccine. In cynomolgus macaques, GG delivery of UFlu on weeks 0, 6, 19, and 43 induced robust antibody and mucosal and systemic NP-specific T cell responses in the lungs and blood and afforded protection from clinical disease after challenge with an H3N2 strain (A/Texas/71/2017) that is moderately virulent in macaques and after re-challenge with the highly virulent pandemic H1N1 strain A/California/04/2009. Peak viral loads in bronchoalveolar lavages measured 3 days post-challenge were also 2-3 Logs lower than in control macaques challenged with the same viruses. UFlu is being advanced to phase I human trials using an optimized clinical gene gun (MACH-1TM) engineered by Orlance with innovations that are user friendly and increase penetration and distribution of the DNA/gold particles. When compared to traditional gene guns, we found that MACH-1 improved local gene/antigen expression and immunogenicity. Together, these studies support clinical development of a MACH-1 GG-delivered UFlu DNA vaccine.

P80 Hypertonic intranasal vaccines gain nasal epithelia access to exert strong immunogenicity

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Intranasal vaccines potentially offer superior protection against viral infections compared with injectable vaccines. The immunogenicity of intranasal vaccines including the leading candidate; adenovirus vector (AdV), has room for improvement, while few options are available for safe execution. In this study, we show that modifying a basic parameter of vaccine formulation, namely osmolarity, can significantly enhance the immunogenicity of intranasal vaccines. Firstly, we screened several viscous additives to enhance the immunogenicity of intranasal adenoviral vector (AdV) vaccines, since “mucoadhesive” which prolong intranasal vaccine retention against the mucociliary clearance might promote AdV infection to result in stronger immunogenicity. We found that glycerol, but not other viscous additives, enhanced systemic and mucosal antibodies as well as resident memory T cells in the nasal tissues several-to-100-fold compared to AdV intranasal vaccine in PBS. Unexpectedly, we revealed viscous glycerol did not have capacity to prolong intranasal retention of vaccines, while we confirmed that it still promoted AdV infection of nasal epithelial cells. This enhanced immunogenicity was induced by the hypertonicity of vaccine preparations and hypertonic vaccines prepared with sodium chloride, glucose, and mannitol also demonstrated the capacity to enhance immunogenicity. We revealed that the hypertonic preparation facilitated solutes’ access to the nasal epithelial cell surface, which is limited under the condition of the appropriate osmotic pressure of the mucus. Moreover, although hypertonic glycerol did not enhance the immunogenicity of subunit intranasal vaccines without adjuvant or injectable AdV vaccines, it did enhance the immunogenicity of adjuvanted subunit intranasal vaccines. These data suggest that the hypertonic preparation does not exhibit adjuvanticity and does not enhance the immunogenicity of injectable vaccines but could allow vaccines better access to nasal epithelial cells to increase the immunogenicity of intranasal vaccines that already demonstrate certain immunogenicity. Thus, the immunogenicity of intranasal vaccines could be safely improved by a simply applicable way.

P81 Evaluation of Attenuation Phenotype of the Live-Attenuated Rift Valley Fever Candidate Vaccine, RVax-1, in Preweaning and Pregnant C57BL/6 Mice

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Background: Rift Valley fever (RVF) is a mosquito-borne zoonotic disease endemic to Africa and the Middle East, causing high rates of abortion and fetal malformations in livestock, and hemorrhagic fever, retinitis, and encephalitis in humans. In the USA, the live-attenuated MP-12 vaccine, developed via chemical mutagenesis of the pathogenic ZH548 strain, has received conditional veterinary licensure and undergone Phase 1 and 2 trials for human use. MP-12 is attenuated through modifications in the M-segment and carries temperature-sensitive mutations in the L-segment. We developed RVax-1, a next-generation vaccine, using reverse genetics. It includes a deletion of the 78kD and NSm genes, along with 566 silent mutations in the MP-12 background. These modifications minimize viral dissemination in mosquitoes and reduce viral RNA fitness. Previous studies showed that reassortant ZH501 strains encoding either the S-, M-, or L-segment of RVax-1 exhibit an attenuated phenotype in adult mice. This study aimed to assess the attenuation of RVax-1 in two highly susceptible mouse models: 19-day-old C57BL/6 mice and pregnant C57BL/6 mice. Nineteen-day-old CD1 mice have been utilized as a model to evaluate the virulence of MP-12 vaccine and the variants, given their high susceptibility (MP-12 LD50 = 75.9 PFU). To minimize variations in host genetic background, we used inbred C57BL/6 mice in this study. Previously, we evaluated the susceptibility of pregnant Sprague-Dawley rats to 1×105 PFU of rMP-12 or RVax-1, but this model did not demonstrate detectable viral infection in placenta or fetuses. Therefore, we chose pregnant C57BL/6 mice to characterize the differences in attenuation between rMP-12 and RVax-1.

Methods: Nineteen-day-old mice were infected intraperitoneally with 1,000, 50, or 10 PFU of recombinant MP-12 (rMP-12), RVax-1, or ΔNSs-ΔNSm-rZH501 to assess survival rates and histopathological changes. Meanwhile, pregnant mice at embryonic day 14 (E14) received intramuscular injections of 1×105 PFU of either rMP-12 or RVax-1, or PBS as a control. The delivery of newborn pups was monitored, while viral RNA was detected from dams and pups by RT-qPCR.

Results: Survival rates for 19-day-old mice following 1,000, 50, or 10 PFU were as follows: rMP-12 (50%, 33.3%, 57.1%), RVax-1 (42.9%, 18.2%, 57.1%), and ΔNSs-ΔNSm-rZH501 (57.1%, 14.3%, 28.6%). The 1,000 PFU dose resulted in higher survival rates compared to the 50 PFU group. Viral RNA was predominantly detected in the brains of infected mice. Brain lesions in mice infected with rMP-12 or RVax-1 showed minimal inflammatory cell infiltration and abundant viral antigens in neurons and astrocytes, while ΔNSs-ΔNSm-rZH501 induced significant neutrophil infiltration and neuronal damage. Three out of five pregnant dams infected with rMP-12 exhibited reduced pup numbers, while two out of five infected with RVax-1 showed fetal demise. The rMP-12 or RVax-1 RNA were detected in the uterus of affected mice, but not in any newborn pups or unborn fetuses.

Conclusion: RVax-1 demonstrated a similar attenuation profile to rMP-12 in 19-day-old C57BL/6 mice but showed distinct pathological outcomes in pregnant C57BL/6 mice. Further studies on the mechanisms of viral infection in the placenta by rMP-12 or RVax-1 are underway.

P82 Innate immune responses against mRNA vaccine promote cellular immunity through IFN-Î² at the injection site

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in2019 and caused the global coronavirus disease 2019 (COVID-19) pandemic. mRNA vaccines against SARS-CoV-2 have become effective prophylactic agents, but the immunological mechanisms underlying their efficacy are not fully understood. Here, we investigated injection site responses of mRNA vaccines by generating comprehensive single-cell transcriptome profiles to lipid nanoparticle (LNP) or LNP-mRNA challenge. We show that LNP-induced interstitial pro-inflammatory responses and mRNA-induced type I interferon responses dominate in the initial injection site. By tracking the fate of the delivered mRNA, we showed that injection-site fibroblasts induce the Cxcl5 chemokine, which is involved in leukocyte recruitment, leading to antigen-presenting via MHC class I. Also we found that fibroblasts specifically expressed IFN-β in response to the mRNA component, which was highly enriched with delivered mRNA and not the LNP component of the mRNA vaccine. Moreover, the mRNA-LNP, but not LNP alone, induced migratory dendritic cells highly expressing IFN-stimulated genes (mDC_ISGs) at the injection site. When IFN-β was co-injected with LNP-subunit vaccine, it substantially enhanced antigen-specific cellular immune responses. Furthermore, blocking of IFN-β at the injection site significantly decreased mRNA vaccine-induced cellular immune responses. Collectively, these data highlight the importance of injection site fibroblasts and IFN-β signaling during early immune responses against mRNA vaccine and provide detailed information on the initial chain of immune reactions elicited by mRNA vaccine injection.

P83 L-pampo™, a TLR2/3 agonist, can be a potent vaccine adjuvant targeting respiratory infectious diseases

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Introduction: Vaccine adjuvants are crucial for effectively protecting against respiratory infectious diseases by enhancing immune responses. Toll-like receptor (TLR) agonist-based adjuvants have garnered significant interest due to their ability to activate innate immunity and promote robust adaptive immune responses. Current vaccines are predominantly administered intramusculaly. However, there is growing recognition of the importance of enhancing mucosal immunity at the primary infection site of the virus in respiratory infectious diseases as a critical vaccine strategy. This study aims to assess the efficacy of L-pampo™ when administered via the intramuscular, intranasal, or sublingual route for targeting Influenza or SARS-CoV-2. Additionally, we evaluated L-pampo™'s potential in enhancing humoral, cellular, and mucosal immune responses to develop effective vaccination strategies.

Methods: In the study of Flu-COVID combination vaccine, BALB/c mice received two doses of vaccines three weeks apart. Influenza-specific antibody responses were assessed from serum using ELISA and hemagglutination inhibition (HI) assays, while IFN-γ production from splenocytes was measured by ELISPOT assay. For the COVID-19 vaccine, neutralizing antibody (nAb) levels and ACE2 receptor-blocking antibodies against the SARS-CoV-2 receptor binding domain (RBD) were determined. Protective efficacy was evaluated in a virus challenge model using hACE2 transgenic mice. Additionally, the immune responses of sublingual vaccine formulations containing L-pampo™ and SARS-CoV-2 RBD were assessed in saliva, BALF, serum, and cervical lymph nodes using ELISA, ELISPOT, and flow cytometry.

Results: For the Flu/COVID-19 combination vaccine, intramuscular injection of L-pampo™ significantly increased Influenza or SARS-CoV-2-specific IgG and HAI titers in serum and IFN-γ-producing cells from splenocytes. Additionally, intranasal administration of L-pampo™ elicited robust mucosal immune responses with higher levels of IgA in the influenza vaccine study. Similarly, in a COVID-19 model, sublingual administration of L-pampo™ augmented RBD-specific IgA in saliva and BALF, IgG in serum, and IFN-γ-producing cells from splenocytes. Moreover, L-pampo™ promoted tissue-resident memory T (TRM) cells crucial for mucosal immunity in the sublingual COVID-19 model.

Conclusion: This study highlights the pivotal role of adjuvant L-pampo™ in enhancing immune responses against respiratory infectious diseases. Our findings underscore the effectiveness of L-pampo™ through intramuscular injection and mucosa-targeting administration, demonstrating its potential as a candidate for mucosal immune vaccines against Influenza and COVID-19.

P84 Immunological and pathological analysis of mpox vaccine, LC16m8

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In 2022, an outbreak of monkeypox virus (MPXV) spread rapidly to over 100 countries, promoting the World Health Organization to declare a public health emergency of international concern on July 23, 2022. Several types of smallpox vaccines, including the LC16m8 attenuated vaccinia virus strain, have demonstrated protective efficacy against MPXV. LC16m8 vaccine was approved in Japan for smallpox in 1975 and for MPXV in 2022. Previous clinical studies have shown the efficacy of LC16m8 vaccines against MPXV with fewer adverse events compared to first-generation smallpox vaccines, contributing to the eradication of smallpox. In this study, we investigated the immunological responses, especially cellular immune responses, of LC16m8 vaccine strain in two mouse strains and its pathological effects in non-human primate model. Additionally, we evaluated the immunogenicity of LC16m8 vaccine using specimens from vaccinated humans. Our results showed that LC16m8-vaccine induced significant antibody and T cell responses against vaccinia virus in mice and humans, but neutralizing antibodies against MPXV were limited. Pathological analysis in non-human primates revealed no significant adverse effects, although skin pox lesions appeared. These findings suggested that the LC16m8 vaccine could induce protective immune responses against MPXV, although its safety for immunocompromised patients requires further consideration.

P85 A New Public Facility That Bridges Vaccine Biomanufacturing for Clinical Trials – The National Research Council (NRC) of Canada's Clinical Trial Material Facility

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National Research Council Canada

The NRC recently completed the commissioning of its new Clinical Trial Material Facility (CTMF) at its Royalmount site in Montréal, Quebec, Canada. This 18,000 sq. ft. facility has a bioreactor capacity of 500 litres (upstream) and downstream suites and a unique uni-directional design for people and material flow, for ease of product change and maintaining multifunctionality. It is designed for the production of viral vector, protein subunit and virus-like particle vaccines and other biologics using cell-based platforms.

With the capacity to replicate drug production processes at a smaller scale that comply with good manufacturing practices (GMP) that are compliment with FDA, Health Canada and EU guidelines, it can produce the quantity of materials required to conduct human phase 1 and 2 clinical trials. It can also be used as a technology transfer hub to complete verification runs and optimize GMP manufacturing processes, enabling testing, analysis and evaluation of the production process, including scaling up and scaling down.

NRC's research expertise includes designing early-stage biologics through pre-clinical evaluation and bioprocess research and development to early process validation at pilot scale. NRC also offers a variety of proprietary cell line platforms such as NRC-HEK293, CHO-BRI and NRC-Vero cells for production of various vaccines and therapeutics. The new CTMF is designed to operate in conjunction with NRC's other R&D labs at the Human Health Therapeutics Research Centre, or separately, depending on the requirements of a particular project. The facility can host a broad range of partners and stakeholders, including industry, hospitals, health networks, academia and government to help advance biologics products through human clinical trials. NRC now offers a one-stop shop to support the design, prototype and scale-up R&D and GMP biomanufacturing of novel biologics.

P86 A novel subunit vaccine Ag85A-LpqH focusing on humoral immunity provides substantial protection against tuberculosis in mice

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Tuberculosis (TB) is an ancient infectious disease that seriously endangers the global public health. With promising developments in subunit vaccines and the recognition of the importance of humoral immunity in combating TB, we aim to create a vaccine that can stimulate both cellular and humoral immunity that can enhance the vaccine's protective efficacy. In this study, a novel subunit vaccine named Ag85A-LpqH (AL) was prepared by fusing the antigen Ag85A proved to induce robust T cells immune responses, and LpqH shown to produce protective antibodies. Aluminum adjuvant and Poly IC adjuvant were selected and tested as booster adjuvants for the recombinant subunit vaccine. The prevention and BCG prime-boost mouse models were established to test the vaccine efficacy. The results indicate that Ag85A-LpqH can induce substantial protection by reducing bacterial loads and pathological lesions in both models. This subunit vaccine can induce robust antibody responses, as well as T cell immune responses especially strong CD8+ T cell responses. The subunit vaccine can generate robust IgG-specific antibodies, especially the ALA (AL with Alum Adjuvants), which not only maintained high levels of antibodies post-infection but also enhanced macrophage-mediated phagocytosis. Moreover, the serum from AL-immunized mice can reduce the bacterial load and lung pathology in mice infected with M.bovis. B cell receptor (BCR) sequencing revealed a notable rise in BCR diversity among mice immunized with the ALA group in comparison to the BCG and control groups. These results indicate that it is rational to design the TB vaccines based on both cellular and humoral immunity, and Ag85A-LpqH can be a promising vaccine candidate for tuberculosis prevention and control.

P87 Coverage and vaccine hesitancy of influenza vaccination among reproductive-age women (18-49 years old) in China

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Background: Influenza is a significant global respiratory infection, and vaccinating reproductive-age women, particularly in densely populated countries like China, cannot be overlooked. In this study, we aimed to determine influenza vaccination coverage, vaccine hesitancy as well as associated factors among Chinese women aged 18-49 years old.
Methods: A cross-sectional survey was conducted in China from March 15 to March 30, 2023, using a random stratified sampling method. The target population was women aged 18-49 years. We collected information such as past-year influenza vaccination, demographic characteristics, health-related factors, COVID-19-related factors, and perceived susceptibility and severity of influenza. Reproductive-aged women who did not receive influenza vaccination in the past year were asked if they would get the flu vaccine in the future. Multivariable logistic regression analyses were employed to investigate the influencing factors of vaccine coverage and vaccine hesitancy.
Results: A total of 1742 Chinese reproductive-aged women were finally included. The past-year influenza vaccine coverage among women aged 18-49 years old was only 39.32% in China. Age ≥35 years (aOR = 0.72, 95% CI: 0.56-0.94), renting accommodation (0.57, 0.44-0.75), and history of COVID-19 infection (0.65, 0.47-0.89) and COVID-19 vaccine hesitancy (0.39, 0.29-0.54) were all identified as negative correlates of influenza vaccine coverage among Chinese reproductive-aged women. While participants with a history of chronic diseases (1.57, 1.23-2.01) and noticeable pandemic fatigue due to COVID-19 (1.45, 1.05-2.00) were prone to have higher vaccination rates. Among reproductive-aged women who did not receive influenza vaccination in the past year, the hesitancy rates regarding future influenza vaccination were 31.79%. Factors such as older age, urban residence, living with others, poor self-rated health status, absence of chronic diseases, completion of full COVID-19 vaccination, COVID-19 vaccine hesitancy, pandemic fatigue, and failure to perceive the susceptibility and severity of influenza might increase influenza vaccine hesitancy.
Discussion: A lower coverage rate of influenza vaccine was notably observed among Chinese reproductive-age women, as well as the hesitancy regarding future vaccination. To effectively mitigate the impact of influenza and reduce the incidence of associated diseases, it is imperative to devise targeted intervention strategies and policies tailored to reproductive-age women.

P88 SARS-CoV-2 Plasma Cells are Largely Excluded from the Bone Marrow Long-Lived Compartment 33 Months after mRNA Vaccination

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The goal of any vaccine is to induce long-lived plasma cells (LLPC) to provide life-long protection. Natural infection by influenza, measles, or mumps viruses generates bone marrow (BM) LLPC similar to tetanus vaccination which affords safeguards for decades. Although the SARS-CoV-2 mRNA vaccines protect from severe disease, the serologic half-life is short-lived even though SARS-CoV-2-specific plasma cells can be found in the BM. To better understand this paradox, we enrolled 19 healthy adults at 2.5-33 months after SARS-CoV-2 mRNA vaccine and measured influenza-, tetanus-, or SARS-CoV-2-specific antibody-secreting cells (ASC) in LLPC (CD19-) and Non-LLPC (CD19+) subsets within the BM. All individuals had IgG ASC specific for influenza, tetanus, and SARS-CoV-2 in at least one BM ASC compartment. However, only influenza- and tetanus-specific ASC were readily detected in the LLPC whereas SARS-CoV-2 specificities were mostly excluded. The ratios of Non-LLPC:LLPC for influenza, tetanus, and SARS-CoV-2 were 0.61, 0.44, and 29.07, respectively. Even in five patients with known PCR-proven history of infection and vaccination, SARS-CoV-2-specific ASC were mostly excluded from the LLPC. These specificities were further validated by using multiplex bead binding assays of secreted antibodies in the supernatants of cultured ASC. Similarly, the IgG ratios of Non-LLPC:LLPC for influenza, tetanus, and SARS-CoV-2 were 0.66, 0.44, and 23.26, respectively. While serum IgG titers specific for influenza and tetanus correlated with IgG LLPC, serum IgG levels for SARS-CoV-2, which waned within 3-6 months after the vaccine, were associated with IgG Non-LLPC. In all, our studies demonstrate that rapid waning of serum antibodies is accounted for by the inability of mRNA vaccines to induce BM LLPC.

P89 Synergistic activation of STING and TLR9 for cancer immunotherapy

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TLR9 and STING agonists act as vaccine adjuvants, capable of enhancing the adaptive immune responses that are triggered by the adjuvant-boosted innate immune response. Although adjuvants can be included in vaccines for infectious diseases or cancer, adjuvants themselves can also be used for cancer immunotherapy without antigen. Our previous study indicated that the combination of STING and TLR9 agonists synergistically induces type I immune responses and subsequent anti-tumor immunity in several mouse tumor models. Although the mode of action of the combination has been elucidated to some extent, the detailed mode of action of the combination as a cancer immunotherapeutic remains to be elucidated. Furthermore, there are still unanswered questions regarding the optimal conditions for the induction of synergistic anti-tumor immunity by the combination of TLR9 and STING agonists. These include the treatment schedule, the most effective combination of TLR9 and STING agonists to use, the appropriate dose and the choice of drug delivery systems (DDS). Therefore, the objective of this study was to identify the optimal combinations of TLR9 and STING agonists that can achieve the desired synergistic anti-tumor effect. A total of 18 different TLR9 and STING combinations, with or without DDS, were administered to tumor-bearing mice. The survival rate, primary tumor size and systemic serum toxicity marker AST were then measured. The results demonstrated a strong positive correlation between tumor size and serum AST levels. Furthermore, three new combinations with the highest anti-tumor effect and the least toxicity were identified. Furthermore, the DDS-containing combination groups exhibited low serum AST levels, irrespective of tumor size. This suggests that DDS can mitigate the toxicity of adjuvants, thus preventing potential adjuvant-induced adverse events. Consequently, the current study provides further insights into the optimization of TLR9 and STING combination-based cancer immunotherapy strategies, which could contribute to the clinical development of combination-based therapies for cancer.

P90 Development of Serum-free Medium Based on Deep-learning Artificial Intelligence Platform to Enhance the Production of Influenza Vaccines with MDCK Cells

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MDCK (Madin-Darby Canine Kidney) suspension cell culture-based influenza vaccine production has become an attractive alternative to the egg-based or adherent cell-based methods, as its scalability and exclusion of serum significantly improves production efficiency and process stability. Especially, the design of serum-free culture medium is critical for the enhancement of influenza virus productivity. However, traditional medium development approach like DOE (Design of Experiment) highly relies on the experience and knowledge of researchers. The confirmation of candidate components and their ranges directly affects the experimental workload and cycle of medium development. Therefore, BioEngine have independently established a deep-learning artificial intelligence platform, which guides the development of serum-free medium formulas by assisting in experimental design, discovering key components of formulas, and establishing predictive models. This platform adopts a deep-learning neural network model to replace the traditional decision tree model, extract complex features from the data, optimize dimensionality reduction methods, introduce dynamic models to improve model expression ability, and thereby improve the accuracy of data analysis and prediction models. Using this platform, a serum-free medium for suspension MDCK cell culture was developed, which was proved to support a stable and rapid cell growth during long-term subculture (over 200 days). Notably, the production capacity for influenza viruses was improved after the long-term culture in certain serum-free medium, and the underlying reasons were further explored by transcriptomic analysis combined with physiological and metabolic investigations. Furthermore, a dilution feed process has been developed to achieve a maximum influenza virus titer of 3.6 lg (HAU/100 μl), and the immunogenicity of the MDCK cell derived vaccines using the serum-free medium developed by our platform were comparable to chicken embryo derived ones. This process has been successfully adopted by many vaccine manufacturers. A company has applied this medium for human influenza vaccine production in the clinical phase; Several avian influenza vaccine companies have achieved large-scale and stable production, with a maximum production scale of 6000 L bioreactor. This high-efficient medium development platform provides a meaningful alternative for upgrading of current viral vaccine manufacturing.

P91 Bacteriophage T4 as a Protein-Based, Adjuvant- and Needle-Free, Mucosal Pandemic Vaccine Design Platform

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We present here a novel protein-based, bacteriophage T4 platform for rapid design of efficacious vaccines against bacterial and viral pathogens.

Bacteriophage T4 infects Escherichia coli bacterium. It is one of the most stable and structurally and genetically well-characterized viruses. The phage has a large 120 x 86 nm prolate icosahedral capsid (head) containing ~171kb packaged double-stranded linear genome. Its exterior is coated with two nonessential outer capsid proteins, Soc (small outer capsid protein) (9.1 kDa; 870 copies per capsid) and Hoc (highly antigenic outer capsid protein) (40.4 kDa; 155 copies per capsid).

Soc binds as a trimer at the quasi-three-fold-axes by clamping two adjacent capsomers and provides additional stability to an already very stable capsid. Hoc is a 18nm-long fiber and acts as an adhesin allowing phage to bind to bacterial and mammalian cell surfaces. Both have nanomolar affinity and exquisite specificity to T4 capsid and can be used as adapters for high density display of pathogen antigens on the surface through in vitro or in vivo assembly.

Using T4 phage as a surface display platform, we have designed a series of nanoparticle vaccines against deadly infectious agents including Bacillus anthracis (anthrax), Yersinia pestis (plague), HIV, SARS-Co-V2 (COVID-19), influenza-A (Flu), and dengue virus. The T4 vaccines are stable at room temperature, do not need an adjuvant, and are effective as needle-free intranasal vaccines. In animal models including mice, rabbits, and macaques, complete protection was observed against lethal challenges with the respective infectious agents (except HIV).

Intranasal or intramuscular administration of two doses of T4 vaccines induced robust systemic humoral and cellular immune responses that include neutralizing antibodies, CD4 and CD8 T cell immunity, and Th1-biased cytokine responses. Additionally, intranasal immunizations elicited mucosal immunity including high secretory IgA titers in sera and bronchoalveolar lavage fluids, and effector (TEM), central (TCM), and tissue-resident memory CD4+ T cells (TRM) at mucosal sites in the case of the T4-Flu vaccine. The nasal vaccines conferred complete protection and also sterilizing immunity against multiple SARS-CoV2 variants.

The modular, temperature-stable, needle- and adjuvant-free, phage T4 nanovaccine platform might be a good candidate for global vaccine development for low and middle income countries, and as a complementary platform for emergency preparedness against epidemic and pandemic pathogens.

P92 Prime-Boost Immunization with Inactivated Human Adenovirus Type 55 combined with an Adjuvant Enhances Neutralizing Antibody Responses in Mice

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Human adenovirus type 55 (hAd55) infection can lead to acute respiratory diseases that often present with severe symptoms. Despite its persistent prevalence in military camps and communities, there are no commercially available vaccines or vaccine candidates undergoing clinical evaluation; therefore, there is an urgent need to address this. In this study, we evaluated the immunogenicity of inactivated hAd55 isolates and investigated the effects of adjuvants and various immunization intervals. To select a vaccine candidate, four hAd55 strains (6-9, 6-15 (AFMRI 41014), 28-48 (AFMRI 41013), and 12-164 (AFMRI 41012)) were isolated from infected patients in military camps. Sequence analysis revealed no variation in the coding regions of structural proteins, including pentons, hexons, and fibers. Immunization with inactivated hAd55 isolates elicited robust hAd55-specific binding and neutralizing antibody responses in mice, with adjuvants, particularly alum hydroxide (AH), enhancing antibody titers. Co-immunization with AH or alum phosphate (AP) also induced hAd14-specific neutralizing antibody responses, albeit at lower levels. Notably, booster immunization administered at a four-week interval resulted in superior immune responses compared with shorter immunization intervals. These findings demonstrate the potential of prime-boost immunization with the inactivated hAd55 isolate, particularly when combined with an AH adjuvant, as a promising approach for preventing hAd55-induced respiratory disease. Further research is warranted to explore the efficacy and safety of these vaccine candidates for preventing hAd55-associated respiratory illnesses.

P93 Combination adjuvants targeting nucleic acid sensors for cancer immunotherapy

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Innate immune sensing of nucleic acids derived from invading pathogens or tumor cells via pattern recognition receptors is crucial for mounting protective immune responses against infectious disease and cancer. Recently, discovery of tremendous amounts of nucleic acid sensors as well as identification of natural and synthetic ligands for these receptors revealed the potential of adjuvants targeting nucleic acid sensing pathways for designing efficacious vaccines. Especially, current data indicated that unique adjuvants targeting TLR9 and stimulator of interferon genes (STING)-dependent cytosolic nucleic acid sensing pathways along with the combinations of already existing adjuvants are promising candidates for this purpose.
Agonists for TLR9 and stimulator of IFN genes (STING) offer therapeutic applications as both anti-tumor agents and vaccine adjuvants, though their clinical applications are limited; the clinically available TLR9 agonist is a weak IFN inducer and STING agonists induce undesired type 2 immunity. Yet, combining TLR9 and STING agonists overcame these limitations by synergistically inducing innate and adaptive IFNγ to become an advantageous type 1 adjuvant, suppressing type 2 immunity, in addition to exerting robust anti-tumor activities when used as a monotherapeutic agent for cancer immunotherapy. Here, we show that combination of TLR9 and STING agonists synergistically induce IL-12 and type I IFN production from murine APCs. Synergistic effect of the TLR9 and STING agonists on IL-12p40 are observed on protein, mRNA and promoter activation levels and transcriptional regulation is mediated by a 200 bp region situated at 983 bp upstream of IL-12p40 transcription initiation site. Moreover, local combination treatment promoted strong anti-tumor immunity in Pan02 peritoneal dissemination model via the mechanisms involving both CD4 and CD8 T cells, as well as co-operative action of IL-12 and type I IFNs. Furthermore, rechallenge studies in the long-term survivors suggested the elicitation of Pan02-specific memory responses that provide protection against secondary tumor challenge.
Nevertheless, combination-adjuvanted peptide vaccine could induce potent Ag-specific Th1-type and CD8 T cell immune responses against synthetic long peptides and neopeptide pools derived from melanoma and mesothelioma tumors. Importantly, combination-adjuvated peptide vaccine exhibited robust anti-tumor effect that was synergistically enhanced by anti-PD-1 treatment in the immune checkpoint blockade-resistant melanoma model B16-F10-OVA. Therefore, combination of TLR9 and STING agonists may have clinical applications as potent anti-tumor agents, and elicitation of the mechanisms mediating the synergism between TLR9 and STING agonists may hold a key in successful cancer immunotherapy and provide further insights into dual agonism of innate immune sensors during host homeostasis and diseases.

P94 K3-SPG-mediated long-term protection against viral infection

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In the face of recurrent global pandemics, rapid and effective vaccine development remains key for saving lives and controlling societal impacts. While effective, conventional approaches to vaccine development are often time-consuming, hindering our ability to respond swiftly to emerging pathogens. In the fight against SARS-CoV-2, the mRNA vaccine development took only approximately 1 year, however, the estimated total number of deaths were at least 3 million by 31 December 2020 (World Health Organization). Furthermore, from the time of the vaccine launch to the completion of the first immunization, additional millions of lives were lost. Moving forward, researchers across the globe are cooperating to achieve the 100-day mission as we prepare for the next pandemic. The missions' primary objective is to produce a vaccine in 100 days upon the emergence of a new pathogen, while also putting in efforts to develop an emergency treatment to further mitigate infection and mortality rates until vaccines become available. A component that has attracted the attention of current research is vaccine adjuvants, such as Toll-like receptor (TLR) 9 agonists CpG deoxynucleotides (CpG ODNs), which has been extensively reported to be immunogenic and has the capability to confer innate immune memory targeting various pathogens. By itself, CpG ODNs have demonstrated significant protection against bacteria, viruses, and parasites, however, their effectiveness against influenza viruses remain limited.
To address this gap, our study focuses on the development of K3-SPG, a novel CpG-ODN complex as an emergency treatment in future pandemics. Here, we report that intranasal administration of K3-SPG alone confers full protection against influenza virus (H1N1) in mice, with potent antiviral effects sustained for at least 80 days. Interestingly, protection against influenza virus requires only 3 days of pre-exposure to K3-SPG with no discernible adverse effects. Moreover, desired effect was enhanced by local administration, suggesting the importance of the route of adminstration depending on the type of pathogen. Using various approaches to investigate underlying mechanisms, we identified rapid changes in immune cell subsets as early as 24 hours after administration, along with correlations between different cell subsets. Collectively, our findings suggest that K3-SPG is a promising candidate for emergency treatment in pandemic responses, effective not only against influenza viruses, but also with potential efficacy against other respiratory viruses.

P95 Quantification of polysaccharides in trivalent iNTS-typhoid glycoconjugate vaccine by high-performance anion-exchange chromatography with pulsed amperometric detection

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The quantification of polysaccharides is a critical aspect of developing and characterizing trivalent iNTS-typhoid glycoconjugate vaccines. This study presents a high-performance anion-exchange chromatography with pulsed amperometric detection (HPAEC-PAD) method optimized for quantifying the polysaccharide content in the final multivalent vaccine product. The method development involved selecting an optimal hydrolysis method to convert O-specific polysaccharides (OSP) to their specific unique monosaccharides, thereby enhancing detection sensitivity and consistency. We compared trifluoroacetic acid (TFA) and hydrochloric acid (HCl) hydrolysis methods, identifying HCl as superior due to its higher signal intensity for abequose and tyvelose, key monosaccharides in the polysaccharides derived from Salmonella typhimurium and Salmonella enteritidis.
To address the interference from aluminum phosphate adjuvants in the vaccine, we evaluated three desorption methods: trisodium citrate, trisodium citrate with trisodium phosphate, and NaOH treatment. NaOH treatment was found to be the most effective, providing complete detachment of the conjugate from the adjuvant without affecting the target monosaccharides. We refined the HPAEC-PAD conditions to ensure accurate quantification and enhance efficiency, with a focus on reducing the elution time and separating overlapping peaks with preservative components.
Validation of the method included testing for accuracy, precision, linearity, and limit of detection (LOD). The method demonstrated high accuracy, with a recovery rate of over 90% for both ST OSP and SE OSP, and precision with relative standard deviations (RSD) below 10%. The LOD was determined to be 2.5 µg/mL for ST OSP and 5 µg/mL for SE OSP, and the linearity was confirmed with R^2 values above 0.99. This HPAEC-PAD method is robust and reliable for quantifying polysaccharides in trivalent iNTS-typhoid vaccine formulations, facilitating efficient product development and quality control.

P96 Structure-based antigen design for serogroup B N. meningitidis vaccine

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Neisseria meningitidis is a human specific pathogen that is a leading cause of meningitis and sepsis in children and young adults. The case fatality rate for meningococcal sepsis remains up to 10%-15% despite optimal medical therapy. Conjugate capsular polysaccharide vaccines have been successfully employed to combat epidemic disease caused by certain serogroups of N. meningitidis (namely A, C, Y and W135). However, these strategies cannot be employed to prevent endemic serogroup B N. meningitidis (MenB) infection because of the particularity of MenB capsular polysaccharides, which resulting in low immunogenicity, and raises concerns about eliciting autoimmune responses in human. fHbp、NHBA、NadA are vaccine candidates verified by reverse vaccinology, which heralded a revolution in approaches to MenB vaccine development.
Here we use structure-based antigen design to generate two types of chimeric antigens (ChAs) against MenB elicit complement-mediated bactericidal activity. One ChAs fuse fHbp and the inter-domain of NHBA together with linker to generate fusion protein. The other ChAs exploit NadA as a molecular scaffold to present the surface exposed PorA VR2 loop. All ChAs in our design retain epitopes from both fHbp、NHBA、NadA and PorA, and can elicit functional immune responses against both antigens. Compare to native fHbp、NHBA、NadA and PorA, the ChAs in our design exhibit good stability and homogeneity, which are conducive to industrial development of MenB vaccine.
Further More, considerate the sequence hypervariability of both antigens, the local antigen variants from China are included in our vaccine candidates to elicit the best Immuno-protective effect. In conclusion, using structure-based antigen design, we verified two ChAs as MenB vaccine candidates, which exhibit good stability and immunogenicity combat endemic serogroup B N. meningitidis (MenB) infection in China.

P97 Safety and immunogenicity of a SARS-CoV-2 mRNA virus-like particle vaccine in adults 18 years of age and older in a Phase 1 randomized clinical trial

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Background: Despite the rollout of effective vaccines against coronavirus disease 2019 (COVID-19), there remains an ongoing need for COVID-19 vaccines with improved potency, lower reactogenicity, broader coverage against emergent variants of SARS-CoV-2, and longer duration of protection. This study examined the safety and immunogenicity of two SARS-CoV-2 mRNA virus-like particle (VLP) vaccines.

Methods: This is an ongoing, Phase I, open-label, randomized, active-controlled study assessing 2 dosages of AZD9838 (BA.4/5 variant) and AZD6563 (XBB.1.5 variant). Participants had previous natural immunity via either prior infection or primary series vaccination and were randomized to receive a single intramuscular injection of AZD9838 (Groups 1 and 2), AZD6563 (Groups 3 and 4), or 30 µg BNT162b2, a licensed SARS-CoV-2 mRNA vaccine (XBB1.5 variant).

SARS-CoV-2 neutralizing antibody (nAb) titers against the ancestral, Omicron BA.4/5, Omicron XBB.1.5, and Omicron JN.1 variants were measured at baseline and Day 29. Solicited adverse reactions (ARs) were collected for 7 days post-vaccination and unsolicited adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs) were collected for 29 days post-vaccination. All comparisons were descriptive.

Results: Overall, 166 healthy adults 18 to 64 years of age and 76 healthy adults ≥65 years of age were vaccinated. nAb geometric mean titers (GMTs) numerically increased from baseline and with increasing dosage of AZD9838 and AZD6563 in all groups. In participants 18 to 64 years of age, vaccination with dosage 2 of AZD6563 resulted in nAb GMTs similar to those observed with BNT162b2, while in adults ≥65 years of age, dosage 2 of AZD6563 generated a nAb GMT ratio of 1.92 (95% confidence interval 0.77, 4.75) for Omicron XBB.1.5 versus BNT162b2 at Day 29.

Both AZD9838 and AZD6563 were well-tolerated at both dosages, with a numerically lower proportion of injection site pain and muscle aches reported among AZD6563 recipients compared with BNT162b2 recipients. Unsolicited AEs were numerically similar between groups; no related SAEs or AESIs were reported up to Day 29.

Conclusion: This study showed that immunogenicity to a SARS-CoV-2 mRNA VLP vaccine was similar to that of BNT162b2. Furthermore, the SARS-CoV-2 mRNA VLP vaccine was well tolerated, with fewer ARs reported compared with BNT162b2.

P98 Development of a thermostable, immunogenic ACM Tunable Platform (ATP) for mRNA delivery using amphiphilic block co-polymers

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Lipid nanoparticles (LNPs) are considered the best-in-class for mRNA delivery, but their thermal instability restricts their duration of use after thawing and their distribution to regions with cold chain infrastructure. Lyophilization is extensively used in the pharmaceutical industry to improve stability and shelf life of many medications but its application to LNPs is not trivial given the need for careful selection of multiple processes and parameters. An alternative approach is the incorporation of specialized ionizable lipids that impart increased stability. Here, we show that replacement of DMG-PEG_{2000} with the block co-polymer PBD-*b*-PEO results in a highly stable ACM Tunable Platform (ATP) formulation that can undergo prolonged storage in liquid format at 4°C with no detriment to its structure and function. Dynamic light scattering (DLS) measurements of mRNA-ATP revealed a stable size distribution profile for 24 weeks at 4°C whereas mRNA-LNPs became unstable after four weeks. Furthermore, mRNA integrity and *in vitro* HEK293 transfection did not show evidence of deterioration. Characterization of tissue distribution by IVIS® imaging after intravenous (IV) or intramuscular (IM) administration of luciferase mRNA-ATP revealed a substantial reduction in liver affinity concomitant with increased deposition in secondary lymphoid organs. Cellular level analysis by flow cytometry showed efficient ATP uptake by macrophages and different subsets of dendritic cells (cDC1, cDC2 and pDCs). Based on these attributes, we evaluated ATP as a carrier for an mRNA vaccine. Mice given two IM injections of mRNA-ATP exhibited mild, transient weight loss two days after each dose but did not present with evidence of systemic toxicity (i.e.: normal serum ALT, CRP and creatinine), indicating good tolerability. Vaccinating with freshly fabricated ovalbumin (OVA) mRNA-ATP generated robust and durable OVA-specific IgG titers and H-2kb/SIINFEKL pentamer$^+$ CD8$^+$ T cells. Notably, SIINFEKL-specific, IFNγ-producing CD8$^+$ T cells were detected in the spleens of ATP-vaccinated mice at twice the frequency as LNP-vaccinated mice, 154 days after study start. Despite its immunogenicity, repeated IV administrations of ATP did not boost anti-PEG antibodies, unlike LNPs which efficiently boosted such antibodies with consecutive doses. Immunogenicity of OVA mRNA-ATP remained intact after prolonged storage at 4°C. Similar frequencies of circulating effector memory, central memory or Pent$^+$ CD8$^+$ T cells were induced by one dose of fresh or aged ATP. Moreover, aged ATP was more immunogenic than freshly fabricated LNPs, based on the significantly higher frequencies of Pent$^+$ CD8$^+$ T cells at multiple time points after one or two doses. Although the OVA-specific IgG titer induced by aged ATP trended lower than fresh ATP, the response was vigorously boosted by the second dose of aged ATP. The potential for clinical translation was determined by vaccinating Golden Syrian hamsters with ATP encapsulating ancestral SARS-CoV-2 spike mRNA. Hamsters developed high levels of spike-specific IgG similar to those generated by the LNP comparator and were strongly protected against weight loss induced by live virus challenge. Cumulatively, we have demonstrated mRNA-ATP to be highly stable, immunogenic and possesses potential for clinical translation.

P99 MONTANIDE™ ISA 51 VG: open access adjuvant dedicated to therapeutic vaccines

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Therapeutic vaccines represent a good alternative for active immunotherapy and are particularly used in the treatment of cancers, autoimmune diseases, and certain chronic infectious diseases. For those vaccines, the use of well defined over expressed self antigens is linked with weak and short term immune response. To enhance the quality of the vaccines in terms of immune response and stability, oily adjuvants can be used.

Indeed, GMP grade oily adjuvants such as MONTANIDE™ ISA 51 VG from Seppic are widely used in humans to formulate stable water-in-oil emulsions based vaccines. When injected, water-in-oil vaccines create a depot effect at the injection site and allow a slow and prolonged release of the antigen. It results in strong activation of CD8+ and CD4+ cells and production of cytokines.

MONTANIDE™ ISA 51 VG is mostly used in immunotherapy for the development of cancer vaccines and has been administered to more than thirty thousands patients worldwide. Thus, this adjuvant has a strong safety database in which local and general adverse events observed are mild to moderate and generally transient, and refer to headache, local pain or redness at injection site.

In conclusion, MONTANIDE technology is a well-known ready-to-use adjuvants platform. It has been proven to be safe and potent thanks to their widely used in clinical trials worldwide for more than thirty years. MONTANIDE adjuvants are also suitable for registration by agencies as MONTANIDE™ ISA 51 VG is used in a licensed vaccine against non-small cell lung cancer, called the CIMAvax-EGF®, registered in eight countries so far.

P100 Cost-Effectiveness Analysis of Hepatitis E Vaccination Strategies for Swine-Related Occupational Workers

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Objectives: Hepatitis E virus (HEV) is a major public health challenge due to its zoonotic potential and widespread presence in animals and humans. Swine-related occupational groups are at higher risk of HEV infection because of their work environment. This study aimed to evaluate the cost-effectiveness of hepatitis E vaccination in these groups in China. Methods: A decision tree-Markov model was utilized to determine the cost-effectiveness of two hepatitis E vaccination strategies (vaccination without screening and vaccination following screening) in a cohort of swine-related workers aged 16-60, compared with no vaccination, using a licensed recombinant hepatitis E vaccine (Hecolin) in China. We calculated the cases and deaths averted, quality-adjusted life years (QALYs) gained, and incremental cost-effectiveness ratios (ICERs) for each strategy compared to no vaccination, from a societal perspective. Willingness to pay (WTP) threshold was set at China's per capita GDP in 2023 ($12,325.24). One-way and probabilistic sensitivity analyses and scenario analyses were conducted to explore the model uncertainty. Results: Compared with no vaccination, both hepatitis E vaccination without screening and vaccination following screening significantly reduced hepatitis E outpatient cases (32.45%, 40.18%) and inpatient cases (32.45%, 40.19%), acute liver failure (ALF) cases (32.52%, 40.18%), and deaths (32.84%, 40.30%). Base-case results showed ICERs of $11,428.16/QALY and $9,830.71/QALY for these two vaccination strategies, indicating good cost-effectiveness. One-way sensitivity analysis identified the discount rate, utility in asymptomatic cases, probability of symptomatic infection, probability of incidence, and utility in outpatient cases as the most important factors affecting ICER. Probabilistic sensitivity analysis showed a 47.5% of cost-effectiveness probability for vaccination following screening, compared to 52.5% for no vaccination. Moreover, in the scenarios of vaccination at age 16-60, 20-60, 30-60, 40-60, and 50-60, vaccination without screening was cost-ineffective after age 30, and vaccination following screening was cost-ineffective after age 40. Furthermore, the ICER of hepatitis E vaccination strategies decreased with vaccine price increased. We estimated the vaccine price that achieved the cost-effectiveness of hepatitis E vaccination. At the price of $124.2 per dose of hepatitis E vaccine, vaccination without screening was cost-ineffective. At the price of $138.0 per dose, vaccination following screening was also cost-ineffective. Additionally, we compared the cost-effectiveness of completing three-dose schedule, partially completing three-dose schedule, and completing two-dose schedule. A complete course of two-dose vaccination schedule and partially completing three-dose vaccination demonstrated the cost-effectiveness, whereas a complete course of three-dose vaccination did not. Conclusion: Hepatitis E vaccination following screening for swine-related workers may be the cost-effective measures against HEV infection. Vaccination at early age and vaccine price reduction may further improve the cost-effectiveness. Additionally, during hepatitis E outbreak, a two-dose vaccination schedule may be prioritized for containment of HEV transmission.

P101 The Development of Sulfated Lactosyl Archaeol (SLA) Archaeosomes as a Vaccine Adjuvant

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Archaeosomes are liposomes traditionally comprised of total polar lipids (TPL) or semi-synthetic glycerolipids of ether-linked isoprenoid phytanyl cores with varied glycol- and amino-head groups. As adjuvants, they induce robust, long-lasting humoral and cell-mediated immune responses to multiple antigens and enhance protection in murine models of infectious disease and cancer. We have developed a semi-synthetic archaeosome formulation based on sulfated lactosylarchaeol (SLA) that can be readily synthesized yet retains strong immunostimulatory activity for induction of humoral and cell-mediated immunity following systemic immunization. Liposomes composed of sulfated lactosyl archaeol (SLA) have been shown to be a safe and effective vaccine adjuvant with a multitude of antigens in preclinical studies including hepatitis C virus E1/E2 glycoproteins, hepatitis B surface antigen (HBsAg), influenza hemagglutinin (HA), Rabbit Hemorrhagic Disease Virus (RHDV) antigens and SARS-CoV-2 spike antigens based on the ancestral strain as well as multiple variants of concern. Given the urgent need for new vaccine technologies and adjuvants in light of the COVID-19 pandemic, SLA's preclinical immunogenicity and safety profile make it a highly promising candidate. Currently, it is progressing towards Good Manufacturing Practice (GMP) manufacturing, bringing us closer to its potential application in combating infectious diseases.

P102 Leveraging the genetic diversity of the live TB vaccine M. bovis bacillus Calmette-Guerin (BCG) to identify novel components of the T7SS ESX-1

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Members of the Mycobacterium tuberculosis-complex (MTBC) express a highly conserved type-7 protein secretion system (T7SS) called ESX-1 to export virulence effector proteins that are also highly immunogenic. The live attenuated TB vaccine M. bovis bacillus Calmette-Guerin (BCG) which is comprised of a dozen genetically distinct strains all have in common however, a conserved deletion in a section of the esx-1 locus that encodes proteins of the multi-component ESX-1 secretion machinery. In this study, we re-introduced into 12 different strains of BCG a fragment of M. tuberculosis DNA containing 24 genes of the entire esx-1 locus, in a bid to reconstitute in the recombinant BCG functional ESX-1 secretion systems. We hypothesized that with the diversity of single nucleotide polymorphisms, genetic deletions and other mutations outside of the esx-1 locus in these different BCG strains, and if any of these mutations are in genes functionally important to optimal ESX-1 activity, not all 12 BCG with esx-1 re-introduced into their genomes will necessarily exhibit full ESX-1 function. We reasoned that such a genetic approach might help identify novel genes essential to the workings of this important MTBC virulence factor. Indeed, we identified 3 such BCG strains – BCG-Russia, BCG-Moreau and BCG-Tice with just such features, that we systematically interrogated to identify the molecular nature of the defects present in them that prevent restoration of ESX-1 activity.

P103 Developing The Next Generation Of Thermal Stable Mrna Vaccines Against Viral And Bacterial Pathogens

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Messenger nucleic acid (mRNA)-lipid nanoparticle (LNP) has been proven to be safe and effective during the COVID-19 vaccination campaign and represents a powerful platform technology for quick pandemic responses. Future improvement of the technology may include simplified multivalent or combination vaccine design and increased stability/shelf-life at non-frozen storage condition. Immorna's proprietary "Read-to-Use lipid nanoparticle (RTU-LNP)" delivery technology features simple bedside mixing with mRNA immediately before administration and is stable at 2-8°C for ≥ 18 months. The RTU-LNP is also resistant to elevated temperatures, such as 40°C. In addition, Immorna's RTU-LNP is universal in nature, can complex with mRNA or self-replicating RNA (srRNA) encoding any Gene-of-Interest, and thus can be stockpiled for rapid pandemic responses.
Here, we present several vaccine candidates that are in development at Immorna, including 1) JCXH-221, a bivalent COVID-19 mRNA vaccine using Immorna's proprietary 'dumbbell' design, 2) JCXH-110, a multivalent seasonal influenza/COVID combo mRNA vaccine using the 'dumbbell' design, and 3) a therapeutic Acne mRNA vaccine. Our antigen design enables vaccine multivalency with a reduced number of mRNA strands to achieve potent immunogenicity, simplified manufacturing and testing complexity as well as reduced cost of goods.
In a Phase 1 randomized, double-blinded, placebo-controlled study, the safety and immunogenicity of JCXH-221 was demonstrated at 20 µg and 50 µg per dose in subjects of 18-64 years and ≥ 65 years of age. Of the 72 healthy subjects enrolled, only low incidence of reactogenicity and very transient solicited reactions were reported. Rapid, strong, sustained neutralizing antibodies were induced against all 4 SARS-CoV-2 strains tested with clear dose dependency; and the immunogenicity appeared comparable between the two age groups at the high vaccine dose. Analysis of antigen-specific T-cell responses showed predominant IFN-γ rather than IL-4 producing T cells, indicating a Th1 profile. These results provide strong clinical proof-of-concept for Immorna's RTU-LNP delivery technology and mRNA vaccine antigen design, which de-risks the development of other multivalent or combination vaccines using the platform technology.
In preclinical studies, JCXH-110 demonstrated strong immunogenicity in mice as measured by serum hemagglutinin inhibition for three influenza viral strains and SARS-CoV-2 pseudo-neutralization. The Acne mRNA vaccine induced strong protective humoral responses that significantly reduced the intradermal inflammation caused by Cutinobacterium acnes in mice.

P104 Development and Preclinical evaluation of Novel Trivalent iNTS/Typhoid Vaccine

SoJung An, International Vaccine Institute

Salmonella infections, particularly those caused by invasive non-typhoidal Salmonella (iNTS) strains such as Salmonella Enteritidis and Salmonella Typhimurium, and typhoidal serotypes like Salmonella Typhi, represent a significant global health burden, especially in low-resource settings. These infections lead to high morbidity and mortality rates, with iNTS causing severe bloodstream infections predominantly in sub-Saharan Africa. Despite the availability of vaccines for typhoid fever, there is currently no licensed vaccine for iNTS. This study aims to address this gap by developing a trivalent vaccine that provides protection against both iNTS and typhoid fever.
The development of the trivalent vaccine involved several key steps:
•Strain Selection and OSP Production: Clinical isolates of S. Enteritidis and S. Typhimurium were utilized to produce O-specific polysaccharides (OSPs).
•Conjugation Process Optimization: Various conjugation chemistries and carrier proteins (Diphtheria toxoid (DT) and Tetanus toxoid (TT)) were tested to determine the optimal conditions for OSP conjugation.
•Immunogenicity: The immunogenicity of different conjugates was evaluated in animal models to identify the most effective formulations.
•Formulation Development: The optimal iNTS OSP conjugates were combined with the Vi-DT typhoid conjugate to create a trivalent vaccine. The formulation was further optimized with an adjuvant and assessed for immunogenicity and stability.
The study successfully identified optimal conjugation methods and carrier proteins, resulting in high-yield and immunogenic OSP conjugates. The trivalent vaccine formulation, which includes both iNTS and typhoid components, demonstrated robust immunogenic responses in preclinical tests. The formulation was also optimized for scalability and stability, with successful technology transfer to manufacturing partners.

P105 A proof-of-concept for a bivalent Paratyphoid and Typhoid vaccine development in animals.

SoJung An, International Vaccine Institute

Enteric fever, caused by Salmonella enterica serovar Typhi and serovar Paratyphi A, B, and C, remains a significant global health burden with approximately 26 million cases reported in 2016. This includes 12 million illnesses and 128,000 deaths due to typhoid and 4 million illnesses and 25,000 deaths due to paratyphoid. The highest incidence of paratyphoid is observed in South Asia. The increasing prevalence of S. Paratyphi A, particularly since the late 1990s, highlights the need for integrated prevention and control strategies, including the development of bivalent vaccines targeting both S. Typhi and S. Paratyphi A.

Building on the successful development and technology transfer of the Vi-DT typhoid conjugate vaccine, the International Vaccine Institute (IVI) initiated the development of a bivalent S. Typhi/S. Paratyphi A vaccine. The development process involved optimizing conjugation chemistries and selecting suitable carrier proteins for the S. Paratyphi A O-specific polysaccharide (OSP) conjugates. CDAP (cyanylation) and reductive amination conjugation methods were evaluated, with the CDAP method demonstrating higher immunogenicity in animal models. Proof-of-concept (POC) studies were conducted to determine optimal formulation and characterization conditions, aiming to induce equivalent or higher anti-OSP/Vi IgG titers compared to monovalent controls.

The POC studies have successfully identified the optimal S. Paratyphi A OSP conjugation process for the development of a bivalent S. Typhi/S. Paratyphi A vaccine. These findings support the next phase of process development and formulation optimization for potential clinical evaluation.

P106 Development of a broadly protective Outer Membrane Vesicle based beta coronavirus vaccine

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After the initial outbreak of SARS-CoV-2, the rapid appearance of variant strains that were able to (partially) avoid the established immune response, showcased the necessity for a more broadly protective vaccine. To this end we have been developing a new vaccine which intends to offer protection not only against SARS-CoV-2 and its variants, but also to other members of the Betacoronavirus genus, which includes MERS and SARS-CoV-1 amongst others. The vaccine is based on Intravacc's established Neisseria meningitidis derived Outer Membrane Vesicles (OMVs). In vaccine concepts based on OMV, the vesicle serves as carrier for antigens and/or directs the immune response via the intrinsic adjuvant properties of the OMV. Intravacc has exploited its Neisseria meningitidis OMV technology to display separately produced antigens from other pathogens, viral as well as bacterial, on OMV using them as carrier as well as adjuvant. Larger antigens, like Spike protein, can also be mixed with OMV, exploiting the intrinsic adjuvant properties of the OMV. We use both strategies to develop OMV based vaccines. Our OMV based subunit vaccine against SARS-CoV-2, containing the ectodomain of the Wuhan Spike protein was shown to be safe and immunogenic in a FIH study, when administered intranasally. To broaden the induced protection of our SARS-CoV-2 vaccine we aim to mix a chimeric Spike protein or an RBD construct with OMV decorated with broadly protective Betacoronavirus T-cell epitopes.

Several Chimeric Spike proteins or RBD constructs were designed and expressed in CHO cells. Subsequently, BALB/c mice were immunized twice intranasally with the combined OMV-antigen vaccines. Neutralizing antibodies specific against SARS-CoV-1, SARS-CoV-2 (Omicron BA.5 strain) and MERS were detected in serum samples by microneutralization assay. Results showed that the combination of OMVs with candidate AV065, a composite of four RBDs originating from different sarbecovirus subgenus strains, yielded the highest VN titers. It protected well against both SARS-CoV-1 (GMT=244) and SARS-CoV-2 (GMT=780) but showed low neutralizing titers against MERS (GMT=56), attributable to the fact that no MERS RBD was included in the construct. Studies in which hamsters, ferrets and rabbits are immunized with a combination of OMVs, AV065 and one of several MERS constructs and subsequently challenged with SARS-CoV-1, SARS-CoV-2 (Omicron BA.5 strain) or MERS, are ongoing. In follow studies, we aim to assess the immune response of AV065 in combination with OMV decorated with broadly protective Betacoronavirus T-cell epitopes and of novel RBD construct composed of 6 RBDs originating from different sarbecovirus as well as merbecovirus subgenus strains.

P107 Artificial and Human Intelligences Combined: Removal of Inhibitory Sequences Improves Vaccine Immunogenicity and Efficacy

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Computational vaccinology has enabled the rapid development of new vaccines, with applications in both infectious disease and oncology. Most approaches use in silico tools predicting HLA Class I and/or HLA Class II restricted epitopes to identify highly immunogenic candidate antigens from the genome of pathogens, or to develop epitope-based immunotherapies such as personalized cancer vaccines. T cell epitope prediction tools mainly focus on modeling the interaction between putative epitopes and HLA molecules but lack the ability to assess how the peptide-MHC (pMHC) complex interacts with T cell receptors (TCR) and whether these epitopes are likely recognized by effector T cells (Teff) or regulatory T cells (Treg). Our group recently discovered that the prediction of epitopes for vaccines is improved when removing T cell epitopes homologous to self-epitopes at the TCR interface, as T cells that recognize these cross-conserved "self-like" epitopes may be tolerant to them or actively tolerogenic. Preclinical studies have shown identifying these self-like epitopes is an important step for the development of vaccines against infectious agents and cancer.

We have developed the JanusMatrix tool to assess pMHC cross-conservation with self-sequences, allowing for the in silico discrimination of immune activating (Teff) and immune dampening (Treg) T cell epitopes. JanusMatrix was employed to identify putative Treg epitopes from influenza (H7N9 HA) and self-antigens (Factor V). These epitopes were subsequently confirmed to suppress Teff responses and activate Tregs when tested in vitro with healthy donor PBMCs. Immune engineering experiments with H7N9 HA showcased that disruption of the validated Treg epitope improved antigen immunogenicity over the wild-type antigen, and enhanced vaccine efficacy in an H7N9 lethal challenge study. In addition, our group demonstrated that inhibitory (suppressor) neoantigen sequences identified in a mouse cancer cell line (CT26) dampened the immune response to a neoantigen-based vaccine by 5-fold and that they should therefore be identified and excluded from cancer vaccine designs. To further exemplify the benefit of JanusMatrix in oncology, we performed retrospective studies of cancer mutanomes highlighting improved prediction of survival when removing putative Treg neoepitopes from neoepitope burden calculations.

Ongoing efforts in pandemic preparedness and precision medicine has highlighted the need for rapid design and manufacturing of novel vaccines. Immunoinformatic pipelines that can rapidly scan the genome of pathogens or cancer cells and identify the "best" antigens are in high demand. We have developed web-based vaccine design platforms for infectious disease and cancer immunotherapy that enable the identification of highly immunogenic antigens and the removal of deleterious sequences that may curtail vaccine efficacy. We showed in in vitro and in vivo studies that screening, removing, and modifying suppressor epitopes improves vaccine immunogenicity and efficacy. Usage of these platforms for vaccine development will enable the generation of better and safer vaccines.

P108 Cancer Vaccine Adjuvant Name Recognition from Clinical Trial Data using Large Language Models

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Adjuvants are substances added to vaccines to modify and improve their effects, either by enhancing the body's immune response or by reducing side effects. By stimulating the immune system and increasing antibody production, adjuvants significantly boost the efficacy of cancer vaccines. Identifying adjuvant names in cancer vaccine clinical trial data is essential for advancing research and improving treatment outcomes. However, manually curating adjuvant names from the rapidly growing biomedical literature is challenging.

This study investigates the automatic identification of vaccine adjuvant names using Generative Pretrained Transformers (GPT), a large language model (LLM), a form of artificial intelligence. We used state-of-the-art language models, specifically GPT-4, to tackle these challenges. We analyzed two distinct subsets of cancer vaccine trials from https://clinicaltrials.gov/. The first subset included 97 clinical trial records annotated by the researchers of the AdjuvareDB website, serving as the gold standard. GPT-4 achieved an impressive F1-score of 81.9% on this dataset. The second subset consisted of 430 cancer vaccine clinical trials, manually curated by our team to cover a diverse range of adjuvant information and their contextual applications. GPT-4 reached an F1-score of approximately 81.0% on this dataset, with a precision of 92.5% and a recall of 72.1%. From this set, we identified nine new adjuvants not included in the AdjuvareDB, such as Matrix-M1, GLA-SE, and Imiquimod.

Our key findings show that GPT-4 is particularly good at recognizing adjuvant names, even rare and novel ones, which are often difficult for traditional named entity recognition approaches. The model's high precision indicates its effectiveness in correctly identifying adjuvant names. However, there is room for improvement in capturing all relevant adjuvant names. Additionally, the model showed robustness in distinguishing adjuvant names from other biomedical entities, reducing false positives and improving overall reliability.

In conclusion, this study highlights the potential of Generative Pretrained Transformers in advancing cancer vaccine research through accurate and efficient adjuvant name recognition from clinical trial data. By leveraging the power of GPT-4, we demonstrate a promising approach that bridges the gap between unstructured clinical trial data and actionable insights, ultimately contributing to the progress of cancer immunotherapy. Future studies will focus on expanding beyond cancer vaccine adjuvants to include vaccines for infectious diseases, and comprehensively processing all records from clinicaltrials.gov instead of subsets. Additionally, we aim to extend our search to biomedical literature in PubMed and PubMed Central. Technically, we plan to utilize open-access large language models, such as LLaMA3 and Google's models, to fine-tune our models with sentences related to vaccines and adjuvants, enhancing their generalizability and effectiveness across various contexts.

P109 Bioprocess improvement to increase manufacturing yield using a fixed-bed bioreactor

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Improving the bioprocess to increase manufacturing yield of a vaccine is crucial in reducing the cost of goods of a product. The goal of this study was to evaluate the potential of using a fixed-bed bioreactor to increase the yield of a vaccine, using a Lassa vaccine as a prototype. This Lassa vaccine candidate is a replication-competent recombinant measles virus expressing the Lassa virus nucleoprotein and glycoprotein precursor (MV-LASV). MV-LASV was manufactured using Vero cells on a microcarrier process platform at up to 10 L bioreactor scales. We have successfully established MV-LASV production in a fixed-bed bioreactor, and demonstrated a volumetric yield increment when a higher compaction bioreactor was used. Finally, we have further increased virus production when the bioreactor was operated in a perfusion mode. In conclusion, fixed-bed bioreactors have a great potential to significantly increase the production of measles virus vector. These bioreactors could significantly improve virus production of vaccines that use adherent cells.

P110 An intranasal Newcastle disease virus (NDV)-based SARS-CoV-2 Omicron vaccine elicits protective immune responses in mice and hamsters

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Many lives have been saved thanks to the rapid development of coronavirus disease 2019 (COVID-19) vaccines during the early phases of the pandemic. The majority of COVID-19 vaccines currently in use are delivered intramuscularly. While intramuscular administration typically induces high levels of serum antibodies preventing severe disease, failing to induce immunity in the respiratory tract may lower the efficacy against asymptomatic COVID-19 infections and transmission. A next-generation of mucosal vaccines is necessary to protect the – often neglected – more vulnerable and immunocompromised segments of the population. Here, we developed an intranasal Newcastle disease virus (NDV)-based vaccine expressing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike stabilized in its pre-fusion conformation (NDV-HXP-S). As new variants of concern (VOCs) with increased immune escape emerged, we updated the NDV-HXP-S vaccine to target the Omicron variants BA.1 and XBB.1.5. We demonstrated, that the immune responses from intramuscular vaccination with mRNA-LNPs is enhanced by the intranasal NDV-HXP-S boosting, resulting in improvement of serum neutralization titers and induction of mucosal immunity in mice. Furthermore, one or two intranasal immunizations with NDV-HXP-S expressing the XBB.1.5 spike induced protective immunity in naïve mice. In addition, intranasal vaccination with NDV-HXP-S XBB.1.5 protected hamsters from variant matched infection. We found significantly reduced virus shedding in vaccinated hamsters, providing complete protection to naïve co-housed animals in a direct contact transmission study. Taken together, this data demonstrates that intranasal vaccination or boosting with variant adapted NDV-HXP-S induces protective mucosal immunity and mitigates viral spread in pre-clinical animal models.

P111 Rapid Vaccine Development Projects to prepare for Pandemics in Republic of Korea

Mi Young Kim, Korea Disease Control and Prevention Agency

As the key to responding to a pandemic is speed, countries around the world are competing to develop mRNA vaccines after COVID-19. With major developed countries and international organizations such as the CEP) are investing heavily in mRNA vaccine technology with the goal of developing a customized vaccine within 100 days of the outbreak of the pandemic.

Korean government also established a mid- to long-term comprehensive plan to prepare for future pandemics In May last year. One of the key goals is to have the capacity to develop a vaccine within up to 100/200 days in the event of a pandemic. In order to secure mRNA technology that can accelerate development speed, we have set a goal of commercializing domestically produced vaccines by 2028.

The goal of setting the COVID-19 vaccine is to continue administering the COVID-19 vaccine in the future to protect high-risk groups such as those aged 65 or older. Also, COVID-19 mRNA vaccine if successful, we will have a platform technology such as mRNA synthesis, modification, and delivery technology. By utilizing the management procedures as is, we will have the ability to quickly respond to new viruses.

The government also support project expenses contributions to research basic infrastructure such as preclinical and clinical studies and rapid development technologies for candidate materials such as priority infectious disease (Influenza, Lassa etc.) vaccines developed by pharmaceutical companies and other private companies to ensure safety, etc. in advance of the outbreak of a pandemic. Prototype vaccines of the priority pathogens will be developed in advance and stored in vaccine libraries.

To achieve the goal, we provide bold R&D budget support to promising companies. Next-stage clinical trials for excellent companies with potential through evaluation at each stage of development from non-clinical to clinical Test costs will be supported. The 'mission-oriented R&D' strategy, which supports all stages from productization to commercialization to solve national problems such as pandemic response, is becoming a global trend. In addition, the government focuses on eliminating regulations and providing technical and institutional support so that private companies can develop vaccines smoothly.

The Korea Disease Control and Prevention Agency plan to create a pan-ministerial integrated support system to support mRNA vaccine and rapid development system to periodically check progress and quickly resolve complex regulations and on-site difficulties in the development process.

P112 Heterologous prime/boost immunization with Newcastle disease virus and modified vaccinia virus Ankara vectors as an improved and effective strategy against SARS-CoV-2 infection

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Effective vaccination strategies quickly adapted to new emerging viruses and capable of inducing robust, broad and durable antigen-specific protective immune responses are necessary. In particular, viral vectors are powerful vaccine platforms against emerging viruses like severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this study, we studied the immunogenicity and efficacy against SARS-CoV-2 infection triggered in transgenic K18-hACE2 mice by different prime/boost vaccination regimens (mucosal and systemic) comprising two vaccine candidates based on Newcastle disease virus (NDV) and Modified vaccinia virus Ankara (MVA) vectors expressing a prefusion-stabilized SARS-CoV-2 spike (S) protein (NDV-HXP-S and MVA-S(3P), respectively). The results showed that the vaccine regimens fully protected K18-hACE2 mice from morbidity and mortality caused by SARS-CoV-2 infection, with the sequential intranasal administration of NDV-HXP-S followed by an intramuscular inoculation of MVA-S(3P) resulting in no detectable viral replication (mRNA and infectious virus) in respiratory tissues, only mild and occasional lung histopathological lesions, and reduced levels of pro-inflammatory cytokines in the lungs. High titers of binding anti-S IgG antibodies, with a Th1 bias, and neutralizing antibodies against the ancestral Wuhan strain of SARS-CoV-2 and different variants of concern were detected in all vaccinated animals. Moreover, antigen-specific CD4+ and CD8+ T-cellular immune responses were induced, with the NDV-HXP-S/MVA-S(3P) combination favoring higher magnitude of S-specific CD8+ T cells. This research demonstrates the potential of heterologous NDV/MVA prime/boost vaccine strategies for the generation of potent and broad SARS-CoV-2-specific humoral and T-cellular immune responses, capable of preventing SARS-CoV-2 infection and disease. The use of such combined prime/boost vaccination regimen should be explored for durability and against other emerging or re-emerging viruses for which effective vaccines are not available.

P113 Vaccine candidates based on the poxvirus MVA vector expressing SARS-CoV-2 prefusion-stabilized spike proteins of the Wuhan, Beta, and Omicron BA.1 variants elicit robust humoral and T-cellular immune responses and protect K18-hACE2 mice against SARS-CoV-2 Omicron infection

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Despite the decrease in mortality and morbidity due to SARS-CoV-2 infection, the worldwide incidence of infections due to Omicron subvariants of SARS-CoV-2 continue unabated. The mutations acquired by these subvariants, mainly concentrated in the receptor-binding domain (RBD), have caused a shift in infectivity and transmissibility, leading to a loss of effectiveness of the first authorized COVID-19 vaccines, among other reasons, by neutralizing antibody evasion. Hence, the generation of new vaccine candidates adapted to Omicron subvariants is of special interest to overcome this immune evasion. Here, an optimized COVID-19 vaccine candidate, termed MVA-S(3P_BA.1), was developed using a modified vaccinia virus Ankara (MVA) vector expressing a full-length prefusion-stabilized SARS-CoV-2 spike (S) protein from the Omicron BA.1 variant. MVA is currently an approved vaccine against smallpox and monkeypox. The immunogenicity and efficacy induced by MVA-S(3P_BA.1) were evaluated in mice in a head-to-head comparison with the previously generated vaccine candidates MVA-S(3P) and MVA-S(3Pbeta), which express prefusion-stabilized S proteins from Wuhan strain and Beta variant, respectively, and with a bivalent vaccine candidate composed of a mixed combination of MVA-S(3P) and MVA-S(3P_BA.1). The results showed that all four vaccine candidates elicited, after a single intramuscular dose, protection of transgenic K18-hACE2 mice challenged with SARS-CoV-2 Omicron BA.1, as confirmed by reduction on viral loads, histopathological lesions, and levels of proinflammatory cytokines in the lungs. The protected mice also elicited anti-S IgG and neutralizing antibodies against various Omicron subvariants, with MVA-S(3P_BA.1) and the bivalent vaccine candidate inducing the highest titers. Additionally, a single intranasal immunization in C57BL/6 mice with the four vaccine candidates induced activation of systemic and mucosal S-specific CD4+ and CD8+ T-cell and of humoral immune responses, with the bivalent vaccine candidate inducing broader immune responses, defined by levels of antibodies against the ancestral Wuhan strain and different Omicron subvariants. These results highlight the use of MVA as a potent and adaptable vaccine vector against new emerging SARS-CoV-2 variants, as well as multivalent MVA vaccine candidates against different pathogens.

P114 Potent immunogenicity and broad-spectrum protection potential of dissolvable-microneedle array patch-based COVID-19 DNA vaccine candidates

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In the face of the ongoing COVID-19 pandemic, the development of effective vaccines is of utmost importance. A recent study has shown promising results in the development of potent COVID-19 DNA vaccine candidates using dissolvable microneedle array patch (D-MAP) technology. These vaccines have the potential to provide broad-spectrum protection against SARS-CoV-2 variants, addressing a critical need in the fight against the virus.

Through the use of engineered plasmids encoding receptor-binding domain chimeras from different variants and microneedle array patches for vaccine delivery, the study assessed the immunogenicity of these constructs. The results showed that intramuscular administration of the DNA constructs led to high levels of anti-RBD-specific IgG responses, with the microneedle array patches further enhancing the immune response.

Of particular significance was the finding that a D-MAP loaded with a DNA construct outperformed an inactivated SARS-CoV-2 virus vaccine in generating specific effector and memory T cells. Additionally, the D-MAP-induced T lymphocytes with unique homing patterns compared to intramuscular injection, and its antisera demonstrated high neutralization efficacy against SARS-CoV-2 pseudoviruses, effectively protecting mice from variants challenge.

In conclusion, the study suggests that D-MAP-based DNA vaccines encoding chimeric RBDs hold great promise as COVID-19 immunization candidates. The demonstrated potent immunogenicity and broad-spectrum protection potential underscore the importance of further research and development to advance these candidates toward clinical use. This research represents a significant step forward in the global effort to combat the COVID-19 pandemic.

P115 Thermoresistant flagellin adjuvanted cancer vaccine synergizes with photothermal therapy of breast cancer

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Cancer immunotherapy, leveraging the immune system to target and eradicate cancer cells, has profoundly transformed cancer treatment paradigms. Among these approaches, cancer vaccines are notable for their capacity to elicit antigen-specific immune responses and establish long-term immune memory. Despite the promising profiles, cancer vaccines often struggle with inducing robust and sustained anti-tumor responses due to tumor heterogeneity, immunosuppressive tumor microenvironments (TMEs), and immune tolerance mechanisms. This study explores a novel combinatorial strategy to enhance vaccine efficacy, integrating photothermal therapy (PTT) with a flagellin-adjuvanted cancer vaccine (FlaB-Vax) and immune checkpoint inhibitors (ICIs). We developed a targeted liposomal formulation (TLIF) encapsulating indocyanine green (ICG) and flagellin to optimize PTT conditions, which induces optimal immunogenic cell death (ICD) liberating tumor specific antigens (TSAs) for epitope expansion. Using the DD-Her2/neu tumor model, we assessed therapeutic efficacy of a combinatorial immunotherapy regimen comprised of FlaB-Vax, TLIF-mediated PTT and immune checkpoint inhibitor. Employing a bilateral tumor implantation model, we evaluated the abscopal effect to measure systemic immune responses. FlaB-Vax aimed to trigger tumor associated antigen (TAA)-specific immune responses. TLIF-PTT aimed to lessen tumor burden and induce ICD-mediated TSA liberation. Our findings reveal that combining TLIF-mediated PTT with FlaB-Vax significantly enhances long-term survival and induces robust antigen-specific immune responses along with longer lasting immune memory. The addition of anti-PD-1 therapy further improves long-term relapse-free survival, highlighting the potential of this combinatorial approach to induce durable antitumor immunity and prevent cancer recurrence at the long run.

P116 ARMY LIPOSOME FORMULATION CONTAINING QS-21 MODULATES PROINFLAMMATORY MILIEU AND INNATE ANTI-VIRAL FACTORS RENDERING HUMAN MONOCYTE-DERIVED MACROPHAGES LESS PERMISSIVE TO HIV-1 INFECTION

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Adjuvants are critical components of many vaccine formulations. We have created a family of adjuvants known as Army Liposomal Formulations (ALF) consisting of saturated phospholipids, synthetic monophosphoryl lipid A and either 43 mol% or 55 mol% (ALF55) cholesterol. An additional immunostimulant the saponin QS21 is incorporated into ALF55 to generate ALFQ, a highly promising adjuvant that has been utilized in three completed Phase 1 human clinical trials, four ongoing trials, and with nine trials in the pipeline. ALFQ has profound immune-stimulatory responses in human monocyte-derived macrophages (MDM). ALF55 comprises small unilamellar vesicles (SUVs, 50nm), while ALFQ is polydisperse with mainly large-giant unilamellar vesicles (GUVs, 50nm to ≥ 30,000nm in diameter). The uptake of GUVs by MDM was time-dependent and could be observed using fluorescent-labeled lipids. Uptake was seen as early as 1 hour and by 18-24h, MDMs were loaded with GUVs. MDMs are highly permissive to HIV-1 infection, potentially due to the downregulation of innate factors during the differentiation process. We evaluated whether exposure of MDM differentiated from PBMCs of HIV-1 seronegative donors (RV229B, WRAIR Protocol #1386) to ALFQ could restrict HIV-1 infection. Primary human monocytes were differentiated into MDM following *in-vitro* culture in media supplemented with M-CSF. The MDMs were infected with purified primary HIV-1 and subsequently exposed to ALFQ or alternatively, MDMs were exposed to ALFQ and then infected with HIV-1. HIV-1 infection was determined by flow cytometry. Pre- and post-treatment of MDMs with ALFQ resulted in a significant decrease in HIV-1 infection and this was dependent on the time of exposure of MDMs to ALFQ. ALFQ upregulated MHC Class II and CD86 molecules on the surface of MDM and downregulated CD163, CD206, and CD14. In addition, MDMs cultured with ALFQ induced higher levels of proinflammatory cytokines, notably IFN-gamma and IL-1beta, compared to MDMs cultured with ALF55. ALFQ and not ALF55 upregulated innate anti-viral factors notably APOBEC3A and IFI16, leading to decreased HIV-1 permissivity. This effect was lost by knockdown with APOBEC3A siRNA. Our findings highlight a relationship between innate immune activation, proinflammatory milieu, and upregulation of anti-HIV proteins. Induction of these responses can switch the HIV-1 permissive MDM into a more refractory phenotype. Thus, ALFQ serves not only as a robust and potent adjuvant when present in vaccines but could also serve as a potential therapeutic agent against HIV-1.

P117 Lipid formulated plasmid DNA drives robust innate immune activation to promote adaptive immunity

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Gene-vectored vaccines have grown in importance over the past several years, exemplified by exemplified by the approvals of lipid nanoparticle-formulated mRNA (mRNA-LNPs), viral-vectored vaccines, and a jet-delivered DNA vaccine for SARS-CoV-2. However, understanding the differences between lipid-based formulations for delivering DNA and mRNA-LNPs in particular has not been studied, and characterization of lipid-formulated DNA could build upon current genetic delivery approaches. Here, we study a lipid-based plasmid DNA vaccine formulation which we demonstrate induces potent innate and adaptive immunity at low doses with similar potency to mRNA-LNPs and adjuvanted protein. Using an influenza virus hemagglutinin-encoding construct (HA), we show that lipid-formulated plasmid DNA drives potent inflammation dependent on the cGAS-STING-TBK1 pathway but independent of TLR9. Priming with a HA-expressing lipid-formulated DNA construct demonstrated robust activation in migratory DC (mDC) subpopulations and significant upregulation of mDCs and neutrophils. Transcriptomics elucidated activation and upregulation of pro-migration factors among multiple innate immune populations after priming with lipid-formulated DNA. HA-expressing lipid-formulated DNA uniquely induced superior HA-specific CD8+ T cell responses relative to other platforms. HA-expressing lipid-formulated DNA additionally induced robust germinal center responses attenuated in frequency to mRNA-LNPs and adjuvanted protein, but with humoral immune responses equivalent in titer, durability, and function. Extending these findings to an additional pathogen antigen, a SARS-CoV-2 spike-encoding lipid-formulated DNA construct elicited protective efficacy comparable to spike mRNA-LNPs. Thus, this study identifies priming mechanisms and characterizes immune phenotypes after lipid-formulated DNA immunization, suggesting additional avenues for vaccine development.

P118 Virus-free Recombinant VLP Vaccine for Polio Virus Eradication

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Global eradication of polio is at hand by a combined use of live attenuated oral polio vaccine (OPV) and inactivated polio vaccine (IPV). Despite continued efforts, however, poliovirus remains endemic in some regions such as Pakistan and Afghanistan. Because of rare occasions of adverse effects - circulating vaccine-derived poliovirus (cVDPV) and Vaccine-associated Paralytic Polio (VAPP)-, IPV have replaced OPV. Uncertainties remain, however, on IPV's role as part of a global polio eradication strategy in impacting on fecal- oral transmissions in developing countries. Additionally, all polio vaccines in current use relies on cell culture in high-level biosafety containments. After eradication, a stockpile of virus-free polio vaccine (VfPV) is required to keep the globe as a polio-free status. Replacing the pre-existing cell-culture of infectious viruses, a 'virus-free' recombinant production is highly recommended as a low-cost vaccine platform.
This study aims to overcome the limitations of conventional cell-culture based polio vaccines by developing a bacterially production of Virus-Like Particle (VLP) vaccine. A major drawback of bacterial systems is that antigens are often produced as insoluble aggregates hampering mass production. A novel chaperone system – RNA-based chaperone (Chaperna) - was adopted to overcome this technical hurdle to ensuring that vaccine antigens are produced as soluble and immunologically relevant conformation. Thus, three major surface proteins, VP0, VP1, and VP3, were produced individually as soluble form, and subsequently assembled into VLP in vitro. The physicochemical properties of these VLPs were confirmed by tunneling electron microscopy (TEM) and dynamic light scattering (DLS). The 'D-antigen' content, which indicates the potency of the poliovirus vaccine, was evaluated by ELISA assay. This innovative approach aims to contribute to global poliovirus eradication by delivering a safe, effective, low-cost vaccine to the affected area. The project was supported in part by RIGHT Foundation and seeks further support from international organizations to fulfill its goal.

P119 Bacterially Production of Recombinant Pentamer Scaffolded West Nile Virus Vaccine

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West Nile Virus (WNV) is an arthropod-borne pathogen that poses a significant threat to human health, potentially leading to life-threatening conditions. This virus belongs to the family Flaviviridae and the genus Flavivirus including dengue, Zika, and Japanese encephalitis viruses. Although there are WNV vaccines designed for veterinary use, no vaccines have been developed for human application. This presents a significant gap in public health protection, given the potential severity of WNV infections in humans. To address this gap, this study introduces a prototype WNV recombinant subunit vaccine candidate which specifically targets the ED3 region of the viral envelope protein.
West Nile virion is assembled into icosahedral assembly of envelope proteins (E) where immunologically important domain III (EDIII) is placed at the edge of the dimer, converging to a pentamer interface. Cholera toxin B (CTB) was employed as dual purpose: structural scaffold for the five-fold symmetry of EDIII and built-in adjuvant. Thus, harnessed with RNA-dependent chaperone ('Chaperna'), the CTB-ED3 fusion antigen, was expressed in E. coli predominantly as soluble form pre-assembled into pentamer. The protein was purified by affinity chromatography (IMAC) followed by size-exclusion chromatography (SEC). Pentamer formation is crucial as it mimics the natural structure of viral proteins, enhancing the immune response. All experiments involving neutralization assay with infectious virus was conducted in the BSL3 containment of Korea Disease Control and Prevention Agency (K-DCA). Upon immunization of mice, the purified antigen induced robust neutralizing the virus, comparable to formalin-inactivated viral vaccine.
This approach, which avoids the need for high-level biological containment for virus culture, suggests that a bacterial production platform could offer equitable access to a low-cost vaccine for endemic areas in low- and middle-income countries (LMICs). By leveraging this innovative approach, the development of a human vaccine against WNV could fill a critical gap in global public health, providing a significant tool in the fight against this potentially severe virus.

P120 A Novel Green Technology Platform for Inactivated Vaccines: EGCG (Epigallocatechin-3-gallate)-Inactivated Zika Virus Vaccine

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Zika virus (ZKV) is a reemerging flavivirus that causes severe neurological complications such as microcephaly in newborns through vertical transmission and Guillain-Barré syndrome in adults. Traditionally, toxic chemical agents such as formalin (FA) have been utilized for the preparation of inactivated vaccines or toxoids. However, FA extensively modifies vaccine antigens, adversely affecting their immunogenicity profiles and often compromising their protective efficacy and safety. Consequently, formalin-inactivated (FAi) Zika vaccine shows very low efficacy in pre-clinical evaluation. Here, we introduce Epigallocatechin-3-gallate (EGCG), a major catechin from green tea, as a novel inactivating agent for ZIKV, aiming to overcome the limitations of FAi vaccines.
EGCG is known to inhibit viral entry and cell attachment of enveloped viruses by binding to envelope proteins and viral membranes inducing cross-linking without extensive antigen denaturation. This mechanism preserves antigenic structure while enhancing immunogenicity. We demonstrated that EGCG irreversibly inactivates ZIKV while preserving its antigenic integrity. The inactivating process was optimized by treating ZIKV with varying concentrations of EGCG under controlled pH conditions, and the results showed a complete and irreversible loss of virus infectivity.
Immunogenicity assessments were conducted in murine models to compare the immune response elicited by EGCG-inactivated (EGCGi) ZIKV and FAi ZIKV. Mice were immunized with the inactivated viruses, and serum samples were collected to measure ZIKV-specific IgG antibody responses. The results revealed that the EGCGi ZIKV vaccine elicited significantly higher neutralizing antibody titers than the FAi counterpart. Neutralization assays further confirmed that these antibodies effectively neutralized ZIKV, suggesting that the inactivated virus retains critical epitopes necessary for immune recognition and responses. A notable finding was the dramatic isotype switching observed with the EGCGi ZIKV vaccine, resulting in a balanced Th1/Th2 response, which is crucial for comprehensive viral immunity. This balanced response ensures robust protection and reduces disease severity. Our study demonstrates that EGCG offers a robust inactivated vaccine platform, providing a safer and more efficient alternative to conventional vaccine strategies. The green technology platform could be extended for improving the efficacy and safety, and the proven doss-sparing effects could contribute to equal access to low-cost viral vaccines.

P121 Engineering E. coli Nissle 1917 for Enhanced Mucosal Vaccine Development: Stable Expression of HIV-1 MPER in Outer Membrane Protein F and Outer Membrane Vesicles

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Mucosal vaccines can induce protective immune responses directly at infection sites. Utilizing bacterial surface proteins to display recombinant bacterial or viral epitopes holds substantial promise for vaccine development. Additionally, the outer membrane vesicles (OMVs) of probiotic Gram-negative bacteria, which contain immunogenic viral epitopes, have the potential to enhance the immunogenicity of recombinant probiotic bacteria. This dual expression on the surface and within OMVs underscores their pivotal role in the advancement of effective vaccines. We utilized CRISPR/Cas9 gene editing to modify a probiotic strain of E. coli Nissle 1917 (EcN) to stably express the HIV-1 envelope (gp41) membrane-proximal external region (MPER) within the bacterial outer membrane protein OmpF. It was shown that the MPER epitope was successfully integrated into the surface-expressed OmpF, and the expression of the protein remained stable under non-selective conditions for at least 30 consecutive subcultures.

The study measured MPER expression in the recombinant EcN-MPER lysate, reporting approximately 0.143 pg of the protein per CFU. Furthermore, whole-cell ELISA of the EcN-MPER highlighted differences in antigenicity between live and heat-killed recombinant bacteria. MPER expression in viable bacteria is approximately 7.0×10^{-4} pg per CFU, while in heat-killed EcN-MPER, it is around 4.0×10^{-3} pg per CFU.

The MPER epitope was also detected in the OMV fraction of EcN-MPER. The OMV fraction was examined using Dynamic Light Scattering (DLS) and transmission electron microscopy (TEM), revealing that OMVs of EcN-MPER ranged from approximately 15 to 75 nm in diameter.

The successful integration and stable expression of the MPER epitope in E. coli Nissle 1917, both on the bacterial surface and within OMVs, offer a promising strategy for mucosal vaccine development. This approach enhances antigen presentation and immunogenicity, underscoring its potential for advancing live probiotic vaccines. Future work should focus on evaluating the in vivo efficacy of this system.

P122 VFI Adjuvants for Global Health

Falko Apel, Vaccine Formulation Institute

The Vaccine Formulation Institute (VFI) is an R&D institute based in Switzerland and dedicated to the development of clinically relevant adjuvants and to the provisionof these adjuvants under open access terms to the vaccine community. VFI has developed a portfolio of adjuvants comprising Sepivac SWETM (a squalene-in-water emulsion), as well as three new saponin-based adjuvants: SQ (squalene-in water emulsion with QS21 saponin), LQ (liposome-based adjuvant with QS21 saponin) and LMQ (liposome-based adjuvant with a TLR4 ligand and QS21 saponin). VFI adjuvants are compatible with various antigen types and have established their efficacy across a diverse range of indications and preclinical models.

The three VFI saponin-containing adjuvants SQ, LQ and LMQ not only drive functional antibody responses but also induce Th1-biased cellular immune responses. The opportunity to compare these saponin-containing adjuvants simultaneously in head-to-head comparative studies ensures optimal antigen-specific downselection for selecting a lead adjuvanted vaccine candidate. VFI adjuvants LQ, SQ and LMQ are now available at Good Manufacturing Practice (GMP) grade under open-access terms (i.e., without any licencing agreement required) for vaccine developers and manufacturers worldwide, to support the clinical development of their adjuvanted vaccines.

P123 Pandemic Fatigue and Vaccine Hesitancy among People Who Have Recovered from COVID-19 Infection in the Post-Pandemic Era: A Cross-Sectional Study in China

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Background: At present, the COVID-19 pandemic is still ongoing globally and the virus is constantly mutating. The herd immunity barrier established by past infections or vaccinations gradually weakens and reinfections occur. Therefore, it is essential to understand the status and correlates of pandemic fatigue and vaccine hesitancy toward the next dose among people who have recovered from COVID-19 during the post-pandemic era.

Methods: An anonymous cross-sectional survey was conducted in China from 4 July to 11 August 2023, nearly 6 months after the last large-scale nationwide infection. Basic sociodemographic characteristics, health-related factors (smoking, drinking, and chronic disease history), COVID-19 vaccination history, and self-reported long COVID were obtained as potential covariates. Pandemic fatigue of COVID-19 was assessed by the Pandemic Fatigue Scale and divided into "Low (6-18 points)", "Moderate (19-30 points)", and "High (31-42 points)" levels based on the total scores (6-42 points). A series of logistic regression models were performed to examine the association between pandemic fatigue and vaccine hesitancy toward the next dose of COVID-19 vaccines via crude relative risks (cORs) and adjusted relative risks (aORs) with 95% CIs.

Results: According to our results, of the 2942 participants who have recovered from COVID-19, 1242 (42.2%) were hesitant (unwilling or not sure) to receive the next dose of COVID-19 vaccines. Those who are single, non-smokers, have low perceived severity of reinfection, did not report long COVID symptoms, and have a longer time since their last COVID-19 vaccination were more likely to be vaccine-hesitant ($p < 0.05$). 1166 (39.6%) and 580 (19.7%) participants reported moderate and high levels of pandemic fatigue, respectively. The average score on the Pandemic Fatigue Scale was 21.67 ± 8.86 (25.26 ± 8.52 in the vaccine-hesitant group vs. 19.04 ± 8.17 in the vaccine-accepting group), and the scores of all items in the vaccine-hesitant group were significantly higher than those in the vaccine-accepting group. Additionally, compared to the low level of pandemic fatigue, the higher the pandemic fatigue level among people who have recovered from COVID-19, the more likely they were to be hesitant to receive the next dose of the COVID-19 vaccines (moderate: aOR = 2.94, 95% CI: 2.46-3.53; high: aOR = 6.88, 95% CI: 5.49-8.64).

Conclusion: Overall, more than 40% of the recovered participants were unwilling or uncertain about the next COVID-19 vaccine dose, with varying degrees of pandemic fatigue. Pandemic fatigue is a potentially relevant factor for vaccine hesitancy and may hinder the translation of vaccination intention into behavior. Considering the ongoing reinfection situation, implementing a health education plan to reduce pandemic fatigue and prioritizing vaccination issues for people who have recovered from COVID-19 may be key to promoting the reduction of the COVID-19 disease burden and ensuring the health and well-being of the population.

P124 Transient innate immune responses induced by DNA/LION™ vaccine shape long-lasting immunity against different antigens

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Background

Induction of durable adaptive immunity requires combinations of both cellular and humoral immune responses. We evaluated a novel DNA/nanoparticle formulation vaccine for its ability to deliver DNA and monitored innate responses and adaptive cellular and humoral immune responses in rhesus macaques (RM).

Methods

RM were vaccinated via the IM route using SARS-CoV-2 Spike or HIV Env DNA formulated with a cationic nanocarrier (Lipid InOrganic Nanoparticle; LION™). Innate and vaccine-specific immune responses were monitored in blood and lymph nodes (LN) using plasma proteomics, flow cytometry and antibody-based assays.

Results

The DNA/LION vaccine induced strong and long-lasting (>2 yrs) antigen-specific humoral and cellular immunity. Interestingly, vaccine-induced T cell responses were predominantly CD8+ cells, in contrast to other DNA vaccination regimens. The vaccine induced a rapid (4 hrs) transient cytokine/chemokine response with peak by 24hrs in plasma, including biomarkers associated with cell proliferation, trafficking and LN activation. Immunophenotyping showed increased proliferation and dynamic changes between blood and lymph nodes of myeloid-derived, dendritic, B and T cell subsets monitored at days 1, 3, 8, 22 after vaccination. Significant increases in proliferating myeloid cell subsets were found to associate with CCL13/MCP-4, CXCL12/SDF-1a, FLT3L, G-CSF, IL-9 increases supporting their functional connections. We also found significant changes in biomarkers associated with LN and germinal center (GC) cell activation including CXCL13, FLT3L, IL-7, and IL-6, associated with CD4 Tfh, GC-Tfh, CD8 Tfh cell changes, and CXCL12 with B cell changes. In vitro Activation-Induced Marker (AIM) assay revealed strong antigen-specific responses in draining LNs. Thus, DNA/LION vaccination resulted in great induction of antigen-specific activated T cells both in blood and in lymph node GC as well as a general activation of lymphocytes and myeloid cells in both compartments.

Conclusion

DNA/LION™ vaccination resulted in induction of robust cellular and humoral responses against different immunogens, serving as an effective platform for nucleic acid vaccine delivery. Transient rapid and coordinated cytokine responses, including IL-15, contributed to strong and sustained activation of draining lymph nodes and determined effective and long-lasting adaptive cellular and humoral immunity. This formulation may achieve an optimal balance for protective immunity against some difficult vaccine targets, including HIV.

P125 RNA as Chaperone (Chaperna) for the Assembly of Virus-like Particles and Nanoparticle Vaccines

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Significant advances have been made in the design and manufacture of nanoparticle vaccine, as vital alternative to traditional cell-culture vaccines. Assemblages of key immunologic features of viruses as highly repetitive particulate structures are essential for inducing potent and long-lasting antibody responses. The folding of monomeric antigens and their subsequent assembly into higher ordered structure is crucially important for robust and faithful production in a timely and reproducible manner. The current vaccine design approach basically relies on the thermodynamic stabilities on the final multimeric assemblages without due consideration on the kinetic stabilities on folding/assembly intermediates. Consequently, an elaborate design of chimeric nanoparticle vaccines inevitably increases the kinetic complexities on folding pathway, leading to a 'collapse' of antigen structure into immunologically compromised aggregates. The problem can be circumvented in part in eukaryotic hosts, but vexingly rampant in bacterial hosts.

Capitalizing on a novel function of RNAs as chaperone (Chaperna), here we provide a robust protein folding vehicle that could be implemented for virus-like particle (VLP) or nanoparticle (NP) assemblies in bacterial host. Thus, a viral target surface antigen is fused with and RNA-interaction domain (RID) and expressed in E. coli as soluble form. The removal of RID by site-specific protease prompted the assemblage of monomers into regular multimeric complex. We confirm that RNA is crucial for the folding of monomers and subsequent assembly into VLPs. The mutations that affect the RNA binding to RBD greatly increases the soluble aggregation into amorphous structures, reducing the overall yield of nanoparticles of defined size, confirming the importance of RNA interaction for the assembly into highly ordered complex. The results suggest that RNA functions as a 'pacemaker' for the assembly by controlling the overall kinetic network of antigen folding pathway into immunologically relevant conformation. The Chaperna platform holds promise to develop and deliver VLP and NP vaccines as a high-priority vaccine strategy against emerging viral infections.

P126 Autophagy as a therapeutic target for innate host defense during mycobacterial infections

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Mycobacterial infections, caused by Mycobacterium tuberculosis and non-tuberculous mycobacteria (NTM), pose significant challenges in treatment due to their increasing resistance to conventional antibiotics. Consequently, research has increasingly focused on host-directed therapies, which involve modulating the host's immune responses to combat these infections. Autophagy, a vital cellular process responsible for lysosomal degradation is a crucial effector mechanism in the innate immune defense against M. tuberculosis, the formidable pathogen responsible for tuberculosis in humans. Our recent investigations have centered on understanding the roles of autophagy and the underlying mechanisms through which it activates host protective immunity against M. tuberculosis and NTM infection. Activation of selective autophagy through p62/SQSTM1 results in the enhancement of antimicrobial responses against multidrug-resistant mycobacteria. Additionally, we found that myeloid ATG7 plays a major role in non-cell-autonomous protection against pulmonary infections caused by NTM by alleviating neutrophil-associated pathological inflammation and cell death. During this presentation, I will discuss our ongoing research, which is focused on targeting autophagy-related genes to enhance the antimicrobial host defenses against mycobacterial infections. A deeper understanding of the molecular mechanisms through which autophagy-related genes function in host defense will illuminate the development of innovative host-directed therapeutic approaches against tuberculosis and nontuberculous mycobacterial infections.

P127 Recombinant Pertussis Vaccine as an Alternative to Traditional Acellular Vaccine

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Whooping cough, or Pertussis, is a highly contagious respiratory disease caused by the bacterium *Bordetella pertussis*. Initially, the whole-cell pertussis (wP) vaccine, containing inactivated bacterial cells, was used for vaccination. Although effective, the wP vaccine was associated with significant side effects, leading to the development of the acellular pertussis (aP) vaccine. The aP vaccine, which includes purified components such as pertussis toxin, pertactin, and fimbriae, is considered safer but does not match the efficacy of the wP vaccine. This is due to its induction of a Th2-biased immune response and shorter-term immunity, resulting in waning protection over time. Additionally, the antigen purification process for the aP vaccine is associated with low yield, posing another challenge in production process.

In response to these limitations, we have developed a recombinant pertussis (rP) vaccine assisted by an RNA-mediated chaperone ('Chaperna') to enhance the solubility and expression of antigens. Via this novel approach, three pertussis antigens—genetically detoxified pertussis toxin (PTx), pertactin (Prn), and filamentous hemagglutinin (FHA)—were successfully expressed in *Escherichia coli*. This method not only streamlines the purification process and increases yield but also demonstrates improved immunogenicity.

Our study compared the rP vaccines' immunogenicity and efficacy with those of existing aP vaccines. Mice immunized with rP vaccines showed significantly lower bacterial burdens in their lungs following exposure to *B. pertussis* and exhibited enhanced immune responses. Unlike the aP vaccines, which tend to promote a Th2-biased response, the rP vaccines elicited a Th1/Th17-mediated immune response, crucial for strong and long-lasting immunity against *B. pertussis*.

The findings suggest that the recombinant vaccine strategy using Chaperna technology offers a promising alternative to both wP and aP vaccines. The improved solubility and increased antigen yield provided by Chaperna technology, highlight the potential of rP vaccines to offer a more effective and safer solution for pertussis prevention. As the first recombinant pertussis vaccine comprising all three PTx, Prn and FHA, the rP vaccines could overcome the limitations of current production process of aP vaccine, as an option for providing long-lasting immunity against *B. pertussis* infection.

P128 Chaperna Assisted Self-Assembly of Foot and Mouth Disease Virus (FMDV) Virus Like Particle (VLPs) Vaccine

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Foot and Mouth Disease Virus (FMDV) is a highly contagious pathogen that severely impacts cloven-hoofed domesticated animals, leading to substantial economic losses in the agricultural sector. Current prevention strategies rely on inactivated vaccines, which, although effective, are expensive and labor-intensive to produce. The process involves culturing live FMDV and subsequently inactivating it, which requires high level BSL containment. Consequently, there is a pressing need to develop safer and more efficient vaccines that do not involve live virus cultivation.

This study focuses on the development of subunit vaccines, particularly those utilizing virus-like particles (VLPs) to mimic the structure of the virus and elicit an immune response. VLPs are advantageous as they do not contain viral genetic material, thus eliminating the risk of infection. Specifically, we investigated the production of FMDV VLPs in Escherichia coli by employing Chaperna technology. This method involves fusing an RNA interaction domain to the FMDV structural proteins, facilitating their correct folding and assembly into VLPs in an RNA-dependent manner.

Our findings indicate that the three essential structural proteins of FMDV were successfully expressed in the E. coli system and self-assembled into VLPs. Transmission Electron Microscopy (TEM) confirmed that the produced VLPs were approximately 30nm in diameter, which was corroborated by Dynamic Light Scattering (DLS) analysis. Immunological assays, including ELISA and blocking ELISA (Competitive ELISA), demonstrated that sera from mice immunized with the E. coli-expressed FMDV VLPs showed a significant reaction with coated neutralizing antigens. This suggests that the antibodies produced had potential capable of neutralizing FMDV, highlighting this FMDV VLP could be an effective vaccine candidate.

In conclusion, the successful production and immunogenicity of FMDV VLPs in an E. coli expression system using Chaperna technology represents a promising step forward in the development of safe and effective vaccines. This approach could significantly contribute to the global efforts to control FMDV, providing a significant protective measure for domesticated animals against this devastating disease.

P129 An economical adjuvant without a production limit to induce potent cell-mediated immunity in subunit vaccines

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Compared with humoral immunity which blocks pathogen infection, cell-mediated immunity (CMI) clears infected cells to limit the replication and spread of pathogens. This increases vaccine efficacy against highly contagious (e.g., severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) or latent (e.g., herpesvirus) pathogens. Although FDA-approved AS01B, AS01E and matrix-M adjuvants can induce potent CMI in subunit vaccines, they rely on QS21, a polysaccharide extracted from the bark of Quillaja saponaria. Because massive synthesis of QS21 is infeasible and Q. saponaria occurs only in South America, the supply of these CMI-inducing adjuvants is limited (e.g., approximately 20 million doses annually for AS01B), resulting in higher prices for the corresponding vaccines (approximately 150-200 USD per dose of ShingrixTM compared with other vaccines normally sold at 10-40 USD per dose).
The FDA has recently approved ionizable lipid nanoparticles (LNPs) for COVID-19 mRNA vaccines as carriers and oligodeoxynucleotides containing CpG motifs (CpG ODNs) for hepatitis B subunit vaccine as immunostimulators, both could be synthesized economically. We developed a novel LNP-CpG ODN adjuvant and tested its potency in different subunit vaccines. In varicella-zoster virus (VZV) vaccines, which use glycoprotein E as an antigen, this vaccine induced levels of CMI, which plays a decisive role in the efficacy of zoster vaccines, comparable to those of ShingrixTM in a VZV-primed mouse model that was adopted for preclinical studies of ShingrixTM and in non-human primates. In addition to potent humoral responses (approximately 10 times greater than those induced by alum adjuvants after 2 injections), Th1-oriented CMI was induced in respiratory syncytial virus (RSV) vaccines via the use of stabilized fusion glycoprotein (F) as an antigen, which may be helpful for lowering the risk of antibody-dependent enhancement of immunopathology. For rabies virus (RABV) vaccines, the surface glycoprotein (RABV-G) was used as an antigen, and IgG antibodies were induced within 7 days of primary vaccination (compared with 14 days with alum as an adjuvant). Prompt-induced humoral immunity and potent CMI that are helpful for eradicating infected viruses may work synergistically for increasing RABV vaccine efficacy. In conclusion, LNP-CpG ODN adjuvants are helpful for inducing prompt, potent humoral immunity and potent CMI for subunit vaccines.

P130 Phylogenetic and genetic analysis of the Hendra virus and Nipah virus

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Hendra virus (HeV) and Nipah virus (NiV) are highly virulent, prototypic members of the henipavirus genus in the Paramyxoviridae family. HeV and NiV are bat-borne zoonotic viruses identified as the causative agents of severe disease outbreaks in the mid- to late-1990s in the vicinity of Hendra in Australia and Kampung Sungai Nipah in Malaysia, respectively. NiV continues to cause outbreaks in South Asia (Bangladesh and India), while HeV re-emerges periodically in Australia. These viruses remain ongoing transboundary threats. NiV and HeV are listed as high priority pathogens by the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and the Coalition of Epidemic Preparedness Innovations (CEPI), highlighting the urgent need for medical countermeasures, especially vaccines. NiV and HeV have envelopes with filamentous nucleocapsids containing genomes encoding six major structural proteins (N-P-M-F-G-L). In this study, we evaluated design options for NiV and HeV vaccine candidates, focusing on the fusion protein respectively. For vaccine design, we generated consensus sequences of the NiV Fusion (F) protein and HeV Fusion (F) protein antigen, respectively. All NiV and HeV F protein sequences available as of December 2023 in the National Center for Biotechnology Information (NCBI) GenBank database (http://www.ncbi.nlm.nih.gov/genbank/) were included in the analysis. This dataset comprised 27 sequences of HeV F proteins and 70 sequences of NiV F proteins, which were aligned and assembled using CLC Main Workbench software version 6.9 (CLC Bio, Aarhus, Denmark). The NiV F consensus sequences exhibited 99.33% to 93.97% homology with the reference NiV F sequences. Similarly, the HeV-F consensus sequences showed 100% to 87.26% homology with the reference HeV F sequences. A phylogenetic tree was constructed using the Maximum-Likelihood method based on the Tamura-Nei model in MEGA 7 software. The analysis involved 107 nucleotide sequences of NiV and HeV. Our NiV-F consensus sequences and HeV F consensus sequences hold promise as candidates for human and animal vaccines, potentially mitigating NiV and HeV outbreaks.

P131 '100 Days Mission' Speedy Delivery of Disease X Vaccines: Chaperna platform based Bacterially Produced Highly Pathogenic Avian Influenza Virus Nanoparticle Vaccine

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The global outbreak of COVID-19 asks us to develop and deploy vaccines in a timely manner. In contrast to mRNA vaccine that affords speedy delivery, the protein-based vaccines that has long been used for the prevention of variety of infectious diseases could not be tailored for speedy delivery. In particular, for newly discovered viruses, conventional mammalian cell culture often fails to produce enough vaccine doses in a timely manner. While bacterial cells provide an easy and economical system for the production of HA proteins, viral proteins expressed in Escherichia coli cells are usually expressed as insoluble aggregates and require a refolding process which is highly empirical rending compromised quality of antigens.
Highly pathogenic avian influenza viruses (HPAIVs) pose a significant threat to human health, with high mortality rates. Recent reports indicate that H5N1 can cross-infect dairy cows, with the virus detected in the milk of infected animals, posing a significant public health concern. Therefore, it is crucial to develop rapid and safe methods for producing vaccines effective against potential HPAI H5 virus outbreaks.
We showed that, harnessed with novel RNA-mediated chaperone ('Chaperna') function, hemagglutinin (HA) of H5N1 HPAIV could be expressed predominantly as soluble form, self-assembled into chimeric nanoparticles (cNP) displaying HA as an immunologically relevant conformation. A tri-partite monomeric antigen was designed including: i) an RNA-interaction domain (RID) as a docking tag for RNA to enable chaperna function (chaperna: chaperone + RNA), ii) globular head domain (gd) of HA as a target antigen, and iii) ferritin as a scaffold for 24 mer-assembly. The immunization of mice with the nanoparticles (~46 nm) induced a 25–30 fold higher neutralizing capacity than monomeric antigen, and provided cross-protection from homologous and heterologous lethal challenges. This study suggests that cNP assembly is conducive to eliciting antibodies against the conserved region in HA, providing potent and broad protective efficacy.
The chaperna platform holds promise to meet the mandate of 'just-in-time' delivery of low cost vaccines against 'just-in-case' pandemic outbreaks, amenable to meet the '100 Days Mission'. This platform could be harnessed for a fast delivery of recombinant vaccines to LMICs in time of unexpected outbreak, contributing to equitable access to vaccines as public goods.

P132 In vitro and in vivo studies of plant-produced Atezolizumab as a potential immunotherapeutic antibody

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Imcheckpoint inhibitors are a well-known class of immunotherapeutic drugs that have been used for effective treatment of several cancers. Atezolizumab (Tecentriq) was the first antibody to target immune checkpoint PD-L1 and is now among the most commonly used anticancer therapies. However, this anti-PD-L1 antibody is produced in mammalian cells with high manufacturing costs, limiting cancer patients' access to the antibody treatment. Plant expression system is another platform that can be utilized, as they can synthesize complex glycoproteins, are rapidly scalable, and relatively cost-efficient. Herein, Atezolizumab was transiently produced in Nicotiana benthamiana and demonstrated high expression level within 4-6 days post-infiltration. After purification by affinity chromatography, the purified plant-produced Atezolizumab was compared to Tecentriq and showed the absence of glycosylation. Furthermore, the plant-produced Atezolizumab could bind to PD-L1 with comparable affinity to Tecentriq in ELISA. The tumor growth inhibitory activity of plant-produced Atezolizumab in mice was also found to be similar to that of Tecentriq. These findings confirm the plant's capability to serve as an efficient production platform for immunotherapeutic antibodies and suggest that it could be used to alleviate the cost of existing anticancer products.

P133 Engineering Pickering emulsion for the advanced vaccine adjuvant

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To better provoke the responses, it is becoming increasingly important to strengthen the delivery efficacy of the antigenic and immunogenic components. Particles, such as liposomes, polymeric particles, protein aggregates etc, were engineered with multi-scale structures and tuneable physicochemical properties to load and deliver the vaccine components. To address this, we develop a particle-stabilized emulsion (Pickering emulsions), which was densely packed with nanoparticles to offer the high specific surface area for antigen loading and cellular interactions, and processed an oily core to demonstrate the softness to deform on the cellular surface, enlarging the contact area for higher uptake efficacy. Additionally, the soft droplets can also demonstrate the force-dependent deformation, which allow for the droplets to pass through the intercellular gaps with the interstitial flow, evidently increasing the lymph node accumulation of the delivered antigens. Compared with solid particles and conventional surfactant-stabilized emulsions, the optimized Pickering emulsions enhance the recruitment, antigen uptake and activation of antigen-presenting cells (APCs). In H1N1 influenza and SARS-CoV-2 vaccines, Pickering emulsion induced robust neutralizing antibody titer, IFN-r secreting T cells and the increased survival of mice upon lethal challenge, compared with the clinical-relevant adjuvants. By engineering the softness, Pickering emulsion were demonstrated with the enhanced lymph node accumulation, cellular uptake and immunogenicity, which may offer an alternative strategy for the efficient vaccine delivery system.

P134 Immunogenicity in Recombinant Protein Vaccine Candidates Targeting Nipah virus

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Nipah virus (NiV) is a highly pathogenic virus that causes severe neurological and respiratory diseases, belongs to the Paramyxoviridae family, and causes outbreaks in Southeast Asia. NiV has a high mortality ranging from 40% to 75% in humans, but there is currently no approved treatments or vaccines. The key antigens that induce protective immunity against NiV infection are known to be the fusion glycoprotein (F) and the major attachment glycoprotein (G), which are surface proteins for membrane fusion and receptor binding during viral entry. This study focuses on evaluating NiV vaccine antigen design options centered around these antigens. There are two strains of NiV, Malaysia (NiVM) and Bangladesh (NiVB), which are composed of several proteomes. The G and F proteins, which are involved in virus-host cell binding, are very similar in both NiVM and NiVB. Therefore, we developed and evaluated recombinant subunit vaccines by synthesising G proteins from NiVM and NiVB as monomers and tetramers, and F proteins as monomers and trimers in various combinations. Additionally, Chimeric proteins containing both forms were also expressed, resulting in 17 distinct NiV recombinant protein vaccine candidates. These vaccine candidates were then immunised in BALB/c mice to gauge their capacity to induce immune responses against NiV antigens. The results showed that most neutralizing antibodies were induced by tetra G bivalent (NiVM + NiVB) group. The findings demonstrated robust humoral immune responses elicited by nearly almost all of the vaccine candidates, notably with the tetrameric G bivalent (NiVM + NiVB) group eliciting the highest response. This research underscores the potential of tetrameric formulations combining G proteins from different NiV strains as effective vaccine candidates. These studies demonstrate the composition of NiV vaccine candidates designed to address pandemic threats, highlighting the use of prototype pathogens as an approach to enhance pandemic response and preparedness against deadly virus.

P135 An intranasal parainfluenza virus 5 (PIV5)-based vaccine for Lyme Disease induces protection against multi-strain Borrelia burgdorferi tick challenge in mice

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Parainfluenza virus 5 (PIV5) viral vectored vaccines for COVID-19 and RSV have been developed and are currently undergoing phase 2 clinical trials. In addition to targeting viral pathogens, PIV5 has been utilized as a vector to develop bacterial vaccines against *Mycobacterium tuberculosis*, *Burkholderia mallei*, and *Burkholderia pseudomallei*, all of which have shown efficacy in mouse models. Here, we detail the creation, immunogenicity, and efficacy of an intranasal PIV5-based vaccine for Lyme Disease (PIV5-A_{BPBPk}) in mice. CDC records indicate that Lyme Disease cases in the United States have steadily increased since the late 2000s, yet no human Lyme Disease vaccine is currently available on the market. The PIV5-A_{BPBPk} vaccine was engineered by incorporating a modified *Borrelia burgdorferi* OspA protein, A_{BPBPk}, between the SH and HN genes in the PIV5 genome. The vaccine's immunogenicity and efficacy were evaluated in C3H-HeN mice, a Lyme Disease mouse model, using a homologous prime/boost vaccination regimen. Serological data demonstrated that mice vaccinated with PIV5-A_{BPBPk} maintained anti-OspA antibodies in their serum for up to 1-year post-immunization, similar to mice vaccinated with recombinant rOspA+Alum. We assessed the borreliacidal activity of PIV5-A_{BPBPk}-vaccinated mice and found it persisted up to 18 months post-immunization, with a stronger response than that induced by rOspA+Alum vaccination. A multi-strain *B. burgdorferi* tick challenge was conducted at 9- or 15-months post-immunization. Results indicated an increase in breakthrough infections in mice vaccinated with rOspA+Alum compared to those vaccinated with PIV5-A_{BPBPk}, as determined by qPCR of *B. burgdorferi* bacterial load and tissue culture, as well as antibodies against *B. burgdorferi* protein VlsE by ELISA. The data demonstrates that an intranasal PIV5-based vaccine can offer longer-lasting protection than a recombinant protein-based vaccine. Given that current Lyme Disease vaccine candidates in clinical trials are primarily based on a recombinant protein platform, we decided to evaluate our PIV5-based vaccine in a heterologous prime/boost vaccination study. The study involved either an intranasal PIV5-A_{BPBPk} prime followed by a subcutaneous rOspA+Alum boost, or a subcutaneous rOspA+Alum prime followed by an intranasal PIV5-A_{BPBPk} boost. The data showed that a heterologous prime/boost vaccination (IN/SC or SC/IN) fully protected against multi-strain *B. burgdorferi* challenge in mice, suggesting that this regimen is a viable option for vaccine administration. These results further underscore the versatility and effectiveness of PIV5 as a viral vector for bacterial vaccines.

P136 Psychological determinants of HPV vaccine hesitancy among females of catch-up generations in Japan: Internet survey

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Background: Preventive human papillomavirus (HPV) vaccines have been demonstrated to be highly effective and safe, primarily in preventing the development of cervical cancer. In Japan, the Ministry of Health, Labor and Welfare suspended active HPV vaccination recommendations in June 2013. It resumed its recommendation in November 2021 and began catch-up vaccination for women who missed the opportunity to receive HPV vaccination from fiscal year 2022 to 2024. However, as of January 2024, very few women had received catch-up vaccination, and it is expected that these generations have anxiety and hesitancy about vaccination. Therefore, this study aimed to examine the differences in knowledge about HPV, cervical cancer, and HPV vaccines between women who have received and have not received the HPV vaccine, and their association with psychological determinants of vaccination using the widely used and updated 7C model.

Methods: In January 2024, an internet survey was conducted targeting women born between 1997 and 2007. The questionnaire surveyed knowledge of cervical cancer, HPV vaccines, whether they had been vaccinated and the reasons for doing so, and psychological antecedents regarding vaccination intentions based on the 7C model.

Results: 600 valid responses were received. 15.2% (91/600) had completed the HPV vaccination, while 37.5% (225/600) had never received them. Of the women who answered regardless of whether they had been vaccinated, less than half had specific knowledge of cervical cancer, HPV vaccines, and cervical cancer vaccines. Knowledge was particularly low in the unvaccinated group. Among those who had not completed the HPV vaccine, 34.4% (175/509) were unsure whether they would vaccinate during the catch-up period, and 17.1% (13/509) had no intention of getting vaccinated. The most common factor was fear of side effects of the HPV vaccine. Some of the 7C psychological antecedents, particularly Complacency, Confidence, and Constraints were expected to be strongly associated with HPV vaccination behavior. Conclusion: It is necessary to continue to strategically provide information on the effectiveness and importance of vaccines and the need for cancer screening to the catch-up generation.

P137 Development of stabilized Rift Valley Fever Virus immunogens

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Rift Valley Fever Virus (RVFV) is a zoonotic pathogen with significant implications for human and animal health, causing substantial morbidity and mortality. The glycoproteins Gn and Gc are displayed on the surface of the RVFV viral particles and are essential for viral entry, making them key targets for vaccine development. Our research addresses the challenge of stabilizing these antigens for enhanced vaccine efficacy and manufacturability. We combine rational design with deep learning tools for protein design to identify mutations that enhance the thermal stability and secretion efficiency of monomeric Gn antigens. Additionally, we engineer a scaffold that improves the secretion of a soluble heterodimeric Gn/Gc complex. Our optimized antigens demonstrate strong binding to neutralizing antibodies. These redesigned antigens represent a crucial first step towards the development of a next-generation vaccine against RVFV, with the potential to significantly mitigate the virus's impact on global health.

P138 Lung eosinophil recruitment and type 2 host immune responses in vaccinated mice is non-pathological and correlates with protection during influenza infection in mice with infection-permissive or sterilizing immunity

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Type 2 host immune responses to virus infection are characterized by a typical IL4/5/13 cytokine response and granulocytes like eosinophils. These immune features are typically driven by Th2 cells during host immune responses to infection and homeostasis. Lung eosinophilia after respiratory viral infection has been linked to aberrant Th2 responses like vaccine-associated enhanced respiratory disease, but has been decoupled from pathology in some models of respiratory viral infection, with or without prior vaccination. We characterized mouse lung eosinophils after a sublethal, vaccine-matched influenza challenge (breakthrough infection). Post-challenge, we observed CD101+ Siglec-Fhi lung eosinophils in mice that received trivalent inactivated influenza vaccine. This group did not have strong inflammatory cytokine expression, detectable viral titers, allergic levels of total IgE, severe lung pathology, goblet cell hyperplasia, or enhanced morbidity. In contrast, unvaccinated mice exhibited no eosinophilia, despite ¬high viral titers, strong pro-inflammatory cytokine profiles, and significant pathology with infiltrating immune cells like inflammatory monocytes and neutrophils. Longitudinal analyses at days 1, 3, 7, 10, and 28 post-challenge revealed no overt Th2 cytokine signal in the lungs of breakthrough infection mice, suggesting that non-canonical mechanisms and cell circuits promoted lung eosinophilia in this model. Furthermore, lung eosinophils correlated with protection and not pathology in breakthrough influenza infection of mice. In a similar type 2 fashion, but without the eosinophil influx, lungs of AddaVax-adjuvanted influenza vaccinated mice with sterilizing immunity show strong IL4/5/13 cytokine profiles upon infection. Again, this type 2 response correlates with full protection. The outcome of these studies suggests that the host immune response to infection is skewed by vaccination and leans towards type 2 host immune responses that correlate with infection rather than pathology.

P139 Accurate Transcutaneous Immunization of High-dose Live Vaccines using Multi-coated Microneedle Array Patches

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Coated microneedle (MN) platforms have been widely investigated for effective intradermal vaccination due to their fast delivery kinetics and simple fabrication process. However, limited coating amount and difficulty of precise and selective vaccine coating on MN shafts remain significant challenges for developing MN-based inoculation methods. In addition, the stability of bioactive agents such as live vaccines during MN fabrication is an important factor to be considered for vaccination and stockpiling. In this study, we will report a transcutaneous vaccination using a live vaccine-coated MN patch prepared by low-temperature multiple micro-dispensing system. To achieve selective and precise coating of vaccine solutions on base MN arrays, we used a contact dispensing method after selective surface treatment of plain MN arrays. The plain base MN arrays (8×8 MNs/patch) was prepared by injection molding, and each bullet-shaped MN had a base diameter of 350 μm and a height of 900 μm. The contact dispensing technique accurately transferred single microdroplets of the coating solution containing live vaccines from the nozzle to the MN tip and provided multiple coating after drying previous layers. Thus, the target amount of drug to be delivered into skin can be easily adjusted according to the number of dispensing coatings. We will present two transcutaneous immunization results using live vaccine-coated MN array patches (vaccinia-coated MN for smallpox vaccination and Bacillus Calmette-Guérin-coated MN for tuberculosis) to demonstrate the efficacy of MN-mediated transcutaneous vaccination in experimental animals.

P140 Novel rabies vaccine offers potential for population wide pre-exposure prophylaxis in rabies endemic areas

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Despite the existence of effective vaccines, rabies causes 60,000 deaths annually. Current vaccines are mostly used for post-exposure prophylaxis (PEP) but are often not available when needed. Vaccines are recommended for pre-exposure prophylaxis (PrEP) for high-income travellers entering rabies-endemic countries, but are not available to those most at risk; children who reside in such countries. The use of rabies vaccines as PrEP for those who can afford it underlines its benefits, and the lack of access to those most at risk remains a striking health inequality. The relatively high costs of current rabies vaccines and the need for multiple doses means delivery of rabies PrEP programmes is considered too expensive for cost-effective use on a population level.
RAB002 is a phase Ib/II clinical trial of a new rabies vaccine, ChAdOx2 RabG, including Tanzanian adults and children aged 2-6 years old. In both age groups, we compared participants receiving a single dose of ChAdOx2 RabG to those receiving a single dose of Verorab, a currently licenced rabies vaccine. In the paediatric age group, we also compare those receiving a single dose of ChAdOx2 RabG to those receiving two doses of Verorab according to a currently WHO-recommended PrEP schedule deployed locally. ChAdOx2 RabG was found to be well tolerated and highly immunogenic in both age groups. Using the accepted correlate of protection for rabies, virus neutralising antibody (VNA) levels, this new vaccine was found to be superior to the administration of a single dose of a currently licensed vaccine. In children, a single dose of ChAdOx2 RabG trended to superiority compared to a currently approved PrEP schedule requiring two doses of Verorab.
A single-dose PrEP regime against rabies has the potential to address health inequality and prevent tens of thousands of rabies deaths each year. When coupled with the lower costs of manufacturing this vaccine, ChAdOx2 RabG performing at least as well as the currently approved PrEP schedule means single dose PrEP to control rabies is now within reach.

P141 Development of HIV mRNA Lipid Nanoparticles (LNPs) Vaccine Formulation

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Lipid nanoparticles (LNPs) are a drug delivery system for nucleic acids that protect the nucleic acids from degradation and enable a safe and efficient delivery of the RNA/DNA at the target site. The structure of LNPs consists of four major components that serve a specific purpose including cationic ionizable lipids, cholesterol, and helper lipids, such as DSPC, and PEGylated lipids. The aim of this study was to encapsulate HIV-1 protein envelope, gp-120-A244 mRNA in LNPs and adjuvant the formulation to increase vaccine efficacy and durability. Here, we developed and optimized LNP formulations using several ionizable lipids including DLin-KC2-DMA, ALC-0315, DAP, DODMA, and SSOP. DLin-KC2-DMA gave the best immune responses in pilot studies and was selected to encapsulate the gp-120-A244 mRNA. The formulation was tested in vitro in HEK 293 cells and in vivo in BALB/C female mice. Three doses of 1 or 2 µg mRNA-LNP with or without adjuvants ALF (20 µg 3D-PHAD®), ALFQ (20 µg 3D-PHAD®, 10 µg QS-21), or QS-21 (1 µg) were administered to mice (n = 5/group) every 3 weeks intramuscularly. We found that both mRNA-LNP doses (1 or 2 µg) induced high antibody titers in all the groups except the mRNA-LNP mixed with ALFQ groups, and the titers remained high, ranging from 50 – 80% up to four months. Loss of antibody durability was evident six months post the last immunization. Furthermore, the titers were not significantly enhanced in the presence of adjuvants, ALF or QS-21 compared to the control and the addition of ALFQ to the mRNA-LNPs completely abrogated the antibody response.

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P142 NVX-CoV2373 Vaccine Exposure During Pregnancy and Risk of Adverse birth outcomes: Korean Nationwide Population Study

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Abstract: *Background:* Evidence on the association between NVX-CoV2373 COVID-19 vaccine exposure and preterm birth and congenital anomaly is limited. Prior studies reported receiving a COVID-19 vaccine during pregnancy has not been associated with a higher risk of adverse birth outcomes such as stillbirth, preterm birth, or congenital anomaly. This study estimates the association of NVX-CoV2373 vaccine exposure during pregnancy with preterm birth and congenital structural anomalies. *Method:* This retrospective cohort study used national data from the National Health Insurance System, linking maternal and neonatal records with COVID-19 vaccination registries. Eligible pregnancies included those with recorded births among women 15–49 years old occurring between February 14 and July 31, 2022. Preterm births were identified via diagnosis codes of neonates (ICD-10 codes under the categories 'P07.2' and 'P07.3') and mothers ('O60.1', 'O42.91'). We defined structural anomalies of neonates based on the ICD-10 codes of neonates listed by the EUROCAT network (https://eu-rd-platform.jrc.ec.europa.eu/eurocat), excluding those for chromosomal anomalies, and maternal diagnostic code of fetal congenital anomalies ('O35'). Women who were vaccinated with NVX-CoV2373 during pregnancy were matched at a 1:4 ratio to those who were not vaccinated during pregnancy based on year and month of conception, women's age, living outside of the Seoul capital area, employment, level of income, disability, pre-pregnancy history of smoking, obesity, anemia, and SARS-CoV-2 infection during pregnancy. Adjusted odds ratios (AORs) of preterm birth and structural anomalies were calculated using logistic regression and reported with corresponding 95% confidence intervals (95% CI). Result: Among the mothers of 106,692 live births in South Korea between February and December 2022, 466 (0.4%) mothers received the NVX-CoV2373 vaccine during pregnancy and met inclusion/exclusion criteria. Prior to matching, the NVX-CoV2373 vaccine group was more likely to be older (≥35 years old; 40.8% versus 29.0%), live outside of the Seoul capital area, have higher income, and lower incidence of SARS-CoV-2 infection during pregnancy in comparison to women who were not vaccinated during pregnancy. There were zero cases of stillbirth in mothers who received the NVX-CoV2373 vaccine during pregnancy. Of the newborns in the matched sample of controls (n=1864) and NVX-CoV2373 recipients (n=466), 136 (7.3%) and 42 (9.0%) were preterm birth, respectively. Structural anomaly was identified in 143 (7.7%) of matched control and 29 (6.2%) of NVX-CoV2373 recipients. The AOR of preterm birth comparing NVX-CoV2373-exposed and unvaccinated women during pregnancy was 0.94 (95% CI: 0.57–1.55), and the adjusted OR for structural anomalies was 1.06 (95% CI: 0.68–1.64). *Conclusion:* Among pregnant women exposed to the NVX-CoV2373 vaccine during pregnancy, there were not significant differences in the risk of adverse birth outcomes (preterm birth or structural anomaly) compared to women who were not exposed to any COVID-19 vaccines during pregnancy. The reported rates of preterm birth and structural anomalies are similar to published rates for the Korean population. These findings provide evidence regarding the safety of NVX-CoV2373 vaccination during pregnancy. *Keywords*: COVID-19, vaccine, stillbirth, preterm birth, congenital structural anomaly, pregnancy, safety

P143 A protein-based multivalent cholera vaccine candidate broadly protects against Vibrio cholerae serogroup infections

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Abstract: Cholera remains a deadly and persistent threat to public health. Current oral cholera vaccines (OCVs) prequalified by WHO confer ~60% protection to adults and children over five years of age but unfortunately poor or no protection to children <5 years in cholera-endemic countries or regions. In this study, we applied a novel epitope- and structure-based multiepitope fusion antigen (MEFA) vaccinology platform to construct a polyvalent protein to target multiple virulence determinants across *V. cholerae* serogroups and developed a protein-based injectable vaccine for cross-protection against *V. cholerae* infections. By integrating conservative immunodominant B cell epitopes of *Vibrio cholerae* toxin coregulated pilus A, cholera toxin (CT), sialidase, hemolysin A, flagellins B, C, and D, as well as lipopolysaccharide O-antigen mimotopes into backbone immunogen FlaB and mimicking epitope native antigenicity, we constructed a polyvalent protein immunogen, cholera MEFA. Mice and rabbits IM immunized with cholera MEFA protein developed robust IgG antibody responses to all target virulence factors except for LPS. Mouse and rabbit antibodies exhibited *in vitro* protection against CT enterotoxicity, CT binding to GM_1, as well as motility and adherence of *V. cholerae* O1, O139, and non-O1/non-O139 bacteria. Moreover, rabbits IM immunized with this immunogen prevented >99% *V. cholerae* colonization in small intestines when challenged with *V. cholerae* O1 El Tor or a non-O1/non-O139 strain. Furthermore, infant rabbits born to the mother rabbits IM immunized with cholera MEFA protein remained healthy, prevented from >99% bacteria intestinal colonization, and protected 100% from severe diarrhea, and 88% from mild diarrhea, when challenged with O1 El Tor (N16961), O1 Classical (O395), O139 Bengal, or a non-O1/non-O139 strain. These results indicated that cholera MEFA protein is broadly immunogenic and cross-protective against O1, O139, and non-O1/non-139 infection preclinically, suggesting cholera MEFA protein can be the antigen of a cross-protective cholera subunit vaccine. Additionally, an infant rabbit passive protection model and an adult rabbit colonization model may fill a crucial gap in cholera vaccine preclinical efficacy studies and overcome a significant hurdle in cholera vaccine development.

P144 System Vaccinology Approach Identifies an Early Innate Immune Signature as a Correlated of Humoral and Cell-mediated Immune Responses to the rVSVΔ-LASV-GPC in Phase 1 Clinical Trial

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Predicting vaccine immunogenicity and efficacy remains a challenge. We used a systems vaccinology to identify early biomarkers and immune signatures that are associated with antigen-specific antibody and T-cell responses in humans receiving the Lassa Virus (LASV) vaccine candidate rVSVΔ-LASV-GPC. Plasma samples obtained from vaccinated individuals at days 0, 1, 3, 7, 14 and 28 were analysed for changes in 44 different cytokines, chemokines and growth factors using a Meso Scale Discovery (MSD) platform. We identified a signature of early innate markers correlating with LASV GPC IgM and IgG binding and neutralizing antibody levels on day 28 and beyond. Among those, IP-10, MCP-1, MIP-1a, MIP-1b, TNF-a, TSLP, IL-12/23p40, IFN-g, IL1-RA, IL-10 and Eotaxin-3 were independent correlates. Consistently, we also found an early cytokine signature linked to anti vector antibodies and vaccine-specific T cell responses, as measured by IFN-γ T cell ELISPOT, flow cytometry and multiplex cytokine release assays. Overall, our results show the replication-competent rVSV-vector induces a milieu of innate antiviral responses that can orchestrate the rapid development of durable adaptive immunity against Lassa virus.

P145 Development of Novel Recombinant Vaccine against Re-emerging Genotype V Japanese Encephalitis Virus

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Japanese encephalitis (JE) is a severe and potentially fatal disease caused by the Japanese encephalitis virus (JEV). The virus is primarily transmitted by Culex mosquitoes and has a significant impact in many Asian countries. Although vaccines against JE have been developed, the emergence of genotype V (GV) JEV presents a new challenge, as existing vaccines are predominantly based on genotype III (GIII) and may not provide adequate protection against GV strains.

This study aims to evaluate the efficacy of a newly developed GV-based vaccine in comparison to the traditional GIII-based vaccines. Harnessed with Chaperna system (RNA as chaperone), we developed a pentameric recombinant antigen using cholera toxin B as a scaffold and mucosal adjuvant, genetically fused with the E protein domain III of GV. This novel vaccine antigen was produced in E.coli as pre-assembled pentamer, and tested in mice for its immunogenicity and protective efficacy against GV JEV isolates. The results demonstrated that the GV-based vaccine induced a stronger immune response and provided better protection against GV JEV compared to the GIII-based vaccine. Additionally, we explored a bivalent vaccine strategy, combining both GIII- and GV-based antigens. This approach was tested for its ability to provide comprehensive protection against both GIII and GV JEV strains. The bivalent vaccine induced robust immune responses and protected mice from lethal challenges with both genotypes, suggesting its potential as a more effective vaccination strategy in regions where multiple JEV genotypes co-circulate. The results highlight the importance of developing genotype-specific vaccines to address the evolving threat of JEV. The GV-based vaccine and the bivalent approach offer promising solutions for enhancing JE control and prevention, particularly in areas with emerging GV strains.

Further research and clinical trials are needed to confirm these results and facilitate the deployment of these vaccines in affected regions. Our study underscores the dynamic nature of viral pathogens and the need for continual adaptation of vaccine strategies to maintain effective disease control. The implementation of genotype-matched vaccines could significantly reduce the incidence of JE and improve public health outcomes in endemic areas.

P146 Protective efficacy of a non-proliferative attenuated vaccinia virus DIs strain against mpox virus infection in mice

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Background: Mpox is a zoonotic disease caused by the mpox virus (MPXV), previously found to be endemic in West and Central Africa. Unexpectedly, since 2022, mpox has been transmitted human-to human through sexual contact, primarily in a group of males who have sex with men (MSM), resulting in large global outbreaks in over 110 countries. Currently, three vaccines MVA-BN, LC16, and OrthopoxVac has been approved for prevention of mpox. However, given the large number of HIV-infected individuals in the MSM group, the development of a new safe and effective mpox vaccine would be important. In this study, we investigated the protective efficacy of a *host range-restricted* and highly attenuated vaccinia virus (VACV) DIs strain against mpox infection in mice.

Methods: CAST/EiJ mice, which are susceptible to infection with MPXV, were used in this study. The CAST/EiJ mice were immunized epidermally twice with VACV-DIs at 1E+08 PFU at 4-week intervals. The humoral immune response elicited by vaccination was evaluated by neutralization assay. Two weeks after the 2nd vaccination, the efficacy of VACV-DIs vaccination was examined in challenge infection with two variants, Zr-5991 (Clade I) and TK-006 (Clade IIb).

Results: Mice immunized twice with VACV-DIs induced neutralizing antibody against both Zr-599 and TK-006 strains. After intranasal infection with MPXV, PBS(-)-treated control mice showed significant decrease in the body weight and developed pneumonia, while all VACV-DIs-immunized mice did not show any decrease in body weight and alleviated pneumonia. When assessed 9 days after infection, the titer of infectious MPXV titer in the lungs of VACV-DIs-immunized mice was below the detection limit, whereas the virus was detected in the lungs of all control mice.

Conclusion: We demonstrated that VACV-DIs protects mice from infection with both Clade I and Clade IIb MPXV without any decrease in body weight. Therefore, the non-proliferative attenuated VACV-DIs may be a promising vaccine candidate against mpox. The detailed protection mechanisms of VACV-DIs, including cell-mediated immunity, will be analyzed in the future.

P147 Introduce a novel proprietary Lipid Nanoparticle (LNP)

Chunlin XIN
VP of External R&D, CanSinoBIO

RNA-based therapies, including mRNA, siRNA, and antisense oligonucleotides (ASO), have shown great promise in preventing and treating a broad spectrum of diseases such as infections, tumors, and rare diseases. Due to the negative charges and inherent instability of RNA drugs, various delivery systems, including lipid nanoparticles (LNPs), have been developed to overcome these barriers. To date, three mRNA vaccines encapsulated by LNPs—mRNA-1273, BNT162b2 for COVID-19, and mRNA-1345 for RSV—have been licensed for market use.

Conventional LNPs are formulated with four lipid components: ionizable lipids, cholesterol, PEG-lipids, and helper lipids. The functional delivery of mRNA by LNPs greatly depends on the inclusion of ionizable lipids. However, the structure-function relationships between ionizable lipids and mRNA delivery are poorly understood. Moreover, the risk of mRNA delivery to off-target tissues highlights the necessity for LNPs with enhanced tissue selectivity. For instance, mRNA delivered by conventional LNPs after intramuscular administration often partly goes to the liver, resulting in substantial expression of the target proteins in the liver.

In this context, our presentation introduces the iterative design of novel proprietary LNP formulations. These formulations exhibit high efficiency in mRNA encapsulation and delivery, a good safety profile, and excellent stability during storage. Furthermore, the novel LNPs are identified as effective local mRNA delivery systems through intramuscular administration. They demonstrate high transfection efficiencies at the local site without systemic exposure, thereby minimizing systemic side effects. Additionally, these LNPs enable efficient delivery of mRNA vaccines, such as those for herpes zoster and COVID-19, triggering both strong humoral and cellular immune responses. Notably, with the delivery of the optimized LNPs, the candidate mRNA vaccines could elicit much stronger CD8+ T cell responses compared to LNPs used in commercial mRNA vaccines. These results indicate that the novel LNPs have great potential for mRNA vaccine delivery, particularly for applications that prioritize CD8+ T cell activation, such as mRNA tumor vaccines.

Moreover, the local delivery feature of these LNPs introduces a promising approach for safe and effective gene therapy targeting muscle tissue. This local delivery minimizes off-target effects and maximizes therapeutic benefits at the intended site of action. Notably, these LNPs also show promising potential for inhalation applications, offering a new avenue for respiratory drug delivery. The structure of the LNPs demonstrated good tolerance during nebulization, whereas conventional LNPs were destroyed in this process. In mouse models, including those that evaluate systemic immune responses, mRNA vaccines delivered by the novel inhalable LNPs also robustly elicited mucosal immune reactions, inducing high levels of secreted IgA and IgG in the bronchoalveolar lavage fluid (BALF).

The combination of these attributes positions this proprietary LNP as an advanced development in the field of mRNA delivery. By ensuring localized, efficient, and safe delivery of mRNA, these novel LNPs offer significant improvements over existing delivery systems. Their potential applications in various therapeutic areas, from vaccines to gene therapy, highlight their importance in advancing RNA-based treatments. This presentation will delve into the special attributes and promising data of our LNP, and the broad implications for future prophylactic and therapeutic applications.

P148 Novel multi-genotypic E2E1 nanoparticle HCV vaccines

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Hepatitis C virus (HCV) infection affects approximately 58 million people and causes ~300,000 deaths yearly. A high proportion of HCV patients can be cured with new direct acting antiviral agents (DAAs). However, these individuals can be re-infected and DAA resistance is emerging as a barrier to therapy. Therefore, it has become clear that, without an effective HCV vaccine, it will not be possible to meet the World Health Organization targets of HCV viral elimination. DNA vaccines represent a viable promising solution, as they are simple and inexpensive to produce. They are stable at room temperature, simplifying vaccine handling and distribution, ensuring that lowto middle income countries, with the greatest need can benefit. Primary target for HCV neutralizing antibodies (nAbs) is the highly diverse E1E2 glycoprotein. Eliciting broadly nAbs that recognize conserved cross-neutralizing epitopes is important for an effective HCV vaccine. However, most DNA vaccines encoding E1/E2 have not been highly immunogenic in the past. To improve immunogenicity, we developed a novel DNA vaccine encoding multi-genotypic soluble E1E2 immunogens that were generated by permutation of the E1 and E2 subunits; and deletions of E2 hypervariable domains, hypervariable region (HVR) 1 and HVR2, and intergenotypic variable region. We displayed the E2E1 immunogens into nanoparticles by fusion with the β-annulus peptide which participates in the formation of the dodecahedral internal skeleton of the tomato bushy stunt virus (TBSV). These nanoparticles vaccines induced high antibody titers against E2 from genotype 1, 2 and 3. Furthermore, the E2E1 nanoparticles elicited high-magnitude T-cell responses against E1/E2 from genotype 1 or 3. Further evaluation is underway to assess the ability of the antibodies induced by immunisation to cross-neutralise HCV particles. These results provide a roadmap for the generation pan-genotype HCV vaccine to elicit T cells and nAbs for future assessment in humans

P149 Targeting immunosubdominant epitopes via antigen monomerization

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The nature of the interplay between human immunity and viral escape is infinitely adaptive. Frequent infections or vaccinations typically induce immune responses against escape-prone variable epitopes, rather than against hidden conserved epitopes. It thus remains a substantial challenge to elicit the immune responses to the conserved epitopes providing broad-spectrum immunity. Molecular characterization of human serum antibody (Ab) repertoires revealed a prevalence of cross-reactive Abs that bind to the conserved stem or the monomer-monomer interface occluded inside the hemagglutinin (HA) trimer. The interface-specific Abs conferred full cross-protection *in vivo* and were able to dissociate HA trimers into monomers upon binding *in vitro*. The observation is seemingly contrary to that of conventional epitope binding and neutralization that would require HA trimerization to attain full antigenicity. We showed previously that the recombinant HA from a pandemic strain was monomeric in solution and that a stable HA monomer by mutations at the monomer-monomer interface induced *in vivo* protective immunity, comparable to the trimer. In this study, we developed an approach of scaffold-mediated mosaic display to present monomeric influenza virus HAs. Stable HA monomers were rationally engineered from H1 and H3 subtypes and B type HA trimers, with amino acid changes at the monomer-monomer interface and for disulfide bond formation, which were then fused to a self-assembling scaffold to form a mosaic HA monomer-displaying nanoparticle, 3HA-np. *In vivo* immunization with 3HA-np in mice induced broadly neutralizing Abs and conferred significant protection against both H1N1 and H3N2 influenza virus challenges. Competitive immunoassays revealed that 3HA-np induced high titers of Abs specific to conserved stem regions and monomer-monomer interfaces, regardless of influenza virus subtypes. Our results suggest that targeting immunosubdominant and conserved epitopes by monomer-displaying nanoparticles is a promising approach to generate a universal influenza vaccine.

P150 A chimeric vaccine based on a fusion protein combining RBDs from Wuhan and Omicron SARS-CoV-2 variants protects against Omicron infection in Syrian hamsters

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Derivates of Omicron SARS-CoV-2 variant are dominating in circulation for the last two years. The mortality rates of the COVID-19 caused by Omicron variants is only approximately half that of previous variants, vaccines effective against Omicron are needed. Moreover, a generally safe, easily adapted, cheap and stable construct for the future vaccine variations for routine immunization would be appreciated. Demonstrating that a SARS-CoV-2 vaccine can protect against Omicron in an *in vivo* infection model, particularly in that of Syrian hamsters, is important for the preclinical characterization of COVID-19 vaccines. We performed an evaluation of W-PreS-O vaccine for its ability to protect Syrian hamsters against infection by Omicron SARS-CoV-2 variant. W-PreS-O is a chimeric vaccine based on a single fusion protein (W-PreS-O), combining receptor-binding domains (RBDs) from Wuhan and Omicron variants' virion surface (S) proteins adsorbed to aluminum hydroxide. Syrian hamsters were immunized three times at three-week intervals with W-PreS-O or with aluminum hydroxide (placebo), and then infected with Omicron BA.1 strain. Non-infected and non-vaccinated animals served as intact controls. Neutralizing antibody (nAB) titers, weight, lung symptoms (i.e., edema and pneumonia index), and viral loads, measured with RT-PCR in the upper and lower respiratory tracts, were determined. In addition, infectious virus titers from the lungs were measured using a plaque-forming assay. W-PreS-O-vaccinated hamsters developed robust nABs against Omicron, showed almost no macroscopic or microscopic signs of pneumonia, and had significantly reduced infectious virus titers in the lungs. Importantly, the viral loads in the nasal cavities of W-PreS-O-vaccinated hamsters were close to or above the PCR cycle threshold considered to be non-infectious. Our data provide compelling evidence demonstrating that the fusion W-PreS-O vaccine protects against challenge with Omicron SARS-CoV-2 in a Syrian hamster *in vivo* infection model. W-PreS-O is therefore a highly promising candidate vaccine for SARS-CoV-2 infections, and it should be further evaluated in clinical studies.

P151 iVDPV2: a threat for the polio-free world or not?

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Poliomyelitis is a neurological disease for a long time controlled by the vaccination with live oral poliovaccine (OPV) with continues efforts from Global Polio Eradication Initiative. Regretfully, vaccine polioviruses can mutate into vaccine-derived polioviruses during human-to-human transmission or multiplication in immunodeficient persons. VDPVs restore neurovirulent properties of wild polioviruses, can circulate in human population and cause poliomyelitis outbreaks. The formation of VDPV in a person with primary immunodeficiency (iVDPV) is a very rare event, and cases of longtime silent carrier state is even rarer. However, in these cases the virus can mutate silently for years, without any clinical manifestation. There were a number of surveys aimed to identification of such individuals, but longtime carriers were not identified. Nevertheless, from time to time polio laboratories all over the world, including polio-free countries not using OPV for several decades, isolate highly diverged VDPVs from sewage, indicating that such individuals exist. Do this people pose a threat? It is assumed that vaccination protects against all polioviruses. However, iVDPVs evolve in absence of immune response and can acquire unexpected mutations in antigenic sites that possibly can evade immune response. Since switch from tOPV types 1, 2, 3 to bOPV types 1, 3 the immunity to polioviruses type 2 is maintained by IPV vaccination, which includes only 1-2 doses in the most of the world countries. This leads to a decline of population immunity to polioviruses type 2, and raises the risk of VDPV2 circulation.

The main aim of the study was to evaluate the neutralizing antibodies spectrum against iVDPV2 induced by immunization with different combination of the vaccines.

Three isolates of VDPV2 were isolated from wastewater samples as part of the National Polio Surveillance Program in Russia in 2015-2023. The level of divergence from the Sabin2 vaccine strain varied between viruses from 7 to 17%. All isolates were classified as iVDPV2. Antibody titers were determined in neutralization test with sera from children under 15 years of age vaccinated according to various schemes (tOPV, IPV+bOPV, IPV) against studied viruses in comparison with the wild strain MEF and the vaccine strain Sabin2. In general, fully vaccinated children (4+ poliovaccine doses) had antibodies against all studied iVDPV2 viruses, although up to 50% children vaccinated with 1-2 IPV doses did not have antibodies against at least one of the variants. Moreover, in 2 out of 80 samples collected from children with 5 tOPV doses there were no antibodies against the most diverged iVDPV2 variant. Therefore, iVDPV2 can be escape mutants evading poliovaccine immunity. Undervaccinated children form a risk group, in which the virus can circulate and possibly cause a disease. However, vaccination with bOPV can boost the IPV induced immunity to polioviruses type 2 and help to solve the problem.

2024 Awards

The International Society for Vaccines is pleased to provide Awards to support PhD Students, Early Career Researchers, and scientists from low and middle-income countries (LMICs). Applications were reviewed by the ISV Awards & Prizes Committee and the Congress Co-Chairs. Awards are based on quality of abstract and application. Awardee abstracts are to be presented in-person and virtually.

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The International Society for Vaccines (ISV) Membership

The International Society for Vaccines (ISV) is a not-for-profit organization of professional members in the diverse disciplines of vaccinology. ISV engages, supports and sustains its membership through education, communication, and public information with the goal to advance human and animal health through immunization science and vaccination. Founded in 1994, Re-Organized in 2008.

Income from membership fees is vital to enable the ISV to accomplish valuable activities and support our members and the global vaccine community. To name just a few:

- ISV is the only international society whose sole purpose is to engage with, support, and connect people in the vaccine community.
- ISV is the only non-profit organization to lead an Annual International Conference dedicated to the science and the clinical development of vaccines.
- ISV awards program provides funding for Early Career Researchers from Low Middle-Income Countries (LMIC) and Non-LMIC to attend the ISV Annual Scientific Conference.
- ISV has been a go-to source of information for scientists, health care providers, policymakers, and science journalists of the global vaccine community.

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We encourage you to consider submitting a multi-year membership.

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- Reduced registration fee for the in-person ISV Annual Congress (US$100 savings).
- Receive regular ISV member-only newsletter.
- Access to career mentorship and a Next Generation Vaccinology network for ECR's.
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- Eligibility for ISV Officer and Board positions.
- Access to online version of journal Vaccine (upon request).
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NOTES

NOTES

The International Society for Vaccines is pleased to announce the 2025 ISV Annual Congress
will occur in South Africa, Protea Hotel, Stellenbosch
28-30 October 2025

2025 ISV Annual Congress Co-Chairs

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University of Cape Town,
South Africa

Michelle Groome
University of the Witwatersrand,
South Africa

Michael Schotsaert
Icahn School of Medicine, Mount Sinai,
United States

AT A GLANCE PROGRAM

MONDAY 21 OCTOBER 2024

09:00-10:00	WELCOME COFFEE *Sponsored by Afrigen Biologics & Vaccines*	(Hanra Foyer)
10:00-10:10	OPENING SESSION	(Hanra 1 & 2)
10:10-10:40	STANLEY PLOTKIN LECTURE: **Jerome Kim,** *International Vaccine Institute (IVI), South Korea*	(Hanra 1 & 2)
10:40-12:00	PLENARY SESSION 1: CLIMATE CHANGE AND EMERGING INFECTIONS	(Hanra 1 & 2)
12:00-13:30	LUNCH *Sponsored by Pfizer*	(Hanra 1 & 2)
12:15-13:25	Cutting Edge: AI/ML and Computational Vaccinology Workshop *Organized by EpiVax, Inc.*	(Hanra 3)
13:30-14:50	PLENARY SESSION 2: VACCINES WITH BROAD IMPACT	(Hanra 1 & 2)
15:00-15:30	COFFEE BREAK *Sponsored by Arcturus Therapeutics*	(Hanra Foyer)
15:30-17:30	• CONCURRENT SESSION 1 (Hanra 1): VIRAL VACCINES OF CONTEMPORARY INTEREST • CONCURRENT SESSION 2 (Hanra 2): STRATEGIES FOR IMPROVED PROTECTION • CONCURRENT SESSION 3 (Hanra 3): VACCINES AGAINST CHALLENGING TARGETS • Bright Sparks in Vaccinology: PhD Students (Rendezvous 2nd floor)	
17:30-20:00	POSTER SESSION 1	(Shilla 1-5)
18:00-18:20	ISV CONGRESS AWARDS CEREMONY	(Shilla 1-5)
18:00-20:00	WELCOME RECEPTION *Sponsored by Epivax, Inc.*	(Shilla 1-5/Hanra/Shilla Foyers/Hanra 1)

TUESDAY 22 OCTOBER 2024

08:00-08:30	MORNING COFFEE *Sponsored by SK bioscience*	(Hanra Foyer)
08:30-08:55	KEYNOTE SPEAKER: **Peter Lawaetz Andersen,** *Novo Nordisk Foundation, Denmark*	(Hanra 1 & 2)
08:55-10:15	PLENARY SESSION 3: AI AND MACHINE LEARNING FOR VACCINE R&D	(Hanra 1 & 2)
10:15-10:45	COFFEE BREAK *Sponsored by GPN Vaccines*	(Hanra Foyer)
10:45-12:25	• CONCURRENT SESSION 4 (Hanra 1): MUCOSAL VACCINES • CONCURRENT SESSION 5 (Hanra 2): THE MYSTERY OF MERS: VACCINES & IMMUNOLOGY • CONCURRENT SESSION 6 (Hanra 3): ROUNDTABLE: REGULATORY ISSUES FOR VACCINE DEVELOPMENT • Bright Sparks in Vaccinology: Early Career Researchers (Rendezvous 2nd floor)	
12:30-14:00	LUNCH *Sponsored by Vaxxas*	(Hanra 1 & 2)
12:45-14:00	Current Status and Future Prospects of New Vaccine Development Workshop *Organized by Global Vaccine Leading Technology Center (GVLTC)*	(Hanra 3)
12:45-13:30	MENTORSHIP PROGRAM: LEARN ABOUT THE ISV'S NEW PROGRAM	(Rendezvous 2nd Floor)
13:30-15:00	POSTER SESSION 2	(Shilla 1-5)
14:00-15:00	ISV ANNUAL GENERAL MEETING	(Hanra 1)
15:00-15:30	COFFEE BREAK *Sponsored by BioNTech*	(Hanra Foyer)
15:30-17:35	PLENARY SESSION 4: DELIVERY & NEW ADJUVANTS	(Hanra 1 & 2)

WEDNESDAY 23 OCTOBER 2024

08:00-08:30	MORNING COFFEE *Sponsored by CanSinoBIO*	(Hanra Foyer)
08:30-08:55	KEYNOTE SPEAKER: Albert Osterhaus, *University of Veterinary Medicine Hannover (TiHo), Germany*	(Hanra 1 & 2)
08:55-10:00	PLENARY SESSION 5: THERAPEUTIC VACCINES AGAINST CANCER	(Hanra 1 & 2)
10:00-10:30	COFFEE BREAK *Sponsored by EuBiologics*	(Hanra Foyer)
10:30-12:30	• CONCURRENT SESSION 7 (Hanra 1): VACCINE PRODUCTION AND EVALUATION • CONCURRENT SESSION 8 (Hanra 2): NEW VACCINES AGAINST OLD BUGS • CONCURRENT SESSION 9 (Hanra 3): INNOVATIVE RNA VACCINE TECHNOLOGY	
12:30-14:00	LUNCH *Sponsored by Valneva Austria GmbH*	(Hanra 1 & 2)
12:45-13:45	Canadian Government Workshop: Health Emergency Readiness Canada; Life Sciences and Biomanufacturing Capacity Building and Opportunity for Global Cooperation in Vaccine Development	(Hanra 3)
12:45-13:45	CAREER DEVELOPMENT: HAVE YOUR QUESTIONS ANSWERED ABOUT DIFFERENT CAREER PATHS	(Rendezvous 2nd Floor)
14:00-14:30	ISV AWARDS CEREMONY	(Hanra 1 & 2)
14:30–14:55	PAPER OF THE YEAR PRESENTATION	(Hanra 1 & 2)
14:55- 15:45	PLENARY SESSION 6: VACCINES FOR ONE HEALTH AND PANDEMIC PREPAREDNESS	(Hanra 1 & 2)
15:45–16:00	CLOSING SESSSION & INTRODUCTION TO 2025 ISV ANNUAL CONGRESS	(Hanra 1 & 2)