A Welcome from the ISV Congress Co-Chairs

Dear Delegates,

On behalf of the International Society for Vaccines (ISV), it is a great pleasure and honor to welcome experts from around the globe and across diverse disciplines to the 2018 ISV Annual Congress in Atlanta. We are particularly thrilled this year to have the 2018 ISV Annual Congress in the city that is home to U.S. Centers for Disease Control and Prevention, the heart of Public Health in the USA.

The ISV Congress occupies a unique position of being the world’s largest non-profit scientific conference in the field of vaccines. The program covers all aspects of research and development for vaccine and immunotherapies and is organized to facilitate presentation of the latest scientific findings from around the world as well as providing a forum for determining and advancing the best means to expedite vaccine development. It encourages interactions amongst leading scientists as well as young trainees representing diverse aspects of the vaccine field. The Congress also features a career development and mentoring session for young scientists to obtain advice from senior vaccinologists from the varied sectors (academia, industry, government, NGO), and explore career options.

The 2018 ISV Congress is delighted that Dr. Julie Gerberding, M.D., M.P.H., Executive Vice President - Communications, Global Policy, and Population Health and Chief Patient Officer at Merck will be the Opening Keynote Speaker. Dr. Gerberding was recently honored as the Healthcare Businesswomen's Association (HBA) 2018 Woman of the Year. She was recognized for her remarkable contributions to health as a physician, infectious disease expert, first female director of the CDC, and for her leadership roles at Merck. This Opening Keynote Lecture will honor of Dr. Adel Mahmoud. Dr. Mahmoud was an infectious-disease expert who played a vital role in the development of lifesaving vaccines. He served as president of Merck Vaccines from 1998 until 2006. Dr. Mahmoud oversaw the creation and marketing of several vaccines that have brought major advances in public health. These include a vaccine which prevents rotavirus infection, a potentially fatal cause of diarrhea in babies, a vaccine for HPV, combination vaccines (MMRV), among others. Dr. Mahmoud was also a champion of global health issues and the need for new approaches to develop vaccines for emerging markets.

We would like to thank the many individuals from ISV, the Scientific Committee, the invited speakers, and the volunteer leaders for their efforts throughout the year in developing and contributing to this outstanding program. Special thanks are due to our Dr. Shan Lu and Ted Gibson at the ISV Congress Secretariat for their enormous efforts with all aspects of the Congress and handling the many logistical issues that arise with such a complex undertaking.

Gratitude is also due our partners, sponsors, and the numerous organizations who have enabled the ISV to both provide financial assistance enabling trainees and scientists from Lower and Middle-Income Countries to attend and to keep registration costs low for all attendees. We would also like to recognize the Georgia Research Alliance for its sponsorship and special support to bring the Congress to Atlanta in 2018.

Everyone is encouraged to attend the ISV annual general meeting on Monday afternoon, Oct. 29th. The Society welcomes members and non-members alike. We are continually expanding the areas of information and benefits offered to members and the greater vaccine community. Your personal involvement in the Society promotes collaboration and your scientific visibility.

Welcome to Atlanta! Enjoy the science and the people.

Ted M. Ross, ISV Congress Co-Chair, University of Georgia, USA
Denise Doolan, ISV Congress Co-Chair, James Cook University, Australia
Rafi Ahmed, ISV Local Co-Chair, Emory University, USA
Julia Hilliard, ISV Local Co-Chair, Georgia State University, USA
Mark Prausnitz, ISV Co-Chair, Georgia Tech University, USA
Co-chairs of the 2018 ISV Congress will select presentations for possible publication in Human Vaccines & Immunotherapeutics

Details will be announced during the congress
Contents

Welcome

General Information

Conference Program

Julie Gerberding and Adel Mahmoud
Photos and Biographies

Invited Speaker Photos

Invited Speaker Biographies & Abstracts

Oral Presenter Abstracts

Poster Presenter Abstracts

Award Recipients

Oral and Poster Number Index

Note Paper
ISV CONGRESS co-CHAIRS

Ted Ross, University of Georgia, USA  
Denise Doolan, James Cook University, Australia

CONGRESS LOCAL co-CHAIRS

Rafi Ahmed, Emory University, USA  
Julie Hilliard, Georgia State University, USA  
Mark Prausnitz, Georgia Tech University, USA

SCIENTIFIC COMMITTEE

Randy Albrecht, Icahn School of Medicine at Mount Sinai, USA  
Guirakhoo Farshad, GeoVax, USA  
Lars Frelin, Karolinska Institutet, Sweden  
Davinder Gill, Hilleman Laboratories, India  
Ali Harandi, University of Gothenburg, Sweden  
Stephen Hoffman, Sanaria, USA  
Linda Klavinskis, King’s College London, UK  
Karl Ljungberg, Karolinska Institutet, Sweden  
Janet McNicholl, Centers for Disease Control and Prevention, USA  
Ed Mocarski, Emory University, USA  
Marty Moore, Meissa Vaccines, USA  
Mark Schleiss, University of Minnesota, USA  
Sean Tucker, Vaxart, USA  
Jeffrey Ulmer, GlaxoSmithKline, USA  
Thiru Vanniasinkam, Charles Sturt University, Australia  
Vish Nene, ILRI, Kenya  
Heather Wilson, University of Saskatchewan, Canada  
Anna-Lise Williamson, University of Cape Town, South Africa  
Suh-Chin (Samuel) Wu, National Tsing Hua University, Taiwan

CONGRESS SECRETARIAT

Shan Lu, UMass Medical School, USA  
Email: shan.lu@umassmed.edu  
Tel: +1-508-856-6791  
Ted Gibson, UMass Medical School, USA  
Email: edward.gibson@umassmed.edu  
Tel: +1-508-856-1179

CONGRESS VENUE

Atlanta Marriott Marquis  
265 Peachtree Center Ave, Atlanta, GA 30303  
Tel: +1-404-521-0000

CONGRESS WEBSITE

Conference website: www.isvcongress.org  
ISV website: www.isv-online.org
REGISTRATION DESK
The registration/information desk will be located in the Imperial Foyer area and will remain open throughout the conference staffed during the following times:

- Sunday, 28 October  8:00am-8:00pm
- Monday, 29 October  7:30am-6:00pm
- Tuesday, 30 October  7:30am-2:00pm

BADGES
For security reasons and catering purposes please make sure you wear your conference badge. Replacements for lost badges are available from the registration desk.

CONFERENCE BAGS & DELEGATE BOOKS
Please make sure that you insert a business card or name tag in your bag. Please also write your name in your delegate book and do not leave either your book or bag unattended at the conference at any time.

ORAL ABSTRACT PRESENTATIONS
Your presentation has been allocated a total of 15 minutes; this includes time for questions, so please keep the actual talk to 10-12 minutes to allow time for questions. Chairpersons will eliminate questions for speakers whose talk runs the full 15 minutes. The day of your talk please take your presentation on a USB flash drive directly to the AV technician in the room listed in the program for your session. ISV staff will be available if you have any questions with this process.

POSTER SESSIONS
Please plan to set up your posters anytime between 6:00AM-9:45AM on Sunday, October 28th prior to the start of the opening remarks. The poster stands will be located in Imperial Room B. There will be poster numbers posted at each stand. Please refer to your program to see your poster designation number.

The dedicated poster session will take place on Sunday, October 28th from 6:10PM-8:00PM as well as Monday, October 29th from 1:00PM-2:30PM. Poster presenters should ensure that they stand by their posters during this time.

Please remove your posters on Tuesday, October 30th at the conclusion of the program if you wish to bring with you. Any posters left after 5:00PM will be discarded.

WELCOME RECEPTION
A welcome reception will take place on Sunday, October 28th in the Imperial Foyer area and Imperial B during the poster session. Complimentary hors d’oeuvres and drinks will be provided.
**LUNCH**

Lunch will be provided on Sunday, Monday, and Tuesday at the Skyline Level 10 (10th Floor) at no cost for all attendees.

**COFFEE BREAKS**

Coffee breaks will be available in the Imperial Foyer and Imperial Room B Sunday, Monday and Tuesday at no cost for all attendees.

**WI-FI**

Wi-Fi will be available at the conference free of charge. The Wi-Fi network name is **Marriott_CONFERENCE** and the password is **ISV2018**. This information is also located on the back of your badge.

**GALA DINNER**

The Gala Dinner will take place on the evening of Monday, October 29th at the Fernbank Museum of Natural History (tickets are required). The buses will begin loading at the main entrance of the hotel at 6:00PM. Staff will be available to escort you to the pick-up area. The dinner will take place from 6:30PM -10:00PM. Buses will begin loading at 10:00PM to bring you back to the hotel.

Pre-purchased tickets are located in your badge holder.

**RECORDING OF SESSIONS**

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

**EVALUATION FORM**

Your comments and views on the content and organization of the conference are highly valued and we would encourage you to complete an online evaluation form which will be emailed to you after the conference.

**MESSAGES**

Messages for delegates received at the registration desk will be posted on the message board in the Imperial Foyer. You are welcome to use the message board to contact fellow delegates.
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:00-09:15</td>
<td>REGISTRATION</td>
<td></td>
</tr>
<tr>
<td>08:30-09:45</td>
<td>WELCOME COFFEE <em>(Imperial Foyer)</em></td>
<td>SPONSORED BY: <em>GlaxoSmithKline (GSK)</em></td>
</tr>
<tr>
<td>09:45-09:55</td>
<td>CONGRESS CO-CHAIRS OPENING REMARKS <em>(Imperial Salon A)</em></td>
<td>ISV Congress co-Chairs: Ted Ross, University of Georgia; Denise Doolan, James Cook University</td>
</tr>
<tr>
<td>9:55-10:00</td>
<td>INTRODUCTION OF OPENING SESSION AND SPEAKER <em>(Imperial Salon A)</em></td>
<td>David Weiner, ISV President</td>
</tr>
<tr>
<td>10:00-10:45</td>
<td>Creating Vaccine Confidence: Courage, Conviction, and Compassion <em>(Imperial Salon A)</em></td>
<td>Julie Gerberding, Merck and Co. and US CDC Director (2002-2009)</td>
</tr>
<tr>
<td>10:45-12:00</td>
<td>PLENARY SESSION 1: Influenza 1918 to 2018 <em>(Imperial Salon A)</em></td>
<td>Ted Ross, University of Georgia; Rafi Ahmed, Emory University</td>
</tr>
<tr>
<td>10:45-11:10</td>
<td>[PL1.1] Where did the Spanish Influenza come from and could its killing power have been thwarted by</td>
<td>John Oxford, Queen Mary College</td>
</tr>
<tr>
<td></td>
<td>the “new” vaccines in 1918?</td>
<td></td>
</tr>
<tr>
<td>11:10-11:35</td>
<td>[PL1.2] Pathogenesis of the 1918 Pandemic Virus</td>
<td>Terrence Tumpey, Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>11:35-12:00</td>
<td>[PL1.3] Influenza Vaccine Effectiveness: What’s the Problem with H3N2?</td>
<td>Edward Belongia, Marshfield Clinic Research Institute</td>
</tr>
<tr>
<td>12:00-13:30</td>
<td>LUNCH <em>(Skyline – 10th Floor)</em></td>
<td>SPONSORED BY: <em>INOVIO PHARMACEUTICALS</em></td>
</tr>
<tr>
<td>13:30-15:45</td>
<td>CONCURRENT SESSION 1: Vaccine Technologies, Formulations, and Delivery <em>(International 8)</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[O1.1] Developing Vaccines that Elicit Broadly Neutralizing Antibodies</td>
<td>Ravi Kane, Georgia Tech University</td>
</tr>
<tr>
<td></td>
<td>[O1.2] Microneedle Patch as a New Vaccine Delivery Method</td>
<td>Nadine Rouphael, Emory University</td>
</tr>
<tr>
<td>13:30-13:55</td>
<td>[O1.3] Immunogenicity of a protective intradermal DNA vaccine against Lassa Virus in Cynomolgous</td>
<td>Jingjing Jiang, Inovio Pharmaceuticals</td>
</tr>
<tr>
<td></td>
<td>[O2.1] Immunogenicity of Neoantigen Cancer Vaccines</td>
<td>Hyewon Phee, Amgen</td>
</tr>
<tr>
<td></td>
<td>[O2.2] Advances in the field of in-silico methods for the identification of (neo)epitopes.</td>
<td>Morten Nielsen, The Technical University of Denmark</td>
</tr>
<tr>
<td></td>
<td>[O2.3] Beyond Adjuvants: Vaccines for Cancer Immunotherapy and Infectious Disease</td>
<td>Young Taik Lim, Sungkyunkwan University</td>
</tr>
<tr>
<td></td>
<td>[O3.1] Toward licensure of the first and future generations of live parasite</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[O3.2] Autophagy: a New Strategy for Host-directed Therapy of Tuberculosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[O3.3] Replicating Single Cycle Adenovirus Vaccine against Clostridium Difficile</td>
<td></td>
</tr>
<tr>
<td>14:20-14:35</td>
<td></td>
<td>William Matchett, Mayo Clinic</td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
<td>Title</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>14:35-14:50</td>
<td>[O1.4]</td>
<td>Genomic DNA as a damage-associated molecular pattern increases the immunogenicity of influenza vaccines given by a dissolvable microneedle patch</td>
</tr>
<tr>
<td></td>
<td>[O3.4]</td>
<td>Vaccine-induced immunity in the immunocompromised host: Evaluating antifungal vaccine efficacy in a non-human primate model of drug-induced immunosuppression</td>
</tr>
<tr>
<td></td>
<td>[O2.5]</td>
<td>Development of Vaccines for Infectious Diseases and Cancer Using a Novel MVA-VLP Vector</td>
</tr>
<tr>
<td></td>
<td>[O3.5]</td>
<td>To what Extent Are Recent Pertussis Epidemics Due to Under Vaccination or to Waning of Pertussis Vaccine Immunity?</td>
</tr>
<tr>
<td>15:05-15:20</td>
<td>[O1.6]</td>
<td>Immunogenicity and Efficacy of a Thermostable Live-Attenuated Influenza Vaccine in Ferrets</td>
</tr>
<tr>
<td></td>
<td>[O2.7]</td>
<td>A DNA-based immunotherapy induces receptor-blocking antibodies that can neutralize HBV in humanized mice</td>
</tr>
<tr>
<td>15:45-16:15</td>
<td></td>
<td>COFFEE BREAK (Imperial Foyer/Imperial Salon B)</td>
</tr>
<tr>
<td>16:15-16:40</td>
<td>[PL2.1]</td>
<td>Vaccines and Immune Memory</td>
</tr>
<tr>
<td></td>
<td>[PL2.2]</td>
<td>Profiling the IgOme - the repertoire of antibodies in serum: principles and applications</td>
</tr>
<tr>
<td>16:40-17:05</td>
<td>[PL2.3]</td>
<td>Understanding Innate Immune Mechanisms Dictating Vaccine Responses</td>
</tr>
<tr>
<td></td>
<td>[PL2.4]</td>
<td>The History of Pertussis and Pertussis Vaccines; Mistakes Made during a 112-Year Odyssey and What some of those Mistakes Bode for the Future</td>
</tr>
<tr>
<td>17:05-17:30</td>
<td>[PL2.5]</td>
<td>Skin immunisation harnesses networks of protective immune connectivity in peripheral tissues</td>
</tr>
<tr>
<td>17:30-17:55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17:55-18:10</td>
<td>[PL2.5]</td>
<td>Skin immunisation harnesses networks of protective immune connectivity in peripheral tissues</td>
</tr>
<tr>
<td>18:10-20:00</td>
<td></td>
<td>POSTER SESSION # 1</td>
</tr>
<tr>
<td>18:30-20:00</td>
<td></td>
<td>WELCOME RECEPTION (Imperial Foyer/Imperial Salon B)</td>
</tr>
<tr>
<td>Time</td>
<td>Event</td>
<td>Room</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>07:30-08:30</td>
<td>MORNING COFFEE (Imperial Foyer)</td>
<td>SPONSORED BY: MERCK</td>
</tr>
<tr>
<td>08:30-10:10</td>
<td>PLENARY SESSION 3: Human Vaccine Trials</td>
<td>(Imperial Salon A)</td>
</tr>
<tr>
<td></td>
<td>Session Chairs: Julia Hilliard, Georgia State University; Annie DeGroot, EpiVax, Inc.</td>
<td></td>
</tr>
<tr>
<td>08:30-08:55</td>
<td>[PL3.1] The State of Vaccine Development Against the Human Cytomegalovirus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stanley Plotkin, Vaxconsult</td>
<td></td>
</tr>
<tr>
<td>08:55-09:20</td>
<td>[PL3.2] Lymphoid tissue fibrosis is associated with impaired vaccine responses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tim Schacker, University of Minnesota</td>
<td></td>
</tr>
<tr>
<td>09:20-09:45</td>
<td>[PL3.3] Vaccines for Herpes Zoster</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tony Cunningham, The Westmead Institute for Medical Research and University of Sydney</td>
<td></td>
</tr>
<tr>
<td>09:45-10:10</td>
<td>[PL3.4] Epstein-Barr Virus Vaccine for the Prevention of Infectious Mononucleosis—and What Else?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hank Balfour, University of Minnesota Medical School</td>
<td></td>
</tr>
<tr>
<td>10:10-10:40</td>
<td>COFFEE BREAK (Imperial Foyer/Imperial Salon B)</td>
<td>SPONSORED BY: GC PHARMA</td>
</tr>
<tr>
<td>10:40-12:30</td>
<td>CONCURRENT SESSION 4 Viral Vaccines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(International 8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Session Chairs: Mark Connors, NIAID, Lars Frelin, Karolinska Institutet</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tong Ming Fu, Merck Research Laboratories</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Martin Moore, Meissa Vaccines</td>
<td></td>
</tr>
<tr>
<td>11:05-11:30</td>
<td>[O5.1] Innovative vaccination methods</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gary Kobinger, Université Laval</td>
<td></td>
</tr>
<tr>
<td>11:05-11:30</td>
<td>[O5.2] Rift Valley Fever control through vaccination: an ongoing challenge in endemic regions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baptiste Dungu, MCI Sante Animale</td>
<td></td>
</tr>
<tr>
<td>11:30-11:45</td>
<td>[O6.1] Composite Virus-like particles (VLP) by constructing intelligent artificial nano/micro “chassis” assembled with antigens</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Guanghui Ma, Chinese Academy of Sciences</td>
<td></td>
</tr>
<tr>
<td>11:30-11:45</td>
<td>[O6.2] Development of therapeutic vaccines for cardiovascular diseases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hironori Nakagami, Osaka University</td>
<td></td>
</tr>
<tr>
<td>11:45-12:00</td>
<td>[O6.3] Is the current dose of normal human immunoglobulin for post-exposure prophylaxis of measles in Australia too low?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Megan Young, Griffith University</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Julia Baker, Emory University</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| 12:00-12:15  | [O4.5] Unraveling the respiratory syncytial virus (RSV) antibody functional repertoire in adult healthy donors  
Emanuele Andreano, University of Siena (IT)  |
|              | [O5.5] A Universal Dengue Vaccine Elicits Neutralizing Antibodies Against Strains from All Four Dengue Serotypes  
Naoko Uno, University of Georgia  |
|              | [O6.5] Estimating the population-level effect of pediatric norovirus vaccination: A model simulation study  
Elizabeth Sajewski, Emory University  |
| 12:15-12:30  | [O4.6] Elicitation of protective antibodies against 20 years of future H3N2 co-circulating influenza virus variants in ferrets imprinted to historical H3N2 influenza viruses  
James Allen, University of Georgia  |
|              | [O5.6] Multiroute morbillivirus entry: disease informs delivery  
Paul Duprex, Boston University  
School of Medicine  |
Joseph Opare, Ghana Health Service/Ministry of Health  |
| 12:30-13:30  | LUNCH (Skyline – 10th Floor)  |
| 13:00-14:30  | POSTER SESSION # 2 (Imperial Salon B)  |
| 14:00-15:00  | ISV ANNUAL MEETING (Imperial Salon A)  |
| 15:00-15:30  | COFFEE BREAK (Imperial Foyer/Imperial Salon B)  |
|              | SPONSORED BY: HIVF  |
| 15:30-17:50  | PLENARY SESSION 4: Vaccines for Influenza Viruses (Imperial Salon A)  
Session Chairs: Mark Tompkins, University of Georgia; Sang-Moo Kang, Georgia State University  |
|              | [PL.4.1] Systems Profiling of Fluzone™ Vaccinees – Biomarkers of Breadth & Durability  
Harold Kleanthous, Sanofi Pasteur  |
|              | [PL4.2] New insights into mucosal vaccine adjuvant functions that can be explored for developing broadly protective influenza vaccines  
Nils Lycke, University of Gothenburg  |
|              | [PL4.3] VaxArray Neuraminidase: A new assay for neuraminidase quantification of seasonal influenza vaccines  
Rose Nash, InDevR  |
|              | [PL4.4] An alternative strategy as a quadrivalent live attenuated influenza virus vaccine  
Zhimin Wan, University of Georgia  |
|              | [PL4.5] Molecular Dissection of the Antibody Response Elicited by a Computationally Optimized Broadly Reactive Antigen (COBRA) H1 Hemagglutinin Influenza Vaccine  
Giuseppe Andrea Sautto, University of Georgia  |
|              | [PL4.6] Pan-influenza A protection by prime-boost vaccination with X-31 cold-adapted live attenuated influenza vaccine  
Baik Seong, Yonsei University  |
|              | [PL4.7] Development of paradigm-shifting T cell-targeting universal influenza vaccines  
Daniel Hoft, Saint Louis University  |
<p>| 17:50-18:20  | BUS PICK UP FOR GALA DINNER  |
| 18:30-22:00  | GALA DINNER (TICKETS REQUIRED)  |
|              | SPONSORED BY: VGXI, Inc. and GEORGIA RESEARCH ALLIANCE  |</p>
<table>
<thead>
<tr>
<th>Time</th>
<th>Session/Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>07:30-08:30</td>
<td>MORNING COFFEE (Imperial Foyer) SPONSORED BY: CELLULAR TECHNOLOGY LIMITED (CTL)</td>
</tr>
<tr>
<td>08:30-10:10</td>
<td>PLENARY SESSION 5: Public Health, Public Policy, and Vaccine Acceptance (Imperial Salon A) Session Chairs: Margaret Liu, ProTherImmune; David Weiner, The Wistar Institute</td>
</tr>
<tr>
<td>08:30-08:55</td>
<td>[PL5.1] Vaccine hesitancy – the global landscape Pauline Patterson, London School of Hygiene &amp; Tropical Medicine (LSHTM)</td>
</tr>
<tr>
<td>08:55-09:20</td>
<td>[PL5.2] Fostering Vaccine and Immunization Acceptance: Insights from Communication Practice and Research Glen Nowak, University of Georgia</td>
</tr>
<tr>
<td>09:20-09:45</td>
<td>[PL5.3] Vaccine associated-hypersensitivity Michael McNeil, Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>09:45-10:10</td>
<td>[PL5.4] Global strategy of Polio eradication: Russian experience Aydar Ishmukhametov, Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products</td>
</tr>
<tr>
<td>10:10-10:40</td>
<td>COFFEE BREAK (Imperial Foyer/Imperial Salon B)) SPONSORED BY: SANOFI PASTEUR</td>
</tr>
<tr>
<td>10:40-12:20</td>
<td>CONCURRENT SESSION 7 Immunodulators and Vaccines (International 8) Session Chairs: Ali Harandi, University of Gothenburg Joon Haeng Rhee Chonnam National University Medical School</td>
</tr>
<tr>
<td></td>
<td>CONCURRENT SESSION 8 One Health and Vet Vaccines (International 9) Session Chairs: Anna-Lise Williamson, University of Cape Town Dennis Klinman, National Cancer Institute</td>
</tr>
<tr>
<td></td>
<td>CONCURRENT SESSION 9 HIV/AIDS (International 10) Session Chairs: Janet McNicholl, Centers for Disease Control and Prevention Barbara Felber, National Cancer Institute</td>
</tr>
<tr>
<td>10:40-11:05</td>
<td>[O7.1] Vaccination against chronic diseases using virus-like particles Martin Bachmann, Jenner Institute</td>
</tr>
<tr>
<td></td>
<td>[O8.1] Nanoparticle technologies that help drive bovine immune responses in East Coast fever vaccine development Vish Nene, International Livestock Research Institute (ILRI)</td>
</tr>
<tr>
<td></td>
<td>[O9.1] Humoral responses to HIV-1: building the paths to a protective vaccine Guido Ferrari, Duke University School of Medicine</td>
</tr>
<tr>
<td></td>
<td>[O8.2] African Horse Sickness Virus-Like Particle Vaccine Candidate Made in Plants Edward Rybicki, Biopharming Research Unit, University of Cape Town</td>
</tr>
<tr>
<td></td>
<td>[O9.2] Needle-free injection of the sublingual and buccal tissues with an HIV-1 vaccine induces strong systemic and mucosal immune responses and protects from SHIV challenge in rhesus macaques Andrew Jones, Emory University</td>
</tr>
<tr>
<td>11:20-11:35</td>
<td>[O7.3] Human clinical data on use of Advax delta inulin adjuvants in infectious disease, allergy and cancer vaccines Nikolai Petrovsky, Flinders University</td>
</tr>
<tr>
<td></td>
<td>[O8.3] Vaccination and intra-cage transmission of a recombinant parainfluenza virus 5 expressing Rabies lyssavirus glycoprotein in the big brown bat (Eptesicus fuscus) Kelsey Briggs, University of Georgia</td>
</tr>
<tr>
<td></td>
<td>[O9.3] DNA+Protein HIV vaccine protection against SHIV challenge upon same site administration in macaques Barbara Felber, National Cancer Institute</td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>[O8.4]</td>
</tr>
<tr>
<td></td>
<td>[O9.4]</td>
</tr>
<tr>
<td>11:50-12:05</td>
<td>[O7.5]</td>
</tr>
<tr>
<td></td>
<td>[O8.5]</td>
</tr>
<tr>
<td></td>
<td>[O9.5]</td>
</tr>
<tr>
<td>12:05-12:20</td>
<td>[O7.6]</td>
</tr>
<tr>
<td></td>
<td>[O8.6]</td>
</tr>
<tr>
<td></td>
<td>[O9.6]</td>
</tr>
<tr>
<td>12:20-13:20</td>
<td></td>
</tr>
<tr>
<td>13:20-14:00</td>
<td></td>
</tr>
<tr>
<td>14:00-14:30</td>
<td></td>
</tr>
<tr>
<td>14:30-15:15</td>
<td></td>
</tr>
<tr>
<td>14:30-15:55</td>
<td>[PL6.1]</td>
</tr>
<tr>
<td>15:10-15:25</td>
<td>[PL6.3]</td>
</tr>
<tr>
<td>15:40-15:55</td>
<td>[PL6.5]</td>
</tr>
<tr>
<td>16:00-16:15</td>
<td></td>
</tr>
</tbody>
</table>
Dr. Julie Gerberding

The 2018 ISV Congress is pleased to announce the Opening Keynote Speaker as Dr. Julie Gerberding, M.D., M.P.H., Executive Vice President - Communications, Global Policy, and Population Health, and Chief Patient Officer at Merck. Dr. Gerberding was recently honored as the Healthcare Businesswomen's Association (HBA) 2018 Woman of the Year. Julie was recognized for her remarkable contributions to health as a physician, infectious disease expert, first female director of the CDC and for her leadership roles at Merck.

Dr. Adel Mahmoud

Julie will present the Opening Keynote Lecture on Sunday morning, October 28th at the Congress in honor of Dr. Adel Mahmoud (24 August 1941 – 11 June 2018). Dr. Mahmoud was an infectious-disease expert who played a vital role in the development of lifesaving vaccines. He served as president of Merck Vaccines from 1998 until 2006, Dr. Mahmoud oversaw the creation and marketing of several vaccines that brought major advances in public health. These include a vaccine which prevents rotavirus infection (a potentially fatal cause of diarrhea in babies), a vaccine for HPV, combination vaccines (MMRV), among others. He was also a champion of global health issues and the need for new approaches to develop vaccines for emerging markets.
Rafi Ahmed

Dr. Rafi Ahmed received his Ph.D. in microbiology from Harvard University and is currently the Director of the Emory Vaccine Center and the Charles Howard Candler Professor of Microbiology and Immunology. Dr. Ahmed, a member of the National Academy of Science, is a world-renowned immunologist whose work during the past decade has been highly influential in shaping our current understanding of memory T cell differentiation and anti-viral T and B cell immunity. His work has revealed mechanisms by which immunological memory is maintained after infection and vaccination. His seminal work defined the cellular and molecular basis of T and B cell memory providing a framework for the rational design of vaccines against infectious diseases. He identified long-lived plasma cells and showed that these cells were critical for the maintenance of humoral immunity. He then documented an essential role for CD4 T cells and the SLAM-associated protein in the generation of these long-lived plasma cells. Ahmed’s studies on T cell memory established that memory cells could persist in the absence of antigen resolving a long-standing and much debated issue in immunology. His subsequent work defined the transcriptional and functional changes that occur during memory CD8 T cell differentiation and delineated how cell fate decisions are made and how memory CD8 T cells acquire the ability to undergo self-renewal and rapidly respond to re-infection. Ahmed’s studies comparing T cell differentiation during acute versus chronic infection resulted in ground-breaking discoveries on T cell dysfunction. He showed that the lack of T cell responses during chronic infection was not due to deletion of the reactive cells but due to functional exhaustion of virus specific CD8 T cells. Ahmed’s subsequent discovery linking T cell exhaustion with the PD-1 inhibitory receptor and showing that \textit{in vivo} blockade of this inhibitory pathway can restore function in exhausted T cells and reduce viral load has been highly influential in the clinical development of PD-1 directed immunotherapy for the treatment of human chronic infections and cancer.

Abstract [PL2.1]:

Central questions regarding the origin of memory CD8 T cells, their turnover and longevity \textit{in vivo} are not well-defined in humans. Here, we have used the highly efficacious live yellow fever virus vaccine (YFV-17D) to address these issues in the context of a primary acute viral infection. We used \textit{in vivo} labeling with vaccinees drinking heavy water (D2O) thereby marking all CD8 T cells proliferating in response to the virus with deuterium. We then assessed cellular turnover and longevity by quantifying deuterium dilution kinetics in YFV-specific tetramer+ CD8 T cells by mass spectrometry. Remarkably, the YFV-specific CD8 T cells detected more than 1-2 YEARS after vaccination had minimal dilution of deuterium; the labelled cell replacement half-life of \~450 days indicated that the population divided less than once every year. These data show that the memory pool originates from CD8 T cells that have divided extensively during the effector stage and is then maintained by intrinsically long-lived cells that undergo slow turnover with a long intermitotic interval. These YFV-specific memory CD8 T cells had a transcriptional program that was much more similar to naive CD8 T cells than to effector cells but their DNA methylation profile at effector genes and open chromatin map based on ATAC-seq analysis was highly similar to effector CD8 T cells. This open chromatin profile was maintained in memory cells isolated even a decade after vaccination showing that these quiescent long-lived memory cells remain epigenetically poised for rapid activation upon re-encounter with antigen. Taken together, these data provide compelling evidence that long-lived human virus specific memory CD8 T cells retain an epigenetic imprint of their effector history. This addresses a fundamental and much debated issue in memory T cell differentiation.
Martin Bachmann

Martin Bachmann (50) grew up near Winterthur and studied Cell Biology at the ETH Zurich. He then went on to perform his doctoral studies in Immunology at the lab of Rolf Zinkernagel in Zurich. Both his diploma and doctoral thesis were honored with a silver medal from the ETH. After graduating he worked for two year as a post-doc in the lab of Prof Pam Ohashi in Toronto and then became a member at the Basel Institute for Immunology. From the end of 1999 to 2012 Martin Bachmann was the CSO for Cytos Biotechnology in Schlieren. After leaving Cytos, he held various positions as guest lecturer at the University of Zurich, research director of the cancer center in Doha, Qatar and before becoming chair of immunology in Bern and associate professor of Immunology in Oxford.

The focus of his research is the translation of novel immunological insights into therapeutics with clinical applications. He has helped develop 7 immune therapeutics from bench to bedside and clinical efficacy of several vaccines and immune modulators has been proven. CAD106, a vaccine against Alzheimer’s disease, is currently in phase III trials with Novartis at the moment.

Martin is the author of over 250 scientific publications, his work has been cited over 29’000 times and his h-Index is 95. He is the inventor on more than 40 filed or granted patents.

Abstract [O7.1]:

Researchers working on the development of vaccines face an inherent dilemma: to maximize immunogenicity without compromising safety and tolerability. Early vaccines often induced long-lived protective immune responses, but tolerability was a major problem. Newer vaccines have very few side effects but can be of limited immunogenicity. One way to tackle this problem is to design vaccines that have all the properties of pathogens with the exception of causing disease. Key features of pathogens can be mimicked by virus-like particle (VLP) based delivery systems. Here we discuss the use of immunologically optimized VLPs for the generation of therapeutic vaccines ranging from Alzheimer’s disease in humans to atopic dermatitis in dogs.

Hank Balfour

Henry H. Balfour, Jr. (Hank) is a graduate of Princeton University and Columbia College of Physicians and Surgeons. After serving as Captain, USAF MC from 1968 to 1970, Hank began a career in herpesvirus research, particularly in the detection, diagnosis and treatment of herpesvirus-associated diseases. He has 290 peer-reviewed articles and his h-index is 71. In 1989, he published a landmark paper on prevention of posttransplant CMV disease with acyclovir. His present focus is on primary infection by EBV in both the immunocompetent and immunocompromised host. Hank has been working on an EBV vaccine since 2007, which he believes could prevent infectious mononucleosis, posttransplant lymphoproliferative disorder, certain cancers, and even multiple sclerosis.

Abstract [PL3.4]:

A vaccine to prevent Epstein-Barr virus (EBV) diseases has been painfully slow in coming. The title of this talk is the same as that of an editorial I wrote all the way back in 2007, the year we began research on EBV vaccine. The incidence of primary EBV infection among EBV-naïve University of Minnesota undergraduates is 25% during freshman year, and the majority of these infections manifest as infectious mononucleosis (Mono) with a median duration of illness of 17 days. Besides acute Mono, which is a significant disease itself, Mono may linger for many months or years as a chronic debilitating disease. EBV is also associated with cancers and autoimmune diseases such as multiple sclerosis. A prophylactic EBV vaccine could reduce the incidence and severity of all of these EBV-spurred disorders.

We have partnered with industry to continue development of a subunit gp350 EBV vaccine. The rationale for this approach is that antibody against gp350 is closely associated with EBV neutralizing antibody, and a very similar vaccine prevented Mono among young adults (the topic of my 2007 editorial). Soluble gp350
was produced from transfected CHO cells in our Molecular and Cellular Therapeutics Laboratory and is currently being purified by ion exchange chromatography. Quantitative assays for EBV gp350 and EBV neutralizing antibodies have been validated and used to document immunogenicity in C57BL6 mice vaccinated with EBVgp350 combined with a TLR4 agonist, glucopyranosyl lipid adjuvant (GLA), formulated in a squalene-in-water emulsion (SE).

Next steps will be to show that our gp350 is comparable to data previously generated in mice, and perform the toxicology studies required for submission of an IND. Our goal is to perform a phase 1 or a phase 1/2 study in EBV-naïve college freshmen as soon as practical.

Edward Belongia

I am an infectious disease epidemiologist and Director of the Center for Clinical Epidemiology & Population Health (CCEPH) at the Marshfield Clinic Research Institute (MCRI). I served as a CDC Epidemic Intelligence Service officer and was a member of the CDC Advisory Committee on Immunization Practices (ACIP) from 2014-18. I am a current member of the ACIP Influenza Work Group and the ACIP Herpes zoster work group. I have 18 years of experience leading vaccine-related research, including studies of influenza vaccine effectiveness, repeated vaccination effects, waning protection, vaccine immune response, and vaccine safety. Our vaccine research team includes five PhD/MD epidemiologists, two Masters-level epidemiologists, research coordinators, interviewers, programmer/analysts, and laboratory technicians. I have coauthored over 90 publications on influenza, and we have conducted annual CDC-funded studies of influenza vaccine effectiveness since 2004-05.

Abstract [PL1.3]:

Susceptibility to infections, disease severity, and response to vaccines are highly variable from one individual to another. Medical practices and public health policies typically take a ‘one size fits all’ model for disease management and vaccine development. This approach ignores individual heterogeneity in immune responses that likely impacts the response to therapy or the efficiency and development of side effects secondary to vaccine or treatment administration. Due to the complexity of immune responses at the individual and population level, it has been challenging thus far to define the borders of a healthy immune system as well as the parameters (genetic, epigenetic, and environmental) that drive its naturally-occurring variability. In particular, such assessments require large sample sizes, consensus for defining “healthy”, and standardized protocols for sample recruitment. In this context, the Milieu Intérieur Consortium initiated in September 2012 a cross-sectional healthy population-based study of 1,000 healthy volunteers, split equally by sex (1:1 sex ratio) and stratified across five-decades of life. The overall aim of the Milieu Intérieur study is to assess the factors underlying immunological variance within the general healthy population. The primary objective is to define genetic and environmental factors that contribute to the observed heterogeneity in immune responses. This is being realized through the characterization and integration of (i) lifestyle and medical history (ii) genome-wide SNP genotyping and whole-exome sequencing (iii) metagenomic diversity based on sequence analysis of bacterial, fungal and viral populations in fecal and nasal samples; (iv) induced transcriptional and protein signatures by whole microbes, microbial-associated molecular pattern (MAMP) agonists, medically relevant cytokines, or stimulators of the T cell response; and (v) variability in levels of circulating immune cell populations based on flow cytometry. In parallel a number of disease specific studies lead by consortium members, and a pilot study on healthy donors in collaboration with Institut Pasteur Senegal have been initiated. These results will lay the foundations for a better understanding of immune response variability helping to support new precision vaccination strategies.
James Cherry

James D. Cherry, MD, MSc is a member of the past Chief of Division of Infectious Diseases at Mattel Children's Hospital UCLA and a Distinguished Research Professor of Pediatrics at the David Geffen School of Medicine at UCLA.

Dr. Cherry received his bachelor’s degree from Springfield College in Springfield, Massachusetts, his master of science in epidemiology from London School of Hygiene and Tropical Medicine, London, England, and his medical degree from the University of Vermont, Burlington, Vermont. He received his pediatrics training at Boston City Hospital and Kings County Hospital and his infectious disease training at the Thordinke Memorial Laboratory at Boston City Hospital.

Dr. Cherry is a senior member of the American Academy of Pediatrics and he has been a member for over 53 years. He has been the recipient of several awards including the selection as a John and Mary B. Markle Scholar in Academic Medicine in 1964, and the Distinguished Physicians Award of the Pediatric Infectious Disease Society in 2003. Dr. Cherry was the President of the Pediatrics Infectious Diseases Society in 1989-1991.

Dr. Cherry served on the committee on Infectious Disease of the American Academy of Pediatrics from 1977 to 1983 and on the Advisory Committee on Immunization Practice (ACIP) from 1987 to 1991. From 1983 to 1992, he was a consultant to the Red Book and he has been a frequent consultant to CDC since 1991. Dr. Cherry was the American Regional Editor of “Vaccine” from 1991 to 2000. He was an associate editor of the 19th edition of the Red Book in 1982.

Dr. Cherry has published more than 700 papers and chapters in scientific journals and textbooks. The majority of these have been related to vaccines and vaccines preventable diseases. He is the senior editor of Feigin and Cherry’s Textbook of Pediatrics Infectious Disease. The 8th edition of this book is published and available as of spring 2018.

Dr. Cherry has been studying pertussis (vaccines, epidemiology, and clinical disease in children and adults) over the last 43 years. He has authored or co-authored more than 160 research papers, articles, and book chapters relating to pertussis and its prevention.

Abstract [PL2.4]:

*Bordetella pertussis* was isolated in 1906 and because pertussis was such a severe and fatal disease, investigators, so there after, tried to develop vaccines for treatment and prevention. Effective DTwP vaccines became available in the 1930s and they were put into routine use in the 1940s in the U.S. Their use reduced the average rate of reported pertussis from 157/100,000 in the pre-vaccine era to <1/100,000 in the 1970s. Because of alleged reactions (encephalopathy and death), vaccine use in several countries was discounted (Sweden) or markedly decreased (UK, Germany, Japan). During the 20th century, *B. pertussis* was extensively studied in animal model systems and many “toxins” and protective antigens were described. A leader in *B. pertussis* research was Margaret Pittman at NIH/FDA; she published two papers suggesting that pertussis was a pertussis toxin (PT) mediated disease. Dr. Pittman’s views led to the idea that less reactogenic acellular vaccines could be produced. The first DTaP vaccines were developed in Japan and put into routine use. Following this, DTaP vaccines were developed in the Western World and definitive efficacy trials were carried out in the 1990s. These vaccines were all less reactogenic than DTwP vaccines and in the spite of the fact that their efficacy was less than DTwP vaccines; they were approved in the U.S. and many other countries. DTaP vaccines replaced DTwP vaccines in the U.S. in 1997. During the last 13 years, major pertussis epidemics have occurred in the U.S. and numerous studies have demonstrated the deficiencies of the DTaP vaccines. Two of these deficiencies are the small number of antigens that the vaccines contain and the type of cellular immune response that they elicit. The type of cellular response (Th ½) results in less good and shorter duration of protection. Because of the small number of antigens (3-5 in DTaP vaccines vs >3000 in DTwP vaccines) linked-epitope suppression occurs. Because of linked-epitope suppression, all children who were primed by DTaP vaccines will be more
susceptible to pertussis throughout their lifetimes and there is no easy way to decrease this increased lifetime susceptibility.

Tony Cunningham

Professor Anthony Cunningham AO is Executive Director, The Westmead Institute for Medical Research (“Westmead Institute”) and Director of the Westmead Institute’s Centre for Virus Research, Professor of Research Medicine Sydney Medical School, Westmead, The University of Sydney and Director, Australian Centre for HIV and Hepatitis Virology Research (ACH2).

He trained in infectious diseases, clinical virology and virology research at the University of Melbourne and as a postdoctoral fellow at Stanford University. His major research interests are in HIV and Herpes virus biology and immunology, especially in relation to the development of vaccines and microbicides.

He has also published numerous original and review articles on epidemiology, antiviral therapy and vaccines for Herpes simplex and varicella/zoster viruses, has participated in numerous international roundtables and often consults for global pharma on these topics. Recently, he has played a leading academic role in trialling and immunologic analysis of the highly efficacious GSK recombinant Zoster Vaccine (HZ/Su).

He has published more than 330 primary refereed scientific articles and 70 invited reviews or chapters in various journals or books, and has been cited ~20,000 times.

In 2010, Tony was made an Officer in the Order of Australia (AO) for “service to medicine, particularly in the field of viral research and through the development and leadership of medical and biomedical research”. In 2014 he was elected as a fellow of the Australian Academy of Health & Medical Sciences and in 2017 as President of The Association of Australian Medical Research Institutes.

Abstract [PL3.3]

Herpes zoster (HZ) results from the reactivation of latent varicella zoster virus (VZV) in the dorsal root or cranial nerve ganglia, usually decades after initial infection, causing pain and rash in the innervated dermatome. VZV-specific antibody, innate immune cells and proteins and CD4 and CD8 T cells control initial infection at the level of nerve ganglia and skin. Over 90% of adults have been infected with VZV and, therefore, are at risk for HZ. HZ occurs in 50% of adults >85 years of age or older owing to declining cell mediated immunity or immunosenescence. However, HZ can occur at any age, especially when cell-mediated immunity is decreased by disease or drug therapy. Rash and pain usually resolve within 4 weeks. The commonest complication is prolonged pain or post-herpetic neuralgia (PHN).

Oral antivirals are effective in acute HZ but have a limited effect on PHN and low prescription levels exacerbate their lack of impact. The licensed concentrated live attenuated vaccine Zostavax (Merck) boosts antibody and T cell immunity and provides 51% and 66% protection against HZ and PHN respectively, but efficacy against disease incidence decreases with age and declines over 4 - 8 years. The newly licensed HZ subunit vaccine (Shingrix, GSK) combines a key surface VZV glycoprotein (E) with an antibody and T cell boosting adjuvant combination (AS01B consisting of MPL and QS21). It is highly efficacious in protection (~90%) against HZ and PHN in immunocompetent subjects, with no decline in advancing age and protection maintained for >3 years. Local injection site pain and swelling can be severe in a minority (9.5%) but lasts only 1-3 days. After immunization, 98% and 93% of subjects had specific antibody and CD4 T cell responses respectively lasting for the study duration. (CD4 T cell responses were mostly polyfunctional, an important predictor of vaccine efficacy). In severely immunocompromised patients both inactivated VZV Vaccine and Shingrix were safe and showed 64% and 68% efficacy respectively against HZ.
Baptiste Dungu

I am a South African veterinarian and vaccinologist, currently Head of Strategy and Business Development for MCI Santé Animale, a large African biopharmaceutical company, and previously Senior Director: Research and development for GALVmed, based in Edinburgh, Scotland, UK. I am also the Vice-President of the World Animal Health Organisation, OIE (Paris, France), Scientific Commission. I qualified as a veterinarian in the DR Congo in 1988, worked as a junior lecturer, before moving to South Africa in 1992, where I obtained all my post-graduate and research qualifications at the University of Pretoria: BVSc-Hons, MSc and PhD. I also hold a Professional Management certificate from UNISA. I worked for 10 years as senior researcher at the Onderstepoort Veterinary Institute (OVI), covering different aspects such as R&D of recombinant antigen-based ELISA tests. As project leader, I established the first multidisciplinary nucleic acid-based diagnostic laboratory at OVI and developed a number of diagnostic tools on a wide range of animal diseases. I also established the Bovine spongiform encephalopathy (BSE) diagnostic laboratory.

I then moved into senior Management, serving as Program Manager of the FMD vaccine development and production unit of ARC-OVI. From 2002 until 2008, I worked at Onderstepoort Biological Products Ltd. (OBP Ltd.) as General Manager: Operations, R&D, and later as Chief Operating Officer, overseeing the production and development of more than 50 different vaccines and biologics, as well as related R&D activities. From 2008 and 2014, in my capacity as Senior Director R&D for GALVmed, based in Edinburgh, UK, I was in charge of program development and scientific strategic direction of the organisation. I was overseeing all product development, registration and production, developing partnerships for vaccine and other product development involving biopharmaceutical industry, academic & research organizations for GALVmed. I had developed a number of projects including a program funded to the tune of 8 million Euros by the EU, aimed at Capacity building into vaccine production for African state livestock vaccine manufacturers. I managed a pipeline portfolio of 24 products (vaccine, drugs and diagnostic tests), through partnerships with more than 50 institutions around the world, including research, academic, pharmaceutical and international organisations. For the past 15 years, I have conducted consultancies in more than 20 African countries for different international organizations such as IAEA, FAO, as well as the African Union-IBAR and SADC.

In my current position, I am working with the largest and most advanced African veterinary biopharmaceutical company, MCI Santé Animale based in Morocco, to develop strategies for increasing the African business and overall develop the sector on the continent and other markets (Middle East, Central Asia, Europe).

I also have consulted in a number of Biotechnology related processes nationally and internationally. I am a reviewer for the South African National Research Foundation (NRF) and evaluator for the Technology and Innovation Agency (TIA). I have more than 30 peer-reviewed articles to my credit, a patent filed in South Africa and more than 50 congress contributions and other publications.

Abstract [O5.2]:

Rift Valley fever (RVF) is a zoonotic mosquito-borne multispecies disease caused by the RVF virus, a negative single stranded RNA virus of the Phlebovirus genus in the Bunyaviridae family, which is associated with high abortion rates, neonatal deaths, and foetal malformations in susceptible animals, and mild to severe disease in humans, leading to cases of fatal haemorrhagic disease. Considerable economic losses are associated with outbreaks of RVF, together with important public health damages and human mortalities. The disease is endemic in countries in Africa and the Arabian Peninsula, and usually manifests in irregular outbreaks with long interepidemic periods; some countries have no large-scale outbreaks but rather serological evidence of more frequent virus circulation. The disease is also considered to be a threat to currently unaffected regions and classified by many countries as a potential bioterrorist pathogen. The irregular occurrence of the disease in endemic regions has brought veterinary authorities to device different control strategies, based on local circumstances. To date, vaccines constitute the most effective RVF control tool. Three approaches are broadly employed for livestock in endemic regions: continuous yearly vaccination, emergency vaccination at the first signs of an outbreak or when advised by specific early warning systems, and no vaccination. Although several vaccine strategies and candidates have been
developed and evaluated, only two live attenuated and one inactivated vaccines are licensed for use in livestock and none for human use. To minimise the impact of this devastating disease, effective vaccination strategies, and functional national and international multi-disciplinary networks, remain crucial for ensuring availability of effective and safe vaccines in the right quantity at the required times. They are also important to support effective vaccination and control in high risk areas for efficient response to RVF alerts and outbreaks, but also for preparedness during interepidemic periods.

Guido Ferrari

Dr. Guido Ferrari, M.D., is Associate Professor at Duke University in the Department of Surgery and Molecular Genetics and Microbiology. He is also affiliated faculty at the Duke Global Health Institute, Duke Human Vaccine Institute, and University of Cape Town Department of Immunology. Dr. Ferrari has worked on testing samples from vaccine recipients for cytotoxic T lymphocyte (CTL) and antibody dependent cellular cytotoxic (ADCC) responses since 1995 initially for the AIDS Vaccine Evaluating Group (AVEG) and, subsequently for the HIV Vaccine Trial Network (HVTN) where he is currently working as director of the ADCC laboratory. Dr. Ferrari was the first to characterize vaccine-induced cross-clade clade CD8 CTL responses and the difference in class I-restricted epitope recognition between HIV-1 infected individuals and vaccine recipients. He followed this initial epitope mapping of cellular responses with the epitope mapping of ADCC responses to identify the anti-C1C2 epitope as the most recognized epitope by ADCC Ab responses in infected individuals. Dr. Ferrari has also been the director of the ADCC core laboratory for the Comprehensive Antibody-Vaccine Immune Monitoring Consortium (CA-VIMC) and for the Primate AIDS Vaccine Evaluation Group (PAVEG). Dr. Ferrari has gained unique insights in exploring the cytotoxic aspects of the anti-HIV-1 cellular and humoral immune responses that can be exploited for the design of AIDS vaccines.

Abstract [O9.1]:

In the history of vaccine development against HIV-1, induction of protective humoral immunity have been both in the spotlight and held back stage roles for immunogen design strategies. More recently with the identified humoral correlates of decreased HIV risk of infection in the RV144 phase 3 vaccine efficacy trial, there is a renewed interest in understanding the complexity of vaccine-induced humoral responses required to achieve protection from HIV-1 infection. It is evident that we should pursue and balance qualitative aspects of these responses including: 1) antibody subclasses and isotypes; 2) neutralizing and antibody Fc effector functions; and 3) breadth and epitope specificity to the virus target. In addition to the qualitative aspects, we need to determine how to achieve long-lasting protective antibody responses at concentrations capable of protecting against HIV acquisition at the genital mucosa. Success is likely to be achieved from combined immunogen design approaches that elicit multiple antibody effector functions in concert with cellular immunity.

Tong-Ming Fu

Dr. Tong-Ming Fu obtained his medical doctor degree at Peking University Health Science Center, formerly Beijing Medical University, in China, and Ph.D. at Pennsylvania State University, Hershey Medical Center. He joined Merck Research Laboratories after his academic trainings, and has been working at Merck Vaccines Research for over 20 years. His research focus is mainly on novel vaccine candidates for challenging infectious disease targets such as pandemic flu and HIV-1. He started Merck cytomegalovirus vaccine program in 2006 and led the discovery and early clinical development efforts for a novel candidate designated V160; V160 is currently under Phase 2 evaluation for prevention of CMV acquisition in women.

Abstract [O4.1]:

Congenital cytomegalovirus (CMV) infection is one of the leading causes of birth defects in the United States, and developing a prophylactic vaccine is a high priority for public health. Naturally acquired CMV immunity in women prior to conception is effective in preventing CMV transmission to fetus during
pregnancy; both humoral and cellular immunity to CMV are likely playing a role in blocking the transmission. However, a live attenuate CMV vaccine is difficult to develop since the CMV is known to establish persistent and life-long infection in host. Aiming to develop an effective and safe CMV vaccine incapable of establishing productive and persistent infection, we first restored expression of viral gH/gL/pUL128-131 pentameric gH complex, and then applied a genetic/chemical switch to two viral proteins essential for replication. This design would allow regulation of viral replication with a small synthetic molecule; the vaccine virus cannot replicate without the chemical in culture. Vaccine virus, however, can infect cells and express viral antigens de novo upon vaccination, thus, eliciting both arms of adaptive immunity. Phase 1 demonstrated that 1) the vaccine is safe and well tolerated and the virus can't replicate in human volunteers, and 2) it is effective in induction of durable neutralizing Abs as well as CD4 and CD8 T-cell responses. The vaccine is under Phase 2 evaluation for efficacy against CMV acquisition in women age 16-35 years.

Jonathan Gershoni

Prof. Jonathan M. Gershoni completed his BSc in Biology and PhD in Biochemistry at the Hebrew University of Jerusalem. He then did Post-doctoral training with Prof. George E. Palade at Yale School of Medicine where he began his research on the interplay of viruses and their targets and the defense mechanisms of the immune system. Returning to Israel in 1983 he joined the Department of Biophysics at the Weizmann Institute of Science where he continued his study of the molecular events that govern viral infection. He subsequently joined the Laboratory of Tumor Cell Biology at the National Institutes of Health in Bethesda, MD to work with Dr. Robert C. Gallo on developing new approaches to AIDS therapy and prevention. In 1990 he returned to Israel as one of the founders of the new Department of Cell Research and Immunology at Tel Aviv University where he has served as chairman (2003-2006). Over the last decade Prof. Gershoni has focused on developing new methods for the rational design of vaccines to such pandemic diseases as AIDS, Hepatitis C, influenza, SARS and MERS. Prof. Gershoni continues to investigate the humoral response towards viral pathogens; developing computational methods to profile the IgOme - the complete repertoire of antibodies in polyclonal sera, and developing novel approaches for epitope based vaccines and next generation diagnostics.

Abstract [PL2.2]:

Polyclonal serum consists of vast collections of antibodies. The spectrum of antibody specificities is dynamic and varies with age, physiology, and exposure to pathological insults. The complete repertoire of antibody specificities in blood, the IgOme, is therefore an extraordinarily rich source of information – a molecular record of previous encounters, as well as a status-report of current immune activity. The ability to profile antibody specificities of polyclonal serum at exceptionally high resolution is an important and serious challenge which can now be met. Here we describe "Deep Panning" a methodology that merges the flexibility of combinatorial phage display peptide libraries with the power of Next Generation Sequencing to enable high resolution / high-throughput interrogation of the IgOme.

Aydar Ishmukhametov

Prof. Aydar Ishmukhametov, MD, member of the Russian Academy of Sciences, is currently the CEO of the Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products (Moscow, Russia). The Chumakov Center is the oldest Russian research institution developing vaccines and immunomodulating substances. As the Director, Prof. Ishmukhametov introduced the concept of streamlined production path from research projects to the large-scale manufacturing of immune biological products. This led to a successful launching of several new products and a 60% increase in the sales. The Chumakov Center is the only Russian scientific and production facility with WHO prequalification. By now, its products are exported to more than 60 countries. Since 2015, Prof. Ishmukhametov leads the project of inactivated polio vaccine development based on the Sabin strains. This new polio vaccine has successfully passed clinical trials and will be out on the market by the end of 2018.
Abstract [PL5.4]:

Paralytic poliomyelitis caused by the poliovirus became a global epidemic disease in the first half of XX century. The development and application in the late 50s of effective poliovirus vaccines, namely inactivated polio vaccine (IPV) and live attenuated oral polio vaccine made from Sabin strains (OPV) led to a sharp decline in polio-related morbidity and mortality. In 1988, WHO adopted the Global Program for Eradication of Poliomyelitis. The "vaccine of choice" to ensure vaccination coverage of at least 95% of children and stop circulation of the wild poliovirus was the oral trivalent OPV (tOPV). The vaccination strategy was based on the experience in control of poliomyelitis of the USSR and the WHO American Region, as well as on the properties of the vaccine made from Sabin strains. In the beginning of the XXI century, the incidence of polio infections reduced to single cases and poliovirus type 2 has been eradicated. At the same time, serious problems associated with the continued use of tOPV were identified, namely the outbreaks and incidents of the disease caused by circulating vaccine-derived polioviruses (VDPV), and persistent excretion of VDPV by persons with primary immunodeficiency. This scenario demanded for a change in the vaccination strategy with simultaneous global transition from the use of tOPV to OPV which included only poliovirus types 1 and 3 (bivalent OPV, bOPV) followed by the global replacement of OPV by IPV. The Chumakov FSC R&D IBP RAS has more than 60 years of experience in the development, production of various poliovirus vaccines and implementation of vaccination programs, which allows timely response to the challenges of the epidemic situation and the vaccine market ensuring the epidemiological safety of the Russian Federation. In 1959, evidence of the safety and high effectiveness of tOPV were obtained and the scientific basis for its production control was developed that later formed the basis for the WHO international requirements for OPV. The use of tOPV in immunisation programs in the Russian Federation and many other countries of the world has made a significant contribution to the certification of the WHO European Region as “polio-free” in 2002. At the time of global shift from tOPV to bOPV, clinical trials and registration of bOPV and monovalent OPV type 2 have been conducted. The existing global shortage of IPV carries a significant threat to the world's epidemiological well-being, so the Chumakov FSC R&D IBP RAS has developed and performed preclinical studies of IPV from Sabin strains (the choice of strains was determined by the requirements of poliovirus containment) which is now in the stage of registration.

Eun-Kyoung Jo

Eun-Kyeong Jo has led the “Medical Research Center (MRC)” at Chungnam National University (CNU, Korea) since 2007. She gained her M.D. (1991) and Ph.D. degree (1996) from College of Medicine, CNU. After postdoctoral training at Imperial College London, she was promoted to professor at CNU in 2008. She has published over 110 publications in highly peer-reviewed journals (Nat Immunol, Immunity, Cell Host Microbe, Nat Commun, Autophagy, etc) and currently serves as Director of MRC (Infection Control Convergence Research Center) at CNU. Her research interests are innate immune regulation and autophagy in mycobacterial infection. She also focuses on several key functions of orphan nuclear receptors in regulation of innate immunity and inflammation.

Abstract [O3.2]:

Tuberculosis remains a major public health problem worldwide. In developing countries, tuberculosis is highly endemic, and the global incidence is increasing as a consequence of the human immunodeficiency virus epidemic. *Mycobacterium tuberculosis* (Mt) is a successful pathogen that enhances its own intracellular survival by arresting phagolysosomal fusion. Autophagy is an essential process for lysosomal degradation to eliminate protein aggregates and damaged organelles, thus maintaining intracellular homeostasis against various stress conditions. It is now becoming clear that autophagy is crucial in the host immune defense against infection with intracellular bacteria, including Mt, through enhancement of phagosomal maturation. Emerging evidences have shown that autophagy is involved in potential therapeutics for various human disorders, including metabolic conditions, neurodegenerative diseases, cancers, and infectious diseases. For the last several years, we have focused on the roles of autophagy and the mechanisms by which activation of autophagy promotes innate host defense against Mt infection. In this talk, I will discuss our recent findings showing that estrogen-related receptor α (ERRα; NR3B1), operates in a feed-forward loop with sirtuin 1, in the activation of autophagy and antimicrobial responses,
via both transcriptional and post-translational control of autophagy genes. Our current research interest of unveiling the functional GABAergic system upon autophagy regulation will be briefly introduced in terms of controlling intracellular bacterial infection. Targeting autophagy may modulate host defenses, and could be beneficial in certain types of infection and inflammation.

Ravi Kane

Ravi Kane is the Garry Betty/ V Foundation Chair and GRA Eminent Scholar in Cancer Nanotechnology. He received a B.S. in Chemical Engineering from Stanford University in 1993. He then received an M.S. in Chemical Engineering Practice and a Ph.D. in Chemical Engineering from MIT, working with Bob Cohen and Bob Silbey. After postdoctoral research with George Whitesides in the Department of Chemistry and Chemical Biology at Harvard University, he joined Rensselaer Polytechnic Institute (RPI) as an assistant professor in 2001. He was promoted to associate professor in 2006, to full professor in 2007, and to the P.K. Lashmet Professor in 2008. He served as the head of RPI's Howard P. Isermann Department of Chemical and Biological Engineering before moving to Georgia Tech in 2015. Prof. Kane has graduated 29 Ph.D students and contributed to over 140 scientific publications.

Abstract [O1.1]:

Vaccines constitute one of the most effective tools to prevent disease. For many important diseases, however, currently available vaccines do not provide broad and durable protection. For instance, in several cases, immunodominant regions of protein antigens are highly variable in sequence and elicit narrow and strain-specific immune responses. We will discuss approaches for engineering antigens to focus the immune response on targeted (conserved) epitopes and elicit broadly neutralizing antibodies.

Hiroshi Kiyono

Dr. Kiyono obtained his dental degree (D.D.S.) from Nihon University, and Ph.D. from the University of Alabama at Birmingham (UAB). His background as a dentist combined with extensive research experience in the field of Mucosal Immunology at UAB, Max-Planck Institute, Osaka University and at present, the University of Tokyo and Chiba University makes him exceptionally well qualified to discuss the current and future directions of mucosal immunology and mucosal vaccine development. To reflect his scientific contribution, he was listed in ISI Highly Cited Researchers’ List and received several prestigious awards such as NIH New Investigator Research Award, NIH Research Career Development Award, The Japanese Society for Vaccinology Takahashi Award and Hideyo Noguchi Memorial Medical Science Award.

He was the former President of Society for Mucosal Immunology. He also contributed to scientific Journals such as Vaccine, Mucosal Immunology, Human Vaccines and Frontiers as the editorial board members. He himself has a total of 528 publications in peer review journals and edited a total of 20 books.

He served as the Dean of the Institute of Medical Science, The University of Tokyo and is currently Director and Project Professor for International Research and Development Center for Mucosal Vaccines, and Project Professor for Division of Mucosal Immunology, IMSUT Distinguished Professor Unit at the same institute. He is also holding a Project Professorship at Chiba University in Japan.
Abstract [PL6.1]:

The mucosal surfaces of the aero-digestive tract are continuously exposed to countless opportunities for the invasion of pathogens. These mucosal surfaces are thus equipped with the mucosal immune system which provides the first line of immune surveillance and defense against pathogen invasion. Nasal immunization with an appropriate vaccine delivery vehicle prompts the induction of protective immunity in both the mucosal and systemic compartments, leading to a double layer of protection against pathogens. To harness the benefits of mucosal vaccines, a cationic cholesteryl-group-bearing pullulan nanogel (cCHP nanogel) has emerged as a potent nasal vaccine delivery vehicle for the induction of protective immunity against respiratory infections. The pneumococcal surface protein A (PspA) antigen is a highly immunogenic and conserved surface protein that is expressed on all clinical isolates of \textit{S. pneumoniae}. A nasal vaccine formulation of cCHP nanogel containing PspA (cCHP–PspA nanogel) has been developed as a new form of \textit{S. pneumoniae} vaccine. When cCHP–PspA nanogel was nasally administered to experimental animals, PspA antigen was efficiently delivered to the nasal epithelium and subsequently taken up by dendritic cells for the initiation of an antigen-specific immune response. Nasal vaccination with cCHP–PspA nanogel thus resulted in the elevation of antigen-specific IgG and IgA antibodies in the serum and bronchial fluids, and antigen-specific IgA levels in nasal fluids. Consequently, bacterial growth was suppressed both in the lung and nasal cavities of the vaccinated animals, which then were protected against lethal challenge with \textit{S. pneumoniae}. The protective immunity elicited through cCHP–PspA nanogel was accompanied by the production of both Th2- and Th17-type cytokines by antigen-specific CD4+ T cells, a feature that is known to be associated with protective immunity against \textit{S. pneumoniae}. Taken together, the use of cCHP nanogel as an antigen delivery system for nasal vaccination induces effective \textit{S. pneumoniae} -specific immune responses in both the systemic and mucosal compartments.

Harry Kleanthous

Dr. Kleanthous has over 24 years industry experience in the research & development of recombinant live attenuated and subunit-based vaccines against viral and bacterial pathogens.

He is currently the Scientific Officer for FluNXT, a virtual biotech initiative within Sanofi Pasteur, with responsibility for developing Broadly Protective Influenza Vaccines in humans. He joined Sanofi Pasteur as the North American Head of Discovery Research in 2008 with responsibility for evaluating and developing novel viral vaccine platforms and delivering novel targets to the Development pipeline. Previously, Dr. Kleanthous was Vice President of Research at Acambis Inc. (formerly OraVax) with responsibility for developing a new exploratory portfolio.

His research interests have been in the field of replication-defective viral vaccine platforms, targeting Flaviviruses, Papilloma and Herpes viruses, as well as their use for foreign antigen delivery. In recent years Dr. Kleanthous has focused efforts on the research and development of Universal Influenza Vaccines and presented strategies currently being explored at Sanofi Pasteur at WHO, the World Vaccine Congress, ISV, EDUFLUVAC.

Prior to joining industry, Dr. Kleanthous was a scientific investigator at academic teaching hospitals and the Central Public Health Laboratory Service in the UK, where he developed his expertise in the area of infectious diseases. He obtained his Ph.D. in the field of Molecular Microbiology from the University of London and has published over 40 scientific papers.
Abstract [PL4.1]:

Most humans have pre-existing immunity to influenza viruses. In this study, volunteers (ages of 18-85 years) were vaccinated with split, inactivated influenza vaccine (Fluzone™) over four consecutive influenza seasons. The impact of repeat vaccination on breadth and durability of immunity was assessed as a function of this pre-existing immunity in response to vaccine strain changes. Hemagglutination-inhibition (HAI) antibody was measured against both influenza A and B HA components in the vaccine post-vaccination, with HAI activity demonstrated to increase in all age groups. However, younger subjects maintained their sero-protective titers to the vaccine strains, resulting in higher seroconversion rates compared to the elderly, whose HAI titers were more likely to decline prior to the next season. Regardless of age, immunological recall or 'back-boosting' to antigenically related strains were associated with seroconversion to the vaccine strain. Overall, both younger and older people have the ability to mount a breadth of immunity following influenza vaccination. This report describes how influenza exposure differs across age groups, and how immunological imprinting influences antibody cross-reactivity to past hemagglutinin antigenic variants, and shapes immune responses elicited by current split inactivated influenza vaccines. Understanding how current influenza vaccines are influenced by pre-existing immunity in people of different ages is critical for designing the next-generation of 'universal' or broadly-protective influenza vaccines.

Gary Kobinger

Gary Kobinger is a professor in the Department of Microbiology and Infectious Diseases and the Director of the Research Centre on Infectious Diseases, Faculty of Medicine at Université Laval. He is also an adjunct professor in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania, and an associate professor in the Department of Medical Microbiology at the University of Manitoba. His work focuses on developing and testing new vaccine platforms and immune treatments against emerging and re-emerging viruses of high consequences to public health. Gary’s goal as Director is to develop a research framework that can respond rapidly to emerging and re-emerging pathogens.

Abstract [O5.1]:

The yearly emergence and re-emergence of infectious diseases is an issue that appears to be intensifying as the global population increases, ages, and as international travel, urbanization and climate change continue to rise. These factors promote the emergence, evolution and dispersion of new pathogens and diseases. Thus, research on novel vaccines and delivery technologies is increasingly needed to help prevent outbreaks from occurring and to mitigate those that due commence.

This presentation will focus on novel vaccine delivery systems with a potential for rapid immunization of humans and animals with both viral- and non-viral-based vaccines. It will also discuss the possible applications of DNA-based and viral VSV-based vaccines against CCHFV and HIV, respectively. Recent findings suggest that protective immune responses as potent as the ones induced by natural infections can be obtained using these rapid vaccination platforms.

Young Taik Lim

Professor in Sungkyunkwan University (SKKU). SKKU Advanced Institute of Nanotechnology, Department of Nano Engineering, and School of Chemical Engineering.

After he received his Ph.D. from the Department of Chemical and Biomolecular Engineering of the Korea Advanced Institute of Science and Technology (KAIST) in 2002, he joined John V. Frangioni’s group at Harvard Medical School as a postdoctoral research fellow. He contributed to the development of lymph node targeting nanomaterials for cancer diagnosis.
He continued his researches in two Korea government supported research institutes, ETRI and KRIBB. In KRIBB, he started to design and synthesize nanomaterials that can not only modulate the function of therapeutic immune cells but also track them in vivo through molecular imaging technologies.

He started professorship at Chungnam National University at 2009 and expanded his research fields to the development of vaccine adjuvants for infectious diseases. He moved to SKKU at 2014 and is focusing on the development of bioengineered/nanoengineered synthetic immune niches for enhanced cancer immunotherapy as well as the control of infectious diseases.

Abstract [O2.3]

Adjuvants can be defined as pharmacological and immunological components that are able to modify and/or enhance antigen-specific immune responses. Based on the interdisciplinary research between immunology and material science/engineering, various vaccine adjuvant materials have been developed. In this talk, I will present the progress of bioengineered prophylactic and/or therapeutic vaccine adjuvants that were developed in my laboratory for cancer and/or infectious disease, and discuss the prospect of future vaccine adjuvant materials. By rational design and engineering of antigen or adjuvant materials, immune-modulatory vaccine systems were generated to antigen-specific immune responses. The optimal combination of antigens, adjuvants and delivery carriers is very important to maximize the effectiveness both in cancer immunotherapy and infectious disease control. Any single immuno-stimulant or delivery system will not be sufficient to induce both broad and long-lasting immunity. Therefore, the future effective adjuvant systems can be developed by combining one or more immuno-stimulants and delivery system.

Karin Loré

Karin Loré is a professor in vaccine immunology at the Division of Immunology and Allergy, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.

She trained in immunology and received her PhD from the Karolinska Institutet. She did her postdoctoral training at the Vaccine Research Center (VRC), NIH, USA where she still has several collaborations and is a visiting scientist. Karin is a tenured professor at the Karolinska Institutet. Her research focus is the immunological mechanisms by which different vaccine platforms interact with the innate immune system to regulate adaptive vaccine responses. A major part of her research has been on the mode of action of vaccine adjuvants. She has published several original and review articles on the topic and is highly cited.

Karin has extensive experience in leading large late-stage preclinical studies of vaccines in non-human primates both in collaboration with academia, the vaccine industry and funding agencies such as the Gates foundation. She is also managing the B cell assays in ongoing clinical studies investigating co-vaccination of selected licensed vaccines for synergistic effects as well as testing of a novel live pertussis vaccine.

Abstract [PL2.3]:

The innate mechanisms priming vaccine responses and why different vaccine formulations induce quantitatively and qualitatively different responses are largely unknown, yet represent a fundamental element in vaccinology. Most vaccines are delivered by needle into the muscle. However, normal muscle contains few immune cells like dendritic cells that are critical for initiating and priming adaptive immunity. We have recently established a non-human primate (NHP) model to in vivo illustrate the first immune processes after vaccine administration. By using fluorescently-labelled vaccines we can track the biodistribution after delivery. Recruitment of cells to the site of injection, efficiency of vaccine targeting of immune cell subsets, cell activation profiles, migration to draining lymph nodes and subsequent priming of T cell and B cell responses can be monitored. We have utilized this model to evaluate the responses from different types of vaccine formulations such as protein antigen in various adjuvants and mRNA-based vaccines. In addition, different delivery routes such as intramuscular, intradermal and subcutaneous administration have been compared. As there is much resemblance in immune cell subsets and innate
pathways between NHPs and humans, this is a powerful model for studies of how vaccines may work in humans and can help in understanding the innate immune mechanisms shaping vaccine responses and be translated into optimizing future vaccine formulations and delivery.

Nils Lycke

Dr Lycke has published over 170 original peer-reviewed papers and 29 reviews or book chapters. Lycke et. al. have pioneered the development of mucosal vaccines with important contributions to the field in adjuvant construction, including the patented CTA1-DD adjuvant. Basic mechanism of mucosal immune regulation, vaccine development and clinical assessment of safety & efficacy are other main research areas. Of lately, a universal flu vaccine has been a challenging effort in the laboratory. Other infectious diseases that has captured the interest over the years have been Helicobacter pylori and Chlamydia trachomatis. He has been the coordinator of 6 EU-sponsored projects and received financial support from EU, NIH, Wellcome Trust, Swedish Cancer foundation, The Wallenberg Foundation, The Swedish Foundation for Strategic Research, Novo Nordisk Foundation, the Swedish Research Council, and others. He has served as a member of several International committees among them the WHO Transdisease Vaccinology Committee and is currently Chief editor of Mucosal Immunity section of Frontiers of Immunology and associate editor of Mucosal Immunology.

Abstract [PL4.2]:

The search for a broadly protective influenza vaccine is ongoing. We have developed a candidate intranasal vaccine based on the conserved M2e-peptide and the adjuvant properties of a cholera toxin (CT) derived fusion protein-CTA1-DD. Here, I will discuss the mechanism of action of the adjuvant and give a detailed account on the multifunctional features of M2e-specific lung resident CD4 T cells that convey protection against a heterosubtypic virus challenge. Firstly, adjuvanticity is achieved through two different pathways; one affecting the germinal center reaction as the adjuvant targets follicular dendritic cells (FDC) and stimulates CXCL13 gene transcription and the second acting to enhance functions of migratory dendritic cells leading to better priming of CD4 T cells in the draining mediastinal lymph node. The effects on these dendritic cells included augmented endosomal processing and required ERK-dependent phosphorylation of CREB, but was independent of cAMP changes, typical for CT. The resulting lung resident M2e-specific memory CD4 T cells were predominantly Th17 cells and their expansion and functions upon a challenge infection were monitored. Single cell RNAseq analysis of M2e-specific CD4 T cells revealed unique patterns of activity at the early and late stages of infection. A critical cytotoxic function on day 3 correlated with a reduced virus expansion and later more classical Th17 functions dominated the resolution phase. These studies reveal the complexity of immune protection against influenza and conveys optimism as to the design of a universal vaccine against influenza infections.

Guanghui Ma

Prof. Guanghui Ma graduated from Gunma University, Japan (1988) as a scholarship student of China Education Ministry, and received her Ph.D. (1993) in Polymer Chemistry from Tokyo Institute of Technology. She started his academic career at Tokyo University of Agriculture and Technology as Assistant Professor (1994). She moved to Institute of Process Engineering, Chinese Academy of Sciences as a full professor (2001), and was appointed as Vice Director of State key Laboratory of Biochemical Engineering (2002), Vice Director of Institute of Process Engineering (2005). She has been appointed current position since 2012. Prof. Ma is one of the earliest women scientists who have won the China National Science Fund for Distinguished Young Scholars. She has been engaged in the area of functional nano-microparticles for systematic theoretic study and innovative biomedical applications. For example, 1) She established the Membrane Emulsification Technique to prepare uniform sized nano-microspheres; 2) She discovered a variety of new merits of polysaccharides particles including the autofluorescence property, environmental sensitive response; 3) She established large-scale preparation platform of uniform nano-microparticles, which have been successfully designed for bio-separation media, drug release carrier and particle adjuvant.
Prof. Ma has published 352 papers (180 first/corresponding author), such as *Nature Materials*, *Nature Commun*, *JACS*, *Adv Materials*, *ACS Nano*, *Biomaterials*. She edited/wrote 12 books, such as "Microspheres and Microcapsules in Biotechnology". She is also an invited editor for special issue of Small, Vaccine, etc. She has been authorized 82 patents, some of them have been transferred to companies and developed to a series of commercialized products.

She has received Outstanding Contribution Award from federation of Biotechnology (AFOB), the First Prize of Beijing Science and Technology Award, and the Second Prize of National Technological Invention Award, TWAS-TWOWS-SCOUPS Regional Young Women Researcher Award, and so forth.

**Abstract [O6.1]:**

Subunit antigen such like virus-like particle (VLP) and protein/peptide antigen has high safety compared with conventional inactivated vaccine, however, its immune-response usually became lower with increasing safety. Furthermore, VLP is unstable, it is easy to dissociate and aggregate and lose its activity. Based on synthetic biology concept, we proposed to construct artificial “chassis”, and assembled antigen and other biomolecules such like CPG adjuvant, targeting molecule on it to form composite virus-like particle (cVLP), which can not only increase the antigen stability but also enhance the immune-response of antigen. We have designed various nano/micro “chassis”, including nanoparticle, pH-sensitivity particle, 2D particle. Recently, we designed a PLGA nanoparticle-stabilized Pickering emulsion (PPAS) as an intelligent “chassis”, where the antigen was loaded in gap among PLGA nanoparticles (Fig1a) to form cVLP. PPAS chassis showed force-dependent deformation and antigen lateral mobility, which mimicking pathogen behavior. Compared with conventional emulsion or solid nano/microparticle chassis, the force-dependent deformation and dynamic fluidity of PPAS stimulated the multivalent three-dimensional interaction with antigen-presenting cells. By contrasting with the clinical-relevant adjuvants, including alum, MF59, and AS04, the developed “chassis” loaded with different subunit antigens exerted potent immune protections against influenza virus challenge (Fig.1b) and enhanced efficiency in both E.G7/OVA (Fig.1c) and B16/MUC1 anti-tumor therapies.

Michael McNeil

Michael M. McNeil, MD MPH, is Senior Medical Officer in the Office of the Director, Immunization Safety Office, Division of Healthcare Quality Promotion, at the Centers for Disease Control and Prevention. He has specialist experience in infectious diseases and epidemiology and a broad background in infectious disease and public health. He is author/co-author of more than 150 publications. Over the last 20 years, his research has focused on the safety of vaccines administered primarily in the U.S. military (e.g., anthrax and smallpox), the monovalent pandemic influenza A (H1N1) 2009 vaccine, and newer vaccines included in the childhood and adolescent immunization schedules. He currently serves as CDC vaccine safety subject matter expert for the anthrax, arbovirus and respiratory syncytial virus workgroups of the Advisory Committee on Immunization Practices (ACIP), CDC liaison to the Advisory Commission on Childhood Vaccines (ACCV), and co-mentor for the Emory/CDC T-32 vaccine safety fellowship which is now in its sixth year. He has led several safety investigations using the national Vaccine Adverse Event Reporting System (VAERS) and the collaborative Vaccine Safety Datalink (VSD) project. His research interests include vaccine-associated hypersensitivity and the investigation of rare, serious adverse outcomes following immunization.

**Abstract [PL5.3]:**

Vaccines have been recognized as one of the most effective public health interventions. Routine immunization has resulted in major reductions in vaccine-preventable infectious disease and death. The Advisory Committee on Immunization Practices (ACIP) recommends an immunization schedule for the United States in which children receive 10 vaccines to protect against 14 diseases before the age of 2 years. Vaccine-associated hypersensitivity reactions are not infrequent, although fortunately, most reported vaccine-associated reactions are not serious. Post vaccination acute-onset hypersensitivity reactions
include self-limited localized adverse events and, rarely, systemic reactions ranging from urticaria or angioedema to full-blown anaphylaxis with multisystem involvement. Serious acute-onset, presumably IgE-mediated or IgG and complement-mediated anaphylactic or serious delayed-onset T cell-mediated systemic reactions are considered extremely rare. Although rare after vaccination, estimated to be 1.31 (95% CI, 0.90-1.84) per million vaccine doses, anaphylaxis can occur among persons with no history of hypersensitivity; most persons recover fully with treatment, but serious complications, including death may occur. Hypersensitivity can occur because of either the active vaccine component (antigen) or one of the other components. Evaluation of immunization-associated, potentially immunologically mediated hypersensitivity is important to help determine the mechanism or mechanisms of the reaction. If acute hypersensitivity is confirmed, it allows future exposure to the needed vaccine through desensitization or in split doses if low risk. Serious hypersensitivity reactions after influenza vaccines are particularly important because of the large number of persons vaccinated annually. Recently, novel influenza vaccine types were introduced in the United States (recombinant vaccines, some with higher antigen content and a new adjuvanted vaccine). Providers should be aware of changing recommendations on the basis of recent published evidence for persons with a history of egg allergy to receive annual influenza vaccination. Further research is also needed to determine whether repeated annual inactivated influenza vaccination increases the risk for allergic reactions and if the number of vaccine antigens administered at the same time and the timing of routine infant vaccinations are optimal for overall population well-being.

**Martin Moore**

Dr. Martin Moore received his PhD in Genetics from the University of Georgia in 2002, studying mouse adenovirus in Kathy Spindler’s lab. He was a postdoctoral fellow in the laboratory of Stokes Peebles at Vanderbilt from 2004 to 2008, investigating RSV strains and pathogenesis. In 2008, Marty joined the faculty of Pediatric Infectious Disease at Emory University, where his group developed mouse models of RSV infection and a plasmid-based RSV genetic system. His laboratory developed a novel codon-deoptimization technique for RSV in order to generate vaccine candidates. This technology was recognized as Emory University’s innovation of the year in 2013. Marty founded Meissa Vaccines, Inc in 2014. In 2016, Marty was named Director of the Emory and Children’s Healthcare of Atlanta Center for Childhood Infections and Vaccines. Dr. Moore left academics to be full-time CEO of Meissa in 2018.

**Abstract [O0.2]:**

Respiratory syncytiar virus (RSV) is a leading cause of lower respiratory tract infection in infants worldwide. Live-attenuated RSV vaccines have a demonstrated track record of safety in pediatric populations. However, classically attenuated candidates thus far have failed due to low immunogenicity and genetic instability. We sought to engineer an RSV live attenuated vaccine candidate with enhanced immunogenicity. First, genetic mapping identified strain line 19 fusion (F) protein residues that correlate with pre-fusion antigen maintenance by ELISA and thermal stability of infectivity in live RSV. We then generated a live attenuated RSV vaccine candidate (MV-012-968) that expresses line 19 F and is attenuated by codon-deoptimization of non-structural (NS1 and NS2) genes, deletion of the small hydrophobic (SH) gene, codon-deoptimization of the attachment (G) gene, and ablation of the secreted form of G. The live attenuated RSV vaccine candidate exhibited elevated pre-fusion antigen levels, thermal stability, immunogenicity, and efficacy despite heavy attenuation in the upper and lower airways of cotton rats. As a strategy for developing vaccines against human metapneumovirus (hMPV), a version of MV-012-968 expressing a chimeric hMPV/RSV F protein was rescued and characterized.
Hironori Nakagami

Dr. Hironori Nakagami is Professor, Department of Health Development and Medicine, Osaka University Graduate School of Medicine.

He graduated from Nara Medical University and got Ph.D. from Osaka University Graduate School of Medicine. He spent two years as a postdoctoral fellow at Harvard Medical School, Brigham and Women's Hospital. His research field includes Geriatric Medicine, Cardiology and Gene Therapy with a number of original and review papers, but he is recently interested in the immunotherapy and started the vaccine project.

Although vaccines are commonly used to prevent infectious diseases, their application has recently been expanded to treat conditions such as cancer or Alzheimer’s diseases by targeting self-antigens. Vaccines for hypertension has a long history for more than 30 years which targets the renin-angiotensin system (RAS). Based on these knowledge, we try to develop the angiotensin II vaccine for hypertension toward clinical application as an initial platform, and apply these system for several diseases in collaboration with venture company.

He is a board member of several journals such as Scientific Reports. He has published 120 original scientific articles and 30 reviews or chapters in various journals or books

Abstract [O6.2]:

Vaccines are commonly used worldwide as a preventive medicine for infectious diseases and have recently been applied to cancer. We and others have developed therapeutic vaccines designed for cardiovascular diseases that are notably different from previous vaccines. In the case of cancer vaccines, a specific protein in cancer cells is a target antigen, and the activation of cytotoxic T cells (CTLs) is required to kill and remove the antigen-presenting cancer cells. Our therapeutic vaccine mainly induces the antibody, but not CTLs, which could be used as therapies against common diseases, such as Alzheimer’s disease or hypertension. In our system, an immunogenic molecule (i.e., KLH) with adjuvants provides an antigen that supports the activation of helper T cells in the combination of adjuvants. We have already reported the Angiotensin II vaccine for hypertension and related diseases (PLoS One, 2013, Hypertension 2015, Stroke 2017, Sci Rep 2017), DPP-4 vaccine for Diabetes (PNAS 2014) and PCSK9 vaccine for Dyslipidemia (PLoS One 2018) in each animal model. In terms of Angiotensin II vaccine project, the phase I clinical trial has been designed and first-in-patient was enrolled in 2018.

The therapeutic target of our therapeutic vaccine is similar to that of antibody therapy. Recently, multiple antibody-based drugs have been developed for cancer, immune-related diseases and dyslipidemia, which are efficient but expensive. If the effect of a therapeutic vaccine is nearly equivalent to antibody therapy as an alternative approach, the lower medical cost and improvement of drug adherence can be advantages of therapeutic vaccines. In this session, we will introduce our concept of therapeutic vaccines for cardiovascular diseases and the future directions of therapeutic vaccines as novel immunotherapy.

Vish Nene

Vish Nene is at the International Livestock Research Institute (ILRI) and is based in Nairobi, Kenya. He graduated from the University of Southampton (UK) and carried out post-doctoral research at the University of Nottingham and Cambridge. He has worked at the Institute for Genome Sciences, University of Maryland, The Institute for Genomic Research & J. Craig Venter Institute, USA. He has a broad range of research interests that converge on developing improved or novel methods of infectious disease control and in the use of whole genome sequence data and genomic technologies to underpin laboratory research, primarily in the field of veterinary vaccines.
**Abstract [08.1]:**

A tick-transmitted protozoan in the phylum Apicomplexa called *Theileria parva* is only found in sub-Saharan Africa. The mammalian hosts of the parasite include cattle and the Cape buffalo. Infection of cattle usually results in a fatal lymphoproliferative disease, while buffalo exhibit disease tolerance. Cattle that recover from infection exhibit solid immunity to re-infection, but this immunity can breakdown due to parasite antigenic diversity. These observations have led to development of a parasite-based infection and treatment method (ITM) of immunization, and the spectrum of immunity can be increased by immunizing with a cocktail of sporozoites derived from different parasite isolates.

There is good evidence that MHC class I-restricted cytotoxic T lymphocytes (CTLs) that lyse autologous schizont-infected lymphocytes *in vitro* play a major role in mediating immunity induced by the ITM vaccine. In addition, parasite antigens that are the target of sporozoite neutralizing antibodies can induce immunity. With several collaborators, we have identified a number of CTL antigens and the sequence of peptide epitopes presented by different BoLA class I alleles. Similarly, epitopes that are the target of some neutralizing antibodies have been mapped. We have explored different viral vectored systems and protein-adjuvant formulations in experimental vaccine trials. An emphasis will be placed on recent results obtained with nanoparticle based technologies to focus antibody responses to an 80 amino acid section of a candidate vaccine antigen. Antigen-delivery systems that we have tested in cattle include mesoporous silica based nanoparticles and virus-like-particles (VLPs) made by fusing antigen with hepatitis B core protein. In addition, studies using antigen-fusions in a novel two-protein component artificial VLP platform are underway. The latter are made from distinct proteins that are not of viral origin, but which have been designed to self-assemble into either a homo-dimer, a homo-trimer or a homo-pentamer. Co-expression of two different proteins results in the assembly of icosahedral shaped VLPs, each one consisting of 120 protein monomers. This system allows the display of multiple antigens.

**Morten Nielsen**

Morten Nielsen holds a shared position as Professor of Bioinformatics at the Department of Bio and Health Informatics, at the Technical University of Denmark, and the Universidad Nacional de San Martin, Argentina. MN graduated with a master in physics from the University of Copenhagen. Obtained his PhD (also in physics) from the University of McGill, Canada. The core of Morten Nielsen’s research deals with the development of novel and advanced data-driven prediction methods for pattern recognition in biological systems. Morten Nielsen is a pioneer in the field of immunological bioinformatics and a key inventor of several state-of-the-art methods for T and B cell epitope discovery including NetMHC and NetMHCpan. He has been a partner in several large epitope discovery grants and has published numerous articles and book chapters within the fields of immunology, immunological bioinformatics and neural networks.

**Abstract [02.2]:**

The immune system reacts to foreign molecules in a highly specialized manner. T cells play a central role in the cell-mediated immunity. T cells scrutinize small peptide fragments presented in complex with major histocompatibility complexes (MHCs) on the surface of most cells in the host. Identifying which peptides will be presented in complex with a given MHC molecule therefore is of pivotal importance for understanding cellular immunity.

Each MHC molecule is highly specific, binding only a minor fraction of the set of possible peptides. Due to the high selectivity of the MHC molecules, major efforts have been dedicated to characterize their binding specificity and several *in-silico* methods have been developed to predict this event. However, other factors including antigen processing, peptide:MHC binding stability, peptide similarity to self etc. have been claimed to impact peptide T cell immunogenicity.

In my talk, I will give an overview of the advances during the last decade in prediction methods for rational epitope discovery. I will demonstrate how MS MHC peptidomics data has substantially advanced our ability to predict both MHC class I and MHC class II ligands and epitopes. I will argue why in my view no factor
other than MHC binding is critical when predicting antigen presentation in the context of CD8 epitopes but demonstrate how the processing signal contained within MHC class II MS peptidome data can be used to improve the predictive accuracy for MHC class II ligands and CD4 epitopes.

I will demonstrate how peptide similarity to self serves as an important factor for predicting neopeptide immunogenicity, and discuss how T cell receptor data can be used to refine our understanding of peptide immunogenicity, and present results suggesting that the cognate target of a T cell can be predicted from the sequence of its T cell receptor.

Finally, I will discussion limitations of the state-of-the-art tools, and suggest solutions for how to move the field forward dealing with these limitations.

Glen Nowak

Glen Nowak, Ph.D., is a Professor of Advertising and Public Relations at the University of Georgia Grady College of Journalism and Mass Communication and Director of the Grady College’s Center for Health and Risk Communication. For over 20 years, Professor Nowak has provided senior-level leadership in vaccine and immunization-related communications programs, projects, and research, including to the U.S. Centers for Disease Control (CDC), the U.S. National Vaccine Program Office (NVPO), the Task Force for Global Health, and the World Health Organization (WHO).

Prior to re-joining the University of Georgia (UGA) faculty in January, 2013, Dr. Nowak spent 14 years at the U.S. CDC, including six years as the Communications Director for the National Immunization Program and six years as the agency’s Director of Media Relations. He also spent two years as a senior health communication specialist and senior advisor to the director of CDC’s National Center for Immunization and Respiratory Diseases.

During his time at the CDC, Dr. Nowak provided leadership and expertise in communication science, health communications, risk communication, vaccine safety communications, news media relations, social marketing and public engagement. He was involved in projects and collaborations designed to increase vaccine confidence and acceptance, address vaccine coverage disparities and to promote adoption of vaccination recommendations. Dr. Nowak also directed and collaborated on vaccine and immunization research and evaluation projects. He was also extensively involved in NCIRD and CDC’s pandemic influenza preparedness and response efforts. In 2003, he was recognized by the CDC’s Communicators’ Roundtable with their “Lifetime Achievement in Health Communication” award in recognition of over 10 years of work contributing to furthering the mission of CDC through communication leadership.

For the past five years, Dr. Nowak has continued to be extensively involved in vaccine and immunization-related acceptance and communication research projects, including those designed to increase understanding of vaccination acceptance and hesitancy, improve vaccine and immunization communication, and assess the value of new communication technologies for vaccination education. He is an author or co-author of over 35 peer-reviewed journal articles, and in the past 5 years, has served as a reviewer for over 20 leading vaccine, health communication, and medical or health-related journals.

Dr. Nowak received his BS in 1982 from the University of Wisconsin-Milwaukee, with majors in both economics and communications. He continued his studies at the University of Wisconsin-Madison, where he subsequently earned an MA degree in journalism (1987) and a PhD in the field of mass communications (1990).

Abstract [PL5.2]:

There is much interest in increasing vaccine acceptance and compliance with public health immunization recommendations. There is also much need to identify and understand the knowledge, beliefs, and attitudes that foster or inhibit acceptance and compliance, including for new vaccines and vaccines that may be recommended for use in response to a public health emergency. Although vaccines have enormous public
value and individual health benefits, significant communication and education efforts are needed to foster acceptance, reduce hesitancy, and achieve high immunization rates.

As beneficial as vaccines and immunization recommendations are, many parents of young children, people for whom vaccinations are recommended, and policy makers who make immunization program funding decisions have questions, concerns, or inadequate knowledge about which vaccines are recommended, the basis for recommendations, the benefits and risks of vaccinations, and need or value of vaccines. Communication and education are essential for increasing knowledge, understanding, confidence, and compliance, but are not as easy to do as many imagine or would like.

Much has been learned, including in recent years, from communication-related research, practice, and experiences regarding vaccine and immunization acceptance, hesitancy, and confidence. This presentation will highlight some of the primary communication challenges associated with vaccines and immunization recommendation, recent findings that can inform vaccine-related communication and education efforts, and communication approaches that can increase the effectiveness of vaccine-related communication and education. Communication best practices and key findings from recent studies will be discussed.

The objectives of this presentation include 1) increasing understanding of the communication issues and challenges associated with vaccines and immunization recommendations, 2) increasing awareness of recent communication-research efforts and findings that can help inform and strengthen vaccine and immunization-related communication and education, 3) increasing recognition of the value of communication-related research when it comes to fostering vaccine-related confidence and reducing vaccine-related hesitancy, and 4) fostering of greater use of communication research and principles in vaccine and immunization promotion efforts.

John Oxford

I trained as a Virologist with Dr G Schild and Professor Sir Charles Stuart-Harris at Lodge Moor Hospital in Sheffield. I was appointed Lecturer in Medical Microbiology there and later moved to the Australian National University in Canberra to work on Influenza with Drs R. Webster and G Laver. I returned to England to work with Dr G Schild at the World Influenza Centre at Mill Hill, London, and later at NIBSC. I accepted the Chair of Virology at the London Hospital Medical College with Professor David Williams. My publications include 300 scientific papers and 3 text books, including “Human Virology” OUP, now in its 5th Edition.

I founded a small biotech company called Retroscreen, now H Vivo.

I was trained for TV Radio and Science programmes, particularly involving influenza pandemics. More recently I have been working with two large EU grants on Universal Influenza Vaccines. I was awarded a DSc (University of Kingston) and FRCPE.

Abstract [PL1.1]:

“The Spanish Pandemic” has bequeathed us very detailed clinical descriptions as well as thousands of well-preserved tissue blocks of lungs. This latter resource has been used to recreate the actual influenza A (H1NI) virus which caused the outbreak, whilst the pathology slides can also be probed to discover new cytokines, bacteria and co-infections. The virus has been resurrected by reverse genetics and showed increased growth rates in cell cultures and virulence in mice and ferrets but not enough, alone, to be the main cause of the catastrophic deaths of 50 million 18-40-year olds. Rather, we identify a number of special features perhaps unique to that period which could allow a conclusion that such a juxta position of the movement of 10 million young soldiers and the Great War and perhaps their unique immune memory of preceding pandemics could not happen again. However, we strongly recommend more research including ‘gain of function’ experiments, until recently suspended, to better understand virus genetics and transmission dynamics, as well as deepened research into Universal Influenza Vaccines and the discovery of a new generation of inhibitory drugs perhaps blocking host cell proteins necessary for viral replication and therefore able to ‘resist’ mutations to make them inactive.
We have also emphasised new molecular clock studies on the time of origin of the virus in 1916 and a possible conduit to the USA from the Western Front during 1916 to 1917 of the newly described 'purulent bronchitis' via the Harvard volunteer doctors and nurses. We note the very similar pathology between influenza victims described in the antibiotic era of 2009 and those in the pre-antibiotic era of a hundred years before, with over half of the patients dying with bacterial pneumonia. But a combination of the modern pneumococcus vaccines, Universal Influenza Vaccines, new antivirals based on human genome studies, and updated pandemic plans will see the world enter a safer era.

Pauline Paterson

Dr. Pauline Paterson is a Research Fellow in the Department of Infectious Disease Epidemiology at the London School of Hygiene & Tropical Medicine (LSHTM), UK and is co-director of The Vaccine Confidence Project with Dr. Heidi Larson.

Dr. Paterson has been researching issues of public confidence in immunisations since 2010. Specific research activities include application of the WHO Tailoring Immunization Programmes (TIP) tool to explore reasons for childhood under-vaccination in a Jewish orthodox community in London, UK, qualitative research on parental reasons for not vaccinating their child with influenza vaccine in England, and factors influencing vaccination uptake during pregnancy among ethnic minorities in London.

Dr. Paterson is a member of the National Institute for Health Research (NIHR) Health Protection Research Unit in Immunisation and has an honorary academic contract with Public Health England. Dr. Paterson has a PhD in Epidemiology, MBA and MSc from Imperial College London.

Abstract [PL5.1]:

Whilst most people vaccinate, some groups or individuals delay or refuse vaccines. Episodes of public concerns about vaccines have occurred around the world, spreading quickly and sometimes seriously eroding public confidence in immunisation and ultimately leading to vaccine refusals and disease outbreaks. Dr Pauline Paterson, Assistant Professor and Co-Director of The Vaccine Confidence Project at the London School of Hygiene & Tropical Medicine, will present on the global vaccine hesitancy landscape.

The presentation will explore the need to pay attention to vaccine confidence based on surveys and case studies, including non-vaccination of measles containing vaccine (MCV), influenza vaccine, and vaccines in pregnancy.

Dr Paterson will introduce and describe the term ‘vaccine hesitancy’, and present findings from a 67-country survey on vaccine confidence, a literature review on trust and confidence in vaccines during pregnancy, and a literature review of healthcare provider’s individual vaccine hesitancy and their role in addressing vaccine hesitancy in their patients. We will then examine the decision-making processes in regards to vaccination. Dr Paterson will finish by discussing effective tools and activities focused on measuring and maintaining confidence in vaccines and addressing vaccine hesitancy.

This talk will highlight the importance of maintaining and improving vaccine confidence, and the diversity of concerns and perceptions about vaccines by time, context, geographical region and sub-population.

Hyewon Phee

I started my career in academia as a T cell immunologist, then made a career transition to pharmaceutical Industry joining Amgen in 2015. Prior to joining Amgen, I was trained in the laboratory of Dr. Art Weiss at UCSF as a postdoctoral fellow and continued my research in the field of T cell signal transduction and Immunology. In 2012, I moved to Chicago to lead a research laboratory in the Department of Microbiology and Immunology at Northwestern University as a tenure-track Assistant professor and continued my research in immune tolerance and regulatory T cell biology. In 2015, I joined Amgen to pursue a target discovery research in Inflammation and Oncology. I believe that, by harnessing our body’s tumor-specific
T cell responses to kill tumor, cancer vaccine has great potential to be a critical component of effective Cancer Immunotherapy.

Abstract [O2.1]:

One of the challenges in the field of neoantigen cancer vaccine is to predict immunogenicity of the neoantigens and generate a vaccine that can elicit potent neoantigen-specific, tumor-controlling T cell responses. In order to learn how to construct a neoantigen cancer vaccine that induces potent immunogenicity towards cancer neoantigens, we first performed whole exome sequencing and RNA sequencing of the four cancer cell lines commonly used in pre-clinical cancer models. I will discuss our approach to construct immunogenic neoantigen cancer vaccines using a pre-clinical cancer model. Furthermore, I will discuss lessons learned from this approach—immunogenicity, pharmacodynamic effect, and efficacy of the neoantigen cancer vaccine as well as importance of the vaccine platform to produce robust immune responses towards cancer in the pre-clinical cancer model.

Stanley Plotkin

Dr. Stanley A. Plotkin is Emeritus Professor of the University of Pennsylvania, and Adjunct Professor of the Johns Hopkins University. Until 1991, he was Professor of Pediatrics and Microbiology at the University of Pennsylvania, Professor of Virology at the Wistar Institute and at the same time, Director of Infectious Diseases and Senior Physician at the Children’s Hospital of Philadelphia. He maintained laboratories at both CHOP and Wistar. In 1991, Dr. Plotkin left the University to join the vaccine manufacturer, Pasteur-Mérieux-Connaught (now called Sanofi Pasteur), where for seven years he was Medical and Scientific Director, based at Marnes-la-Coquette, outside Paris. He left France in 1998, and is now consultant to many vaccine manufacturers, biotechnology companies and non-profit research organizations as principal of Vaxconsult. He also continues to teach at the University of Pennsylvania.

Dr. Plotkin attended New York University, where he received a B.A. degree, and then the State University of New York Medical School in Brooklyn, where he received an M.D. degree in 1956. His subsequent career included internship at Cleveland Metropolitan General Hospital under Fred Robbins, residency in pediatrics at the Children’s Hospital of Philadelphia and the Hospital for Sick Children in London and three years in the Epidemic Intelligence Service of the Centers for Disease Control of the US Public Health Service. While in EIS in the 1950s he worked on the development of oral polio vaccine and on the efficacy of a vaccine against inhalation and cutaneous anthrax.

He has been chairman of both the Infectious Diseases Committee and the AIDS Task Force of the American Academy of Pediatrics, liaison member of the Advisory Committee on Immunization Practices and Chairman of the Microbiology and Infectious Diseases Research Committee of the National Institutes of Health.

Dr. Plotkin received the Bruce Medal in Preventive Medicine of the American College of Physicians, the Distinguished Physician Award of the Pediatric Infectious Diseases Society, the Clinical Virology Award of the Pan American Society for Clinical Virology, the Richard Day Master Teacher in Pediatrics Award of the Alumni Association of New York Downstate Medical College, and the Marshall Award of the European Society for Pediatric Infectious Diseases. In June 1998, he received the French Legion of Honor Medal; in June 2001, the Distinguished Alumnus Award of the Children’s Hospital of Philadelphia, in September 2006 the gold medal from the same hospital; the Sabin Gold Medal in May 2002, in September 2004 the Fleming (Bristol) Award of the Infectious Diseases Society of America, in May 2007 the medal of the Fondation Mérieux, in 2009 the Finland Award of the National Foundation for Infectious Diseases and the Hilleman Award of the American Society for Microbiology, and in 2013 the Career Achievement Award from the Association for Clinical and Translational Medicine, as well as the Caspar Wistar Medal of the Wistar Institute of Biological Research. In 2014 he received the Charles Mérieux Award of the National Foundation for Infectious Diseases and the Sheikh Hamdan (Dubai) Award for Medical Sciences.
He was elected to the National Academy of Medicine of the National Academy of Sciences in 2005, to the French Academy of Medicine in 2007, to the French Academy of Pharmacy in 2013, and to the Thai Pediatric Infectious Diseases Society in 2015. Dr. Plotkin is the Founder and a Fellow of the Pediatric Infectious Diseases Society. He is also a Fellow of the Infectious Diseases Society of America, of the International Society for Vaccines, the American Academy of Pediatrics and the College of Physicians of Philadelphia.

Dr. Plotkin holds honorary doctoral degrees from the University of Rouen (France) and the Complutense University of Madrid (Spain). He is on the board of the Rostropovich Foundation. Named lectures in his honor have been established at the Pediatric Academic Societies annual meeting, at the International Advanced Vaccinology Course in Annecy, France, and at the DNA Vaccines Society. A professorship in his name was established at the Children’s Hospital of Philadelphia. His bibliography includes over 800 articles and he has edited several books including the standard textbook on vaccines, now in its 7th edition and now titled “Plotkin's Vaccines.” In 2000, Plotkin proposed and helped organize an Advanced Course in Vaccinology at the Fondation Mérieux, now in its 19th year. In 2015, in the New England Journal of Medicine, he proposed an international fund for development of vaccines against emerging diseases, which now exists as the Coalition for Epidemic Preparedness and Innovation.

Dr. Plotkin developed the rubella vaccine now in standard use throughout the world, is codeveloper of the pentavalent rotavirus vaccine also used in the United States and elsewhere, and has worked extensively on the laboratory development and application of other vaccines already licensed or in development including anthrax, oral polio, rabies, varicella, pertussis, Lyme disease and cytomegalovirus.

Abstract [PL3.1]:

The human cytomegalovirus (HCMV) is the most important cause of congenital abnormalities now that rubella is controlled, and is also the most common infectious complication of transplantation. Attempts to develop a vaccine against HCMV go back to the 1970s, when it was shown that serious CMV disease post-transplant could be significantly reduced by vaccination with a live attenuated strain. Subsequently, vaccine development has focused on antibody responses to two surface antigens: the gB glycoprotein and a pentameric complex consisting of gH and gL glycoproteins together with the UL128, 130 and 131 proteins. Antibodies and CD4+ T cells against gB have been shown to prevent acquisition of HCMV by seronegative women, whereas antibodies to the pentamer have been shown to correlate with non-transmission of the virus from infected mothers to their fetuses. gB antibodies have also been shown to protect solid organ transplant recipients against HCMV transmission from seropositive donors. Hematogenous stem cell transplant recipients need induction of CD8+ T cell responses, and one of the most potent viral stimulators of those responses is the pp65 tegument protein of HCMV. There are now many candidate vaccines against HCMV, with indications against congenital infection and/or infection after transplant. Among them are a replication-defective virus, purified gB and pentameric proteins, peptides from those proteins, DNA plasmids, mRNA constructs, lentivirus particles coated with gB, and various vectors producing CMV proteins. Demonstration of efficacy against congenital infection may require large trials, whereas efficacy against maternal acquisition can be shown easily because of the ubiquitous infection and excretion of HCMV by toddlers. Efficacy against transplant infection should also be easily demonstrated, but with greater difficulty in hematogenous stem cell recipients than recipients of solid organs. Clinical trials conducted in the near future will determine whether a vaccine against HCMV, the cause of many disease syndromes, is feasible.

Thomas Richie

Dr. Richie earned PhD and MD degrees from the University of Pennsylvania. He completed a residency in internal medicine at Massachusetts General Hospital and a fellowship in Infectious Diseases at Johns Hopkins Hospital. He directed the US Navy Malaria Program 2004-13, focusing on gene-based malaria vaccines. In 2014 he joined Sanaria as Chief Medical Officer where he is responsible for the clinical development of whole sporozoite-based vaccines. In 2018-9, Dr. Richie is providing oversight for multiple
clinical trials of Sanaria’s products including trials conducted in the USA, Germany, the Netherlands, Mali, Kenya, Tanzania, Gabon, Equatorial Guinea and Indonesia.

Abstract [O3.1]:

In 2016, malaria caused 216 million cases and claimed 445,000 lives worldwide, both increases from the year prior, with the large majority of severe disease and death caused by *Plasmodium falciparum* (Pf), indicating an urgent need for a vaccine. Sanaria Inc. has developed methods to manufacture, purify and cryopreserve aseptic Pf sporozoites (SPZ), and is using this platform technology to develop an injectable PfSPZ-based product that provides high-grade, durable protection against infection with Pf malaria. Several candidate PfSPZ-based vaccines are being developed and tested, including PfSPZ Vaccine (radiation-attenuated PfSPZ), PfSPZ-CVac (fully infectious PfSPZ attenuated *in vivo* by concomitant administration of an anti-malarial drug), and PfSPZ-GA1 (PfSPZ attenuated by gene knockout). Multiple trials have shown the vaccines to be extremely safe and well tolerated including in infants, children and HIV-infected adults, and documented 90-100% protection against controlled human malaria infection (CHMI). The lead candidate, PfSPZ Vaccine, has demonstrated sustained (6 month) protection against naturally transmitted Pf in the field in 4 separate trials. More than 40 research groups and government institutions from 18 countries, organized as the International PfSPZ Consortium (I-PfSPZ-C), are collaborating to advance this program by providing intellectual, clinical, and financial support. Twenty clinical trials of these vaccine products have been completed in the USA, Europe and Africa, 4 more are underway (Germany, Equatorial Guinea, Gabon, Mali), and several more will start in 2019, including a first Phase 3 trial in Equatorial Guinea. Sanaria anticipates application to the US FDA and the EMA to license a first generation vaccine to prevent Pf malaria in 2021-2, initially to protect adults, and a year later to protect all persons ≥6 months of age. Improved vaccine candidates will be advanced as needed until the following requirements have been met: adequate protection against natural transmission, excellent safety and tolerability, and operational feasibility for population-wide administration. The presentation will describe the three most developed whole PfSPZ vaccine candidates, associated clinical trials, initial plans for licensure and deployment, and long-term objectives for a final product suitable for mass vaccination programs (MVPs) to achieve regional malaria elimination and eventual global eradication. The presentation will also describe key innovations associated with PfSPZ development: direct venous inoculation as the route of administration, liquid nitrogen vapor phase cryostorage, use of cryopreserved, non-attenuated PfSPZ to conduct CHMI, and *in vitro* SPZ production.

Nadine Rouphael

Dr. Nadine Rouphael (MD) is an Associate Professor of Medicine at the Emory University in Atlanta, USA. She graduated from Saint Joseph University School of Medicine in Lebanon (2001). She completed her internal medicine residency (2005) and infectious diseases fellowship (2008) at Emory University. She serves as the Director of the Hope Clinic and the Emory co-principal investigator for the NIH funded Vaccine Treatment and Evaluation Unit (VTEU) and the Clinical Core principal investigator and Director of the Hope Clinic for NIH funded Human Immunology Project Consortium (HIPC). She is also an investigator for HIV Clinical Trials (HVTN). She has served as the national chair/co-chair as well as overall PI/site PI of 30 clinical studies and an investigator on more than 100 studies. She has interest in antimicrobial resistance, vaccine clinical trials (pandemic influenza, Zika, Ebola…), vaccine delivery methods (NIH funded phase 1 trial on microneedle patch), translational research on innate immunity and systems biology, immune aging and correlates of protection. She has published more than 60 peer reviewed publications (New England Journal of Medicine, The Lancet, JAMA, Nature Immunology, Cell…) and has received 9 awards including the Robert Austrian Research award from the International Symposium on Pneumococci and Pneumococcal Diseases in 2014.

Abstract [O1.2]:

Microneedle patch (MNP) is a micron-scale solid conical structures made of dissolvable excipients on a patch backing that delivers vaccine antigens across the stratum corneum into the epidermis and dermis. We have recently shown that a single application of dissolvable MNP can safely and effectively deliver
seasonal influenza vaccine in healthy adults. MNP are currently being tested as a vaccine delivery method for other vaccines. MNP could have a public health impact by simplifying vaccine delivery, thereby enabling distribution and storage outside the cold chain, disposal as non-sharps waste, and possible self-administration under medical supervision or even at home and potential enhancement of immunogenicity by targeting the skin, an immunologically rich organ.

Tim Schacker

Dr. Schacker received his M.D. from the University of Minnesota in 1987 and completed a residency in Internal Medicine at Oregon Health Sciences University in 1990. He then completed a fellowship in Infectious Disease at the University of Washington in 1992 and then joined the faculty of the University of Washington. His early research focused on herpes simplex virus interactions with HIV and on the natural history of acute HIV infection. During his time at the University of Washington he started one of the first clinics designed to recruit and follow patients in acute HIV infection. In 1996, he moved to the University of Minnesota where he is now a Professor of Medicine in the Division of Infectious Diseases. His work now focuses on the immune-pathogenesis of HIV infection, particularly in lymphatic tissues where the main reservoir of infection resides. Dr. Schacker has made significant contributions to the field and his laboratory was the first to describe lymphoid tissue fibrosis as a mechanism of T cell loss in HIV infection. He maintains his interest in studying the pathogenesis of acute infection and has active studies in this area.

Abstract [PL3.2]:

There are numerous examples of a vaccine that results in neutralizing antibodies in one population, but not others. Rotavirus, polio, cholera, and tuberculosis (TB) are examples. BCG vaccination for TB has significantly higher rates of protection the further north the vaccine is used. Reasons for differences in vaccine efficacy are unknown with genetic or environmental factors thought to be important factors. An interesting parallel observation is that population based measures of CD4 T cells also vary geographically, with people living in northern latitudes having significantly greater numbers of CD4 T cells than people living close to the equator. In our studies of mechanisms of loss of CD4 T cells in HIV infection, we showed that HIV replication in lymphoid tissues caused inflammatory damage to the Fibroblastic Reticular Cell network (FRCn) in the form of collagen deposition into the network. The FRCn is the primary source of IL-7 outside of the thymus and loss of the network results in decreased production of IL-7 with a net result of increased T cell apoptosis and this process is a significant mechanism of CD4 loss in HIV infected people. Because there are significant differences in population based measures of CD4 T cell count that seem to parallel differences in vaccine efficacy infections we speculated that infections other than HIV might cause inflammatory damage to the FRCn that lead to T cell depletion which might be a contributing factor to poor vaccine efficacy rates. To explore this hypothesis, we studied lymph nodes in HIV negative people living in Kampala, Uganda and show fibrotic changes to the FRCn and a depleted T cell population. We also found elevated levels of inflammatory cytokines, including TGFβ which we have shown is a cause of LN fibrosis in HIV infection. We then vaccinated the individuals with yellow fever vaccine (YFV) and found that the peak neutralizing antibody titers were blunted and correlated to our quantitative measures of the FRCn, fibrosis, CD4 T cell populations (including T Follicular helper cells), and inflammatory cytokines. These data suggest that LN fibrosis is not limited to HIV infection and may be associated with impaired immunologic responses to vaccines and also provide insight into potential mechanisms that prevent appropriate immunologic responses to vaccine administration in some settings. This may have an impact on vaccine development, especially for infectious diseases prevalent in the developing world.
Terry Tumpey

Terrence M. Tumpey earned his Bachelor of Arts degree in biology from the University of Minnesota and his Ph.D. in Microbiology/Immunology from the University Of South Alabama School Of Medicine in Mobile, Alabama. He was a recipient of the American Society for Microbiology (ASM) Postdoctoral Fellowship award and conducted his postdoctoral training at the Influenza Division, Centers for Disease Control and Prevention (CDC). He later served the U.S. Department of Agriculture (USDA) as a Microbiologist at the Southeast Poultry Research Laboratory in Athens, Georgia. His interests lie in elucidating the molecular determinants of virulence and transmission of influenza viruses, including the 1918 pandemic virus. Since 2003, Dr. Tumpey has been with the CDC and served as the Team Leader of Pathogenesis and currently is the Chief of the Immunology and Pathogenesis Branch. His research on pathogenesis and immunity during the last 30 years is documented in over 230 total peer-reviewed publications. In 2006 he was honored with the Lancet Award for the top scientific paper of 2005 presented by Lancet. He also received the 2006 and 2008 Shepard Award from the CDC for Outstanding Research Papers. Dr. Tumpey has been serving as editor with Virology for 5 years. In 2007, Dr. Tumpey was inducted into the University of Minnesota, Duluth Academy of Science and Engineering and he received the Distinguished Alumni Award presented by the University of South Alabama.

Abstract [PL1.2]:

The pandemic influenza virus of 1918-1919 killed an estimated 20-50 million people worldwide. As influenza viruses continue to evolve and pose a threat to human health, studying past pandemic viruses can be key to future preparedness efforts. Infectious virus containing complete coding sequences of the eight gene segments from the 1918 pandemic virus was completed and first published in 2005, permitting for the first time in vivo and in vitro examination of the fully reconstructed strain. The 1918 virus replicated to high titers in human airway cells and was highly virulent in mammals. Studying the molecular determinants of virulence and transmission for this virus, in comparison with other contemporary viruses with pandemic potential, has afforded us a window into understanding why the 1918 pandemic was so devastating. Most of the initial research emphasis on the 1918 virus was placed on the hemagglutinin (HA), which demonstrated that the 1918 HA enhanced the virulence of both H1N1 and H3N2 subtype viruses in mammals. The 1918 HA along with a second influenza protein, the polymerase basic protein (PB2) appears to contribute to the transmissibility of this virus by allowing increased replication at lower temperatures found in the airway of mammals. Reconstruction of the 1918 influenza virus has facilitated considerable advancements in our understanding of this extraordinary pandemic virus. It is hopeful that continued examination of and reference to this notorious strain will further enable public health efforts to mitigate the burden of influenza virus infection worldwide.
Immunogenicity of a protective intradermal DNA vaccine against Lassa Virus in Cynomolgus macaques

Jingjing Jiang1*, Stephanie J. Ramos1*, Preeti Banglore1, Kathleen A. Cashman2, Connie S. Schmaljohn2, Katherine Schultheis1, Holly Pugh1, Jacklyn Nguyen1, Laurent M. Humeau1 and Kate E. Broderick1

1 Inovio Pharmaceuticals Inc., Plymouth Meeting, PA
2 United States Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD

* J.J. and S.J.R. contributed equally to this study

Lassa virus (LASV) is a hemorrhagic fever virus of the Arenaviridae family with high rates of mortality and co-morbidities, including chronic seizures and permanent bilateral or unilateral deafness. LASV is endemic in West Africa and Lassa fever accounts for 10-16% of hospitalizations annually in parts of Sierra Leone and Liberia according to the CDC. An ongoing outbreak in Nigeria has resulted in 114 deaths and 365 cases confirmed as LASV as of March 2018, with many more suspected, highlighting the urgent need for a vaccine to prevent this severe disease. We previously reported on a DNA vaccine encoding a codon-optimized LASV glycoprotein precursor gene, INO-4500, that completely protects Guinea pigs and nonhuman primates (NHPs) against viremia, clinical disease, and death following lethal LASV challenge. Herein we report on the immunogenicity profile of the LASV DNA vaccine in protected NHPs. Antigen-specific binding antibodies were generated in 100% (6/6) NHPs after two immunizations with INO-4500. These antibodies bound predominantly to the assembled LASV glycoprotein complex and had robust neutralizing activity in a pseudovirus assay. INO-4500-immunized NHPs (5/6) also developed T cell responses as measured by IFNγ ELISpot assay. These results demonstrate that the INO-4500 DNA vaccine is capable of generating functional, LASV-specific T cell and antibody responses, and the assays developed in this study will provide a framework to identify correlates of protection and characterize immune responses in future clinical trials.

Genomic DNA as a damage-associated molecular pattern increases the immunogenicity of influenza vaccines given by a dissolvable microneedle patch.

Teena Mohan1, Song Li2, Gilbert X. Gonzalez1, Mark Prausnitz2, and Bao-Zhong Wang1

1 Center for Inflammation, Immunity & Infection, Institute for Biomedical Sciences, Georgia State University, Atlanta, GA 30303, USA.
2 School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA.

Background: Microneedle patch (MNP)-based influenza vaccines demonstrate increased immunogenicity and additional benefits including acceptability, accessibility, and thermostability. However, unlike conventional influenza vaccines, adjuvants for MNP-based skin vaccinations are not sufficiently studied. When cells undergo necrosis/apoptosis during an infection, the genomic DNA released by the injured cells acts as a ‘danger signal’ which promotes antigen-presenting cell (APC) maturation and other immune-stimulatory effects. Here, we have studied mouse genomic DNA (mGD) as a novel adjuvant to enhance the potency of MNP-based influenza vaccines.

Methods: We made MNPs encapsulating inactivated Pr8 virus (10μg) with and without the various contents of mGD (0.1μg, 0.5μg, or 1μg) by a two-step fabrication process. Mice were skin-immunized with the resulting MNPs or empty MNPs (placebo). A naïve group was included as a negative control group. Another group was immunized by Pr8 only MNPs followed by mGD (0.5μg) only MNPs with an interval of 20 minutes. MNPs were applied on the dorsal surface of 6–8-week-old BALB/c mice at week-0 with a booster dose at week-4.

Results: The Pr8 HA and mGD in MNPs retained their physical and functional properties with a delivery efficiency of 80-85%. The Pr8-mGD MNP vaccination induced significantly (p<0.001) higher Pr8-specific serum IgG (IgG2-dominant) antibody levels and antibody secreting cells than other groups. We found increased Th1/Th2 cytokine levels and enhanced cytokine secreting cells in the Pr8-mGD MNP groups. The Pr8 MNPs co-formulated 0.5μg mGD group showed the greatest enhancement in the antigen-specific antibody and cellular immune responses when compared with other vaccine formulations. The Pr8-mGD
MNP-immunized animals demonstrated elevated hemagglutinin inhibition and serum neutralization titers compared with other groups —indicating an improved protection in these animals. At 4-week post-boost, animals were challenged intranasally with 10×LD₅₀ of mouse adaptive A/PuertoRico/8/1934 (Pr8;H1N1) or A/California/7/2009 (CaH;H1N1) viruses. Animals immunized with Pr8-mGD MNPs showed the greatest protection with minimum body weight loss against both virus challenges. Immunization with Pr8-mGD MNPs also inhibited viral replication and inflammatory responses in lungs and enhanced viral clearance from the respiratory system. In passive immune sera transfer experiments, we found that mice received immune sera from the Pr8-mGD MNP-immunized mice showed complete protection against both virus challenges compared with other control groups —demonstrating that the serum antibodies conferred protective immunity.

To understand the involved mechanism, we evaluated the activation of bone marrow dendritic cells (BMDCs), dermal dendritic cells (dDCs), and Langerhans cells (LCs) in the vaccinated animals. The Pr8-mGD MNP groups had significantly (p<0.05) increased CD11c⁺CD40⁺ BMDCs with increased levels of IL-6, IL-12p40, and TNF-α cytokines. Results showed that the mGD added in Pr8 MNPs encouraged BMDCs to mature phenotypically and functionally. The Pr8-mGD MNP groups demonstrated a significantly (p<0.01) higher percentage of activated dDCs (CD103⁺CD80⁺;28.5%) and LCs (CD103 CD80⁺;9.65%) compared with other groups. These results confirm that the activated BMDCs, dDCs, and LCs play a crucial role in immune protection.

**Conclusion:** The mGD in Pr8 MNPs acted as a strong immunostimulator and enhanced protective immunity in immunized mice by activating APCs in bone marrow and epidermal and dermal layers of the skin.

---

**Replicating Single-cycle Adenovirus Vaccine against Ebola Virus**

**Stephanie S. Anguiano-Zarate¹**, William E. Matchett², Pramod Nehete⁴, K. Jagannadha Sastry⁴,⁵, Andrea Marzi⁶, and Michael A. Barry³

Clinical Translational Sciences Graduate Program¹, Virology and Gene Therapy Graduate Program², Department of Internal Medicine, Division of Infectious Diseases³, Department of Immunology³, Department of Molecular Medicine³, Mayo Clinic, Rochester, MN, Department of Immunology⁴, Departments of Veterinary Sciences⁴ and Immunology⁵, The University of Texas M.D. Anderson Cancer Center, Houston and Bastrop, TX, Laboratory of Virology, Division of Intramural Research⁶, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, MT

The latest resurgence of Ebola virus (EBOV) affirms the need for more strategies to prevent and combat EBOV outbreaks. Only two investigational vaccines have been field-tested and there is currently no FDA-approved vaccine. Among promising gene-based vaccine vectors are adenoviruses (Ads). The vast majority of Ad vaccines are RD-Ad vectors, which do not amplify the antigen genes they carry, and upon infecting a cell, express only "1X" antigen per cell. One of the field-tested vaccines in the 2014 outbreak was the chimpanzee-derived replication-defective adenovirus (RD-Ad), ChAd3-EBOV. While RD-Ads elicit robust protection, they require increased particle delivery and their efficacy wanes when tested in humans. Alternatively, replication-competent Ads (RC-Ad) can replicate genes up to 10,000-fold to amplify antigen expression and immune responses. While RC-Ads are more potent, they run the risk of causing adenovirus disease due to uncontrolled viral replication. To circumvent these pitfalls, we recently described a “single cycle” adenovirus (SC-Ad) vector that amplifies antigen genes like RC-Ad, but avoids the risk of adenovirus infection. We have tested an SC-Ad6 vector expressing the glycoprotein from a 2014 Zaire EBOV strain in mice, hamsters, and rhesus macaques. We show that SC-Ad6-EBOV gp induces high serum antibodies after single intranasal or intramuscular immunization and the production of binding and neutralizing antibodies in rhesus macaques. We show that SC-Ad6-EBOV gp mediates protection against pseudo-challenge. These data suggest that SC-Ad6-EBOV gp is a potent vaccine and may provide value during future EBOV outbreaks.
Immunogenicity and Efficacy of a Thermostable Live-Attenuated Influenza Vaccine in Ferrets

Jasmina M Luczo1, Tatiana Bousse2, Cheryl A Jones1, Scott K Johnson1, Carlie A. Neiswanger1, Constantinos S. Kyriakis1, Nicholas Pearce2, Min-Xuan Wang3, Erin A Miller3, Nickolai Pertovskiy4, David E Wentworth2, Victor Bronshtein4, Mark Papania2, and S. Mark Tompkins1

1 Center for Vaccines and Immunology, University of Georgia, Athens, Georgia, USA
2 Centers for Disease Control and Prevention, Atlanta, Georgia, USA
3 Universal Stabilization Technologies, Inc., San Diego, California, USA
4 Vaxine Pty. Ltd., Flinders Medical Center, Adelade, South Australia, Australia

Human seasonal influenza epidemics occur yearly, with an estimated 25-50 million infections occurring in the United States alone. Annual vaccination is the most effective strategy for the prevention and control of seasonal influenza. Seasonal influenza vaccination strategies include live-attenuated and inactivated influenza vaccines (LAIV and IIV, respectively), having trivalent and quadrivalent vaccine formulations. While LAIV may have some benefits over IIV, thermostability is a concern and potency of these vaccines can be negatively affected if not maintained at adequately cold temperatures. Here, we thermostabilized LAIV (tLAIV), created with the A/Leningrad/134/17/1957 master donor virus, at ambient temperatures using Preservation by Vaporization (PBV, Patent No. US 9,469,835). Subsequently, a ball mill was used to micronize the dry formulation for respiratory powder delivery, the infectivity of the tLAIV over one year was determined, immunogenicity assessed, and the efficacy of the dry powder vaccine in ferrets was examined. Infectivity studies demonstrated essentially no loss in titer of tLAIV lots stored at room temperature over one year. Moreover, there were only modest decreases in titer of tLAIV lots stored at 37°C. Immunogenicity of tLAIV was assessed in ferrets vaccinated intranasally with the dry powder vaccine and compared to liquid LAIV stored at -80°C. Replicating LAIV was detected in nasal washes of tLAIV vaccinated ferrets and vaccination elicited robust mucosal antibodies, and serum hemagglutination-inhibition titers comparable to standard liquid LAIV, indicative of protection. Ferrets vaccinated with tLAIV were protected when challenged with an antigenically matched strain, A/TX/50/2012 (H3N2). These results support the use of PBV stabilization for LAIV to reduce cold-chain requirements and improve stability of LAIV, as well as dry powder intranasal delivery of tLAIV as an effective immunization strategy eliciting protective influenza-specific immune responses.

Double-layered protein nanoparticles induce broad protection against divergent influenza A viruses

Lei Deng

Current influenza vaccines provide limited protection against matched circulating influenza A viruses. Mismatches cause epidemics in some seasons. An occasional pandemic can cause deaths in millions. A universal influenza vaccine will eliminate these threats. The relatively conserved ectodomain of matrix protein 2 (M2e) and stalk domain of hemagglutinin (HA) are ideal candidates for such vaccines. Here we generated double-layered protein nanoparticles by desolvating tetrameric tandem M2e into protein nanoparticle cores and coating these cores by crosslinking structure-stabilized headless HA. Representative headless HAs of two HA phylogenetic groups were constructed to include the conserved stalk region of the receptor binding HA1 subunit and modified HA2 subunit. Vaccinations with the double-layered protein nanoparticles in mice induced robust and long-lasting immunity, fully protecting the mice against challenges by divergent influenza A viruses of the same group or both groups. The results demonstrate the importance of incorporating both structure-stabilized HA stalk domains and M2e into a universal influenza vaccine to improve its protective potency and breadth. These potent disassemblable protein nanoparticles indicate a wide application in protein drug delivery and controlled release.

Joshua Tobias¹, K. Bailer¹, M. Drinic¹, K. Amoroz¹, E. Garner-Spitzer¹, C. C. Zielinski², M. Kundis³, U. Wiedermann³

¹ Institute of Specific Prophylaxis and Tropical Medicine, Medical University of Vienna, Austria
² Division of Oncology, General Hospital, Vienna, Austria
³ Department of Environmental Hygiene, Center for Public Health, Medical University of Vienna, Austria

The extracellular domains of the oncogene product Her-2/neu, which is overexpressed in breast, gastric and other cancers, have been the focus for immunotherapy. The monoclonal antibodies (mAbs) Trastuzumab and Pertuzumab in combination have shown to synergistically result in a significant improvement in clinical outcomes of patients with Her-2/neu-positive metastatic breast cancer. Unlike application of mAbs however, active immunotherapy provides advantages like induction of humoral, cellular and memory responses leading to achievement of anti-tumor activity.

Our group has earlier constructed two generations of anti-Her-2/neu vaccine consisting of three B-cell epitope peptides singularly conjugated to virosomes (first generation), and after fusing the single peptides into a hybrid peptide conjugated to CRM197 and in conjunction with the adjuvant Montanide (P467-CRM-Montanide; second generation) which was shown to induce enhanced and long term humoral and Th1-biased cellular responses with antitumor activity. To broaden the number of biologically active epitopes in the next generation of our vaccine, cellular tools and overlapping peptides spanning the extracellular domains of Her-2/neu were applied and the binding site epitopes (mimotopes) of Trastuzumab and Pertuzumab were identified.

The specificity of the identified mimotopes was observed by ELISA assays and immunization of BALB/c mice with the mimotopes was shown to induce polyclonal humoral and cellular responses. Additionally, when evaluating the anti-tumor effect of the identified mimotopes in transgenic mice spontaneously developing rat Her-2/neu, we have shown that combination of the mimotopes has notably reduced the tumor progression in the corresponding immunized mice compared to naïve mice. Towards our goal to construct a third generation of our anti-Her-2/neu vaccine based on our newly established mimotope platform technology, the antitumor effect of Trastuzumab and Pertuzumab mimotopes, in combination with either the hybrid peptide P467 or the selected B-cell epitope peptides, is now being evaluated. Moreover, as a proof of principle, the impact of anti-mouse PD1 mAb as an immune checkpoint inhibitor on enhancement of the anti-tumor effect of our 3rd generation cancer vaccine is also being assessed.

Construction of a vaccine targeting different active epitopes/mimotopes of Her-2/neu or other cancer vaccine antigens, possibly in combination with an immune checkpoint inhibitor, may potentially result in an effective novel multi-level vaccine against Her-2/neu overexpressing and other cancer entities.

Development of Vaccines for Infectious Diseases and Cancer Using a Novel MVA-VLP Vector

Arban Domi

Summary: GeoVax MVA platform technology is built on a 4th generation MVA vector system that is improved for high expression and stable transgenes during manufacture. It has the advantages of being a live replication-competent vector in avian cells for manufacturing, yet replication-deficient in mammalian cells for vaccination, thus inherently safe. Importantly, MVA vaccines elicit protective T cell as well as antibody responses in animals and humans. Our MVA platform is combined with the potent immunogenicity of Virus Like Particles (VLPs) (e.g. MVA-VLP-HIV, -Ebola, -Marburg, -Sudan, -Lassa fever, -HBV, -HPV, -malaria, -MUC1+ cancers) to express proteins in their native conformations enabling vaccines that induce full protection after a single dose. The MVA-VLP-HIV vaccine has completed 7 clinical trials with proven safety and induction of robust antibody and T cell responses in Ph2a clinical trials.

In this talk, we present preclinical single dose efficacy data for vaccines against Ebola, Lassa fever and Zika and briefly discuss the pipeline of all other MVA-VLP vaccines in progress, including combination therapy for treatment of HBV chronic infection and MUC1+ cancers.
Anti –Energy based Unconventional Prophylactic HIV/AIDS Vaccine provide Proof of Concept in Human

Uniyal Bandana, M.Sc.
Secretary: Shri Radheykrishna Oaj (AIDS) Vaccine Organization, bandana_uni9@yahoo.co.in
9012356136

The human immunodeficiency virus (HIV) pandemic is now in its fourth decade. With more than 35 million people infected in over thirty years, the HIV pandemic has been an unique challenge to the scientific community. The development of effective anti-retroviral therapy has decreased morbidity and mortality of those infected with HIV, but a comprehensive approach that includes effective preventive strategies will be needed to curb this unique pandemic. Vaccine remains the best option, but the development of a safe and effective preventive HIV vaccine has defied decades of research. Understanding the unique obstacles in development of HIV vaccine is provided the roadmap for future HIV/AIDS vaccine development. The complexity of this challenge has required innovative approach to vaccine development.

A new unconventional (Innovative) basic research study finds a proof of concept in human when 1:2 dilutions of HIV-1 infected (positive) serum with anti –energy substance lost its infectivity when left for two weeks. This vaccine strategy based on energy utilized by the HIV -1 virus for replication inside host rather than proteinious nature of virus. No chemical treatment for inactivation and killing of HIV -1 virus. Prototype HIV – 1 vaccine injected intramuscularly into HIV negative person at 0 month and 22 months. A fourth-generation HIV-1 antibody immunoassay were performed to confirm HIV infection at 21 days, 3 months, 6 months, 12 months and repeats after 22 months. After 4.0 years of follow up study vaccine subject do not show any symptoms of HIV – 1 infection that confirm HIV – 1 infection. All blood parameters (Complete Blood Count) are normal in range. The sexual transmission of HIV – 1 virus during study period does not occur without any prevention methods were used. Prototype HIV – 1 vaccine does not show antibody response. Protection was occurred due to cellular immunity and some mysterious cause. The nature of HIV infections argues strongly that an effective vaccine must block infection such that it never becomes established in vaccinated individuals (i.e., sterilizing protection). This basic research study provides proof of concept for prophylactic HIV – 1 vaccine in human. The study vaccine is safe and effective. The prototype vaccine based on anti –energy hypothesis is safe and effective for desired study questions.

A DNA-based immunotherapy induces receptor-blocking antibodies that can neutralize HBV in humanized mice

Lars Frelin1, Panagiota Maravelia1, Neetu Jagya1, Lieven Verhoye2, Georg Verch3, Yi Ni3, Gustaf Ahlén1, Stephan Urban3, Philip Meuleman2, Matti Sallberg1
1) Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden
2) Laboratory of Liver Infectious Diseases, University of Gent, Belgium
3) Molecular Virologie, University of Heidelberg, Heidelberg, Germany

Background: In chronic hepatitis B and D virus (HBV/HDV) infection the virus evades host immune responses by inducing a severe T cell dysfunction/tolerance, and by secreting HBV surface antigen (HBsAg) to inhibit HBsAg-specific neutralizing antibodies. As the infectious HBV virions, in contrast to circulating HBsAg, predominantly display the PreS1/2 proteins, the presence of PreS1 antibodies can block viral entry and spread of infection. To circumvent, rather than to overcome or break, immunological tolerance in chronic HBV, we used the large HDV capsid antigen (HDAg) as a heterologous carrier of T cell help. Thus, genetic immunization with HDAg, linked to PreS1 sequences, will prime healthy T cells that support B cell activation and production of neutralizing PreS1 specific antibodies also in a host with chronic HBV.

Methods: We designed various combinations of DNA vaccine candidates that induce receptor-blocking antibodies to the preS1 domain of HBV and HDV, and specific T cells. The DNA vaccines are composed of PreS1 sequences fused to HDAg genotype (gt) 1 and gt2 sequences, which were injected in C57BL/6 and BALB/c mice or rabbits by intramuscular immunization followed by in vivo electroporation. Induction of
antibodies and specific T cells were analysed by ELISA and ELISpot. The elicited antibodies were further evaluated for their ability to neutralize HBV by an *in vitro* neutralization assay.

**Results:** We found that the HDAg-induced T cells are genotype specific in both C57BL/6 and BALB/c mice, suggesting that the vaccine needs to contain both HDV gt1 and gt2 sequences. Upon vaccination of mice and rabbits, broadly cross-reactive preS1-antibodies were effectively induced that recognized HBV of genotypes A to F. Importantly, the vaccine-primed high levels of PreS1 antibodies in mice and rabbits that effectively neutralized HBV *in vitro*. Antibodies purified from vaccinated and non-vaccinated rabbits were tested for their ability to prevent receptor-binding and infection in uPA-SCID mice with humanized livers. Only immunoglobulin from vaccinated rabbits showed protection against HBV infection.

**Conclusion:** The current therapeutic vaccine candidate, using a strategy of circumventing immunological tolerance by inducing healthy heterologous T cells, induced functional and neutralizing HBV- and HDV-specific immune responses. We show that our DNA-based vaccination strategy may represent an important constituent for future combination immunotherapies against chronic HBV and possibly also HDV infection.

---

**[O3.3]**

**Replicating Single Cycle Adenovirus Vaccine against Clostridium Difficile**

Authors: William E. Matchett, and Michael A. Barry, Ph.D.

*Clostridium difficile* (*C. difficile*) caused almost half a million infections in patients in the United States in a single year. This makes *C. difficile* infection (CDI) the most common cause of healthcare associated infections. In that same year, 29,000 patient deaths were associated with CDI.\(^1\) Infection can develop when antibiotic treatment disrupts normal host commensal microbiota. *C. difficile* colonize the large intestine. Symptoms arise from CDI do to the release of two toxins, Toxin A (TcdA) and Toxin B (TcdB). These toxins cause inflammation and diarrhea that can result in life-threatening disease. Standard CDI therapies use antibiotics. Broad spectrum antibiotics can cause further disruption of the intestinal microbiota. This continued disruption results in 20% rate of recurrence.\(^2\) One new approach to CDI treatment that has shown some promise in clinical trials is fecal transplantation. Yet, most studies using fecal transplants administered them using invasive delivery methods.\(^3\) While new treatments like this are needed, vaccines have been the most effective means to fight infectious diseases. Additionally, vaccines delivery uses less invasive methods. For CDI, a vaccine may offer the best opportunity for sustained, long-term protection. We developed a novel single cycle adenovirus (SC-Ad) gene-based vaccine against *C. difficile*. Unlike replication-defective Ad vaccines, SC-Ad vectors replicate antigen genes thousands of times to amplify immune responses. Yet, unlike replication-competent Ads, SC-Ad cannot cause dangerous adenovirus infections. We engineered our SC-Ad to express fused and secreted receptor-binding domains from *C. difficile*’s two toxins. Western blot analysis of transduced mammalian cells demonstrated that the vaccine produced and secreted both TcdA and TcdB as fused and cleaved proteins. Unlike toxoid vaccines currently in clinical trials that need at least three immunizations, a single intramuscular immunization with our SC-Ad vaccine generated TcdA and B binding antibodies that climbed over one half of a year to reciprocal titers above 10^5 against both toxin A and B.\(^4\) Samples collected 6 months after single immunization had an average reciprocal TcdB neutralizing titer of 160. We challenged mice with a lethal dose of TcdA after the single-immunization, all PBS and control SC-Ad vaccinated animals succumbed to the toxin within 48 hours. In contrast, all animals in the SC-Ad *C. difficile* vaccine group survived. These data suggest that this vaccine may have utility as a single mucosal or systemic vaccine against CDI.

---

**[O3.4]**

**Vaccine-induced immunity in the immunocompromised host: Evaluating antifungal vaccine efficacy in a non-human primate model of drug-induced immunosuppression**

Viviana Cobos Jiménez, Whitney Rabacal, Emily Rayens, Brenda Noble, Lauren Lacefield, Rebecca Tarantelli, Karen A. Norris.

Center for Vaccines and Immunology, Department of Infectious Diseases, University of Georgia, Athens, GA, USA

Immunocompromised patients, like those undergoing organ transplant or chemotherapy, are at high risk of acquiring life-threatening infections caused by opportunistic fungal pathogens, such as *Pneumocystis* (Pc). Although *Pneumocystis* Pneumonia (PCP) has a high mortality rate (30-50%) in these patients, there are no vaccines available, and therapeutic alternatives are limited. To better understand and improve vaccination strategies for immunocompromised patients, we have established a pre-clinical non-human
primate (NHP) model for drug-induced immunosuppression, which allows us to examine the prophylactic and therapeutic efficacy of anti-fungal vaccination strategies. Rhesus Macaques were administered an immunosuppressive drug regimen consisting of 2mg/kg/day of FK506 (Tracolimus) and a 40mg/day Methylprednisolone dose tapered to 4mg/day over two weeks. After 2 months of receiving this immunosuppressive regimen, there was evidence of persistent pulmonary Pc colonization, which could be sustained over time. In the context of this pre-clinical drug-induced immunosuppression model, we were also able to examine the effectiveness of our KEX-1 protein-subunit vaccine candidate (Kling and Norris, 2016). We have previously shown that KEX-1 can establish a robust anti-Pc immune response that is maintained during SIV-induced immunosuppression, and is able to confer protection from the development of Pneumocystis Pneumonia (PCP). In this current study, we were able to evaluate the duration and potency of the anti-KEX 1 immune response during the course of a FK506/Methylprednisolone regimen. This pre-clinical model of drug-induced immunosuppression opens numerous possibilities to study prophylactic and therapeutic vaccines candidates against opportunistic pathogens, such as Pneumocystis, in a highly relevant primate model that is able to recapitulate disease course and immune responses in humans. Our NHP pre-clinical model allows us to evaluate vaccine efficacy when vaccination takes place before immunosuppression, as well as to develop strategies for vaccination of patients already undergoing immunosuppressive regimens that do not have access to other therapeutic alternatives.

To what Extent Are Recent Pertussis Epidemics Due to Under Vaccination or to Waning of Pertussis Vaccine Immunity?

Ousseny Zerbo, PhD; Joan Bartlett, MPH, M.P.P; Kristin Goddard, MPH; Bruce Fireman, MA; Ned Lewis, MPH; and Nicola P. Klein, MD, PhD
Kaiser Permanente Vaccine Study Center, 1 Kaiser Plaza, 16th Floor, Oakland, CA 94612

**Background:** Children who are not age-appropriately vaccinated are at increased risk of pertussis. However, children who are age-appropriately vaccinated are also at risk due to waning of Diphtheria, Tetanus, and acellular Pertussis vaccine (DTaP) immunity. The objective of this study was to examine the risk of pertussis by DTaP vaccination status and waning of DTaP vaccine immunity to better understand the contribution of each factor to recent pertussis outbreaks.

**Method:** We conducted a cohort study among children born between 1999 and 2016 who were members of Kaiser Permanente Northern California (KPNC) at 2 months of age. We started follow-up at 3 months of age, or January 1, 2006, whichever was later, and continued until the first occurrence of a positive polymerase chain reaction (PCR) test for Bordetella pertussis, disenrollment from KPNC, 11th birthday, or the end of study follow-up (June 30, 2017). We categorized DTaP vaccination status based on the number of DTaP doses received in relation to the number of DTaP doses expected according to the ACIP-recommended ages for the 5-dose series (2, 4, 6, 12 - 18 months, and 4 - 6 years). We classified children as fully vaccinated if they received the expected number of DTaP doses by one-month after the ACIP-recommended age. Children with fewer doses than expected for their age were undervaccinated, and children with 1 more dose than expected were timely fully vaccinated. Children with no DTaP doses were classified as unvaccinated at all ages. We estimated pertussis risk by multivariable Cox regression models on a calendar timeline, stratified by month and year of birth, which, together, closely adjust for age. We further adjusted risk estimates for sex, race/ethnicity, facility where children received care, and type of insurance. In models restricted to vaccinated children, we also examined pertussis risk in relation to the number of years since the last DTaP dose.

**Results:** Among 469,982 children ages 3 months to 11 years, who contributed 2,138,835 person-years of follow-up, we identified 738 PCR-confirmed pertussis cases. Among pertussis cases, 99 (13.4%) were unvaccinated, 36 (4.9%) undervaccinated, 515 (69.8%) fully vaccinated, and 88 (11.9%) timely fully vaccinated. Pertussis risk was 13 times higher among unvaccinated children (adjusted hazard ratio [aHR]= 13.53, 95% CI 10.64 - 17.21) compared with fully vaccinated children. Pertussis risk was 1.9 times higher (aHR =1.86, 95% CI 1.32 - 2.63) among undervaccinated children. Among vaccinated children ages 19 to < 84 months, pertussis risk was 5 times higher (aHR= 5.04, 95% CI 1.84 - 13.80) 3+ years versus <1 year after vaccination after controlling for undervaccination. Similarly, among children ages 84 to 132 months, pertussis risk was 2 times higher (aHR = 2.32, 95% CI 0.97 - 5.59) 6+ years versus <3 years after vaccination.
Conclusion: Undervaccinated and unvaccinated children were at greater risk of pertussis. However, most pertussis cases occurred among fully vaccinated children who were further away from their last DTaP dose. These results indicate that waning of DTaP immunity was the primary cause of recent pertussis epidemics.

O3.6 Microneedle-based Novel Transdermal Gonorrhea Vaccine
Lotika Bajaj1, Rikhav Gala1, Cherilyn D’Souza1, Carmen Popescu2, Susu Zughaier3 and Martin D’Souza1
1. Mercer University, Center for Drug Delivery, College of Pharmacy, Atlanta, GA 30341
2. Roquette America Inc., Geneva, IL 60134
3. Qatar University, College of Medicine, Doha, Qatar

Purpose: Gonorrhea is one of the most common sexually transmitted infections, caused by Gram-negative Diplococcus bacteria, Neisseria gonorrhea. The treatment for gonorrhea involves use of antimicrobials but development of drug resistance is a great threat to public health and hence, novel methods for prevention of gonorrhea infection are needed. Langerhans cells (specialized dendritic cells) in the skin are phagocytic cells that signal T-cells. Upon activation, T cells and macrophages drain into nearby lymph nodes causing an increased immune response.

Methods: Spray dried microparticles with pre-crosslinked BSA loaded with formalin fixed whole cell of gonorrhea bacteria as vaccine were prepared. The microparticles were characterized for percent yield, size, charge and poly dispersity index (PDI). The sugar-based microneedles containing the gonorrhea vaccine microparticles were prepared using the mold casting method. Swiss webster mice (6-8 weeks old) were administered one prime dose at day 0 followed by two booster doses at week 2 and 4. There were five groups (n=6) in this study; naïve group received nothing (control), blank microneedles group without any vaccine (Blank MN or microneedle control group), gonorrhea subcutaneous vaccine suspension group (GnH Susp SubQ), gonorrhea vaccine suspension loaded into the microneedles (GnH Susp MN) via transdermal delivery group and gonorrhea vaccine microparticles loaded in the microneedles (GnH MP MN) group. Blood samples collected bi-weekly, were analyzed for serum antibody titers using ELISA. Animals were sacrificed at week 10, spleens were collected and levels of the immune cells such as the CD4+ and CD8+ T cells in the spleens were counted using BD Accuri™ C6 Plus (BD Accuri Cytometers, Ann Arbor, MI).

Results: The percent yield for vaccine particles was 89 % w/w. Vaccine particles were 4.5 μm and PDI was 0.447 with a charge of -25 mV. The group which received the GnH vaccine microparticles in microneedles (GnH MP MN) showed significantly higher antibody titers than the other two vaccine groups at week 6 and 8. The group that received the vaccine, showed significantly higher CD4+ and CD8+ T cells than compared to the controls – naïve and blank microneedles.

Conclusion: Since the bacteria is formalin fixed, all the surface proteins, antigenic domains are conserved in their native form which are presented by antigen presenting to the immune cells of the body. Generation of antibodies post vaccination was seen in mice using microneedle based transdermal route of administration. The vaccine produced both CD4+ and CD8+ T cell based immune response, which is an important factor for the success of a vaccine.

O3.7 Design of a multi-antigenic, multi-stage and multi-epitope potential vaccine candidate against onchocerciasis and related filarial diseases: adding immuno-informatics to immunomics
Robert Adamu Shey1,3, Esoh Kum Kevin2, Neba Derrick Nebangwa3, Shintouo Cabirou Mouchili3, Nkemngo Francis Nongley3, Fru Asa Bertha3, Ferdinand Ngale Njumé1,3, Luc VanHamme1, Stephen Mbigha Ghogomu5, Jacob Souopgui1.
1Université Libre de Bruxelles, Gosselies Campus, Belgium, 2Jomo Kenyatta University of Agriculture and Technology, Juja, Kenya, 3University of Buea, Cameroon.
Corresponding author: robert.adamu.shey@ulb.ac.be

Onchocerciasis (river blindness) is a disabling yet neglected tropical disease with enormous socio-economic burden on 34 affected African countries. The disease is caused by the parasite Onchocerca volvulus and transmitted by blackflies of the genus Simulium. It is the second leading cause of infectious blindness after trachoma worldwide, with over 90% of cases occurring in Africa. Recent estimates from the Global Burden of Disease Study 2015 indicate that approximately 15.5 million people currently live with onchocerciasis, including 12.2 million people with Onchocerca skin disease (OSD) and
1.025 million with vision loss (river blindness). An additional 187 million people are living in disease-endemic areas. The disease has also lately been associated with higher rates of epilepsy and mortality in affected populations. The plan of elimination by 2020 in selected African countries and by 2025 in 80% of African countries by the WHO-created Expanded Special Project for the Elimination of Neglected Tropical Diseases (ESPEN) is hampered by many obstacles including increasing reports of drug resistance to ivermectin, restrictions to mass drug administration in regions of disease co-endemicity with loiasis, the serious challenges to development of new reliable drugs amongst others. Needed, and needed as a matter of urgency, in the fight to eliminate onchocerciasis are new tools, including preventive and therapeutic vaccines.

A multi-epitope prophylactic/therapeutic vaccine targeting the parasite infective L3 and microfilaria stages is invaluable for onchocerciasis elimination since these two stages are respectively responsible for infection and disease pathology. Consequently, an immuno-informatics approach was applied to design a filarial conserved multi-epitope subunit vaccine construct consisting B- and T-cell epitopes of proteins earlier reported to exhibit considerable vaccinogenic properties. Conservation of the selected proteins and predicted epitopes across related parasites suggests that the generated construct could be helpful in cross-protection. The 3D structure of the construct and its adjuvant was predicted, refined and validated bioinformatically. Protein-protein docking of the construct with TLR4 (which is reported to implicated in protection) predicted favourable binding. Immune simulation showed significantly high levels of IgG1, T-helper, T-cytotoxic cells, INF-γ and IL-2 responses. Overall, the construct demonstrated superior antigenicity to the current vaccine candidate leads and could be a vital tool in onchocerciasis elimination programs. Following results from in-silico studies, there is therefore a need to further determine the immunogenicity and safety profile of the construct experimentally.

Skin immunisation harnesses networks of protective immune connectivity in peripheral tissues.

Linda S. Klavinskis

Department of Infectious Disease, School of Immunology and Microbial Sciences, King’s College London, London, SE1 9RT, United Kingdom

A remarkable feature of skin vaccination is the generation of protective immunity in remote barrier tissues including the respiratory and female genital tract, yet the mechanism driving recruitment and retention of antigen-specific CD8+ T-cells to these tissues is unclear. To delineate the cellular/molecular changes that instruct CD8 T-cell migration to barrier tissues following skin vaccination, we have used intradermal injection and a ‘needle-free’ skin vaccination system using dissolvable ‘microneedle arrays’ (MA) fabricated to contain a replication-defective adenovirus (Ad) vector encoding HIV-1 CN54 gag (Ad HIV-1 CN54gag) as an exemplar vaccine within the dissolvable needles for skin delivery in B6 mice.

We found that, irrespective of the anatomic skin site used for vaccine delivery, high frequency Db/CN54 gag tetramer+ CD8+ T-cells (specific to the Db/HIV-1 CN54 gag308-318 epitope) tracked to the female reproductive tract (FRT). The recruited CD8+ T cells were functional, as demonstrated by in vivo killing of peptide pulsed syngeneic targets injected into the vaginal wall, and controlled a vaginal challenge with vaccinia virus expressing the cognate HIV-1 CN54 gag sequence. In studies to explore how skin primed CD8+ T-cells migrated to the FRT, we found Db/CN54 gag tetramer+ CD8+ T-cells isolated from the FRT expressed a panel of inflammatory chemokine receptors including CXCR3. In a search for mediators that might condition the FRT and recruit skin primed CXCR3+CD8+ T-cells we found a significant increase in the frequency of innate cells infiltrating the FRT in skin vaccinatated mice relative to naïve controls, notably an early wave of NK cells followed by Ly6C+ monocytes that expressed CXCL9, the cognate ligand for CXCR3. NK cell depletion during vaccination significantly reduced the frequency of CXCL9+ monocytes as also the frequency of Db/CN54 gag tetramer-specific CD8+ T-cells in the FRT (but not in blood). Immunisation of Rag2−/−;γc-deficient mice and Rag1−/− deficient mice treated with neutralising anti-interferon gamma antibody revealed NK cells orchestrate CXCR3-dependent CD8+ T cell recruitment by priming CXCL9 production by Ly6C+ monocytes via cell intrinsic IFNγ.

Collectively, the data demonstrate a novel mechanism for skin vaccination to induce low-level inflammation
in the FRT that is sufficient to promote CD8$^+$ T-cell recruitment through a CXCR9 dependent mechanism licenced by NK cells and has important implications for vaccine designs against pathogens transmitted across epithelial barrier tissues.

**[O4.3]**

**Efficacy of RSV Maternal Immunization Varies with the Version of the Pre-fusion F Antigen in Virus-like Particles (VLPs)**

Trudy G. Morrison$^1$, Lori McGinnes-Cullen$^1$, Gretel M. Torres$^1$, Adam J. Longwich$^1$,
Lioubov M. Pletneva2, Raymonde O. Otoa2, Lurds R. Fernando2, Marina S. Boukhvalova2, Jorge C. G. Blanco2,

$^1$Department of Microbiology and Physiological Systems, Program of Immunology and Microbiology,
University of Massachusetts Medical School, Worcester, MA, 01655

2Sigmovir Biosystems Inc., 9610 Medical Center Drive, Suite 100, Rockville, MD 20850

**Background:** Respiratory syncytial virus (RSV) is a significant human pathogen severely impacting infants and young children, but no vaccine exists for this vulnerable population. Direct vaccination of infants is likely ineffective and potentially unsafe. Maternal vaccination is the best and safest approach to infant protection through the passive transfer of neutralizing antibodies (NA) in utero to the fetus or after birth through lactation. Using RSV primed, pregnant cotton rats as a surrogate human model, we showed that a single immunization with our novel RSV pre-fusion F protein (DS-Cav1 pre-F)-containing virus-like particles (VLPs) stimulated high titers of NA, protected their offspring from RSV challenge, and decreased pup lung pathology compared to that observed after RSV infection of offspring of mock-immunized dams (Nat. Commun. (2018) 9:1904).

**Methods:** Several reports indicate that soluble DS-Cav1 pre-F is unstable. Thus, we prepared four new VLPs containing pre-F proteins different than DS-Cav1 and assessed their stability and immunogenicity in mice and cotton rats.

**Results:** We determined that VLP associated DS-Cav1 pre-F as well as the four new VLP associated pre-Fs were stable under a variety of conditions. The new pre-F VLPs bound, in ELISA, to pre-F specific monoclonal antibodies, AM14 and D25, at levels different from DS-Cav1 pre-F VLPs. Upon immunization of mice, two of these new pre-F VLPs stimulated serum NA titers 2 to 3-fold higher than the DS-Cav1 pre-F VLPs. These two new pre-F VLPs were used as immunogens in RSV-primed, pregnant cotton rats to test their efficacy in protection of their 4-week-old pups from RSV challenge. The levels of NA induced in dams by the new VLPs as well as DS-Cav1 VLPs were similar. However, immunization of dams with the new pre-F VLPs reduced lung titers in the pups upon RSV challenge to lower levels than DS-Cav1 VLP immunization and immunization with one of these new pre-F VLPs reduced virus lung titers 10-fold over that detected after DS-Cav1 pre-F VLP dam immunization. Levels of serum NA and total anti-F antibodies in pups correlated with protection from challenge.

**Conclusions:** Different versions of pre-F protein containing VLPs varied significantly in binding pre-fusion F-specific monoclonal antibodies suggesting some variations in the pre-F protein conformation. Furthermore, one version of pre-F VLPs tested impacted the induction of NA titers in mice and, significantly impacted the efficiency of transfer to pups and/or half-life of the NA received from immunized cotton rat dams.

**[O4.4]**

**Novel RSV vaccine development protect adult and neonate animals**

**Authors:** Chaofan Li$^1$, Suren Zhang$^1$, Yiwei Zhong$^1$, Gan Zhao$^2$, Aihua Dong$^2$, and Bin Wang$^1$.

$^1$Key Laboratory of Medical Molecular Virology of MOH and MOE, Shanghai Medical College, Fudan University, Shanghai, China

$^2$Beijing Advaccine Biotechnology Co. LTD, Beijing, China

**Background:** Respiratory syncytial virus (RSV) infection is a major cause of respiratory tract disease in children under 5 years old. It leads to 64 million cases of bronchiolitis and viral pneumonia and causes approximately 200,000 deaths annually. Moreover, there are direct correlations between RSV infection in childhood and development of asthma in adulthood. The infections have become a heavy medical and economic burden around the world, particularly in developing countries, yet no vaccine for the prevention of RSV in early life is available. The effectiveness and particularly safety issues of RSV vaccines have puzzled researchers for more than 50 years, since the first formalin-inactivated RSV vaccine (FI-RSV)
caused recipient children severe lung injuries and two infants died in a phenomenon that was then called vaccine-enhanced disease (VED) in the 1960s. A recent study has demonstrated that FI-RSV-induced VED was due to expel away Treg cells from lung since the Treg cells are important immunoregulatory cells to control inflamed reactions and minimize tissue damage.

**Methods:** We developed a novel strategy of immunizing neonate animals with a recombinant RSV G protein formulated with cyclosporine A (CSA) twice subcutaneously. The vaccinated animals were further challenged by RSV A2 strain. Levels of neutralizing antibodies, B cell activation and maturation, IL-10 producing Treg cells and lung tissue pathological assessments were analyzed and evaluated after RSV challenge. Adults animals were vaccinated as the same protocol above and repeated challenged to assess the protection.

**Results:** This novel vaccine induced not only a higher level of NAb against RSV infection, but most importantly, also significantly higher levels of Treg cells that suppressed VED in the lung after RSV infection not only in adult, but importantly in these neonate animals. The induced responses provided protection against RSV challenge with no sign of pneumonia or bronchitis in both adult and neonate animals. Treg cell production of IL-10 was one of the key factors to suppress VED. This vaccine can also protect animals from repeat RSV challenges.

**Conclusion:** The study suggests that this new approach could be a promising vaccine candidate against RSV infection in animals, and lead to the development of novel RSV vaccine for children and older people against this important pathogen.

---

**Unraveling the respiratory syncytial virus (RSV) antibody functional repertoire in adult healthy donors**

**Emanuele Andreano1,2, Ida Paciello2, Monia Bardelli2, Simona Tavarini2, Chiara Sammicheli2, Elisabetta Frigimelica2, Silvia Guidotti2, Giulia Torricelli2, Ugo D’Oro2, Rino Rappuoli2, Oretta Finco2 and Francesca Buricchi2**

1 University of Siena, Department of Life Sciences, Italy
2 GSK, Siena, Via Fiorentina 1, Italy

Human RSV is a RNA virus belonging to the Paramyxoviridae family (subfamily Pneumovirinae) against which no vaccine is currently available and passive immunization is the only preventive strategy in high risk populations. RSV is responsible for over 33 million cases of acute low respiratory tract infection leading to up to 199,000 deaths annually. Among the 11 proteins encoded by this virus, the fusion protein in its prefusion state (preF) is considered the most immunogenic antigen, capable to elicit highly neutralizing antibodies (nAbs).

While infants and older adults are the populations at highest risk of acute RSV infection, healthy adults present the strongest and most mature immune system capable to naturally resolve infection against this pathogen. Therefore, deep characterization of adult healthy donors preF antibody functional repertoire is a “must do” to better understand the effective natural response against this highly antigenic protein.

In order to unravel the preF-induced antibody functional repertoire, the methodology named by Rappuoli and coworkers as reverse vaccinology 2.0 was applied. This allowed to single cell sort and to interrogate over 1200 IgG+ preF-binder memory B cells isolated from four adult healthy donors. From these cells, over 200 nAbs were retrieved and brought us to shed light on the predominant RSV F-protein specific heavy and light chain gene rearrangement (IGHV1-18;IGHJ4-1 and IGKV2-30) which was shared by almost 15% of nAbs. This rearrangement is associated to a high binding capability towards the preF and recognition of a specific epitope region. Furthermore, up to 20 nAbs identified were selected and expressed as full length IgG for in-depth functional characterization and will be also expressed as Fab for structural analysis of predominant rearrangement derived-nAbs.

This work meticulously defines the preF functional repertoire elicited by RSV natural infection in healthy adults and leads to novel insights for the development of a much needed RSV vaccine.
Elicitation of protective antibodies against 20 years of future H3N2 co-circulating influenza virus variants in ferrets preimmune to historical H3N2 influenza viruses.

James D. Allen1*, Hyusen Jang1, and Ted M. Ross1,2#

1Center for Vaccines and Immunology, 2Department of Infectious Diseases, University of Georgia, Athens, GA, USA

The vast majority of people already have pre-existing immune responses to influenza viruses from one or more subtypes. However, almost all preclinical studies evaluate new influenza vaccine candidates in immunologically naïve animals. Recently, our group demonstrated that priming naive ferrets with broadly reactive H1 COBRA HA based vaccines boosted pre-existing antibodies induced by wild-type H1N1 virus infections. These H1 COBRA HA antigens induced antibodies with HAI activity against multiple antigenically different H1N1 viral variants. In this study, ferrets, preimmune to the historical H3N2 virus, A/Panama/2007/1999, were vaccinated with virus-like particle (VLP) vaccines expressing either an HA from a wild-type H3 influenza virus or a COBRA H3 HA antigen. The elicited antisera had the ability to neutralize virus infection against a panel of viruses representing vaccine strains selected by the World Health Organization (WHO) between 1995 and 2016 or a set of viral variants that co-circulated during the same time period. Preimmune animals vaccinated with H3 COBRA T10 HA antigen elicited sera with higher HAI antibody titers than antisera elicited by VLP vaccines with wild-type HA proteins in preimmune ferrets. However, while the T11 COBRA vaccine did not elicit HAI activity, the elicited antibodies did neutralize antigenically distinct H3N2 influenza viruses. Overall, H3 COBRA-based HA vaccines were able to neutralize both historical H3 and contemporary, as well as future, H3N2 viruses with higher titers than vaccines with wild-type H3 HA antigens. This is the first report demonstrating the effectiveness of a broadly reactive H3N2 vaccine in a preimmune ferret model.

Towards the development of influenza virus vaccines: insights from the ferret animal model

Randy A. Albrecht1

1Department of Microbiology, and Global Health and Emerging Pathogens Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.

Influenza A viruses (IAV) pose major threats to public health with substantial social and economic impacts resulting from epidemics of seasonal influenza. These burdens would be further exacerbated by an influenza pandemic caused by a global outbreak of an antigenically novel IAV. Our mitigation approach to prevent infection by seasonal or pandemic IAV is centered on sequential immunization strategies which focus adaptive immune responses on the antigenically conserved, but immunosubdominant, IAV hemagglutinin stalk domain. The domestic ferret, Mustela putorius furo, is the gold standard small animal model for studying the transmission, biology, and pathogenesis of influenza A viruses. We have demonstrated in the ferret model that our sequential immunization strategies can induce robust hemagglutinin stalk-specific antibody responses in ferrets, and can induce sufficient levels of humoral immunity that substantially suppresses virus replication throughout the respiratory tract. Towards exploring the immunological basis for this protection, we have engaged in collaborative efforts to develop immunological reagents and assays to examine B and T cell responses of ferrets to influenza virus infection or vaccination. These immunological reagents will advance biomedical research, in particular viral respiratory disease research, with this animal model.

Age-Related Modulation of Immune Response to Vaccination with a Chikungunya Virus-Like Particle Vaccine and Chikungunya Viral Infection

Maria T. Arévalo1,2, Ying Huang1, Matthew J. Prellberg1, Cheryl A. Jones1, and Ted M. Ross1,2

1Center for Vaccines and Immunology, 2Department of Infectious Diseases, University of Georgia, Athens, GA, USA

Chikungunya virus (CHIKV) is a re-emerging pathogen that is responsible for causing outbreaks of febrile disease accompanied with debilitating joint pain. Symptoms typically persist for two weeks, but more severe and chronic chikungunya illnesses have been reported, especially in the elderly. Currently, there are no licensed vaccines or antivirals against CHIKV available. In our studies, we combined a CHIK virus-like
particle (VLP) vaccine with different adjuvants to enhance immunogenicity and protection in both, adult and aged mice. CHIK VLP-based vaccines were tested in 6-8-week-old (adult) and 18-24-month-old (aged) female C57BL/6 mice. Formulations contained CHIK VLP alone or adjuvants: Imject Alum, QuilA, or R848. Animals were vaccinated by intramuscular or subcutaneous injections. CHIKV-specific antibody responses were measured in sera by IgG ELISA and by microneutralization assays. We also characterized CHIKV infections in adult mice versus aged mice and assessed protection of vaccinated animals against CHIKV infection. In adult mice, CHIKV infection resulted in significant swelling of the CHIKV-infected right hind foot, which peaked by day 8, at 175% of initial size. Viral titers peaked on day 2 post-infection at $2-3 \times 10^9$ CCID50/ml. Mice vaccinated with CHIK VLP-based vaccines developed robust anti-CHIKV-specific IgG antibody responses that were capable of neutralizing CHIKV in vitro. CHIK VLP alone or CHIK VLP plus QuilA delivered via intramuscular injections were 100% protective against CHIKV as determined by lack of viral loads and disease. In contrast, the antibody responses elicited by the VLP-based vaccines in aged mice were attenuated, with negligible neutralizing antibody responses. Naive aged mice were resistant to CHIKV infection, while vaccination exacerbated disease. CHIK VLP alone provides 100% protection against CHIKV infection in adult mice, however, improved adjuvant and/or vaccine combinations are needed to enhance the protective immune responses against CHIKV in the aged.

---

**A Universal Dengue Vaccine Elicits Neutralizing Antibodies Against Strains from All Four Dengue Serotypes.**

Naoko Uno1, Maria T. Arévalo1,2, and Ted M. Ross1,2

1Center for Vaccines and Immunology, 2Department of Infectious Diseases
University of Georgia, Athens, GA, USA

Developing a vaccine for Dengue virus (DENV) has been difficult to achieve. Any potential vaccine needs to protect against all four serotypes of the virus to avoid antibody dependent enhancement (ADE). ADE is thought to occur when pre-existing antibodies to one DENV serotype do not neutralize, but enhance a heterotypic infection. Therefore, it is critical to produce a vaccine against viruses representing all four DENV serotypes without enhancing disease. In the current study, we developed and tested DENV subviral particle (SVP) vaccine targeting the envelope (E) glycoprotein by designing consensus sequences using computationally-optimized broadly reactive antigen (COBRA) methodology. DENV E sequences were obtained from GenBank and a layered, consensus-building approach was used to derive four final COBRA DENV sequences. COBRA and wild-type SVPs were expressed from 293T cells using a mammalian expression vector encoding prM-E genes. Female C57BL/6 mice (age 6-8 weeks) were vaccinated intramuscularly three times at 4-week intervals with 100µg total SVP plus Imject Alum. Vaccines were prepared as individual or tetravalent SVP formulations. Immune sera were collected and total IgG antibody titers to DENV E were analyzed by ELISA and the ability to prevent virus infection in vitro was assessed in a focus reduction neutralization test (FRNT50) against a panel of 12 prototype and modern strains from all four serotypes. Mice vaccinated with wild type DENV SVPs expressed anti-E IgG antibodies that were specific to strains in each homologous serotype. The elicited antibodies neutralized serotype specific viruses. COBRA DENV SVPs elicited a broader breadth of antibodies that neutralized various strains across all four serotypes. The COBRA DENV E immunogen neutralized all 12 strains of DENV in vitro, comparable to tetravalent SVP vaccination. This is a promising vaccine candidate based on broad protection against strains representing all four serotypes of DENV.

---

**Multiroute morbillivirus entry: disease informs delivery**

Linda J Rennick, Sham Nambulli Natasha L Tilston-Lunel, , Rory D de Vries, Rik L de Swart and W Paul Duprex

1 Department of Microbiology, Boston University, Boston, United States
2 Department of Viroscience, Erasmus Medical Center, Rotterdam, The Netherlands

Morbilliviruses represent some of the most transmissible pathogens on the planet. Attaining an understanding of primary pathogenesis and tropism is critical for the development of novel countermeasures. To extend standard reverse genetics approaches we developed a pipeline for the de novo synthesis of morbillivirus genomes based on sequences obtained directly from clinical material. To dissect multiroute morbillivirus entry we generated virologically identical but phenotypically distinct
recombinant (r) canine distemper viruses (CDV) and measles viruses (MV) expressing different fluorescent reporter proteins for in vivo competition and airborne transmission studies in ferrets and macaques. Animals simultaneously received three expressing green, red or blue fluorescent proteins via conjunctival (ocular, Oc), intra-nasal (IN) or intra-tracheal (IT) inoculation. Single lymphocytes expressing multiple fluorescent proteins were abundant in peripheral blood and lymphoid tissues, demonstrating the occurrence of double and triple virus infections for MV and CDV. Multicolor fluorescence in situ hybridization was used to determine if RNA persisted in vivo following virus clearance, seroconversion and disappearance of clinical signs of disease. We show both morbilliviruses can use multiple entry routes in parallel, that co-infection of cells during viral dissemination in the host is common, that cell-to-cell spread in vivo is the norm and that airborne transmission resulted in replication of a single-colored virus, which was the dominant virus in donor animals. Intranasal infection was inefficient, paralleling what is seen when rMV vaccines are delivered using this delivery route in macaques.

[O6.3]
Is the current dose of normal human immunoglobulin for post-exposure prophylaxis of measles in Australia too low?
Megan Young1 Shu-Kay Ng1, Graeme Nimmo1,2 Allan Cripps1
Email: megan.young@griffith.edu.au
Griffith University
Immunoglobulin, measles, post-exposure prophylaxis, pharmacokinetics
1School of Medicine and Menzies Health Institute – Queensland, Griffith University, Southport, Queensland, Australia
2Pathology Queensland, Queensland Health, Brisbane, Queensland, Australia

Background: Passive immunisation with immunoglobulin is an important means of post-exposure prevention of measles, particularly for subpopulations at highest risk of complications from this disease. It is unclear whether currently recommended doses of intramuscular polyvalent immunoglobulin are optimal for both effectiveness and efficiency of disease prevention in Australia when administered post-exposure to measles.

Methods: The peak concentration and decay of disease-specific antibodies after intramuscular dosing of polyvalent immune globulin in adults was modelled using published pharmacokinetic parameters and Australian immunoglobulin product disease-specific antibody concentrations. Models simulated dosing according to current Australian guidelines, then adjusted the dose in clinically relevant increments to estimate the optimal dose of disease-specific immunoglobulins for post-exposure prophylaxis of non-immune individuals against measles. Optimal dosing assumed a target serum concentration of disease-specific antibodies of the correlate of protection for measles plus a 10% margin of error (equivalent to 132mIU/mL) at an incubation period.

Results: Current Australian guidelines appeared to underdose a measles naïve subpopulation, with serum concentrations of measles-specific antibodies at an incubation period estimated between 95 and 108mIU/mL. The optimal dose of measles-specific antibodies was 17.5 IU/kg assuming 75% bioavailability and 25.5 IU/kg assuming 50% bioavailability of intramuscular immunoglobulin.

Conclusions: The recommended dose of intramuscular polyvalent immunoglobulin should be increased following measles exposure for recommended subgroups. These models may be adapted for use internationally.

[O6.4]
Variation in direct and indirect effectiveness and total impact of infant rotavirus vaccination among children in the United States: analysis of national claims data from 2001-2016
Julia M. Baker, Rebecca M. Dahl, Umesh D. Parashar, Benjamin A. Lopman

Background and aims: Introduction of the infant rotavirus vaccine in 2006 altered the epidemiologic patterns in rotavirus illness in the United States and provided indirect benefits to unvaccinated children. Since vaccine introduction, a biennial pattern in rotavirus rates has emerged with higher rates of illness in odd post-vaccine calendar years. We aimed to assess the longer-term impacts of rotavirus vaccination among children in the United States by estimating the annual direct and indirect vaccine effectiveness (VE) as well as the total impact of infant rotavirus vaccination on rotavirus hospitalizations among children under 5 years of age.
**Methods:** Monthly data on rotavirus gastroenteritis hospitalizations from MarketScan, a national claims and encounters database of commercially insured individuals in the United States, were analyzed from July 2001 through June 2016. Events were identified using ICD-9 and ICD-10 codes identified in inpatient admissions claims records among children 0-4 years of age. Negative binomial regression models were fitted to estimate rate ratios and 95% confidence intervals from which VE and vaccine impact were calculated. Annual direct VE was estimated by comparing rotavirus hospitalization rates among vaccinated and unvaccinated children for each year beginning in 2008. Annual indirect VE was estimated by comparing rates among unvaccinated children in each individual post-vaccine year to the pre-vaccine era overall. Total vaccine impact for the entire post-vaccine period was estimated by comparing rates among unvaccinated children in the pre-vaccine era overall to vaccinated children in the post-vaccine period overall.

**Results:** Direct VE for the entire post-vaccine period was 87% (95% CI: 0.83-0.90) with substantial direct VE in each individual post-vaccine year. A subtle biennial pattern was observed with larger direct effectiveness in odd post-vaccine years (range: 0.84 – 0.91) compared to even post-vaccine years (range: 0.67 – 0.87). A more extreme and opposite biennial pattern was observed for indirect effects with stronger effectiveness in even post-vaccine years (range: 0.62, 0.83, 0.88, 0.94, 0.94 in 2008, 2010, 2012, 2014 and 2016, respectively) and non- or less-significant effectiveness in odd years. The total vaccine impact was 95% (95% CI: 0.93-0.96).

**Conclusions:** In this analysis, we demonstrate the longer-term effectiveness of infant rotavirus vaccination and the annual variation in VE during the post-vaccine period. Year-to-year fluctuation in indirect VE, opposite to the pattern of rotavirus gastroenteritis rates, suggests larger indirect VE during periods of low rotavirus incidence. Patterns in direct VE, which mirror those of rotavirus gastroenteritis rates, require further investigation. In the United States, a vaccinated child living in the post-vaccine era has a 95% lower risk of rotavirus hospitalization compared to an unvaccinated child prior to vaccine introduction.

---

**Estimating the population-level effect of pediatric norovirus vaccination: A model simulation study**

Authors: Sajewski, Elizabeth T., Steele, Molly K., Lopman, Benjamin A.

**Background:** Noroviruses cause approximately 23 million cases of acute gastroenteritis annually in the United States. Children under the age of 5 years experience the highest incidence and are also thought to play an outsize role in transmission. While multiple vaccines are moving through the development pipeline, questions remain regarding at what age children should be vaccinated and the vaccine efficacy required to achieve public health goals.

**Methods:** To address these issues, we developed a deterministic mathematical model of norovirus disease, immunity, transmission, and vaccination. The model includes age-structure and compartments to represent susceptible, exposed, symptomatically- and asymptptomatically-infected, and immune individuals with analogous compartments to represent vaccinated individuals. Using maximum likelihood methods, we estimated four age-specific transmission parameters and two seasonality parameters by fitting the model to US norovirus outbreak patterns and age-specific incidence. After fitting the model, we simulated the following four pediatric vaccination schedules: birth; 6 months; 12 months; and 60 months (i.e. school-age vaccination). We assumed 100% vaccine coverage and varied vaccine efficacy (VE) in order to identify the parameter values predicted to reduce symptomatic norovirus cases long-term by 50% in the pediatric age group (<5 years of age) and by 15% in the overall population (all ages). We also considered short-term and long-term direct effects versus indirect effects of vaccination in the pediatric and overall populations.

**Results:** The fitted model successfully captured important factors of the US norovirus dataset, including incidence and seasonal patterns. We simulated VE ranging from 25% to 100% for the four pediatric vaccination schedules. A VE as low as 67% was sufficient to reduce the overall norovirus incidence by 15%; however, a VE of 85% was required to achieve both overall and pediatric public health goals long-term (50% pediatric cases averted, 19% overall cases averted). When age of vaccination was adjusted to 6 and 12 months, overall norovirus reduction goals were met at 85% VE (17% and 16% cases averted, respectively). However, pediatric norovirus reduction goals were not met at any VE level for vaccination at 6 and 12 months and vaccination at 60 months did not achieve either public health goal at any VE level. When considering the indirect and direct vaccination effects for the overall population, we found that indirect effects were responsible for the majority of the total cases averted in both short and long-term settings. In the short-term among the pediatric population (85% VE), 26-36% of the total pediatric cases were averted and of these averted cases, 21-31% resulted directly from vaccination. Conversely, in the long-term, direct
vaccination effects resulted in the majority of adverted pediatric cases.

Conclusions: The model demonstrated that vaccination at birth (85% VE) was most effective in meeting the pre-determined norovirus reduction goals in both pediatric and overall populations. Pediatric vaccination reduced norovirus incidence long-term via direct effects in the pediatric population and via indirect effects in the overall population. As improved vaccine performance estimates become available, this model can be expanded to strengthen our prediction of the population-level effects of norovirus vaccination.

Joseph K. L. Opare12*, John Kofi Odoom3, E. Afari1, F. Wurapa1, C. Ohuaunwo4
1. School of Public Health, FELTP, UG, Legon
2. Regional Health Directorate, Upper East Region, Ghana Health Service, Private Mail Bag, Bolga-Upper East Region, Ghana.
4. Morehouse school of Medicine, Atlanta-GA
*Corresponding author: Email: kwadwolarbiopare@gmail.com

Introduction: Ghana recorded the last case of poliomyelitis caused by wild poliovirus in 2008 and the country was declared polio-free in 2015. High levels of immunity must be maintained to prevent the importation of wild poliovirus. We determined the immunity against poliomyelitis in the population of three geographically representative regions of Ghana to identify possible immunity gaps.

Methods: A cross-sectional, hospital-based study was undertaken in three regions in 2015. Individuals who visited the three teaching hospitals of the regions to have their blood drawn for any reason were invited to participate in our study. Neutralizing-antibody titers to polio serotypes P1, P2, and P3 were assayed by WHO-standards. Antibody titers of ≥8 were considered positive. Antibody titers were measured and seroprotection rates compared in the regions. Bivariate and multivariate analyses were conducted on subject characteristics to assess for potential factors for failure to sero-convert. P-values < 0.05 were considered statistically significant.

Results: Neutralizing-antibodies against poliovirus types 1, 2 and 3 were detected in 86.0% (264/307), 84% (258/307) and 75% (230/307) of samples respectively. Overall, 60.1% (185/307) were seropositive for the three polio serotypes and 2.9% (9/307) sero-negative. Seroprevalence of polio-neutralizing antibodies among males (P1=51.9%, P2= 51.6% and P3= 52.6%) were higher than females. Seroprevalence rates of polio-neutralizing antibodies (P1 and P2) decreased with age [p< 0.001]. Low seroprevalence of polio-neutralizing antibodies was significantly associated with low school attendance of mothers (p<0.001).

Conclusion: Our study population is moderately protected against the three poliovirus serotypes. However, immunity appears to wane with increasing age or low Mother’s education. This might suggest the need for young-adult booster-dose to minimize the risk of wild poliovirus infection.

[PL4.3] VaxArray Neuraminidase: A new assay for neuraminidase quantification of seasonal influenza vaccines
Rose T Nash, PhD1, Jacob H Gillis1, Kathy L Rowien, PhD1
1InDevR Inc, 2100 Central Ave., Suite 106 Boulder, CO 80301, United States

Current evaluation of neuraminidase (NA) content in influenza vaccines is generally limited to confirmation of NA presence via enzymatic activity assays. The VaxArray Influenza Seasonal Neuraminidase Potency Assay (VXI-sNA) is a novel tool for quantification of NA content when matched with an appropriate standard. The assay is built upon the scientific basis of the other VaxArray assays wherein antigen is captured by subtype-specific yet broadly reactive monoclonal antibodies (mAbs) printed on a glass substrate in a microarray format. The captured antigen is subsequently labeled by a broadly reactive label antibody conjugated to a fluorescent dye. The VXI-sNA mAbs are specific to influenza NA protein and do not detect HA or other influenza proteins. Each capture antibody is subtype-specific, enabling simultaneous quantification of seasonal N1, N2, and B-NA antigen in multivalent samples. The VXI-sNA assay is highly sensitive with limits of detection for N1, N2, and B-NA of 9 ng/mL, 3 ng/mL, and 1 ng/mL, respectively. VXI-sNA is also well correlated with enzymatic activity measured by a MUNANA-like assay, with R² correlation
coefficients of 0.993, 0.996, and 0.999 for N1, N2, and B-NA antigen, respectively. The linear dynamic ranges of the VXI-sNA capture mAbs range from 162x - 570x for all NA components within a multivalent seasonal influenza vaccine. The intermediate precision of the VXI-sNA capture mAbs across multiple days, multiple users, multiple reagent lots, and multiple analysis instruments demonstrated a relative standard deviation (RSD) that ranged from 5.7 - 12.2% (n=144). VXI-sNA correlates strongly with immunogenicity and is a good proxy for predicting vaccine immunogenicity as measured by the induction of NA-inhibiting antibodies in a mouse model. VXI-sNA is capable of detecting conformational changes in antigen (i.e. stability indicating) and is not affected by the presence of crude matrices containing potentially interfering agents such as allantoic fluid, tissue culture media, sucrose, alum containing adjuvants, and squalene-based adjuvant. In summary, the VXI-sNA assay is a first-in-kind, commercially available assay for NA concentration determination.

**An alternative strategy as a quadrivalent live attenuated influenza virus vaccine**

Zhimin Wana, Stivalis Cardenas Garciaa, Jing Liuα, Jefferson Santosas, Silvia Carnaccinia, Ginger Geigera, Lucas Ferreriα, Daniela Rajaoa, and Daniel R. Pereza,*

Influenza virus infections continue to pose a major public health threat worldwide associated with seasonal epidemics and sporadic pandemics. Vaccination is considered the first line of defense against influenza. It is commonly accepted that live attenuated influenza virus (LAIV) vaccines provide superior responses compared to inactivated vaccines because the former can better elicit a combination of humoral and cellular responses by mimicking a natural infection. Unfortunately, during the 2013-2014, 2014-2015 and 2015-2016 seasons, concerns emerged about the effectiveness of the only LAIV approved in the U.S. that prevented the CDC from recommending its use. Such drawback opens up the opportunity for alternative LAIV strategies that could overcome such concerns. Previously, we developed a combined strategy of temperature sensitive mutations in the PB2 and PB1 segments and an epitope tag in the C-terminus of PB1 that effectively attenuates influenza A viruses of avian and mammalian origin. More recently, we adopted a similar strategy for influenza B viruses. The resulting attenuated (att) influenza A and B viruses were safe, immunogenic, and protective against lethal influenza virus challenge in a variety of animal models. In this report, we provide evidence of the potential use of our att strategy in a quadrivalent LAIV vaccine (QIV) formulation carrying H3N2 and H1N1 influenza A virus subtype viruses and two antigenic cluster influenza B viruses. In naïve, DBA/2J mice, two doses of the QIV elicited HI responses ≥40 and effectively protected against lethal challenge with prototypical pandemic H1N1 influenza A and influenza B virus strains.

**Molecular Dissection of the Antibody Response Elicited by a Computationally Optimized Broadly Reactive Antigen (COBRA) H1 Hemagglutinin Influenza Vaccine**

Giuseppe A. Sautto1, Greg A. Kirchenbaum1, Jeffrey W. Ecker1, Spencer R. Pierce1, and Ted M. Ross1,2
1Center for Vaccines and Immunology, 2Department of Infectious Diseases, University of Georgia, Athens, GA, USA

We previously described the design and characterization of computationally optimized broadly reactive influenza hemagglutinin (HA) antigens (COBRA) expressed on the surface of viral-like particles (VLP) vaccines. These COBRA HA-expressing VLP elicited a broadly reactive humoral immune response against divergent H1N1 viral strains. In order to dissect and understand the mechanism of antibody breadth elicited by COBRA-based immunogens, a panel of monoclonal antibodies (mAbs) was generated following COBRA HA immunization. Specifically, groups of BALB/c mice were intranasally primed with an influenza virus expressing either a novel H1 COBRA HA (P1) or the wild-type H1 HA (CA/09) and intraperitoneally boosted with the same virus 21 days post-infection. Sera from COBRA P1-immunized groups recapitulated broad HA binding and exhibited hemagglutination inhibition (HAI) activity against a panel of seasonal and pandemic H1N1 viruses, while sera from CA/09-immunized mice displayed more restricted HA binding and HAI activity. In order to better characterize the antibody response at the single cell level, splenocytes from COBRA P1- and CA/09-immunized mice were fused with SP2/0 myeloma cells to generated B-cell hybridomas. A panel of P1- and CA/09-specific hybridomas was obtained and single cell cloned by FACS. Subsequently, the corresponding mAbs were assessed for breadth of HA binding and HAI activity against a panel of seasonal and pandemic H1N1 viruses. Collectively, P1-specific mAbs exhibited a broad spectrum...
of binding and functional activities against multiple H1N1 strains. Specifically, different mAb clusters were identified, spanning from strain-specific to broadly-reactive mAbs, suggesting the targeting of numerous HA epitopes. In contrast, CA/09-specific mAbs displayed restricted epitope recognition and biological activities. These P1 mAbs are endowed with additional biological activities, such as antibody-dependent cell-mediated cytotoxicity (ADCC) and phagocytosis (ADCP), which may contribute to the broad protection conferred by vaccination with the P1 COBRA immunogen. Collectively, these studies will be fundamental not only to understand the mechanism of breadth elicited by COBRA-based immunogens, but also to leverage their optimization for the development of an effective influenza vaccine.

---

Pan-influenza A protection by prime-boost vaccination with X-31 cold-adapted live attenuated influenza vaccine
Yo Han Jang¹, Joo Young Kim², Young Ho Byun¹, Ahyun Son¹, Jeong-Yoon Lee², Yoon Jae Lee¹, Jun Chang², and Baik L. Seong¹,³*
¹Department of Biotechnology, College of Life Science and Biotechnology, Yonsei University, Seoul 03722, South Korea.
²Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul 03760, South Korea.
³Vaccine Translational Research Center, Yonsei University, Seoul 03722, South Korea.

Influenza virus infections continually pose a major public health threat with seasonal epidemics and sporadic pandemics worldwide. While currently licensed influenza vaccines provide only strain-specific protection, antigenic drift and shift occasionally render the viruses resistant to the host immune responses, which highlight the need for a vaccine that provides broad protection against multiple subtypes. In this study, we suggest a vaccination strategy using the cold-adapted, live attenuated influenza vaccines (X-31 CAIVs of H1N1 backbone) to provide a broad, potent, and safe cross-protection covering antigenically distinct hemagglutinin (HA) group 1 and 2 influenza viruses. Using a mouse model, we tested different prime-boost combinations of CAIVs for their ability to induce humoral and T cell responses, and protective efficacy against H1 and H5 (HA group 1) as well as H3 and H7 (HA group 2) influenza viruses. Notably, even in the absence of antibody-mediated neutralizing activity or hemagglutinin inhibitory activity in vitro, CAIVs provided a potent protection against heterologous and hetero-subtypic lethal challenges in vivo. Heterologous combination of prime (H1)-boost (H5) vaccine strains showed the most potent cross-protection efficacy. In vivo depletion experiments demonstrated not only that T cells and NK cells contributed to the cross-protection, but also the involvement of antibody-dependent mechanisms for the cross-protection. Little correlation, if any, was observed between HA stalk-specific antibodies and cross-protection. Vaccination-induced antibodies did not enhance the infectivity of heterologous viruses, addressing to the safety concerns associated with the enhancement of virulence via non-neutralizing antibodies. Our data show that a concerted humoral and cellular immune responses are required for inter-group cross-protection. Augmentation of inter-group cross-protection by boost immunization with X-31 CAIV (H1N1 backbone) could be equivalent to the boosting effect by single immunization on the majority of human population primed by previous exposure (infection or vaccination) by H1 strain that circulated for the last 50 years. The strategy of using X-31 CAIV of H1N1 backbone thus serve as a simple but powerful option for developing a universal influenza vaccine providing pan-A protection. The promising results of potency, breadth, and safety demonstrated in the mouse model support further studies in higher animal models for clinical relevance.

--

Development of paradigm-shifting T cell-targeting universal influenza vaccines
Christopher S. Eickhoff¹, Frances E. Terry², Linda Peng¹, Isaac G. Sakala¹, Daniel Van Aartsen¹, Leonard Moise²,³, William D. Martin², Jill Schreiwer¹, R. Mark Buller¹, Anne S. De Groot²,³, and Daniel F. Hoft¹
¹Saint Louis University, Saint Louis, Missouri, United States
²EpiVax, Inc., Providence, Rhode Island, United States
³University of Rhode Island, Providence, Rhode Island, United States

Influenza is a viral respiratory pathogen which causes significant morbidity and mortality each year. Licensed seasonal influenza vaccines induce protective antibody immunity, typically limited to vaccine-matched strains, but are unable to provide adequate protection against novel pandemic influenza strains, which can be highly lethal. Novel approaches are needed to produce a broadly protective influenza vaccine. We devised a comprehensive strategy to produce a T cell-directed universal influenza vaccine. CD4 and
CD8 T cells that recognize conserved influenza internal proteins are protective against homologous and heterologous influenza strains in both mice and humans. Using immunoinformatic tools, we identified T cell epitopes highly conserved in diverse influenza A strains, including H1, H2, H3, H5, H7, and H9 subtypes predicted to bind to the major human MHC I supertype HLA-A2 and a panel of 8 common HLA-DR alleles. Putative HLA-A2- and panDR-restricted epitopes were synthesized for in vitro assays and for generation of peptide-pulsed dendritic cell vaccines (DC). DNA vaccines encoding the HLA-A2-restricted and panDR-restricted epitopes were generated. HLA-A2 and HLA-DR1 transgenic (Tg) mice were immunized with the A2- and panDR- multi-epitope vaccines, respectively, and T cell responses to individual peptides evaluated via IFN-gamma ELISPOT assay. These vaccines were found to be highly immunogenic in HLA-A2 and HLA-DR1 transgenic mice, inducing robust T cell responses to most of the predicted epitopes. Furthermore, immunization of HLA-A2 and HLA-DR1 Tg mice with the DC and/or DNA vaccines provided protection against influenza A H3N2 challenges. Importantly, significant heterologous protection was observed in vaccinated HLA-A2 Tg animals after challenge with influenza A H1N1 virus. Human immunogenicity of the putative HLA-A2-restricted T cell epitopes was confirmed using HLA-A2+ PBMCs in IFN-gamma ELISPOT assays. These results demonstrate proof-of-concept that universal influenza vaccines targeting highly conserved T cell epitopes can be broadly protective. Furthermore, this work provides strong support for additional studies to broaden the population coverage beyond HLA-A2 to generate universal influenza vaccines for diverse populations that provide protection against both seasonal and pandemic influenza.

**[PL4.8]**

**Robust Cellular Immune Responses and Cross-Protective Anti-Hemagglutination Responses Elicited by Influenza Micro-Consensus DNA Vaccines**

Anna M. Slager1, Sarah T.C. Elliott2, Amelia A. Keaton2, Jacqueline D. Chu2, Charles C. Reed1, Bradley Garman1, Arni Patel2, Jian Yan1, Matthew P. Morrow1, Kate E. Broderick1, David B. Weiner2

1. Inovio Pharmaceuticals, Plymouth Meeting, PA, USA.
2. The Wistar Institute of Anatomy and Biology, Philadelphia, PA, USA.

Despite the routine development and distribution of seasonal influenza vaccines, influenza remains an important pathogen contributing to significant human morbidity and mortality each year. Due to genetic changes in the HA protein, however, new vaccine strains are needed to be developed continually to match the new HA antigen of each seasonal influenza A virus. It would be advantageous if a small group of antigens could be developed to elicit cross-reactive T and B cell immune responses against diverse influenza viruses.

Previously, we developed a micro-consensus influenza H1N1 HA vaccine, which was capable of inducing protective HAI titers (≥1:40) against a wide range of unmatched H1N1 viruses that span the past 25 years of seasonal vaccine strains in guinea pigs and non-human primates when delivered via intradermal CELLECTRA® 3P electroporation. The vaccine-induced protective HAI titers are fully functional and immunized ferrets were completely protected from A/Mexico/InDRE4487/2009 virus infection. Importantly, T cell responses, which are critical for prevention of disease in the elderly, were induced by this vaccine in a clinical trial as well.

H3N2 viruses are very diverse, as detailed sequence analyses indicate that H3HA sequences can differ up to about 20%. Historically, antigenic mismatch between vaccine components and circulating H3N2 viral strains resulted in poor vaccine efficacy. In the 2017-2018 influenza season, the interim estimate of vaccine effectiveness was about 25% (CI = 13% to 36%) against illness caused by the H3N2 virus. In addition, most current influenza vaccine formulations induce poor or no T cell immunity, which is likely particularly impactful in the elderly. In an effort to develop a H3HA vaccine that can elicit broad T and B cell immunity against diverse H3N2 viruses, we used a phylogenetic approach to analyze the diverse H3HA sequence landscape and then down-selected to develop a collection of micro-consensus H3HA antigens (pH3HA). The vaccine delivered via the CELLECTRA® 3P device could induce HAI titers ≥1:40 against diverse seasonal H3N2 viruses that circulated between 1968 and the present. Vaccination with pH3HA also induced a potent antigen-specific IFN-gamma response. Mice immunized with pH3HA were protected against lethal challenge with two distinct H3N2 viruses (A/Philippines/2/1982 X79 and A/Hong Kong/1/1968 X31), highlighting the strong protection afforded by synthetic micro-consensus immunogens.

Taken together, the synthetic DNA platform could play a role in seasonal as well as pandemic outbreaks.
In addition, the technology can be developed for universal influenza vaccine strategies as well. Multiple DNA vaccines against infectious diseases delivered by the CELLECTRA® 3P device have generated consistent immunity in clinical studies showing response rates over 99% with excellent tolerability. Additionally, as shown in our recent clinical trial, we were able to move a Zika vaccine to the clinic in just months and demonstrated high immune potency. The use of this simple and scalable approach has significant implications for rapid development of influenza vaccines that would be of value to the elderly, as well as broader populations.

A Multi-Omics Systems Analysis of Human Vaccine Adjuvants: Of Clouds and Clocks
Ali M. Harandi
Department of Microbiology & Immunology, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Sweden. ali.harandi@microbio.gu.se

A comprehensive understanding of the mechanisms of action of vaccine adjuvants could inform a rational development of next generation vaccines for human use. Decomposing the mammalian response to vaccine and its component at systems level has recently been made possible owing to the recent advancements in Omics technology powered by systems biology approaches. This systems approach has just begun to unravel molecular signatures of human vaccines. We have recently reported transcript signatures of four clinically tested adjuvants in mice, and also identified blood signatures of a synthetic TLR4 agonist adjuvant in humans. Herein, we report integrated transcript-metabolite signature pathways and networks of four clinical grade adjuvants, including CAF01 (a cationic liposome targeting the C type lectin receptor Mincle), IC31 (a TLR9 agonist), GLA-SE (a synthetic TLR4 agonist in squalene) and Alum. Data generated from the longitudinal whole genome transcriptomics and Liquid Chromatography Mass Spectrometry metabolomics analyses of blood response in mice to four clinically tested vaccine adjuvants were subjected to an integrated multi-omics systems analysis approach. Our enhanced framework for investigation includes a modelling strategy based on a combination of Principal Component Analysis, Orthogonal Projections to Latent Structures, and combinatorial biological pathways. This talk reports signature transcript and metabolic pathways and networks, which are shared by or otherwise exclusive to these clinically tested vaccine adjuvants in mice. These results shine a spotlight on the mechanisms of action of human vaccine adjuvants, and may have implications for the use of existing adjuvants, and development of new ones, in rational design of human vaccines.

Human clinical data on use of Advax delta inulin adjuvants in infectious disease, allergy and cancer vaccines
Nikolai Petrovsky

New and improved adjuvants referred to by Charlie Janeway as ‘immunologist’s dirty little secrets” continue to hold great promise to improve vaccine effectiveness. Nevertheless, development of new human adjuvants has been held back by poor understanding of adjuvant mechanisms of action together with safety and tolerability concerns. More than 20 years ago we showed that semicrystalline particles of delta inulin, a natural plant polysaccharide, have unique immune-modulatory activities that translated in animal immunisation models into potent enhancement of humoral and cellular immunity when co-administered with vaccine antigens. Nevertheless, animal data does not necessarily translate into human effectiveness, and hence we sought to undertake clinical trials to assess the effectiveness of a delta inulin adjuvant formulation (Advax) across a range of human vaccine applications including against infectious disease (influenza, hepatitis B), allergy (bee and ant sting anaphylaxis) and cancer. To date over 2000 human subjects have received one or more immunisations with Advax adjuvant across more than 10 different trials, with the maximum number of consecutive doses of Advax received by each single individual being > 50 over 3 years as part of the allergy desensitisation studies. Vaccines containing Advax were well tolerated and no safety issues were identified. The data from the trials confirm the beneficial effects of Advax seen in animal models on both human humoral but also T cell immunity. These human trials have also provided important insights into the mechanism of action of this paradoxical adjuvant, showing that it has predominantly anti-inflammatory effects on human peripheral blood mononuclear cells with ability to suppress production of the prototypic inflammatory cytokine interleukin 1, and upregulation of the anti-inflammatory cytokine, IL1 receptor antagonist. Instead, Advax induces production of dendritic cell chemokines that it turn recruit T
cells to the site of antigen presentation. In turn this enhanced activation of antigen specific T cells leads to increased generation day 7 post-immunisation of antigen-specific plasmablasts which exhibit increased levels of activation-induced cytidine deaminase helping explain their increased B cell receptor affinity maturation. In the context of allergy vaccines, Advax induces a rapid switch to production of allergen-specific IgG4, which then acts as a blocking antibody for allergen-specific IgE mediated mast cell activation. Despite being anti-inflammatory in nature, emerging data from its use in cancer vaccines indicates that it induces a robust CD8 T cell response, implying its ability to engage dendritic cell antigen cross-presentation pathways, a property previously thought to be restricted to only the most inflammatory adjuvants. This data suggests that the danger model of adjuvant action is outdated, and a new paradigm need to be found to explain the potent adjuvant activity of non-inflammatory delta inulin particles.

Vaccine adjuvant effects of dendritic cell-targeting peptides
Kazuki Misato¹, ○Yasuo Yoshioka¹,²,³
¹Vaccine Creation Project, BIKEN Innovative Vaccine Research Alliance Laboratories, Research Institute for Microbial Diseases, Osaka University
²BIKEN Center for Innovative Vaccine Research and Development, The Research Foundation for Microbial Diseases, Osaka University
³Laboratory of Nano-design for Innovative Drug Development, Graduate School of Pharmaceutical Sciences, Osaka University

Subunit vaccines are expected with improved safety compared with other vaccine types. However, subunit vaccines must be delivered to dendritic cells (DC) more efficiently and administered with an adjuvant, because the vaccine antigen alone does not induce sufficient protective immunity. Our group is developing novel targeting peptide as an antigen delivery vehicle by using a phage display system, which is an in vitro screening technique that uses a library of bacteriophages displaying various peptides. In the present study, we tried to identify peptides that bind DC as antigen delivery vehicle for vaccine development by means of phage display system. A bacteriophage library was mixed with bone marrow-derived DC and the bacteriophage clones that bound the DC were recovered. The binding capacity of the recovered bacteriophage clones was determined by flow cytometry: many of the peptides that bound the DC have a common sequence motif. We examined the vaccine adjuvant effects of the DC-binding peptides against Streptococcus pneumoniae in mice by using Pneumococcal surface protein A (PspA) as the antigen. We genetically fused PspA with peptides, and recombinant fusion PspA-peptide proteins were made in E. coli. We confirmed that, among the 20 peptides tested, only FL4 peptide enhanced the antibody response, even though all of these peptides contained same motif. Fusion PspA-FL4 without any adjuvants induced significantly higher PspA-specific antibody levels than did PspA with adjuvants. In addition, we confirmed that PspA-specific antibody response induced by PspA-FL4 was sufficient to protect against pneumococcal infection. Next to understand why only FL4 peptide can induce strong immune responses, we examined the binding mode of peptides to DC. Many of our identified peptides bound to DC via neuropilin1. In contrast, we showed that FL4 peptide could bind to DC independent on neuropilin 1. Furthermore, we succeeded in identifying the cellular receptor of FL4 peptide on DC. Considering all of these data, we conclude that FL4 can deliver an antigen efficiently to DC and induce antigen-specific antibody without the need of adjuvants.

Cellular and Humoral Immune Responses to PENNVAX-GP® HIV DNA Vaccine plus IL-12 are Equivalent or Superior when Delivered by Intradermal vs. Intramuscular Electroporation in Healthy, HIV Uninfected Adults
*presenting author

Background: Several approaches are underway to improve immunogenicity of HIV DNA vaccines. The HVTN 098 study, a randomized, double blind, placebo-controlled trial at four US sites, evaluated immunogenicity of PENNVAX®-GP vaccine (4 plasmids for HIV-1 consensus subtype C Env, subtype A
**Methods:** Participants received PENNVAX®-GP DNA vaccine in the deltoid as: 1.6mg intradermal (n=20), 1.6mg intradermal + 0.4mg IL-12 (n=30), 8mg intramuscular + 1mg IL-12 (n=30) or placebo (n=9) via electroporation at 0, 1, 3 and 6 months. Peak immunogenicity and durability were measured at months 6.5 and 12, respectively, with intracellular cytokine staining (ICS) for cellular immune responses to Env/Gag/Pol, and binding antibody multiplex assay (BAMA) for Env-specific antibodies (Ab).

**Results:** At peak immunogenicity, frequency of CD4+ responders to any HIV protein (Env/Gag/Pol) were 96% in both intradermal+IL-12 and intramuscular+IL-12 groups; CD8+ response rates were 64% and 44%, respectively. Both CD4+ and CD8+ responses were highest to Env>Gag>Pol. IL-12 increased the rate of CD4+ responses from 56% to 96% in the ID group (p=0.002). Frequency of responders were similar (≥90%) for IgG binding Ab to group M gp140 consensus Env in intradermal+IL-12 and intramuscular+IL-12 groups, but the magnitude was significantly higher in the intradermal+IL-12 group (p=0.008). IL-12 did not increase response rate or magnitude at peak but resulted in higher magnitude after the 3rd dose in the intradermal groups. IgG Ab response rates to gp41 were significantly higher in intradermal vs. intramuscular groups (79% vs. 38%, p=0.007). IgG to subtype AE V1V2 (AE.A244) was detected in 56% of intradermal+IL-12 participants, but in only 14% of participants in the intramuscular+IL-12 group. IgG3 responses to group M gp140 Env were higher in the intradermal+IL-12 vs. intramuscular+IL-12 group (89% vs 54%, p=0.006). At the durability time point, 6 months after the 4th vaccine, CD4+ response rates declined to 66% (p=0.0039) and 76% (p=0.01), in the intradermal+IL-12 and the intramuscular+IL-12 groups, respectively, but the magnitude remained robust among responders. CD8+ response rate and magnitudes remained at similar levels between the two time-points in these two groups. IgG and IgG3 response rates and magnitudes declined significantly in all groups (for example, from 56% to 11% IgG V1V2 in the intradermal+IL-12 group), but robust antigen-specific magnitudes were maintained in 20%-85% of the participants.

**Conclusions:** PENNVAX®-GP DNA vaccine given via electroporation induced robust, and durable cellular and humoral immune responses to HIV-1 antigens, demonstrating that immunogenicity of DNA vaccines can be enhanced by electroporation and IL-12, administered either intradermally or intramuscularly. Intradermal electroporation was dose sparing: with only one-fifth of the intramuscular dose, equivalent or in some aspects superior immune responses were noted compared to intramuscular electroporation.

**Augmentation of antigenicity of the C-terminal region of Clostridium perfringens enterotoxin by fusion with the B subunit of Escherichia coli Shiga toxin 2 for the development of bivalent food poisoning vaccine**

Koji Hosomi¹, Atsushi Hinenoya², Hidehiko Suzuki³, Takahiro Nagatake¹, Tomomi Nishino¹, So-ichiro Hirata¹, Masuo Kondoh², Shinji Yamasaki², Jun Kunisawa¹,³,⁶

¹Laboratory of Vaccine Materials, Center for Vaccine and Adjuvant Research, and Laboratory of Gut Environmental System, National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN)
²Division of Veterinary Science, Graduate School of Life and Environmental Sciences, Osaka Prefecture University
³Department of Microbiology and Immunology, Graduate School of Medicine, Kobe University
⁴Graduate School of Pharmaceutical Sciences, Osaka University
⁵Graduate School of Medicine and Graduate School of Dentistry, Osaka University
⁶Division of Mucosal Vaccines, International Research and Development Center for Mucosal Vaccines, The Institute of Medical Science, The University of Tokyo

Food poisonings caused by Clostridium perfringens and Shiga toxin (Stx)-producing Escherichia coli (STEC) frequently occur worldwide and are serious problem of public health. However, no vaccine is currently available. The aim of this study was to develop a bivalent vaccine against C. perfringens and STEC infections. As C. perfringens and STEC cause food poisoning by toxin produced, induction of toxin-specific neutralizing antibody is a key factor to prevent their pathogenicity. C-terminal region of C. perfringens enterotoxin (C-CPE) and Stx2 B subunit (Stx2B) are non-toxic portion and critical for the binding to their receptors, which prompted us to examine a fusion protein of Stx2B and C-CPE (Stx2B-C-CPE) as a vaccine antigen.

We found that subcutaneous immunization of mice with C-CPE either with or without alum adjuvant induced moderate levels of C-CPE–specific IgM, but not IgG in the serum, which was insufficient for the protection of mice from CPE-mediated pathological symptoms such as hyperkalemia and associated paralysis of limbs.
and general weakness. In contrast, high levels of C-CPE-specific IgG were found in the serum of mice immunized with Stx2B-C-CPE, which completely neutralized lethal doses of CPE in Vero cells. Consistently, immunization with Stx2B-C-CPE prevented mice from pathological symptoms induced by CPE. Additionally, comparable and substantial levels of Stx2B-specific neutralizing IgG were induced in mice immunized with Stx2B-C-CPE or Stx2B alone. Consistent with high levels of Stx2B-specific IgG antibody production, immunization with Stx2B-C-CPE or Stx2B prevented mice from kidney dysfunction and death induced by Stx2.

In addition to antibodies, immunization with Stx2B-C-CPE induced antigen-specific T cell responses. Ex vivo stimulation with Stx2B-C-CPE or Stx2B induced cytokine production (e.g., IFN-γ and IL-4) from splenic T cells collected from mice immunized with Stx2B-C-CPE, whereas ex vivo stimulation with C-CPE did not induce any cytokines. Since these IFN-γ and IL-4 cytokines induces Ig-class switching from IgM to IgG, these results indicate that T cells recognized Stx2B, but not C-CPE, plausibly promoted Ig-class switching of Stx2B- and C-CPE-specific B cells from IgM to IgG. Thus, antigenicity of C-CPE was augmented by fusion with Stx2B, which was mediated by T cells recognizing Stx2B.

These findings collectively indicate that Stx2B-C-CPE could be an efficient bivalent vaccine against C. perfringens and STEC infections by inducing protective immunity against both CPE and Stx2.

---

**African Horse Sickness Virus-Like Particle Vaccine Candidate Made in Plants**

Susan J. Dennis¹, Ann E. Meyers¹, Carina Lourens², Inga I. Hitzeroth¹ and Edward P. Rybicki¹

¹ Biopharming Research Unit, Department of Molecular and Cell Biology, University of Cape Town, Rondebosch, 7701, South Africa
² Department of Veterinary Tropical Diseases, Faculty of Veterinary Sciences, University of Pretoria, Onderstepoort 0110, Pretoria, South Africa

African horse sickness is a devastating, infectious, but non-contagious disease that causes great suffering and many fatalities amongst the horse populations in sub-Saharan Africa. It is caused by nine distinct serotypes of African horse sickness virus (AHSV), an orbivirus of the family Reoviridae which is spread by Culicoides spp. midges. The disease has significant economic consequences for the equine industry, both in southern Africa and now also increasingly further afield as the geographic distribution of the midge vector broadens with global warming. Live attenuated vaccines have been in use in southern Africa with relative success for more than five decades, but there is a distinct risk of reversion to virulence as well as reassortment of the segmented genome between outbreak and vaccine strains. Furthermore, the vaccines lack DIVA capacity, the ability to distinguish between vaccine-induced immunity and that induced by natural infection. Several studies have demonstrated the potential for the use of plant expression systems for the production of VLPs, which are excellent vaccine candidates because they do not contain the virus genetic material, there is no risk of reversion to virulence or reassortment with wild virus strains and they are DIVA compliant.

In this study we report on the Agrobacterium tumefaciens-mediated transient expression of all four structural proteins (VP2, -3, -5 and -7) of AHSV serotype 5 in Nicotiana benthamiana plants, purification of virus-like particles (VLPs) containing all four proteins, and testing of the immunogenicity of purified VLPs in horses. Production of these VLPs was scaled up using density gradient ultracentrifugation, and immunogenicity and serum neutralisation was initially tested in guinea pigs. Sera from the guinea pigs were shown to be reactive with all four structural proteins, and able to neutralise live virus after one prime and a single boost inoculation. The ability of plant-produced VLPs to stimulate immunogenicity in horses - the main target animals - was subsequently tested. Sera from horses immunised with 2 doses of plant-produced VLPs (200ug total protein in 5 ml PBS pH 7.4 with 5% Pet Gel A adjuvant, intramuscular) had high anti-AHSV5 reactivity, and were capable of neutralising both live AHSV5 and the cross-reactive AHSV8. A maximum viral neutralization titre of 1:320, comparable to that generally obtained when inoculating horses with the AHS LAV, was achieved for two naïve horses. These results show that there is great potential for the production of novel and effective AHSV vaccines in plants.
Vaccination and intra-cage transmission of a recombinant parainfluenza virus 5 expressing Rabies lyssavirus glycoprotein in the big brown bat (Eptesicus fuscus)

James A. Ellison1, Matthew R. Mauldin1, Clint N. Morgan1, Felix R. Jackson1, William C. Carson1, Huiling Wei2, Kelsey Briggs2, Nadia Gallardo-Romero1, Biao He2, Christina L. Hutson1
1 Poxvirus and Rabies Branch, Division of High-Consequence Pathogens and Pathology, CDC, Atlanta GA USA
2 Department of Infectious Diseases, University of Georgia College of Veterinary Medicine, Athens GA USA

Rabies virus (RABV) is a zoonotic disease that infects several different species and can be transmitted to humans through a bite or scratch, causing its host to have erratic behavior resulting in symptoms like insomnia and an extreme fear of water. Even with an effective vaccine there are roughly 55,000 human deaths worldwide, due to a lack of vaccine availability or post exposure treatment. Since rabies is transmitted from wildlife to domesticated animals and humans, several vaccination programs exist to help reduce the prevalence of rabies in the wild by orally vaccinating animals like skunks, foxes, and raccoons. However, a major reservoir for the virus, the bat, remains unvaccinated. Bats colonies typically consist of several thousand individuals living in confined quarters, which increases the speed and likelihood of disease transmission. This lifestyle allows our viral vectored vaccine to transmit orally/nasally between individual bats, while also inducing an effective immune response to RABV. Parainfluenza virus 5 (PIV5) is thought to contribute to kennel cough and kennel cough vaccines containing live PIV5 have been used in dogs for many years. Previously, we have generated a PIV5-vectored rabies vaccine (PIV5-RAV-G) that has been tested in mice. The mice vaccinated with a single dose of PIV5-RAV-G protected lethal challenge. In this study, we evaluated the efficacy of PIV5-RAV-G in bats against a lethal RABV challenge. Seronegative big brown bats (n=24) were divided into three separate groups, a PIV5-RAV-G vaccine group (n=9), placebo group (n=10), and a challenge control group (n=5). The placebo group did not receive the vaccine but were cohoused with the 9 bats from the PIV5-RAV-G group, while the challenge control group were kept in a separate laboratory until the day of challenge (45 days post vaccination). The challenge control group had a high mortality after 30 days, while the PIV5-RAV-G and placebo group had reduced mortality. In addition, half of the PIV5-RAV-G bats had RABV neutralizing antibodies (rVNA) by day 13 post vaccination. By day 30 post vaccination, 40% of the placebo bats had a detectable rVNA as well. This study demonstrates that a PIV5-vectored vaccine can be administered intranasally and transmit between cohoused bats to induce colony immunity.

Rational design of Lumpy Skin Disease Virus Vaccines

Henry Munyanduki, Niki Douglass, Ruzaiq Omar, Anna-Lise Williamson
Institute of Infectious Disease and Molecular Medicine, University Of Cape Town, South Africa.

Lumpy skin disease virus is a Capripoxvirus that causes economically important cattle disease mainly in Africa and the Middle East. In recent years LSDV has also spread to Europe. The most widely used attenuated LSDV vaccine is based on the Neethling stain of LSDV (nLSDV). There have been anecdotal reports that this vaccine is too virulent in some breeds of cattle but not protective enough in other breeds. We compared another LSDV vaccine (xLSDV) to Neethling to determine if the vaccines differed. Ion Torrent sequencing indicated that the two genome sequences to be almost identical. In xLSDV there were 2 single nucleotide polymorphisms (SNPs) and 1 deletion of 2bp. The SNPs were found in LSDV genes LW056 (hypothetical protein) and LW116 (RNA polymerase subunit). Both these SNPs resulted in conservative amino acid changes which are unlikely to affect the function of the expressed genes. The deletion of 2bp was in the superoxide dismutase (SOD) ORF. In nLSDV SOD is truncated relative to a virulent LSDV (LSDV Neethling 2490). However, in xLSDV a full length SOD gene has been created by the deletion of 2bp and this gene is now more similar to that of SOD from the more virulent Neethling strain 2490 which was sequenced by Tulman (2001) (Genbank: AF325528). On close inspection of the sequences the deletion occurred in a stretch of TA residues; deletions and insertions of small repeated sequences are known to take place in poxviruses. In addition the deletion was only present in 42% of the sequences unlike the SNPs which were present in 100% of the sequences indicating that the deletion in this repeat region may be unstable. The SOD gene was redesigned and synthesized to remove the TA repeat residues (SODis). Knock-out (nLSDVdSOD) and knock-in (nLSDVSiSOD) viruses were constructed and compared with respect to SOD activity, growth of virus in eggs and apoptosis. The newly constructed viruses were
demonstrated to have a different phenotype to each other and nLSDV. nLSDV appeared to grow to higher titres in eggs compared with the other two viruses. nLSDVdSOD-UCT had a significantly lower titre than Neethling on days 1 to 4 of a 5 day growth curve in MDBK cells. There was significant difference in the amount of inflammation at day 5 between nLSDV and nLSDVdSODs compared to nLSDVdSOD. In cell culture there was increased virus induced apoptosis following infection with the SOD knock-in compared to the SOD knock-out. In the presence of camptothecin, the SOD knock-in virus showed inhibition of camptothecin induced apoptotic death. For attenuated poxvirus vaccines a “take” or “major cutaneous reaction” indicates successful vaccination. These recombinant LSDV viruses are being tested in cattle to determine if the “take” differs.

**[08.5]** Laser-assisted skin delivery of immuno-contraceptive rabies nanoparticulate vaccine in poloxamer gel

Amit Bansal¹, Xianfu Wu², Cherilyn D'Souza¹ and Martin J D'Souza¹
¹Mercer University, Vaccine Nanotechnology Laboratory, Center for Drug Delivery Research, College of Pharmacy, Atlanta, GA;
²Poxvirus and Rabies Branch, DHCPP, NCEZID, The Centers for Disease Control and Prevention, Atlanta, GA, 30329 USA

**Purpose:** Rabies is a zoonotic viral diseases causing neurological symptoms with an estimated 60,000 global human deaths. In the present study, we aimed at immunocontraceptive approach to sterilize the animals and control the population of rabies infected animals. In order to achieve the goal of immunocontraception, we used the unique pDNA that has dual function of providing protection against rabies and induce immunocontraception. Limitation of poor uptake of pDNA to antigen-presenting cells and rapid degradation of pDNA encapsulated in nanoparticles prompted us to fabricate an encapsulation free pDNA nanoparticulate vaccine.

**Methods:** Nanoparticles were prepared by the emulsification method using biocompatible polymers. The negatively charge pDNA was adsorbed onto cationic PLGA (poly (d, l-lactide-co-glycolide)-chitosan nanoparticles. Immobilization of pDNA to cationic nanoparticles was determined by agarose gel electrophoresis. Cellular uptake of cationic nanoparticles was determined as a function of time and concentration and intracellular localization was determined by fluorescent microscopy. In-vivo efficacy was evaluated in mice administered with pDNA nanoparticulate vaccine in hydrogel intramuscularly or transdermally. Serum was collected every week up to 12 weeks post-vaccination and analysed for gonadotrophin release hormone (GnRH, a reproductive hormone) specific antibody using ELISA. IgG subclass ELISA (IgG2a and IgG1) was performed to ascertain polarization of TH1 and TH2 immune response. The binding strength of GnRH specific antibodies was measured by avidity sodium thiocyanate-elution ELISA.

**Results:** Nanoparticles were obtained in the size range of 380-500 nm with a zeta potential of 50.0 mV. P/N ratio of 1/50 was found to be optimum resulting in complete immobilization of pDNA and was further validated from the results of agarose gel electrophoresis. Uptake of vaccine particulates by dendritic cells was both time and concentration dependent and followed saturation kinetics with V_max of 11.389 µg/mL.hr and K_m value of 139.48 µg/mL. The results of the fluorescent microscopy study revealed that the labeled nanoparticulate vaccine was distributed in both cytoplasm and nucleus. Both intramuscular and transdermal route of administration showed elevated levels of GnRH specific IgG, IgG2a and IgG1 antibody response and avidity in mice that received pDNA nanoparticulate vaccine and adjuvant (Alum and MF59) compared to pDNA and blank nanoparticles. However, we found that the immune response was higher in mice that received vaccination transdermally compared to intramuscular route of administration.

**Conclusion:** Our findings demonstrate that pDNA nanoparticulate vaccine showed rapid cellular uptake. It generated anti-GnRH specific antibodies when administered along with adjuvants in poloxamer 407 gel and would be effective in inducing immunocontraception and rabies control.

**[08.6]** Identification of candidate *Coxiella burnetii* T cell epitopes for a novel human Q fever vaccine

Guilhem Richard¹, Anja Scholzen², Leonard Moise¹, Patrick M. Reeves³, Susan R. Paul³, Timothy A. Brauns³, Laurie A. Baeten⁴, Richard A. Bowen⁴, Richard Bucala⁵, Christine M. Boyle¹, William D. Martin¹, Ann E. Sluder³, Anja Garritsen⁶, Anne S. De Groot¹, Mark C. Poznansky³
¹EpiVax, Providence, RI, USA
Coxiella burnetii, the causative agent of Q fever, is a Gram-negative intracellular bacterium transmitted via aerosol. Regulatory approval of the Australian whole-cell vaccine Q-VAX® in the US and Europe is hindered by reactogenicity in previously exposed individuals. The aim of this study was to identify and rationally select C. burnetii epitopes for design of a safe, effective and less reactogenic T cell targeted human Q fever vaccine.

Immunoinformatic methods were used to predict 65 HLA class I and 50 HLA class II C. burnetii epitopes sourced from seroreactive antigens and type IV secretion system substrates. HLA binding assays confirmed 89% of class I and 75% of class II predictions, and 11 HLA class II epitopes elicited IFNγ responses following heterologous DNA/DNA/peptide/peptide prime-boost immunizations of HLA-DR3 transgenic mice. Human immune responses to the predicted epitopes were characterized in individuals naturally exposed to C. burnetii during the 2007-2010 Dutch Q fever outbreak. Subjects were divided into three groups: controls that demonstrate no immunological evidence of previous infection and individuals who exhibit responses to heat-killed C. burnetii in a whole blood IFNγ release assay (IGRA) and either remained asymptomatic or experienced acute Q fever during the outbreak. Recall responses to C. burnetii epitopes were assessed by cultured IFNγ ELISpot. While HLA class I epitope responses were scarce in this cohort, we identified 21 HLA class II epitopes that recalled T cell IFNγ responses in 10-28% of IGRA+ subjects. IGRA+ individuals with past asymptomatic and symptomatic C. burnetii infection showed a comparable response pattern and a cumulative peptide response that correlated with IGRA responses. No peptide elicited reactogenicity in a C. burnetii exposure-primed guinea pig model.

These data demonstrate that a substantial proportion of immunoinformatically identified HLA class II epitopes show long-lived immunoreactivity in naturally infected individuals, making them desirable candidates for a novel epitope-based Q fever vaccine.

Needle-free injection of the sublingual and buccal tissues with an HIV-1 vaccine induces strong systemic and mucosal immune responses and protects from SHIV challenge in rhesus macaques

Andrew T. Jones1,2, Korey Walter3, Xiaoying Shen4, Celia C. LaBranche5, Linda S. Wyatt6, Georgia Tomaras4, David C. Montefiori6, Bernard Moss6, Dan H. Barouch7, John D. Clements8, Pamela A. Kozlowski3, Raghavan Varadarajan9, and Rama Rao Amara1,2

1Emory Vaccine Center, Yerkes National Primate Research Center, Emory University, Atlanta Georgia, USA; 2Department of Microbiology and Immunology, Emory School of Medicine, Emory University, Atlanta, Georgia, USA; 3Department of Microbiology, Immunology and Parasitology, Louisiana State University Health Sciences Center, New Orleans, LA, USA; 4Duke Human Vaccine Institute, Duke University Medical Center, Durham, North Carolina, USA; 5Department of Surgery, Duke University Medical Center; Durham, NC, USA; 6Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA ; 7Ragon Institute of MHG, MIT, and Harvard, Boston, MA, USA; 8Department of Microbiology and Immunology, Tulane University School of Medicine, New Orleans, LA, USA; 9Molecular Biophysics Unit, Indian Institute of Science, Bangalore, India,

In the immediate hours post mucosal transmission, Human Immunodeficiency Virus (HIV)-1 exists in a vulnerable state due to localized replication and a small or unestablished viral reservoir. Thus, the generation of mucosal immunity against HIV-1 via mucosal vaccination may be ideal for combating HIV-1 in this early state. Mucosal vaccines are primarily delivered directly to mucosal surfaces and have several advantages over conventional vaccine routes as they are generally non-invasive, easily administered, and are potentially suitable for mass vaccination. Oral vaccination is a common route of mucosal vaccination in which antigens delivered orally pass through the stomach and are sampled by the gut-associated lymphoid tissue (GALT). To avoid the harsh conditions of the stomach, an alternative strategy of oral vaccination targets the sublingual (below the tongue) and buccal (inner cheek) tissues in the oral cavity. Here we evaluate the sublingual and buccal (SL/B) tissue as a route of oral vaccination against HIV-1 in rhesus macaques. We show that rhesus macaque SL/B tissue contains numerous antigen presenting cell
subsets, including Langerhans cells and conventional myeloid dendritic cells. To aid in antigen uptake, we utilized a modified needle-free injector to deliver immunizations efficiently across the oral epithelium into the underlying tissue. Female rhesus macaques were immunized twice with modified vaccinia Ankara (MVA-HIV) expressing clade-B ADA HIV-1 antigens followed by two boosts with a recombinant clade-B JRFL- trimeric gp120 immunogen (cycP-gp120) adjuvanted with double mutated heat-labile enterotoxin (dmLT) derived from *E. Coli* either via topical SL/B application, needle-free SL/B injection, or the conventional intradermal/subcutaneous (ID/SC) route. Needle-free SL/B immunization resulted in a strong systemic and mucosal vaccine-specific IgG response, comparable to ID/SC immunization, as well as class-switched rectal, vaginal, and saliva localized IgA responses, not observed in ID/SC immunized animals. In contrast, topical SL/B immunization resulted in minimal or undetectable immune responses. Additionally, needle-free SL/B and ID/SC immunization generated vaccine-specific T-cell responses, neutralizing antibodies, and broadly reactive V1V2-directed antibodies, a major correlate of protection in the RV144 vaccine trial. To test vaccine efficacy, we challenged the immunized animals fifteen weeks after final immunization intrarectally weekly with a low-dose pathogenic SHIV-SF162P3. Needle-free SL/B and ID/SC, but not topical SL/B immunization resulted in a significant delay of infection when compared to unvaccinated controls with an estimated vaccine efficacy of 78% (ID/SC) and 58% (Needle-free SL/B) per exposure. Correlates of protection include serum and rectal IgG responses against HIV-1 gp120, V2-loop specific antibodies, and non-neutralizing antibody effector functionality. These results demonstrate both the potential of MVA-HIV/cycP-gp120 + dmLT as a vaccine candidate for future HIV-1 vaccine trials, as well as needle-free SL/B immunization as a practical, efficient, and non-invasive route of both systemic and mucosal vaccination.

[O9.3]

DNA+Protein HIV vaccine protection against SHIV challenge upon same site administration in macaques

BK Felber1, A Valentin2, Z Lu1, X Hu1, M Rosati2, W Williams3, S Shen3, GD Tomaras3, G Ferrari3, C LaBranche3, DC Montefiori3, SG Reed4, N. Sardesai5, DJ Venzon6, P Aye7, B Bahar7, PA Marx7, GM Shaw8, BF Haynes3, GN Pavlakis2

1HRPS and HRS, NCI, Frederick, MD
2Duke U. Med Center; Durham, NC
3DRI, Seattle, WA
4Inovio, Plymouth Meeting, PA
5CCR, NCI, Rockville, MD
6Tulane, New Orleans, LA
7UPenn, Philadelphia, PA

**Background:** We developed methods of simultaneous vaccination with DNA and protein to increase humoral responses and improve protection against SIV infection in macaques. We found that combination of DNA and adjuvanted protein induces high and potent cellular and humoral responses that efficiently disseminate to mucosal sites. Here, we compare immunogenicity and protective efficacy of a DNA+Protein vaccine delivered following two different strategies: co-administration in the same site or separate delivery of DNA and protein in opposite anatomical sites.

**Methods:** Rhesus macaques were immunized with HIV gp145 env DNA and SIV gag DNA by IM electroporation followed by administration of HIV gp120 Env protein adjuvanted with GLA-SE (TLR-4 agonist). The HIV Env vaccine comprised matching sequentially isolated clade C CH505 Env as both DNA and protein. The DNA+Protein vaccine was administered either together by co-immunization in the same muscle, or by immunization in separate anatomical sites (20 animals/group). RMs received 6 vaccinations in 4 month intervals and were challenged weekly with low dose T/F tier-2 SHIV CH505 via the IVAG route.

**Results:** The co-immunization group developed higher vaccine-induced Env Ab and T cell responses. Only the co-immunization group showed significant delay in SHIV acquisition (p=0.011) with a 67% reduction in per exposure acquisition risk relative to the controls after 15 weekly IVAG challenges. These data indicate that simultaneous recognition of the two vaccine components (DNA and protein) by the draining LN plays a critical role in the development of protective immunity.

**Conclusions:** Co-immunization of DNA+Protein in the same muscle is superior for inducing responses able to provide protection against repeated tier-2 R5 autologous SHIV challenge. The advantage of co-immunization vaccine regimens targeting immunogens to the same draining LN could be applicable to other
vaccine modalities and other pathogens.

Direct Detection of Cross-clade ADCC activities in human volunteer sera elicited by a polyvalent DNA prime-protein boost HIV vaccine DP6-001

Shixia Wang¹, Justin Pollara², Sherry Stanfield-Oakley², Diego J. Farfán-Arribas¹, Shuying Liu¹, Guido Ferrari², Shan Lu¹
¹University of Massachusetts Medical School, Worcester, MA
²Duke University, Durham, NC

Background: The landmark RV144 trial has demonstrated that Env-specific antibodies with antibody-dependent cellular cytotoxicity (ADCC) activities correlated with the partial protection against HIV-1 acquisition, which indicated eliciting ADCC is a major objective of candidate HIV-1 vaccines. We previously reported that Env-specific human mAbs isolated from a phase I clinical trial volunteers who received a polyvalent DNA prime-protein boost DP6-001 vaccine showed potent and broad ADCC activities. In the current study, we further analyzed the ADCC activities in vaccinee sera collected from the same DP6-001 trial.

Methods: Two types of assay systems were performed to evaluate the ADCC activities in the DP6-001 vaccinee sera: 1) ADCC-GranToxiLux (ADCC-GTL) assay using CEM.NKRCCR5 target cells coated with autologous or heterologous gp120 protein from subtype A (A2), B (B, Bal and MN), C (TV1) and AE (E, CM235 and A244); and 2) HIV-1 infectious molecular clone-luciferase (IMC-Luc) based assay using target cells infected with heterologous HIV-1 subtype B (Ba-L), subtype C (TV-1, 1086.C), or subtype AE (CM235) molecular clones. Human PBMCs were used as source of effector cells.

Results: Among 19 DP6-001 vaccinee serum samples tested, 12 (63.2%) had positive ADCC activities by the ADCC-GTL assay against target cells coated with 8 individual gp120 proteins from subtypes A, B, C and AE; and 87% of the samples with ADCC positive activities had ADCC antibody titers greater than 1:10,000. More importantly, 16 of 19 (84.3%) serum samples demonstrated ADCC activities against HIV-1 IMC infected target cells by the INC-Luc assay, in particular against subtype AE CM235-IMC, with ADCC antibody titers up to 1:37,959.

Conclusion: A polyvalent Env DNA prime-protein boost vaccination regimen is capable of eliciting high level and cross subtype ADCC-mediating antibody responses in sera of human vaccinees.

NIH Grants AI-087191, AI-082274, AI-082676, HHSN27201100016C

Synthetic DNA Delivery by Electroporation Promotes Robust in vivo Post-Translational Modification of Broadly Neutralizing anti-HIV Immunoadhesin

Ziyang Xu, 1,2 Megan C. Wise, 3 Hyeree Choi, 1 Alfredo P. Puchalet, 1 Ami Patel, 1 Edgar Tello-Ruiz, 1 Jacqueline D. Chu, 1 Kar Muthumani, 1 and David B. Weiner1
1 Vaccine Center, Wistar Institute, Philadelphia, PA 19104
2 Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104
3 Inovio Pharmaceuticals, Plymouth Meeting, PA 19422

Despite ongoing efforts, no vaccines have yet succeeded in inducing antibodies that are considered broadly neutralizing (bNabs) against HIV-1 in NHPs and humans. Passive transfer of bNabs is an important alternative preventive or therapeutic strategy for HIV-1. While exciting, this approach has only recently entered clinical evaluation and warrants further investigation. For these mAbs to be efficacious in preventing HIV-1 infection, neutralization breadth remains a key issue. Accordingly, novel molecules possessing broader neutralization activity have been designed. Among these, the broadest and the most potent are immunoadhesins that contain extracellular domains of CD4 which impart these molecules neutralization breadths, and a peptide that mimics either the N-terminus of CCR5 or crucial binding site of CD4 inducible antibodies to enhance the neutralization potency. The biological production of these complex molecules can be challenging as these immunoadhesins frequently require post-translational sulfation by enzymes to interact with the HIV envelope and achieve their full in vivo potency. Here, we report using synthetic DNA and electroporation (DNA/EP) to promote in vivo expression of an anti-HIV-1 immunoadhesin for at least 6 months. Additionally, we engineered a Tyrosylprotein Sulfotransferase 2 (TPST2) variant enzyme that efficiently trafficked to Trans-Golgi Network (TGN) to colocalize with the immunoadhesin. Binding ELISA
assay was used to demonstrate that the engineered TPST2 variant delivered by synthetic DNA/EP optimally sulfated the target molecule in vivo at a low plasmid dose (1:1000 relative to plasmid immunoadhesin dose). Additionally, post-translational sulfation enhanced the potency of the immunoadhesin, decreasing its IC50 in neutralizing global panel HIV isolates (CE1176, 0.57 to 0.05 ug/mL; 25710, 1.09 to 0.16 ug/mL; X2278, 0.77 to 0.16 ug/mL; TRO, 0.38 to 0.18 ug/mL; BJOX, 0.56 to 0.19 ug/mL; X1632, 0.75 to 0.27 ug/mL; CH119, 1.66 to 0.52 ug/mL; CNE55 1.92 to 0.75 ug/mL; 246F3, 2.11 to 1.07 ug/mL). This work provides a proof-of-concept for delivering anti-HIV immunoadhesins and other engineered complex molecules in vivo by advanced nucleic acid technology. This work also highlights the feasibility and potential for using plasmid-encoded enzymes to modulate the post-translational modifications and activities of their target proteins in vivo, demonstrating a platform with diverse applications (half-life prolongation for biologics, effector function enhancement for antibodies, or immunogenicity modulations for antigens).

Liposome-Encapsulated HIV-1 gp120 Induces Potent V1V2-Specific Antibodies in Humans

Mangala Rao1, Sayali Onkar1,2, Kristina K. Peachman1,2, Yohann White1,2, Hung V. Trinh1,2, Ousman Jobe1,2, Yingjun Zhou3, Peter Dawson1,2, Gary R. Matyas1, and Carl R. Alving1
1United States Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA. 2Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA. 3The Emmes Corporation, Rockville, MD, USA.

In the RV144 trial, HIV-1 gp120 V1V2 antibodies correlated inversely with risk of HIV-1 infection; however the titers waned quickly. Potential approaches to improving the magnitude and durability of the V1V2 antibody responses include additional boosts of the vaccine and/or combining the antigen with more potent adjuvants. To examine these approaches, we utilized available archived samples from a phase I randomized, double blind placebo-controlled trial AVEG015 (ClinicalTrials.gov NCT00001042), conducted in 1992 in HIV-1-uninfected individuals with HIV-1 SF-2 gp120 combined separately with seven adjuvants. Archived sera from two arms of AVEG015 were of special interest; HIV-1 SF-2 gp120 either adsorbed to aluminum hydroxide (AH arm) or encapsulated in liposomes containing monophosphoryl lipid A (MPL®) and then adsorbed to aluminum hydroxide (liposomal arm). The geometric mean IgG titers against gp120 subtype B at weeks 26 and 74 were 82,732 and 94,810, respectively, in the liposomal arm. These titers were much higher than the peak titers of 10,383 observed in the RV144 trial. In the liposomal arm of AVEG015, a 4-fold drop in the titers (94,810 to 21,945) was observed at 40 weeks post-final boost, compared to a 14-fold decrease in the geometric mean titers at 24 weeks post-last boost in the RV144 trial. The median IgG antibody titers across weeks 10-112 were higher in the liposomal arm against subtypes B (2-16-fold), AE (4-8-fold) and C (4-16-fold) V1V2 proteins with half-life’s of 20 and 24 weeks for gp70V1V2 CaseA2 and gp70V1V2 A/E in the liposomal arm compared to 11 and 10 weeks, respectively for the AH arm. In addition to V1V2-specific antibody responses, significantly higher antibodies were also obtained to cyclic V2 and V3 peptides belonging to subtypes B and C in the liposomal arm. Based on the prediction of the secondary structure of the V2 and V3 peptides from the circular dichroism data, we speculate that the % of coil and β-sheet might influence the magnitude of the antibody response, with the liposomal formulation favoring a random coil conformation resulting in higher antibody titers. The antibodies also exhibited ADCC activity and inhibited the binding of α4β7-integrin receptor to cyclic V2 peptide. Thus, the AVEG015 study highlights the importance of adjuvant combinations and precedence for adjuvant combinations in vaccine formulations is now being increasingly appreciated for durable and functional antibody responses. Therefore, inclusion of two adjuvants in the vaccine formulation, aluminum hydroxide and liposomal MPL®, an additional boost, and longer interval between boosts should prove to be promising in the design and development of an effective HIV-1 vaccine.

Stabilized HIV-1 Envelope Designs Expressed in a Replication Competent Ad4 Vector Directly Impact Envelope Conformation, Expression, and Immunogenicity

A Patamawenu1, S Evans1, N Wright1, H Parrington1 C Morris1, P Zhang2, GY Chuang3, G Joyce3, C Cheng3, J Gorman3, YT Lai3, L Vang4, J Alexander4, J Smith4, J Guenaga5, Y Feng5, MC Bonjit6, M Gurwirth4, RW Sanders6, P Russo6, R Wyatt5, P Kwong3, and M Connors1
1HIV-Specific Immunity and 2Viral Pathogenesis Section, LIR, and 3Vaccine Research Center NIAID/NIH, Bethesda MD, USA; 4PaxVax Inc., San Diego, CA, USA; 5IAVI Neutralizing Antibody Center at The Scripps
Replication-competent vectors offer unique advantages over other platforms such as the persistence of antigen and the potential to present HIV-1 Envelope (Env) in a native conformation, glycosylation, and sulfation. In such vaccines, high level expression of uniform, stable Env is likely critical for the induction of antibodies capable of neutralizing diverse isolates. Here varied Env designs expressed by replication competent Ad4 were tested for antigenicity and immunogenicity.

Ad4 shuttle vectors carrying 1086 (clade C) Env genes encoding >100 Envs designed to stabilize or eliminate the need for furin cleavage were transfected into A549 cells. Constructs with the most native-like Env were selected for production of recombinant Ad4. Cell surface Env expression and conformation were characterized by flow cytometry with a panel of 10 antibodies. These antibodies bound epitopes on the apex (PGT145, PG16), V3 (447-52D), the CD4 binding site (VRC01, B12, and F105) and the gp120-gp41 interface (PGT151, 8ANC195, 35022 and 10E8). Constructs that eliminated the endocytosis motif within the Env cytoplasmic tail dramatically increased surface expression. Most constructs bound F105 and 447-52D, implying a non-native-like structure. The 1086c native flexibly linked trimer derived (NFLTD) construct demonstrated the most native-like conformation, nearly eliminating F105 and 447-52D binding while maintaining binding of PG16, PGT145, and PGT151. Native-like conformations were further confirmed by negative stain electron microscopy. Both the NFLTD 1086c and unstabilized 1086c constructs induced durable autologous tier 2 neutralizing antibodies that continued to rise 56 days after the second IM immunization (median 1:264). Our results indicate that stable, native-like Env can be expressed by recombinant Ad4 and induce durable neutralizing antibodies. The NFLTD and unstabilized 1086c Ad4 constructs are in production for clinical trials in early 2019.

An mRNA based trivalent genital herpes vaccine: Sterilizing immunity as a real possibility
Sita Awasthi, Lauren M. Hook, Norbert Pardi, Fushan Wang, Arpita Myles, Michael P. Cancro, Gary H. Cohen, Drew Weissman, Harvey M. Friedman
Perelman School of Medicine and School of Dental Medicine, University of Pennsylvania, Philadelphia, PA, USA 19104

A safe, effective HSV-2 vaccine is a high priority based on the psychological trauma and HIV risks associated with genital herpes. Our laboratory previously evaluated a trivalent HSV-2 gC2/gD2/gE2 subunit antigen vaccine administered with CpG/alum with the goal of producing antibodies that block virus entry, cell-to-cell spread, and immune evasion from antibody and complement. Here we assessed nucleoside-modified mRNA/ lipid nanoparticles (LNP) based trivalent vaccine. The mRNA modifications increase protein translation and prevent mRNA from triggering innate immune sensors that inhibit translation. Mice (n=20-40/group) were immunized with: i) gC2/gD2/gE2 mRNA-LNP; ii) gD mRNA-LNP alone; iii) gC2/gD2/gE2 subunit antigens with CpG/alum; or iv) poly C mRNA-LNP as a control. The mRNA immunizations were given twice at 28-day intervals, while the subunit antigens were administered three times at 2-week intervals, consistent with our prior studies. The trivalent mRNA-LNP elicited potent CD4+ T cells to all immunogens, gE2 CD8+ T cells, germinal center Tfh cells and B cells, and a balanced Th1 /Th2 response. The trivalent mRNA-LNP immunogens produced significantly higher neutralizing antibody titers than the trivalent subunit antigens. After intravaginal challenge with 200 LD50 of HSV-2 strain MS, all animals in the poly C group died. In contrast, the trivalent mRNA vaccine provided sterilizing immunity in 63/64 (98%) mice, based on no vaginal HSV-2 replication on days 2 and 4 post-infection, undetectable DRG HSV-2 DNA on day 4, no seroconversion, no genital disease and no deaths. In the gD2 alone mRNA group, sterilizing immunity was detected in 16/20 (80%) mice, while in the trivalent subunit antigen group, sterilizing immunity occurred in 13/19 (68%). We further evaluated whether the protection provided by trivalent mRNA prevents transmission of virus to naïve mice. We collected vaginal fluids 2 days after HSV-2 challenge from trivalent mRNA and poly C immunized mice and inoculated the fluids into naïve mice. No transmission (0/10) occurred using vaginal fluids from animals immunized with trivalent mRNA, while 6/10 animals inoculated with fluids from the Poly C group became infected. The impressive protection from infection and transmission, and the nearly universal sterilizing immunity in the trivalent mRNA group indicate that nucleoside-modified mRNA immunization is an exciting, novel vaccine approach for preventing genital
**Background:** The CD8 T cell epitopes of human influenza A virus are more conserved than the antibody epitopes and have been proposed for the development of influenza vaccine with broaden efficacy. This conservativeness may be explained by (1) mutations on CD8 T cell epitopes are constrained by their detrimental effect, (2) CD8 T cell-escaping mutants have little advantage because CD8 T cells impose little selection pressure, and (3) the selective advantage of an escaping mutant is limited by the breadth of human major histocompatibility complex (MHC) polymorphism at population level.

**Models:** To explore the interplay of these aspects, we constructed a population genetics model incorporating fitness cost, selective advantage, and MHC allele frequency. Additionally, we accounted for the immunity shift toward escaping mutant by an ordinary differential equation system.

**Experiments:** Guided by the model, a series of experiments was designed to estimate the parameters. Using reverse genetics techniques, we introduced an escaping mutation to the nucleoprotein (NP) under PR8 (H1N1) background. *In vitro* viral growths showed no fitness cost on this mutation. Next, naïve mice, mice primed with HKx31 (H3N2) intranasally or intramuscularly were challenged with a mixture of wild-type PR8 and the escaping mutant on day 30 intranasally. Viral loads in the lungs were measured by digital droplet PCR assay, which is capable of distinguishing mutants from the wild-type on the same host with high specificity. Based on the area under viral growth curves, the selective advantage of escaping mutant is 27% in intranasally- and 9.3% in intramuscularly-primed mice.

**Conclusion:** With the estimates from experimental data, our models predict that even if no fitness cost is accompanied, a CD8 T cell-escaping mutant either cannot invade or invades extremely slowly. The lower selective advantage in intramuscularly-primed mice suggests the lung-resident memory CD8 T cells may be the primary source of selection pressure on influenza virus.

---

**Pandemic Influenza Preparedness: Thailand as part of Global Action Plan to be one of the local Influenza Vaccine Development**

Punnee Pitisuttithum, MBBS, DTM&H,FRCPT
Vaccine Trial Centre, Faculty of Tropical Medicine, Mahidol University

Pandemic influenza is a major health threat due to its potential of rapid global spread and devastating health and socioeconomic impacts. With the Emergence of highly pathogenic avian influenza H5N1 outbreaks in poultry in 2004 and pandemic spread of Influenza A H1N1 2009 around the globe including Thailand, WHO under Global Action Plan(GAP) has worked with developing country manufacturers to increase vaccine production capacity. Thai Government Pharmaceutical Organization (GPO) has been selected to be one of the potential candidates.

Under WHO GAP, a pilot plant was refabricated and equipped. The monovalent live attenuated H1N1 2009 influenza vaccine have been developed, advanced to the clinical trial phase I and II. The LAIV H1N1 was proved to be safe and has received the Emergency Use Authorization (EUA) from Thai FDA. The H5N2 LAIV vaccine was selected and manufactured thereafter as part of pandemic preparedness. As a results of phase I/II clinical trial in the isolation ward at the Vaccine Trial Center. The vaccine was safe, immunogenic, and was able to induce cross clade antibodies after receiving a booster dose of an inactivated H5N2 one year later. The EUA was granted in 2015.

Under WHO GAP, a pilot plant was refabricated and equipped. The monovalent live attenuated H1N1 2009 influenza vaccine have been developed, advanced to the clinical trial phase I and II. The LAIV H1N1 was proved to be safe and has received the Emergency Use Authorization (EUA) from Thai FDA. The H5N2 LAIV vaccine was selected and manufactured thereafter as part of pandemic preparedness. As a results of phase I/II clinical trial in the isolation ward at the Vaccine Trial Center. The vaccine was safe, immunogenic, and was able to induce cross clade antibodies after receiving a booster dose of an inactivated H5N2 one year later. The EUA was granted in 2015.

In parallel, an inactivated trivalent seasonal influenza vaccine development has been initiated. Phase I and Phase II non-inferiority trials with GPO- inactivated trivalent influenza vaccine and marketed product have just finished.

The keys of success include strong commitment and collaboration among local and international partners. Various local universities include Mahidol university and Silpakorn university ,FDA , Department of
Medical Science, MOPH and NVI. The international partners such as WHO, BARDA, IEM, NIBSC, USCDC, KAKETSUKEN and RIVM. An industrial plant has been built by GPO and expected to be completed by 2018. The seasonal influenza vaccine dossier submission to NRA is planned and the approval is expected to be available.
P1 Longitudinal Assessment of Memory B cell and Plasmablast Reactivity Against Influenza A Hemagglutinin in Subjects of Varying Age
Rodrigo B. Abreu1, Greg A. Kirchenbaum2, Emily F. Clutter1 and Ted M Ross1,2
1Center for Vaccines and Immunology, 2Department of Infectious Diseases
University of Georgia, Athens, GA, USA

Influenza is a highly contagious viral respiratory disease that affects millions worldwide each year. Annual vaccination is recommended by the World Health Organization with the goal to reduce influenza severity and limit transmission through elicitation of antibodies targeting the hemagglutinin (HA) glycoprotein. The antibody response elicited by current seasonal influenza vaccines is predominantly strain-specific; however, continuous antigenic drift by circulating influenza virus isolates facilitates escape from pre-existing antibody reactivity and necessitates frequent reformation of seasonal influenza vaccine. Another caveat to successful vaccination that has recently been appreciated is the role of pre-existing influenza immunity. To this end, it remains unclear how the composition of serum antibody and B cell memory is shaped by annual vaccination over the course of multiple seasons, especially in high risk elderly populations. To begin to address these questions, we systematically profiled serum antibody reactivity from a cohort of young (19-34 years old) or elderly (65-85 years old) vaccine recipients that received annual influenza vaccination for 3 or more consecutive seasons. Specifically, we evaluated serum antibody (IgA and IgG) reactivity against recombinant HA (rHA) proteins representing the H1N1 and H3N2 vaccine strains by enzyme-linked immunosorbent assay (ELISA) and hemagglutination-inhibition (HA1) activity against an extensive panel of H1N1 and H3N2 vaccine strains pre/ post-vaccination. Moreover, to assess the impact of sequential influenza vaccination on the memory B cell (Bmem) compartment, we performed in vitro differentiation of donor PBMC collected over the multi-year study to evaluate the breadth of secreted antibody against a panel of H1 and H3 rHA. Lastly, we tracked the precursor frequency and vaccine-elicted expansion of H1 and H3-reactive Bmem by flow cytometry using tetrameric HA probes possessing ablated sialic acid binding activity. Collectively, the coordinated assessment of serum antibody and Bmem reactivity in a cohort of young and elderly donors receiving annual seasonal influenza vaccination will shed invaluable insight into how pre-existing immunity shapes the vaccine response. Ultimately, these studies will advance efforts toward development of broadly protective influenza vaccines with improved efficacy in all populations.

P2 Morbidity benefit conferred by childhood immunisation in relation to maternal HIV status
O. O. Adetokunboh1,2, O. A. Uthman1,2, C. S. Wiysonge1,2
1Cochrane South Africa, South African Medical Research Council, Cape Town, South Africa, 2Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University, Cape Town, South Africa, 3Warwick Medical School - Population Evidence and Technologies, University of Warwick, Coventry, United Kingdom, 4Division of Epidemiology and Biostatistics, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa

Background: The study determined the prevalence of acute respiratory infections and diarrhoea among sub-Saharan African children. It also examined if there was any significant morbidity benefit conferred by three doses of diphtheria-tetanus-pertussis containing vaccines (DTP3) with respect to maternal HIV status. Methods: Data sets were obtained from the Demographic and Health Survey (DHS) program, United Nations Development Programs, World Bank and Joint United Nations Programme on HIV/AIDS. The study included data from 27 countries and were selected based on the availability of DHS data on childhood immunisation coverage, HIV testing; recent symptoms of acute respiratory infection and episodes of acute diarrhoea two weeks prior to the conduct of the surveys. The main outcomes for this study were recent symptoms of acute respiratory infections or episodes of diarrhoea in DTP3 vaccinated children aged 12-23 months. Results: The study shows that 4,523 children developed symptoms of acute respiratory infections among 12,158 children who did not receive DTP3 (37.2%), compared to 8,153 cases out of 21,801 who received DTP3 (37.4%). The study also shows that 6,808 children had episodes of diarrhoea amidst 42,592 children who were not vaccinated with DTP3 (16.0%), compared to 12,845 cases out of 74,186 vaccinated children (17.3%). Children who did not receive DTP3 were likely to develop symptoms of acute respiratory infections compared to children who received DTP3 (poled OR = 1.09; 95% CI 1.02 – 1.17) with low heterogeneity. For the episodes of diarrhoea there was significant difference in the estimates (OR = 0.83; 95% CI 0.74 – 0.92) with significant heterogeneity. The pooled data for symptoms of acute respiratory infections and episodes of diarrhoea show nil significant difference between the children of mothers living with HIV and the children of HIV negative mothers. There was no difference between the estimates of children of HIV seropositive mothers who did not receive DTP3 and those who received DTP3 with respect to symptoms of acute respiratory infections or episodes of diarrhoea. Conclusions: Tackling various causes and risk factors for respiratory tract infections and diarrhoeal diseases should be a priority for various stakeholders in sub-Saharan Africa. There is need for introduction and scaling up the use of newer vaccines such as Haemophilus influenzae type B, pneumococcus, and rotavirus vaccines especially in African countries that are yet to include them in their national immunisation programme. African government officials, policy makers, developmental agencies and healthcare workers should ensure the availability and easy access to routine licensed vaccines. The health systems in some of the African countries are very weak and needed to be strengthened with efforts channelled towards improving the low vaccination coverage in some of the countries.

P3 Vaccine coverage and under-5 mortality in sub-Saharan Africa: analysis of Global Burden of Diseases Study
O. O. Adetokunboh1,2, A. H. Adetokunboh3
1Cochrane South Africa, South African Medical Research Council, Cape Town, South Africa, 2Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University, Cape Town, South Africa, 3Cape Peninsula University of Technology, Cape Town, South Africa

Background: Sustainable Development Goal (SDG) 3.8 targets achieving universal health coverage by access to quality essential health-care services, essential medicines and vaccines for all. Adequate vaccine coverage is critical in protecting children and reducing risks of morbidity and mortality from vaccine-preventable diseases. It is essential to measure the progress made by sub-Saharan African countries towards the health-related SDGs, especially vaccine coverage and reduction in under-5 mortality. This study examined the trend in vaccine coverage of the eight basic vaccines as included in national vaccine schedules in sub-Saharan Africa. The study also examined the relationship between under-5 mortality and vaccine coverage. Methods: Data for this study was obtained from the Institute for Health Metrics and Evaluation, Global Burden of Diseases and Health-related SDGs data visualization tool. Indicator 3.b.1: Coverage of eight vaccines in national vaccine schedules data was obtained for years 1990 and 2016. The 2016 data for the indicator 3.2.1: Under-5 mortality rate (probability of dying before the age of 5 years per 1,000 live births) was also included.

P3 (Continued)

Results: A total of 49 sub-Saharan African countries were included in this study. In 2016, the vaccine coverage ranged from 31% in Somalia to 99.8% in Seychelles. Only 15 countries surpassed the 90% vaccine coverage threshold. Paired t test analysis shows that between 1990 and 2016, the vaccine coverage among the countries progressed from 56.5% (95% CI: 49.8 – 63.2) to 81.4% (95% CI: 76.9 – 85.9) (p < 0.0001). Under-5 mortality ranged from 11.9 per 1000 live births in Seychelles to 130.5 per 1000 live births in Central African Republic. A linear regression established that uptake of the basic eight vaccines could statistically significantly predict under-5 mortality. F(1, 47) = 18.34, p < 0.0001. Vaccine coverage accounted for 26.5% of the explained variance for under-5 mortality. Conclusions: There has been a significant progress made in sub-Saharan Africa in terms of vaccine coverage of basic vaccines for children. However, many countries and sub-Saharan Africa in general performed below the required threshold for vaccine coverage. This study shows that vaccination played a big role in preventing mortality due to vaccine-preventable diseases in Africa. There is need to sustain the support given by Global Alliance for Vaccines and Immunisation in order to meet up with various national targets for vaccination programmes in many African countries. African government also need to prioritise and provide adequate funding for vaccination.
P4 Situation Case Analysis Of Diphtheria In Jakarta
A. Verry; Inggariwati; H. Laili Nur; E. Etrina; Widyastuti
Jakarta Provincial Department of Health

Diphtheria is an infectious disease caused by infections of Corynebacterium diphtheriae. Diphtheria is still endemic in Indonesia with 342 cases reported in 2016 just lower than India and Madagascar with 3380 and 2685 cases respectively. In 2017, a surge of diphtheria cases happened in the country with 591 cases reported from January to November across 20 provinces and 95 districts. Jakarta is one of the provinces undergoing the surge of diphtheria cases. During the period of 2014-2016, there were only 31 reported cases in Jakarta province. Until the end of 2017, there were 120 reported cases of diphtheria with 17 of them were laboratory confirmed. There were 23 new cases reported since the turn of the year until the end of the first week of February 2018. We found that the disease spread across the 5 out of 6 districts (only Thousand Island district reporting zero cases), and 39 out of 44 sub-districts. The disease affected people of all age with children in the 5-10 year old age group and adults in 19-40 year old group contributing the majority of the cases with 43 and 39 cases respectively. Overall, there is no significant difference in total number of cases between men and women. The majority of the cases (45%) were found to have received complete basic three-course of DPT immunization during their first year of life even though the proportion of those with unknown basic immunization status is also quite high (39%). The proportion of cases who received booster vaccination is 12%, 22% of the cases did not receive any booster vaccination while the other 66% have unknown booster vaccination status.

P5 Biofabrication of microencapsulated pancreatic β TC-6 cells for type 1 diabetes mellitus using a spraying nozzle
Amit Bansal1, Sucheta D’Sa1, Cheryl D’Souza1 and Martin J. D’Souza1
1Center for Drug Delivery Research, Vaccine Nanotechnology Laboratory, Mercer University, College of Pharmacy, Atlanta, GA 30341, USA 2Department of Analytical Chemistry, Charles River Laboratories, Ashland, Ohio 44805, USA

Purpose: Type 1 diabetes mellitus (T1DM) is a disease characterized by lack of pancreatic β cell function. Whole tissue transplantation appears to be a viable alternative in the management of T1DM due to limitation of exogenous insulin therapy. Microencapsulation of insulin secreting β TC-6 cells in alginate-chitosan microcapsule polymeric membrane can be used to immunosolating the cells from body’s immune system. Fabrication of microcapsules have been done previously using electrostatic droplet generator or laminar jet break up, but the scale-up of microcapsules always remain a challenge. Therefore, in this study we investigated the potential of automated spraying nozzle employing coaxial air flow to fabricate the microcapsules. This device converts large droplet into small fine droplets at the tip of nozzle due to simultaneous flow of suspension and air. It can produce large quantity of spherical microcapsules in a short span of time with narrow size distribution.

Method: Microcapsules encapsulated with β TC-6 cells were fabricated using a novel spraying device producing uniform spherical microcapsules. The size of microcapsules was optimized by altering the air flow rate. Microcapsules were further characterized for both long and short term stability. Permeability studies were performed using molecular weight markers (i.e. insulin, 5.5 Kd and bovine serum insulin, 65 Kd), and cell viability using Live Dead Staining Kit. In-vitro immunogenicity of microencapsulated β TC-6 cells was evaluated via nitric oxide assay. Microencapsulated β TC-6 cells were transplanted intraperitoneally in streptozotocin (STZ) induced diabetic mice and monitored for lowering in blood glucose levels and immune acceptance.

Result: Spherical microcapsules with a diameter in the range of 250-350 μm were prepared using an air flow rate of 250 L/Hr. Microencapsulated β TC-6 cells in alginate capsules demonstrated prolonged in-vitro viability up to 30 days. More than 90% of microcapsules remained intact in both short and long term stability studies. Results of permeability study showed increase concentration of insulin (5.5 Kd) inside the microcapsules compared to bovine serum albumin (66.0 Kd). Microencapsulated β TC-6 cells released less amount of nitric oxide compared to other groups suggest that microcapsules provide protection to encapsulated cells. In-vivo, the group of mice that received microencapsulated β TC-6 cells maintained normoglycemia for 35±5 days before rejection. However, the group that received naked β TC-6 cells rejected graft within 1 or 2 days and exhibited both cellular and humoral immune responses.

Conclusion: Microcapsules prepared using a specialized nozzle were reproducible, with a narrow size distribution and in addition provides flexibility in producing different sized capsules. Our finding for in-vivo study revealed that transplantation of microencapsulated β TC-6 cells may be a viable alternative in the management of T1DM with acceptable immune response. Importantly, a high level of correlation was achieved for in-vitro microencapsulated β TC-6 cells viability and in-vivo maintenance of normoglycemia.

P6 ZIKA VIRUS MICRONEEDLE VACCINATION CONFERS LONG-TERM PROTECTION TO IMMUNE-PRIVILEGED COMPARTMENTS
Jacob Beaver and Ioanna Skountzou

Zika virus (ZIKV) has garnered global attention since outbreaks in French Polynesia and Brazil were correlated to the development of Guillian-Barré syndrome (GBS) and congenital microcephaly in newborns from infected pregnant women. Since 2013, ZIKV has spread across 20 provinces and 95 districts. Jakarta is one of the provinces undergoing the surge of diphtheria cases. During the period of 2014-2016, there were only 31 reported cases in Jakarta province. Until the end of 2017, there were 120 reported cases of diphtheria with 17 of them were laboratory confirmed. There were 23 new cases reported since the turn of the year until the end of the first week of February 2018. We found that the disease spread across the 5 out of 6 districts (only Thousand Island district reporting zero cases), and 39 out of 44 sub-districts. The disease affected people of all age with children in the 5-10 year old age group and adults in 19-40 year old group contributing the majority of the cases with 43 and 39 cases respectively. Overall, there is no significant difference in total number of cases between men and women. The majority of the cases (45%) were found to have received complete basic three-course of DPT immunization during their first year of life even though the proportion of those with unknown basic immunization status is also quite high (39%). The proportion of cases who received booster vaccination is 12%, 22% of the cases did not receive any booster vaccination while the other 66% have unknown booster vaccination status.

P7 Pandemic origin matrix gene in swine influenza virus contributes to enhanced disease in a murine model of infection
Emily F. Beaver1,2, Shelly J. Samet1,2, Constantinos S. Kyriakis1,3, Jasmina Luczo1, and S. Mark Tompkins1,2
1Center for Vaccines and Immunology, University of Georgia, Athens, GA 2Department of Infectious Diseases, University of Georgia, Athens, GA 3Current address: Department of Pathobiology, Auburn University, AL 36849

Influenza A viruses (IAVs) are negative sense RNA viruses with a segmented genome, containing eight gene segments encoding at least ten proteins. Since the 1990’s, North American swine IAVs (swIAVs) have predominantly contained an internal gene constellation referred to as the triple reassortment internal gene (TRIG) cassette, containing gene segments of human, avian, and swine origin. However, after emergence of the pandemic H1N1 IAV in 2009 in humans (pdmH1N1), reverse-zonotic spillovers into swine have enabled reassortment events with endemic swIAVs resulting in new gene constellations. Specifically, the matrix gene in the TRIG cassette, which originated from the classical swine influenza (swm), was replaced with the pdmH1N1 matrix gene (pdmM). Prior studies have demonstrated increased neuraminidase activity and transmissibility of viruses containing the pdmM suggesting a fitness benefit. Similarly, we demonstrated that the origin of the matrix gene in swIAVs is associated with severity of disease, as demonstrated by increased viral replication and lung pathology in mice infected with viruses containing the pdmM gene segment. We hypothesized that the swIAVs containing the pdmM gene induce dysregulation of the host innate response. To test this, we infected BALB/c mice with a panel of H1 swIAVs containing either the pdmM or the swm matrix gene segment and assessed lung cytokine responses, cellular infiltrates, and cellular responses. We found that infection with swIAVs containing the pdmM elicited greater interferon gamma (IFNγ) responses, as well as increased NK cell and neutrophil infiltration and activation. To confirm the contribution of the matrix gene, we generated reverse genetics viruses containing either the pdmM or swm on a common IAV backbone and assessed replication, disease, and immune responses.

Malaria, the disease caused by mosquito-borne Plasmodium parasites, is transmitted via mosquito bite and manifests as anemia, flu-like symptoms, and sometimes death. A highly efficacious vaccine is not available. During the pre-erythrocytic stage of the life cycle, the *P. falciparum* circumsporozoite protein, or PICSP, is highly expressed on the parasite membrane and is a major target of vaccine efforts. Parainfluenza 5 (PIV5) is a non-segmented, negative-sense RNA virus in the family Paramyxoviridae, and it has been shown to be a safe and effective vaccine vector. We generated multiple PIV5-PICSP vaccines and tested them for their immunogenicity and ability to protect against malaria challenge in mice. We found that PIV5-containing full-length PICSP expressed PICSP on the cell surface. We tested the efficacy of our PIV5-based PICSP vaccine in mice using a transgenic parasite and compared its efficacy to an adenovirus-vector PICSP vaccine. We found that PIV5-PICSP resulted in higher antibody titer post-immunization and protected mice against lethal challenge. Furthermore, we generated a PIVS vaccine containing the Pf625 protein, a protein that is expressed on the parasite surface during the mosquito stage and thought to be critical for parasite transmission. We were able to express Pf625 in a confirmation specific manner in mice. Mice immunized with PIVS-Pf626 generated high levels of Pf625 specific antibodies that were able to block transmission of *P. falciparum* to An. stephensi mosquitoes. The results show that PIV5-vectored vaccines are promising candidates for *P. falciparum*.

**Performance of adjuvant formulations using as model Yellow Fever antigens of different natures**

Cajaraville, AC1; Pierre, M1; Azamor, TCB4; Silva, HC Junior3; Miguez, M3; Pereira RC1; Neves, PC3; Canide, E1; Barbosa, SM1; Gaspar, L1; Medeiros, MA2

1Laboratory of Virological Technology, Biomanguinhos, FIOCRUZ
2Laboratory of Recombinant Technology, Biomanguinhos, FIOCRUZ
3Laboratory of Vaccines and Immunology, Biomanguinhos, FIOCRUZ

The attenuated Yellow Fever vaccine is one of the most successful vaccines ever developed. After a single dose administration, the vaccine can induce balanced Th1/Th2 immune responses and longlasting neutralizing antibodies. For these qualities, YFV17DD vaccine has been studied as a model of how to correctly stimulate the innate immunity to modulate the adaptive immune responses for protection. Despite the success, however, for its attenuated nature, YFV17DD vaccine imposes restrictions of administration to the elderly and block parasite transmission to the mosquito host. We found that the dominant protein hemagglutinin (HA) and the amount of NA is not standardized in current seasonal viruses nor is the breadth coverage known. To better understand the effect of age and pre-existing antibody levels, we conducted an experiment on mice. On following vaccination, subjects were vaccinated with the current split inactivated influenza vaccine. Adults and children (12- 85 years of age) were vaccinated with the quadrivalent (QIV) Fluzone® influenza vaccine. Elderly people (65-85 years of age) were vaccinated with either Standard Dose (SD) (15μg of HA) and High Dose (HD) (60μg of HA) Fluzone® formulations. All other age groups were administered SD QIV vaccine. Sera were collected prior to vaccination and 21 days post-vaccination and tested for anti-neuraminidase antibodies by ELISA or as sessed for neuraminidase-inhibition (NI) activity by enzyme-linked lectin assay (ELLA). All ELLA assays were performed with tetrameric-NA protein, therefore by-passing any potential interference by anti-HA antibodies. Anti-NA antibodies increased against both N1 and N2 NA components in the vaccine between day 0 pre-vaccination and day 21 post-vaccination in all age groups. In addition, there was an increase in NI activity in sera collected at day 21 in the teenager cohort following vaccination with standard dose vaccine and the elderly administered HD vaccine. Both anti-neuraminidase binding antibodies and NI activity increased in teenagers (12-18 years of age) administered the SD of the vaccine. However, there was not a significant increase in anti-NA or N1 titers in the elderly (65-85 years of age) regardless if they were administered SD or HD vaccine.
P12 Interferon and inflammasome networks are associated with lower neutralizing antibody responses to Yellow Fever vaccination
Abdelali Filali-Mouhim, Glenda Canderan, Francois Lefebvre, Enoch Muyanja, Li Pan, Pearlne Cartwright, Robert Balderas, Mark Cameron, Elias K. Haddad, Lydie Trautmann, Pontiano Kaleebu, Laurent Sabbagh, Patricia Fast, Rafick-Pierre Sekaly, Yellow Fever Vaccine Study Group

Immune response to vaccines is critically dependent on multiple host and environmental factors including acute and chronic infections as well as metabolic and/or pathophysiologic states of the host. In this study, we used computational systems biology to analyze a cohort of Ugandan subjects following immunization with the Yellow Fever vaccine (YF-17D) to identify pre-vaccination molecular and cellular mechanisms that can predict the response to the vaccine. By integrating gene expression profiling, cell subset phenotyping and cytokine measurements, we highlight the upregulated levels of interferon and inflammasome genes and proteins as negative correlates of the antibody response to YF-17D vaccine. We show that this innate immune response is associated with higher levels of genes (AOAH, TRIFL) which interact with bacterial components, with dysregulated levels of the interferon signaling inhibitor SOCS-1 and with increased frequencies of Tr1 CD39+ cells producing IL-10. These results underscore the potential role of prevalent commensal or environmental bacteria as an upstream mechanism that could lead to lower YF-17D vaccine response. Our results provide a framework to define the influence of environmental parameters present prior to vaccination on the response to vaccines in human populations.

P13 Protective effect of maternally derived antibodies against highly pathogenic avian influenza H7N3 virus

In the Americas, outbreaks involving highly pathogenic avian influenza (HPAI) H7N3 viruses were reported between 2002 and 2007 in Chile and Canada. In 2012, H7N3 HPAIVs became endemic in Mexico with devastating consequences for the commercial poultry sector. Since then, Mexico has introduced intensive vaccination campaigns to control the outbreaks occurring in different regions of the country. Current vaccines against H7N3 viruses have been shown to be poorly immunogenic. Vaccination of hens against Influenza viruses leads to transfer of maternally derived antibodies (MDA). However, little is known about transfer of H7N3 vaccine-induced MDA, their half-life in chickens after hatch, and their role on protection upon challenge with HPAI virus. Here we evaluated the duration and protective effect of MDA in chickens against HP H7N3. To generate chickens with and without MDA (MDA+ and MDA-, respectively), White Leghorn hens were allocated into two groups: 1) unvaccinated and 2) vaccinated. Group 2 was given an inactivated, Mexican-like LPAI H7N3 vaccine virus, adjuvanted with Montanide ISA 71 VG, and boosted twice. Two weeks after final booster, fertile eggs from both groups were collected and set to incubate. After hatch, MDA+ and MDA- chickens were monitored weekly for MDA status. Three weeks after hatch, chickens were challenged with 10^6 EID50/bird of a homologous Mexican HPAI H7N3 virus. Clinical signs and mortality were recorded for up to two weeks after challenge. MDA specific to the HA were detected mostly on the first week after hatch, while NP antibodies were still detected three weeks after hatch. While 100% of the MDA(-) birds succumbed to disease by day 5 after challenge, 95% of the MDA(+) birds survived. Clinical signs were observed on the MDA(+), however, survivors recovered over time. In conclusion, MDA confers protection against mortality upon challenge with HPAIV H7N3, even three weeks after hatch.

P14 Hemagglutination-Inhibition Activity of Human Antisera Against the Vaccine and Historical Influenza A (H1N1, H3N2) and Influenza B Viruses in Volunteers Vaccinated with FluZone® in Consecutive Influenza Seasons from 2013-2017
Michael Carlock1, Ivette Nuñez1, James D. Allen1, John D. Ingram1, Harold Kleanthous3, and Ted M. Ross1, 2
1Center for Vaccines and Immunology. 2Department of Infectious Diseases University of Georgia, Athens, GA, USA
3Sanofi-Pasteur, Cambridge, MA, USA

Influenza virus infection causes a high disease burden as more than 200,000 people in the United States are hospitalized each year for illnesses associated with influenza virus infection. In seasons where influenza viruses undergo change (drift or shift), the number cases can drastically increase variable vaccine effectiveness. This is especially evident in the elderly population as aging is associated with diminished immunity that affects antibody production, naïve T cell populations, and B-cell activation. Since, influenza vaccine-induced antibody responses in the elderly are often compromised, the vaccine is less effective in this population compared to other age groups. Previously, our group has shown that the breadth of anti-HA antibody to historical vaccine strains is associated with improved vaccine effectiveness leading to increased seroprotection following vaccination. This study investigates the polyclonal antibody-elicited response to the annual inactivated, split influenza vaccine, adjuvanted with dmLT or Lpampo adjuvants compare to the non-adjuvanted group. Moreover, the humoral response intervals. The overall increase in gE specific antibody titers was observed among adjuvanted groups compared to the non-adjuvanted group. Moreover, the humoral response was IgG1-dominated. Hence, a decreasing tendency of IgG1/IgG2c ratio was observed in adjuvanted groups compare to the non-adjuvanted group. Additionally, the humoral response was still detected three weeks after hatch.

P15 A microneedle vaccination with glycoprotein E of Varicella Zoster Virus elicits antibody production and Interferon gamma producing T cells in mice.
Hye-Ran Cha1, Su Jin Hwang1, 2, Hye-Ren Jeong1, Jung-Hwan Park2 and Jae Myun Lee1, 2
1 Department of Microbiology and Immunology, Yonsei University College of Medicine, Seoul, Republic of Korea
2 BK21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Republic of Korea
3 Department of Bionano Technology and Gachon BioNano Research Institute, Gachon University, Gyeonggi-do, Republic of Korea

A microneedle has several benefits in that it is painless, easy to use and preventable from potential cross-contamination by using conventional needle. Despite these advantages, vaccination with microneedle may provide comparable or even higher immune response than vaccination through conventional intramuscular route. Here we have been developing herpes zoster vaccine using microneedle coated with recombinant glycoprotein E (gE) of VZV, which is essential in virus replication and cell-to-cell spread. Microneedles were coated by gE and three different adjuvants: double-mutant heat-labile toxin (dmLT), the combination of TLR1/2 and TLR3 ligands (Lpampo), or mutant cholera toxin A subunit (CTA). C57BL/6 mice were immunized with the coated microneedles two times at 2-week intervals. The overall increase in gE specific antibody titers was observed among adjuvanted groups compared to the non-adjuvanted group. Moreover, the humoral response was IgG1-dominated. Hence, a decreasing tendency of IgG1/IgG2c ratio was observed in gE adjuvanted with dmLT or Lpampo groups whereas relatively high ratio was detected in CTA group. This indicates that Th1 immune response complemented Th2 response in former groups. By conducting ELISPOT, we measured the amount of INF-gamma secretory T cells as cell-mediated immune response is significant in immunogenicity of HZ vaccine. Inconsistent with humoral response, dMLT or Lpampo adjuvanted group exhibited enhanced cell-mediated immune response. Taken together, delivery of HZ subunit vaccine with microneedle may provide a potent immune response against reactivation of VZV.
P16 Informing the Design of Virus-like Particle Glycoconjugate Vaccines: The Immunological Effect of Molecular Linkers

Ashley Chapman
Georgia Institute of Technology

Glycoconjugate vaccines generate protective immune responses against poorly immunogenic glycan antigens by their chemical conjugation to carrier proteins. Virus-like particles (VLPs) are protein nanoparticles that serve as carrier proteins for glycoconjugate vaccines; their immunogenicity and structure allow polyvalent display of antigens which result in immunological memory against conjugated glycans. In this study, the immunogenic effect of the molecular linker connecting glycan antigen to VLP was investigated. Four molecular linkers were explored for two disease-relevant glycan antigens for a total of eight VLP-conjugate vaccines. VLPs derived from bacteriophage Qβ were first acylated using either pentanoate, phenylacetylene, PEGα-alkyne or PEGβ-alkyne linkers. Synthetic glycan antigens identified from Streptococcus pneumoniae and melanoma were then covalently connected to linkers using copper-catalyzed azide-alkyne cycloaddition (CuAAC) “click” chemistry. VLP-glycoconjugate vaccines were administered to CD-1 and C57BL/6 mice, and serum was analyzed by ELISA to determine differences in antibody titers between formulations. Overall, differences in anti-glycan total IgG titers were slightly higher for PEG linkers of both glycan constructs, yet not large enough to suggest antigenicity is linker dependent. However, circulating anti-glycan IgG persisted longer for short linkers and these antibodies demonstrated higher avidity to their cognate antigen than antibodies generated by vaccines containing PEG linkers. Furthermore, IgG subclass data showed slightly higher titers of T-cell dependent subclasses for pentanoate linkers compared to PEG linkers. These data suggest that the composition of the molecular linker may influence antigen presentation in VLP-conjugate carbohydrate vaccines.

P17 Impeding apoptosis activation augments MVA vaccine-induced humoral responses

Lynnette S. Chea1, Linda S. Wyatt2, Bernard Moss2, and Rama R. Amara1
1Emory Vaccine Center, Department of Microbiology and Immunology, and Yerkes National Primate Research Center, Emory University, Atlanta, Georgia, USA; 2Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

The development of an HIV vaccine to protect from infection is critical to prevent the spread of HIV/AIDS. Modified vaccinia Ankara (MVA) is an immunogenic, attenuated poxvirus being developed as a viral vector for multiple vaccines. However, MVA-infected cells undergo rapid apoptosis leading to faster clearance of recombinant antigens. A possible reason for this could be the fragmentation of the anti-apoptotic gene B13R in MVA. Here, we explored the fragmented B13R with a functional version and tested its effects on the immunogenicity of MVA. In vitro MVA or MVA-B13R infected cells were monitored for caspase 3 activation and cell membrane permeability as apoptosis progression markers. MVA-B13R infected Hela cells were protected from chemically induced apoptosis confirming functionality of B13R. Infection of Hela cells and a human muscle cell line demonstrated the ability of MVA-B13R to delay caspase 3 activation compared to MVA through 86 hours post-infection. To determine immunogenicity, BALB/c mice were immunized intramuscularly with recombinant MVA/SHIV or MVA-B13R/SHIV expressing SIV Gag, Pol and HIV clade C Env (SHIV) at weeks 0 and 4. One week after the booster immunization, we observed 3.5-fold higher Env-specific antibody secreting cells in MVA-B13R/SHIV compared to MVA/SHIV mice (p = 0.03). Through four weeks after the booster immunization, we observed 2.5-fold higher Env-specific serum antibodies in the MVA-B13R/SHIV immunized mice (p < 0.01). MVA-B13R/SHIV immunized mice also had 2.5-fold higher frequency of Env-specific memory B cells at four weeks post boost (p < 0.01). Additionally, MVA-B13R/SHIV mice had higher titers of B5R-specific antibodies post boost which are considered to be protective against vaccinia. To determine differences in the innate immune response that may have led to the observed augmented humoral response, we performed RNA-Seq analysis on draining lymph node cells after a single immunization in mice. At day 1 after immunization, we observed 255 differentially expressed genes (DEGs) for MVA/SHIV mice when compared to naive mice while MVA-B13R/SHIV mice showed 66 DEGs. Gene set enrichment analysis from day 1 after immunization for both MVA-B13R/SHIV and MVA/SHIV mice showed significant enrichment for interferon-alpha and interferon-gamma responses relative to naive mice. Unexpectedly, MVA-B13R/SHIV immunizations were associated with a negative enrichment for type I and II interferon responses compared to MVA/SHIV mice indicating MVA-B13R/SHIV induces a less robust interferon response that may lead to the enhanced humoral response observed. Taken together, these results demonstrate that restoring B13R functionality in MVA significantly delays apoptosis induced by MVA which is associated with augmented anti-HIV Env antibody responses in mice and may be due to the reduced interferon-alpha and interferon-gamma responses induced after vaccination.

P18 Putting pre-existing immunity at work: using innate stimuli to enhance protection against influenza virus infection in the immune-trained host

Angela Choi1, Lorenza Itati Ibañez2, Jan Spitael3, Adolfo Garcia-Sastre1,2,3,4, and Michael Schotsaert5
Graduate School of Biomedical Sciences1, Department of Microbiology2, Global Health and Emerging Pathogens Institute3, Department of Medicine4, Icahn School of Medicine at Mount Sinai, New York, New York, USA; Centro de Virología Animal, Dr. César Miltstein Institute, CONICET, Ciudad de Buenos Aires, Argentina

Currently, seasonal vaccines are the best way to provide protection against influenza virus. However due to antigenic drift or shift of the virus, vaccines can be rendered less effective; thus, necessitating yearly updates of influenza vaccines. Due to exposure to the virus and yearly vaccinations, pre-existing immunity to influenza virus is present in the human population. We developed a murine influenza infection model in which we studied host immune responses to influenza infection in the presence or absence of pre-existing immunity provided by seasonal trivalent inactivated virus vaccine (TIV). Through our model, we have shown that pre-existing immunity shifts broad protection against influenza virus from cellular to humoral immunity and affects the establishment of long lasting mucosal cellular immunity. Using this model, we show that an innate stimulus with the RIG-I agonist, sendai virus, shifts immunity in vaccinated mice. At day 1 after immunization, we observed 3.5-fold higher Env-specific serum antibodies in the MVA-B13R/SHIV immunized mice (p < 0.01). MVA-B13R/SHIV immunized mice also had 2.5-fold higher frequency of Env-specific memory B cells at four weeks post boost (p < 0.01). Additionally, MVA-B13R/SHIV mice had higher titers of B5R-specific antibodies post boost which are considered to be protective against vaccinia. To determine differences in the innate immune response that may have led to the observed augmented humoral response, we performed RNA-Seq analysis on draining lymph node cells after a single immunization in mice. At day 1 after immunization, we observed 255 differentially expressed genes (DEGs) for MVA/SHIV mice when compared to naive mice while MVA-B13R/SHIV mice showed 66 DEGs. Gene set enrichment analysis from day 1 after immunization for both MVA-B13R/SHIV and MVA/SHIV mice showed significant enrichment for interferon-alpha and interferon-gamma responses relative to naive mice. Unexpectedly, MVA-B13R/SHIV immunizations were associated with a negative enrichment for type I and II interferon responses compared to MVA/SHIV mice indicating MVA-B13R/SHIV induces a less robust interferon response that may lead to the enhanced humoral response observed. Taken together, these results demonstrate that restoring B13R functionality in MVA significantly delays apoptosis induced by MVA which is associated with augmented anti-HIV Env antibody responses in mice and may be due to the reduced interferon-alpha and interferon-gamma responses induced after vaccination.

P19 Longitudinal Profiling Serum Antibody Reactivity Against Influenza A in Young and Elderly Vaccine Recipients

Emily F. Clutter1, Greg A. Kirchebaum2, Ted M. Ross1,2,3
1Center for Vaccines and Immunology, 2Department of Infectious Diseases University of Georgia, Athens, GA, USA

Seasonal influenza viruses are responsible for substantial morbidity and mortality on an annual basis, especially in select, high risk populations. Annual vaccination is recommended by the World Health Organization with the goal to reduce influenza severity and limit transmission through elicitation of antibodies targeting the hemagglutinin (HA) glycoprotein. However, it remains unclear how serum antibody abundance against the influenza vaccine strains is influenced by repeated vaccination over multiple seasons. In this study, serum IgA and IgG reactivity against recombinant HA (H3N2) proteins representing the H1N1 and H3N2 vaccine strains were evaluated pre/post-vaccination. A cohort of young (n=17) and elderly (n=33) were recruited and received annual split, inactivated influenza vaccination (FluzoneTM) in three consecutive years (2014-2016). The H1N1 strain in the vaccine remained constant for the three seasons, whereas the H3N2 vaccine strains were updated and changed each season. To enable more precise comparisons between the different ages groups, as well as across multiple seasons, the serum abundance of anti-HA specific antibodies was interpolated into µg/mL equivalents based on purified IgA or IgG reference standards. Over the course of multiple seasons, elderly subjects had a consistently greater abundance of both H1N1 and H3N2 strain-specific IgA and IgG when compared to young subjects at both Day 0 and Day 21. The IgG titer at day 21-28 post-vaccination for both vaccine strains was a strong predictor of the day 21 receptor blocking, hemagglutination-inhibition (HAI) titer. These results allow for the characterization of individual antibody responses to annual influenza vaccination over multiple seasons.
**P20** Evaluation of a Multiplex Bead Serological Assay to Assess Population Immunity to Measles and Rubella.
Melissa M. Coughlin1, Alexandrnia Mitchell1, Jeffrey W. Priest1, Gabby P. Smits2, Fiona R. M. van der Klie2, Heather M. Scobie1, James L. Goodson1, Paul A. Rota1, and Bettina Bankamp1
1Centers for Disease Control and Prevention, Atlanta, GA, USA, 2National Institute for Public Health and the Environment, Bilthoven, The Netherlands

Serosurveys are an important tool for the evaluation of population immunity providing information that can help guide measles elimination efforts. However, laboratory testing methods such as enzyme immunoassay (EIA) or the “gold standard” for measuring measles immunity the plaque reduction neutralization test (PRN) assay are time consuming and expensive methods to perform. The multiplex bead assay (MBA) offers multiple benefits over standard serological assays. Here, we report the evaluation of two MBA assays that were multiplexed with rubella antigen. Though the rubella antigen was the same, two preparations of measles antigen were tested, a sucrose gradient purified lysate of measles infected cells (whole virus antigen) and a strong anion exchange column purified baculovirus expressed measles nucleoprotein (N), both multiplexed with rubella antigen. The performance MBA assays was compared to EIA and PRN using serum samples from human vaccines.

Results from the whole virus measles MBA correlated well with results from EIA and PRN assays. The cutoff for the whole virus MBA determined by receiver operator curve analysis was similar to the established correlate of protection as measured by PRN (120 mIU/ml). There was a significant linear correlation when comparing titers obtained by PRN to titers from the whole virus MBA (R²= 0.827, R= 0.964, p< 0.0001), but not for the titers obtained with the MBA using N (R²= 0.431, R= 0.012, p= 0.889). Furthermore, the error rate for the whole virus MBA (11.4%) was lower than for the EIA (13%) and the N MBA (15.7%), respectively, when compared to the PRN assay. To facilitate wider use of the whole virus assay, a commercial antigen source was identified and evaluated.

**P21** Structure-based design of receptor-binding domain immunogens for Middle East Respiratory syndrome coronavirus
Lianpan Dai1, Jinghua Yan2, George Fu Gao1,2
1Research Network of Immunity and Health (RNIH), Beijing Institutes of Life Science, Chinese Academy of Sciences, Beijing 100101, China, 2CAS Key Laboratory of Microbial Physiological and Metabolic Engineering, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China.

Middle East Respiratory syndrome coronavirus (MERS-CoV) is a deadly human pathogen, and have mortality rate more than 30%. The emergence and persistence of MERS-CoV as a cause of severe respiratory disease highlights the need for rapid development of effective prophylactics. MERS-CoV spike (S) protein mediates virus entry and is the major protective immunogen. MERS-CoV binds to cellular receptor CD26 via receptor-binding domain (RBD) of S protein. We and others have demonstrated that the RBD contains many neutralizing epitopes and antibodies recognition of RBD can block the interaction with CD26. Therefore, focusing the antigen-elicited response to RBD is a favorable vaccine strategy. Here, we found, that compared with RBD dimer, the monomer is moderately immunogenic and less protective. Therefore, we then designed a series of RBD dimers as immunogens based on the crystal structure of MERS-RBD. Some of them form unique dimeric form of RBD protein and can be easily purified. By immunogenicity evaluation, the vaccine candidates can elicit high titer of RBD-specific antibodies with potent neutralizing activity against both MERS pseudovirus (>1:1000) and live virus (>500). To evaluate the protection in vivo, we used MERS-CoV susceptible mice with transient CD26 expression as the animal model for MERS-CoV challenge. Indeed, mice administered with the vaccine candidate substantially reduced the virus loads in lungs up to 1000 folds. By histopathological analysis, we also found the vaccine candidate dramatically alleviated the virus-induced severe inflammation in lungs. Subsequently, the crystal structure of dimer form of RBS was determined. Structure analysis showed that RBD-dimer stacks in a head-to-head manner and preserve the space around the subdomain of the receptor-binding motif (RBM) for antibody assess. The dimer form of RBD also reduce the exposure of region in non-RBM and would refocus the vaccine-elicited antibodies to RBM. Our finding highlights the important parameters in the design of RBDbased vaccines to support further clinical assessments.

**P22** Heterosubtypic influenza protection elicited by double-layered polypeptide nanoparticles in mice
Lei Deng
Georgia State University

Influenza is a persistent threat to public health. Here we report that double-layered polypeptide nanoparticles containing a combination of two conserved nucleoprotein (NP) epitopes (NP55 and NP147) and matrix protein 2 ectodomain (M2e) increased the immunogenicity of the peptide antigens. We fabricated layered nanoparticles by ethanol desolvation of a composite peptide of tandem copies of NP55 and NP147 into nanoparticle cores and crosslinking M2e composite peptide of four tandem copies of M2e (4M2e) to the core surface as a coating. The resulting layered nanoparticles induced robust antigen-specific immunity protecting mice against heterotypic influenza A virus challenges. The immune response was further enhanced by a dissolvable microneedle patch-based skin vaccination. Double-layered nanoparticles demonstrated a strong antigen depot effect and migrated into spleens and draining (inguinal) lymph nodes for an extended period compared with the standard two-layered nanoparticles. Double-layered nanoparticles demonstrated a strong antigen depot effect and migrated into spleens and draining (inguinal) lymph nodes for an extended period compared with the standard two-layered nanoparticles. Stronger immune responses in the nanoparticle-immunized group. The protection against infection induced by nanoparticle immunization was transferable by passive immune serum transfusion and depended partially on a functional IgG receptor ForYIV. Using a conditionally cell depletion, we found that CDB positive (CDB+) T cells are involved in the protection. The immunological potency and stability of the layered peptide nanoparticles indicate applications for other peptide-based vaccines and peptide drug delivery.

**P23** Hemagglutinin stalk antibody responses following trivalent inactivated influenza vaccine immunization of pregnant women and association with protection from influenza virus infection
Nisha Dhar1,2, Gaurav Kwatra1,2, Marta C Nunes1,2, Rafael Nachbargauer3, Florian Kramer3, Shahar A Madhi1
1Medical Research Council, Respiratory and Meningeal Pathogens Research Unit, 2Department of Science and Technology, National Research Foundation, Vaccine Preventable Diseases; Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, 3Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, USA

Current seasonal influenza vaccines are poorly effective during seasons when there is antigenic mismatch between the vaccine and circulating virus strains. In previous randomised controlled trials with trivalent influenza inactivated vaccine (IIV3), we observed a disconnect between the observed vaccine efficacy against confirmed influenza illness and haemagglutination inhibition (HAI) responses, especially in HIV-infected women. Antibodies measured in the HAI assays bind the immuno-dominant and highly variable hemagglutinin (HA)-head domain of the virus and have very narrow, strain specific neutralisation potency. Efforts are underway to identify antigens that could induce more broadly protective antibodies and one such target is the immuno-subdominant HA-stalk region. In this study, we retrospectively investigated antibody responses in relation to the H1 HA stalk domain following IIV3 vaccination in pregnant women and evaluated its association with confirmed influenza virus infections. Both H1 HA stalk-specific (H1-S) antibody and HAI responses were significantly elicited post one month IIV3 vaccination in both HIV-uninfected and HIV-infected women. Among the IIV3 recipients, HIV-uninfected women showed no correlation between post one month vaccination H1-S antibody and HAI responses, whereas, HIV-infected women showed significant correlation (p<0.0001). The H1-S antibody concentration was significantly lower among group 1- HIV1N1 infected as compared to -uninfected women (p<0.001).
At H1-S antibody threshold concentration of ≥215 AU/ml, around 90% of women are likely to remain A/H1N1-uninfected (OR=0.09 [95% CI: 0.008-0.04], p=0.005). We also observed H1-S antibody concentration significantly lower among non-group 1 infected as compared to -uninfected women (p=0.04). For the same participants, A/H1N1-HAI titers were also significantly lower among the A/H1N1- infected as compared to -uninfected women (p=0.02). The seroprotective A/H1N1 HAI titer of ≥40 was significantly associated with reduced odds of acquiring an A/H1N1 infection (OR=0.16; [95% CI: 0.03, 0.64], p=0.01). The study results suggest association of both H1-S antibody and H1N1-HAI responses with protection against confirmed 1-A/H1N1 influenza virus infection. However, post IIV3 vaccination H1-S antibody and HAI responses were differentially induced among HIV-uninfected women and synergistically induced among HIV-infected women suggesting a possible coupled effect of both antibody types in protection against influenza virus infections, especially among HIV-infected women. In addition, H1-S antibody responses were associated with protection against non-group 1 influenza infections, suggesting a potential cross-group protective activity of these antibodies.

**P24 Genomic analysis of the immune response to an Ebola DNA vaccine.**
Kelsie Dickerson1, Kimberly A. Kraynak1, Matthew P. Morrow1, Dinah Amante1, Aubree Anton1, Jean Boyer1, Kristine Germar1, Mark Bagarazzi2, David B Weiner2, Scott M. White1

DNA vaccines have demonstrated evidence of strong immune responses and can be targeted to diverse pathogens; however, clinical responses to similar vaccination vary considerably and the molecular basis of this is unclear. Using the NanoString nCounter Immunology Panel, we performed a transcriptomic profiling of unstimulated and peptide-stimulated peripheral blood mononuclear cells (PBMCs) from participants across 3 cohorts enrolled in a Phase I clinical trial. Cohorts received varying doses and schedules of Inovio’s SynCon® vaccine, which encodes for a consensus sequence of the glycoprotein (GP) of Ebola Zaire virus, and two of the cohorts additionally received DNA encoding the adjuvant IL-12. To explore the molecular features associated with a robust antigen-specific T cell response, we compared gene expression data of participants with the highest and lowest IFNγ ELISPot responses two weeks after the third vaccination, or eight weeks after the second vaccination if there was no third vaccination. Luminex was also performed from the supernatant of stimulated cells. We found that participants with the highest IFNy ELISPot responses in each cohort demonstrated a considerably larger number of differentially expressed genes (DEGs) in response to stimulation with Ebola peptides than those with the lowest IFNy ELISPot responses, and that all DEGs involved in theJak-Stat cascade, a signaling pathway activated by IFNg stimulation, were significantly positively correlated with IFNy ELISPot response. Gene sets involved in cytokine-cytokine receptor interaction also demonstrated high Global Significance Scores (GSS), and the CXCL10 molecule was of particular interest due to its significantly high correlation with its encoded protein, IP-10, detected via Luminex. Here we outline some of the molecular features of a robust antigen-specific T cell response and identify potential new targets for future vaccines.

**P25 Longevity of varicella-specific plasma cells in the bone marrow after childhood vaccination**

**Introduction:** Long-lived plasma cells predominantly reside in the bone marrow, constantly produce antibodies against previously encountered antigens and can maintain protective antibody levels for decades or life. Childhood varicella zoster virus (VZV) life-attenuated vaccination was introduced in 1995 and has significantly decreased cases of chickenpox in the US. However, the longevity of varicella-specific plasma cells in the bone marrow induced by this childhood immunization is still unknown.

**Methods:** 14 healthy adults with history of childhood varicella zoster vaccination were enrolled at the Hope Clinic of Emory Vaccine Center, Atlanta, and bone marrow samples were collected. Isolated bone marrow cells were enriched for CD138+ plasma cells, and varicella zoster and Influenza-specific IgG plasma cells quantified by ELISpot. Similarly, Varicella and Influenza-specific memory B cells were enumerated after stimulation with IL-2 and R848. Serum titers of antibodies were determined by ELISA.

**Results:** Of 14 enrolled subjects, 13 had received a total of two vaccine doses according to current recommendations. The interval between last vaccine dose and bone marrow sampling was on average 7 years (range 1 months to 10 years). 12 out of 14 patients had detectable serum IgG antibody titers against VZV lysate. A mean of 0.22% of IgG-producing plasma cells in the bone marrow were specific for VZV, and 0.09% of circulating IgG memory B cells. In comparison, 1.5% of IgG-producing plasma cells were specific for the influenza surface antigens, and 0.94% IgG memory B cells. We observed a positive correlation between numbers of plasma cells and memory B cells for both, Varicella- and Influenza-specific cells (R=0.33 resp. 0.62).

**Conclusion:** Childhood immunization with the life-attenuated Varicella zoster vaccine elicits durable yet low humoral memory responses in terms of bone marrow plasma cells and memory B cells.

**P26 Purification of influenza hemagglutinin and neuraminidases proteins from the stably expressing EXP293 cell lines**
Jeffrey W. Ecker1, Spencer R. Pierce1, Giuseppe A. Sautto1, Dawn L. Taylor-Mulineix1, Greg A. Kirchenbaum1, and Ted M. Ross1,2

1Center for Vaccines and Immunology, 2Department of Infectious Diseases, University of Georgia, Athens, GA, USA

Recombinant proteins have numerous applications in both basic and translational research. For example, expression of recombinant proteins is essential for the development of diagnostic assays and production of therapeutics. Moreover, expression of recombinant proteins is often required for producing experimental vaccine antigens in the laboratory, and for characterizing the immune response elicited by infection or vaccination. However, expression and purification of recombinant proteins can be time-consuming and expensive. To reduce the cost and enable large scale recombinant protein production, we generated EXP293 cell lines stably expressing influenza hemagglutinin (HA) glycoproteins through a multi-step pipeline. Parental EXP293 cells were transfected with pcDNA3.1/Zeocin+ constructs and secretion of recombinant HA (rHA) protein was confirmed by western blot using the hexahistidine (6XHis) affinity tag. Culture medium of transfected EXP293 cells was then replaced with essential growth medium containing the selection drug zeocin, and culture supernatants were analyzed for expression of rHA protein as adherent zeocin-resistant (zeoR) EXP293 lines expanded. ZeoR EXP293 lines with the highest level of rHA expression were identified using a limiting dilution approach and subsequently adapted for suspension growth in serum-free EXP293 expression medium. To date we have generated 20+ EXP293 cell lines that stably express rHA representing numerous influenza subtypes (H1, H3 and H5). Stably expressing EXP293 lines can be expanded to high density in shake flasks and maintain rHA expression after multiple passages. Typical protein yields range from 8 mg/L to as much as 100 mg/L and are consistently above 90% purity following affinity chromatography. Collectively, the establish pipeline confirms the feasibility of generating EXP293 cell lines for production of rHA antigens. Future efforts will focus on generating additional EXP293 cell lines and production of rHA antigens to support reagent development for basic research.
P27 Maternal RSV pre-F + Advax-SM immunization elicits sterilizing immunity to RSV in mothers and offspring without inducing lung pathology
Katherine Eichinger
University of Pittsburgh School of Pharmacy

Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory tract infections in humans, causing severe disease in infants less than 6 months of age. Efforts to develop a direct, infant RSV vaccine have been hampered by the short time frame between birth and first RSV exposure, as well as the immaturity of the infant immune response, and risk of vaccine-enhanced disease. Maternal RSV vaccination is an alternative approach that provides newborns with RSV immunity through the passive, transplacental transfer of maternal anti-RSV antibodies. RSV antibodies resulting from natural infection are predominately directed against the post-fusion form of RSV F protein and fail to provide robust or long-lasting immunity, but stabilized forms of pre-fusion RSV F protein (pre-F) elicit high levels of RSV neutralizing antibodies. However, RSV subunit vaccines, including pre-F, require an adjuvant to boost their immunogenicity, with alum, a Th2 polarizing adjuvant, used most commonly. What remains to be determined is the safety and efficacy in mothers and their offspring of a maternal RSV vaccine combining pre-F immunogen with an adjuvant that provides a more balanced T-helper response. We hypothesized that maternal immunization of BALB/c mice with pre-F in combination with Advax-SM, a potent, non-Th2 polarizing adjuvant, would induce high levels of neutralizing antibodies in mothers that are transferred to their pups, thereby protecting immunized mothers and their passively immunized offspring from RSV infection. Pre-F alone induced only low RSV neutralizing antibody titers in dams that were not sufficient to induce sterilizing immunity to RSV. The immune response of dams immunized with pre-F alone was Th2 biased as evidenced by increased airway concentrations of Th2 cytokines (IL-4, IL-5, and IL-13), a high RSV-specific IgG1 to IgG2a ratio, and significant pulmonary eosinophilia with increased pulmonary pathology, including peri-vascular and -bronchial inflammation and excess mucus production. Moreover, offspring born to dams immunized with RSV pre-F alone had low or undetectable neutralizing antibody titers and had measurable RSV lung titers following challenge. In contrast, dams immunized with pre-F + Advax-SM had a more balanced immune response, characterized by higher neutralizing antibody titers, an RSV-specific IgG1 to IgG2a ratio < 1, elevated airway IFNg concentrations, enhanced RSV-specific CD8+ T cell responses, an absence of pulmonary eosinophilia, and complete, sterilizing immunity following RSV challenge. Importantly, offspring born to pre-F + Advax-SM immunized dams had higher neutralizing antibody titers and demonstrated sterilizing immunity following RSV challenge. Together, these studies provide evidence of Advax-SM’s ability to rebalance the Th2 biased immune response elicited by immunization with pre-F alone. Pre-F in combination with Advax-SM adjuvant is a promising maternal RSV vaccine candidate that warrants further development.

P28 Attenuated Phenotype and Immunogenic Characteristics of a Mutated Herpes Simplex Virus 1 Strain in the Rhesus Macaque
Shengtao Fan
Institute of Medical Biology, Chinese Academy of Medical Sciences

Herpes simplex virus type 1 (HSV-1) presents a conundrum to public health worldwide because of its specific pathogenicity and clinical features. Some experimental vaccines, such as the recombinant viral glycoproteins, exhibit the viral immunogenicity of a host-specific immune response, but none of these has achieved a valid epidemiological protective efficacy in the human population. In the present study, we constructed an attenuated HSV-1 strain M3 through the partial deletion of UL7, UL41, and the latency-associated transcript (LAT) using the CRISPR/Cas9 system. The mutant strain exhibited lowered infectivity and virulence in macaques. Neutralization testing and ELISpot detection of the specific T-cell responses confirmed the specific immunity induced by M3 immunization and this immunity defended against the challenges of the wild-type strain and restricted the entry of the wild-type strain into the tegumental ganglion. These results in macaques demonstrated the potential of the attenuated vaccine for the prevention of HSV-1 in humans.

P29 Intradermal Vaccination Safely Demonstrates Added Cellular and Humoral Immunogenicity Benefit with SynCon® EBOLA GP DNA Vaccines in Healthy Participants

The Ebola virus (EBOV) outbreak that began in 2014 in West Africa resulted in more infections and deaths than all other EBOV outbreaks combined. Therefore, it is imperative to develop a safe and effective vaccine that not only generates potent humoral and cellular responses, but also is easy to deliver and temperature stable for shipment and long-term storage. INO-4201 is a plasmid-based prophylactic vaccine encoding a synthetic consensus Zaire Ebolavirus glycoprotein (GP) that accounts for genetic variability from previous outbreak strains in order to establish a wide breadth of immune coverage for divergent Ebola virus variants. Here, we report results from part of a Phase 1 clinical study (NCT02464670) where INO-4201 was administered to a subset of 30 participants via intramuscular (IM) or intradermal (ID) routes followed by in vivo electroporation with a CELLECTRA®-SP or -3P delivery device, respectively, and evaluated for safety, tolerability and immunogenicity.

INO-4201 was administered to a subset of 30 participants via intramuscular (IM) or intradermal (ID) routes followed by in vivo electroporation with a CELLECTRA®-SP or -3P delivery device, respectively, and evaluated for safety, tolerability and immunogenicity. INO-4201 was administered to a subset of 30 participants via intramuscular (IM) or intradermal (ID) routes followed by in vivo electroporation with a CELLECTRA®-SP or -3P delivery device, respectively, and evaluated for safety, tolerability and immunogenicity. INO-4201 was administered to a subset of 30 participants via intramuscular (IM) or intradermal (ID) routes followed by in vivo electroporation with a CELLECTRA®-SP or -3P delivery device, respectively, and evaluated for safety, tolerability and immunogenicity. INO-4201 was administered to a subset of 30 participants via intramuscular (IM) or intradermal (ID) routes followed by in vivo electroporation with a CELLECTRA®-SP or -3P delivery device, respectively, and evaluated for safety, tolerability and immunogenicity.

INO-4201 was administered to a subset of 30 participants via intramuscular (IM) or intradermal (ID) routes followed by in vivo electroporation with a CELLECTRA®-SP or -3P delivery device, respectively, and evaluated for safety, tolerability and immunogenicity. INO-4201 was administered to a subset of 30 participants via intramuscular (IM) or intradermal (ID) routes followed by in vivo electroporation with a CELLECTRA®-SP or -3P delivery device, respectively, and evaluated for safety, tolerability and immunogenicity. INO-4201 was administered to a subset of 30 participants via intramuscular (IM) or intradermal (ID) routes followed by in vivo electroporation with a CELLECTRA®-SP or -3P delivery device, respectively, and evaluated for safety, tolerability and immunogenicity.
P30 Immune engineering: A strategy to couple B cell and T cell immunity for improved pandemic and universal influenza vaccines

Leonard Moise1,2, Bethany Girard1, Andres Gutierrez1, Christine Boyle1, Nese Kurt Yilmaz2, Shurong Hou1, Hyesun Jang3, Manabu Ato1, Yoshimasa Takahashi4, Celia Schiffer5, Ted Ross5,7, William D. Martin1, Anne S. De Groot1,2

1EpiVax, Inc., Providence, RI, USA
2Institute for Immunology and Informatics, University of Rhode Island, Providence, RI, USA
3Institute of Influenza and Molecular Pharmacology, UMass Medical School, Worcester, MA, USA
4Institute for Influenza and Molecular Pharmacology, University of Georgia, Athens, GA, USA
5National Institute of Infectious Diseases, Tokyo, Japan
6Department of Infectious Diseases, University of Athens, Athens, GA, USA

Rational vaccine antigen design approaches generally focus on antibody-based immunity using consensus sequence and structure modeling methods to produce immunogens with stabilized neutralizing epitopes. While emphasis on antibody targets is critical, attention to the quality of vaccine-induced CD4+ T cell responses is essential to ensure they support mechanisms required for protective antibody responses, including class switch recombination, affinity maturation, and B cell differentiation into long-lived plasma cells and memory cells in germinal centers. We are innovating an approach named immune engineering, that combines immunoinformatic and structure modeling methods, to engineer CD4+ T cell epitopes into protein antigens while preserving native antigen structure.

P30 (Continued)

Here, we apply immune engineering to engineer avian H7N9 influenza hemagglutinin (HA) to recruit broadly reactive seasonal influenza HA-specific memory CD4+ T cells to boost protective antibody responses while maintaining neutralizing antibody epitopes that would be encountered in natural infection with wild type H7- HA. In a first generation immune engineered H7N9 HA, we made three amino acid substitutions that introduced a highly conserved and broadly reactive CD4+ T cell epitope from H3-HA (H3-HA99-103) and simultaneously deleted a regulatory T cell inducing epitope native to H7-HA. Structure modeling showed that the H7-HA structure could accommodate these substitutions without destabilizing the protein. Characterization of the engineered rHA (H7-HA-Opt1) and comparison to the wild type rHA demonstrated both preserved antigenicity and improved immunogenicity in humanized mice. Three monoclonal antibodies raised against wild type H7-HA recognized H7-HA-Opt1 with affinity equivalent to the wild type protein, suggesting that modifications did not induce significant structural perturbations. Similarly, human polyclonal sera demonstrated identical binding profiles against H7-HA-Opt1 and wild type H7-HA.

Importantly, immunizations of NOD/SCID/IL2Rγcnull immune-deficient mice reconstituted with human PBMCs using non-adjuvanted H7-HA-Opt1, stimulated a 5-fold greater anti-H7-HA IgG titer and 20-fold greater anti-H7-HA B cell frequency over mice immunized with wild type protein.

We designed second generation immune engineered H7-HAs capable of harnessing additional HA-specific CD4+ T cell memory generated in seasonal influenza exposure. Using immunoinformatic tools, five seasonal HA CD4+ T cell epitope 9-mers were selected from >34,000 H1-HAs and >38,700 H3-HAs isolated between 1997 and 2017 for (i) conservation across >50% of subtype-specific isolates, (ii) potential to bind ‘A’ HLA class II super-type alleles, (iii) >40% identity and <100% identity with corresponding 9-mer sequences in 803 H7N9 HA human isolates identified between 2013 and 2017, (iv) reported T cell reactivity, and (v) low potential for T cell cross-reactivity with human sequences. A structure model of an H7-HA bearing all five epitopes, as well as the H3-HA296-318 epitope, was generated on a homology model of A/Guangdong/17S/F003/2016 H1N1. Molecular dynamics simulations showed system dynamics and backbone flexibility of the novel antigen were similar to the native protein in terms of root-mean-square deviation and fluctuation of alpha carbon atoms, suggesting the design is stable. The antigen is under production for studies using human and pre-immune mouse models to show how recruitment of a broader repertoire of memory CD4+ T cells can augment B cell and protective antibody responses.

P31 Toolkit for monitoring of immunogen expression and adaptive cellular response in common marmosets following intraderal DNA immunization with electroporation

Gordeychuk Ilya1,2, Tukhvatulin Amir3, Petkov Stefan4, Abakumov Maxim5, Gulyaev Stanislav1, Tukhvatulina Natalia2, Gulyaeva Tatiana1, Mikhailov Mikhail1,2, Logunov Denis2, and Isaigiants Manii1,2,8

1 Chumakov Federal Scientific Center for Research and Development of Immuno-and-Biological Products of the Russian Academy of Sciences, Moscow, Russia; 2 N.F. Gamaleya National Research Center for Epidemiology and Microbiology, Moscow, Russia; 3 Sechenov First Moscow State Medical University, Moscow, Russia; 4 Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden; 5 Pirogov Russian National Research Medical University, Ministry of Health of the Russian Federation, Moscow, Russia; 6 Russian Medical Academy of Continuous Professional Education, Moscow, Russia; 7 Mechnikov Research Institute for Vaccines and Sera, Moscow, Russia; 8 Riga Stradins University, Riga, Latvia.

Common marmosets (Callithrix jacchus, CM) are small New World primates widely used in biomedical research including vaccine studies. In this work, we present a set of optimized procedures for characterization of the expression of immunogens and the consequent adaptive T-cellular immune response in CMs, namely a method of in-vivo visualization of pathways to support recruitment of a broader memory response.

Materials and Methods. Common marmosets A and B were injected intradermally (id) each with 10, 20 and 40 µg of pVaxLuc plasmid encoding luciferase gene (pVaxLuc), two repeats each dose. Immediately after, the injection sites were electroporated using a forked plate electrode (BEX) with 400V poration pulse and three (A) or eight (B) driving pulses of 100V with alternating polarity (CUT12/Edlt/1, BEX Ltd) (Latanova AA et al, 2018). After 3, 72 and 120 hours CMs were sedated by inhalation of 2.5% isofluorane, injected intraperitoneally with luciferin (150 mg/kg; PerkinElmer), placed into Spectrum CT imager (Perkin Elmer) and monitored for the emission of bioluminescence. Heparin-treated blood samples from eight common marmosets were stained with fluorescently labeled monoclonal antibodies to populations marker (CD45, CD3, CD20, CD4, CD8; BioLegend, BD, Beckton Coulter) and lymphocyte maturation and activation markers (CD69, CD62L, CD45RO, CD107A and CD27; BioLegend, BD) and analyzed using flow-cytometry (FACS aria III, BD).

P31 (Continued)

Results. Introduction of 10 ug and 20 ug of pVaxLuc by id injection followed by electroporation with eight driving pulses (protocol optimized for mice; Latanova A et al, 2018) led to luciferase expression peaking at 72 hours, with high residual radiance at 120 hours. Photon emission from 20 ug of pVaxLuc was 10-times higher than from 10 ug. Introduction of 40 ug of pVaxLuc led to signal overload with sharp decrease of emission from 3 to 120 h; luciferase expression level by 120 h was equal to that generated by 10 ug of pVaxLuc. Mild DNA-immunization protocol with few pulses was ineffective. Next, we characterized the immune status of naïve CMs. Within the CD45+ population 22±5.5% were CD3–CD20+ and 67±6.3% were CD3+CD20–. CD3+ subpopulation included 55±5.5% CD3+CD4+CD8– and 34±3.7% CD3+CD4–CD8+. Activation and maturation markers were CD107A and CD27+ cells was found to highly correlate with CM age (r=0.923, p<0.005). Percent of CD3+CD4+CD45RO+ cells (1.9±0.5 in females vs 1.1±0.2 in males; p<0.05). Percent of CD3+CD4+CD107a on 1.6±0.6% of CD3+CD4+ and 1.8±0.7% of CD3+CD8+ cells; CD27 on 94.6±2.1% of CD3+CD4+ and 8.9±3.9% CD20+ cells. Female and male subjects differed in % of CD3+CD4+CD8– and 34.3±3.7% CD3+CD4–CD8+. Activation and maturation markers were CD69 on 2.7±1.2% of CD3+CD4+, and 1.2±0.5% of CD3+CD8+ cells; CD27 on 94.6±2.1% of CD3+ and 8.9±3.9% CD20+ cells. Male and female subjects differed in % of CD3+CD4+CD54R0+ cells (1.9±0.5 in females vs 1.1±0.2 in males; p<0.05). Percent of CD20+CD27+ cells was found to highly correlate with CM age (r=0.923, p<0.005).

Conclusion. Conditions for DNA-immunization and for assessment of the immune status and the adaptive cellular response in common marmosets have been established crucial for the performance of prophylactic and therapeutic DNA immunization in these animals.
P32. HLA binding modeled by in silico tools predicts immunogenic T cell epitopes in vaccinated individuals

Aimee Mattie1, Brian Roberts1, Pooja Hindocha1, Frances Terry1, Guilhem Richard1, Sarah E. Silk3, Carolyn M. Niels3, Rebecca Ashfield3, Simon J. Dryer3, Vinayaka Kotia1, Amy R. Noe3, Mark C. Poznansky6, Ann E. Sluder5, Lenny Moise1,2, William Martin1, Anne S. De Groot1,2
1EpiVax, Inc., Providence, Rhode Island, United States
2University of Rhode Island, Providence, Rhode Island, United States
3Jenner Institute, University of Oxford, Oxford, United Kingdom
4Leidos Life Sciences, Frederick, MD, USA
5Vaccine and Immunotherapy Center, Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Boston, MA USA

The ability of the immune system to develop a response against pathogens relies on the presentation of peptide antigens to CD4+ T-cells in the context of class II human leukocyte Antigen (HLA-II) molecules found on the surface of antigen presenting cells. Allele-specific binding profiles have been elucidated allowing for the development of in silico-based tools, such as EpiMatrix, which predicts the peptides within a given protein that will bind HLA, providing an important first step in immunogenicity screening. JanusMatrix evaluates epitope similarity to the human proteome at the T cell receptor (TCR) interface, which may induce regulatory T cell responses. By screening a pathogen’s proteome, we can rapidly narrow down target epitopes allowing for focused vaccine design. The combination of in silico predictions validated by in vitro assays provides a powerful method whereby vaccines can be developed. We present three case studies to demonstrate the utility of EpiMatrix and JanusMatrix in harnessing T cell immunity for production of safe and effective vaccines.

P32 (Continued)

Case Study 1. Promiscuous class II epitopes with TCR face conservation to the human proteome in R5S, a Plasmodium falciparum blood-stage antigen, were identified and validated with EpiMatrix, JanusMatrix, HLA binding assays, and Interferon gamma (IFNγ) ELISpot assays using PBMC from R5S1 vaccinees. An individualized T cell epitope measure (ITEM) score, and a score adjusted for human cross-conservation (J-ITEM) were calculated based on vaccinees’ HLA-DR haplotype. Peptides inducing positive responses had higher iTEM and J-ITEM scores (p<0.05 and <0.01, respectively) than negative peptides, indicating that patients could present the peptides and respond with IFNγ if the peptide was unique to malaria and hence non-tolerogenic.

Case Study 2. EpiMatrix and JanusMatrix were used to identify 50 promiscuous class II epitopes from Coxiella burnetii (Cb) antigens which were tested in HLA binding assays and screened for immunogenicity in HLA-DR3 transgenic mice. Significant epitope-specific IFNγ responses were found for 11/50 peptides, all of which are predicted HLA-DR3 epitopes (Fisher’s exact p-value: 0.023) and recall IFNγ responses in humans with a history of natural exposure to Cb; all but one bound to HLA-DR3 in vitro.

Case Study 3. Class II T cell epitopes from vaccinia virus proteins were identified in IFNγ ELISpot assays using the PBMCs of smallpox vaccinees by Kennedy & Poland, (Virology 2010). Using EpiMatrix and JanusMatrix, we found that the T cell epitopes identified were predicted to bind to class II HLA alleles more often and had lower JanusMatrix human homology scores than the remainder of the overlapping peptide library (p<0.05), suggesting that in silico binding predictions correlate to T cell responses in vitro. We have shown that EpiMatrix and JanusMatrix algorithms efficiently identify putative T cell epitopes, distinguishing likely inflammatory peptides from regulatory peptides and are adaptable to patient HLA-specific assessment. Applying both tools in the early stages of vaccine design, antigen selection and engineering will result in the advancement of next generation vaccines where the minimal essential components of protection can be delivered without off-target or unintentionally suppressive signals deleterious to vaccine efficacy.

P33. HLA Binding Assay Design: Impact of HLA binding motif centering on HLA binding results and T cell response; Relevance to Overlapping Peptide Analysis

Aimee Mattie1, Brian Roberts1, Pooja Hindocha1, Frances Terry1, William Martin1, Anne S. De Groot1,2
1EpiVax, Inc., Providence, Rhode Island, United States
2University of Rhode Island, Providence, Rhode Island, United States

Peptides that bind to HLA Class II molecules are stabilized by flanking residues, improving binding performance. Poorly centered HLA-binding motifs (at the N- or C-terminal of the binding peptide) may result in absence of binding or T cell response despite the presence of an HLA binding motif. Off-center motifs may also perform poorly due to the degradation of key HLA-binding residues, resulting in poor in vitro performance. The following retrospective analysis from recent publications demonstrates the likely impact of off-centered motifs. Repeating the binding assay with properly centered peptides, and/or removing off-centered motifs from retrospective studies, improved correlations between in silico predictions and in vitro findings. These findings are relevant for developing accurate predictive tools and for proper interpretation of vaccination studies.

Case Study 1. We reviewed a published report describing HLA class II-restricted T cell epitopes from vaccinia virus membrane proteins (Kennedy & Poland, Virology 2010). In this paper, overlapping peptides representing the sequence of four vaccinia membrane proteins were synthesized and tested in IFNγ ELISPOT assays with PBMCs of 29 recent smallpox vaccine recipients. Peptides identified as T cell epitopes were predicted to bind to class II HLA super-type alleles (using EpiMatrix) more often than the remainder of the non-reactive overlapping peptide library (p<0.05). This relationship improved (p<0.03) after removing peptides containing off-centered binding motifs from the analysis, demonstrating the impact of centered binding motifs to T cell response.

Case Study 2. In a recent study describing HLA binding and T cell assay results for two monoclonal antibodies (Hamze et al., Frontiers in Immunology 2017), HLA binding and immunoinformatics results were noted to be discordant. A subset of the original peptides was re-synthesized and optimized (centered) versions of these peptides were also produced. Both sets of peptides were then assayed for HLA class II binding at EpiVax. The repeat assays using peptides that had centered motifs improved the correlation between in silico HLA binding predictions and in vitro performance from a positive predictive value of 65% to 84%.

Both studies described here highlight the impact of off-centered T cell epitope binding motifs in HLA binding assays. Careful attention should be taken to design peptides with optimal features, such as centered motifs, before their usage in in vitro and in vivo experiments.

P34. A trivalent gC2/gD2/gE2 vaccine for herpes simplex virus generates antibody responses that block immune evasion domains on gC2 better than natural infection

Lauren M Hook1, Sita Aswath2, Jonathan Dubin4, Jessica Flechtner4, Deborah Long2, and Harvey M. Friedman4
1Infectious Disease Division, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104-6073; 2Genecoea Biosciences, Cambridge, MA 02140

Vaccines for prevention and treatment of genital herpes are high public health priorities. Our approach towards vaccine development is to focus on blocking virus entry mediated by herpetic simplex virus type 2 (HSV-2) glycoprotein D (gD2) and to prevent the virus from evading complement and antibody attack by blocking the immune evasion domains on HSV-2 glycoproteins C (gC2) and E (gE2), respectively. HSV-2 gC2 and gE2 are expressed on the virion envelope and infected cell surface where they are potential targets of antibodies that bind and block their immune evasion activities. We demonstrate that antibodies produced during natural infection in humans or intravaginal inoculation in guinea pigs bind to gC2 but generally fail to block the immune evasion domains on this glycoprotein. In contrast, immunization of naive or previously HSV-2-infected guinea pigs with gC2 subunit antigen administered with CpG and alum as adjuvants produces antibodies that block domains involved in immune evasion. These results indicate that immune evasion domains on gC2 are weak antigens during infection, yet when used as vaccine immunogens with adjuvants the antigens produce antibodies that block immune evasion domains. We are currently using high throughput biosensor technology to determine the specific epitopes on gC2 that are immunogenic in infected and immunized guinea pigs. A comparison of the epitope specific antibody responses in immunized and infected animals will help identify crucial epitopes on gC2 that produce antibodies that block immune evasion.
**P35 Elicitation of Protective Antibodies Against H1N1 Influenza Viruses using Recombinant Hemagglutinin or Virus-like Particles in a Prime-Boost Regimen**

Ying Huang¹, Greg A. Kirchenbaum¹, Spencer R. Pierce¹, Jeffrey W. Ecker¹, Ted M. Ross¹,²

¹Center for Vaccines and Immunology, ²Department of Infectious Diseases University of Georgia, Athens, GA, USA

Influenza A viruses cause annual, recurring epidemic outbreaks. Vaccination is the most effective way to prevent viral infection. However, the diversity of antigenically distinct isolates is a challenge for developing influenza vaccines. In order to overcome the antigenic variability and improve the protective efficacy of influenza vaccines, our group has developed computationally optimized broadly reactive antigens (COBRA) based on the main influenza virus surface glycoprotein hemagglutinin (HA). COBRA HA proteins were expressed on the surface of a virus-like particle (VLP) and the VLPs were purified from 293T HEK cell supernatants. Mice were vaccinated with these VLPs and the elicited immune responses were compared to mice vaccinated with a soluble recombinant HA (rHA) protein. rHA proteins were expressed and purified from E. coli. These cell lines stably protein that is shed into the supernatant and is then purified. Recombinant H1N1 HA proteins derived from A/California/07/2009, A/New Caledonia/20/1999, pandemic COPRA P1, seasonal COBRA X-6 and X-3, as well as the H3N2 isolate A/Texas/50/2012, were purified and used as immunogens. BALB/c mice (6-8 weeks old, n=10) were vaccinated intramuscularly (3X) with rHA (5µg) or phosphate-buffered saline formulated with Alum as an adjuvant at a 4-week intervals. At week 12 post-vaccination, all the mice were challenged with the A/California/07/2009 (H1N1) virus. All mice vaccinated with rHA derived from A/California/07/2009 or COBRA P1-2 were protected from weight loss and death, while mock-vaccinated and H3 rHA vaccinated animals rapidly lost weight and reached experimental endpoints between 5 and 6 days post-infection. Even though mice vaccinated with X-6 and X-3 lost weight, 70-80% of mice survived the influenza virus infection. The survival rate provided by rHA vaccination was similar with the corresponding VLP vaccination. Collected antisera from mice vaccinated with rHA had similar hemagglutinin inhibitory activity against a panel of H1N1 viruses as antisera collected from mice vaccinated with VLP vaccines. Overall, HHA proteins produced from stable expression cell lines elicited the similar immune responses, with similar protection profiles in mice as mice vaccinated with purified VLP vaccines.

---

**P36 Parainfluenza virus 5 (PIV5)-based vaccines protect mice against lethal challenge with wild-type strains of Burkholderia mallei and Burkholderia pseudomallei**

Maria Cristina Huertas-Diaz, Zhenhai Chen, Jeremy S. Dyke, Tomislav P. Jele-sijevic, Frank Michel, Robert J. Hogan, Eric R. Lafontaine, Biao He

Burkholderia mallei and Burkholderia pseudomallei are both highly pathogenic bacteria that cause glanders and melioidosis, respectively. Due to their ability to be used as biological warfare agents and the lack of a licensed vaccine for either disease, both bacteria have been categorized as Tier 1 organisms by the U.S. Federal Select Agent Program. Our lab has developed vaccines against B. mallei and B. pseudomallei by incorporating the predicted surface-located domains of the autotransporter protein BatA and the outer membrane protein 7 (OMP7) into the PIV5 genome (PIV5-BatA and PIV5-OMP7, respectively). Single-dose immunizations were performed in BALB/c mice to test the efficacy of the vaccines against challenge with wild-type strains of B. mallei and B. pseudomallei. Mice were monitored for up to 55 days post-challenge for signs of illness, and target tissues from surviving animals were collected to determine bacterial burden. Our results showed that vaccines with a single-dose of either PIV5-BatA or PIV5-OMP7 provide excellent protection against challenge with lethal doses of B. mallei and B. pseudomallei strains (up to 92% and 71% survival with PIV5-BatA and B. pseudomallei strains during acute and chronic stages of infection, respectively). Vaccinations with the vaccine candidates also resulted in a significant decrease in bacterial burden from target tissues in the surviving mice. This study highlights the potential of BatA and OMP7 as novel antigens for generating vaccines against B. mallei and B. pseudomallei, as well as the diversity of PIV5 as a viral vector for vaccine development.

---

**P37 Growth of tumors in immunocompetent mice promoted by the expression of HIV reverse transcriptase can be restricted by reverse transcriptase gene immunization**

Jansons J.¹, Pankova E.³,⁴, Pektov S.², Mezale D.¹, Fridrhone I.¹, Skristaina D.², Podschwadt P.³, Abakumov M.⁴, Starodubova E.¹,³,⁴, Strumfa I.¹, Gordeychuk J.¹,³,⁴,⁵, Izagulians M.¹,³,⁴,⁵,⁶

¹- Riga Stradins University, Riga, Latvia; ² - Biomedical Research and Study Center, Riga, Latvia 3 - Chumakov Federal Scientific Center for Research and Development of Immune-and- Biological Products of Russian Academy of Sciences, Moscow, Russia; 4 - Gamaleya Research Center of Epidemiology and Microbiology, Moscow, Russia; 5 - Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden; 6 - Engelhardt Institute of Molecular Biology, Moscow, Russia. 7 - Sechenov First Moscow State Medical University, Moscow, Russia. * Presenting author: maria.issaguliants@rsu.lv

Introduction: HIV infection is accompanied by oncological complications. HIV Tat, Nef, and p17 are directly oncogenic. Oncogenic potential has also been attributed to retroviral reverse transcriptase (RT) from retrotransposons. We have shown that HIV RT induces oxidative stress known to promote cancer. Its oncogenic potential has not been addressed. Aims: Assess RT as a potential tumor-associated antigen and evaluate the possibility to protect immunocompetent mice from challenge with aggressive RT-expressing tumor cells. Materials and Methods: Consensus RT of HIV FSU_A (RT_A) and its variants with mutations of resistance to nucleoside (RT_An) and non-nucleoside (RT_Ann) inhibitors were designed. Their expression-optimized genes were synthesized (Evrogen), cloned in pVAX and expressed in eukaryotic cells. Coding sequences were used to generate RT-expressing lentiviruses (Evrogen). Murine adenocarcinoma 4T1 luc2 cells (Perkin Elmer) were transduced with RT-lentiviruses at varying multiplicity of infection/MOI. RT expression by subclones was assessed by Western blotting. BALB/c mice were orthotopically transplanted with 4T1 luc2RT 1.3, 4T1 luc2RT 5.3, 4T1 luc2RT 20.1, 4T1 luc2RT An10.1, 4T1 luc2RT An10.2 (RT-variant.MOI.clone). Tumor growth was monitored by morpho-metric images and bioluminescence imaging/BLI (Spectrum CT; Living Image4.4). After 20 days, mice were sacrificed; tumors and internal organs were excised, and monitored by ex vivo BLI. Number of Luc-expressing cells in organs was calculated. Directly after, tissues were paraffin-embedded for histological analysis. Area of tumor metastases in the organs was quantified in haematoxylin–eosin-stained slides by computer-assisted morphometry (NIS-Elements, Nikon). Implantation and follow-up were also performed in mice DNA-immunized (Latanova AA, Sci Rep.2018;8(1):8078) with RT_A inactivated by site mutagenesis. At experiment end-points, mice were assessed for in vivo immune response to RT-derived peptides by IFN-g/IL-2 Fluorospot (Mabtech).

**P37 (Continued)**

Results: Within 10 days, all subclones formed palpable tumors. RT_A expressing tumors grew faster and to larger size than tumors expressing drug-resistant RTs, or parental 4T1 luc2 (p<0,05). Mice with RT_A tumors had more metastasis in internal organs than mice implanted with 4T1 luc2 (p<0,05). Aggressiveness and metastatic activity increased with increase of RT_A expression/increased MOI. Aggressiveness and metastatic activity of subclones expressing drug-resistant RT As did not differ from parental clone. Mice with RT_expressing tumors developed no anti-RT immune response. DNA-immunization with inactivated RT_A as induced modest T-cell and potent antibody response, and protected 80 to 100% mice from challenge with 4T1 luc2 clones expressing high levels of respective RTs (RT5.3, RT_Ann10.1). Protection from subclones with low levels of RT expression (RT-1.3, RT_Ann-10.2) did not exceed 30%, however tumors in these mice were smaller than in controls (p<0,05). In vector/PBS-immunized mice, all subclones formed palpable tumors within 10 days post-implantation. Protected/partially protected mice exhibited RT-specific IFN-g/IL-2 response to in vitro stimulation of splenocytes with RT-derived peptides. Unprotected mice demonstrated no such response, and low response to mitogens.

Conclusions: RT expression increases tumorigenic and metastatic activity of malignant cells advancing RT as potential tumor-associated antigen. The effect is abrogated by drug-resistance mutations. RT DNA-immunization can protect against growth of RT-expressing tumors. Degree of protection depends on the level of RT expression by tumor cells. Tumorigenic cell lines expressing HIV-1 antigens are useful in assessing protective potential of therapeutic HIV DNA-vaccines.

Acknowledgments: RFBR#17_54_30002;17_04_00583; RSF#15-15-30039; VACTRAIN #692293.
P38 Sero-surveillance for the Asian Lineage Avian Influenza A (H7N9): A Baseline Study toward the Application of a Novel Vaccine Candidate

Hyeseun Jang1, Michael A. Carlock1, John D. Ingram1, and Ted M Ross1,2
1Center for Vaccines and Immunology, 2Department of Infectious Diseases
University of Georgia, Athens, GA, USA

The poor immunogenicity of H7 HA protein has been a major obstacle to develop efficacious vaccines against Asian lineage avian influenza H7N9 (Asian H7N9). In this study, we examined if people living in the United States had antibodies that cross-reacted with the H7N9 isolates A/Anhui/1/2013 (clade 1) or A/Guangdong/1/2016 (clade 2) influenza viruses. Serum samples were collected from volunteers (n=192) between the age of 12 and 85 years living in Athens, GA, USA. These volunteers were vaccinated with split, inactivated (IV) Fluzone during the 2017-2018 northern hemisphere influenza season. Serology was performed on day of vaccination and 21 days post-vaccination and the serum samples were screened for hemagglutination inhibition (HAI) against H7 strains, as well as against IBV viruses included in the vaccine, but also against both the 2013 and 2016 H7N9 influenza strains. Young subjects had significantly higher HAI activity against historical, as well as contemporary H1 and H3 virus strains from the mid-1980s to present. In contrast, elderly subjects had HAI activity to H1 strains from all years, but were more likely to have HAI activity to older strains from 1918-1950s. They also had a more restricted HAI profile against H3 viruses compared to young subjects recognizing H3N2 influenza viruses from the mid-2000s to present. Almost all volunteers had antibodies against both strains representing the Yamagata and Victoria lineages pre and post-vaccination. In contrast, no serum sample had HAI activity against either of the H7N9 influenza viruses. However, despite the lack of HAI activity, these subjects did have anti-HA antibodies that bound recombinant H7 HA proteins. To determine how these subjects have antibodies that bind to H7 rHA proteins without prior exposure to the H7N9 viruses, we analyzed and correlated the antibody titers with antibody titers to seasonal influenza subtypes (H1, H3, IBV), as well as with the subject's age and gender. In addition, the antiserum was tested for competition with stem-specific antibodies, F6 or CR8020, to determine if the antibody cross-reactivity was focused on the stalk region of the H7 protein. Overall, our findings provide a valuable insights to assist in the development of novel vaccine strategies against the poorly immunogenic H7N9 influenza viruses.

P39 METHOD FOR RAPID EX VIVO ASSESSMENT OF METASTATIC POTENTIAL OF TUMOR CELLS FOR PRECLINICAL TESTING OF CANCER VACCINES

Jansons J1,2, Mezale D1, Petkov S1, Pankova E4,5, Fridrihsoene I1,2, Podschatzd P2, Kilpelaainen A1, Skrastina D2, Abakumov M5, Gordeychuk H4,5, Strunfle I1, Isagulants M1,3,4,5
1Riga Stradins University, Riga, Latvia; 2Latvian Biomedical Research and Study Centre, Riga, Latvia; 3Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden 4Chumakov Federal Scientific Center for Research and Development of Immuno- and Biological Products of Russian Academy of Sciences, Moscow, Russia 5Gamaleya Research Institute of Epidemiology and Microbiology, Moscow, Russia

Challenge with tumor-inducing cell lines stably expressing microbial antigens is a powerful surrogate model to evaluate the protective potential of microbial vaccines, specifically when the microbial challenge is not available. The in-depth characterization of tumorogenic and metastatic activity of tumor cells expressing microbial antigens on the background of antimicrobial immune response helps to identify correlates of protection and better understand its mechanisms. Using tumor cells "labelled" by expression of reporters make such analysis fast, reliable and animal-sparing, allowing to monitor tumor growth in live animals. However, assessment of metastatic activity remains cumbersome and time-consuming. Tumor size and the signal from multiphoton imaging during in vivo evaluation, leaving only the option of histochemical/Immunohistochemical analysis of multiple tissue sections. High throughput methods are required for rapid sensitive assessment of metastatic activity. Here, we propose a method to quantify metastasis of reporter-expressing tumors by ex vivo quantification of reporter activity in excised tissues/organs of tumor-bearing animals. We analyzed metastatic activity in BALB/c mice of murine adenocarcinoma cell line expressing luciferase (4T1luc2; Perkin Elmer) and consensus reverse transcriptase (RT)/protease (PR) enzymes of HIV-1 (HIV-PR or RT/PR) clones were cloned into lentiviral vectors. Resulting lentiviruses were used to transduce 4T1luc2 cells at increasing multiplicity of infection. Presence of RT- and PR-coding insert in genomic DNA was confirmed by PCR, and RT- and PR-expression, by mRNA analysis and Western blotting. Resulting 4T1luc2RT and 4T1luc2PR clones were subcutaneously injected into BALB/c mice. Tumor growth was monitored at 1-3 day intervals morphometrically and by bioluminescence imaging (BLI; Spectrum/Perkin Elmer). After 21 days, mice were sacrificed, tumors were biopsied and excised and subjected to ex vivo BLI. Number of photon-emitting cells in tissues/organs was quantified using calibration curves built using known amount of 4T1luc2 cells, with recalculation of signal loss in excised tissues compared to the same tissues assessed in vivo. After BLI, organs/tissues were fixed, paraffin-embedded, and sectioned. Sections were stained by H&E. Metastases were assessed within five 400x-power microscope fields by computer-assisted morphometry (Nikon; NIS-Elements software). Statistical analysis was done by IBMSPSSv23.

P40 Protection against respiratory syncytial virus (RSV) by recombinant live attenuated influenza virus expressing RSV G protein domain in a chimeric hemagglutinin molecule

Yu-Jin Jung, Yu-Na Lee, Ki-Hye Kim, Youi Lee, Min-Chul Kim, Jongsang Lee2, Cheol Kim2, Manki Song3, Sang-Moo Kang
1Center for Inflammation, Immunity & Infection, Institute for Biomedical Sciences, Georgia State University, Atlanta, GA 30303, USA. 2BEAMS Biotechnology Co. Ltd., Seongnam, Gyeonggi-do, Republic of Korea. 3International Vaccine Institute, Seoul, Republic of Korea.

Respiratory syncytial virus (RSV) is one of the most important pathogens associated with significant morbidity and mortality in infants and the elderly. Live attenuated influenza vaccine (LAIV) is a licensed platform for vaccination in humans. RSV G attachment receptors mediate virus binding to the target cells and contain a conserved central domain with neutralizing epitopes. Here, we generated recombinant LAIV based on the attenuated A/PR8/34 virus backbone, expressing a RSV G conserved domain in a chimeric hemagglutinin (HA) fusion molecule (HA-G). The attenuated phenotypes of chimeric HA-G LAIV were evident by restricted replication in the upper respiratory (nose) but not in the lower respiratory tract lungs tissues of the mice. In addition, chimeric HA-G LAIV did not cause weight loss or illness in mice even after inoculation with 100 to 1000 fold higher doses than the control wild type backbone virus causing severe weight loss. Prime and boost intranasal vaccination of mice with HA-G LAIV induced G protein-specific IgG and IgG2a (Th helper type 1) isotype antibodies. The protection against RSV was confirmed by the significant reduction in the lung viral load below the detection limit after RSV infection. Mice immunized with chimeric HA-G LAIV showed significant increases in G-protein specific IgG antibodies in lung, bronchiolarveolar fluid, bone marrow, and spleens. Histopathology is being investigated to assess the safety of vaccination after RSV infection. In future, the community of chimeric HA-G LAIV against influenza virus was not compromised. These results in this study suggest a novel approach of developing RSV vaccine candidates using LAIV, potentially dual vaccines confering protection against both pathogens.
P41 Development of Recombinant Adenovirus-based Vaccine Targeting MERS-CoV Spike(S) Protein.

Myung Hee Kim, Jeong-Yoon Lee, Jung Ok Kang and Jun Chang*
Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul, Republic of Korea

Middle East respiratory syndrome coronavirus (MERS-CoV) causes an acute and severe lower respiratory illness as well as vomiting, diarrhea and renal failure. Since there are no licensed MERS-CoV vaccines currently available, preventive and therapeutic measures are urgently needed. The surface spike (S) glycoprotein of MERS-CoV, which binds to the cellular receptor, dipeptidyl peptidase 4 (DPP4), is considered a major target for development of the MERS-CoV vaccine. In this study, we designed recombinant replication-deficient adenovirus-based vaccines expressing the full-length S protein (rAd/spike) and receptor binding domain (RBD) of the MERS-CoV S1 subunit (rAd/RBD). We found that immunization with both candidate vaccines via the intranasal route induced S1-specific IgG antibodies and neutralizing antibodies against MERS spike-pseudotyped virus. Especially, rAd/spike induced higher neutralizing antibody titer than rAd/RBD. To compare the immune responses induced by different routes of administration, rAd/spike was administered via intranasal, sublingual or intramuscular route. All of these routes of administration exhibited neutralizing effects in the serum. The MERS-CoV-specific neutralizing IgA antibodies in the bronchoalveolar lavage fluid (BALF) were only induced by intranasal or sublingual administration but not by intramuscular administration. Taken together, our results show that both the S1-specific IgG antibodies and neutralizing antibodies are highly induced by rAd/spike administration, suggesting that rAd/spike may confer protection against MERS-CoV infection.

P42 Adjuvant effects of BCG cell-wall skeleton on improving influenza vaccination by enhancing effector humoral and CD4 T cell responses

Ki-Hye Kim1, Young-Tae Lee1, Soojin Park1, Eun-ju Ko, Yu-Jin Jung1, Eun-Yeong Jo1, Sang-Moo Kang1
1Center for Inflammation, Immunity & Infection, Institute for Biomedical Sciences, Georgia State University, Atlanta, GA 30302, USA. 2Department of Medical Science, College of Medicine, Chungnam National University, Munhwa-ro 266, Dungku, Daejeon, 35015, Republic of Korea

Bacillus Calmette-Guérin cell wall skeleton (CWS) consists of mycolic acids, arabinogalactan, and peptidoglycan, which has been used as an adjuvant for immunotherapy to stimulate anti-cancer immunity in a variety of cancer patients. Here, we investigated the adjuvant effects of CWS on mediating protective immune responses to influenza vaccination in a mouse model. The ptkovine was inactivated split influenza virus (named sCal) derived from 2009 H1N1 pandemic strain (A/California/2009). A single intramuscular immunization of mice with a low dose of sCal vaccine in the presence of CWS induced total IgG and isotype IgG antibodies by over 16 folds compared to the vaccine only group. CWS adjuvanted sCal prime vaccination induced enhanced protection against lethal challenge with A/California/2009 virus, which was evidenced by low airway resistance, several hundreds fold reduction in lung viral loads, 100% survival rates and prevention of weight loss compared to the sCal vaccine alone group displaying severe weight loss and 0% survival rates. Higher levels of lung CD4 T cells expressing cytokines (IFN-γ, TNF-α) and in vitro antibody secreting cell responses were observed as a result of CWS adjuvanted sCal prime vaccination. As a further evidence of improved protection, lung histopathology due to challenge viral infection was prevented in CWS adjuvanted sCal vaccination whereas more severe histopathology with high inflammatory infiltrates was observed with ineffective sCal vaccinated mice than unvaccinated naive mice with lethal infection. The results in this study warrant further studies of developing BCG CWS as an effective vaccine adjuvant.

P43 Replication Kinetics of Swine Influenza Field Viruses in Primary Swine Respiratory Epithelial cells and Normal Human Bronchial Epithelial (NHBE) cells to Assess their Zoonotic Potential

Madelyn Krunkosky1,2, Constantinios S. Kyriakisk1,2, Ian Padykula1,2, Jasmina Luczo1, and S. Mark Tompkins1,2
1Center for Vaccines and Immunology, University of Georgia, Athens, GA
2Department of Infectious Diseases, University of Georgia, Athens, GA 30602

Influenza A viruses (IAVs) are single stranded negative sense RNA viruses containing eight gene segments. IAVs have two genetic traits: (a) drift, resulting from mutations, usually in gene segments expressing the surface glycoproteins hemagglutinin and neuraminidase and (b) shift, re-assortment, which occurs when two viruses co-infect the same host and exchange gene segments. Pigs, susceptible to avian and human IAVs, are proposed as the “mixing vessel” linked to the generation of novel IAVs that may infect humans. Swine IAVs exchange gene segments from swine, avian, or human viruses: H1N1, H3N2 and H1N2. To investigate the zoonotic capacity of swIVs, we compared the replication properties of human and swIVs in swine primary nasal, tracheal, and bronchial epithelial cells and normal human bronchoalveolar (NHBE) cells. We used human seasonal H1N1 and H3N2 IAVs as comparators and tested their replication against older and contemporary swIVs of different subtypes, isolated before and after the emergence of the pdmH1N1 virus. SwIVs were sequenced to identify differences within the internal genes, and viruses were classified based on the presence of a matrix gene of classical swIV origin (swIVm) or pdmH1N1-origin (pdmIV), which was established in swine populations after the 2009 H1N1 pandemic. We hypothesized that swIVs containing the pdmIV gene would replicate more efficiently in swine primary respiratory epithelial cells and NHBEs than swIVs containing the swIVm gene, suggesting a greater pandemic potential. Our results indicate specific gene constellations, including but not limited to the pdmIV gene, do result in enhanced swIV replication in swine primary respiratory epithelial cells and NHBE cells and may increase the zoonotic potential of swine influenza viruses.

P44 A chimeric yellow fever-Zika virus vaccine virus fully protects against lethal zika and yellow fever virus diseases in stringent murine challenge models

Dieudonné B. Kuma1, Robert Boudevin2, Ji Maa, Ivan Gladwyn-Ngb3, Christian Alfanob, Niraj Mishraa, Li Hsin Lia, Michael A. Schmidaa, Rafael E. Marguesc, d, Dominique Scholse, Suzanne Kapteina, Laurent Nguyenb, Johan Neyts2* and Kai Dallmeiera*
akU Leuven, Department of Microbiology and Immunology, Rega Institute for Medical Research, Laboratory of Virology, Antiviral Drug and Vaccine Development, Division of Virology and Experimental Chemotherapy, Leuven, Belgium
bGIGA-Neurosciences, Interdisciplinary Cluster for Applied Genoproteomics (GIGA-R), University of Liége, C.H.U. Sart Tilman, Liége, Belgium
cUniversidade Federal de Minas Gerais, Belo Horizonte, Brazil
dLaboratorio Nacional de Biotecnologia, Campinas, Brazil
eRega Institute for Medical Research, K.U. Leuven, 3000 Leuven, Belgium
*Correspondence: Kai Dallmeier (kai.dallmeier@kuleuven.be) and Johan Neyts (johan.neyts@kuleuven.be)

Introduction: The recent Zika virus (ZIKV) epidemic in the Americas, followed by the yellow fever virus (YFV) outbreaks in Angola and Brazil highlights the urgent need for safe and efficient vaccines against the ZIKV virus but as well as a much greater capacity for the production of the yellow fever virus vaccine. Given that the ZIKV and YFV are largely prevalent in the same geographical area, vaccines that would be able to protect against both pathogens at the same time would offer a significant benefit.

Methods: Employing our recently developed and proprietary (WO/2014/174078) PLLAV (Plasmid-Launched live-Attenuated Virus) platform technology, we engineered a chimeric vaccine candidate by swapping the sequences encoding the YFV-17D surface glycoproteins by those of the corresponding prototypic Asian lineage ZIKV strain (Yap Island isolate 2007).
P44 (Continued)

**Results:** A chimeric YF-ZIKprM/E virus was constructed that is highly attenuated in vitro and in interferon-deficient AG129 mice. A single vaccine dose of YF-ZIKprM/E conferred complete protection against a lethal challenge with 1x105 PFU of a heterologous wild-type ZIKV. In addition, vaccination of female NMRI mice followed by intra-placental challenge with ZIKV completely protected pups from congenital ZIKV infection and brain malformations. Surprisingly, this vaccine candidate also efficiently protected against lethal (1x104 PFU) YFV-17D challenge in different mouse models. ZIKV structural and YFV-17D non-structural proteins were targets of both CD4+ and CD8+ T cell responses, indicating that multi-functional (memory) T cell responses may contribute to the protective efficacy. We also demonstrated that CD8+ but not CD4+ T cells, nor ZIKV neutralizing antibodies were required to confer protection against YFV-17D. More so, our vaccine candidate could significantly reduce viremia in dengue challenged mice.

**Conclusion:** The chimeric YF-ZIKprM/E vaccine, which resembles the recently licensed chimeric Japanese encephalitis and dengue vaccines Imojev® and Dengvaxia®, respectively, can be considered as a promising vaccine candidate against both the ZIKV and the YFV. This may be particularly important in rational vaccine design against flaviviruses especially in areas where both viruses co-circulate.

---

P46 Antigenic properties and immunogenicity of human respiratory syncytial virus fusion protein constructs with mutations in the cleavage sites and transmembrane domain presented on virus-like particles

Young-Man Kwon1, Hye-Suk Hwang, Youri Lee1, Ki Hye Kim, Yu-Jin Jung, Min-Chul Kim, Sang-Moo Kang

Institute for Biomedical Sciences, Georgia State University, Atlanta, Georgia, USA

Human respiratory syncytial virus (RSV) causes significant hospitalizations and mortality in young children and the elderly. There is no licensed vaccine against RSV. Palivizumab, the only prophylactic licensed drug is a monoclonal antibody against RSV fusion protein (F), suggesting that F is a promising target for developing RSV vaccines. The palivizumab-reactive epitope is known to be present in pre-fusion and post-fusion F proteins. The effects of oligomer stabilizer and cleavage site mutations on displaying neutralizing epitopes remain largely unknown in the F-proteins presented in a membrane-anchored native-like form mimicking RSV. In this study we better display RSV neutralizing epitopes on F present in a membrane-anchored form on virus-like particles (VLP) mimicking RSV, we introduced various modifications and mutations into F proteins. (1) Oligomer stabilizing sequences (GCN3; GCN4; GCN4; GCN4tet) linked to the hemagglutinin transmembrane (TMpr8) domain replacing RSV F TMsv. (2) Mutations deleting 10 amino acids within the fusion domain and in the cleavage site 1 or site 2 (F1, F1d, F2, F12d). The palivizumab-reactive epitope appeared to be well exposed in F proteins with GCN4-linked TMpr8 than with GCN3 or wild type RSV F. Combination mutations F1d-GCN4TMpr8 was found to better display the palivizumab reactive epitope than wild type F or F12d-GCN4TMpr8, and more immunogenic for inducing RSV binding and neutralizing antibodies than wild type F or other mutant F constructs after immunization in cotton rats. These GCN4 and cleavage site mutations did not expose pre-fusion specific epitopes even in combination with pre-fusion stabilizing mutations. Further studies are ongoing to better stabilize and display pre-fusion and post-fusion epitopes in the F constructs presented on VLP.

---

P47 Effects of novel combination adjuvants on improving the efficacy of inactivated split Respiratory syncytial virus vaccine in mice

Youri Lee, Eun-Ju Ko, Young-Tae Lee, Ki-Hye Kim, Soojin Park, Sang-Moo Kang*

Center for Inflammation, Immunity, and Infection, Institute for Biomedical Sciences, Georgia State University, Atlanta, Georgia, USA

Human respiratory syncytial virus (RSV) causes severe disease of pneumonia and bronchiolitis leading to hospitalizations and mortality of over 160,000 pediatric deaths worldwide. There is no licensed vaccine on the market despite extensive effort on developing a safe and effective RSV vaccine for several decades. Alum adjuvanted formalin-inactivated whole RSV vaccine (FI-RSV) failed in clinical trials in young children due to vaccine-enhanced pulmonary disease, which is also recapitulated in animal models. In this study, we investigated different adjuvants and combinations which would improve RSV vaccine efficacy as well as modulate immune responses preventing vaccine-enhanced pulmonary histopathology after vaccination and RSV infection in mice. We found that inactivated and detergent-split RSV (SRSV) vaccines expose neutralizing epitopes reactive to palivizumab at higher levels than inactivated whole virus. Split RSV vaccination of mice induced more desirable immune responses towards T helper type 1 (Th1) and less lung histopathology compared to FI-RSV after RSV challenge. Next, we tested the efficacy and pulmonary histopathology after Split or FI-RSV vaccination in the presence of different adjuvants (alum salts, AddaVax oil-in-water emulsion, fucoidan carbohydrates, poly IC TLR 3 agonist, MPL TLR 4 agonist, CpG TLR 9 agonist, or combination MPL+CpG). We used 2 weeks old infant or adult BALB/c mouse models after prime vaccination and RSV challenge. Low dose combination of monophosphoryl lipid A (MPL) + CpG adjuvants was found to be most effective in increasing Th1 type IgG antibodies, neutralizing activity, and lung viral clearance as well as modulating balanced immune responses to prevent pulmonary histopathology after RSV vaccination and challenge. Whereas, many other common vaccine adjuvants did not attenuate lung histopathology in mice after RSV vaccination and challenge, despite their effects on increasing the immunogenicity of RSV vaccines. This study demonstrates adjuvant candidates that would improve the efficacy and safety of subunit RSV vaccines.

---

P45 Association between mucosal immune response and Group B Streptococcus colonization in pregnant women

Gaurav Kwatra 1,2, Peter V Adrian 1,2, Claire Cutland 1,2, Shabir Madhi 1,2

Authors’ affiliations: Medical Research Council: Respiratory and Meningeal Pathogens Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. Department of Science and Technology/ National Research Foundation: Vaccine Preventable Diseases, University of the Witwatersrand, Faculty of Health Sciences, Johannesburg, South Africa.

**Background:** Establishing association between mucosal immunity and Group B Streptococcus (GBS) colonization in pregnant women could contribute to the evaluation of GBS vaccines. We studied the association of serotype-specific mucosal antibodies on new acquisition and clearance of recto-vaginal GBS colonization in pregnant women and association between serum IgG and mucosal IgG.

**Methods:** Serotype-specific GBS capsular mucosal IgG and IgA concentrations were measured by multiplex Luminex assay in vaginal mucosal secretions. Recto-vaginal swabs for GBS colonization was undertaken at 20-25 weeks of gestation and thereafter at 5-6 weekly intervals. Standard microbiological methods were used for GBS culture and serotyping undertaken by latex agglutination and PCR if non-typeable by latex agglutination.

**Results:** Mucosal IgG correlated significantly with serum IgG (Rho =0.839, 0.621 and 0.426 for serotypes Ia, III and V, respectively (p<0.001 for all). Serotype-specific capsular mucosal IgG GMC’s were higher in pregnant women who remained uncolonized compared to those who acquired homotypic GBS serotype, albeit no statistical significance was achieved for any serotype, serotype Ia (0.90 ng/ml vs. 0.47ng/ml; p=0.10), serotype III (0.97ng/ml vs. 0.72ng/ml; p=0.33), serotype V (1.91 ng/ml vs 1.21 ng/ml; p=0.21). For Mucosal IgA, a similar trend was observed only for serotype V (2.15 ng/ml vs. 1.03 ng/ml; p=0.06).

**Conclusion:** The results suggest that IgG in mucosal secretions is derived from serum IgG. We were, however, unable to establish a correlation for either mucosal serotype-specific IgG or IgA and risk of homotypic GBS colonization.
P48 EcoCRM® A Recombinant CRM197 Carrier Protein

A. Lees1, R. Simon2, S. Balibam1, I. Krauss3, D. Nguyen1, M. Pravetoni4, N. Oganesyan1
1,2Fina Biosolutions, Rockville, MD; 3U Maryland School of Med, Baltimore; 4Brandeis U, Waltham, MA; 5Hennepin Healthcare Research Institute; 6Center for Immunology, U Minnesota

CRM197, a genetically detoxified diphtheria toxoid, is widely used as a carrier protein in conjugate vaccines. It was first expressed as a secreted protein in Corynebacterium diphtheria but, until recently, both “native” and recombinant CRM197 have been difficult to obtain and/or expensive. There is a need for a low-cost CRM197 to support vaccine development and to provide affordable conjugate vaccines for low-income countries. Fina BioSolutions has developed a new CRM197, EcoCRM®, expressed as a soluble protein in the cytoplasm of BL21, an E.coli expression strain widely used in bioproduction. High expression levels and a simple purification method allow low-cost production and the promise of significantly reducing the cost of this component of conjugate vaccines. In this study, we present immunological data demonstrating that EcoCRM® is an excellent carrier protein for a variety of antigens: (1) Immunization of mice with opioid-based hapten conjugated to EcoCRM® reduced oxycodone and heroin uptake to the brain as effectively as opioid conjugate vaccines containing KLH. (2) Mice immunized with a S. Typhimurium core O-PS conjugate were protected from wild type infection of the bacteria and (3) Conjugates of an HIV glycoprotein with EcoCRM® or recombinant CRM from Pseudomonas (PFlexen Reagent Proteins) induced similar antibody titers in rabbits. To support the clinical use of EcoCRM®, physiochemical characterization of the protein has been completed (Hickey et al. Analytical Comparability Assessments of Five Recombinant CRM197 Proteins from Different Manufacturers and Expression Systems. J Pharm Sci., 107:1806, 2018) and GMP manufacture is underway. As an affordable carrier protein, EcoCRM® can reduce the cost of goods for conjugate vaccines and promote the use of conjugate vaccines in low-income countries.

P49 Bacillus toyonensis spores improve the immune response to Clostridium perfringens recombinant epsilon toxin in sheep

Francisco Denis Souza Santos, Marcos Roberto Alves Ferreira, Lucas Reichert Maubrigades, Fabricio Rochedo Conceição, Felipe Maisiro Salvarami, Fábio Pereira Leivas Leite
Centro de Desenvolvimento Tecnológico, Núcleo de Biotecnologia, Universidade Federal de Pelotas 96160-900 Capão do Leão RS, Brazil; fabio@leivasleite.com.br

The use of probiotic supplementation in sheep is a safe alternative to improve animal health, productivity and immunity. However, its administration generally needs to be continuous. The objective of this study was to evaluate the effect of B. toyonensis as a probiotic supplement on the immune response to a recombinant vaccine containing Clostridium perfringens epsilon toxin (ETX) in sheep. Ewes were vaccinated with a 2 ml subcutaneous dose of a vaccine formulated with 200 µg of C. perfringens rETX adjuvanted with 10 µl alum hydroxide. A group of 8 ewes were supplemented orally with 30 ml of B. toyonensis spore suspension containing 3 x 105/ml for 5 days before the prime and boost vaccination. Another group of 8 ewes served as a control group and were vaccinated and given 30 ml of PBS instead of the probiotic supplement. The supplemented ewes had a significant (p<0.05) 4-fold increase in immunoglobulin levels after the prime vaccine and kept this ratio after the boost. This included a significant (p<0.05) increase in C. perfringens ETX neutralizing antibodies, which was 1.7 U/ml higher than the control group. Peripheral blood mononuclear cells from the supplemented sheep also had significant (p<0.05) higher levels of expression of BOB3 transcription factor, IL-2 and IFN-Υ cytokines. The results presented in this study show that supplementation of sheep with B. toyonensis over a short period (5 days) improved the efficacy of a C. perfringens rETX vaccine. This research highlights a novel alternative for improving vaccine efficacy in sheep management.

P50 Zika Subviral Particle Vaccines Induce Protective Immune Responses

Liyun Liu1, Maria T. Arévalo1,2, and Ted M. Ross1,2
1, 2Fina Biosolutions, Rockville, MD; 2U Maryland School of Med, Baltimore; 3PATH US, Seattle, WA 98121, United States, 4Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States, 5PATH US, Seattle, WA 98121, United States, 6Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States

Zika virus (ZIKV) is an arthropod-borne virus and although ZIKV infection is usually asymptomatic, it has been associated with more severe disease outcomes in humans in recent outbreaks, including Guillain-Barre syndrome in adults. In pregnancy, ZIKV infection has been linked with intrauterine growth retardation and fetal microcephaly. As a result, developing an effective ZIKV vaccine is an urgent need. In the current study, we developed a Zika subviral particle (SVP) vaccine to elicit immune responses and protection against ZIKV in mice. Zika SVPs were designed to form the prM-E region of SPH2015 (Asian lineage) and were expressed and purified from mammalian cells. Female BALB/c mice (6-8 weeks of age) were vaccinated intramuscularly with Zika SVPs (2.2mg E per mouse) formulated with Imject Alum on days 0, 28, and 56. Sera was collected 14 days after each dose, and evaluated for anti-ZIKV-specific antibody subclass es, as well as the ability to neutralize viral infection in vitro. Finally, mice were treated with anti-mouse IFNAR-1 (MAR1-5A3) antibody and challenged with ZIKV DAK AR 41671 strain (African lineage). Mice vaccinated with Zika SVPs had high anti-ZIKV IgG2a antibodies with lower IgG1 and then IgG3 responses. Sera from mice vaccinated with Zika SVP neutralized both homologous and heterologous ZIKV strains in vitro, with FRNT50 titers varying from 102 to 103. However, these mice were not protected against heterologous challenge with ZIKV strain DAK AR 41671. Therefore, we generated SVPs expressed from Zika DAK AR 41671 prM-E sequence to test if protection by Zika SVP vaccines was lineage-specific. Our ongoing studies show that sera from mice vaccinated with SPH2015 and DAK AR 41671 SVPs differentially neutralize a panel of Asian and African-lineage Zika viruses, and the protection against in vivo challenge viruses may be lineage-specific.

P51 Live-attenuated universal influenza virus vaccine candidates confer heterosubtypic immunity against influenza A viruses in a preclinical ferret model

Wen-Chun Liu1,2, Raphael Nachbagauer1, Daniel Stadlbauer1, Alicia Solorzano1,2, Francesco Berlanda-Scorzal3, Adolfo Garcia-Sastre1,2, Peter Palese1,4, Florian Kramer1, Randy A. Albrecht1,2,4
1Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States, 2Global Health and Emerging Pathogens Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States, 3PATH US, Seattle, WA 98121, United States, 4Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States

Due to continuous antigen drift or shift, influenza viruses may escape from human adaptation and immunity resulting in significant morbidity and mortality in humans. Therefore, to avoid the demand for annual reformulation/readministration of seasonal influenza vaccines, we are developing a novel chimeric hemagglutinin (cHA)-based universal influenza virus vaccine, which is comprised of a conserved stalk domain derived from a circulating pandemic H1N1 (pH1N1) Cal09 strain in combination with “exotic” head domains. Through prime-boost sequential immunization strategies, we redirected antibody responses toward the conserved stalk region. We compared the vaccine effectiveness elicited by distinct vaccination approaches in the preclinical ferret model of influenza. All cHA-based vaccinated ferrets developed stalk-reactive and broadly cross-reactive antibody responses. Two consecutive vaccinations with live-attenuated influenza viruses (LAIV-LAIV) conferred the superior protection against pH1N1 and H6N1 challenge infection in comparison to LAIV followed by split inactivated influenza virus (IVI) vaccine regimen, standard of care, or mock control groups. Importantly, the LAIV-LAIV immunization regimen also induced greater HA stalk-specific CD4+TGFβ- and CD8+TGFβ+ effector T cell responses in peripheral blood that were recalled by pH1N1 viral challenge. Sequential immunization with LAIV followed by IVI vaccine (LAIV-IVI regimen) also induced robust antibody responses. The findings from this preclinical study support inclusion of a LAIV-LAIV regimen in the design of universal vaccine would be beneficial to induce superior protective immunity against pan-groups influenza A and/or influenza B virus infection.
P52 Mycobacterium tuberculosis H37Rv encoded poly L-glutamine peptides acts as a potential Th1-type adjuvant
Rajesh Mani1,2, Manish Gupta1, Rajendra Prasad 3, Rakesh Bhatnagar 4, Nirupama Banerjee*1
1BSL-3, Molecular Biology and Genetic Engineering laboratory, School of Biotechnology, Jawaharlal Nehru University, New Delhi, India. 2 Amity University, Amity Education Valley, Gurgaon, Haryana, India. *Author contributed equally.

Objective: The immunomodulatory properties of Mtb cell wall (CW) components are well-known and classically highlighted by their use in Freund’s adjuvant. Here we aim to explore the adjuvant potential of poly-L-glutamine (PLG), a lesser-known component of Mtb CW, that are present in abundance, only in pathogenic mycobacteria.

Methods: Immunomodulatory properties of PLG were evaluated using Mtb ESAT-6 protein as vaccine candidate in C57BL/6J mice model. Different parameters of antigen specific immunity-humoral response, T cell development, recall memory etc., were monitored using ELISA and flow cytometry. The potency of PLG as adjuvant is compared with known Th1-immunity inducing adjuvant, dimethyl-dioctadecyl ammonium bromide-monoophosphoryl lipid A (DDA-MPL). Effect of PLG in modulating protective efficacy of ESAT-6 in the mice model is examined after challenge with Mtb, by recording clearance/reduction of bacillary load in the lung and spleen, and long-term survival of the host, in comparison to BCG.

Results: PLG adjuvanted triggered a strong humoral response against ESAT-6 antigen and resulted in significantly elevated levels of total IgG and its isotypes IgG1, IgG2-a and IgG2-b). The splenocytes from PLG vaccinated mice upon antigenic stimulation, displayed robust increase in Th1 specific IFN-γ, TNF-α, IL-2 and Th2 specific IL-4 and IL-10 cytokines. Additionally, PLG also activated Th17 response, leading to secretion of significantly high levels of IL-17 cytokine by the splenocytes. The PLG adjuvanted mice recorded 97.4 % and 92.43% reduction in bacterial counts in the lungs and spleens respectively, six weeks after Mtb challenge. The magnitude of reduction is statistically not different from BCG vaccinated mice. PLG as adjuvant appears better than DDA-MPL in enhancing protective efficacy of ESAT-6 (P < 0.05).

Conclusions: The strong Th1 and Th17 immune response generated by PLG makes it a promising adjuvant candidate for developing effective vaccines against Th1 response dependent diseases like Tuberculosis, Typhoid, Brucellosis, etc.

P53 Army Liposome Formulations, ALFA and ALFQ, Are Potent Adjuvants
Gary R. Matyas1, Sheelji Dutta1, Renee M. Laird2,3, Amritha Ramakrishnan1, Andrea J. McCoy4 and Zoltan Beck1,2
1 Walter Reed Army Institute of Research, United States, 2 Naval Medical Research Center, United States, 3 Henry M. Jackson Foundation for the Advancement of Military Medicine, United States, 4 Naval Medical Research Unit 6, Peru

Background: Army Liposome Formulations (ALF) are liposomes containing phospholipids and cholesterol (43 mol %) in which monophosphoryl lipid A is incorporated as the adjuvant. QS-21 is a saponin that has potent adjuvant activity, but when used alone, has considerable toxicity. Incorporation of QS-21 into ALF containing 55 mol % cholesterol to form ALFQ detoxifies the QS-21, while maintaining potent adjuvant activity. ALF and ALFQ, when used together with Aluminum hydroxide (AH), designated as ALFA or ALFQA, also are potent adjuvants. Current studies using mice with HIV antigens and non-human primates with malaria and Campylobacter jejuni were conducted.

Methods: ALF and ALFQ were prepared using rotary evaporation to remove lipid solvents, suspension of dried lipids in buffer, and microfluidization. Multiple antigens were formulated with ALFQ using ALFQA, also are potent adjuvants. Current studies using mice with HIV antigens and non-human primates with malaria and Campylobacter jejuni were conducted. ALFQ was developed using QS-21 from Tolypocladium inflatum to detoxify QS-21, while maintaining potent adjuvant activity.

Results: Immunization of mice with HIV antigens formulated with ALFQ produced predominantly a Th2 response, while ALFQ immunized animals had a mixed Th1-Th2 response. Immunization with CSP formulated with ALFQ protected mice from transgenic malaria challenge. Immunization of Rhesus macaques with FMP013-ALFQ induced high titer antibodies to both the NANP-repeat region and C-terminal repeat region of CSP. The highest antibody titers to CSP were induced with the ALFQ. The efficacy of C. jejuni challenge was 86% with the ALFQ compared to 29% with AH. No vaccine induced toxicities were observed.

Conclusion: The ALFQ adjuvants are potent adjuvants for vaccines against viral, bacterial and parasitic diseases.

P54 Archaeal Lipid Adjuvant Systems
Bassel Akache, Felicity C. Stark, Yimei Jia, Umar Iqbal, Renu Dudani, Lise Deschatelets, Blair Harrison, Vandana Chandan, Yimei Jia and Lakshmi Krishnan, Michael J. McCluskie
Human Health Therapeutics, National Research Council Canada; Ottawa, ON K1A 0R6, Canada

Archaeosomes are liposomes comprised of ether lipids derived from various archaea which, as adjuvants, can induce robust, long-lasting humoral and cell-mediated immune responses to entrapped antigens. Traditional total polar lipid (TPL) archaeosome formulations were relatively complex and semi-synthetic archaeosomes involved many synthetic steps to arrive at the final desired glycolipid composition. We have recently developed a novel archaeosome formulation comprising a sulfated saccharide group covalently linked to the free sn-1 hydroxyl backbone of an archaeal core lipid (sulfated S-lactosylarchaeol, SLA) that can be more readily synthesized yet retains strong immunostimulatory activity for induction of cell-mediated immunity following systemic immunization. Herein, we have evaluated the immunomodulatory effects of SLA archaeosomes when used as adjuvant with different types of antigen and compared this to commercially available adjuvants including TLR3/4 agonists, oil-in-water and water-in-oil emulsions and aluminum hydroxide. Overall, we have found that semi-synthetic sulfated glycolipid archaeosomes are a safe and effective novel class of adjuvants capable of inducing strong cell-mediated immune responses against a range of different antigens. A key step in their mechanism of action appears to be the recruitment of immune cells to the injection site and the subsequent trafficking of antigen to local draining lymph nodes.

P55 Designing Precision Cancer Immunotherapies with Streamlined and Accurate CD4 and CD8 T cell Neo-epitopes Analysis
Guilhem Richard1, Leonard Moise1,2, Matthew Ardisio1, Frances Terry1, William Martin1, Gad Berdugo2, Anne S. De Groot1,2
1EpiVax, Inc., Providence, Rhode Island, United States
2University of Rhode Island, Providence, Rhode Island, United States

Precision cancer immunotherapy targeting mutations expressed by cancer cells have proven to effectively control the tumor of patients in multiple clinical trials (Sahin et al., Nature 2017; Ott et al., Nature 2017). However, the selection of immunogenic T cell neo-epitopes remains challenging and many epitopes selected using traditional methodologies fail to induce effector T cell responses. Poor performance may partially be due to inclusion of mutated epitopes cross-conserved with self-epitopes recognized by regulatory (Treg), anergic, or deleted T cells. Vaccination with self-epitopes can lead to weak effector responses, active immune suppression, and toxicity due to immune-mediated adverse effects. In addition, most cancer vaccine studies focus on the selection of CD8 T cell neo-epitopes due to an apparent lack of robust and accurate CD4 T cell epitope prediction tools.

We have developed Ancer, an advanced cancer T cell epitope identification and characterization tool, that streamlines the selection of both CD4 and CD8 T cell neo-epitopes from Next Generation Sequencing data. Ancer leverages EpiMatrix and JanusMatrix, state-of-the-art predictive algorithms that have been extensively validated in prospective vaccine studies for infectious diseases (Moise et al., Hum. Vaccines ImmunoInmunothera 2015; Wada et al., Sci. Rep. 2017). Distinctive features of Ancer is its ability to accurately predict Class II HLA ligands, or CD4 epitopes, with EpiMatrix, and to identify tolerated or Treg epitopes with JanusMatrix. In addition, screening candidate sequences with JanusMatrix enables to the removal of neo-epitopes that may trigger off-target events, which have in some cases abruptly halted the development of promising cancer therapies.
The performance of Ancer was assessed by retrospectively analyzing multiple published datasets. First, we evaluated HLA-Class-I-bound peptides detected by mass spectrometry and published by Abelin et al., Immunity 2017. Our analysis showed that 95% of eluted peptides were correctly predicted by EpiMatrix to bind to their respective HLA, while only 88% of these sequences were accurately predicted by NetMHCPan. In addition, the majority of eluted peptides were specifically identified by EpiMatrix as strong HLA ligands.

Second, we performed a retrospective analysis of a cancer immunogenicity study published by Stranen et al., Science 2016 where HLA A2-restricted neo-epitopes were validated in T cell assays. Immunogenic sequences had significantly higher binding potentials, as estimated by EpiMatrix, compared to non-immunogenic sequences (p=0.0020). In contrast, no significant differences in predicted binding affinities were observed between these two subsets of sequences using public in silico prediction tools (p=0.0561). Lastly, Ancer divided immunogenic and non-immunogenic sequences from Stranen et al. with 72% accuracy outperforming the results obtained with public tools (21% accuracy) or with lengthy and costly in vitro characterization techniques (65% accuracy).

These results suggest that higher quality candidate targets are retrieved by Ancer, as compared to other conventional algorithms. CD4 and CD8 neo-epitopes with low Treg activation potential may then be used to support the development of safer and more effective personalized cancer vaccines. Future steps include the design of prospective studies to test the efficacy of Ancer-derived vaccines in the CT26 and GL261 murine cancer models.

A vaccine potentially effective for the reduction of severe diseases associated with the interdependent relationship between HIV and TB

André J Nahmias, MD, MPH, Emer Prof, Ped ID, Emory Univ., Atlanta, GA

To identify and prevent HIV and TB infections remains universally important, but the more recent increase in dual infections demand more concern for diagnostics and vaccine prevention studies.

**Diagnosis:** As regards improving identification of the two agents, the results already obtained with the direct ELISPOT method provide already a ~80% positivity, (and studies could be extended for better results). Studies included the early diagnosis of infants born to HIV+ mothers, and the diagnosis of TB in adults. The direct ELISPOT provides several advantages: a) it can detect the efficacy of the therapy used, as the original spots will decrease with time in case of effective treatments; and b) the indirect ELISPOT technique has already been used widely to detect TB with a gamma interferon assay.

**Immunology:** Of note are the immunologically parallel outcomes between (1) the inability of most children until the age of 2-4 years to stimulate lipopolysaccharides antigens e.g. of pneumococci or of TB and other mycobacterial antigens e.g. lipoprotein (LAM), and (2) HIV infected older children, and adults with CD4 cells less than 200, who will most often have lost their immune ability to stimulate LAM antibodies (such patients will also have positive blood cultures if several blood specimens are obtained). Our earlier studies of BCG performed in young children from birth-3 years in Chile, confirmed in children from Finland, and revealing the vaccine stimulation of LAM antibodies, different from those controls not vaccinated with BCG. As more data have been obtained more recently on the humoral system regarding mycobacteria, LAM has been demonstrated to be an important mycobacterial factor that is likely to be transmitted by blood, with the potential of producing blood disseminated disease. .
P58 (Continued)

Vaccine: Clearly, consideration of using BCG in the immunodeficient HIV patients would face safety concerns, in that the vaccine may produce severe diseases (BCGIOSIS). An alternative to BCG, however, is based on recent advances of important basic and practical studies. Some of the vaccines against microbial agents with polysaccharide antigens e.g. H.influenzae have been conjugated with proteins, thus providing very effective protection by an early age (~ 6 months). Fortunately, LAM conjugated vaccines against TB have already been developed by Swedish investigators 15 years ago. The LAM/protein vaccines, administered only in animals (guinea pigs and rabbits), were found to mimick several, if not most, beneficial BCG effects (B. Hams et al. Vaccinf 21(4081-93), 2003 'M.tuberculosis arabinomannan-protein conjugates protect against tuberculosis').

Conclusion: The current problems of dual infections with HIV and TB demand more rapid solutions with their growing impact on disease and mortality. The studies noted need to be extended - for the diagnostic (and prognostic) beneficial effects of the direct ELISPOT assay, and for the possibility to expedite clinical trials in humans with the LAM protein/conjugate vaccine, as several studies have already been performed in animals

P59 VaxArray v2.0: An example of the rapid adaptation of the VaxArray Influenza Seasonal HA Potency Assay to vaccine strain changes

Rose T Nash, PhD1, Jacob H Gillis1, Kathy L Rowlen, PhD1
InDevR Inc, 2100 Central Ave., Suite 106 Boulder, CO 80301, United States

In response to recent antigenic changes to the H3 and B-Victoria components in seasonal influenza vaccines, the VaxArray Influenza Seasonal Hemagglutinin Potency Assay (VXI-sHA) reagent kit was upgraded with new monoclonal antibodies (mAbs) to ensure detection of the newly recommended vaccine strains from the WHO. Within 2 months of the WHO consultation meeting in February 2018, antibodies were evaluated and downselected, and the new VXI-sHA v2.0 reagent kit was formulated, verified, and commercialized - for the diagnostic (and prognostic) beneficial effects of the direct ELISPOT assay, and for the possibility to expedite clinical trials in humans with the LAM protein/thiol conjugate vaccine, as several studies have already been performed in animals

P60 Effects of Primary and Secondary Flavivirus Exposure on Immune Responses and Antibody Dependent Enhancement in Zika-infected subjects

Muktha S Natrajan, Dmitri Kazmin, Vinit Karmali, Joanne Altieri-Rivera, Yongxian Xu, Lilin Lai, Nadine Rouphael, Mark J Mulligan

Background: Zika virus (ZIKV), an emerging flavivirus that led to a global epidemic in 2015, causes symptoms of fever and rash and has been associated with microcephaly, birth defects, and Guillain Barre syndrome. The purpose of this study is to understand the humoral immune response to ZIKV in order to develop better diagnostic and vaccine strategies, both of which have been complicated by several factors related to the immune response to the virus. Cross-reactivity among antibodies against flaviviruses (particularly ZIKV and dengue viruses (DENV)) has limited the utility of antibody (Ab) assays in diagnosis. There is also uncertainty about disease protective vs enhancing effects of cross-reactive antibodies in flavivirus-exposed subjects (secondary Zika) vs flavivirus naive subjects (primary Zika). In this study, we aimed to study cytokine responses, transcriptomic changes, antibody-dependent enhancement and serological profiling to determine the effects of cross-reactive responses from prior flavivirus immunity, e.g., DENV infection or yellow fever vaccination, on the immune response to Zika infection.

Methods: We collected sera from 13 subjects, 7 with secondary Zika infection and 6 with primary Zika infection (5 enrolled at acute and 8 enrolled at convalescent timepoints) and measured their ZIKV and DENV IgM and IgG binding Ab by ELISA as well as their neutralizing antibody (nAb) titers by focus reduction neutralization test across several timepoints. We also characterized their transcriptomic profiles by RNASequencing and serum cytokine profiles by 38-plex Luminex, and determined antibody dependent enhancement (ADE) in vitro.

Results & Conclusions: In primary vs secondary Zika, there are notable differences in cytokine and transcriptomic profiles after infection, with an increase in the anti-inflammatory cytokines IL4 and IL6 at acute timepoints in secondary cases as well as large increases in certain pro-inflammatory cytokines and innate cell chemokines in two pregnant secondary cases. Pro-inflammatory cytokines increase earlier after infection in primary cases compared to secondary, specifically IL-10, TNF-a, and IL17a. There was no difference in ZIKV or DENV IgM between primary vs secondary groups; this result was in contrast to the literature on secondary Dengue cases, where almost no IgM is produced on a secondary DENV infection. ZIKV vs DENV IgG responses differed significantly after Zika infection; secondary subjects had much higher ZIKV and DENV IgG binding antibodies from acute to convalescent phases of infection, while primary Zika subjects produced little to no DENV IgG antibodies and lower ZIKV IgG after infection. However, ZIKV nAb showed no difference between the two groups over time, suggesting a significant proportion of IgG produced in secondary infections is non-neutralizing. In acute stages (<30 days post onset of symptoms), ADE of ZIKV was not seen in sera from primary subjects but was significantly enhanced in secondary flavivirus subjects, potentially driven by production of the non-specific ZIKV and DENV binding antibodies in secondary flavivirus infections. The magnitude of antibody responses in secondary flavivirus infections appears to correlate well with ADE in vitro. Overall, prior exposure to highly homologous flaviviruses appears to affect not only the type of antibody response to ZIKV but also the early cytokine response.

P60 (Continued)
P61 Factors of the Bone Marrow Microniche that Support Human Plasma Cell Survival and Immunoglobulin Secretion
Emory University & Georgia Institute of Technology, Atlanta, GA; University of Wisconsin-Madison, Madison, WI; University of Toronto, Toronto, ON; University of Alabama at Birmingham, Birmingham, AL
(*Equally contributed)
Department of Global Health, Stellenbosch University, Stellenbosch, South Africa
3Department of Medicine, University of Cape Town - Cape Town, South Africa
1South African Cochrane Centre, South African Medical Research Council, Cape Town, South Africa

Objective: Persistent yellow fever endemicity and continued outbreaks have continued to increase vaccine demand, while straining global vaccine supply. Fractional dose vaccination is being considered as a dose-sparing strategy to mitigate current global vaccine shortages.

Methods: We registered this systematic review in the prospective register of systematic reviews; PROSPERO (Registration Number: CRD42018084214); published the protocol; conducted a comprehensive search of electronic databases and reference lists of relevant publications; and followed the guidance contained in the statement on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). We included studies comparing safety and immunogenicity between fractional and standard doses of the yellow fever vaccine. Included studies were appraised for risk of bias. We pooled dichotomous data using risk ratios (RR) with their corresponding 95% confidence intervals (CI). We assessed statistical heterogeneity using the Chi-square test of homogeneity (with significance defined at the 10% α-level), quantified it using the Higgins’ I² statistic and conducted subgroup analyses where appropriate. We analyzed data using Review Manager 5.3.

Results: & Discussion: We retrieved 2494 records from the literature search, 9 of them potentially eligible. Six studies (3 randomised controlled trials and 3 quasi-randomised controlled trials) met our inclusion criteria, with a total of 2371 participants. Immunogenicity (sero-conversion rates and antibody geometric mean titres) did not differ between participants who received fractional doses of 1/3rd, 1/5th and 1/10th of standard or undiluted yellow fever vaccine compared with those who received the standard (undiluted) doses of the reference vaccine (RR = 1.00, 95% CI: 0.99 – 1.01, n = 1334). There was no statistically significant difference in immunogenicity between fractional and standard doses across vaccine arms. We didn’t detect substantial heterogeneity between studies. However, there was statistically significant lower immunogenicity in fractional doses lower than 1/10th (1/50th, 1/100th, 1/1000th and <1/1000th) of the standard dose, compared with the reference standard dose vaccine (RR = 0.85, 95% CI: 0.79 – 0.92, n = 1921). In terms of safety, no serious adverse events following vaccination was reported in all vaccine arms. The combined data provide moderate certainty evidence that there is non-inferiority in immunogenicity and safety between 1/3 – 1/10th fractional doses and standard doses of the yellow fever vaccine.

Conclusion and Implications for practice: These findings support the use of fractional-dose yellow fever vaccination as a dose-sparing strategy to mitigate current global vaccine shortages.

P62 Extracellular Vesicles from Bone Marrow-Derived Mesenchymal Stromal Cells Support Ex Vivo Survival of Human Antibody Secreting Cells
Emory University & Georgia Institute of Technology, Atlanta, GA; University of Wisconsin-Madison, Madison, WI
(*Equally contributed)
Division of Pulmonary Allergy, Critical Care, & Sleep Medicine, Emory University, Atlanta, GA, USA
2Departments of Pediatrics and Hematology & Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA
3International Center for Malaria Research, Education and Development, Emory Vaccine Center, Yerkes National Primate Research Center, Emory University, Atlanta, GA, USA
4School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA, USA
5Emory Vaccine Center and Department of Urology, Emory University, Atlanta, GA, USA
6Department of Medicine and University of Wisconsin Carbone Cancer Center, University of Wisconsin in Madison, Madison, WI, USA

Extraglomerular vesicles from bone marrow-derived mesenchymal stromal cells (MSC) are novel mechanisms of cell-cell communication over short and long distances. MSC have been shown to support human antibody secreting cells (ASC) survival ex vivo, but whether crosstalk between MSC-ASC occurs via EVs is not known. We evaluated the role of EVs in ASC survival and IgG secretion. EVs were isolated from irradiated and non-irradiated primary MSC and were quantified. They were further characterized by electron microscopy (EM) and CD63 and CD81 immuno-gold EM staining. Human ASC were isolated via FACS and cultured ex vivo with EV fractions, EV-reduced fractions, or conventional medium. IgG Elispots were used to measure survival and functionality of ASC. Contents of EV fractions were evaluated by proteomics. We saw that both irradiated and non-irradiated MSC secretome preparations afforded vesicles of a size consistent with EVs. Both preparations appeared comparable in EM morphology and CD63 and CD81 immuno-gold EM. Both irradiated and non-irradiated EV fractions supported ASC function, at 88% and 90%, respectively, by day 3. In contrast, conventional media maintained only 4% ASC survival by day 3. To identify the specific factors that provided in vitro ASC support, we compared proteomes of irradiated and non-irradiated EV fractions with conventional media. Pathway analysis of these proteins identified factors involved in the vesicle-mediated delivery of integrin signaling proteins. These findings indicate that MSC EVs provide an effective support system for ASC survival and IgG secretion.

P63 A Systematic Review and Meta-analyses of the Safety and Immunogenicity of Fractional Doses of the Yellow Fever Vaccine: Mitigating Global Vaccine Shortages
C. Nnaji 1,2, M. Shey 2, O. Adetokunboh 1,4, C. Wiysonge 1,2,4
1South African Cochrane Centre, South African Medical Research Council, Cape Town, South Africa
2School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa
3Department of Medicine, University of Cape Town - Cape Town, South Africa
4Department of Global Health, Stellenbosch University, Stellenbosch, South Africa

Background: Persistent yellow fever endemicity and continued outbreaks have continued to increase vaccine demand, while straining global vaccine supply. Fractional dose vaccination is being considered as a dose-sparing strategy to mitigate current global vaccine shortages.

Objectives: To assess and compare safety and immunogenicity between fractional and standard doses of the yellow fever vaccine.

Methods: We conducted a comprehensive search of electronic databases and reference lists of relevant publications; and followed the guidance contained in the statement on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). We included studies comparing safety and immunogenicity between fractional and standard doses of the yellow fever vaccine. Included studies were appraised for risk of bias. We pooled dichotomous data using risk ratios (RR) with their corresponding 95% confidence intervals (CI). We assessed statistical heterogeneity using the Chi-square test of homogeneity (with significance defined at the 10% α-level), quantified it using the Higgins’ I² statistic and conducted subgroup analyses where appropriate. We analyzed data using Review Manager 5.3.

Results & Discussion: We retrieved 2494 records from the literature search, 9 of them potentially eligible. Six studies (3 randomised controlled trials and 3 quasi-randomised controlled trials) met our inclusion criteria, with a total of 2371 participants. Immunogenicity (sero-conversion rates and antibody geometric mean titres) did not differ between participants who received fractional doses of 1/3rd, 1/5th and 1/10th of standard or undiluted yellow fever vaccine compared with those who received the standard (undiluted) doses of the reference vaccine (RR = 1.00, 95% CI: 0.99 – 1.01, n = 1334). There was no statistically significant difference in immunogenicity between fractional and standard doses across vaccine arms. We didn’t detect substantial heterogeneity between studies. However, there was statistically significant lower immunogenicity in fractional doses lower than 1/10th (1/50th, 1/100th, 1/1000th and <1/1000th) of the standard dose, compared with the reference standard dose vaccine (RR = 0.85, 95% CI: 0.79 – 0.92, n = 1921). In terms of safety, no serious adverse events following vaccination was reported in all vaccine arms. The combined data provide moderate certainty evidence that there is non-inferiority in immunogenicity and safety between 1/3 – 1/10th fractional doses and standard doses of the yellow fever vaccine.

Conclusion and Implications for practice: These findings support the use of fractional-dose yellow fever vaccination as a dose-sparing strategy to mitigate current global vaccine shortages.
The neglected tropical disease Leishmaniasis continues to pose a significant public health concern despite major efforts both in therapeutic development and vector control. Consequently, vaccination remains the most promising strategy to treat or eliminate this disease, yet to date, attempts to develop a vaccine have proven unsuccessful. Glycoconjugate vaccines represent a new strategy that expands the list of available target antigens to include carbohydrate moieties that oftentimes dominate host-pathogen interactions. In the case of the Leishmania spp. glycoalyx, lipophosphoglycan (LPG) represents an ideal target given its high accessibility and unique structure. In this study, a series of synthesized antigens consisting of variations on the LPG cap saccharide (Gal β1-4Man, Man α1-2Man, Man α1-2Man) were screened for antigenicity to determine the functionally relevant structural features of LPG that could provide protection upon a challenge infection. First, bacteriophage-derived Q β VLPs were functionalized with an azide-containing linker that then underwent copper-catalyzed alkynyl-azole cycloaddition with the various alkyne-modified glycans. These polyvalent glycoconjugates were administered in BALB/c mice and the total IgG response in serum was measured by ELISA. Initial results indicated a low anti-glycan response, although it was seen that the Gal β1-4Man antigen produced a greater IgG response than the pure mannoscontaining antigens. Ongoing studies are investigating the incorporation of a ceramide-based NKT cell adjuvant to boost titers and antibody affinities. If successful, these constructs could provide evidence that glycoconjugate vaccines displaying functionally relevant portions of LPG may be considered as vaccine candidates.

Zika virus (ZIKV) is a member of the Flaviviridae viral family, transmitted by mosquitoes between human hosts. Originally discovered in 1947, it has recently garnered attention as a pathogen of great importance after an epidemic in 2015. The virus swiftly spread through South America and the Caribbean, and was implicated as the causative agent of microcephaly in newborns in these regions. This concerning pathogenic effect has since been demonstrated extensively and has verified as an effect of viral replication within a pregnant female host. While humans are generally accepted as the major reservoir for the virus, it remains unknown if farm animals might serve as an underappreciated reservoir for the virus. Knowledge of how ZIKV infects animal models other than mice would also be a crucial tool in developing therapeutics for the disease. In order to investigate what animal model might serve best, bone marrow-derived mesenchymal stem cells (BM-MSCs) were obtained from ovine, equine, porcine, and bovine donors. These were infected with two strains of ZIKV: Nigeria/1968 and Puerto Rico/2015 at MOIs of 0.1 and 1. Cell culture supernatants were collected at multiple timepoints over a 120 hour course of infection and assayed for virus by TCID₅₀. These experiments showed ovine, bovine, equine and porcine BM-MSCs to be permissive hosts to ZIKV of the pandemic lineage, Puerto Rico/2015, with the highest titers being found in ovine cell cultures. These results were similar between the two viral strains used, and across three biological replicates. Based upon these findings, an ovine model of ZIKV infection and pathogenesis can be used to study the virus outside of the mouse model, and in a model of pregnancy that more closely corresponds to human pregnancy.

Using a methodology termed computationally optimized broadly reactive antigen (COBRA), novel hemagglutinin (HA) proteins were derived using HA sequences from H5N1 isolated viruses. Two candidates were developed from HA sequences from derived from H5N1 viruses isolated in 2005-2007 from human infection (Human COBRA-2) and one derived from human and avian infections (Human-Avian COBRA-2). Approximately 99% of the amino acids are identical between the Human-COBRA 2 HA and the Human-Avian COBRA 2 HA antigens. Four amino acids differed in the HA globular head (sites 140-141 and sites 155-156). Each of these HA proteins were expressed on the surface of a virus-like particle (VLP) and used to vaccinate mice and chickens. When challenged with an H5N1 isolate from a future drifted clade 2.3.2.1B A/Duck/Vietnam/N1CVD/672/2011 (VN11) virus, animal vaccinated with the Human-COBRA 2 HA VLP vaccine protected morbidity and mortality, whereas the Human-Avian COBRA-2 was less effective. Animals vaccinated with a VLP expressing a wild-type HA isolated from A/Whopper swan/Mongolia/244/2005 (WS05) did not protect any of the animals against heterologous challenge. In order to determine which amino acids are critical for these phenotypes, site directed mutagenesis was performed in order to exchange 4 amino acids between the two HA antigens in a VLP vaccine. BALB/c mice (n=120) were vaccinated with VLP vaccines expressing one of these COBRA or wild-type HA antigens to determine the ability to elicit antibodies with distinct HAI profiles and protect against H5N1 influenza virus challenge. VLP vaccines that contained the Human-COBRA 2 HA amino acid sequence asparagine and threonine, which results in an N-glycosylation motif at site 155-156, elicited a broader protection against viruses than vaccines that did not contain this site. The combination of an N-linked glycan and a serine at amino acid position 141, significantly enhanced antibody binding and neutralization of the H5N1 viruses: WS/05, A/Hubei/1/2010, A/Egypt/N0307/2010, A/Egypt/321/2007, A/Cambodia/X0810300/2013 and A/Chicken/Egypt/CAL3-RLOP/2017. The p-epitope value predicted that these mutated HA antigens would elicit a broader neutralization profile than the original HA proteins. We hypothesize that the glycosylation of the antigenic site located near the receptor binding domain hinders the elicitation of neutralizing antibodies and therefore redirects the immune dominant epitope that elicits neutralizing antibodies to the immune response to a site located on the HA globular head that is more likely to neutralize viral infection.

Current live attenuated and inactivated influenza vaccines based on immunity to the hemagglutinin (HA) hypervariable protein are effective when vaccine strains and circulating viruses are well matched. However, HA-based current vaccines are ineffective in providing cross protection against antigenically distinct drift and new pandemic viruses. Universal influenza virus vaccines based on the highly conserved antigenic targets such as the extracellular domain of M2 (M2e) confer cross protection but are not sufficient to serve as a standalone vaccine due to low efficacy of protection via non-neutralizing immune mechanisms. As a new approach to improve the efficacy of HA-based current vaccines by inducing both HA and cross protective M2e immunity, we generated recombinant influenza virus vaccines platform, which express chimeric H3 (A/Scotland/2013/62) HA-M2e conjugate proteins in the N-terminus (HA-4xM2e). The backbone of recombinant influenza virus was derived from A/Puerto Rico/8/34 H1N1 (A/PR8) virus with high growth property in egg substrates. The reassortants H3N2 chimeric viruses (HA and NA from A/Puerto Rico/8/34 (H1N1) and A/Scotland/2013/62 with NA from A/PR8, respectively) were found to be highly attenuated in mice, as shown by restricted replication in the upper respiratory (nose) but not in the lower respiratory tract lung tissues of the mice. In addition, chimeric H3 HA-4x-M2e did not cause weight loss in mice even after inoculation with 100 to 1000 folds higher doses than the control wild type A/PR8 virus causing severe weight loss. Recombinant H3N2 virus containing chimeric H3 HA-4xM2e was found to be effective in inducing cross protective M2e specific IgG antibody responses as well as HA immunity in mice. Mice that intranasally inoculated with chimeric H3-A/PR8 protected against both antigenically different viruses after one or two doses. The results in this study support a novel approach to improve the efficacy of current influenza vaccine platforms by recombinant influenza virus vaccines inducing immunity to both HA and cross protective M2e antigens.
P68 Influenza virus like particle vaccines containing multiple antigenic proteins of Toxoplasma gondii
Su-Hwa Lee1, Ha-Ji Kang2, Dong-Hun Lee1, Ki-Bac Chu1, Fu-Shi Quan2,3
1Department of Biomedical Engineering, School of Engineering, Kyung Hee University, Seoul, Korea; 2Department of Medical Zoology, Kyung Hee University School of Medicine, Seoul, Korea; 3Biomedical Science Institute, Kyung Hee University

Influenza virus-like particle (VLP) as a highly efficient vaccine has been used vaccine delivery platform to present single or multiple antigenic proteins. In this study, we generated VLPs (multi-antigen VLPs, TG146) by infecting three baculoviruses expressing IMC, ROP18, or MIC8 of Toxoplasma gondii and influenza matrix protein 1 (M1) as a core protein. We also generated three VLPs expressing IMC, ROP18, or MIC8 together with M1 for combination VLPs (TG1/TG4/TG6). A total of four kinds of VLPs generated were characterized by TEM. Higher number of VLPs particles per μm2 were observed in multi-antigen VLPs compared to combination VLPs. Mice (BALB/c) were intranasally (IN) immunized with multi-antigen VLPs or combination VLPs and challenged with T. gondii tachyzoites (GT1) intraperitoneally (iP). Compared to combination VLPs, multi-antigen VLPs showed significantly higher levels of CD4+ T cell and germinal center B cell responses with reduced apoptosis responses, resulting in significant reduction on parasite burden. These results indicate that higher efficacy of VLPs generated by multi-antigen VLPs can induce better protection than that by combination VLPs, providing important insights into vaccine design strategy for VLP vaccine expressing multiple antigenic proteins.

P69 A therapeutic vaccine strategy to prevent Pneumocystis pneumonia in immunocompromised non-human primate model of HIV/AIDS
Whitney Rabacal, Finja Schweitzer, Heather Kling, Rebecca Tarantelli and Karen Norris

It has long been the goal in this field to develop an effective vaccine for the prevention of the opportunistic infection, Pneumocystis pneumonia (PCP) and Pneumocystis-related pulmonary sequelae in HIV infected individuals and other immunocompromised populations. To achieve these goals, our laboratory has established non-human primate models of PCP in simian immunodeficiency virus (SIV)-infected non-human primates (NHP). We have identified a recombinant protein sub-unit vaccine, KE1X, that induces robust anti-Pc immunity in immune-competent macaques that is durable and prevents Pc pneumonia following simian immunodeficiency virus (SIV)-induced immunosuppression and Pc challenge (Kling and Norris, 2016). In clinical studies, we have shown that immunity to KE1X is reduced in NHPs with decreased risk of PCP in SIV-infected individuals (Gingo et al., 2011). In the present study, we used the SIV model of HIV infection to addressed whether therapeutic vaccination with KE1X can be effective following virus-induced immunosuppression. To compensate for immune deficits of HIV infection, development of effective vaccines for immunocompromised populations requires innovative vaccination strategies and/or novel adjuvants. Type I, or invariant natural killer T (iNKT) cells are a subpopulation of lymphocytes bearing the invariant T cell receptor chain (Vα24-Jα18, in humans) that recognize glycolipids presented by the non-classical MHC class I b molecule CD1d. When activated, iNKT cells are capable of rapidly expressing a wide array of cytokines and co-stimulatory molecules that can enhance humoral response. The central hypothesis is that effective immunity to KE1X can be elicited in the context of HIV-induced immune dysregulation and that alternative, CD4-independent vaccination strategies can induce invariant natural killer (iNKT) cell-B cell help for enhance immunity to Pneumocystis.

We have tested the effectiveness of the KE1X vaccine as a therapeutic immunologic booster in immunocompromised, SIV-infected rhesus macaques. SIV-infected macaques were vaccinated and boosted once with KE1X adventured with the INKT-ligand α-galactocerebroside (α-GC). Vaccination with KE1X+α-GC induced a robust increase in KE1X-specific antibody titers that occurred even in SIV-infected animals with circulating CD4+ T cells <500/μl. KE1X+α-GC vaccinated macaques were protected from PCP compared with mock α-GC immunized animals (P=0.0471). These data support the concepts that 1) INKT-mediated alternatives to CD4 T cell help can induce effective humoral immunity in immunocompromised hosts and that 2)humoral immunity to Pneumocystis during HIV-induced immunosuppression may be effectively augmented via INKT-related vaccination strategies.

P70 Live-attenuated virus vaccine provides complete protection against antigenically distinct H3N2 influenza A viruses
Daniela S. Rajaio1,2, Jefferson Santos2, Bryan S. Kaplan1, Tracy L. Nicholson3, Susan L. Brockmeier1, Phillip C. Gauger3, Daniel R. Perez2, Amy L. Vincent1, Eugenio J. Abente1
1Virus and Prion Diseases of Livestock Research Unit, National Animal Disease Center, Agricultural Research Service, USDA, Ames, Iowa, United States of America; 2Department of Population Health, Poultry Diagnostic and Research Center, College of Veterinary Medicine, University of Georgia, Athens, Georgia, United States of America; 3Department of Veterinary Diagnostic and Production Animal Medicine, College of Veterinary Medicine, Iowa State University, Ames, Iowa, United States of America

Influenza A virus in swine (IAV-S) circulating in the United States are phylogenetically and antigenically distinct. A human H3 hemagglutinin (HA) was introduced in the IAV-S gene pool in the late 1990s, sustained continued circulation, and evolved into five monophyletic genetic clades after 2009, H3 IVA-E. Among these phylogenetic clades, distinct antigenic clusters were identified, with three clusters (cyan, red and green) among the most frequently detected antigenic phenotypes. Although it was demonstrated that antigenic diversity of H3N2 IAV-S was associated with changes at a few amino acid positions in the head of the HA, the implications of this diversity on vaccine efficacy was not tested. Using antigenically representative H3N2 viruses, we compared whole inactivated virus (WIV) and live attenuated influenza virus (LAIV) vaccines for protection against challenge with antigenically distinct H3N2 viruses in pigs. WIV provided partial protection against antigenically distinct viruses, but did not prevent virus replication in the upper respiratory tract. In contrast, LAIV provided complete protection from disease and virus was not detected after challenge with antigenically distinct viruses.

P71 Developing a DNA Vaccine for Canine Distemper Virus
Sophia Reeder, Emma Reuschel, Kevin Kim, La'Toya Latney, Tim Georoff, David Weiner

Canine Distemper is a viral disease caused by Canine Distemper Virus (CDV), a single stranded RNA virus of the family Paramyxoviridae which is highly contagious by inhalation or by contact with infected bodily fluids. Canine distemper affects many animal families, including Canidae, Mustelidae, Ailuridae, Ursidae, and large Felidae with high morbidity, affecting multiple body systems, including the lymphoid, epithelial, and nervous tissues. Symptoms include lymphoid depletion (causing immunosuppression and leading to secondary infections), interstitial pneumonia, encephalitis with demyelination, and hyperkeratosis of the nose and foot pads. CDV presents a major threat to endangered animal populations. There have been several documented instances of free-ranging large fells succumbing to the disease, often in large numbers, after exposure to an animal with uncontrolled infection. In the context of conservation and zoos, there is a persistent concern regarding endangered animals contracting CDV infection from interloping wild dogs, raccoons, and foxes. “Exotic” animals such as large fells and mustelids are extremely susceptible to CDV infection, so much so that it is dangerous for them to receive the modified-live vaccine that is commercially available for domestic dogs. In lieu of the MLV, exotic animals in zoos often receive a canarypox vectored vaccine Puravax, which was designed for domestic ferrets. However, data has shown that large fells and red pandas often require 3 or more vaccinations with Puravax before seroconversion and this is a limited vaccine. Development of a non live more robust vaccine would be important for protection of potentially many species. The goal of this project is to develop an optimized DNA vaccine to provide protection against CDV through induction of an antibody response as well as cell mediated immunity. Constructs were developed for H, F and N antigens and in vitro expression was demonstrated. Animals were immunized with the constructs, separately and in combination and studied for immune induction. Serum was collected after each and tissues were immunized for histological analysis one week after the final immunization. ELISPOTs and flow cytometry were used to assess the cell mediated immunity elicited by vaccination with anti-CDV constructs. Microscopy and ELISAs were used to assess antibodies elicited against the H, F, and N constructs. We show that a novel synthetic DNA CDV vaccine elicits both a humoral and a cell-mediated immune responses against multiple CDV antigens. We observe that one or two immunizations elicit anti CDV immunity. Functional immune responses will be described. Overall, our data suggests that a DNA vaccine against Canine Distemper Virus is important for further study to provide a new alternative safe and potent vaccine to protect against Canine Distemper in high risk populations in zoo and conservation settings, as well as possibly in domestic dogs.
Influenza is a common disease that affects millions of people each year. Waterfowl and swine serve as the primary reservoirs for influenza virus that could cause a potential pandemic in humans. While there are several strains of influenza viruses currently circulating in animal reservoirs, viruses of the H2 subtype are of particular concern. The 1957 “Asian Flu” pandemic was caused by viruses in the H2N2 subtype, which circulated among humans in the late 1950s until 1968 when it was replaced with viruses of the H3N2 subtype. Today, more than half the human population was born after the last H2N2 virus circulated in people and therefore, could be susceptible to infection caused by viruses of the H2 subtype, if they began circulating in the human population again. In this study, sera were collected from people between the ages of 12 and 85 years of age and tested for hemagglutination-inhibition (HAI) antibodies titers against a set of H2 influenza viruses that circulated in humans as well as viruses collected between 1968-2016 from birds and different mammalian species. People under the age of 51 had no HAI titers against any of the 16 H2 viruses in the panel. The vast majority of people over the age of 57 had HAI titers to the 1957 H2N2 vaccine strain, as well as several more modern H2 viral isolates. However, no one under the age of 50 had any HAI activity to any of the 16 H2 influenza viruses in our panel. This lack of pre-existing immunity to H2 influenza viruses in the younger population demonstrates the need for a broadly reactive H2 vaccine. To address this need, computationally optimized broadly reactive antigen (COBRA) vaccines were designed and tested in mice to determine their breath of immune reactivity. Mice were vaccinated with virus-like particles (VLPs) expressing either COBRA or wild-type H2 HA antigens. These mice were subsequently boosted at day 21 and day 42 and were bled at day 64 post-vaccination (two weeks after the final boost). Mice vaccinated with COBRA HA VLP vaccines elicited antibodies with more broadly reactive HAI activity than the mice that were vaccinated with any of the 16 wild-type HA VLP vaccines. The lack of pre-existing immunity in the human population demonstrates the need to stockpile a broadly-reactive vaccine in preparation for a global H2 influenza virus pandemic. COBRA mouse vaccination results demonstrate the effectiveness of COBRA vaccines and their potential use as a pre-pandemic stockpile vaccine.

Norovirus causes acute and debilitating gastroenteritis, characterized by vomiting and diarrhea. We recently reported a recombinant GII.4 P domain particle (Pd) vaccine adjuvanted with a flagellin, Vibrio vulnificus FlaB, effectively promoting both humoral and cellular-mediated immune responses. In the previous study, we found that sublingual (SL) immunization induced higher fecal secretory IgA (sIgA) responses while intranasal (IN) route provided higher amplitude of humoral and cellular immune responses in the systemic compartment. We hypothesized that the combination of IN and SL routes should induce more potent and sustained sIgA responses in the gut. In this study, we tried combinatorial prime-boost immunization employing both IN and SL routes. The IN priming and SL boosting with the Pd+FlaB vaccine enhanced highest sIgA responses in feces, encompassing increased Pd-specific memory B cells and plasma cells in spleen and bone marrow, respectively. Notably, the strongest long-lasting secretory IgA response in feces was induced by combined IN prime and SL boost vaccination, which was sustained for more than 3 months. Significantly enhanced gut-homing B cell and follicular helper T cell responses in mesenteric lymph nodes (mLNs) were observed in the IN prime and SL boost combination. IN priming was a requisite for the robust induction of Pd-specific IFNγ, IL-2, IL-4 and IL-5 cytokine responses in the systemic immune compartment. Collectively, the IN prime and SL boost combination was the best option for inducing balanced long-lasting immune responses against the norovirus antigen in both enteric and systemic compartments. These results suggest that immune responses in specific mucosal compartments may be programmed by employing different prime-boost immunization routes.

Flagellin-based recombinant divalent vaccine inhibits periodontitis induced by Fusobacterium nucleatum and Porphyromonas gingivalis mixed infection in a mouse system

Flagellin, a virulence factor produced by many pathogenic bacteria, has the dual role of a TLR5 agonist and a radioprotective adjuvant for radiation therapy. We recently reported that flagellin-based combinatorial vaccines could elicit protective immune responses in mouse models of periodontitis, cervical cancer and glioblastoma multiforme. In the present study, we evaluated the dual effect of flagellin on bacterial infection and tumor development in murine models of periodontitis and cervical cancer. We found that flagellin-based combination vaccines significantly reduced periodontal disease and tumor growth. Surprisingly, the combination therapy of flagellin-adjuvanted F. nucleatum and P. gingivalis infection resulted in tumor suppression indicating flagellin is a potent vaginal adjuvant for a therapeutic peptide cancer vaccine. In this regard, we examined whether flagellin can be used as an adjuvant performing dual role of radioprotection and immunomodulation in an RT/IT combinatorial cervical cancer therapeutic model. When the tumor-bearing mice (5–8 mm in mean diameter) were locally received 20 Gy single dose irradiation, tumor growth was significantly reduced. Additional administration of flagellin-adjuvanted peptide vaccine showed inhibitory effect on tumor growth. Surprisingly, the combination therapy of flagellin-adjuvanted cancer vaccine and radiotherapy induced eradication of tumor mass and long-term memory protection against the re-challenge of the same tumor. These results suggest that flagellin is a promising radioprotective adjuvant for RT/IT combination therapeutic modalities against intractable cancers.
P76 M2e-specific monoclonal antibodies bind to and protect against infection with diverse influenza A viruses
Sydney Ronzulli,1 Lynn Blimler,1,2,3 Amber Song,1,2 Bailee Kain,1,2 Duy Tri Le,1,2,4 Jansen Smith,1,2
Kevin Aviles-Padilla,3,4 Rana Nikzad,3,4 Laura Angelo,3,4 Cheryl Jones,1 S. Mark Tompkins,1 and Silke Paust2,3,4,5,6,7
1Center for Vaccines and Immunology, University of Georgia, 2Graduate Program in Immunology, Baylor College of Medicine, 3Department of Pediatrics, Center for Human Immunobiology, Baylor College of Medicine and Texas Children's Hospital, 4Developing Investigative Scholar's Program (DISP), Rice University, 5Dan L Duncan Cancer Center, Department of Pediatrics, Texas Children's Hospital, 6Department of Molecular Virology and Microbiology, Baylor College of Medicine, 7The Scripps Research Institute, Department of Immunology and Microbiology, La Jolla, CA

Influenza A virus (IAV), an acute illness of global importance, appears virtually every year in which it causes contagious respiratory illness and significant morbidity and mortality. Disease incidence is high annually because neither vaccination nor infection elicits durable, protective immunity, as the hemagglutinin (HA) and neuraminidase (NA) antigens, proteins on the surface of virion and immunodominant targets, undergo antigenic shift and drift, resulting in strains that evade protective antibody responses. Also found on the extracellular surface of the influenza virion is the matrix protein 2 (M2) proton channel, which has a 23-amino acid ectodomain (M2e) and can be a non-neutralizing antibody target. While only having about 30-60 copies per virion, the M2 protein is 98% conserved across influenza A subtypes, has a low mutation rate, and is essential for viral entry and replication, making the M2 ion channel an ideal antigenic target for a universal therapeutic. However, while humans generate robust immune responses to the HA and NA proteins, less than 20% of infected individuals generate M2e-specific antibodies in response to influenza A infection. As antibodies can mediate a variety of complementary effector functions that contribute to host protection, we hypothesize that a M2e-specific MAb individually or in combination will bind to M2 on IAV and/or virus-infected cells and reduce infection and disease through multiple mechanisms including elicitation of ADCC, phagocytosis and complement activation.

Moreover, as M2e-specific MAbs will bind to a broad spectrum of IAVs independent of subtype and species of origin. To test these hypotheses, a panel of M2e-specific murine MAbs were generated in collaboration with the Baylor College of Medicine Hybridoma Core and assayed for breadth of reactivity and efficacy in a murine model of IAV infection. Using a panel of human, avian and swine IAVs with distinct M2e sequences, we show these MAbs bind to all the viruses tested. In mouse challenge studies, we show that a single treatment of MAb can protect against lethal IAV infection, including H5N1 highly pathogenic avian influenza challenge. Ongoing studies focus on mapping the precise epitopes of each M2e-specific MAb as well as determining mechanism(s) of action for reduction in virus titer and protection from disease.

P77 Impact of respiratory dysbiosis on influenza virus infection in the ferret model
Dawne K. Rowe1, Iliassou Hamidou Soumana2, Christopher A. Darby2, Scott K. Johnson1, Cheryl A. Jones1, Anne-Gaelle Bebin-Blackwell1, Jasmina M. Luczo1, Eric T. Harvill2, Ted M. Ross1,2, and S. Mark Tompkins1,2
1Center for Vaccines and Immunology, College of Veterinary Medicine, University of Georgia, Athens, GA 30602; 2Department of Infectious Diseases, College of Veterinary Medicine, University of Georgia, Athens, GA 30602

The healthy microbiota is comprised of commensal bacteria and any microorganism present on surface of exposed tissues, including the integumentary system, respiratory, reproductive, and gastrointestinal tracts. This microbial population, also referred to as the microbiome, develops with the host and may have broad effects on the immune response, playing an important role in both health and disease. Disruption of the microbiota, or dysbiosis, through antibiotic use, infection, or disease may affect susceptibility to and outcomes developing from other infections, including influenza virus. Here, we utilized the ferret model to probe the effects of respiratory microbiome disruption and bacterial infection on influenza virus disease. Preliminary studies were conducted to characterize the respiratory microbiome in healthy, antibiotic-treated and Streptococcus pneumoniae colonized ferrets, and assess the impact of these modifications on IAV infection and shedding. These represent models of intact, reduced (antibiotic-treated), and perturbed (pathogen-infected) microbiomes in animals, establishing them as models for disease and transmission studies. While antibiotic treatment alone did not affect IAV infection, prior infection with nonpathogenic levels of Streptococcus pneumoniae was significantly enhanced following IAV infection, leading to secondary effects and worsening of clinical disease.

P78 Infection-induced heterosubtypic immunity against influenza virus correlates better with humoral than cellular immunity in TIV-vaccinated mice
Angela Choi1, Lorena Itati Ibáñez2, Jan Spithals1, Florian Krammer1, Adolfo Garcia-Sastre1,2,3, Michael Scholsaert1
1Department of Microbiology, Global Health and Emerging Pathogens Institute, 2Department of Medicine, 3Icahn School of Medicine at Mount Sinai New York, New York, USA
Centro de Virología Animal (CEVAN), Instituto de Ciencia y Tecnología Dr. César Milstein, CONICET, Ciudad de Buenos Aires, Argentina

Conventional influenza vaccines aim at the induction of virus-neutralizing antibodies. However, influenza vaccine efficiencies are often low. We investigated to what extent infection-permissive immunity provided by a seasonal trivalent inactivated influenza virus vaccine (TIV) could modulate disease and virus-induced host responses after infection with H1N1 virus that matches the vaccine. More than one TIV vaccination is needed to induce high serum H1 titers efficiently in mice. Contrary to negative control mice, complete loss of alveolar macrophages, as well as presence of Ly6c+ monocytes and release of pro-inflammatory cytokines and chemokines was prevented in TIV-vaccinated animals. We also show that induction of germinal center B cells and tissue-resident CD8+ T cells in the lung after H1N1 infection correlates with protection during reinfection with a lethal dose of a H3N2 virus but is negatively impacted by TIV vaccination. On the other hand, sera from TIV vaccinated animals that received H1N1 infection outperform sera from animals that either received H1N1 infection or a TIV vaccine, but not both, in an in vivo microneutralisation assay with H3N2 virus. Cross-protective sera were not able to inhibit red blood cell hemagglutination by H3N2 virus. These results suggest that, contrary to H1N1 virus-exposed non vaccinated animals, TIV vaccinated animals that were exposed to H1N1 virus rely more on cross-reactive serum antibodies than on cellular immunity for protection during lethal H3N2 reinfection.

P79 Broadly Reactive Hemagglutinin-based Vaccine Designed for Swine Protections Against All Human and Swine H1N1 Influenza Viruses
Amanda Skarupka1,2, Simon O. Owino1, Donald M. Carter1, Ted M. Ross1,2
1Center for Vaccines and Immunology, 2Department of Infectious Diseases, University of Georgia, Athens, GA, USA

Swine Influenza is a respiratory disease of pigs caused by type A influenza virus (SIV) implicated in outbreaks regularly for pigs and rarely for humans. Swine flu viruses exhibit high morbidity – but low mortality – and contribute to economic loss for pig producers. Vaccination against SIV with commercially available influenza vaccines is partially effective at reducing clinical signs, viral shedding, and transmission between pigs. However, as the genetic diversity of the influenza virus increases, cross-protection from one strain to another decreases, negatively affecting vaccine effectiveness. Therefore, commercial vaccines have often failed to provide satisfactory protection. In recent years, swine producers have resorted to including autogenous vaccines to provide immune stimulation with a ‘homologous’ influenza subtype with some positive results (Rodbaugh, 2008). Vaccination not only decreases economic loss, but can also protect against the emergence of pandemic strains following the reassortment of human, swine and/or avian H1 hemagglutinin (HA) influenza viruses during co-infection in pigs. No current vaccine protects pigs against human and swine H1 influenza viruses. In this study, we generated a cross-reactive computationally optimized broadly reactive antigen (COBRA) based on both human and swine (SW) H1 HA sequences. BALB/c mice (n=11) were vaccinated with virus-like particles (VLP) expressing COBRA or wild-type H1 HA proteins. Mice vaccinated with VLP expressing SW2 or SW4 COBRA HA antigens, based upon swine HA sequences, elicited antibodies with hemagglutinin-inhibition (HAI) activity against a panel of swine influenza viruses representing all four clades of SIV. Mice were protected against challenge with the A/SW/NC/152702/15 swine virus when vaccinated with the homologous vaccine, SW2 VLP vaccine, or SW4 VLP vaccine. Mice vaccinated with the P1 COBRA VLP vaccine, developed from human and swine H1 HA sequences, elicited HAI reactivity against both human and swine viruses and protected mice against challenge with either human H1N1 or swine H1N2 influenza viruses. Overall, these COBRA-based HA vaccines elicit broadly protective antibodies that will benefit both human health and the swine industry.
P80 ACCEPTANCE OF HETEROLOGOUS PRIME-BOOST VACCINATION REGIMENS – AN ASSESSMENT

Oriol Mathieu V.1, Steinmann P.2,3, Ivol S.1, Prytherch H.2,3, Bosch-Capblanch X.2,3

1Janssen Vaccines & Prevention B.V., Leiden, the Netherlands
2Swiss Tropical and Public Health Institute, Basel, Switzerland
3University of Basel, Basel, Switzerland

Background: Heterologous prime-boost vaccination regimens deliver antigens through different vaccine types, aiming at inducing both robust humoral and cellular immune responses. These bear the potential for development of vaccines against infectious diseases for which no efficacious vaccines are available or where former approaches failed, for example HIV, tuberculosis and Filovirus diseases, and anti-cancer vaccines. With early clinical development showing promising immune responses, several heterologous prime-boost candidates are moving to potential licensure in the coming years. Therefore, exploring potential future acceptance and uptake of heterologous prime-boost vaccination among key global stakeholders was timely.

Methods: Based on results from a literature review and exploratory interviews with global stakeholders including National Medicines Regulatory Authorities, vaccination programs, academics and non-governmental organizations, we developed a quantitative online survey. The questionnaire consisted of four sections: (1) Awareness of and knowledge about heterologous prime-boost by the participant; (2) Rating of heterologous prime-boost associated benefits and challenges; (3) Challenge identification in three hypothetical vaccine introduction scenarios: (a) when offered to adults and adolescents to protect against a disease for which currently no vaccine is available; (b) an alternative to an existing childhood vaccine requiring more than 2 appointments as part of the EPI schedule; and (c) replacement of an existing vaccine in advance or in reaction to an outbreak with improved efficacy; (4) Identification of acceptance and uptake benefits and challenges at different levels: policy, health care, community and general public.

Results: The online questionnaire was completed by 50 respondents from four continents. Most indicated that they were unfamiliar with heterologous prime-boost vaccination, 15% reported to be well informed. When asked about their perceived benefits and challenges, the majority (80%) rated the potentially enhanced immune responses and an expected longer duration of the protective effect as a benefit. Participants expressed reservations towards feasibility, costs, handling by health workers and the compliance of recipients and rated these aspects as potential challenges. These aspects were also foreseen as challenging in 2 of the 3 scenarios. Suitability of deploying such vaccines in anticipation of epidemics was dependent on improved effectiveness and duration of protection. In contrast, deploying heterologous prime-boost vaccines in reaction to an epidemic was perceived as the most challenging. Regarding licensure and uptake at country level, it was highlighted that these innovative vaccine regimens need to be assessed holistically, taking safety, potential impact, delivery concepts, and communications into account. Limitations of the survey such as a limited number of participants and representativeness will be discussed along with tools in development to support acceptance and compliance.

Conclusion: With several heterologous prime-boost vaccines in development to potentially address unmet prevention needs, transparent and scientifically solid communication plans are needed to proactively prepare the public health community, to increase awareness, avoid potential concerns and ultimately optimize acceptance and uptake.

P81 Characterization of vaccine constructs containing multiple conserved domains for cross protection against influenza virus

Subbiah Jeeva, Young-Man Kwon, Ki-Hye Kim, Bo Ryoug Park, Young-Tae Lee, Min-Chul Kim, Sang-Moo Kang

Center for Inflammation, Immunity & Infection, Institute for Biomedical Sciences, Georgia State University, Atlanta, GA 30302, USA

Current influenza virus vaccines confer strain-specific protection based on neutralizing immunity against the globular head domain of hemagglutinin (HA) surface glycoproteins. Extreme antigenic variations in the HA head domain often makes the current vaccination strategy ineffective when antigenically different virus strains or pandemic viruses emerge. A strategy of developing universal vaccine candidates is to design and include conserved antigenic targets in the influenza vaccination. The HA subtypes are clustered into group 1 (H1, H2, H5, H6, H9, H11, H12, H13, H16, H17, and H18) and group 2 (H3, H4, H7, H10, H14, and H15) based on structural similarity in the HA2 fusion-stalk domain of HA, which is relatively well conserved within the same group among the different influenza A viruses. Also, other conserved antigenic targets include the extracellular domain (M2e) of influenza A virus M2 ion channel protein and nucleoprotein (NP) T cell epitopes.

In this study, we designed and made vaccine constructs composed of multiple conserved antigenic domains. The construct FP-M2e is composed of group 1 and 2 fusion HA2 domains, NP-T cell epitope, and M2e epitopes. The construct Stem-M2e is composed of group 1 and 2 fusion-stem domains and M2e epitopes. The gene constructs were expressed in a membrane-anchored form and presented on virus like particles (VLP) as evidenced by antigenic reactivity to M2e epitopes. Immunogenicity and efficacy of these new constructs containing multiple conserved domains are being evaluated in comparison with VLP containing M2e epitopes only in a mouse model.

P82 Self-replicating RNA vaccines against emerging diseases

Inga Szurgot, Karl Ljungberg, Peter Liljeström

Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden

We describe a generic vaccine platform based on a self-amplifying RNA molecule derived from an alphavirus genome. The RNA encodes the genes for the viral RNA replicase but lacks the genes coding for the structural genes of the alphavirus. Instead the replicase carries the gene(s) encoding the antigen of interest. Self-replicating RNA vaccines can be implemented as a rapid response to emerging diseases as all of their components and entire production process are fully synthetic. This makes this RNA platform robust, controllable and affordable. The vaccine RNA is highly stable and large numbers of vaccine doses for which no efficacious vaccines are available or where former approaches failed, for example HIV, tuberculosis and Filovirus diseases, and anti-cancer vaccines. With early clinical development showing promising immune responses, several heterologous prime-boost candidates are moving to potential licensure in the coming years. Therefore, exploring potential future acceptance and uptake of heterologous prime-boost vaccination among key global stakeholders was timely.

In the present study we evaluated the platform using self-replicating RNA expressing envelope proteins from Chikungunya virus (CHIKV). CHIKV is a mosquito-borne alphavirus that re-emerged in Africa, southern Asia, and the Indian Ocean Islands as the cause of large outbreaks of human disease. There is currently no CHIKV-specific treatment and no licensed vaccine that can prevent CHIKV infection, and a vaccine that could raise long-term protective immunity after a single immunization would be preferable. Human symptoms include acute febrile illness, severe encephalitis and debilitating polyarthritis which can prolong for years and fatality is 1 per 1000 cases. Morbidity due to this virus is a serious threat to global health and has been listed as a priority pathogen by the National Institutes of Allergy and Infectious Disease (NIAID) and WHO.

P82 (Continued)

Our experiments show that RNA replicon vaccines expressing CHIKV envelope protein after a single immunization of mice induced high levels of antibody and T-cell responses. The use of self-replicating RNA vaccines allowed for a significant dose sparing effect in comparison to conventional plasmid DNA expressing the same antigen. Moreover, mice challenged with a high dose of CHIKV, after a single immunization with the replicon vaccine candidates, were completely protected against the induction of viremia. In contrast, a majority of the mice immunized with conventional plasmid DNA induced high levels of viremia, similar to that of naïve mice. Overall, the RNA replicon-based vaccines offer a safe, attractive technology, and our study supports the further clinical development of self-replicating RNA vaccines as a generic vaccine platform.
P83 AUTOMATED, TILT-FREE INTERPRETATION OF HEMAGGLUTINATION INHIBITION (HAI) ASSAYS WITH CYPHER ONE
Garrett Wilson, Erica Dawson, Kathy Rowlen

Hemagglutination (HA) and hemagglutination inhibition (HAI) assays have been utilized for 70+ years and play a critical role in influenza vaccine development. In particular, HAI is critical in antigenic characterization of flu viruses and in evaluating immunogenicity of cell-based and traditional egg-based vaccines. HAI assays are prone to poor lab-to-lab consistency due to subjectivity in interpretation between human “readers” where a difference in endpoint of ±1 dilution (typically, ~4x change in concentration) is often considered “equivalent.” In addition, the presence of non-specific inhibition (NSI) can further complicate analysis. To aid in the interpretation of samples which exhibit NSI, human readers will commonly “tilt” the plate at a 45° angle for 30-60 seconds and look for a “tear drop” formation of the settled red blood cells (RBCs). Here we investigate whether the use of an automated imaging and interpretation system, the Cypher One, can generate accurate results without the need to “tilt” the plate.

We compared performance of the Cypher One automated interpretation to the visual interpretation of a human expert reader for a HAI dataset of 2200 samples. The samples consisted of de-identified human sera subjected to H1, H3 and B influenza strains. This particular experiment utilized both avian and mammalian RBCs for determining the serological response of samples in H1/B antigens or H3 antigens respectively. Although the mammalian RBC subset did not require plate tilting prior to the human interpretation, all plates within the avian RBC subset did require tilting by the human reader. The Cypher One automated interpretation was obtained without tilting and compared to the interpretation obtained by the human reader.

The comparison yielded 95.6% agreement between the expert reader and automated interpretation method (within ± 1 dilution) for the complete dataset. Importantly, ~25% of clinical samples within the avian RBC subset exhibited NSI, which is known to complicate the manual interpretation and is often cited as a cause for the need to tilt the plate for accurate interpretation. Even in the presence of NSI, Cypher One showed high agreement (94.3% ± 1 dilution) without the need to tilt the plate. The Cypher One system thus achieved high accuracy and consistency while providing the additional benefit of a digital database of plate images and associated results to meet data integrity requirements.

P84 Recombinant hemagglutinin proteins formulated in a CpG plus squalene-based oil-in-water emulsion for H7N9 vaccine development
Ting-Hsuan Chen1, Ying-Yu Liu1, Jia-Tsrong Jan2, Ming-Hsi Huang3, Maureen Spearman4, Michael Butler5, Suh-Chin Wu6.*
1Institute of Biotechnology, National Tsing Hua University, Hsinchu 30013, Taiwan; 2Genomics Research Center, Academia Sinica, Taipei 11529, Taiwan; 3National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Zhunan, Taiwan; 4Department of Microbiology, University of Manitoba, Winnipeg, Canada; 5Department of Medical Science, National Tsing Hua University, Hsinchu 30013, Taiwan

Humans infected with H7N9 avian influenza viruses can result in severe pneumonia and acute respiratory syndrome with an approximately 40% mortality rate, and there is an urgent need to develop an effective vaccine to reduce its pandemic potential. In this study, we used a novel PELC/CpG adjuvant for recombinant H7HA (rH7HA) subunit vaccine development. After immunizing BALB/c mice intramuscularly, rH7HA proteins formulated in this adjuvant instead of an alum adjuvant elicited higher IgG, hemagglutination-inhibition, and virus neutralizing antibodies in sera; induced higher numbers of H7HA-specific IFN-γ secreting T cells and antibody secreting cells in spleen; and provided improved protection against live virus challenges. Our results indicate that rH7HA proteins formulated in PELC/CpG adjuvant can induce potent anti-H7N9 immunity that may provide useful information for H7N9 subunit vaccine development.

P85 Bridging systemic and gastrointestinal immune responses for enhanced vaccinations
Yufei Xia1, Guanghui Ma1,*
1 State Key Laboratory of Biochemical Engineering, Institute of Process Engineering, Chinese Academy of Sciences, Beijing, P.R. China
*Email: yfxia@ipe.ac.cn; ghma@ipe.ac.cn

As peripheral lymphocytes are typically excluded from the gastrointestinal lymph tissues, current parenteral vaccinations failed to simultaneously induce systemic and mucosal responses. To break the natural barrier, we developed and heralded “immunoticket” capsules, which were designed with positive charged shells and oily core to spatiotemporally deliver antigens and all-trans retinoic acid (RA). After intramuscular vaccinations, these capsules functioned as immunoticket to cultivate the peripheral DCs with chemokine receptor 9 (CCR9). By hitchhiking on the concentration gradient of chemokine (C-C motif) ligand 25 (CCL25), the primed DCs would home to the gut associated lymphoid tissues (GALTs) and induced antigen-specific IgA secretion and T cell engagements. Compared with the currently employed RA-involved formulations, the immunoticket capsules stimulated enhanced RA-mediated gut-tropism by mounting the inflammatory innate immunity. Through controlling RA payloads, the potential regulatory T cell engagement was circumvented. In OVA and E7V1 vaccinations, the immunoticket capsules induced potent serum IgG titer, antigen-specific cytotoxic T cells in the peripheral lymph tissues, as well as robust IgA secretion and T cell engagements on gastrointestinal sites. Our data suggested the potential of the immunotickets to serve as facile, effective and safe strategy to provide comprehensive immune responses against gastrointestinal infections and diseases.

P86 Rapid vaccine development against Zika virus infection based on multi-platforms
Jinghua Yan1, Lianpan Dai2, Kun Xu3, Qingrui Huang1, George Fu Gao1,3
1CAS Key Laboratory of Microbial Physiological and Metabolic Engineering, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China. 2Research Network of Immunity and Health (RNIH), Beijing Institutes of Life Science, Chinese Academy of Sciences, Beijing 100101, China. 3Chinese Center for Disease Control and Prevention, Beijing, China.

The recent outbreak of Zika virus (ZIKV) has emerged as a global health concern. ZIKV can persist in human semen and be transmitted by sexual contact, as well as by mosquitoes, as seen for classical arboviruses. ZIKV infection is associated with microcephaly and neurological complications, such as Guillain-Barré syndrome. Moreover, we along with others have previously demonstrated that ZIKV infection leads to testis damage and infertility in mouse models. So far, no prophylactics or therapeutics are available; therefore, vaccine development is urgently demanded. Here we develop the candidate vaccines against ZIKV infection based on two platforms. One is purified inactivated ZIKV vaccine (ZPIV), the other is adenovirus vectored vaccine. The ZPIV is based on the SMGC-1 strain as we isolated a patient infected with ZIKV. Besides, due to the low preexisting immunity against the vector among the human population, recombinant chimpanzee adenovirus has been explored as the preferred vaccine vector for many pathogens. We therefore harnessed the recombinant chimpanzee adenovirus type 7 (AdC7) expressing ZIKV M/E glycoproteins as the vaccine. Two doses of ZPIV or a single vaccination of AdC7-M/E was sufficient to elicit potent neutralizing antibodies which could cross-neutralize heterologous ZIKV strains and protective immunity against ZIKV in both immunocompetent and immunodeficient mice. Additionally, AdC7-M/E could rapidly induce neutralizing antibody with high titer within 1 week post-vaccination and elicited ZIKV M- and E-specific T cell responses. Moreover, both ZPIV and AdC7-M/E conferred mouse sterilizing immunity to eliminate viremia and viral burden in tissues against ZIKV challenge. Further investigations showed that vaccination with either ZPIV or AdC7-M/E completely protected against ZIKV induced testicular damage. These data demonstrate that both ZPIV and AdC7-M/E are highly effective and represent promising vaccine candidates for ZIKV prophylactics. So far, the ZPIV-developing technology has been transferred to Changchun Changsheng Life Sciences Limited for pre-clinical developments.
ISV Trainee Awards

Emanuele Andreano, Italy
Lotika Bajaj, United States
Amit Bansal, United States
Emily Beaver, United States
Keegan Braz Gomes, United States
Zheng-Rong Li, United States
Jasmina Luczo, United States
Sydney Ronzulli, United States
Amanda Skarlupka, United States
Megan Young, Australia

LMIC Awards

Olatunji Adetokunboh, South Africa
Verry Adrian, Indonesia
Anna Carolina Cajaraville, Brazil
Nisha Dhar, South Africa
Gaurav Kwatra, South Africa
Rajesh Mani, India
Nida Mubin, India
Chukwudi Nnaji, South Africa
Joseph Opare, Ghana
Robert Adamu Shey, Belgium
Bandana Uniyal, India

Vaccine Renaissance Scholarships for Women and Minority Delegates

Rama Akondy, United States
Stephanie Anguiano-Zarate, United States
Katherine Eichinger, United States
Teena Mohan, United States
Dawn Taylor-Mulneix, United States

(Vaccine Renaissance Scholarships for Women and Minority Delegates sponsored by the National Institute of Allergy and Infectious Diseases, 5 R13 AI 094946-08)
<table>
<thead>
<tr>
<th>Name</th>
<th>Surname</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randy</td>
<td>Albrecht</td>
<td>05.3</td>
</tr>
<tr>
<td>James</td>
<td>Allen</td>
<td>04.6</td>
</tr>
<tr>
<td>Emanuele</td>
<td>Andreano</td>
<td>04.5</td>
</tr>
<tr>
<td>Stephanie</td>
<td>Anguiano-Zarate</td>
<td>01.5</td>
</tr>
<tr>
<td>Maria</td>
<td>Arévalo</td>
<td>05.4</td>
</tr>
<tr>
<td>Lotika</td>
<td>Bajaj</td>
<td>03.6</td>
</tr>
<tr>
<td>Julia</td>
<td>Baker</td>
<td>06.4</td>
</tr>
<tr>
<td>Amit</td>
<td>Bansal</td>
<td>08.5</td>
</tr>
<tr>
<td>Kelsey</td>
<td>Briggs</td>
<td>08.3</td>
</tr>
<tr>
<td>Viviana</td>
<td>Cobos-Jimenez</td>
<td>03.4</td>
</tr>
<tr>
<td>Mark</td>
<td>Connors</td>
<td>PL6.2</td>
</tr>
<tr>
<td>Lei</td>
<td>Deng</td>
<td>01.7</td>
</tr>
<tr>
<td>Arban</td>
<td>Domi</td>
<td>02.5</td>
</tr>
<tr>
<td>Paul</td>
<td>Duprex</td>
<td>05.6</td>
</tr>
<tr>
<td>Srilatha</td>
<td>Edupuganti</td>
<td>07.5</td>
</tr>
<tr>
<td>Barbara</td>
<td>Felber</td>
<td>09.3</td>
</tr>
<tr>
<td>Lars</td>
<td>Frelin</td>
<td>02.7</td>
</tr>
<tr>
<td>Harvey</td>
<td>Friedman</td>
<td>PL6.3</td>
</tr>
<tr>
<td>Ali</td>
<td>Harandi</td>
<td>07.2</td>
</tr>
<tr>
<td>Daniel</td>
<td>Hoft</td>
<td>PL4.7</td>
</tr>
<tr>
<td>Koji</td>
<td>Hosomi</td>
<td>07.6</td>
</tr>
<tr>
<td>Jingjing</td>
<td>Jiang</td>
<td>01.3</td>
</tr>
<tr>
<td>Andrew</td>
<td>Jones</td>
<td>09.2</td>
</tr>
<tr>
<td>Linda</td>
<td>Klavinskis</td>
<td>PL2.5</td>
</tr>
<tr>
<td>Zheng-Rong</td>
<td>Li</td>
<td>PL6.4</td>
</tr>
<tr>
<td>Jasmina</td>
<td>Luczo</td>
<td>01.6</td>
</tr>
<tr>
<td>William</td>
<td>Matchett</td>
<td>03.3</td>
</tr>
<tr>
<td>Teena</td>
<td>Mohan</td>
<td>01.4</td>
</tr>
<tr>
<td>Lenny</td>
<td>Moïse</td>
<td>08.6</td>
</tr>
<tr>
<td>Trudy</td>
<td>Morrison</td>
<td>04.3</td>
</tr>
<tr>
<td>Rose</td>
<td>Nash</td>
<td>PL4.3</td>
</tr>
<tr>
<td>Joseph</td>
<td>Opare</td>
<td>06.6</td>
</tr>
<tr>
<td>Nikolai</td>
<td>Petrovsky</td>
<td>07.3</td>
</tr>
<tr>
<td>Punnee</td>
<td>Pitisuttithum</td>
<td>PL6.5</td>
</tr>
<tr>
<td>Mangala</td>
<td>Rao</td>
<td>09.6</td>
</tr>
<tr>
<td>Ed</td>
<td>Rybicki</td>
<td>08.2</td>
</tr>
<tr>
<td>Elizabeth</td>
<td>Sajewski</td>
<td>06.5</td>
</tr>
<tr>
<td>Giuseppe</td>
<td>Sautto</td>
<td>PL4.5</td>
</tr>
<tr>
<td>Baik</td>
<td>Seong</td>
<td>PL4.6</td>
</tr>
<tr>
<td>Robert Adamu</td>
<td>Shey</td>
<td>03.7</td>
</tr>
<tr>
<td>Anna</td>
<td>Slager</td>
<td>PL4.8</td>
</tr>
<tr>
<td>Joshua</td>
<td>Tobias</td>
<td>02.4</td>
</tr>
<tr>
<td>Name</td>
<td>Last Name</td>
<td>Score</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------</td>
<td>-------</td>
</tr>
<tr>
<td>Bandana</td>
<td>Uniyal</td>
<td>O2.6</td>
</tr>
<tr>
<td>Naoko</td>
<td>Uno</td>
<td>O5.5</td>
</tr>
<tr>
<td>Zhimin</td>
<td>Wan</td>
<td>PL4.4</td>
</tr>
<tr>
<td>Bin</td>
<td>Wang</td>
<td>O4.4</td>
</tr>
<tr>
<td>Shixia</td>
<td>Wang</td>
<td>O9.4</td>
</tr>
<tr>
<td>Anna-Lise</td>
<td>Williamson</td>
<td>O8.4</td>
</tr>
<tr>
<td>Ziyang</td>
<td>Xu</td>
<td>O9.5</td>
</tr>
<tr>
<td>Yasuo</td>
<td>Yoshioka</td>
<td>O7.4</td>
</tr>
<tr>
<td>Megan</td>
<td>Young</td>
<td>O6.3</td>
</tr>
<tr>
<td>Ousseny</td>
<td>Zerbo</td>
<td>O3.5</td>
</tr>
</tbody>
</table>
## Poster Presenter Abstract Index

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodrigo Abreu</td>
<td></td>
<td>P1</td>
</tr>
<tr>
<td>Olatunji Adetokunboh</td>
<td></td>
<td>P2, P3</td>
</tr>
<tr>
<td>Verry Adrian</td>
<td></td>
<td>P4</td>
</tr>
<tr>
<td>Amit Bansal</td>
<td></td>
<td>P5</td>
</tr>
<tr>
<td>Jacob Beaver</td>
<td></td>
<td>P6</td>
</tr>
<tr>
<td>Emily Beaver</td>
<td></td>
<td>P7</td>
</tr>
<tr>
<td>Ashley Beavis</td>
<td></td>
<td>P8</td>
</tr>
<tr>
<td>Anne-Gaelle Bebin-Blackwell</td>
<td></td>
<td>P9</td>
</tr>
<tr>
<td>Keegan Braz Gomes</td>
<td></td>
<td>P10</td>
</tr>
<tr>
<td>Ana Carolina Cajaraville</td>
<td></td>
<td>P11</td>
</tr>
<tr>
<td>Glenda Canderan</td>
<td></td>
<td>P12</td>
</tr>
<tr>
<td>Stivalis Cardenas Garcia</td>
<td></td>
<td>P13</td>
</tr>
<tr>
<td>Michael Carlock</td>
<td></td>
<td>P14</td>
</tr>
<tr>
<td>Hye-Ran Cha</td>
<td></td>
<td>P15</td>
</tr>
<tr>
<td>Ashley Chapman</td>
<td></td>
<td>P16</td>
</tr>
<tr>
<td>Lynette Chea</td>
<td></td>
<td>P17</td>
</tr>
<tr>
<td>Angela Choi</td>
<td></td>
<td>P18</td>
</tr>
<tr>
<td>Emily Clutter</td>
<td></td>
<td>P19</td>
</tr>
<tr>
<td>Melissa Coughlin</td>
<td></td>
<td>P20</td>
</tr>
<tr>
<td>Lianpan Dai</td>
<td></td>
<td>P21</td>
</tr>
<tr>
<td>Lei Deng</td>
<td></td>
<td>P22</td>
</tr>
<tr>
<td>Nisha Dhar</td>
<td></td>
<td>P23</td>
</tr>
<tr>
<td>Kelsie Dickerson</td>
<td></td>
<td>P24</td>
</tr>
<tr>
<td>Christiane Eberhardt</td>
<td></td>
<td>P25</td>
</tr>
<tr>
<td>Jeffrey Ecker</td>
<td></td>
<td>P26</td>
</tr>
<tr>
<td>Katherine Eichinger</td>
<td></td>
<td>P27</td>
</tr>
<tr>
<td>Shengtao Fan</td>
<td></td>
<td>P28</td>
</tr>
<tr>
<td>Elisabeth Gillespie</td>
<td></td>
<td>P29</td>
</tr>
<tr>
<td>Bethany Girard</td>
<td></td>
<td>P30</td>
</tr>
<tr>
<td>Ilya Gordeychuk</td>
<td></td>
<td>P31</td>
</tr>
<tr>
<td>Pooja Hindocha</td>
<td></td>
<td>P32, P33</td>
</tr>
<tr>
<td>Lauren Hook</td>
<td></td>
<td>P34</td>
</tr>
<tr>
<td>Ying Huang</td>
<td></td>
<td>P35</td>
</tr>
<tr>
<td>Cristina Huertas Diaz</td>
<td></td>
<td>P36</td>
</tr>
<tr>
<td>Maria Issagouliantis</td>
<td></td>
<td>P37</td>
</tr>
<tr>
<td>Hyesun Jang</td>
<td></td>
<td>P38</td>
</tr>
<tr>
<td>Juris Jansons</td>
<td></td>
<td>P39</td>
</tr>
<tr>
<td>Yu-Jin Jung</td>
<td></td>
<td>P40</td>
</tr>
<tr>
<td>Myunghee Kim</td>
<td></td>
<td>P41</td>
</tr>
<tr>
<td>Ki-Hye Kim</td>
<td></td>
<td>P42</td>
</tr>
<tr>
<td>Madelyn Krunkosky</td>
<td></td>
<td>P43</td>
</tr>
<tr>
<td>Dieudonné Buh</td>
<td></td>
<td>P44</td>
</tr>
<tr>
<td>Name</td>
<td>First Name</td>
<td>Last Name</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Gaurav Kwatra</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young Man Kwon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Youri Lee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andrew Lees</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fábio Leite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liyun Liu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wen-Chun Liu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rajesh Mani</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gary Matyas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mike McCluskie</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenny Moise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jarrod Mousa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>André Nahmias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rose Nash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mukthaa Natrajan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doan Nguyen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chukwudi Nnaji</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeff Noble</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivette Nuñez</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ian Padykula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bo Ryoung Park</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fu-Shi Quan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whitney Rabacal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daniela Rajao</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sophia Reeder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beau Reneer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joon Haeng Rheee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sydney Ronzulli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dawn Rowe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michael Schotsaert</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amanda Skarlupka</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peter Steinmann</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeeva Subbiah</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inga Szurgot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garrett Wilson</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suh-Chin (Samuel) Wu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yufei Xia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jinghua Yan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The International Society for Vaccines is an organization of professionals in the diverse disciplines of vaccinology. It 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

Membership Benefits

- Reduced registration fee for annual congress (USD$100 savings)
- Access journal Vaccine online free
- Access to ISV newsletter
- Eligibility to run for ISV officer and Executive Board positions and increase your visibility through involvement in ISV Committees
- Opportunity to collaborate with global vaccine organizations
- Participation in the mentoring program, either as an early career scientist or as a mentor

ISV 2019 Full Membership Plans

- 12-month full membership plan - USD $100
- 36-month full membership plan - USD $250
- 60-month full membership plan - USD $400
- Graduate or Post-doctoral fellow membership: USD $35 (12-month)

www.isv-online.org
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:30-09:45</td>
<td>Welcome Coffee (Imperial Foyer)</td>
<td>(Imperial Foyer)</td>
<td>Sponsored by GlaxoSmithKline (GSK)</td>
</tr>
<tr>
<td>09:45-09:55</td>
<td>Congress Co-Chairs Opening Remarks</td>
<td>(Imperial Salon A)</td>
<td>ISV Congress Co-Chairs: Ted Ross, University of Georgia; Denise Doolan, James Cook University</td>
</tr>
<tr>
<td>9:55-10:00</td>
<td>Introduction of Opening Session and Speaker</td>
<td>(Imperial Salon A)</td>
<td>David Weiner, ISV President</td>
</tr>
<tr>
<td>10:00-10:45</td>
<td>ADEL Mahmoud Memorial Lecture</td>
<td>(Imperial Salon A)</td>
<td>Julie Gerberding, Merck and Co. and US CDC Director (2002-2009)</td>
</tr>
<tr>
<td>10:45-12:00</td>
<td>Plenary Session 1: Influenza 1918 to 2018</td>
<td>(Imperial Salon A)</td>
<td></td>
</tr>
<tr>
<td>12:00-13:30</td>
<td>Lunch (Skyline – 10th Floor)</td>
<td>(Skyline – 10th Floor)</td>
<td>Sponsored by Inovio Pharmaceuticals</td>
</tr>
<tr>
<td>13:30-15:45</td>
<td>Concurrent Session 1: Vaccine Technologies, Formulations, and Delivery</td>
<td>(International 8)</td>
<td></td>
</tr>
<tr>
<td>13:30-15:45</td>
<td>Concurrent Session 2: Neoantigens, Cancer Vaccines, and More</td>
<td>(International 9)</td>
<td></td>
</tr>
<tr>
<td>13:30-15:45</td>
<td>Concurrent Session 3: Non-Viral Vaccines</td>
<td>(International 10)</td>
<td></td>
</tr>
<tr>
<td>15:45-16:15</td>
<td>Coffee Break (Imperial Foyer/Imperial Salon B)</td>
<td>(Imperial Foyer/Imperial Salon B)</td>
<td>Sponsored by Georgia Research Alliance</td>
</tr>
<tr>
<td>16:15-18:10</td>
<td>Plenary Session 2: Host Immune Response to Vaccination</td>
<td>(Imperial Salon A)</td>
<td></td>
</tr>
<tr>
<td>18:10-20:00</td>
<td>Poster Session #1</td>
<td>(Imperial Salon B)</td>
<td></td>
</tr>
<tr>
<td>18:30-20:00</td>
<td>Welcome Reception (Imperial Foyer/Imperial Salon B)</td>
<td>(Imperial Foyer/Imperial Salon B)</td>
<td>Sponsored by EpiVax, Inc.</td>
</tr>
</tbody>
</table>

**Monday October 29, 2018**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>07:30-08:30</td>
<td>Morning Coffee (Imperial Foyer)</td>
<td>(Imperial Foyer)</td>
<td>Sponsored by Merck</td>
</tr>
<tr>
<td>08:30-10:10</td>
<td>Plenary Session 3: Human Vaccine Trials</td>
<td>(Imperial Salon A)</td>
<td></td>
</tr>
<tr>
<td>10:10-10:40</td>
<td>Coffee Break (Imperial Foyer/Imperial Salon B)</td>
<td>(Imperial Foyer/Imperial Salon B)</td>
<td>Sponsored by GC Pharma</td>
</tr>
<tr>
<td>10:40-12:30</td>
<td>Concurrent Session 4: Viral Vaccines (International 8)</td>
<td>(International 8)</td>
<td></td>
</tr>
<tr>
<td>10:40-12:30</td>
<td>Concurrent Session 5: E-RID Vaccines (International 9)</td>
<td>(International 9)</td>
<td></td>
</tr>
<tr>
<td>10:40-12:30</td>
<td>Concurrent Session 6: Vaccine Evaluation (International 10)</td>
<td>(International 10)</td>
<td></td>
</tr>
<tr>
<td>12:30-13:30</td>
<td>Lunch (Skyline – 10th Floor)</td>
<td>(Skyline – 10th Floor)</td>
<td>Sponsored by VGXI, Inc.</td>
</tr>
<tr>
<td>13:00-14:30</td>
<td>Poster Session #2</td>
<td>(Imperial Salon B)</td>
<td></td>
</tr>
<tr>
<td>14:00-15:00</td>
<td>ISV Annual Meeting</td>
<td>(Imperial Salon B)</td>
<td></td>
</tr>
<tr>
<td>15:00-15:30</td>
<td>Coffee Break (Imperial Foyer/Imperial Salon B)</td>
<td>(Imperial Foyer/Imperial Salon B)</td>
<td>Sponsored by HIVF</td>
</tr>
<tr>
<td>15:30-17:50</td>
<td>Plenary Session 4: Vaccines for Influenza Viruses</td>
<td>(Imperial Salon A)</td>
<td></td>
</tr>
</tbody>
</table>

**Tuesday October 30, 2018**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>07:30-08:30</td>
<td>Morning Coffee (Imperial Foyer)</td>
<td>(Imperial Foyer)</td>
<td>Sponsored by Cellular Technology Limited (CTL)</td>
</tr>
<tr>
<td>08:30-10:10</td>
<td>Plenary Session 5: Public Health, Public Policy, and Vaccine Acceptance</td>
<td>(Imperial Salon A)</td>
<td></td>
</tr>
<tr>
<td>10:10-10:40</td>
<td>Coffee Break (Imperial Foyer/Imperial Salon B)</td>
<td>(Imperial Foyer/Imperial Salon B)</td>
<td>Sponsored by Sanofi Pasteur</td>
</tr>
<tr>
<td>10:40-12:20</td>
<td>Concurrent Session 7: Immunodulators and Vaccines (International 8)</td>
<td>(International 8)</td>
<td></td>
</tr>
<tr>
<td>10:40-12:20</td>
<td>Concurrent Session 8: One Health and Vet Vaccines (International 9)</td>
<td>(International 9)</td>
<td></td>
</tr>
<tr>
<td>12:20-13:20</td>
<td>Lunch (Skyline – 10th Floor)</td>
<td>(Skyline – 10th Floor)</td>
<td>Sponsored by Pfizer, Inc.</td>
</tr>
<tr>
<td>13:20-14:00</td>
<td>Career Development Panel</td>
<td>(International 8)</td>
<td></td>
</tr>
<tr>
<td>14:00-14:30</td>
<td>ISV Award Ceremony</td>
<td>(Imperial Salon A)</td>
<td></td>
</tr>
<tr>
<td>14:30-15:15</td>
<td>Plenary Session 6: The Future of Vaccines</td>
<td>(Imperial Salon A)</td>
<td></td>
</tr>
<tr>
<td>16:00-16:15</td>
<td>Closing Remarks and Introduction to 2019 Congress</td>
<td>(Imperial Salon A)</td>
<td></td>
</tr>
</tbody>
</table>