# Table of Contents

Conference Overview ...................................................... 2  
Conference Objectives ..................................................... 2  
Acknowledgments ........................................................ 3  
Conference Committee Members. ............................................. 4  
NFID Staff .............................................................. 5  
Invited Presenters ......................................................... 6  
Disclosure Index .......................................................... 8  
General Information ....................................................... 11  
    American with Disabilities Act .......................................... 11  
    Conference Information Desk ........................................... 11  
    Conference Location .................................................. 11  
    Continuing Education ............................................... 11  
    Exhibit Hall ........................................................... 12  
    Messages .................................................................. 12  
    No Smoking Policy .................................................... 12  
    Poster Sessions ....................................................... 12  
    Press Room .......................................................... 12  
    Program and Abstracts ................................................. 13  
    Registration Fees and Hours ........................................... 13  
    Speaker Ready Room and Audiovisual Equipment .................... 13  
    Verification of Attendance ............................................ 13  
Affiliated Events and Other Meetings ...................................... 13  
Hotel Floorplan ........................................................... 14  
Program At-A-Glance. ..................................................... 15  
Program Agenda .......................................................... 16  
Note-taking Outlines ...................................................... 29  
Poster Session Program ................................................... 103  
Meet the Experts Biographies ............................................... 112  
Abstracts 
    Abstracts of Invited Presentations ..................................... 116  
    Abstracts of Submitted Oral Presentations ............................. 125  
    Abstracts of Submitted Poster Presentations ......................... 141  
Author Index ............................................................. 170
Conference Overview

The remarkable growth of vaccine biotechnology continues apace in basic science discovery, product development, market introduction, and adoption into immunization programs. New cytokines are identified, innate and induced immune regulatory pathways unraveled, novel adjuvants and antigen constructs prove effective, and recently-licensed products achieve high coverage, already yielding noticeable decreases in disease incidence. One can envision a growing number of challenging maladies – including chronic, non-infectious, and neoplastic – that may become vaccine-preventable or vaccine-treatable in the years ahead.

The Annual Conference on Vaccine Research (ACVR) aims to provide high-quality, up-to-date reports of such scientific progress in its unique mix of invited presentations by acknowledged international experts in symposia of topical interest, and via its sessions and posters of peer-reviewed submitted abstracts. The ACVR encourages the participation of all the disparate fields of vaccinology in both its human and veterinary domains in order to facilitate valuable cross-fertilization of ideas and approaches among researchers often narrowly focused on their specific diseases or methods.

The Twelfth ACVR promises to maintain its position as the largest scientific meeting devoted exclusively to research on vaccines and associated technologies for disease prevention and treatment through immunization. It is a premier venue for cutting-edge learning, effective data-sharing, and convenient networking for scientific collaboration.

The conference organizers and its volunteer committees enthusiastically invite registrants to participate in its audience discussions, poster presentations, meet-the-expert breakfast sessions, special luncheon lectures, evening receptions and ceremonies, and its sponsored exhibits, and to provide the helpful feedback essential for further evolution and improvement. Welcome to the Twelfth Annual Conference on Vaccine Research.

Conference Objectives

Overall Conference Objectives
At the conclusion of this conference, participants should be able to meet the following objectives:

- Discuss recent scientific advances that are contributing to progress in the development of vaccines
- Identify research opportunities and scientific challenges associated with vaccine development, production, and distribution
- Discuss the assertion that the measles-mumps-rubella (MMR) vaccine and thimerosal-containing vaccines cause autism and how best to communicate issues to the public
- Describe the current status of the polio eradication initiative, its remaining challenges; discuss the ongoing pre-eradication and post-eradication research agenda
- Describe the problem of epidemic Group A meningococcal meningitis in Africa and discuss an affordable, safe and immunogenic vaccine to combat these epidemics that has been developed
- Discuss sustainable financing of new vaccine introduction in developing countries and the coming challenges in this area

Symposia Objectives

Keynote Address
- Describe the aims and objectives of GIVS, its priorities and challenges faced by GIVS and its progress to date

Symposium 1: Recent Issues in Vaccine Safety
- Review considerations of safety versus efficacy for the rhesus rotavirus vaccine (Rotashield) and discuss how this event impacted the development, testing, and monitoring of new rotavirus vaccines
- Explain approaches being used to assess infrequent adverse events following immunization and the challenges in both assessment and development of responsibility responding to possible vaccine safety signals
- Review the state-of-the-art design in genome wide association study (GWAS) design, with special attention to vaccine-specific considerations

Symposium 2: Immunization Programs and Global Health
- Explain the origins of the Expanded Program on Immunization (EPI) and suggested changes needed for optimal incorporation of new vaccines
- Discuss sustainable financing of new vaccine introduction in developing countries and the coming challenges in this area
Symposium 3: Synergies Between Veterinary and Human Vaccine Development
- Explain current status of melanoma vaccine development and clinical trials
- Discuss the challenges which remain for the future introduction of cancer vaccines in general
- Discuss challenges faced by animal and human health sectors in developing vaccines against influenza and review how these efforts have been a major driving force in the One World, One Health initiatives
- Describe the current status of TB vaccine development for both cattle and humans and discuss the potential synergies in a linked program of vaccine testing in cattle and humans
- Review the basic epidemiology of Rift Valley fever virus (RVFV) and explain why only vaccines can control the disease

Symposium 4: Update on Tuberculosis Vaccines
- Explain the differential protective efficacy observed after BCG vaccination of diverse populations, and reasons underlying this observation
- Review the immune response induced by BCG vaccination, how this relates to protection, and differential immune responses observed in diverse populations
- Describe the scientific rationale for the design of TB subunit vaccine development and review the status of recent progress in clinical trials
- Discuss the protective immunity to TB and the clinical development path for new TB vaccines
- Review veterinary tuberculosis vaccine research and development
- Discuss the challenges which remain for the future introduction of tuberculosis vaccines intended for wildlife and livestock

Symposium 5: Malaria Vaccines
- Review recent developments in the malaria vaccine field and discuss the status of advanced malaria vaccine candidates
- Describe strategies for exploiting genomic-scale datasets to advance the identification of therapeutic targets, focusing on the malaria parasite Plasmodium falciparum, and experience with the Eukaryotic Pathogen Genome Database
- Discuss malaria vaccine development, clinical trials, and the challenges of developing vaccines that can protect against genetically diverse malaria parasites
- Review current status of attenuated Plasmodium falciparum malaria sporozoite vaccine development, clinical trials, and the challenges for moving from initial manufacturing and clinical trials to licensure

Acknowledgments (as of April 1, 2009)
This conference is supported, in part, through unrestricted educational grants from:
- Aeras Global TB Vaccine Foundation
- Becton Dickinson
- Celldex Therapeutics
- CSL Biotherapies
- DynPort Vaccine Company
- EpiVax, Inc.
- Foundation Mérieux
- Integrated BioTherapeutics
- LigoCyte Pharmaceuticals, Inc.
- MedImmune, Inc.
- Merck & Co., Inc.
- NanoBio Corporation
- Novartis Vaccines and Diagnostics, Inc.
- Novavax, Inc.
- sanofi pasteur
- U.S. Food and Drug Administration
- VaxInnate Corporation
- Wyeth Pharmaceuticals
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The intent of this disclosure is not to prevent a speaker or program planner with a relevant financial or other relationship from making a presentation or assisting in conference organization. The intent is to provide listeners with information on which they can make their own judgments. It remains for the audience to determine whether the speaker's interests or relationships have influenced the presentation with regard to exposition or conclusion.

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- Huang, Wan-Ting
- Idika, Nneoma
- Ikekami, Tetsuro
- Jang, Seung
- Janju, Naveed
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- Waters, W. Ray
- Wichit, Sineewanlaya
- Winter, Kathleen
- Wolchok, Jedd
- Xu, Lin
- Yu, Lihua

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- Bagley, Kenneth
- Ballou, W. Ripley
- Baxter, Roger
- Belshe, Robert
- Black, Steven
- Caulfield, Michael
- dela Cruz, Tracy

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- GlaxoSmithKline
- Protein Sciences, MedImmune
- Merck & Co., Inc.
- GlaxoSmithKline, sanofi, Novartis
- Wyeth, Merck & Co.
- Dynavax

**Relationship**

- B
- A, C
- A, G
- B
- B
- E
- A, C
- A, C

(continued)
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<table>
<thead>
<tr>
<th>Presenter</th>
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<th>Relationship*</th>
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<td>Cooper-Kerr, Sharon</td>
<td>Ero, Lauren</td>
<td>A, F, E</td>
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<td>Curlin, George</td>
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<td>Deir, Stephanie</td>
<td>Hill, George</td>
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<td>Duma, Richard J.</td>
<td>Pfizer, Cubist, Wyeth, Macrogenics</td>
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<td>Durack, David T.</td>
<td>Becton Dickinson</td>
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<td>Edwards, Kathryn</td>
<td>CSL, GlaxoSmithKline, Novartis, Wyeth, sanofi Pasteur</td>
<td>B</td>
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<td>File, Thomas</td>
<td>Cerexa</td>
<td>B, E</td>
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DISCLOSURE INDEX

Fisher, John  Pfizer, Merck  E
Gay, Cyril G.  Pfizer  A
Goff, Debra  Merck, Wyeth  B, E
                    Cubist  E
Jackson, Marguerite  Cellestis, Inc.  A
Lambert, Paul-Henri  GlaxoSmithKline, sanofi Pasteur,  Novartis  E
                    Lambert, Paul-Henri  GlaxoSmithKline, sanofi Pasteur,  Novartis  E
                    Lambert, Paul-Henri, sanofi Pasteur,  Novartis  E
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Nara, Peter  CSC/Dynaport  E
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                    Bayhill Therapeutics  A, E
Ruben, Fred  sanofi Pasteur  C
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The Baltimore Marriott Waterfront Hotel is fully accessible to the public in accordance with the Americans with Disabilities Act guidelines. If you have any special meeting needs or requirements, please contact either Sharon Cooper-Kerr or a member of the hotel staff.

Conference Information Desk
The Conference Information Desk is located in the foyer area outside the Harborside Ballroom. Conference staff will be available at the desk throughout the conference.

Conference Language
The official language for the conference is English.

Conference Location
All sessions of the conference will be held at:

Baltimore Marriott Waterfront Hotel
700 Aliceanna Street
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Continuing Education

Continuing Medical Education
The National Foundation for Infectious Diseases (NFID) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide Continuing Medical Education (CME) for physicians. NFID takes responsibility for the content, quality, and scientific integrity of this CME activity.

NFID designates this CME activity for a maximum of 16.5 AMA PRA Category 1 credit(s)™. Each physician should only claim credit commensurate with the extent of their participation in the activity.

Continuing Nursing Education
NFID is an approved provider of continuing nursing education by the Maryland Nurses Association, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation. This educational activity has been approved for 16.5 contact hours. To earn contact hours, each participant must attend the entire program, sign-in daily, and complete the conference evaluation form.

Designated Continuing Education Activities
Sessions designated with a CE symbol have been approved for credit. No other sessions are eligible for credit hours.
CME and Nursing Certificates

In order to ensure that you receive the credits to which you are entitled, complete and return the Continuing Education and Evaluation form to conference staff at the Conference Information Desk, or mail to:

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FOR NURSES ONLY: you must also sign in daily and attend the entire conference.

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Exhibit Hall

Visit the Exhibit Hall in Harborside Ballroom A&B to meet with representatives from companies displaying the latest technologies in vaccine-related products and services. The exhibit hall hours are Monday, April 27, 5:00 pm – 7:00 pm, and Tuesday, April 28, 7:30 am – 1:00 pm. A prize drawing will be held on Tuesday, April 28, at 1:15 pm. Be sure to get your exhibitor passport stamped by each of the exhibitors and return it to the conference registration desk by 1:00 pm, Tuesday, April 28, to qualify for the drawing.

Messages

All sleeping rooms in the Baltimore Marriott Waterfront Hotel are equipped with a voice mail system. This system is accessible via the hotel operator using the house phone. In case of emergencies requiring immediate attention, your party should call the general hotel number listed below and instruct the switchboard to deliver a message to Sharon Cooper-Kerr or Lauren Ero at the Vaccine Research Conference Information Desk outside of the Harborside Ballroom. The general hotel number is 1-410-385-3000.

No Smoking Policy

The Baltimore Marriott Waterfront Hotel is a non-smoking facility. No smoking is allowed in any of the session rooms, coffee break area, in the foyer adjoining the session rooms or sleeping rooms.

Poster Sessions

Posters will be on display from 10:00 am, Monday, April 27, until 10:00 am, Wednesday, April 29. Presenters will be at their boards to answer questions and discuss their research during the official poster session on Monday, April 27, 10:00 am-11:30 am, and during the poster reception that day at 5:00 pm. General Posters will be located in the Harborside Ballroom Foyer. Posters for Travel Grant recipients and Maurice R. Hilleman Early-stage Career Investigator Award semifinalists will be located in the Laurel Room.

Press Room

NFID will have a Press Room located in the Falkland Room on Monday and Tuesday and in the Chausseur Room on Wednesday. Members of the press should sign in at the Conference Information Desk during registration hours.
**Program and Abstracts**

Each registered participant will receive one complimentary copy of the Program Agenda and Abstract Book as part of his/her registration fee. Additional copies, if available, may be purchased for $25. Orders for additional copies will be taken at the Conference Information Desk starting Tuesday, April 28, 2009 and after the conference by e-mail to vaccine@nfid.org, phone at (301) 656-0003 x19, or by fax at (301) 907-0878. **PLEASE NOTE THAT WE ARE UNABLE TO REPLACE LOST OR STOLEN PROGRAMS.**

Handouts of the presentations will not be provided. Notetaking outlines may be found immediately after the Program Agenda, beginning on page 30. With the permission of each faculty member, the slides presented at the conference will be posted on NFID’s website after the conference. Registered attendees will be notified by email when the slides are posted, and they will be available for one month. Please use this resource to supplement your notes.

**Registration Fees and Hours**

The onsite registration fee: **US $500 (Non Member) and $450 (NFID Supporting Member)**

Space is limited to the first 525 registrants. The registration fee includes a program/abstract book, continental breakfast on each day of the conference, all scheduled coffee breaks, lunch presentations on Monday and Tuesday, and the receptions on Monday and Tuesday. Accommodations and additional meals are not included.

Individuals interested in registering onsite may do so at the Conference Information Desk between the following times:
- Sunday, April 26 .................. 6:00 pm - 8:00 pm
- Monday, April 27 ................. 7:00 am - 5:00 pm
- Tuesday, April 28 ............... 7:00 am - 5:00 pm
- Wednesday, April 29 ............ 7:30 am - 12:00 pm

**Speaker Ready Room**

A room has been set aside for speakers to preview their slides. All speakers should check in at the Conference Information Desk to be directed to the speaker ready room. The room will be open during the registration hours and will be equipped with a laptop for preview of your PowerPoint presentation.

**Verification of Attendance**

International attendees may obtain a letter of attendance verification from the staff at the Conference Information Desk during registration hours.

**Affiliated Events and Other Meetings**

**Monday, April 27, 2009**

Conference on Vaccine Research Organizing and Scientific Program Committees Meeting
(Closed meeting)
6:00 pm – 9:00 pm, Essex A&B

**Tuesday, April 28, 2009**

Albert B. Sabin Vaccine Institute Gold Medal Award Ceremony and Reception
5:00 pm – 6:00 pm, Harborside Ballroom Foyer
6:00 pm – 7:00 pm, Harborside Ballroom, C-E
Hotel Floor Plan
## Program At-A-Glance

<table>
<thead>
<tr>
<th>SUNDAY, APRIL 26</th>
<th>MONDAY, APRIL 27</th>
<th>TUESDAY, APRIL 28</th>
<th>WEDNESDAY, APRIL 29</th>
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<tr>
<td>7:00 am Registration</td>
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<tr>
<td>7:30 am Poster Set-up</td>
<td>Continental Breakfast/Exhibits</td>
<td>Symposium 2: Immunization Programs and Global Health</td>
<td>Coffee Break</td>
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<tr>
<td>8:00 am Continental Breakfast</td>
<td>Mary Lou Clements-Mann Memorial Lecture</td>
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<td>8:30 am Welcome and Introductions</td>
<td>Keynote Address</td>
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<tr>
<td>11:30 am</td>
<td>Charles Mérieux Award Luncheon</td>
<td>Maurice R. Hilleman Early-stage Career Investigator Award</td>
<td>Lunch (on your own)</td>
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<td>11:45 pm</td>
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<td>Robert Austrian Memorial Lecture and Luncheon</td>
<td>Symposium 5: Malaria Vaccines</td>
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<tr>
<td>1:00 pm</td>
<td>Symposium 1: Recent Issues in Vaccine Safety</td>
<td>Symposium 3: Synergies Between Veterinary and Human Vaccine Development</td>
<td>Adjournment/Participant Evaluation</td>
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<td>Coffee Break</td>
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<td>3:30 pm</td>
<td>Concurrent Submitted Presentations 1 and 2</td>
<td>Concurrent Submitted Presentations 3 and 4</td>
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<tr>
<td>5:00 pm</td>
<td>Adjournment</td>
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<td>5:00 pm</td>
<td>Poster Reception</td>
<td>Albert B. Sabin Vaccine Institute Reception</td>
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<tr>
<td>6:00 pm</td>
<td>Exhibit Hall Opens</td>
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<td>Presentation of the Albert B. Sabin Gold Medal</td>
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<td>6:00 pm</td>
<td>Early Registration</td>
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PROGRAM AGENDA

SUNDAY, APRIL 26, 2009

6:00 pm - 8:00 pm  Early Registration  Harborside Ballroom Foyer

MONDAY, APRIL 27, 2009

7:00 am - 5:00 pm  Registration  Harborside Ballroom Foyer

8:00 am  Poster Set-Up  Harborside Foyer and Laurel A-E

8:00 am  Continental Breakfast  Harborside Ballroom Foyer

8:30 am  Welcome and Introductions  Harborside Ballroom, C-E

Susan J. Rehm, MD  National Foundation for Infectious Diseases  Bethesda, MD

Keynote Address  CE  Harborside Ballroom, C-E

Moderator:  Susan J. Rehm, MD  National Foundation for Infectious Diseases

8:35 am  1 World Health Organization’s Global Immunization Vision and Strategy  [Note taking outline on page 30]

David M. Salisbury, MB, BS  Department of Health  London, United Kingdom

9:10 am  Questions and Answers

9:30 am  Coffee Break  Harborside Ballroom Foyer

10:00 am  Poster Session  Harborside Foyer and Laurel A-E

Charles Mérieux Award Luncheon*

11:30 am  Paul A. Offit, MD  Children’s Hospital of Philadelphia  Philadelphia, PA

Symposium 1: Recent Issues in Vaccine Safety  CE  Harborside Ballroom, C-E

Moderators:  Hana Golding, PhD  U.S. Food and Drug Administration

Paul-Henri Lambert, MD  Centre Medical Universitaire de Genève

*This session is supported by a grant from sanofi pasteur
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Presenter(s)</th>
<th>Location</th>
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<tbody>
<tr>
<td>1:00 pm</td>
<td><strong>Efficacy versus Safety: Lessons from Rotavirus Vaccines</strong></td>
<td>Umesh Parashar, MBBS, MPH</td>
<td>Centers for Disease Control and Prevention, Atlanta, GA</td>
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<tr>
<td>1:25 pm</td>
<td>Questions and Answers</td>
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<tr>
<td>1:30 pm</td>
<td><strong>Assessment of Low-Frequency AEFI Through New Epidemiological Approaches</strong></td>
<td>Steven Black, MD</td>
<td>Center for Global Health, Cincinnati Children's Hospital, Cincinnati, OH</td>
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<tr>
<td>1:55 pm</td>
<td>Questions and Answers</td>
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<td>2:00 pm</td>
<td><strong>Screening for Genetic Predisposition to Adverse Events Following Immunization</strong></td>
<td>Christopher Carlson, PhD</td>
<td>Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA</td>
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<tr>
<td>2:55 pm</td>
<td>Questions and Answers</td>
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<tr>
<td>2:30 pm</td>
<td><strong>Vaccination and Mitochondrial Diseases: Real or False Issue?</strong></td>
<td>Paul A. Offit, MD</td>
<td>The Children's Hospital of Philadelphia, Philadelphia, PA</td>
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<td>2:55 pm</td>
<td>Questions and Answers</td>
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<td>3:00 pm</td>
<td>Coffee Break</td>
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<td>Harborside Ballroom Foyer</td>
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**Submitted Presentations 1:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Presentation Title</th>
<th>Authors</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:30 pm</td>
<td><strong>Immune Stimulatory Interleukin HMGB1 Induces Dendritic Cell (DC) Maturation and Immune Enhancement In Vivo</strong></td>
<td>G. Muthumani, P. Fagone, S. Kannan, J. Yan, B. Huihui, D. J. Shedlock, K. M. Lankaraman, K. Muthumani, D. B. Weiner</td>
<td>University of Pennsylvania School of Medicine, Philadelphia, PA</td>
</tr>
<tr>
<td>3:45 pm</td>
<td><strong>Preclinical and Clinical Safety Evaluation of Adjuvant Systems for the Design of Prophylactic Vaccines. A Case Study: AS04-adjuvanted HPV16/18 Cervical Cancer Vaccine</strong></td>
<td>N. Garçon</td>
<td>GVD Global Adjuvant Center, GlaxoSmithKline Biologicals, Wavre, BELGIUM</td>
</tr>
</tbody>
</table>
4:00 pm

S3  Emulsion-adjuvanted Clade 2 Influenza A/H5N1 Vaccine: A Randomized, Placebo-Controlled Antigen and Adjuvant Dose-ranging Phase 1 Trial in Healthy Adults

G. Foglia¹, E. Sheldon²
¹Clinical Development, Sanofi Pasteur, Swiftwater, PA, ²Miami Research Associates, Miami, FL

4:15 pm

S4  W₈₀SEC, a Nanoemulsion Adjuvant, Provides Robust Anti-Influenza Immunity in Ferrets after a Single Immunization

T. Hamouda¹, A. Myc¹, N. Mank³, J. Knowlton³, N. Mytle³, J. Sutcliffe¹, J. R. Baker, Jr.¹
¹NanoBio Corp, Ann Arbor, MI, ²University of Michigan, Ann Arbor, MI, ³Southern Research Institute, Birmingham, AL

4:30 pm

S5  Randomized, Double Blind, Controlled Phase I Trial of the Safety, Tolerability and Immunogenicity of Fluzone® Inactivated Trivalent Influenza Virus Vaccine Administered with Ascending Doses of JVRS-100 Adjuvant

J. Fairman¹, M. Sisti¹, J. F. Warner¹, V. Knobel¹, M. Lay¹, C. Johnson³, E. Sheldon³, M. Co⁴, F. Emnis⁴, T. Monath¹

4:45 pm

S6  IL-15 Enhances the Vaccine Efficacy of 3-1E DNA Vaccine against Eimeria acervulina Infection

G. Li¹, D. Ma¹, X. Ren¹, H. Lillehoj²
¹Department of Veterinary Pathology, College of Veterinary Medicine, Northeast Agricultural University, Harbin, CHINA, ²Animal Parasitic Diseases Lab, Animal and Natural Resource Institute, USDA-ARS, Beltsville, MD

Submitted Presentations 2:
Influenza Vaccines - Old and New  
Moderator: Georges Peter, MD  
Warren Alpert Medical School of Brown University

3:30 pm

S7  Trivalent Influenza Vaccine Effectiveness (VE) Measured Through Sentinel Physician Network in Canada during the 2007-08 Season of A & B Mismatch

N. Z. Janjua¹, D. M. Skowronska¹, G. De Serres², L. T. Kwindt¹, J. Dickinson³, M. Petric¹, K. Fonseca¹, H. Charest², S. J. Drews², A. Winter³, E. Bontovics⁴, N. Crowcroft⁴, N. Bastien⁷, T. S. Hottes¹, Y. Li¹
¹British Columbia Centre for Disease Control, Vancouver, CANADA, ²Institut National de Santé Publique du Québec, Québec, CANADA, ³University of Calgary, Alberta, Calgary, CANADA, ⁴Alberta Provincial Laboratory, Calgary, CANADA, ⁵Ontario Provincial Laboratory, Toronto, CANADA, ⁶Ontario Ministry of Health, Toronto, CANADA, ⁷National Microbiology Laboratory, Winnipeg, CANADA
3:45 pm  S8  Expansion of a School-based Influenza Vaccination and Herd Protection Trial in Central Texas - Second Year of VIPS: Vaccines for Influenza Prevention in Schools

S9  Evaluation of Mixed Schedules of Live Attenuated and Inactivated Influenza Vaccines in Children

S10  A Comparative Study of Intramuscular (IM), Subcutaneous (SC), Intradermal (ID) Routes of Administration for VAX102 (STF2.4xM2e) Influenza Vaccine in Healthy Adults

S11  Escalating Dose-Ranging Study to Evaluate the Safety and Immunogenicity of the VAX125 (STF2.HA1(SI)), a Recombinant Hemagglutinin Influenza Vaccine, in Healthy Young Adults

S12  Safety, Tolerability, and Immunogenicity of Bivalent Influenza Peptide Conjugate Vaccine (BIPCV) in Healthy Adults
PROGRAM AGENDA

TUESDAY, APRIL 28, 2009

7:00 am - 5:00 pm  Registration  
Harborside Ballroom Foyer

7:00 am - 7:45 am  Meet the Experts Breakfast Session*
Essex A&B

Vaccine Safety Datalinks: Where to Next?
Steven Black, MD
Center for Global Health
Cincinnati Children’s Hospital
Cincinnati, OH

Current Vaccine Controversies
Neal A. Halsey, MD
John Hopkins University
Bloomberg School of Public Health
Baltimore, MD

Publishing Your Results - Tips from a Journal Editor
Gregory A. Poland, M.D.
Mayo Clinic and Foundation
Rochester, MN

Introducing HPV Vaccine
David M. Salisbury, MB, BS
Department of Health
London, United Kingdom

7:30 am  Continental Breakfast/Exhibits
Harborside Ballroom A&B

Mary Lou Clements-Mann Memorial Lecture in Vaccine Sciences  
Harborside Ballroom C-E

Moderator:  Bruce G. Weniger, MD  
Centers for Disease Control and Prevention

8:00 am  Progress and Promise on the Long Road to a Dengue Vaccine
[NOTE TAKING OUTLINE ON PAGE 52]
Harold S. Margolis, MD
International Vaccine Institute
Seoul, Korea

8:40 am  Questions and Answers

9:00 am  Coffee Break/Exhibits  
Harborside Ballroom A&B

*This session is supported by a grant from Wyeth Pharmaceuticals
Symposium 2: Immunization Programs and Global Health

**Moderator:** Myron M. Levine, MD, DTPH
*University of Maryland School of Medicine
Center for Vaccine Development*

9:30 am  
**7 Global Polio Eradication and Related Research**
Stephen L. Cochi, MD, MPH
*National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA*

9:55 am  
**Questions and Answers**

10:00 am  
**8 Eliminating Serogroup A Meningococcal Meningitis Epidemics in Africa**
F. Marc LaForce, MD
*PATH
Voltaire, France*

10:25 am  
**Questions and Answers**

10:30 am  
**9 Extending the Expanded Program on Immunization (EPI) Schedule into the Second Year of Life**
Neal A. Halsey, MD
*John Hopkins University
Bloomberg School of Public Health
Baltimore, MD*

10:55 am  
**Questions and Answers**

11:00 am  
**10 Sustainable Financing of New Vaccine Introduction in Developing Countries**
Andrew Jones, MSc
*Adeni Consulting
Philadelphia, PA*

11:25 am  
**Questions and Answers**

*Maurice R. Hilleman Early-stage Career Investigator Award and Robert Austrian Memorial Lecture and Luncheon*

11:30 am  
**Hilleman Award Presentation**
Austrian Lecture presented by Steven Black, MD

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*This session is supported by grants from Merck & Co., Inc.*
Symposium 3: Synergies Between Veterinary and Human Vaccine Development

Moderator: Cyril G. Gay, DVM, PhD
U.S. Department of Agriculture

1:00 pm  11 Melanoma Vaccines
Jedd D. Wolchok, MD, PhD
Memorial Sloan-Kettering Cancer Center
New York, NY

1:25 pm  Questions and Answers

1:30 pm  12 Avian Influenza Vaccines
Richard J. Webby, PhD
St. Jude Children’s Hospital
Memphis, TN

1:55 pm  Questions and Answers

2:00 pm  13 Development of Vector Vaccine for Tuberculosis
Adrian V.S. Hill, DM
The Jenner Institute
Oxford University
Oxford, United Kingdom

2:25 pm  Questions and Answers

2:30 pm  14 Rift Valley Fever Vaccines
Clarence J. Peters, MD
University of Texas Medical Branch
Galveston, TX

2:55 pm  Questions and Answers

3:00 pm  Coffee Break/Exhibits
Submitted Presentations 3

Assessing Immunologic Response and Disease Protection

(Concurrent Session)

Moderator: George R. Siber, MD
Genocea Biosciences, Inc.

3:30 pm

S13 Pandemic Influenza Preparedness: Identification of Serological Epitopes for Use in the Evaluation and Development of Broadly Protective Vaccines

[Note taking outline on page 66]
H. Golding, S. Khurana, K. Subbarao, C. Simmons, K. Edwards
1CBER, US Food and Drug Administration, Bethesda, MD, 2Lab of Infectious Diseases, NIAID, NIH, Bethesda, MD, 3University of Oxford, Ho Chi-Minh City, VIET NAM, 4Vanderbilt University Medical Center, Nashville, TN

3:45 pm

S14 Live Attenuated Influenza Vaccine (LAIV), but not Trivalent Inactivated Influenza Vaccine (TIV), Induces Functional CD4+, CD8+ and γδ T cell Responses in Children Relevant for Pandemic Influenza

[Note taking outline on page 67]
1Saint Louis University, St. Louis, MO, 2Vanderbilt University, Nashville, TN, 3Cincinnati Children’s Hospital Medical Center, Cincinnati, OH

4:00 pm

S15 Selection Bias in the Measure of Vaccine Protection against Serious but Non-Specific Influenza Outcomes in Seniors: Examination through Linked Manitoba Databases

[Note taking outline on page 68]
T. S. Hottes, D. M. Skowronski, B. Hiebert, L. L. Roos, P. Van Caeseele, R. Walld, N. Janjua, G. De Serres
1British Columbia Centre for Disease Control, Vancouver, CANADA, 2Manitoba Centre for Health Policy, Winnipeg, CANADA, 3Cadham Provincial Laboratory, Winnipeg, CANADA, 4Institut National de Santé du Québec, Quebec, CANADA

4:15 pm

S16 Effectiveness of the Influenza Vaccine at Preventing Death in the Elderly: a New Approach

[Note taking outline on page 69]
R. Baxter, B. Fireman, J. Lee
Kaiser Permanente, Oakland, CA

4:30 pm

S17 Effect of Maternal Pneumococcal (Spn) Antibody (Ab) on Infant Ab Response to Spn Conjugate Vaccine (PCV7)

[Note taking outline on page 70]
M. C. Steinhoff, K. Zaman, E. Roy, R. Raqib, S. E. Arifeen
1Global Health Center, Cincinnati Children’s Hospital and Medical Center, Cincinnati, OH, 22International Centre for Diarrhoeal Disease Research, Dhaka, BANGLADESH

4:45 pm

S18 Immunome-derived Epitope-driven Vaccines (IDEDV) Protect against Viral or Bacterial Challenge in Humanized Mice

[Note taking outline on page 71]
A. De Groot, L. Moise
EpiVax, Providence, RI
Submitted Presentations 4
(Concurrent Session) New and Novel Vaccines
	Moderator: Gregory A. Poland, MD
	Mayo Clinic and Foundation

3:30 pm S19 Phase 1 Safety and Immunogenicity Results of Vaxfectin®-Formulated Plasmid DNA Vaccines Encoding Influenza Virus H5 Hemagglutinin
[Note taking outline on page 72]
L. R. Smith, M. Wloch, A. Rolland, A. Chu, R. Moss
Vical Incorporated, San Diego

3:45 pm S20 Safety, Tolerability, Immunogenicity, and Protective Efficacy of a Multi-stage, Multi-antigen Adenovirus-vectored P. falciparum Malaria Vaccine, in Healthy, Malaria-Naïve Adults
[Note taking outline on page 73]
1 US Military Malaria Vaccine Program, Naval Medical Research Center/Walter Reed Army Institute of Research, Silver Spring, MD, 2National Naval Medical Center, Bethesda, MD, 3GenVec, Gaithersburg, MD, 4United States Agency for International Development (USAID), Washington, DC

4:00 pm S21 Safety and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants Given with Routine Pediatric Vaccinations in Canada
[Note taking outline on page 74]
J. D. Kellner, D. Girgenti, S. A. Halperin, D. Scheifele, W. A. Gruber, D. Scott
1Pediatrics, University of Calgary, Calgary, CANADA, 2Wyeth Vaccines Research, Pearl River, NY, 3Dalhousie University, Halifax, CANADA, 4University of British Columbia, Vancouver, CANADA

4:15 pm S22 Improved Potency of Codon-optimized Encephalitic Alphavirus DNA Vaccines Delivered by Electroporation
[Note taking outline on page 75]
L. C. Dupuy, M. Richards, B. Ellefsen, D. Hannaman, B. Livingston, C. S. Schmaljohn
1U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD, 2Ichor Medical Systems, San Diego, CA

4:30 pm S23 Preliminary Phase 2 Immunogenicity Results of a CMV DNA Vaccine in Hematopoietic Cell Transplant (HCT) Recipients
[Note taking outline on page 76]
L. R. Smith, M. Wloch, D. Guterwill, A. Rolland, A. Chu, R. Moss
Vical Incorporated, San Diego, CA

4:45 pm S24 Immune Responses in Humans to AERAS-402, Crucell Adeno35-vectored TB Vaccine Candidate
[Note taking outline on page 77]
J. C. Sadoff
Aeras Global TB Vaccine Foundation, Rockville, MD

5:00 pm Adjournment

5:00 pm Albert B. Sabin Vaccine Institute Reception
Harborside Ballroom Foyer

6:00 pm Presentation of the Albert B. Sabin Gold Medal
Harborside Ballroom C-E
on Vaccine Research

PROGRAM AGENDA

WEDNESDAY, APRIL 29, 2009

7:00 am - 12:00 pm  Registration  
Harborside Ballroom Foyer

7:00 am - 7:45 am  Meet the Experts Breakfast Session*  
Essex A&B

Bill and Melinda Gates Foundation: Activities in Vaccine Development for Infectious Diseases
W. Ripley Ballou, MD  
Bill and Melinda Gates Foundation  
Seattle, WA

How to Measure the T Cell Response in Field Studies of Novel Vaccines
Willem A. Hanekom, MB, ChB  
South African Tuberculosis Vaccine Initiative  
University of Capetown Health Sciences  
Capetown, South Africa

Affordable Vaccines for Developing Countries Using a Push Business Strategy
F. Marc LaForce, MD  
PATH  
Voltaire, France

How to Develop a New Tuberculosis Vaccine: What are the Challenges?
Helen McShane, FRCP, PhD  
The Jenner Institute  
Oxford University  
Oxford, United Kingdom

7:30 am  Continental Breakfast/Exhibits  
Harborside Ballroom A&B

Symposium 4:  Update on Tuberculosis Vaccines CE  
Harborside Ballroom C-E

Moderator:  Cyril G. Gay, DVM, PhD  
U.S. Department of Agriculture

8:00 am  15 Reasons for BCG Failures in Developing Countries  
[NOTE TAKING OUTLINE ON PAGE 78]  
Willem Hanekom, MBChB  
South African Tuberculosis Vaccine Initiative  
University of Cape Town  
Cape Town, South Africa

8:25 am  Questions and Answers

*This session is supported by a grant from Wyeth Pharmaceuticals
8:30 am  
16  **Progress Made with Subunit Vaccines**  
Peter Andersen, DVM, DMSc, Professor  
Statens Serum Institute  
Copenhagen, Denmark  
[Note taking outline on page 80]

8:55 am  
Questions and Answers

9:00 am  
17  **Clinical Trials with MVA85A, Virally Vectored New Tuberculosis Vaccines**  
Helen McShane, FRCP, PhD  
The Jenner Institute  
Oxford University  
Oxford, United Kingdom  
[Note taking outline on page 82]

9:25 am  
Questions and Answers

9:30 am  
18  **Update on Veterinary Tuberculosis Vaccines**  
W. Ray Waters, DVM, PhD  
National Animal Disease Center  
U.S. Department of Agriculture  
Ames, IA  
[Note taking outline on page 84]

9:55 am  
Questions and Answers

10:00 am  
Coffee Break  
Harborside Ballroom Foyer

Submitted Presentations 5  
**Vaccine Safety**  
Harborside Ballroom C  
(Concurrent Session)  
Moderator:  Georges Peter, MD  
Warren Alpert Medical School of Brown University

10:30 am  
**S25 Post-licensure Safety Evaluation of a Combination Diphtheria, Tetanus, Acellular Pertussis, Hepatitis B, and Inactivated Poliovirus Vaccine (DTaP-HepB-IPV)**  
W. Huang, P. Gargiullo, E. Weintraub, J. Baggs, K. Broder, J. Iskander  
Centers for Disease Control and Prevention, Atlanta, GA  
[Note taking outline on page 86]

10:45 am  
**S26 Rates of Autoimmune Diseases in Kaiser Permanente for Use in Vaccine Adverse Event Safety Studies**  
1Kaiser Permanente, Oakland, CA, 2 Cincinnati Children’s Hospital, Cincinnati, OH, 3 GlaxoSmithKline Biologicals, Rixensart, BELGIUM  
[Note taking outline on page 87]
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
<th>Authors</th>
<th>Affiliations</th>
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<tr>
<td>11:00 am</td>
<td>S27</td>
<td>A Panel Assessment of Causality among Passively Reported Vaccine Adverse Events</td>
<td>A. M. Loughlin¹, C. D. Marchant¹, W. Adams¹, E. Barnett¹, R. Baxter², S. Black³, C. Casey⁴, C. Dekker⁵, K. M. Edwards⁶, J. Klein⁷, N. P. Klein⁸, P. LaRusza⁹, K. Jakob⁠¹⁰, R. Sparks⁠¹¹</td>
<td>¹Boston Medical Center and Boston University School of Medicine, Boston, MA, ²Kaiser Permanente Vaccine Study Center, Oakland, CA, ³Center for Global Health, Cincinnati Children’s Hospital, Cincinnati, OH, ⁴Centers for Disease Control and Prevention, Atlanta, GA, ⁵University School of Medicine, Stanford, CA, ⁶Vanderbilt University, Nashville, TN, ⁷Columbia University Medical Center, New York, NY</td>
</tr>
<tr>
<td>11:15 am</td>
<td>S28</td>
<td>Exact Sequential Analysis for Vaccine Safety Surveillance</td>
<td>E. Lewis, B. Fireman, N. Klein, R. Baxter</td>
<td>Kaiser Permanente Vaccine Study Center, Oakland, CA</td>
</tr>
<tr>
<td>11:30 am</td>
<td>S29</td>
<td>Defining 5-Year Research Needs for the Centers for the Disease Control and Prevention’s (CDC) Immunization Safety Office (ISO) Scientific Agenda</td>
<td>K. Broder¹, J. Iskander¹, E. Skillen¹, B. Slade¹, J. Gidudu¹, J. Gee¹, J. Donahue², K. Edwards³, D. Salmon⁴, B. Schwartz⁵, A. Pavia⁶, B. Hibbs⁷, N. Levine⁷, C. Richards⁸, D. Snider⁹</td>
<td>¹Centers for Disease Control and Prevention, Atlanta, GA, ²Marshfield Clinic Research Foundation, Marshfield, WI, ³Vanderbilt University, Nashville, TN, ⁴National Vaccine Program Office, Washington DC, ⁵University of Utah School of Medicine, Salt Lake City, UT</td>
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Submitted Presentations 6  Immune Memory and Recall CE  (Concurrent Session)  
Moderator: Susan J. Rehm, MD  
National Foundation for Infectious Diseases

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<th>Session</th>
<th>Title</th>
<th>Authors</th>
<th>Affiliations</th>
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<tr>
<td>10:30 am</td>
<td>S30</td>
<td>Maintenance of T Cell Memory in Airway Lumen following Mucosal Immunization Requires both de novo Antigen Presentation and Cell Proliferation</td>
<td>M. Jeyanathan, S. McCormick, C. Small, Z. Xing</td>
<td>McMaster University, Hamilton, CANADA</td>
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<tr>
<td>10:45 am</td>
<td>S31</td>
<td>Plasmid-based IL-12 Used in Combination with in vivo Electroportation and a Heterologous pDNA Prime, rVSV Vector Boost Vaccination Regimen Preferentially Improves the Induction of Antigen-specific T cell with a Polyfunctional Effector Memory Phenotype in Rhesus Macaques</td>
<td>M. A. Egan</td>
<td>Profectus Bioscience, Tarrytown, NY</td>
</tr>
<tr>
<td>11:00 am</td>
<td>S32</td>
<td>Mucosal Vaccination with a Recombinant H5 Antigen and Nanoemulsion Adjuvant Potentiates Immune Response against Pandemic Avian Influenza</td>
<td>N. J. Mank¹, A. Myc¹, J. Sutcliffe¹, T. Hamouda¹, J. Baker, Jr.¹</td>
<td>¹University of Michigan Medical School, Ann Arbor, MI, ²NanoBio Corporation, Ann Arbor, MI</td>
</tr>
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</table>
11:15 am  
**S33 Validation of the Vaccine Population Studies: Consistent Associations of HLA Genotypes with Rubella Vaccine Humoral Immunity**  
I. G. Ovsyannikova, R. M. Jacobson, R. A. Vierkant, M. M. O’Byrne, V. S. Pankratz, G. A. Poland  
*Mayo Clinic and Foundation, Rochester, MN*

11:30 am  
**S34 The Decennial Administration of a Reduced Antigen Content Diphtheria, Tetanus, Acellular Pertussis Vaccine (Boostrix™) in Young Adults**  
J. Mertsola¹, O. Van Der Meeren², Q. He¹, A. Linko-Parvinen¹, G. Ramakrishnan³, L. Mannermaa¹, M. Soila¹, M. Pulkkinen⁴, J. Jacquet²  
¹University of Turku and National Public Health Institute, Turku, FINLAND, ²GlaxoSmithKline Biologicals, Rixensart, BELGIUM, ³GlaxoSmithKline Biologicals, Bangalore, INDIA, ⁴GlaxoSmithKline Biologicals, Espoo, FINLAND

11:45 am  
**Lunch (on your own)**

11:45 am-1:15 pm  
**Symposium 5: Malaria Vaccines**  
*Harborside Ballroom C-E*

**Moderator:** George Curlin, MD  
*National Institute of Allergy and Infectious Diseases*

12:45 pm  
**19 Interventions to Control Malaria, Including Vaccines in the Pipeline**  
W. Ripley Ballou, MD  
*Bill and Melinda Gates Foundation*  
*Seattle, WA*

1:10 pm  
**Questions and Answers**

1:15 pm  
**20 Genomic-Based Identification and Prioritization of Vaccine Targets**  
David S. Roos, PhD  
*University of Pennsylvania*  
*Philadelphia, PA*

1:40 pm  
**Questions and Answers**

1:45 pm  
**21 Application of Genomics to the Evaluation of Malaria Vaccines in Clinical Trials**  
Christopher V. Plowe, MD, MPH  
*Center for Vaccine Development*  
*University of Maryland*  
*Baltimore, MD*

2:10 pm  
**Questions and Answers**

2:15 pm  
**22 Metabolically Active, Non Replicating Plasmodium Falciparum Sporozoite Vaccines: Rationale, Manufacturing Challenges and Clinical Trials**  
Stephen L. Hoffman, MD  
*Sanaria, Inc.*  
*Rockville, MD*

2:40 pm  
**Questions and Answers**

2:45 pm  
**Adjournment/Participant Evaluation**
NOTE TAKING OUTLINES
GIVS has Four Main Aims

GIVS Goals

By 2015 or Earlier (as the case may be)

By 2015 or Earlier (as the case may be)

The Component Strategies

Strategic Area II: Introducing New Vaccines and Technologies

Strategic Area IV: Immunizing in the Context of Global Interdependence

Progress Against the GIVS Objectives

Challenges Faced by GIVS

Vision: A World in 2015 in Which:


Countries Achieving >=90% DTP3 Coverage, 2007

Countries with all Districts Achieving at Least 80% DTP3 Coverage, 2007

Countries with Most Unvaccinated Infants DTP3 Coverage, 2005-2007 (in millions)
“Return Routine Immunization to the centre stage”

Are we on Track?

Estimated Measles Deaths 2000, 2007

Status of Measles Control

Polio Eradication: New Strategic Plan 2009-2013

Critical to Achieve Soonest the Disease Initiatives Goals

Are we on Track?

Global Coverage Estimates, 1980-2007 DTP3, HepB3 and Hib3

Countries Having Introduced Hib Vaccine and Infant Hib Coverage, 2007

Implementation of Other New Vaccines

Accelerating the Widespread Use of New Vaccines

World Health Assembly Resolution on GIVS Report, 24 May 2008 (WHA61.15)

In Brief, All Immunization Stakeholders Should Help to…

GIVS Funding Gap for 72 Poorest Countries

Conclusions
Causes of Severe Acute Gastroenteritis among Children <5 Years

RV Disease Burden

Estimated Global Distribution of the 600,000 Annual Deaths Caused by Rotavirus

Burden of Rotavirus in the US

Rhesus Rotavirus Vaccine -- Rotashield®

Recommended Childhood Immunization Schedule United States, January – December 1999

Intussusception Rates by Week of Age in US Infants, 1993-2004

Interval between Rotashield Vaccine and Intussusception

Risk of IS after Rotashield

Risk of IS after Dose 1, by Age at Vaccination

Studies of the Risk of Intussusception Following RotaShield®

Risks and Benefits of Rotashield in US

US Decision

The Risk Benefit Equation in Developing Countries

The Demise of Rotashield®

The $100 Million Question

Develop Other Rotavirus Vaccines?
2006- Two New Vaccines

Rotarix Intussusception (IS) Data

RotaTeq Intussusception (IS) Data

Will the Risk of IS Ever be Eliminated for Rotavirus Vaccines?

Why Continue to Monitor IS?

US Safety Monitoring

IS Reports to VAERS, Feb 2006-Jan 2008

Comparison of IS Reports to VAERS with Rotashield and RotaTeq

Interpreting VAERS Data

Observed versus Expected 1 to 7 Days (dose 1)*

IS after RotaTeq™, VSD

Post-Licensure Cohort Sample Size

US ACIP Recommendation

Age Restrictions and Vaccine Impact in Developing Countries
What is The Issue?

Approaches to Post-Licensure Evaluation of Vaccine Safety

Passive Reporting: VAERS as an Example

Passive Reporting: Intussusception Cases Reported to VAERS

Empirical Bayesian Geometric Mean Score Following Rotashield

Passive Reporting: Intussusception and VAERS

Phase Four: Post Marketing Surveillance

Considerations of Statistical Power

Studies Based Upon Computerized Data

What Computerized Data?

US VSD Population Characteristics
Types of Studies Possible on Computerized Data

The Utility of Case Series Approaches

Rapid Cycle Techniques

Rapid Cycle Techniques: Intussusception in VSD

VSD Rapid Cycle Evaluation of MMRV

What Do You Do If You Observe a Signal?

What to Do If You Observe a Possible Signal?

What Happens Without Vaccines?

What about Capacity Globally?

Global VSD Planning Meeting Participants

Assessment Survey September 2007

Overview

GVSD Overall Assessment

Conclusions: Where to From Here?
Screening for Genetic Predisposition to Adverse Events Following Immunization: Genomics and Vaccine Safety
Christopher Carlson, PhD
Monday, April 27 at 2:00 pm

Outline

GWAS?

How to GWAS

Study Design

Heritability

Prior Hypotheses

Target Phenotypes

How to GWAS

SNP Selection for Association Studies

Parameters for SNP Selection

Why Common Variants?

How to GWAS
Power Analysis

Replication

Study Design Summary

How to GWAS

Multiple Testing

Bonferroni

Multiple Testing

Permutation Analysis

Permutation Analysis

Permutation Analysis

Multiple Testing Summary

Finishing a GWAS

Generic Conclusions

Vaccine Specific GWAS Considerations
Vaccination and Mitochondrial Diseases: Real or False Issue? Communicating Science to the Public
Paul A. Offit, MD
Monday, April 27 at 2:30 pm

MMR-Autism: Scientific Studies I

MMR-Autism: Scientific Studies II

Thimerosal-Autism: Scientific Studies

Defeating Epidemiology

The Fallacy of Balance

Epidemiological Studies Cannot Detect Rare Events

“Vaccines might cause autism in a small group of genetically susceptible individuals.”

Power of Epidemiological Studies

Epidemiological Studies Don’t Prove Anything

Epidemiological Studies and Proof

Anecdote Trumps Epidemiology

Cultural Biases

The Media Defends the Weak against the Powerful
Players in Vaccine-Autism Controversy

Players in Autism Controversy are Miscast

The Media Loves Mavericks

“While Galileo was a rebel, not all rebels are Galileo.”

The Media Falls into the Single-Study Trap

The Media Doesn’t Understand Science

What Science Isn’t

Explaining Cause and Effect

The Lay of the Land

Conflicts of Interest

Ad Hominem Attacks

Easy Appeal to Toxic, Environmental Hell

Easy to Scare People; Harder to Un-scare Them

Poor Understanding of Risk
HIV Infections Worldwide – 2008 (CDC) report

Vaccination and Basic Notion on DNA Vaccines

Conceptual Advantages of DNA Vaccines

DNA Vaccines in the Clinic

Molecular Adjuvants to improve DNA vaccine

DNA vaccine & Antigen Presentation

HMGB1 and Vaccine

HMGB1 DNA constructions and HMGB1 DNA cloning

Expression of HMGB1 protein and HMGB1 protein localization

Role and Effect of HMGB1 on DCs maturation

Immunization Schedule

HMGB1 induces strong antibody response and ELISpot Assay

Cellular immunity: IFN-γ response

HMGB1 protects a lethal influenza challenge in vivo
**Vaccinology: an evolving science**

Learning from nature

Selecting from nature

Building upon nature

**Case Study: AS04-Adjuvanted Human Papilloma Virus Vaccine**

GSK Human Papillomavirus vaccine

**AS04 mechanism of action**

Safety profile

Vaccine efficacy

Vaccine general safety

**AS04 integrated safety analysis on AID Overall studies involved**

**AS04 Safety: Meta-analysis of Autoimmune Disorders**

**Observed vs Expected Comparison**

**Limitations**

**Conclusions**
Phase 1 multicentre RCT in healthy US adults, April-June 2008

Immunogenicity methods

Background

Homologous antibody response Day 42*


Safety up to Day 42

Conclusions
Nanoemulsion (NE) InTRANasal Vaccine adjuvant Platform

NE adjuvanted Influenza Antigen

How Does it Work?

NE Enhances Delivery to Immune System

NE Influenza Vaccine Ferret Study Design

NE Vaccine induces Robust HAI Titers After One Dose

Robust HAI Titers Maintained After 2\textsuperscript{nd} Dose

NE Vaccine Protects Against Influenza Challenge

Cross Protection

Conclusions

Next Steps
Overview of Study Design

Platform Technology

Demographics and Baseline Characteristics

Systemic Adverse Events

Local Adverse Events

Comments on Adverse Events

Reverse Cumulative HAI Distribution* HAI Antibody Titers: Inverse Dose Response

Antibody Responses - HAI & Seroconversion

Neutralizing Antibody Responses*

T-Cell Responses to Flu A – H3N2

T-Cell Responses to Flu B

Poly-Functional T-Cell Responses

Conclusions
Coccidiosis: The Continuing Problem

Novel prophylactic method for coccidiosis needed urgently

Experimental Group

Cell Transfection

Proliferative Response of T Cells in Thymus, Spleen and PBL

CD4+ and CD8+ T Cell Subpopulation in Thymus

CD4+ and CD8+ T Cell Subpopulation in Spleen

CD4+ and CD8+ T Cell Subpopulation in PBL

ChIL-2 and ChIFN-\gamma mRNA Expression in Thymus

ChIL-2 and ChIFN-\gamma mRNA Expression in Spleen

Body Weight Gaining

Ocyst Per Gram Fece

Anti-Coccidia Index

Conclusions
Introduction

Trivalent Vaccine

Sentinel Surveillance and Test-Negative Controls

Sentinel Physician Contribution

Results: Fig 1. Recruitment of study participants

Table 1. Participant Description (N=1408)

Influenza Detection Profile

Table 2. Influenza subtype distribution by province

Table 3. Strain characterization*

Table 4. Overall and component-specific VE estimates (95% confidence interval)

Changes in amino acid sequence encoded by the Haemaglutinin (HA1) gene from vaccine strain A/Solomon Islands/03/06 (H1N1) for 2007-08 influenza season

Table 5. Overall and component-specific VE estimates (95% CI) for children <9 yrs*

Lessons

Limitations
Background

Study Design

Methods

Results

Results: Elementary Schools by ISDs - 2007 and 2008

Results: Middle and High Schools by ISDs - 2008

Results: Public, Private and Home Schools - 2008

Conclusion
Background

Goals

Methods

Post-dose 2 HAI Antibody Geometric Mean Titer

4 Fold Rise in HAI Titer Post-Dose 2

Virus Shedding After LAIV as Dose 1 or Dose 2 or After TIV Priming

Systemic and Local Reactogenicity (Subjects Positive/Subjects Total)

Conclusions

Limitations
Vaccine background

Influenza M2e Vaccine Conservation of Sequence

Influenza M2e Vaccine: STF2.4xM2e

Study background

VAX102-03 Study Design

Clinical Study Design

Universal (M2e) Vaccine VAX 102-03: Study Design

Demographic characteristics

M2e Immune response

Symptoms after intradermal injection of VAX102

Symptoms occurring after the first 2.0 ug dose of VAX102 by intramuscular (im) or subcutaneous (sc) injection, 8 subjects per group

Universal (M2e) Vaccine VAX 102-03: CRP by dose & route

Universal (M2e) Vaccine VAX 102-03: M2e antibody and CRP

Conclusions
S11  Escalating Dose-Ranging Study to Evaluate the Safety and Immunogenicity of the VAX125 (STF2.HA1(SI)), a Recombinant Hemagglutinin Influenza Vaccine, in Healthy Young Adults
John J. Treanor, MD
Monday, April 27 at 4:30 pm

VAX 125 vaccine product

HA Globular Head Vaccines: VAX125 Vaccine Design

VAX125-01: Phase I, Part I Study Design

VAX125-01: Phase I, Part I Geometric mean HAI titers and fold rise

VAX125-01: Phase I, Part I GMT, seroresponse (SR) and seroprotection (SP) rates

VAX125-01: Phase I, Part I Safety

VAX125-01: Phase I, Part 2 Study Design

VAX125-01: Phase I, Part 2 GMT, seroresponse (SR) and seroprotection (SP) rates

VAX125 part 2: Local and systemic reactogenicity reported post immunization

C reactive protein responses after one IM dose of VAX125

VAX125 part 1 and 2: HAI GMT, GMT fold rise, seroresponse and seroprotection rates by dose group

Vax125 Phase 1: Conclusions
Design of Investigational Influenza Vaccine (Merck)

Summary of Preclinical Studies

Phase I Clinical Studies

Protocol 001: Incidence of Injection-site Adverse Experiences

Protocol 001: Incidence of Systemic Adverse Experiences

Protocol 001: Safety Summary

Protocol 002: Study Population

Protocol 002: Incidence of Injection-site Adverse Experiences

Protocol 002: Incidence of Systemic Adverse Experiences

Protocol 002 - BIPCV/MAA + Adjuvant: Safety Summary

Preliminary Immunogenicity Results: A/M2-Specific Antibody Responses

Preliminary Immunogenicity Results: B/HA₀-Specific Ab Responses

Protocol 001 – BIPCV/MAA: Immunogenicity Summary

Immunogenicity Summary (Preliminary Results)

Conclusions
| 6 | Progress and Promise on the Long Road to a Dengue Vaccine |
|   | Harold S. Margolis, MD |
|   | Tuesday, April 28 at 8:00 am |

*Dr. Margolis did not submit a note taking outline*
The Global Polio Eradication Initiative:


Current Areas of Active Transmission

OPV status of children, by country, 2003-2008

Confirmed Polio Cases India, 2008-2009

Confirmed Wild Poliovirus cases by type and month of onset, India Jan 2006 – Dec 2008

Wild Poliovirus, 2008

Routine Immunization Reported OPV3 Coverage Jan – Nov 2007/2008

Afghanistan and Pakistan Wild Poliovirus, 2008

Population immunity

Importations & Outbreaks, 2008

Conclusions - I

Focus of GPEI Research & Product Development

GPEI Research Acceleration

To Address sub-Optimal OPV Efficacy

Efficacy of monovalent OPV1 vs tOPV

Efficacy of higher-potency mOPV1 (virus titre of 106.2 vs 106.7)
Bivalent (1&3) OPV Development

bOPV Trial Design

New Initiatives, 'bivalent OPV'

Conclusions - new OPV Vaccines

Products for Post-Eradication Era

IPV Project, Yojakarta Province, Indonesia (MOH, Provincial Health, sanofi pasteur, WHO)

Safe for Production” in Developing Countries/Affordable IPV -- I

Safe for Production” in Developing Countries” and Affordable IPV -- II

Alternate Seed Strains for IPV Production

Oman Clinical Trial with Fractional IPV Dose: Study Overview

Oman Clinical Trials with Fractional IPV Doses: Efficacy Endpoints

Seroconversion, Median Titer, After 3 Doses of IPV

Overall Median Titer to Poliovirus Type 1

Overall Median Titer to Poliovirus Type 2

Overall Median Titer to Poliovirus Type 3

Excretion Rates by Group (excluding SB SITE), Pre-mOPV1 Challenge Dose (DAY 0)

Summary
Epidemic Meningitis in Africa

Burkina Faso Meningitis Epidemic Curve

Distribution of Meningococcal Groups in Epidemic Districts, 2003-2007

The Meningitis Vaccine Project

Discussions with African Public Health Officials and WHO/AFRO Fall 01-Spring 02

MVP Men A Vaccine Development Model

Lee/Frasch Conjugation Method: Activation of Raw Materials

Conjugation Reaction

Men A Conjugate Vaccine - “MenAfriVac”

PsA-TT002 Study Design Primary Vaccination 12-23 Month Olds (Mali and The Gambia)

Pivotal Phase II in Africans (12-23 months of age) Week 4 - Men A rSBA Titres
Group A IgG Geometric Mean Concentrations and percentage of subjects (12-23 month olds) with IgG ≥ 2 μg/ml at week 4 after vaccination

PsA-TT002 Study Design PsBooster

Pivotal Phase II in Africans (12-23 months of age)

MVP Phase II/III in African Children & Adults 2-29 yrs of age

Conclusions from Clinical Trials

Introduction Strategies

Proposed Men A Conjugate Vaccine Introduction

Expected Public Health Outcomes of Men A Conjugate Vaccine Introduction Strategy

Lessons Learned

MVP Team


The Meningitis Vaccine Project
### Extending the Expanded Program on Immunization (EPI) Schedule into the Second Year of Life

Neal A. Halsey, MD

Tuesday April 28 at 10:30 am

*Dr. Halsey did not submit a note taking outline*
Overview

Financing Challenges

Bridging the Gap

Financing as an Incentive

Sustainable Financing

New Vaccines Pipeline

Package of Solutions
How IFFIm Works

IFFIm Donor Base

IFFIm

Package of Solutions

Funding the Pipeline

Product Development Cycle

AMC is an Incentive

AMC Implementation

An AMC Pilot: Pneumococcal

Conclusions
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<th>Melanoma Vaccines</th>
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<tr>
<td></td>
<td>Jedd D. Wolchok, MD, PhD</td>
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<td>Tuesday, April 28 at 1:00 pm</td>
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*Dr. Wolchok did not submit a note taking outline*
H5N1 Bird Flu-the Next Pandemic?

1997-1998 Hong Kong H5N1 Avian Influenza Outbreaks in Humans

Not Just Hong Kong

Reemergence of H5N1 in Humans

Inactivated Flu Vaccines

The Pol-I/Pol-II8 Plasmid System for Reverse Genetics of Influenza

H5N1 Pathogenicity

Seed Strain

Results in Ferret Attenuation

Progress

Current Status

Preclinical Efficacy of NIAID Vaccine
Seroconversion

Homologous Challenge

Cross Reactivity of NIAID Vaccine

Seroconversion

Viral Titers

Survival

Problem

Current WHO Approach

Efficacy of Ancestral Vaccine

Efficacy against Clade 1

Efficacy against Clade 2.1

Efficacy against Clade 2.2

Summary
13 Development of Vector Vaccine for Tuberculosis
Adrian V.S. Hill, DM
Tuesday, April 28 at 2:00 pm

*Dr. Hill did not submit a note taking outline
Biomedical Impotence

Why is RVF a Concern?

Egypt, Zagazig Fever Hospital, 1977

RVF Patient, Zagazig, Egypt

RVF Encephalitis, Abassiya Fever Hospital

RVF: Ocular Lesions

RVF Pathogenesis

MP-12 RVF Vaccine

Progressive Attenuation of MP-12 for Mice

One Third of Nucleotide Substitutions are Present in Multiple Lineages

Nucleotide Substitutions in the Lineages

Polymorphisms Change Gradually on Serial Passage
S Segment Reassortants

M Segment Reassortants

L Segment Reassortants

Frequency of Headaches by Day of Onset

Neutralization Titers (PRNT 80)

Overall Antibody Response to RVF MP12 Vaccine

Analysis of Human Serum from Vaccines

Sequence Results of Virus Isolates

Presence of Mutations in Virus Isolates

Summary of Mutations in MP-12 Recovered from Vaccines

MP-12 Mouse Age Virulence Model

Mouse LD50 : Clinical Re-Isolates (serum)

Mouse LD50 of Human MP-12 Clinical Re-Isolates (from serum)

MP-12 Vaccine for Rift Valley Fever Virus
S13  Pandemic Influenza Preparedness: Identification of Serological Epitopes for Use in the Evaluation and Development of Broadly Protective Vaccines
Hana Golding, PhD
Tuesday, April 28 at 3:30 pm

*Dr. Golding did not submit a note taking outline
S14  Live Attenuated Influenza Vaccine (LAIV), but not Trivalent Inactivated Influenza Vaccine (TIV), Induces Functional CD4+, CD8+ and γδ T cell Responses in Children Relevant for Pandemic Influenza
Daniel F. Hoft, MD, PhD
Tuesday, April 28 at 3:45 pm

Background and Hypotheses

Trial Design

% >1:32 Seroprotective Titer Post-vaccination (% >1:32 pre-vaccination)

LAIV Shedding Post-vaccination

Bioinformatic & CMI Assay Approaches

PP2: Conserved HLA class II binding epitopes from M1, M2 & NP proteins

Schematic of Ag-specific Flow Assay Linking Proliferation & Effector Function

Influenza-specific CD4+ T cell Responses

Influenza-specific CD8+ T cell Responses

Flu-Specific γδ T cell Response

Overall CFSE Results (n=10-13/group)

Peptides Induced Suboptimal T cell expansion

IFN-γ ELISPOT?

ON Peptide Pool IFN-γ ELISPOT Assays

Key Points/Questions
Rationale

Evidence: RCT

Other Evidence: Observational

Background

Objective

Methods

Results

Summary

Implications
How well does the flu vaccine prevent mortality in the elderly?

Usual observational studies

Can selection bias be overcome by adjusting for confounders? Probably not

We tried a new approach

Proportion of decedents vaccinated by week after October 1, only looking at weeks OUTSIDE of flu season

Proportion of living people vaccinated (age and sex matched to those who died).

The difference between dead and alive person vaccination rates OUTSIDE FLU SEASON. This has been called “vaccine effectiveness” but is really an indication of selection bias.

Case-centered method

The smooth curve is the “VE” fit to our case-centered logistic regression model

The lower curve is the case-centered regression of VE during Flu season (same dates in years when flu was not circulating)

True Vaccine Effectiveness is the difference-in-differences, in and outside of flu season

Flu Vaccine effectiveness

4.6% seems low
S17  Effect of Maternal Pneumococcal (Spn) Antibody (Ab) on Infant Ab Response to Spn Conjugate Vaccine (PCV7)
Mark C. Steinhoff, MD
Tuesday, April 28 at 4:30 pm

*Dr. Steinhoff did not submit a note taking outline
Components of an Effective Vaccine: Payload + Delivery Vehicle + Adjuvant

Genome-derived Epitope-driven Vaccines

New Tools for Vaccine Design

EpiMatrix

ClustiMer (Promiscuous/Supertype Epitopes)

Conservatrix (Conserved Epitopes)

EpiAssembler (Immunogenic Consensus)

BlastiMer (Avoiding “Self” Autoimmunity)

OptiMatrix (Improving Epitope Binding)

Vaccine-CAD (Processing and Assembly)

Aggregatrix (Optimizing the Coverage of Vaccines)

Report on EpiVax Pipeline

Genome-derived Epitope-driven *F. tularensis* Vaccine

HelicoVax Post Infection Vaccine for *H. pylori*

VennVax Smallpox Immunome “Venn” Vaccine
H5N1 Pandemic Influenza DNA Vaccines Development Pathway

DNA Vaccine Composition

Vaxfectin® Adjuvant

Phase 1 H5 DNA Trial Designs

Summary of Phase 1 Safety Data

Immune Assays: Immune Responses by Day 56

Response Rate Summary: Trivalent Cohorts

H5 Antibody Titers: Monovalent

HI Responses: Monovalent Cohorts

IFN-γ ELISPOT HA1 Responses

IFN-γ ELISPOT HA2 Responses

Summary of Immune Responses

Future Directions
Development of Multi-valent Multi-stage Malaria Vaccine

M3V-Ad-PfCA Vaccine

Study Design

Part A Results: Tolerability and Safety

IFNγ ELISpot Assay PfCSP (summed peptide pools)

IFNγ ELISpot Assay PfAMA1 (summed peptide pools)

Part A RESULTS Immunogenicity

Part B Results Tolerability and Safety

ELISpot: 2nd Dose – No Boost Relative to 1st Dose

ELISA: 2nd Dose – No Boost Relative to 1st Dose

Ad5 Seropositivity: No Effect on ELISpot Responses

Ad5 Seropositivity: No Effect on ELISA Titers

Part B Results Immunogenicity

Time to Parasitemia

Summary
Background

Objectives and Measurements

Study Design and Subjects

Study Protocol

Subjects

Proportion of Subjects with Predefined Levels of Concomitant Vaccine Antigens

Concomitant Vaccine Antigen Geometric Mean Concentrations

Percentage of PCV13 Subjects with Pneumococcal IgG Antibody Concentrations ≥0.35 μg/mL.*

Pneumococcal IgG Geometric Mean Concentrations in PCV13 Subjects

Tenderness

Swelling

Redness

Fever

Other Systemic Reactions

Adverse Events

Conclusions
Encephalitic Alphaviruses

Attributes of DNA Vaccines

Alphavirus DNA Vaccines

Electroporation Delivery of DNA

VEEV DNA Immunogenicity in Mice

VEEV DNA Protection in Mice

VEEV DNA in Nonhuman Primates

Combined Alphavirus DNA in Mice

Summary and Conclusions
Human Cytomegalovirus (CMV)

CMV Plasmid DNA Constructs

Poloxamer CRL1005 Delivery System

Phase 1 Clinical Trial Results

CMV Phase 2 HCT Trial

Phase 2 Clinical Trial: Hypothesis and Assumptions

HCT Vaccine Strategy: Recipient Immunization

Recipient Immune Responses: Pre-vaccination

Recipient Immune Responses: Day 56

Recipient Immune Responses: Day 84

Summary
Immune Responses in Humans to AERAS-402, Crucell Adeno35-vectored TB Vaccine Candidate
Jerald C. Sadoff, MD
Tuesday April 28 at 4:45 pm

*Dr. Sadoff did not submit a note taking outline
On the Menu…

BCG Protects against Disseminated Forms of TB in Infants

Conclusion 1: BCG works!

BCG-Induced Protection against Pulmonary TB is Variable

Reasons cited for variable protection against TB after BCG

Effect of Route and Strain of BCG on the Induced Immune Response

Effect of Route of BCG on Efficacy: Design

Effect of Route of BCG on Efficacy: Results

Effect of Age of Delivery of BCG on the Induced Immune Response: Design
Preparation, Transport to Clinic

Lab: Transfer to Water Bath

Effect of Age of Delivery of BCG on the Induced Immune Response: Results

Conclusion 2: We know Very Little about BCG

To Determine Biomarkers of Protection against TB, Following BCG Vaccination Biomarker Approach

IFN-γ is not a BCG-Induced Immune Correlate of Protection

Neither is Any Other Cytokine on its Own

Models Asking Combinations of Cytokines may Delineate Protection

Models from UNstimulated Blood also Delineate Protection

Conclusions 3: Plasma Cytokines as Biomarkers of Protection
<table>
<thead>
<tr>
<th>Progress Made with Subunit Vaccines</th>
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<tbody>
<tr>
<td>Peter Andersen, DVM, DMSC</td>
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<tr>
<td>Wednesday, April 29 at 8:30 am</td>
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</tbody>
</table>

- BCG – An Efficient Vaccine for Children
- Blocking BCG Replication in Sensitized Donors
- BCG boost – 3 Different Strategies
- Success Criteria for BCG Booster Vaccines
- Subunit Vaccines in Clinical Trials
- The Esat-6 Gene Family
- The H1/H4 Subunit Vaccines
- H1/H4 Vaccines – Animal Model Data
- Vaccine Dose and T Cell Responses
- Vaccine Dose and T Cell Subpopulations
- Dose and Protection in The Mouse Model
Development of Ag85B/ESAT6 Specific Responses

Cytokine Expression Patterns – TB Infection Versus Vaccination

Multifunctional T Cells Express More Cytokine/Cell

Ag85B-ESAT6 Vaccine- Single-Centre, Open Label, Phase 1 THYB Trials

Ag85B-ESAT6 Vaccine-Single-Centre, Exploratory THYB-01 Trial

Ag85B-ESAT6 Vaccine-Single-Centre, Exploratory THYB-01 Trial

Ag85B-ESAT6 Vaccine-THYB-01 Immunogenicity Overview

Ag85B-ESAT6 Vaccine-THYB-01: Phase I in 36 Volunteers

From The Lab to The Clinic

Preclinical and Clinical Evaluation of a Post-Exposure TB Vaccine

Four Stages in The Natural History of Tuberculosis

The Ideal Solution – a Multi-Stage Vaccine
### Clinical Trials of MVA85A, Virally Vectored New Tuberculosis Vaccines
Helen McShane, FRCP, PhD
Wednesday, April 29 at 9:00 am

MVA85A

Design of Studies with MVA85A

Summary of Clinical Trials with MVA85A Since 2002

Outcome Measures in All Trials

Safety data

BCG – MVA85A Induces High and Sustained Antigen 85A-Specific Immune Response

Broad Range of CD4+ T Cell Epitopes

Peak and Plateau Responses are Independent of Interval Between BCG and MVA85A

MVA85A Induced Antigen Specific CD4+ T Cells are Highly Polyfunctional

CFSE Dilution Studies

Comparison of Different Methods for Quantifying IFN-γ Secretion Used in TB Vaccine Trials

Ex Vivo ELISPOT Responses in High Dose UK Trial

Cultured, Diluted Whole Blood Total IFNγ Responses - ELISA
Ex Vivo Whole Blood ICS – CD4+ T Cell Responses

BCG – MVA85A Vaccination Induces Antigen 85A-Specific CD8+ T Cell Responses

TGF-β1

Studies with MVA85A in M.tb Latently Infected Adults

MVA85A is as Immunogenic in Latently Infected Subjects as in BCG Vaccinated Subjects

Quantitative Increase in 85A

UK Studies in HIV Infected Subjects

Immunogenicity of MVA85A in HIV Infected Subjects in the UK (n = 10): Summed Peptide Pools

South African Phase IIa Studies

Ex-vivo IFN-γ Elispot Responses in Adults in South Africa: Ag85A Peptides

Sustained Responses in South African Adults (n = 24)

Polyfunctional Cells in South African Adults (n = 13)

Dose Finding and Non Interference in Gambian Infants

Summary of Findings to Date

Does it Work?

Infant Phase IIb Efficacy Trial
18  Update on Veterinary Tuberculosis Vaccines  
Ray Waters, DVM, PhD  
Wednesday, April 29 at 9:30 am

Presentation Outline

Co-Discovery (Human and Bovine TB)

BCG Efficacy

Bovine TB

Bovine TB Vaccines

Vaccine Approaches with Cattle

Vaccine Approaches with Wildlife

Michigan, Proposed Field Strategy
Neonatal Calf Vaccine Model

TB Vaccine Testing

Opportunities / Relevance, Calf Model

Gross and Histopathology, Disease Scoring

Radiographic Morphometry, Mean ± SEM

Quantitative Culture, Tracheobronchial Lymph Node

Cultured ELISPOTs: A Method to Assess Memory T Cells

Central Memory Responses

Future Studies
Background Pediarix® (DTaP-HepB-IPV)

Background Advisory Committee on Immunization Practices (ACIP) preference for combination vaccines

Background Fever (≥38°C) within 4 days after vaccination in pre-licensure studies

Background Manufacturer-sponsored phase IV study

Objectives

Study design

Study population

Number of DTaP-HepB-IPV or DTaP (Infanrix*) doses administered, by calendar year, 2000-2006

Number of DTaP-HepB-IPV or DTaP (Infanrix*) doses administered, by age of child, 2000-2006

Risk of MAF and seizure day 0–3 after vaccination, any dose, 2000–2006

Risk of MAF day 0–3 after vaccination, by dose number, 2000–2006

Strengths

Limitations

Conclusions
Financial Disclosures

Impact of Autoimmune diseases (AD)

Study Aims

METHODS - Database

METHODS-Should be a Picture

Cases: 11 AD Categories-Abstract Only had 4 Diseases

Identification of Cases

Identification of Cases

Identification of Cases

Identification of Cases

Incidence of Autoimmune Diseases Using Medical Records Review

Incidence of Autoimmune Diseases Using Medical Records Review
Rationale

Objectives

Selection of VAERS Cases

Standard Assessment

Process

Agreement Score

Case Discussion & Resolution of Discrepancies

108 Adverse Events Evaluated from the 100 VAERS

Independent Agreement Scores for 108 Adverse Events

Post-discussion Agreement Scores for 108 AE’s

Causality Assessment by Severity of 108 Adverse Events

Conclusions
Goals of Vaccine Safety Surveillance

VSD and RCA

Key Features of Our Method

Key Features (cont.)

Aspects of the Alpha Spending Plan

Lan DeMets Alpha Spending

Thresholds for Nominal p-values, by Total Number of Looks Planned, Log-Linear Spending

Thresholds for Nominal p-values, by Total Number of Looks Planned (continued)

Graphs and Charts:

Issues We’re Working On:

Summary
Outline

Immunization Safety Office (ISO): Scientific Functions and Infrastructures

Background

Methods: Identifying Possible 5-year Research Needs

ISO Agenda Draft Recommendations

ISO Agenda Draft Recommendations

ISO Agenda Draft Recommendations

ISO Agenda Draft Recommendations

ISO Agenda Draft Recommendations

ISO Agenda Draft Recommendations

Possible 5-Year Priority Research Need Case Example A-II:

Summary Published Pediatric LAIV Studies and Wheeze

Vaccine Safety Datalink (VSD): LAIV and Wheezing Study*

VSD LAIV and Wheezing Study Definitions*

Clinical Immunization Safety Assessment (CISA) Network Pilot Study:

Summary
New Vaccine Platforms for Tuberculosis

Recombinant replication-deficient Adenoviral

Single respiratory mucosal

Single respiratory mucosal AdAg85A immunization

Single respiratory mucosal AdAg85A immunization

Single respiratory mucosal AdAg85A immunization

Following AdAg85A intranasal immunization

Kinetics and phenotype of airway luminal Ag85A-specific CD8 T cells

Proliferative status of airway luminal Ag85A-specific CD8 T cells

Do airway luminal Ag85A-specific memory CD8 T cells proliferate in situ?

Do airway luminal Ag85A-specific memory CD8 T cells proliferate in situ?

Does in situ proliferation of airway luminal Ag85A-specific CD8 T cells require specific Ag stimulation?

Does in situ proliferation of persisting Ag85A-specific CD8 T cells depend on continuous Ag-presentation?

Conclusions
Plasmid Encoded Rhesus IL-12 Improves SIVgag

Total HIV-specific IFN-g ELISPOT Responses

Questions:

Rational for monitoring the quality of the immune response:

Approach to monitoring the quality of the immune response:

Rh-036: Study design

Mean (±SE) Total HIV-specific IFN-g/IL-2 ELISPOT responses over time

Polyfunctionality of the Total HIV-16101 env gp160 peptide pool

Magnitude and polyfunctionality of the env-specific memory T cell response

WLV-Rh-053b: Study design

Post-boost HCV-specific IFN-g ELISPOT responses

Polyfunctionality of the Total HCV NS3 peptide pool-specific CD8+ T cell response

Quality of NS3 peptide pool-specific central memory (CM)

Summary
Threat of Pandemic Avian Influenza

Recombinant H5 Antigen – Influenza A/Indonesia/05/05

Nanoemulsion Adjuvant –

Dose Ranging and Vaccination

End Titer of Serum IgG - ELISA

Avian Influenza – Classification

Cross Clade Reactivity - ELISA

IgA in Bronchial Aveolar Lavage Fluid

Conclusions
Introduction

Study Purpose

Study Subjects

HLA Genotyping and Rubella EIA

Statistical Methods

Statistical Methods – HLA Haplotypes

Characteristics of the Study Populations

Demographic and Clinical Variables in a Combined Cohort

Rubella Antibody and HLA Supertypes*

Rubella Antibody and HLA Haplotypes*

Conclusions

Limitations
Background

Subjects

Design

Demography

Seroprotection/seropositivity rates (95% CI) before and one month after the booster dose

Anti-diphtheria and anti-tetanus geometric mean concentrations

Booster response rates (95% CI) one month after the booster dose

Anti-pertussis geometric mean concentrations

Solicited local and general symptoms within 4 days of vaccination

Safety results

Conclusions
The Impact of Malaria – A Pressing Global Issue

We Have Important New Tools to Control Malaria

And There Are Encouraging Results from Scale-Up Scale of These Interventions

But Sustainable Impact Will Be Costly and Difficult to Maintain in High Transmission Areas

Vaccines Should Work Seamlessly with Other Proven Interventions Malaria Interventions

What Is the Global Health Community Doing?

Global Malaria R&D Investments Are Increasing

Investments Required Across the R&D Spectrum

Malaria Life Cycle Reveals Promising Vaccine Mosquitoes Strategies

Clinical Development is a Long & Complex Process

The Global Malaria Vaccine Pipeline

RTS,S/AS – The Most Advanced Malaria Vaccine Candidate

Protection Is Dependent On Adjuvantaion

Clinical Trials of RTS,S in Malaria-Naïve Adults

Typical RTS,S Experimental Challenge Results Show Complete or ≈ 60% Partial Protection
Quantitative Analysis of Challenge Model

Proof of Concept Trial in Gambian Adults

A Paradigm Shift for Pre-Erythrocytic Vaccines

Goals of MVI/GSK RTS,S Development Program

RTS,S Pediatric Clinical Development Plan

Selecting the Optimal Adjuvant Formulation

Promising Safety Profile Across RTS,S in Controlled Trials Children

Immunogenicity Profile Across Age Groups

Vaccine Efficacy Across Four Phase IIb Trials

Four Year Follow-up of Vaccine Efficacy, Mal 026

RTS,S Phase III Program

Phase III Study Design

Primary Analysis Plan - 12 Months Post Dose 3

Regulatory Pathway

Malaria Eradication Must Encompass Both Pf and Pv

MVI’s Portfolio of Second Generation Strategies

Big Challenges Lie Ahead for the Development of Next Generation Malaria Vaccines (2016+)

Conclusions
The Challenge

Designing and Mining Pathogen Genome Databases

The Philosophy Behind PlasmoDB

Computational Strategies for Identifying & Prioritizing Candidate Vaccine Antigens

Gene Pages: Structure, Expression, Antigenicity, Phenotypes, etc

Genome Browser Shows SNP Location in Greater Detail (zoomable)

Identifying Candidate Vaccine Antigens

Vaccine Target Query

Vaccine Target Query: Signalpeptide

Vaccine Target Query: Transmembrane Domain

Vaccine Target Query: Combine Queries: SP ± TM Domains
Vaccine Target Query: Transcribed in Schizonts

Vaccine Target Query: Pf + Pv, but Not Mammals

Vaccine Target Query: Diversifying Selection

Vaccine Target Query: Combine Queries & Download Results

Nature

brccentral

EuPath DB

Functional Inference, Based on Orthology

Identification of Ortholog Groups:

Computational Identification and Prioritization of Candidate Drug Targets

Think Globally, Act Locally:
Vaccine Resistant Malaria

Genetic Diversity and Vaccine Efficacy

Genetic Diversity in Leading Malaria Vaccine Antigens

Importance of Molecular Epidemiology Investigations

No Selection of Non-Vaccine CSP Alleles by RTS,S

The Approach

Blood Stage Vaccines

MSP-1

FMP1/AS02A: 3D7-based MSP1 Vaccine

Genotyping Results

MSP-119 Haplotypes in Bandiagara 1999-2001

Variation over Time and Age

Hypothesis:

Within-Host Dynamics:

Reducing MSP-1 Haplotypes to “Serotypes” to Select Strains for Multivalent Vaccines

Implications for Malaria Vaccine Design, Efficacy, and Testing

Apical Membrane Antigen 1 (AMA-1)

AMA-1
AMA-1 Candidate Malaria Vaccine FMP2.1/AS02A

FMP2.1/AS02A Immunogenicity

Molecular Epidemiology of AMA-1: Study Objective

Study Design

Genotyping and Analysis

Genotyping Results

214 AMA-1 Haplotypes in Bandiagara

AMA-1 Polymorphism in Mali Mapped on Crystal Structure

Identifying Immunologically Relevant Diversity

Within-Host Dynamics of AMA-1 Polymorphism in Prospective Longitudinal Cohort Study

Within-Host Dynamics of AMA-1 Polymorphism

Identifying Immunologically Relevant Diversity

Distribution of AMA-1 c1L Haplotypes in Bandiagara

Global Distribution of AMA-1 c1L Haplotypes

Identifying Immunologically Relevant Diversity

Population Structure Approach: Whole Ectodomain

Population Structure Approach: Domain I-c1

Narrowing the Amount of Diversity?

Alternative Approaches to Developing a Broadly Protective Malaria Vaccine
22  Metabolically Active, Non Replicating Plasmodium Falciparum Sporozoite Vaccines: Rationale, Manufacturing Metabolically Active, Non Replicating Plasmodium Falciparum Sporozoite Vaccines: Rationale, Manufacturing Challenges and Clinical Trials
Stephen L. Hoffman, MD
Wednesday, April 29 at 2:15 pm

*Dr. Hoffman did not submit a note taking outline
POSTER SESSION
P1 Selected prfA* Mutations in Recombinant Attenuated Listeria monocytogenes Strains Augment Expression of Foreign Immunogens and Enhance Vaccine-Elicited Humoral and Cellular Immune Responses

L. Yan
University of Illinois at Chicago, Chicago, IL

P2 The Use of Vaccine Coverage Surveys to Assess and Improve the Quality of Immunization Programs

S. O. Sow¹, E. N. Dembele¹, J. B. Milstien², K. Kotloff²
¹Centre pour le Développement du Mali (CVD-Mali), Ministry of Health, MALI, ²University of Maryland School of Medicine, Baltimore, MD

P3 Functional Studies of Enterotoxigenic Escherichia coli (ETEC) CS6, with the View to Vaccine Development for Use in Humans

J. Tobias
The Sahlgrenska Academy of Göteborg University, Institute of Biomedicine, Göteborg, SWEDEN

P4 Rotavirus Diarrhoeal Disease Vaccine Coverage in Nigeria: Perceived Barriers and Potential Solutions

N. Idika, P. Anochie, A. Adesanmi, A. Adeiga
National Institute of Medical Research, Lagos, NIGERIA

P5 Evaluation of the Immunogenicity and Efficacy of Inactivated Venezuelan Equine Encephalitis Virus (VEEV) Vaccine Candidates in BALB/c Mice

S. Martin¹, M. Parker², P. Glass², R. Bakken², C. Lind², P. Garcia², E. Jenkins¹, M. Hart¹, D. Fine¹
¹DynPort Vaccine Company, Frederick, MD, ²United States Army Medical Research Institute of Infectious Diseases, Frederick, MD

P6 Validation of a Mouse Assay for Evaluation of Recombinant Botulinum Vaccine Potency

J. Shearer¹, M. Vassar², N. Niemuth², K. Metcalfe¹, I. Henderson¹
¹DynPort Vaccine Company LLC, a CSC company, Frederick, MD, ²Battelle Biomedical Research Center, West Jefferson, OH

P7 A Five Year Follow up of Antibody Response in Children Vaccinated with Single Dose of Live Attenuated SA-14-14-2 Japanese Encephalitis Vaccine: Immunogenicity and Anamnestic Response

J. B. Tandan¹, Y. M. Sohn²
¹Japanese Encephalitis Support Group, Kathmandu, NEPAL, ²Yonsei University, Seoul, REPUBLIC OF KOREA

P8 Intranasal Immunization against Mycobacterium tuberculosis Infection Using Bacillus subtilis Spores as the Delivery Vehicle

L. Yu, S. Cutting
University of London, Surrey, UNITED KINGDOM

P9 Adjuvant-Free Vaccine Potentiation Technique Demonstrated with Influenza Peptide M2e in Mice

P. M. Simon¹, B. Selling²
¹Paul Simon Consulting, LLC, Wilmington, DE, ²Impact Biologics, Inc., Wallingford, PA
General Posters (P1-P44), Harborside Foyer

P10 Safety, Tolerability and Immunogenicity of Recombinant Protective Antigen (rPA) Anthrax Vaccine compared with Anthrax Vaccine Adsorbed (AVA) in a Healthy Population
M. Duchars¹, I. Gray², A. Lockett², L. Curry¹
¹PharmAthene, Annapolis, MD, ²PharmAthene UK, Billingham, UNITED KINGDOM, ³Quintiles, South Bend, IN

P11 Evaluation of a Ricin Vaccine Candidate (RVEc) for Human Toxicity Using an In Vitro Vascular Leak Assay
A. I. Porter, L. DaSilva
US Army Medical Research Institute for Infectious Diseases, Frederick, MD

P12 Rift Valley Fever Virus NSs Protein Promotes Post-transcriptional Downregulation of Protein Kinase PKR and Inhibits eIF2α Phosphorylation
The University of Texas Medical Branch, Galveston, TX

P13 Nasal Administration of W805EC-Adjuvanted Influenza Vaccine in Mice
T. Hamouda¹, A. Myc², N. Mank², J. Knowlton², J. Sutcliffe³, J. R. Baker, Jr.¹
¹NanoBio Corp, Ann Arbor, MI, ²University of Michigan, Ann Arbor, MI

P14 Intramuscular Delivery of a Cholera DNA Vaccine Primes Both Systemic and Mucosal Protective Antibody Responses Against Cholera
G. Xu¹, S. Wang², L. Zhuang³, A. Hackett², L. Gu¹, L. Zhang¹, C. Zhang¹, H. Wang³, Z. Huang¹, S. Lu²
¹1st Affiliated Hospital, Nanjing Medical University, Nanjing, CHINA, ²U. Mass. Med. School, Worcester, MA, ³Jiangsu CDC, Nanjing, CHINA

P15 A Global Cost-Effectiveness Evaluation of the Impact of Potential Innovations in Measles Vaccination in Developing Countries
L. P. Garrison¹, C. T. Bauch², B. W. Bresnahan¹, T. K. Hazlet¹, S. Kadiyala¹, D. L. Veenstra¹
¹University of Washington, Seattle, WA, ²University of Guelph, Guelph, CANADA

P16 Eimeria-derived Macrophage Migration Inhibitory Factor (MIF)-mediated Immunoregulation of Host Innate Immunity
S. I. Jang, S. H. Lee, Y. H. Hong, D. K. Kim, M. Pages, H. S. Lillehoj
Animal and Natural Resources Institute, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, MD

P17 Assess Kinetics of HDP Depot Effect and Trafficking via Distinct Routes of Administration in Mice
T. Dybvig
VIDO, Saskatoon, CANADA

P18 Chitosan Encapsulated Multivalent DNA Vaccine for RSV
S. Boyoglu¹, K. Vig¹, T. Murtada¹, S. Pillai¹, V. Dennis², S. R. Singh¹
¹Alabama State University, Montgomery, AL, ²Tulane National Primate Research Center, Louisiana State University, Covington, LA

P19 Evaluation of Systemic and Mucosal B Cell Immune Response to the Oral Challenge with Shigella Dysenteriae 1 in Cynomolgus Macaques
M. Maciel, Jr.¹, A. Khan¹, J. K. Simon¹, R. Wahid¹, W. D. Picking², M. B. Sztein¹
¹Center for Vaccine Development, University of Maryland, Baltimore, MD, ²University of Kansas, Lawrence, KS
P20  A Universal Influenza Vaccine: Generating Broad Immunity using an M2e/NP Fusion Protein
T. dela Cruz*, H. Ge†, B. Milley†, D. Yalda†, C. Amuε†, D. Higgins†
†Dynavax Technologies, Berkeley, CA, ‡Dynavax-Europe, Düsseldorf, GERMANY

P21  The A1 Subunit of Cholera Toxin as an Adjuvant for DNA Vaccines
K. C. Bagley
Profectus Biosciences, Baltimore, MD

P22  Vaccination Strategies Tailored to Regions with Different Endemicity for Hepatitis B
Netherlands Vaccine Institute, Bilthoven, NETHERLANDS

P23  Neurovirulence and Immunogenicity of Highly Attenuated rVSV/HIV-1 Vaccine Vectors in Non-Human Primates
D. Clarke
Profectus Biosciences, Tarrytown, NY

P24  Protection against Heterologous SHIV Challenge Offered by Immunization of Rhesus Macaques with a Subunit Immunogen that Mimics the Transition State Structure Presented by CD4 Bound HIV Envelope
T. R. Fouts†, R. Pal‡, G. Lewis‡, A. DeVico³
†Profectus BioSciences, Baltimore, MD, ‡Advanced BioSciences Laboratory, Rockville, MD, ³Institute of Human Virology, Baltimore, MD

P25  Cytokine Production by Naïve Murine Dendritic and Spleen Cells in Response to Neospora Caninum Stimulation
X. Feng
U.S. Department of Agriculture, Animal Parasitic Diseases Lab, Beltsville, MD

P26  Size and Shape Specific Particle Delivery System for Vaccines
A. Murphy†, L. Copp†, A. Galloway†, J. Kindig†, S. Roth†, J. White†, J. DeSimone², B. Hubby²
†Liquidia Technologies, Research Triangle Park, NC, ²The Departments of Chemistry and Pharmacology, University of North Carolina, Chapel Hill, NC

P27  The Effect of Cefpodoxime on Neisseria meningitidis Carriage
K. Winter†, K. Harriman†, R. Schechter†, L. Wasson², S. Schmink³, C. Hatcher³, K. Emery³, T. Clark³
†California Department of Public Health, Richmond, CA, ²Kern County Department of Public Health, Bakersfield, CA, ³Centers for Disease Control and Prevention, Atlanta, GA

P28  Modeling the National Pediatric Vaccine Stockpile: Supply Shortages, Health Impacts, and Cost Consequences
S. S. Shrestha, G. S. Wallace, M. I. Meltzer
Centers for Disease Control and Prevention, Atlanta, GA
P29  NK Cells Mediate Cytotoxicity of Parasitized Host Cells and Induce the Egression of *Eimeria* Sporozoites

X. Dong¹, G. H. Abdelnabi¹, H. Jin¹, M. H. Abdillea¹, H. S. Lillehoj², X. Suo³
¹China Agricultural University, Beijing, CHINA, ²Animal and Natural Resources Institute, Agricultural Research Service, United States Department of Agriculture, Beltsville, MD

P30  LEAPS Immunogens Direct the Immune Response by Promoting Development of Human Immature Dendritic Cells into IL12 Producing Dendritic Cells (DC1s)

K. S. Rosenthal¹, P. R. Taylor¹, G. K. Koski², D. H. Zimmerman³
¹Northeastern Ohio Universities Colleges of Medicine and Pharmacy, Rootstown, OH, ²Cleveland Clinic Foundation, Cleveland, OH, ³Cel-Sci Corporation, Vienna, VA

P31  Retrospective Study of *N. meningitidis* Serogroup B-specific SBA Activity in Sera from Peruvian Infants Vaccinated with PedvaxHIB® or ActHIB®

M. J. Caulfield¹, A. Payne¹, L. Indrawati¹, J. Heinrichs¹, C. Przybylecki¹, M. Penny², J. Dargan³, T. Mast¹, W. Strauss¹, J. Boslego⁴
¹Merck Research Labs, West Point, PA, ²Instituto de Investigacion Nutricionalb, Lima, PERU, ³CNN, Atlanta, GA, ⁴PATH, Washington, DC

P32  Persistence of Influenza Antibody Seroprotection in Lung Transplant Patients Over Five Seasons

J. J. M. Moran, A. J. Darga, K. A. Rohde, M. J. Faber, M. S. Hayney
University of Wisconsin School of Pharmacy, Madison, WI

P33  Dynamics of Maternal Neutralizing Antibody against Enterovirus 71 in Taiwanese Young Infants

S. Luo¹, P. Chiang¹, A. Chao¹, G. Liou¹, R. Lin², T. Lin², M. Lee¹
¹National Health Research Institutes, Zhunan, TAIWAN, ²Chang-Gung Children Medical Center, Lincou, TAIWAN

P34  Development of a Challenge Model to Evaluate Vaccine Candidates Against African Trypanosomiasis in Cattle

E. Knapp¹, R. Flores¹, G. Lubega², A. Nanteza², S. Eyanu², M. Namayanza², R. Prichard³, D. Holtzman⁴, V. Yusibov¹
¹Fraunhofer USA Inc., Center for Molecular Biotechnology, Newark, DE, ²Dept. for Veterinary Parasitology and Microbiology, Makerere University, Kampala, UGANDA, ³Institute of Parasitology, McGill University, Montreal, CANADA, ⁴The Bill and Melinda Gates Foundation, Seattle, WA

P35  Prophylactic HIV-1 Vaccine Candidates Based on Structured gp41 N-heptad Repeat Peptides

J. G. Joyce¹, E. Bianchi², M. Miller¹, X. Liang¹, M. Finotto², P. Ingallinella², P. McKenna², M. Citron¹, E. Ottinger¹, R. Hepler¹, R. Hrin¹, D. Nahas¹, C. Wu¹, M. Caulfield¹, A. Pessi², J. Shiver¹, P. Kim¹
¹Merck and Company, West Point, PA, ²Merck and Company, Rome, ITALY

P36  Human Complement Bactericidal Activity in a Phase 2 Safety and Immunogenicity Study following Vaccination with a New Meningococcal A Conjugate Vaccine in Healthy West African Toddlers

B. Mocca¹, S. Sow², B. Okoko³, M. P. Preziosi³, E. Marchetti³, M. Tapia², R. Adegbola², F. C. Haidara², A. Akinsola³, R. Borrow⁴, G. Carlone⁵, P. Kilkarni⁵, M. Hassan-King⁶, M. LaForce⁶, S. Viviani³, M. C. Bash⁷
¹PATH, Bethesda, MD, ²Centre pour les Vaccins en Development, Bamako, MALI, ³Medical Research Council, Basse, GAMBIA, ⁴WHO, Geneva, SWITZERLAND, ⁵PATH, Ferney-Voltaire, FRANCE, ⁶Health Protection Agency, Manchester, UNITED KINGDOM, ⁷Centers for Disease Control and Prevention, Atlanta, GA, ⁸Serum Institute of India Ltd, Pune, INDIA, ⁹Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD
P37  A Multisystem Approach for the Evaluation of Inactivation Efficiency for Venezuelan Equine Encephalitis Virus (VEEV) Vaccine Candidates

E. Jenkins¹, M. Parker², R. Bakken², P. Glass², P. Garcia², B. Grimm³, S. Martin¹, D. Fine¹
¹DynPort Vaccine Company LLC, a CSC company, Frederick, MD, ²U.S. Army Medical Research Institute for Infectious Disease, Fort Detrick, Frederick, MD, ³SAFC Pharma, Carlsbad, CA

P38  B. Pertussis Transmission in Household and Duration of Protection of DTaP Immunizations

Boston Medical Center and Boston University School of Medicine, Boston, MA

P39  In Vivo Immunogenicity of Mycobacterium Tuberculosis T-cell Epitopes Discovered using Immunoinformatics

L. Moise
EpiVax, Inc., Providence, RI

P40  T-cell Epitope Vaccine Protects HLA Transgenic Mice Against Lethal Vaccinia Challenge

L. Moise
EpiVax, Inc., Providence, RI

P41  A Randomized, Double-blind, Controlled Trial of the Comparative Viremia, Immunogenicity and Safety of Live, Attenuated 17D Yellow Fever Vaccine Given in Combination with Human Immune Globulin or Placebo

S. Edupuganti
Emory University School of Medicine, Decatur, GA

P42  Thermal Stabilisation of Influenza Haemagglutinin Using Proprietary Stabilisers

J. Drew
Stabilitech, London, UNITED KINGDOM

P43  Papillomavirus-Based Vaginal Delivery of DNA Vaccine Plasmids Expressing Respiratory Syncytial Virus Antigens

K. Corbett¹, R. Kines², J. Nicewonger¹, T. Johnson¹, M. Chen¹, J. Schiller², C. Buck², B. Graham¹
¹Vaccine Research Center, National Institutes of Health, Bethesda, MD, ²National Cancer Institute, Bethesda, MD

P44  A B Cell-deficient Pig Model Produced By Knock-out of the Immunoglobulin Heavy Chain Locus

M. Mendicino¹, J. Ramsoondar¹, C. Phelps¹, T. Vaughan¹, S. Ball¹, T. LeRoith², J. Monahan¹, S. Chen¹, A. Dandro¹, J. Boone¹, P. Jobst¹, A. Vance¹, N. Wertz¹, I. Polejaeva¹, Y. Dai¹, J. Butler³, K. Wells¹, D. Ayares¹
¹Vaccine Research Center, National Institutes of Health, Bethesda, MD, ²National Cancer Institute, Bethesda, MD
on Vaccine Research

Maurice R. Hilleman Early-stage Career Investigator Award Semi-Finalists
(P45 – P53), Laurel Room

P45 Revisiting Original Antigenic Sin Response to Influenza Virus
J. Kim, I. Scountzou, R. Compans, J. Jacob
Emory University, Atlanta, GA

P46 Hospitalizations Associated with Pneumonia and Influenza in the Philippines, 2004-2006: Implications for Prevention Using Vaccine and Non-vaccine Interventions
S. Kim1, P. Kilgore1, G. S. Diaz2, L. C. Bravo3, M. R. Z. Capeding4, J. A. Santos5
1International Vaccine Institute, Seoul, REPUBLIC OF KOREA, 2Philippine Health Insurance Corp., Pasig, PHILIPPINES, 3Philippine General Hospital, Manila, PHILIPPINES, 4Research Institute for Tropical Medicine, Muntinlupa, PHILIPPINES, 5Philippine Children’s Medical Center, Quezon, PHILIPPINES

P47 Leptosomes: Immune Response and Prophylactic Efficacy in Hamster Model of Leptospirosis
S. M. Faisal, Y. Chang
Cornell University, Ithaca, NY

P48 Needle-Free Intranasal Immunization with P. falciparum CS Protein Conjugated to Flagellin, a Potent TLR5 Agonist, Elicits Protective Systemic Humoral Responses
D. Carapau1, R. Mitchell1, A. Price2, E. Nardin1
1Medical Parasitology Dept., NYU School of Medicine, New York, NY, 2VaxInnate Corporation, New Haven, CT

P49 Production of the Live Sporozoite Vaccine ITM: Protection against East Coast Fever
E. Patel, P. Toye
International Livestock Research Institute, Nairobi, KENYA

P50 Bacterial Co-Infections in Canadian Children Hospitalized With Influenza, 2004 - 2008
L. J. Sauvé1, J. BETTINGER1, W. Vaudry2, D. Moore3, S. Halperin4, R. Bortolussi5, B. Law5
1University of British Columbia, Vancouver, CANADA, 2University of Alberta, Edmonton, CANADA, 3McGill University, Montréal, CANADA, 4Dalhousie University, Halifax, CANADA, 5Public Health Agency of Canada, Ottawa, CANADA

P51 Epidemiological, Clinical, and Laboratory Features of Varicella Zoster CNS Disease 10 Years after Introduction of the Varicella Vaccine
1Stanford University School of Medicine, Stanford, CA, 2California Department of Public Health, Richmond, CA, 3Kaiser Permanente Vaccine Study Center, Oakland, CA, 4Centers for Disease Control and Prevention, Atlanta, GA

P52 Prevalence of Rotavirus Infection in Nicaraguan Children Following a Universal Rotavirus Immunization Program
S. Becker-Dreps1, M. Paniagua2, M. G. Hudgens1, D. Morgan1, F. Espinoza2
1University of North Carolina at Chapel Hill, Chapel Hill, NC, 2University of Nicaragua, Leon, NICARAGUA
P53  Evaluation of Combined Effects of Influenza Vaccine to Mothers and Pneumococcal Conjugate Vaccine to Infants: Results from a Randomized, Double-blind, Controlled Trial

S. B. Omer1, K. Zaman2, E. Roy3, S. E. Arifeen2, R. Raqib2, M. C. Steinhoff3

1Global Health, Emory University, Atlanta, GA, 2International Centre for Diarrhoeal Disease Research, Dhaka, BANGLADESH, 3Johns Hopkins University, Baltimore, MD

P54  Response to a Booster Dose of Hepatitis B Vaccine Administered 6-11 years after Primary Immunization in Moldova

A. Vranceanu-Benes1, P. Iarovoi1, C. Spínu1, O. Benes1, N. Gaisan3, V. Ribalco1, E. Pascal4, L. Cimpoi5, V. Sofronie6, G. Baleac1, J. Drobeniuc1

1National Center for Preventive Medicine, Chisinau, REPUBLIC OF MOLDOVA, 2Center for Preventive Medicine, Cahul, REPUBLIC OF MOLDOVA, 3Center for Preventive Medicine, Comrat, REPUBLIC OF MOLDOVA, 4Center for Preventive Medicine, Hincesti, REPUBLIC OF MOLDOVA, 5Center for Preventive Medicine, Telenesti, REPUBLIC OF MOLDOVA, 6Center for Preventive Medicine, Edinet, REPUBLIC OF MOLDOVA, 7Center for Preventive Medicine, Singeriei, REPUBLIC OF MOLDOVA, 8Centers for Disease Control and Prevention, Atlanta, GA

P55  Enhancement of Mucosal and Cellular Immune Response in Mice by Vaccination with Respiratory Syncytial Virus DNA Encapsulated with Transfersome

J. Xu

Pediatric Institute, Children's Hospital, Fudan University, Shanghai, CHINA

P56  Safety and Immunogenicity of a Candidate Tuberculosis (TB) Vaccine, MVA85A, in Healthy Gambian Infants Previously Vaccinated with BCG

M. O. Ota1, O. A. Owolabi1, O. A. Odutola1, P. K. Owiafe1, R. A. Adegbola1, H. McShane2

1Medical Research Council Laboratories (United Kingdom), Banjul, GAMBIA, 2Centre for Clinical Vaccinology and Tropical Medicine, Headington, UNITED KINGDOM

P57  Development and Preclinical Evaluation of Ad5-based Plasmodium vivax Vaccines derived from the Blood Stage Merozoite Surface Protein 1 (MSP-1)

C. O. Esimone1, A. Valderrama A2, D. N. Onah3, J. Steitz4, S. Herrera2, A. Gambotto4

1Department of Pharmaceutics and Pharmaceutical Microbiology, University of Nigeria, Nsukka, NIGERIA, 2Malaria Vaccine and Drug Development Center, Cali, COLOMBIA, 3Department of Veterinary Parasitology & Entomology, University of Nigeria, Nsukka, NIGERIA, 4Department of Surgery, University of Pittsburgh, Pittsburgh, PA

P58  Dengue Virus Type 2 Recognizes Carbohydrate Moiety of Glycosphingolipids in Mammalian and Mosquito Cells

S. Wichit

Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, THAILAND
P59 Antibody and Cytokine Responses to *P. falciparum* Glutamate Rich Protein (GLURP) and Merozoite Surface Protein (MSP3) in Ghanaian Children

H. Lamptey
Noguchi Memorial Institute for Medical Research, Immunology Department, University of Ghana, Accra, GHANA

P60 Construction and Evaluation of a Candidate DNA Vaccine against Psittacine Beak and Feather Disease in South Africa

K. Kondiah, J. Albertyn, R. R. Bragg
University of the Free State, Bloemfontein, SOUTH AFRICA

P61 A Complex Formation of Rhopty Neck Protein 2 with a Microneme Protein, AMA1, in *Plasmodium falciparum*

J. Cao¹, O. Kaneko², A. Thongkukiatkul³, M. Tachibana⁴, H. Otsuki⁴, T. Tsuboi⁵, M. Torii⁵
¹Jiangsu Institute of Parasitic Diseases, Wuxi, CHINA, ²Institute of Tropical Medicine, Nagasaki University, Nagasaki, JAPAN, ³Faculty of Science, Burapha University, Chonburi, THAILAND, ⁴Ehime University Graduate School of Medicine, Toon, JAPAN, ⁵Cell-Free Science and Technology Research Center, Ehime University, Matsuyama, JAPAN

P62 The Expression and Characterization of Cholera Toxin B subunit-Pneumolysin Toxoid Fusion Protein

A. P. M. Arêas¹, M. L. S. Oliveira², E. N. Miyaji², L. C. C. Leite², P. L. Ho²
¹Universidade Federal do ABC, Santo André, BRAZIL, ²Instituto Butantan, São Paulo, BRAZIL

P63 Emergence of G12 Rotavirus Strains with Detection of a Rare G8 Genotype in Delhi, India, 2000 to 2007

P. Ray, S. Sharma, V. K. Paul, M. K. Bhan
All India Institute of Medical Sciences, New Delhi, INDIA

P64 Withdrawn

P65 Mucosal and Systemic Immune Responses to an Oral Killed Bivalent Vibrio cholerae 01/0139 Whole Cell Cholera Vaccine in Bangladeshi Adults

S. Shamsuzzaman
University of Dhaka, Dhaka, BANGLADESH

P66 Rotavirus Vaccination in Nicaragua and Infant Mortality by Acute Diarrhea in 2007

K. J. Amador Sánchez¹, S. D. Flores González²
¹PATH Nicaragua, Managua, NICARAGUA, ²Monte España Hospital, Managua, NICARAGUA
MEET THE EXPERT BIOGRAPHIES
Steven Black, MD  
Tuesday, April 28, 2009  
7:00 am – 7:45 am

Dr. Steven Black is Adjunct Professor of Pediatrics and Pediatric Infectious Diseases in the Center for Global Child Health at Children's Hospital in Cincinnati, Ohio. Dr. Black is a pediatrics infectious disease specialist who has spent more than 20 years conducting clinical trials and safety studies of vaccines, including being the principal investigator in five pivotal licensure trials and six phase four post-marketing trials. He received his medical degree from the University of California San Diego and specialty training in pediatric infectious diseases at the University of San Francisco. He is a long time member of ESPID and PIDS. His academic interests include the use of clinical databases to evaluate vaccine safety and efficacy both within the US and globally, and the conduct of vaccine clinical trials.

Neal A. Halsey, MD  
Tuesday, April 28, 2009  
7:00 am – 7:45 am

Dr. Neal A. Halsey is the Director of the Institute for Vaccine Safety and is a Professor in the Department of International Health, Disease Prevention and Control Program, at the Bloomberg School of Public Health. He has a joint appointment in the Department of Pediatrics at the Johns Hopkins University School of Medicine. Dr. Halsey received his medical degree from the University of Wisconsin Center for Health Sciences in Madison. He completed a residency in pediatrics and a fellowship in pediatric infectious diseases at the University of Colorado, Denver. He is board certified in pediatrics and pediatric infectious diseases. Dr. Halsey has served for two years with the Indian Health Service at Fort Yates, North Dakota, and as medical epidemiologist and chief of surveillance activities for the immunization division at the Centers for Disease Control and Prevention, Atlanta. He was a faculty member in the departments of pediatrics and tropical medicine at Tulane University, New Orleans for five years before joining the faculty at Johns Hopkins University in 1985 where he served as director for 17 years. Dr. Halsey has authored or co-authored more than 200 peer reviewed publications on the prevention and treatment of infectious diseases. His research interests have focused on vaccine-preventable diseases. He served for seven years with the research and development group for the World Health Organization’s Expanded Programme on Immunization. He has been a member or liaison member of the Advisory Committee for Immunization Practices (ACIP) for ten years and he served on the Committee of Infectious Diseases (The Red Book Committee), for ten years, including four years as chair.

Gregory A. Poland, MD  
Tuesday, April 28, 2009  
7:00 am – 7:45 am

Dr. Gregory A. Poland is the Director of the Mayo Clinic’s Vaccine Research Group. Dr. Poland is a Professor of Medicine and Infectious Diseases and Molecular Pharmacology and Experimental Therapeutics; Associate Chair for Research for the Department of Medicine; the Director of the Immunization Clinic; and Director of the Program in Translational Immunovirology and Biodefense at the Mayo Clinic. He also serves as the President of the International Society for Vaccines and the American Editor for the journal Vaccine.

In March 2005, Dr. Poland was elected as the President of the Armed Forces Epidemiological Board. He was appointed as the Mary Lowell Leary Professor in Medicine by Mayo Clinic’s Board of Trustees in February 2004, and in May 2003 he was awarded the Secretary of Defense Medal for Outstanding Public Service. In 2000, he was appointed as the American Editor for the prestigious medical journal Vaccine. In 1998, he received a joint award from the Centers for Disease Control and Prevention and the Health Care Financing Administration for his contribution to increasing adult immunization rates in the United States. Also of major significance, in 1997 he was honored as the “Outstanding Clinical Investigator of the Year” by the Mayo Clinic.

Additionally, Dr. Poland participates on many national and academic review committees and actively peer-reviews journal articles for over 26 different publications such as The Lancet, Annaus of Internal Medicine and New England Journal of Medicine. A prolific writer, Dr. Poland has published over 160 peer-reviewed scientific articles and book chapters. Dr. Poland received his medical degree from the Southern Illinois University School of Medicine in Springfield, Illinois, and completed his residency and advanced post-graduate work at the University of Minnesota/Abbott-Northwestern Hospital, Minneapolis, MN.
Professor David M. Salisbury, CB
Tuesday, April 28, 2009
7:00 am – 7:45 am

Professor David M. Salisbury is Director of Immunization at the Department of Health in London, with responsibility for the national immunization program. Professor Salisbury graduated from London University in 1969. He trained as a pediatrician at the Hospital for Sick Children, London. He is a fellow of the Royal College of Physicians, and a fellow of the faculty of Public Health. He has an honorary chair at Imperial College, London. Professor Salisbury was made a companion of the Order of the Bath in the Queen’s 2001 birthday honors. In addition to his U.K. responsibilities, Professor Salisbury works extensively for the World Health Organization (WHO) on the Global Program for Vaccines. He is the Chairman of the WHO Strategic Advisory Group of Experts on Vaccines, Chairman of the European Region Certification Commission for Poliomyelitis Eradication, and is a member of the Eastern Mediterranean Polio Elimination Certification Commission and the South East Asian Polio Elimination Certification Commission. He is an adjunct member of the Global Advisory Committee on Vaccine Safety and is a liaison member of the U.S. Advisory Committee on Immunization Practices. He is Co-Chairman of the Influenza Pandemic Preparedness Group for the Global Health Security Action Group of G7 countries.

W. Ripley Ballou, MD
Wednesday, April 29, 2009
7:00 am – 7:45 am

Dr. W. Ripley Ballou is Deputy Director for Vaccines, Infectious Diseases Development, Global Health, at the Bill & Melinda Gates Foundation. He has been involved in malaria vaccine development for more than two decades. Trained in internal medicine and infectious diseases, he began his work in tropical diseases at the Walter Reed Army Institute of Research in the early 1980s. He became part of the team to develop and test the world’s first subunit vaccine against Plasmodium falciparum. As a key member and eventually leader of the U.S. Army’s malaria vaccine research team, he oversaw the development and testing of more than a dozen vaccine candidates that led, in collaboration with scientists at GlaxoSmithKline, to the creation of the RTS,S vaccine, now considered the world’s most advanced malaria vaccine.

Ballou retired from the Army in 1999. He was instrumental in the creation of the Malaria Vaccine Initiative at PATH which is dedicated to accelerating the development of a safe and effective malaria vaccine. Dr. Ballou spent the next eight years in the vaccine industry, including five years at GlaxoSmithKline Biological in Belgium where he was responsible for their clinical development programs for malaria, TB, HIV, seasonal and pandemic influenza vaccines. He has authored more than 150 scientific publications in the field of vaccine development and infectious diseases. In April 2008 he joined the Bill & Melinda Gates Foundation.

Willem Hanekom, MB, ChB
Wednesday, April 29, 2009
7:00 am – 7:45 am

Dr. Willem Hanekom is Associate Professor at the University of Cape Town and Laboratory Director of the South African Tuberculosis Vaccine Initiative. His clinical training was in pediatrics and pediatric infectious diseases, both in South Africa and the United States. He subsequently trained in immunology at Rockefeller University in New York.

Dr. Hanekom’s laboratory focuses on clinical immunology studies in tuberculosis (TB) vaccinology. The largest efforts aim to delineate immune correlates of vaccination-induced protection against TB. Other studies aim to characterize immunity induced by BCG and by four novel boost vaccines in phase I/IIa trials and on the best strategies to deliver these vaccines to infants.

Additionally, Dr. Hanekom is active in the WHO/Stop TB initiative to delineate optimal approaches to measuring TB vaccination-induced immunity. His group takes part in three large consortia (two Gates funded and one NIH funded) which pool resources from various African, European and North American centers to advance TB research.
F. Marc LaForce, MD  
Wednesday, April 29, 2009  
7:00 am – 7:45 am

Dr. F. Marc LaForce joined PATH and the Meningitis Vaccine Project (MVP) as Director in August 2001. The MVP is a Gates Foundation-funded partnership between the World Health Organization (WHO) and PATH aimed at eliminating meningitis epidemics from Sub-Saharan Africa through the development, testing, licensure and introduction of meningococcal conjugate vaccines.

Dr. LaForce earned his Doctor of Medicine degree from Seton Hall College of Medicine and Dentistry, Jersey City, NJ. He completed his internal medicine and infectious disease training on the Harvard Service at Boston City Hospital. He is board-certified in internal medicine and infectious diseases and is Fellow of the American College of Physicians and the Infectious Diseases Society of America. Dr. LaForce served as Epidemic Intelligence Service Officer in the Meningitis and Special Pathogen units at Centers for Disease Control and Prevention, Atlanta, GA. He has research and academic positions at the University of Colorado School of Medicine and the University of Rochester School of Medicine and Dentistry. Dr. LaForce has published over 180 papers and book chapters in the area of pulmonary defense mechanisms, clinical infectious disease, epidemiology, and vaccinology.

Helen McShane, FRCP, PhD  
Wednesday, April 29, 2009  
7:00 am – 7:45 am

Helen McShane trained in medicine at Guy’s Hospital, London, and after junior hospital positions in London, Brighton and Oxford, she was awarded an MRC Clinical Training Fellowship in 1997. She undertook a PhD with Professor Adrian Hill in Oxford, investigating prime-boost immunization strategies in the murine model of tuberculosis. In 2001, she was awarded a Wellcome Trust Clinician Scientist Fellowship, to evaluate these promising immunisation strategies and candidate vaccines in a series of Phase I clinical trials. In 2003, she became a consultant in HIV and genito-urinary medicine, and in June 2005 was awarded a Wellcome Trust Senior Clinical Fellowship. She now runs the TB vaccine programme at Oxford University and is working on a BCG challenge model. In September 2008, she was appointed a Reader in Vaccinology by the University of Oxford.
ABSTRACTS OF INVITED PRESENTATIONS
Objective: Describe the aims and objectives of GIVS, its priorities and challenges, and its progress to date.

The World Health Organization (WHO) Global Immunization Vision and Strategy (GIVS) is a joint initiative with UNICEF. Its purpose is to identify opportunities that can be created to improve immunization service delivery and accelerate the availability of new vaccines or vaccines that were previously not available to the poorest countries of the world. Unlike previous immunization initiatives of WHO, GIVS includes vaccines for individuals of all ages, thereby breaking out of the previous constraints on vaccines for young children. GIVS has four main aims: immunize more people against more diseases, introduce a range of newly available vaccines for young children, and manage vaccination programs within the context of global interdependence. The period over which GIVS will operate spans 2006 to 2015.

Reference:

Objective: Review considerations of safety versus efficacy for the rhesus rotavirus vaccine (Rotashield) and discuss how this vaccine impacted the development, testing, and monitoring of new rotavirus vaccines.

Rotavirus is the most common cause of severe acute gastroenteritis in infants and young children worldwide. It is responsible for approximately half a million childhood deaths each year in the developing world and remains a major cause of childhood morbidity in industrialized countries. Rotavirus vaccine development has been a priority for international health agencies, and in 1998 a rhesus rotavirus vaccine (Rotashield) was licensed in the United States following nearly two decades of research. However, Rotashield was withdrawn within a year of its introduction because of a rare association of the vaccine with the development of intussusception that was identified after more than 1 million doses of vaccine had been administered as part of routine immunization. This abrupt and unanticipated setback led to much scientific and ethical debate about the potential benefits and risks of using Rotashield in the developing world. Furthermore, two other rotavirus vaccines in development at the time had to undergo large and expensive trials of >60,000 infants to evaluate pre-licensure safety with respect to intussusception. Following successful completion of these trials, both these new vaccines have recently been introduced into routine immunization programs. However, to evaluate a potential risk of intussusception smaller in magnitude than that could be detected in clinical trials, post-licensure monitoring of this adverse event is ongoing. Future challenges to rotavirus vaccine development include the lack of efficacy data in infant populations in Africa and Asia that are most at risk of the disease and safety issues such as the risk of intussusception in developing country settings and administration to HIV-infected infants.

Reference:

Objective: Explain approaches being used to assess infrequent adverse events following immunization and the challenges in both assessment and development of responsibility responding to possible vaccine safety signals.

Vaccines are one of the most effective public health interventions. However, concerns about vaccine safety, both real and imagined, can have undermined what would otherwise be effective public health interventions. Vaccine safety scares can spread rapidly because of the Internet and other global communication methods. Efficiently responding to public concerns regarding a possible vaccine safety concern is critical to assuring the safety of the vaccine supply and also reassuring the public when no true safety concern exists. Methods have been developed to use passive and active surveillance to meet this need. However, much work needs to be done to fully understand these techniques and more importantly on how to appropriately respond to a possible vaccine safety signal when one is observed. Because many reported possible vaccine safety questions arise with regard to rare events, separating chance occurrences from true associations can be difficult. Although much attention has been given to development of new techniques to assess safety of vaccines with regard to rare events, less attention has been given as to how to efficiently respond to potential signals when they are observed. Lack of this capacity in and of itself can threaten vaccines which are safe and effective.

Reference:
Screening for Genetic Predisposition to Adverse Events Following Immunization
Christopher Carlson, PhD
Fred Hutchinson Cancer Research Center
University of Washington
Seattle, WA

Objective: Review the state of the art in Genome Wide Association Study (GWAS) design, with special attention to vaccine-specific considerations

Genome Wide Association Studies (GWAS) are an approach to the identification of risk factors for diseases and traits of medical interest. GWAS studies have recently become technically and economically feasible, and results from such studies are reported with increasing frequency in the literature. This study design was developed to assess correlations between common polymorphism in the human genome and common diseases/trait, such as cardiovascular disease and cancer. Ironically, the richest findings from GWAS have been in the realm of relatively infrequent autoimmune diseases, such as Crohn’s disease, rheumatoid arthritis, and type 1 diabetes, although type 2 diabetes and quantitative traits like lipid levels have achieved significant success. While dozens of loci have been mapped for these diseases, the vast majority of reproducibly disease-associated polymorphism identified to date through GWAS are low risk loci with allelic odds ratios below 2. Thus, although immune-related phenotypes are promising targets for GWAS, serious consideration needs to be given to power analyses prior to the application of these tools to rare AEFI. Given the rate with which technical innovations are carrying the GWAS field forward, with the anticipation of a $1000 genome sequence within the next decade, collecting and carefully phenotyping adequate numbers of cases is presently of much greater value than GWAS genotyping in underpowered sample sizes. This presentation will discuss these issues and other vaccine specific considerations in the implementation of GWAS analysis in the field of vaccine research.

Reference:

Vaccination and Mitochondrial Diseases: Real or False Issue?
Paul A. Offit, MD
The Children’s Hospital of Philadelphia
Philadelphia, PA

Objective: Describe the assertion that the measles-mumps-rubella (MMR) vaccine and thimerosal-containing vaccines cause autism and how best to communicate issues to the public

In 1998 a paper published in the British medical journal, Lancet claimed that the combination MMR vaccine caused autism. The author claimed that measles vaccine given in combination with mumps and rubella vaccines damaged intestinal epithelial cells, allowed entrance of encephalopathic proteins, and eventually damaged the central nervous system, causing autism. Since that original publication, twelve separate studies have examined the incidence of autism in children who did or did not receive the MMR vaccine—all with the same result; MMR didn’t cause autism. More recently, the use of an increasing number of thimerosal containing vaccines has led to the fear that the mercury containing preservative caused neurodevelopmental damage, including autism. Six separate studies have now examined this relationship, again showing no association between vaccines and autism. Strategies and challenges for communicating this information to the public will be discussed.

References:

Progress and Promise on the Long Road to a Dengue Vaccine
Harold S. Margolis, MD
International Vaccine Institute
Seoul, Korea

Objective: Describe the challenge of developing a dengue vaccine and the recent progress with several vaccine candidates in clinical evaluation

Dengue is an emerging, mosquito-borne disease caused by four related but distinct dengue viruses (DENV). Dengue produces significant morbidity and consumes considerable health care resources in tropical and subtropical countries. An estimated 3.6 billion people (55% of world’s population) live in areas at risk for DENV transmission. Each year, an estimated 36 million cases of dengue occur, which result in 2.3 million cases of severe dengue and 20,000 deaths. Vector control has been the only method to prevent dengue, a strategy that suffers from poor sustainability and effectiveness due to the unique ecology of the Aedes mosquito vector of DENV.

Prevention of dengue by immunization appears to be antibody mediated and technically feasible. Infection with a single DENV-type produces long-term protection against subsequent disease from that virus-type. Although dengue vaccine development began over 70 years ago, only recently have several vaccine candidates progressed into clinical evaluation. Dengue development has been quite challenging and has resulted in a number of unique approaches for development of these candidates. Other challenges facing dengue vaccines include they must provide durable protection against infection by the four DENVs, which will require a tetravalent formulation, ensuring high levels of long lasting immunity to minimize the theoretical potential for antibody dependent enhanced disease (AED) in partially immune persons, and the need to conduct clinical trials in multiple sites to determine protection against the virus types and the wide range of age groups affected by dengue.

Reference:
No reference provided.

Global Polio Eradication and Related Research
Stephen L. Cochi, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA

Objective: Explain the current status of the polio eradication initiative, its remaining challenges, and discuss the ongoing pre-eradication and post-eradication research agenda

Global incidence of polio has declined more than 99% from an estimated 350,000 cases at the beginning of the Polio Eradication Initiative in 1988 to 1,655 cases in 2008. New tools and tactics, in addition to more...
aggressive outbreak-response guidelines, have contributed greatly to maintaining confidence that polio eradication can be achieved. However, significant challenges remain to complete the effort.

The program of polio research to address the continuing challenges of achieving and sustaining polio eradication - strategically guided by independent advisory Polio Research Committee (PRC) and coordinated by the Research and Product Development team at the World Health Organization (WHO) - has two objectives: first to identify, develop and evaluate new tools and tailored eradication tactics to maximize the impact of eradication efforts and to more rapidly interrupt wild poliovirus transmission globally; and second to broaden and deepen the knowledge base necessary for policy decisions associated with the post-eradication era, thereby ensuring that the long-term risks of polio, once wild poliovirus transmission has been interrupted globally, are minimized and appropriately managed.

Reference:
2. www.polioeradication.org

8

Eliminating Serogroup A Meningococcal Meningitis Epidemics in Africa
F. Marc LaForce, MD
PATH
Voltaire, France

Objective: Describe the problem of epidemic Group A meningococcal meningitis in Africa and discuss the development of an affordable, safe and immunogenic vaccine to combat these epidemics.

Epidemic Group A meningococcal meningitis continues to be a major public health problem in Sub-Saharan Africa. Waves of epidemic Group A meningococcal meningitis occur periodically in Africa and are superimposed on high endemic rates of disease. Reactive vaccination campaigns using meningococcal polysaccharide vaccines have not eliminated these epidemics. The Meningitis Vaccine Project (MVP), a partnership between WHO and PATH, was established in 2001 with Gates Foundation support with the goal of eliminating epidemic meningitis through the development and widespread introduction of an affordable Group A meningococcal (MenA) conjugate vaccine. Using an innovative partnership model (Serum Institute of India; CBER/FDA, Bethesda and SyntoBioPartners, Amsterdam) MVP has developed a Men A conjugate vaccine (MenAfriVac®) with a target price of less than $US 0.50 per dose. In Phase I and Phase II and II/III clinical trials in India and Africa (1-29 years) the vaccine has been shown to be safe, highly immunogenic and able to prime immunological memory when compared to polysaccharide vaccine. Widespread use of the vaccine is expected to generate broad herd immunity. Introduction of the vaccine at public health scale is planned for 2009/2010 and is expected to eliminate Group A meningococcal meningitis epidemics from Sub Saharan Africa.

Reference:

9

Extending the Expanded Program on Immunization (EPI) Schedule into the Second Year of Life
Neal A. Halsey, MD
John Hopkins University
Baltimore, MD

Objective: Explain the origins of the Expanded Program on Immunization (EPI) and suggested changes needed for optimal incorporation of new vaccines.

The EPI was started in 1976, but a standard schedule was not proposed until 1984. The original vaccines recommended—BCG, DTP, OPV, and measles—have been supplemented by several other vaccines and new vaccines are being considered for addition to schedules throughout the world. Primary immunization schedules of 6, 10, and 14 weeks without booster doses are not optimal for new vaccines. The entire EPI schedule needs to be reassessed in order to use new vaccines in the most effective and efficient manner possible.

References:

10

Sustainable Financing of New Vaccine Introduction in Developing Countries
Andrew Jones, MSc
Adeni Consulting
Philadelphia, PA

Objective: Discuss sustainable financing of new vaccine introduction in developing countries and the coming challenges in this area.

Over the past decade, with the increased focus on health sector aid by donors, support to vaccination and the accompanying immunization system has significantly increased. This includes the creation of GAVI in 1999, and with it, the associated growth of innovative financing. Two tools in particular are the IFFIm which raises money from the capital markets through the long-term commitments of funds from donors, and the Advanced Market Commitment (AMC) which helps pull forward the development of new vaccines by legally committing funds to purchase a specific vaccine at a pre-agreed price once it is developed. Both of these have raised several billion dollars for immunization. GAVI has also sought to create an environment for long-term sustainability by requiring countries to contribute small co-payments for each vaccine to enable the eventual financing of vaccines by national governments at some point in the future. Taken together, these financing tools provide a significant incentive for researchers that are focused on developing vaccines for the world's poorest.

Despite this success, many countries that are not eligible for GAVI support (beyond the 72 countries) but remain relatively poor, find it difficult to finance many of the new, relatively expensive vaccines. Finding mechanisms to support these lower-middle income countries will be a significant challenge in the coming years.

Reference:
No reference provided.
Melanoma Vaccines
Jedd D. Wolchok, MD, PhD
Memorial Sloan-Kettering Cancer Center
New York, NY

Objective: Explain the current status of melanoma vaccine development and clinical trials, and discuss the challenges which remain for the future introduction of cancer vaccines in general.

Melanoma is a major public health problem, being the cancer with highest yearly increase in incidence in the US and >60,000 expected cases in 2009. Although most patients with stage I (thin) melanomas are cured with outpatient surgery, patients with lymph node involvement can have approximately 50% risk of recurrence and death in 5 years. Novel therapeutic approaches to treatment and prevention of recurrence are therefore sorely needed. Various approaches to cancer vaccine development have paralleled advances in infectious disease vaccines. However, to date, whole cell or carbohydrate-based vaccines have not been shown to result in prolonged survival when evaluated in prospectively randomized phase 3 clinical trials.

There has been a recent focus on plasmid DNA vaccines encoding melanosomal differentiation antigens in mouse models and clinical trials in dogs with oral melanoma and humans with high risk melanoma in the adjuvant setting. The canine studies have revealed a significant increase in life expectancy in dogs vaccinated with xenogeneic tyrosinase DNA vaccines, leading to conditional licensure by US Department of Agriculture of the human tyrosinase DNA vaccine (Merial) as the first therapeutic cancer vaccine in the United States. Pilot studies of this approach in humans have demonstrated safety and immunogenicity. Attempts to increase the immunologic potency of this approach in various ways including: use of cytokine genes as molecular adjuvants, recombinant virus constructs and addition of immunomodulatory antibodies.

References:

Avian Influenza Vaccines
Richard J. Webby, PhD
St. Jude Children’s Research Hospital
Memphis, TN

Objective: Describe the current state-of-the-art as it pertains to influenza vaccines

Influenza is a zoonotic disease with a number of possible animal reservoirs. This number of possible reservoirs and the diversity of viruses within them pose substantial difficulties for those vested in public health. Although some antiviral drugs are available for influenza viruses, vaccination is the primary means of protecting the human population. The majority of human influenza vaccines used today are derived using an overall process that has remained fundamentally unchanged for decades. This process does, however, have its weaknesses and some viruses are not amenable without modification. Driven to a large extent by the emergence of H5N1 viruses on a global scale, newer generation vaccines and technologies are being developed. Some of these approaches have already been implemented in the veterinary world and these experiences, as well as those obtained from experimental animal models, are helping advance these developments toward use in the human population.

References:
ABSTRACTS OF INVITED PRESENTATIONS

14 Rift Valley Fever Vaccines
Clarence J. Peters, MD
University of Texas Medical Branch
Galveston, TX

Objective: Review the basic epidemiology of Rift Valley Fever Virus (RVFV) and explain why only vaccines can control the disease.

RVFV, from the family Bunyaviridae, causes mosquito-transmitted epidemics in sub-Saharan Africa and has shown a disturbing trend to spread to adjacent geographic areas. Conditions in the U.S. are thought to be receptive to its transmission. In addition, it has potential as a terrorist agent for animals or humans. Epidemics in Africa arise during rainy season primarily from highly viremic sheep and cattle, both of which also suffer significant mortality and abortion. Humans are infected by mosquitoes as well as by contact with slaughtered animals or abortion. An inactivated vaccine was developed for humans in the 1960’s and, although it protected laboratory workers, it was impractical for large scale use. Furthermore, no really satisfactory domestic animal vaccine exists.

USAMRIID undertook development of a live attenuated human vaccine in the early 1980’s resulting in a candidate called MP-12. The usual preclinical studies, including monkey neurovirulence, were performed without untoward events. Because of the zoonotic nature of the virus, we also tested it in domestic animals confirming both immunogenicity and safety. Since RVFV is arthropod transmitted, it was also studied in mosquitoes for reversion, infection, and transmission. The vaccine was later administered to 43 human volunteers without serious adverse events and with a favorable immunogenicity profile. Further development was abandoned for funding reasons.

Under the impetus of 9/11 and the example of West Nile virus introduction into the U.S., NIAID funded the further development of MP-12 which has enhanced our understanding of the molecular biology and safety of the vaccine and has mapped out a path to new seeds and production of a trial lot. In addition, funding from DHS has allowed us to explore veterinary vaccines. It appears likely that MP-12 will be produced commercially on a modest scale as an animal vaccine licensed in the U.S. and that there may be further development to permit distinguishing infection from vaccine immunity.

This illustrates the synergy and parallel development of human and veterinary vaccines. Under realistic scenarios we will need both vaccines to deal optimally with RVFV in Africa and in areas where it might be introduced.

References:

15 Reasons for BCG Failures in Developing Countries
Willem Hanekom, MBChB
South African Tuberculosis Vaccine Initiative
University of Cape Town
Cape Town, South Africa

Objective: Explain the differential protective efficacy observed after BCG vaccination of diverse populations and reasons underlying this observation; review the immune response induced by BCG vaccination, how this relates to protection, and differential immune responses observed in diverse populations.

BCG is approximately 80% effective in preventing tuberculosis (TB) meningitis and miliary disease in infants. The vaccine’s variable efficacy in preventing pulmonary TB has been ascribed to vaccine strain differences, dose, geographic location, and nutritional status, interference by environmental mycobacterial and helminthic infection, and host genetic factors. Presence of specific CD4 T cells able to make type 1 cytokines is thought to be critical for protection against TB. BCG induces multiple, diverse subsets of CD4 T cells, based on capacity to produce IFN-γ, IL-2, TNF or IL-17, in infants. Other groups have compared BCG vaccine uptake between populations in Malawi and in the UK, and African individuals have a lower response. The vaccination-induced immune correlates of protection against TB are not known. In ongoing studies, measuring IFN-γ alone correlates poorly with protection against TB, following newborn BCG vaccination. By delaying BCG vaccination from birth to 10 weeks of age results in an enhanced, and functionally optimal, memory T cell response at 1 year of age. The route of Japanese BCG vaccination does not determine protective efficacy. These results underscore the importance of further study into how optimally to use of BCG, as this vaccine is likely to form the cornerstone of future prime-boost vaccination strategies to prevent TB.
Objective: Describe the scientific rationale for the design of tuberculosis subunit vaccine development and review the status of recent progress in clinical trials

Tuberculosis (TB) kills 2–3 million people every year. The current TB vaccine Mycobacterium bovis bacillus Calmette-Guérin (BCG) is the most widely used vaccine worldwide, but it does not prevent the establishment of latent TB or reactivation of pulmonary disease in adults. The development of subunit vaccines has now reached the point where single antigens as well as poly-protein fusion molecules have been found to provide efficient protection against tuberculosis, and an impressive track record is available for the leading candidates that include data from various animal models including non-human primates. The most advanced of these vaccines such as the fusion between ESAT6/TC10.4 and Ag85B administered in the adjuvant IC31 are now in clinical trials and the first data on safety and immunogenicity are very promising with very robust and long lived responses. Currently the focus is on evaluating the influence of different adjuvants, routes and prime-boost regimes for optimum expression of immunity in the lung, boosting of BCG and maintenance of immunological memory. Subunit vaccines can be used to boost BCG immunity either administered together (tandem administration), shortly after BCG (early boost) or in adolescence when BCG immunity starts to wane (late boost). A late BCG boost would frequently be administrated post-exposure to latently infected individuals, and ongoing efforts are focused on understanding the impact this would have on existing vaccines and for the design of efficient booster vaccines.

Reference:

Objective: Discuss the protective immunity to tuberculosis (TB) and the clinical development path for new TB vaccines

MVA85A is a recombinant modified vaccine Ankara expressing the immunodominant antigen 85A from M. tuberculosis. It has been developed as a vaccine to enhance BCG. Vaccination with MVA85A enhances BCG induced protection against aerosol challenge in mice, guinea pigs, non-human primates and cattle, compared with BCG alone. MVA85A was the first new TB vaccine to enter clinical trials in 2002 and is currently in Phase II clinical trials in the UK, The Gambia and South Africa.

When used alone in BCG naïve subjects, MVA85A enhances pre-existing immunity induced by environmental mycobacteria and induces high levels of antigen specific T cells. When administered to subjects previously vaccinated with BCG, significantly higher levels of antigen specific T cells are seen. In subjects who are latently infected with M. tuberculosis, MVA85A is as safe and as immunogenic as it is in BCG vaccinated subjects. To date this vaccine is also safe and immunogenic in Gambian adults and infants; and South African adults, adolescents, children and infants. This vaccine is also safe and immunogenic in HIV infected adults in the UK and Africa.

The main immunological readout in these clinical trials has been the ex-vivo interferon-gamma Elispot assay. We have now used a variety of cellular immunological assays including polychromatic flow cytometry, intracellular cytokine staining, CFSE proliferation and whole blood assays to characterize in more detail the vaccine induced immune responses. From this data, we see that MVA85A induces highly polyfunctional T cells which also proliferate.

The protective efficacy of MVA85A administration to subjects previously vaccinated with BCG will be evaluated in a Phase Ib proof-of-concept trial in South African infants, commencing in early 2009. A review of the immunological data and clinical development of this promising vaccine will be presented.

References:
elicited antibody and effector recall IFN-γ responses positively correlate with pathology. Together, these findings suggest significant advances in experimental approaches to development of bTB vaccines; however, translation of these advances to large-scale field studies is yet to be realized.

Reference:

19 Interventions to Control Malaria, Including Vaccines in the Pipeline
W. Ripley Ballou, MD
Bill and Melinda Gates Foundation
Seattle, WA

Objective: Review recent developments in the malaria vaccine field and discuss the status of advanced malaria vaccine candidates

Recent efforts to scale-up the introduction of insecticide-treated bed nets and the increasing availability of artemisinin-containing drugs are having a major impact on the global burden of malaria, but better tools are still urgently needed. RTS,S is the world’s most advanced malaria vaccine candidate and is intended to protect infants and young children living in malaria endemic areas of sub-Saharan Africa against clinical disease caused by Plasmodium falciparum. In 2009, it is expected to enter the pivotal Phase III program designed to support licensure in Sub-Saharan Africa. The goal of the program has been to develop a vaccine that will be safe and effective when administered via the Expanded Program for Immunization (EPI) and significantly (>50%) reduce the risk of clinically important malaria disease during the first five years of life. If a similar reduction in the risk of severe malaria and an important impact on other important co-morbidities associated with malaria infection can be achieved, then the vaccine could become a major new tool for reducing the burden of malaria in this region. Encouraging data from the ongoing Phase II program suggest that these goals may indeed be achievable: recent trials conducted in Tanzania and Kenya have shown vaccine efficacy against infection of 62.5% (95%CI:20.7-84.7, p=0.01) in infants and vaccine against clinical malaria disease of 56% (95%CI:31.72, p<0.001) in children 5-17 months of age. The Phase III program will be described. The status of the RTS,S vaccine will be compared with that of other malaria vaccine candidates in development.

References:

20 Genomic-Based Identification and Prioritization of Vaccine Targets
David S. Roos, PhD
University of Pennsylvania
Philadelphia, PA

Objective: Describe strategies for exploiting genomic-scale datasets to advance the identification of therapeutic targets, focusing on the malaria parasite Plasmodium falciparum, and experience with the Eukaryotic Pathogen Genome Database

Genomic-scale projects yield vast datasets: genome and EST sequences, transcript and protein expression patterns, antigenicity data, interactome results, metabolic and signaling pathways, genetic polymorphisms, epidemiological data, comparative genomics results gleaned from cross-species analysis, etc. How can we effectively capture, maintain, update, annotate, integrate, and query these resources to advance biomedical research, including the development of new diagnostics and therapeutics? While genome informatics and database development is a challenge for all biologists, certain consistent features apply to pathogen species. Research questions include: What antigens are expressed at the desired time and are likely to be accessible for antibody recognition and/or MHC presentation? What can evolutionary patterns tell us about selective pressures, including immune selection? What genes distinguish the host from the pathogen? What genes modify virulence and the host response? The Eukaryotic Pathogen Bioinformatics Resource Center (EuPathDB.org) supports diverse data types relevant to a wide range of bio-defense and (re)emerging protozoan pathogens, enabling researchers to formulate their own questions. Integrating sequence data with a variety of automated analyses and manually curated annotation enables interrogation of the Plasmodium falciparum genome to identify candidate vaccine targets based on sub-cellular localization, timing of expression, immunogenicity, essentiality, indicators of evolutionary selection, cross-species conservation, and other attributes, highlighting antigens that may be appropriate to add to the list of antigens already under evaluation.

References:
The development of effective subunit malaria vaccines may be hindered by extensive genetic diversity in the surface proteins being employed as vaccine antigens. Understanding the extent and dynamics of genetic diversity in vaccine antigens can help guide rational vaccine design and will be necessary to interpret the results of vaccine efficacy trials conducted in malaria endemic areas. Molecular epidemiological, population genetic, and structural approaches are being employed both to measure allele-specific efficacy in vaccine trials and to try to identify immunologically relevant polymorphism in vaccine antigens. The results of these studies will inform choices of which alleles to include in multivalent or chimeric vaccines; however, additional molecular and immuno-epidemiological studies will be needed in a variety of geographic locations if these approaches are to succeed. Alternative means of overcoming antigenic diversity are also being explored, including boosting responses to critical conserved regions of current vaccine antigens; identification of new, more conserved and less immunodominant antigens, and whole-organism vaccines. Continued creative application and integration of tools from multiple disciplines, including epidemiology, immunology, molecular biology, and evolutionary genetics/genomics, will likely be required to develop broadly protective vaccines against Plasmodium and other antigenically complex pathogens.

Reference:

Objective: Review current status of attenuated Plasmodium falciparum malaria sporozoite vaccine development, clinical trials, and the challenges for moving from initial manufacturing and clinical trials to licensure.

Efforts to reduce sporozoite-infected mosquito contact with humans and provide effective treatment of malaria are substantially reducing the morbidity and mortality of malaria all over the world. Based on these successes there is now enthusiasm for the possibility of eliminating Plasmodium falciparum from many areas, including high transmission areas of sub-Saharan Africa. There is little question that a vaccine would be an ideal intervention to reduce the morbidity and mortality caused by P. falciparum. We believe that a vaccine is likely to be required to eliminate P. falciparum from high transmission areas, and that the ideal vaccine would be one that prevents infection entirely and therefore also prevents transmission. Currently being developed is a practically manufactured and administered, safe, non-toxic, metabolically active, non-replicating (live attenuated) whole parasite P. falciparum sporozoite vaccine that prevents infection and thereby prevents illness and transmission. This approach is based on the published observations that when radiation attenuated P. falciparum sporozoites are administered as immunogens via the bites of infected mosquitoes, they elicit immune responses that completely protect greater than 90% of human recipients against experimental P. falciparum challenge for at least 10 months. Despite this excellent protective immunity, it was thought for many years that it was impossible to practically produce, administer, and commercialize such a vaccine. Recently, a manufacturing process has been developed, with multiple clinical lots of its PfSPZ Vaccine being manufactured, and Phase 1 clinical trials with experimental challenge beginning in 2009. The first generation PfSPZ Vaccine is attenuated by radiation. Work is progressing on establishing that genetic alteration can also be used to produce attenuated sporozoites. Plans for moving rapidly from establishment of the safety, immunogenicity and efficacy of the PfSPZ Vaccine in the first clinical trials to successful licensure and launch of the PfSPZ Vaccine will be presented.

Reference:
on Vaccine Research

ABSTRACTS OF ORAL SUBMITTED PRESENTATIONS
Immune Stimulatory Interleukin HMGB1 Induces Dendritic Cell (DC) Maturation and Immune Enhancement in vivo

University of Pennsylvania School of Medicine, Philadelphia, PA

Objective: Discuss how the administration of a HMGB1 DNA may lead an enhanced immune response to DNA plasmid vaccination

DNA vaccination is a novel immunization strategy that has great potential for the development of vaccines and immune therapeutics. This strategy has been highly effective in mice, while less immunogenic in nonhuman primates and humans. Enhancing DNA vaccine potency remains a challenge. It is likely that antigen-presenting cells (APCs), and especially dendritic cells (DCs), play a significant role in the presentation of the vaccine antigen to the immune system. A new study reports the synergistic recruitment, expansion, and activation of DCs in vitro by high-mobility group box 1 protein (HMGB1).

Such combinational strategies for delivering vaccine in a single, simple platform will hypothetically bolster the cellular immunity in vivo. Here, we have coimmunized HIV-1 DNA vaccines with an HMGB1 plasmid as a DNA adjuvant for vaccine therapy by intra-muscular immunization of Balb/C mice by electroporation. Immune responses were measured. Coadministration of this potent immunostimulatory adjuvant HMGB1 strongly enhanced cellular and humoral immune response compared to that obtained in mice immunized with vaccine only. In an influenza DNA vaccine model, coimmunization with plasmid expressing influenza A PR8/34 gNp with the HMGB1 generated improved long term CD8+ T cell immunity and protected the mice against a lethal mucosal challenge with influenza virus. Our results show that coimmunization with HMGB1 can have strong adjuvant activity, driving strong cellular and humoral immunity that may be an effective immunological adjuvant in DNA vaccination against infectious diseases.

References:
a few subjects had detectable SN titers. Non-adjuvanted vaccine elicited almost no response at the tested doses, whereas all adjuvanted formulations induced marked responses by D42, with a clear adjuvant-dose/response relationship: the GMT of HI titers on D42 in the 2.5μg/0.5%, 2.5μg/1% and 2.5μg/2.5% groups were 30.8, 37 and 86.3. In the 6μg/0.5%, 6μg/1% and 6μg/2.5% group, these values were 30.8, 60.3 and 99.7. D42 SN titers followed a similar pattern to HI titers with approximately 4-fold higher values. Antibodies crossreacted to a clade 1 strain. There were no immediate reactions or vaccine-related serious adverse events. Solicited injection site reactions, but not systemic reactions, were more frequent with higher doses of adjuvant. Conclusions: Two injections of a dose-sparing H5N1 vaccine are immunogenic when combined with this new emulsion adjuvant. Immunogenicity increased with the amount of antigen and adjuvant.

Reference:

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**S4**

**W**₈₀EC, a Nanoemulsion Adjuvant, Provides Robust Anti-Influenza Immunity in Ferrets after a Single Immunization

T. Hamouda¹, A. Myc², N. Manik³, J. Knowlton⁴, N. Mytle⁴, J. Sutcliffe⁵, J. R. Baker, Jr.⁶
¹NanoBio Corp, Ann Arbor, MI, ²University of Michigan, Ann Arbor, MI, ³Southern Research Institute, Birmingham, AL

**Objective:** Review a novel nanoemulsion that inactivates influenza virus and provides adjuvant activity for nasal vaccination in ferrets

**Background:** W₈₀EC is an oil-in-water emulsion adjuvant composed of nanometer-sized droplets stabilized by surfactants. The nanodroplets kill enveloped viruses via membrane destabilization, thereby providing an alternative for viral inactivation. Viral antigenicity is preserved through incorporation of antigen epitopes in the nanodroplets. The W₈₀EC-adjuvanted vaccine is preferentially taken up by mucosal dendritic cells where antigen processing triggers maturation and trafficking of these cells to secondary lymphoid tissues. Methods: Naïve ferrets were immunized intranasally (IN) on two occasions, at time 0 and four weeks later with influenza A/Wisconsin/67/05 (H3N2) virus inactivated with 20% W₈₀EC. Sera from experimental animals were collected on days 27 and 48 and tested for antibodies to A/Wisconsin and to other H3N2 subgroups using the hemagglutination inhibition assay (HAI). Immune protection was assessed by challenging vaccinated animals intranasally with 10⁶ EID₅₀ (egg infectious dose) Wisconsin virus on day 49 followed by titration of the viral load in the nasal washes. Results: A single IN vaccination in ferrets with W₈₀EC-inactivated influenza vaccine (7.5 HA units) provided a HAI geometric mean titer of 3620 (1280-10240) and 100% seroconversion, with no detectable viral particles in the nasal washes. The vaccine resulted in cross-reacting antibodies against A/California but not against A/Panama. Commercial vaccine administered intramuscularly (IM) did not result in specific or cross-specific immunity. Excretion of virus was found in the ferrets’ nasal washes following the viral challenge in the group receiving commercial vaccine IM. Conclusions: The W₈₀EC-inactivated influenza vaccine elicited a robust immune response in naïve ferrets following a single IN immunization. This vaccine strategy could provide immunization against seasonal influenza in more vulnerable populations or against pandemic influenza in the general population.

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**References:**

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**S5**

Randomized, Double Blind, Controlled Phase I Trial of the Safety, Tolerability and Immunogenicity of Fuzone™ Inactivated Trivalent Influenza Virus Vaccine Administered with Ascending Doses of JVRS-100 Adjuvant

J. Fairman¹, M. Sisti¹, J. F. Warriner, V. Knobel, M. Loy, C. Johnson, E. Sheldon, M. Co, F. Ennis, T. Monath
¹Juvaris Biotherapeutics, Inc., Burlingame, CA, ²Johnson County Clin-Trials, Lenexa, KS, ³Miami Research Associates, South Miami, FL, ¹University of Massachusetts Medical School, Worcester, MA

**Objective:** Discuss the safety and immunogenicity of seasonal flu vaccine with a novel adjuvant

**Background:** JVRS-100 is a novel cationic lipid-DNA complex adjuvant. Addition of vaccine antigens to JVRS-100 strongly enhances CD4⁺ and CD8⁺ T-cell and antibody responses [1]. Studies in mice and monkeys indicate that influenza vaccines could be greatly improved by the JVRS-100 adjuvant. A clinical study assessed safety and immunogenicity of JVRS-100 with TIV versus TIV alone in healthy adults, 18-49 years. Methods: Six groups of 20-24 subjects were randomized to receive 1) TIV half-dose (22.5 μg); 2) TIV (45 μg); or TIV (22.5 μg) with 4 ascending dose levels of JVRS-100. Adverse events, hemagglutination-inhibiting (HAI) and neutralizing (N) antibody levels and T-cell responses were monitored. Results: Increased HAI and N antibody responses were observed in subjects receiving JVRS-100 and vaccine versus vaccine alone 28 days post-vaccination. There was also an enhancement of CD4⁺ and CD8⁺ T-cell responses (including multifunctional cells) in study participants receiving JVRS-100 and vaccine. JVRS-100 at the most efficacious dose was well tolerated, with no increase in injection site or systemic adverse events (AEs) compared to TIV. The most immunogenic dose of JVRS-100 was the lowest dose used in the study (7.5 μg), suggesting that optimal adjuvant activity may occur at lower dose levels. Conclusions: The increase in HAI antibody response of JVRS-100 adjuvanted vaccine was higher than reported for other adjuvants tested in this population. The low dose requirement and absence of AEs appear to be favorable attributes of this adjuvant. The T-cell response suggests that JVRS-100 may have utility in antigenically drifted influenza or with prophylactic and therapeutic vaccines for other indications. Larger trials, dose optimization, and testing of the adjuvant with various vaccines including TIV in the elderly are warranted.

**Reference:**


Background: Eimeria acervulina is an intracellular protozoan which infects primarily the duodenum of poultry. Development of an effective peptide vaccine against this pathogen has been difficult mainly due to a weak immunogenicity of Eimeria peptide antigens. IL-15 has been shown to promote both cellular and humoral immune functions, and enhances host memory response when used in vaccines. In this study, we constructed several different kinds of DNA vaccines carrying 3-1E gene which encodes a potential TLR ligand protein of Eimeria, and chicken IL-15 (chIL-15). Methods: SPF chickens were immunized intramuscularly with the following DNA vaccines with or without IL-15 with some groups receiving IL-15 with a different signal peptide (NchIL-15): 100 μg pcDNA3.1/3-1E (E), 100μg pcDNA3.1/3-1E-linker-chIL-15 (S), 50μg pcDNA3.1/chIL-15 plus 100μg pcDNA3.1/3-1E (C), 50μg pcDNA3.1/NchIL-15 plus 100 μg pcDNA3.1/3-1E (N). Some groups received PBS and pcDNA3.1 vector alone as controls. Challenge infection with live E. acervulina was given orally and cell-mediated immunity (CMI) was assessed by measuring T-cell subpopulations, T-cell proliferation, and cytokine transcripts. Results: The percentages of CD4+ and CD8+ T-cell subsets and T-cell proliferation response were significantly increased in all immunized groups compared to the control group. The expression of IL-2 and IFN-γ mRNA in the thymus and spleen of S and N groups were significantly higher than that of other groups at 7 and 14 day post infection, respectively. Conclusions: These studies demonstrated that chIL-15 enhanced the immunogenicity of 3-1E DNA Eimeria vaccine against E. acervulina infection and induced significant level of CMI. These results suggest a potential use of IL-15 as an immunomodulator to enhance immunogenicity of DNA vaccines in poultry.

References:

Objective: Describe the immune function of cytokines and their application in disease resistance

Background: Eimeria acervulina is an intracellular protozoan which infects primarily the duodenum of poultry. Development of an effective peptide vaccine against this pathogen has been difficult mainly due to a weak immunogenicity of Eimeria peptide antigens. IL-15 has been shown to promote both cellular and humoral immune functions, and enhances host memory response when used in vaccines. In this study, we constructed several different kinds of DNA vaccines carrying 3-1E gene which encodes a potential TLR ligand protein of Eimeria, and chicken IL-15 (chIL-15). Methods: SPF chickens were immunized intramuscularly with the following DNA vaccines with or without IL-15 with some groups receiving IL-15 with a different signal peptide (NchIL-15): 100 μg pcDNA3.1/3-1E (E), 100μg pcDNA3.1/3-1E-linker-chIL-15 (S), 50μg pcDNA3.1/chIL-15 plus 100μg pcDNA3.1/3-1E (C), 50μg pcDNA3.1/NchIL-15 plus 100 μg pcDNA3.1/3-1E (N). Some groups received PBS and pcDNA3.1 vector alone as controls. Challenge infection with live E. acervulina was given orally and cell-mediated immunity (CMI) was assessed by measuring T-cell subpopulations, T-cell proliferation, and cytokine transcripts. Results: The percentages of CD4+ and CD8+ T-cell subsets and T-cell proliferation response were significantly increased in all immunized groups compared to the control group. The expression of IL-2 and IFN-γ mRNA in the thymus and spleen of S and N groups were significantly higher than that of other groups at 7 and 14 day post infection, respectively. Conclusions: These studies demonstrated that chIL-15 enhanced the immunogenicity of 3-1E DNA Eimeria vaccine against E. acervulina infection and induced significant level of CMI. These results suggest a potential use of IL-15 as an immunomodulator to enhance immunogenicity of DNA vaccines in poultry.

References:
Expansion of a School-based Influenza Vaccination and Herd Protection Trial in Central Texas - Second Year of VIPS: Vaccines for Influenza Prevention in Schools

M. Gaglani1, P. Piedra2, P. Gregor1, D. Harvey1, L. Newman1, L. Thomas1, W. Glezen2
1Scott & White Memorial Hospital and Clinic, Texas A&M Health Sciences Center, Temple, TX, 2Baylor College of Medicine, Houston, TX

Objective: Describe a program to increase the influenza immunization coverage of schoolchildren by school-based vaccination

Background: A school-based trial was implemented in 2007 for elementary schools and expanded to middle and high schools in 2008, to increase influenza immunization coverage in schoolchildren. Methods: Study information in English or Spanish was mailed to or sent home with each child, 4 years or older, from 45 elementary, middle and high schools from 7 public-school districts, 5 parochial schools and intervention area home schools. Influenza vaccine permission forms containing child’s demographic and health information were completed, signed and dated by parent and child, 7 years or older and capable of assent, and collected by schools. School staff organized student flow and research staff triaged students for live or inactivated influenza vaccine. Research, public health and student nurses, and investigators administered influenza vaccines during school hours. Immunization was also performed in the pediatric clinic and during a community event. Results: Study information packets were sent to ~22,914 students. From 09/22/08 to 12/18/08, one immunization day was conducted at 50 schools and at a church for home schooled students. Influenza immunization coverage was 48% (26%-73%) for 26 elementary, 28% (19%-34%) for 10 middle and 22% (19%-30%) for 8 public high schools. It was 52% (45%-60%) for parochial schools, 34% for home schools and 10% for a K-12 public school. Additional 648 students were immunized at the pediatric clinic and a community event, and 358 students were reported to be vaccinated elsewhere. Live nasal spray influenza vaccine was administered to 77% of a total of 9,007 students enrolled, and 23% received inactivated vaccine. We also vaccinated 1,878 school staff. Conclusion: Expansion of a school-based immunization trial from elementary to middle and high schools improved influenza immunization coverage in school-age children to ~40%.

References:

Evaluation of Mixed Schedules of Live Attenuated and Inactivated Influenza Vaccines in Children

E. Babusis1, R. B. Belshe2, K. M. Edwards2, C. B. Creech, H1, M. A. Gerber3, D. I. Bernstein2, F. Newman1, I. Graham1, E. L. Anderson1
1Saint Louis University, St. Louis, MO, 2Vanderbilt University, Nashville, TN, 3Cincinnati Children’s Hospital, Cincinnati, OH

Objective: Describe the antibody responses to influenza vaccines in mixed schedules

Background: Two vaccine types (LAIV and TIV) are available for prevention of influenza in children with two doses separated by at least 4 weeks recommended for all children <9 years who are previously unimmunized. We sought to evaluate the interchangeability of live attenuated with inactivated vaccine within the two dose regimens.

Methods: During 2 years, a randomized, open label study of the interchangeability of LAIV and TIV was conducted in children ages 6 mos - 35 mos (Year 1) and children 12 - 35 mos (Year 2). Subjects were equally assigned to the following vaccine combinations; LAIV/LAIV, TIV/TIV, LAIV/TIV or TIV/LAIV. Results: 53 of 55 children received both doses of vaccine and 52 of 55 had serum obtained post-vaccination. No serious adverse were reported.

Post Dose 2 HAI Antibody Geometric Mean Titer (95% CI)

<table>
<thead>
<tr>
<th>Group</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIV/TIV</td>
<td>16</td>
<td>84</td>
<td>13</td>
<td>181</td>
<td>23</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>(3.4 - 76)</td>
<td>(40 - 178)</td>
<td>(2.8 - 88)</td>
<td>(11 - 309)</td>
<td>(0.6 - 878)</td>
<td>(16 - 76)</td>
</tr>
<tr>
<td>LAIV/LAIV</td>
<td>23</td>
<td>32</td>
<td>27</td>
<td>64</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>(3 - 153)</td>
<td>(13 - 77)</td>
<td>(16 - 47)</td>
<td>(30 - 137)</td>
<td>(15 - 94)</td>
<td>(7 - 452)</td>
</tr>
<tr>
<td>TIV/LAIV</td>
<td>14</td>
<td>43</td>
<td>64</td>
<td>128</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>(4 - 43)</td>
<td>(16 - 114)</td>
<td>(7 - 574)</td>
<td>(23 - 726)</td>
<td>(3 - 210)</td>
<td>(10 - 123)</td>
</tr>
<tr>
<td>LAIV/TIV</td>
<td>10</td>
<td>74</td>
<td>76</td>
<td>91</td>
<td>45</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>(3 - 27)</td>
<td>(29 - 186)</td>
<td>(9 - 614)</td>
<td>(92 - 354)</td>
<td>(6 - 374)</td>
<td>(40 - 178)</td>
</tr>
</tbody>
</table>

*Note: H1 antigens for TIV and LAIV were different variants of A/New Caledonia/28/99 (H1N1) and homologous titers are reported here, i.e. WT antigen was used for TIV assays and CA antigen was used for LAIV assays since there is a four amino acid difference in these antigens that is significant for immunogenicity testing.

Seventeen of 28 subjects shed virus after dose 1 compared with only 1 of 13 after the second dose of LAIV (p = 0.002, Fisher’s exact test). Of 12 subjects given TIV (dose 1) followed by LAIV (dose 2), four shed virus after LAIV. Conclusions: Differences in immunogenicity of TIV were noted across years. One dose of LAIV protected significantly better against subsequent vaccine viral shedding. One dose of TIV did not significantly reduce subsequent LAIV shedding. A larger study is needed to evaluate TIV/LAIV as a vaccine schedule in children <24 mos (the lower age approved for LAIV).

References:
A Comparative Study of Intramuscular (IM), Subcutaneous (SC), Intradermal (ID) Routes of Administration for VAX102 (STF2.4xM2e) Influenza Vaccine in Healthy Adults

D. N. Taylor\textsuperscript{1}, C. Turley\textsuperscript{2}, U. Kavita\textsuperscript{3}, L. Tussey\textsuperscript{2}, A. Krishnappa\textsuperscript{1}, O. Linton\textsuperscript{1}, C. Johnson\textsuperscript{1}, R. Rupp\textsuperscript{1}, A. Show\textsuperscript{1}

\textsuperscript{1}VaxInnate Corporation, Cranbury, NJ, \textsuperscript{2}Sealy Center for Vaccine Development, Galveston, TX, \textsuperscript{3}Johnson County Clin-Trials, Lenexa, KS

**Objective:** Describe the safety profile for alternative routes of vaccine administration.

**Background:** M2e is a promising candidate for a broadly protective influenza A vaccine. We hypothesized that VAX102 would be better tolerated at higher dose when given SC or ID because of slower absorption.

**Methods:** Healthy volunteers received two injections (28 days apart) of VAX102 at doses of 0.3 μg or 1.0 μg either IM, SC or ID; or 2.0 μg of VAX102 IM or SC. There was an assessment of symptoms at each dose level before escalating the dose. C-reactive protein (CRP) assays were performed on Day 0 and 1. Serum IgG anti-M2e antibody concentration (μg/ml) was assessed by ELISA on day 42. Results: VAX102 was administered to 64 subjects in an open label study (Table 1). VAX102 was well tolerated by all subjects in the 0.3 and 1.0 μg doses, and the mean CRP level, range and fold increase were higher in the 2 μg IM group compared to SC. The differences in antibody titer between the IM and SC group was not significant.

**Results:**

<table>
<thead>
<tr>
<th>Dose (μg)</th>
<th>Route of administration</th>
<th>No. of subjects</th>
<th>C-reactive protein (mg/dL)</th>
<th>Gen. Mean M2e antibody (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Geo. mean (range) at day 1</td>
<td>Fold Increase from day 0</td>
</tr>
<tr>
<td>0.3</td>
<td>IM</td>
<td>8</td>
<td>0.8 (0.2-3.4)</td>
<td>1.8 (0.04-4.7)</td>
</tr>
<tr>
<td>0.3</td>
<td>SC</td>
<td>8</td>
<td>0.4 (0.2-1.1)</td>
<td>1.8 (0.05-2.7)</td>
</tr>
<tr>
<td>0.3</td>
<td>ID</td>
<td>8</td>
<td>0.4 (0.2-1.2)</td>
<td>1.3 (0.05-4.8)</td>
</tr>
<tr>
<td>1.0</td>
<td>IM</td>
<td>8</td>
<td>0.8 (0.2-3.8)</td>
<td>3.1 (0.8-2.1)</td>
</tr>
<tr>
<td>1.0</td>
<td>SC</td>
<td>8</td>
<td>0.6 (0.2-2.3)</td>
<td>2.1 (0.8-2.3)</td>
</tr>
<tr>
<td>1.0</td>
<td>ID</td>
<td>8</td>
<td>0.7 (0.2-6.5)</td>
<td>2.0 (0.8-2.3)</td>
</tr>
<tr>
<td>2.0</td>
<td>IM</td>
<td>6</td>
<td>1.4 (0.2-4.9)</td>
<td>5.9 (1.1-13.3)</td>
</tr>
<tr>
<td>2.0</td>
<td>SC</td>
<td>8</td>
<td>0.8 (0.4-1.9)</td>
<td>3.2 (0.9-8.0)</td>
</tr>
</tbody>
</table>

**Conclusions:** VAX102 is better tolerated administered by SC route compared to IM. ID was also well tolerated and produced a good M2e immune response.

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**Reference:**

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Escalating Dose-Ranging Study to Evaluate the Safety and Immunogenicity of the VAX125 (STF2.HA1(SI)), a Recombinant Hemagglutinin Influenza Vaccine, in Healthy Young Adults

J. J. Treanor\textsuperscript{1}, D. N. Taylor\textsuperscript{1}, L. Song\textsuperscript{1}, T. Fitzgerald\textsuperscript{1}, A. Show\textsuperscript{1}, L. Tussey\textsuperscript{2}

\textsuperscript{1}University of Rochester, Rochester, NY, \textsuperscript{2}VaxInnate Corporation, Cranbury, NJ

**Objective:** Describe a new type of influenza vaccine.

**Background:** Current production of influenza vaccines has limitations that impact on national and global supply. We developed a novel influenza vaccine by fusing the globular head domain of the protective hemagglutinin (HA) antigen from A/Solomon Islands/3/2006 (H1N1) with the TLR5 ligand, flagellin, designated VAX125 (STF2.HA1(SI)).

**Methods:** Subjects were healthy adults 18 to 49 years old. VAX125 was given as a single intramuscular dose to 8 subjects at each of 7 dose levels ranging from 0.1 to 8 μg. Clinical and laboratory safety assessments took place at on day 1 and 7 after vaccination. Serum hemagglutination-inhibition (HAI) antibody was assessed at day 0, 7, 14, and 28 after vaccination. Results: A total of 56 subjects were enrolled and received vaccine. Side effects at the site of injection were mild for doses 0.1 to 3 μg and moderate at the 5 to 8 μg doses. Systemic side effects were reported as none or mild in 54 (96%) of 56 subjects. The HAI seroconversion and seroprotection rates and HAI GMT fold rise after one dose VAX125 are seen in the table.

**Reference:**
Objective: Describe novel mechanisms for the development of long-lasting, broad spectrum influenza vaccine

Background: Current influenza vaccine antigens are selected yearly to match circulating strains; this imposes significant burden on production and supply. Novel vaccines capable of inducing long-lasting, broad immunity against divergent strains, including potential pandemic viruses, are highly desirable. We have clinically evaluated the safety and immunogenicity of BIPCV, consisting of conserved M2 surface protein (influenza type A) and HA protein (influenza type B). Methods: 377 subjects enrolled in two studies were to receive three doses of BIPCV intramuscularly at 0, 2, and 6 months. Vaccine was formulated with saponin (ISCOMATRIX™ adjuvant) and/or aluminum. Three dose levels of peptide and 3 concentrations of ISCOMATRIX™ adjuvant were evaluated. Active safety follow-up was 14 days after each vaccination, and overall safety was evaluated for entire study duration. Immune responses to A/M2 and B/HA0 were measured 1 month after each vaccination and up to 18 months after last dose. Results: No vaccine-related serious adverse experiences were reported during these studies. Injection site reactions (pain, redness, and swelling) were mostly transient, mild to moderate in intensity. Solicited flu-like symptoms (headache, myalgia, nausea, and fatigue) were transient, generally mild to moderate and reported by 18% to 60% of subjects. BIPCV containing highest amount of antigen and medium to high concentrations of adjuvant were associated with more local and systemic reactions. Antibody titers were up to 15-fold (A/M2) and 125-fold (B/HA0) higher at postdose 2 than baseline and correlated with saponin content. Antibody titers elicited by the vaccine were similar to levels associated with protection of small animals from lethal challenge. Conclusions: BIPCV is highly immunogenic and low to medium content of ISCOMATRIX™ adjuvant displays an acceptable safety profile in young adults.

References:

Objective: Describe epitope profiles for antibodies elicited by avian influenza exposure and vaccines

Background: Recent spread of highly pathogenic avian influenza viruses among poultry, and transmissions to humans, generated concern of impending pandemic. Efforts are underway to generate stockpiles of vaccines against avian influenza. Adjuvants are evaluated to improve vaccine immunogenicity and to elicit broad heterosubtypic protection. Concomitantly, improved analytical tools are needed for comparing different vaccines and antigen/adjuvant combinations. Methods: Whole-genome-fragment-phage-display libraries (GFPDL) expressing all the open reading frames of avian influenza H5N1 (A/Vietnam/1203/2004 & A/Indonesia/5/05) viruses were constructed. Each GFPDL contains 10^10-10^11 phages expressing influenza sequences of 15-350 aa as fusion & A/Indonesia/5/05) viruses were constructed. Each GFPDL contains 10^10-10^11 phages expressing influenza sequences of 15-350 aa as fusion proteins with the pIII coat protein. The FLU-libraries are used to map: a) broadly neutralizing human MAab derived from H5N1 recovered individuals; b) immune sera from unadjuvanted and adjuvanted pandemic influenza vaccinees. Results: Binding of broadly neutralizing H5 human monoclonal antibodies required large HA1 segments encompassing the RBS to express their conformational epitopes. Critical contact residues, which could explain the cross-clade neutralization, were identified. The HA1 sub-fragment was expressed in bacteria and was purified under conditions that favored proper folding or loss of folding. Using surface plasmon resonance, the MAbs bound only to the properly folded HA1 fragment. First generation inactivated H5N1 vaccine elicited limited repertoire of anti-H5N1 antibodies, while sera from MF59 adjuvanted vaccine recipients demonstrated “Epitope Spreading.” The binding to large HA1 fragments that were properly folded was greatly increased in the adjuvanted vaccine group and correlated with improved cross-clade neutralization. Conclusions: The FLU-GFPDL is a powerful unbiased new tool to identify complete repertoires of antibodies elicited by viral infections and vaccination. It may identify conserved sequences involved in broad cross-protection that could be incorporated into future pandemic vaccines and for serodiagnostic use.

Reference:
Abstracts of Oral Submitted Presentations

S14 Live Attenuated Influenza Vaccine (LAIV), but Not Trivalent Inactivated Influenza Vaccine (TIV), Induces Functional CD4+, CD8+ and γδ T Cell Responses in Children Relevant for Pandemic Influenza


1Saint Louis University, St. Louis, MO, 2Vanderbilt University, Nashville, TN, 3Cincinnati Children’s Hospital Medical Center, Cincinnati, OH

Objective: Describe the cell mediated immune responses to influenza vaccines

Background: LAIV protects children better than TIV, possibly related to the induction of enhanced cell mediated immune responses. Methods: T cell responses were studied in children, aged 6-35 months, given 2 doses of influenza vaccine one month apart in four combinations: TIV/TIV, TIV/ LAIV, LAIV/LAIV and LAIV/TIV. CD8+ and γδ T cells capable of live influenza-specific expansion (CFSE dilution) and effector function (intracellular IFN-γ production) were detected by flow cytometry. In addition, highly conserved M1, M2 and NP flu peptides predicted to bind and be presented by common HLA class I and II were used to stimulate overnight IFN-γ ELISPOT responses. Results: Children given LAIV at least once, but not TIV alone, developed significant increases in influenza-specific CD4+, CD8+ and γδ T cells capable of antigen-specific expansion and IFN-γ production (Figure) by Wilcoxon matched pairs tests. In addition, only LAIV induced enhanced IFN-γ ELISPOT responses specific for flu peptides, which was potentially relevant for protection against all known strains of influenza.

Conclusions: Influenza-specific CD4+, CD8+, and γδ effector T cell responses were induced by LAIV but not TIV, including responses reactive with highly conserved epitopes relevant for protection against pandemic influenza viruses. In work presented by Babusis et al, LAIV induced protection against LAIV shedding. These combined results suggest that T cells may provide additional mechanisms by which LAIV can induce enhanced protection against influenza infection.

References:

S15 Selection Bias in the Measure of Vaccine Protection against Serious but Non-Specific Influenza Outcomes in Seniors: Examination through Linked Manitoba Databases

T. S. Hottes1, D. M. Skowronski2, B. Hiebert3, L. L. Roos2, P. Yan Ceaseke1, R. Wolfa1, N. Janjua1, G. De Serres4

1British Columbia Centre for Disease Control, Vancouver, CANADA, 2Manitoba Centre for Health Policy, Winnipeg, CANADA, 3Cadham Provincial Laboratory, Winnipeg, CANADA, 4Institut National de Santé Publique du Québec, Québec, CANADA

Objective: Describe how to use administrative databases to estimate influenza vaccine effectiveness against serious outcomes in seniors

Background: Observational studies based on administrative databases have provided implausibly high estimates of influenza vaccine effectiveness (IVE) against serious but non-specific outcomes in seniors. Methods: Primary pneumonia/influenza/acute respiratory illness) hospitalization and all-cause mortality were compared between vaccinated/non-vaccinated community-dwelling seniors ≥65 years through linked administrative databases of the Manitoba Immunization Monitoring System and the Manitoba Centre for Health Policy data repository between 2000-01 and 2005-06. Separate annual IVE estimates were compared during pre-, influenza-, and peak- and post-season periods through combinations of exclusion/regression/stratification/propensity score analyses. Covariates explored included age/sex/income/urban or rural residence/prior influenza or pneumococcal immunization/prior medical visits/homecare use and Elixhauser (comorbidity) index. Results: Study population included approximately 140,000 seniors, of whom 54-67% were immunized annually. Unadjusted point estimates of IVE ranged up to 10% for primary hospitalization and up to 60% for all-cause mortality during the influenza-season, unaffected by peak-periods. Only adjustment for prior influenza immunization history influenced IVE estimates, increasing to as high as 40% for primary hospitalization and 80% for all-cause mortality. IVE estimates were paradoxically highest in the pre-season period, a finding only exacerbated through standard regression and propensity score adjustment. Stratified analysis showed that habitual immunizers who failed to be immunized during the study year had the highest risk of hospitalization/death pre-season, which persisted through subsequent analysis periods. Conclusions: IVE against serious outcomes in seniors appears to be largely explained by selection bias, as evidenced by persistent pre-season differences in vaccinated/unvaccinated cohorts. The failure of repeatedly vaccinated seniors to be immunized is a flag for acute hospitalization/death, and no readily-available covariate properly adjusts for this “negative confounding-by-indication.” Selection bias precludes reliable interpretation of vaccine protection in seniors when measured through administrative databases.

References:
S16  Effectiveness of the Influenza Vaccine at Preventing Death in the Elderly: A New Approach

R. Baxter, B. Fireman, J. Lee
Kaiser Permanente, Oakland, CA

Objective: Elucidate new methods for determining the effectiveness of the flu vaccine in preventing death in the elderly

Background: Studies have found that mortality during flu season is much lower in elderly people who were vaccinated than in those who were not vaccinated. Recent reports have called into question the assumption that the vaccine accounts for the difference; rather selection bias may be inherent in studies of observational data. Methods: We examined flu vaccination in relation to mortality in members of Kaiser Permanente (KP) in Northern California, aged 65 and above, from September 1996 to September 2005. Flu seasons were defined each year by lab tests that were positive for influenza. We used a "difference-in-differences" approach, measuring the difference between the following two differences: (a) the difference in the odds of prior vaccination between decedents and survivors when flu is circulating, and (b) the difference between decedents and survivors that would be found at the same time of the year when flu is not circulating. To implement this approach, we fit a logistic regression model with a novel specification that may be useful in other large multi-site population-based studies. Results: We vaccinated over 1.9 million members during the study period, during which our 65+ population grew from 273,000 to 387,000. Overall effectiveness of the vaccine against all-cause mortality in our elderly population was 4.6% (CI 0.7-8.3%). Vaccine effectiveness against cardiovascular and respiratory deaths (combined) was 7.6% (2.4-12.6%). Conclusions: The influenza vaccine appears to provide a modest benefit against all-cause mortality in the elderly. The vaccine effectiveness against all-cause mortality is less than previously reported. Our novel statistical methods can be used to help overcome biases present in earlier observational studies and to better determine effectiveness of the influenza vaccine in large populations.

References:

S17  Effect of Maternal Pneumococcal (Spn) Antibody (Ab) on Infant Ab Response to Spn Conjugate Vaccine (PCV7)

M. C. Steinhoff1, K. Zaman2, E. Roy2, R. Raqib2, S. E. Arifeen2
1Global Health Center, Cincinnati Children’s Hospital and Medical Center, Cincinnati, OH, 2ICDDR, Dhaka, BANGLADESH

Objective: Discuss active and passive immunity in infants

Background: Maternal immunization will protect infants, but may inhibit infant Ab response. We assessed the effect of high levels of passive maternal Spn Ab on the infant’s response to immunization with PCV7. Methods: 170 Bangladesh mothers received Spn polysaccharide (23vPS) vaccine in the 3rd trimester of pregnancy; infants received PCV7 at 6, 10 and 14 weeks. There were 4 study groups: Spn vaccine received by A) Mo and Inf, B) Mo only, C) Inf only, D) neither. Mothers’ serum before and after immunization; infant cord; and 10, 14, 18-22 week serum was tested by Luminex IgG ELISA assay for Ig Ab to serotypes 4, 6B, 9V, 14, 19E GMTs were calculated. Results: See serotype 6B Ab GMT values in figure. Maternal immunization increased mothers’ GMT for most serotypes by 6 to 23-fold and the infant/maternal Ab ratios were 0.8-1.2. Conclusions: This is the first RCT of maternal 23vPS followed by infant PCV7 immunization. Although PCV7-immunized infants of 23vPS-immunized mothers have somewhat lower antibody GMT at 6 months, in general they have protective levels of passive and active Spn Ab throughout the high risk 0-6 months.

References:
**S18 Immuneome-Derived Epitope-Driven Vaccines (IDEDV) Protect Against Viral or Bacterial Challenge in Humanized Mice**

**A. De Groot, L. Moise**
EpiVax, Providence, RI

**Objective:** Describe pre-clinical development of immuneome-derived epitope-driven vaccines

While whole killed, whole protein, or live attenuated vaccines have been the standard bearers for protective vaccines in the last century, concerns about vaccine safety and new vaccine design techniques are contributing to a newer emphasis on vaccines developed using the minimum essential subset of T and B-cell epitopes that comprise the ”immunome.” Accordingly, we have used bioinformatics sequence analysis tools, epitope-mapping tools, microarrays and high-throughput immunology assays to discover the minimal essential vaccine components for smallpox, tularemia, *H. pylori* infection and tuberculosis.[1] This approach has resulted in the development of four IDEDV, of which three have been shown to be protective against viral or bacterial challenge. Protective efficacy of 100% (vaccinia); 90% (*H. pylori*), and 57% (tularemia) has been achieved in HLA-transgenic (humanized) mouse models. Such immuneome-derived vaccines may have a significant advantage over conventional vaccines, as the careful selection of the components may diminish undesired side effects such as have been observed with whole pathogen and protein subunit vaccines. We will provide new data showing IDEDV protection against lethal challenge with vaccinia, tularemia, and tuberculosis and discuss the anticipated clinical development of these and similar vaccines.

**Reference:**

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**S19 Phase 1 Safety and Immunogenicity Results of Vaxfectin®-Formulated Plasmid DNA Vaccines Encoding Influenza Virus H5 Hemagglutinin**

**L. R. Smith, M. Whoch, A. Rolland, A. Chu, R. Mass**
Vical Incorporated, San Diego

**Objective:** Describe how DNA vaccines may be an additional strategy for pandemic influenza control

**Background:** Evolving clades of highly pathogenic H5N1 influenza viruses have become widely distributed in wild and domestic birds and are a reservoir for human infections, resulting in >60% fatality rates. Vaccine development is a key strategy in mitigating a potential pandemic. Adjuvanted protein-based vaccines have demonstrated promising safety and immunogenicity profiles but limitations in vaccine manufacturing time and capacity indicate the need to develop additional approaches such as plasmid DNA vaccines. **Methods:** Two double-blind, placebo-controlled phase 1 trials were conducted in 100 healthy 18-45 year old adults at three sites in the United States to assess the safety and efficacy of increasing Vaxfectin®-formulated plasmid DNA doses escalating from 0.1-1 mg of total DNA/injection. Vaccines were administered on days 0 and 21 by intramuscular injection with needle or needle-free Biojector® 2000 device. **Results:** All doses were well-tolerated; no vaccine-related serious adverse events occurred; and no subjects dropped out due to vaccination. Hemagglutination inhibition (HI) titers ≥40 were observed by day 56 in 50%-67% of subjects receiving the highest H5-encoding plasmid doses and the majority of these subjects maintained ≥40 titers at day 182. A good correlation was observed between HI and neutralizing antibody titers at day 56. Cross-clade HI titers ≥40 to two other H5N1 clades were present in 36% and 50% of responders. Interferon-γ-producing H5-specific T-cell responses were elicited in 75%-100% of subjects by day 42 and remained positive in the majority of subjects at day 182. **Conclusion:** Vaxfectin®-formulated DNA vaccines were well-tolerated and induced H5-specific antibody responses in the range of conventional inactivated protein-based vaccines. These findings warrant further clinical development and suggest DNA vaccines may be an important additional pandemic influenza vaccine strategy.

**Reference:**

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**S20 Safety, Tolerability, Immunogenicity, and Protective Efficacy of a Multi-Stage, Multi-Antigen Adenovirus-Vectored *P. falciparum* Malaria Vaccine in Healthy, Malaria-Naïve Adults**

1US Military Malaria Vaccine Program, Naval Medical Research Center/Walter Reed Army Institute of Research, Silver Spring, MD, 2National Naval Medical Center, Bethesda, MD, 3GenVec, Gaithersburg, MD, 4United States Agency for International Development (USAID), Washington, DC

**Objective:** Describe the clinical outcome of a Phase 1/2a malaria vaccine trial testing the safety, tolerability, immunogenicity, and protective efficacy of an adenovirus vectored malaria vaccine

**Background:** A multi-stage, multi-antigen prototype adenovirus (serotype 5)-vectored malaria vaccine is currently under evaluation by the US Military Malaria Vaccine Program in a Phase1/2a trial. Designated NMRC-M3V-Ad-PfCA, the vaccine comprises two adenovectors encoding the antigens *P. falciparum* (Pf) CSP (expressed in sporozoite and early liver stages) and PfAMA1 (expressed in sporozoite, liver and erythrocytic stages). **Methods:** In Part A (dose selection), two groups of volunteers (n=6/group) received either a single 2x10¹³ particle unit (pu) dose (1x10¹⁰ pu/construct) or a five fold higher 1x10¹⁵ pu dose (5x10¹⁴ pu/construct) of vaccine. In Part B (challenge phase), 14 volunteers received two administrations, given 4 months apart, of NMRC-MV-Ad-PfCA (CSP only) at the low dose. Three weeks later, 12 vaccinees and 6 unimmunized infectivity controls underwent Pf sporozoite challenge. **Results:** The vaccine was generally well tolerated at both doses. Part A: Cell-mediated immune responses summed over 9 (CSP) or 11 (AMA) overlapping peptide pools demonstrated statistically significantly higher interferon gamma ELISpot responses to the CSP antigen in the low (range: 114-1066 sfc/10⁶ PBMCs) compared to the high (range: 52-493) dose group (p<0.05). Antibody responses were induced to both antigens but were low. Part B: ELISpot responses to CSP were similar in magnitude to Part A (low dose) and did not statistically differ between first (range: 71-1128) and second (range: 53-596) immunizations. Following challenge, all 12 vaccinated volunteers became parasitemic with no delay to patentcy relative to the six controls. **Conclusion:** In this regimen (1) CSP given as the sole antigen does not confer protection in human volunteers in spite of significant ELISpot responses; (2) a second dose of adenovector does not increase ELISpot responses compared to a single dose.
S21 Safety and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants Given with Routine Pediatric Vaccinations in Canada

J. D. Kellner, D. Girgenti, S. A. Halperin, D. Scheifele, W. A. Gruber, D. Scott

1Pediatrics, University of Calgary, Calgary, CANADA, 2Wyeth Vaccines Research, Pearl River, NY, 3Dalhousie University, Halifax, CANADA, 4University of British Columbia, Vancouver, CANADA

Objective: Discuss whether a new 13-valent pneumococcal conjugate vaccine is safe and immunogenic when given concomitantly with routine infant vaccines

Background: A 7-valent pneumococcal conjugate vaccine (PCV7; 4, 6B, 9V, 14, 18C, 19F, and 23F) has reduced morbidity and mortality associated with invasive pneumococcal disease in infants and children. We report safety and immunogenicity results for a 13-valent conjugate vaccine (PCV13; additional serotypes 1, 3, 5, 6A, 7F, 19A) when given with routine vaccines in Canada. Methods: Healthy infants were randomized (1:1) to receive PCV7 or PCV13 at age 2, 4, and 6 months with DTaP(5)-IPV-Hib at age 2, 4, and 6 months and tetanus-conjugated meningococcal C vaccine at 2 and 6 months. Antibody responses against meningococcal C, Haemophilus influenzae type b, and pertussis antigens in all subjects, and against pneumococcal serotypes in PCV13 subjects, were measured 1 month after the 6-month dose. Local and systemic reactions and adverse events were evaluated. Non-inferiority of response to concomitant vaccines for PCV13 compared with PCV7 was declared if the lower limit of the 95% CI for the difference in proportions of subjects achieving pre-specified antibody levels was >-0.10. Results: Target antibody responses to the concomitant vaccines were achieved by 95.4%-100% of subjects and 96.8%-100% of subjects in PCV13 and PCV7 groups, respectively (evaluable PCV13 n=285; PCV7 n=278). Non-inferiority criteria between treatment groups were met for each antigen. For PCV13, pneumococcal capsular binding IgG responses (WHO threshold concentration ≥ 0.35µg/mL) were >90.0% for all serotypes common to both vaccines. For additional serotypes, responses were 79.6%, type 3; 87.0%, type 5; and >95.0% for all others. Most local and systemic reactions were mild; adverse event profile was similar between groups. Conclusions: PCV13 is immunogenic and well-tolerated when given at age 2, 4, and 6 months with routine pediatric vaccines.

Reference:

References:
S23 Preliminary Phase 2 Immunogenicity Results of a CMV DNA Vaccine in Hematopoietic Cell Transplant (HCT) Recipients

L. R. Smith, M. Wloch, D. Gutierrez, A. Rolland, A. Chiu, R. Moss
Vical Incorporated, San Diego, CA

Objective: Describe how a CMV DNA vaccine can increase CMV-specific T cells which may impact CMV reactivation in patients undergoing HCT

Background: Approximately 60% of CMV-seropositive patients undergoing hematopoietic cell transplant (HCT) experience CMV reactivation within 100 days after transplant, resulting in significant morbidity and mortality. Antiviral treatment limits CMV disease but is associated with toxicities such as neutropenia. Control of CMV viremia and disease appear to correlate with CMV-specific T-cell responses after HCT. We are evaluating a CMV DNA vaccine for increasing CMV-specific T cells and controlling viral replication after HCT. Methods: A double-blind, placebo-controlled study of CMV-seropositive recipients undergoing allogeneic, matched HCT was designed with several end points including safety, immunogenicity, CMV DNAemia, antiviral use, and CMV disease. HCT patients were randomized 1:1 to receive placebo or VCL-CB01 vaccine containing plasmids encoding gB and pp65 formulated with poloxamer CRL1005. All recipients were immunized at 3-5 days prior to and 3-6, 12, and 28 weeks after transplantation. In one trial arm (D/R), donors were also immunized at 9, 6, and 2 days before transplant. In the other arm (R), only recipients were immunized. CMV-specific T-cells were measured by IFN-γ ELISPOT assays and antibodies to gB were measured by ELISA. Results: Trial enrollment was completed and a preliminary analysis of immunogenicity in 47 recipients (33 R, 14 D/R) showed higher frequencies of CMV-specific pp65 (p<0.05) and gB (p<0.05) T cells at days 56 and 84 after transplant only in the subjects in the R arm compared to placebo. There were no differences in gB antibody levels after transplant. Results from the analysis of additional clinical endpoints are expected in the near future. Conclusion: These preliminary results suggest that a CMV DNA vaccine can increase CMV-specific T cells which may impact CMV reactivation in patients undergoing HCT.

Reference:

S24 Immune Responses in Humans to AERAS-402, Crucell Adeno35-Vectored TB Vaccine Candidate

J. C. Sadoff
Aeras Global TB Vaccine Foundation, Rockville, MD

Objective: Describe the approach and results of evaluating immune responses to a new adeno35-vectored TB vaccine candidate following priming with BCG

Background: AERAS-402 is a replication-deficient adenovirus serotype 35 investigational TB vaccine containing DNA that expresses a fusion protein of the Mycobacterium tuberculosis antigens 85A, 85B and TB10.4. AERAS-402’s ability to induce immune responses was investigated in naïve and BCG immunized US and S. African adults. Methods: Antigen specific CD4 and CD8 T cells producing IFN-γ, TNF-α and IL-2 following peptide stimulation were measured by flow cytometry in three studies. In study C001-402 BCG naïve U.S subjects received 2 doses of AERAS-402. In study C003-402 S. African adults given BCG at birth were given various doses of AERAS-402. In study C008-402 BCG was followed by 2 injections of AERAS-402. Descriptive statistics were used to summarize the percentage CD4 and CD8 responses. Results: In studies C001-402, C003-402 and C008-402 the median % (95% CI) CD4 responses 28 days following the second dose of 3x10^10 viral particles against peptide pools of TB antigen 85A/B were 0.01 (0.00, 0.05), 0.01 (0.00, 0.02), and 0.09 (0.01, 0.27) respectively and the median % CD8 responses were 0.02 (0.01, 0.11), 0.04 (0.00, 0.36) and 0.38 (0.01, 0.69) respectively. Conclusions: AERAS-402 induced measurable TB antigen specific CD4 and CD8 T cell responses in BCG naïve individuals and moderate CD4 T cell responses in naïve US volunteers primed with BCG or S. African adults immunized with BCG at or near birth. The naïve US volunteers primed with BCG developed the highest TB antigen specific CD8 T cell responses reported in humans thus far. BCG therefore appears to be an excellent prime for induction of CD8 T cell responses by an adeno-vectored vaccine and AERAS-402 appears to be a promising TB vaccine candidate.

References:

S25 Post-licensure Safety Evaluation of a Combination Diphtheria, Tetanus, Acellular Pertussis, Hepatitis B, and Inactivated Poliovirus Vaccine (DTaP-HepB-IPV)

W. Huang, P. Gargiullo, E. Weintraub, J. Baggs, K. Broder, J. Iskander
Centers for Disease Control and Prevention (CDC), Atlanta, GA

Objective: Discuss the risk of medically-attended fever and seizures in infants who receive DTaP-HepB-IPV or separate DTaP, HepB, and IPV at the same visit

Background: In 2002, combination DTaP-HepB-IPV vaccine was licensed for children aged 6 weeks through 7 years. Preliminary studies in infants aged ≤6 months suggested higher fever rates 0-3 days after DTaP-HepB-IPV compared with coadministering separate component vaccines. We evaluated risks for fever and seizures after DTaP-HepB-IPV in the Vaccine Safety Datalink (VSD) postlicensure cohort. Methods: A retrospective study was conducted using 2000-2006 automated data in seven managed care organizations (MCOs) in the VSD. We identified infants aged 6 weeks to 7 months who, at the same visit, received either DTaP-HepB-IPV with pneumococcal conjugate vaccine (PCV7), or DTaP with separate HepB, IPV, and PCV7. In the postvaccination 0-3 days of each cohort, we identified ICD-9 codes of 1) fever in any healthcare setting; and 2) seizures in the emergency department/hospital. Incidence rate ratios (IRR) were estimated by unconditional Poisson regression adjusted for MCO, gender, calendar year, influenza season and age. Results: We identified 307,499 visits for DTaP-HepB-IPV with PCV7, and 52,172 visits for the separate vaccines. The adjusted IRR across all doses was 1.43 (95% confidence interval [CI]=1.07-1.91) for fever, comparing DTaP-HepB-IPV (538 fevers) with separate component vaccines (50 fevers). DTaP-HepB-IPV coadministered with PCV7 was associated with 1 additional medically-attended fever per 1,798 doses, compared with separate component vaccines. Few postvaccination seizures were observed; the adjusted IRR was 0.89 (95% CI=0.26-3.07) comparing DTaP-HepB-IPV (17 seizures) with the separate vaccines (3 seizures). Conclusions: Combination vaccines reduce the number of infections and may improve vaccination coverage. These benefits should be considered in the context of excess risk for medically-attended fever when deciding whether to use DTaP-HepB-IPV or DTaP, HepB, and IPV simultaneously.
S26 Rates of Autoimmune Diseases in Kaiser Permanente for Use in Vaccine Adverse Event Safety Studies

N. P. Klein1, P. Ray2, D. Carpenter3, J. Hansen4, N. Lewis5, B. Fireman6, S. Black7, C. Gallindo8, J. Schmidt1, R. Baxter1

1Kaiser Permanente, Oakland, CA, 2Cincinnati Children’s Hospital, Cincinnati, OH, 3GileadSmithKline Biologics, Rixensart, BELGIUM

Objective: Discuss the epidemiology and background incidences of four autoimmune diseases in a large health maintenance organization.

Background: Safety monitoring following introduction of new vaccines includes assessment of potential new onset autoimmune diseases (AID). Interpreting the significance of these cases is difficult because knowledge about AID background incidence rates is limited. This retrospective study evaluated baseline incidence rates of Guillain-Barré syndrome (GBS), transverse myelitis (TM), immune thrombocytopenic purpura (ITP) and thyroiditis in 10-62 year olds. Methods: We used electronic records in Northern California Kaiser Permanente to identify ICD-9 and text AID diagnoses from 1998-2004, excluding diagnoses from 1996-1997. We reviewed medical records of all GBS and TM cases and a random sample of ITP and thyroiditis cases (100 each) to verify initial diagnosis dates and confirm cases. Incidence rates were based on confirmed cases.

Results: Electronic medical review identified 212 cases of GBS and 269 cases of TM; 163 and 194 cases, respectively, were accepted after medical record review. Electronic medical review identified 2537 ITP cases and 8894 thyroiditis cases; 9/100 ITP cases and 41/100 thyroiditis cases were accepted after medical review. Age and gender specific incidence rates are below.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>GBS</th>
<th></th>
<th></th>
<th>TM</th>
<th></th>
<th></th>
<th>ITP</th>
<th></th>
<th></th>
<th>Thyroiditis</th>
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<tbody>
<tr>
<td></td>
<td>Males Rate/100,000 person-years (95% CI)</td>
<td>Females Rate/100,000 person-years (95% CI)</td>
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<td>Males Rate/100,000 person-years (95% CI)</td>
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<td>Males Rate/100,000 person-years (95% CI)</td>
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<tr>
<td>10-17</td>
<td>2.1 (0.8, 4.6)</td>
<td>1.8 (0.6, 4.2)</td>
<td></td>
<td>0.7 (0.1, 2.5)</td>
<td>0.4 (0.01, 2)</td>
<td></td>
<td>0.6 (0.1, 1.3)</td>
<td>1.5 (0.3, 3.2)</td>
<td></td>
<td>4.2 (2.3, 6.6)</td>
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<tr>
<td>18-25</td>
<td>0.8 (0.1, 1.3)</td>
<td>0.4 (0.01, 2.1)</td>
<td></td>
<td>0.4 (0.01, 2.3)</td>
<td>1.1 (0.2, 3.2)</td>
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<td>1.2 (0.3, 2.5)</td>
<td>3.3 (0.7, 6.3)</td>
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<td>3.4 (0.7, 6.4)</td>
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<tr>
<td>26-62</td>
<td>3.3 (2.5, 4.2)</td>
<td>2.3 (1.7, 3.1)</td>
<td></td>
<td>2.4 (1.7, 3.2)</td>
<td>4.9 (4, 6)</td>
<td></td>
<td>3.4 (0.7, 6.4)</td>
<td>3.1 (0.6, 6.6)</td>
<td></td>
<td>2.6 (2.3, 3.6)</td>
</tr>
</tbody>
</table>

Conclusions: Utilizing a two-year disease-free inception cohort and medical review of identified cases increases the specificity of population-based AID incidence rates. Numerous issues relating to methodology and Kaiser Permanente membership influence comparability of the results with published estimates. Nevertheless, these results will facilitate interpretation of observed medical events after new vaccines are introduced into practice.

References:
2. Kaiser Permanente Vaccine Study Center, Oakland, CA, 3Center for Global Health, Cincinnati Children’s Hospital, Cincinnati, OH, 4Centers for Disease Control and Prevention, Atlanta, GA, 5University School of Medicine, Stanford, CA, 6Vanderbilt University, Nashville, TN, 7Columbia University Medical Center, New York, NY.

Objective: Describe the feasibility of assessing causality of vaccine adverse events reported to the Vaccine Adverse Event Reporting System.

Background: Vaccine safety is a major concern for patients, parents, healthcare providers, public health officials and vaccine manufacturers. The Vaccine Adverse Event Reporting System (VAERS) is the principal passive surveillance system for vaccine adverse events in the United States. Vaccination may be coincidentally, not causally, related to the adverse event reported to VAERS. We sought to determine whether causal relationship could be assessed between the vaccine and the adverse events in a random sample of VAERS reports. Methods: A stratified random sample of the 2004 VAERS reports contained 75% severe cases and 25% non-severe cases. Five experts knowledgeable about vaccines and vaccine adverse events independently reviewed each VAERS case report; available medical records, and other supporting material provided by the CDC and FDA personnel. Causality assessment was based on modified WHO criteria that classify the causal relationship between the vaccine and the adverse event. If the reviewers did not reach majority agreement, then the case was discussed on a telephone conference call to achieve majority agreement. Results: For 108 adverse events, majority agreement was achieved in 83% of cases, and 17% required further discussion. A causal relationship was determined to be definite in 2.8%, probable in 20.4%, possible in 20.4%, unlikely in 20.4%, unrelated in 33.3% and unclassifiable in 2.8% of VAERS cases reviewed. Conclusions: In this assessment, a definite causal relationship between a vaccine and adverse event was established only rarely. 54% of adverse events reviewed were either not caused or unlikely to have been caused by the vaccine administered. Accurate reporting to VAERS including review of medical records, and the use standard definitions for adverse events would improve causality assessments.

References:
S28 Exact Sequential Analysis for Vaccine Safety Surveillance

E. Lewis, B. Fireman, N. Klein, R. Baxter
Kaiser Permanente Vaccine Study Center, Oakland, CA

Objective: Discuss a new method for sequential analysis in observational studies of vaccine safety

Background: The Vaccine Safety Datalink is a collaborative effort of eight medical care organizations (MCOs) and the Centers for Disease Control, which conducts post-licensure vaccine safety monitoring. Data from nearly nine million MCO members are evaluated weekly, comparing adverse events (AEs) which occur after vaccination to identical medical outcomes which occur among appropriate controls. Sequential (repeated) data analyses require a balance between the need for timely detection of real vaccine safety risks and the need to minimize false alarms. Here we present a new approach to sequential analysis which uses exact statistics, which are especially helpful when there are small numbers of AEs, and/or variation over time in the ratio of exposed (vaccinated people) to unexposed (controls). Methods: Each week, we examine the distribution of all AEs to date, across pre-specified risk windows following vaccination, relative to the distribution within an appropriate comparison group. Using an efficient exact permutation algorithm, we compute probabilities that a safe vaccine would, by chance alone, be followed by as many apparent AEs as have been observed in the risk window. Our chances of a false alarm are rationed to ensure that they add up to no more than 5% before the study endpoint, which may be specified in terms of AEs, calendar time, or vaccine doses delivered. The method is flexible in adapting to any pre-specified ‘alpha spending’ plan. It also allows for stratification by covariates such as age or calendar week even when the incidence density is sparse. Conclusions: This new method is simple, flexible, consistent with well-established statistical theory and suitable to population-based surveillance where, unlike in clinical trials, vaccine coverage varies in unpredictable ways across subgroups and over time.

References:

S29 Defining 5-Year Research Needs for the Centers for the Disease Control and Prevention’s (CDC) Immunization Safety Office (ISO) Scientific Agenda


Centers for Disease Control and Prevention, Atlanta, GA, 1Marshfield Clinic Research Foundation, Marshfield, WI, 2Vanderbilt University, Nashville, TN, 3National Vaccine Program Office, Washington DC, 4University of Utah School of Medicine, Salt Lake City, UT

Objective: Describe the process ISO used to define the possible research needs for the draft Scientific Agenda and provide four examples of possible vaccine safety research needs

Background: In response to an Institute of Medicine recommendation, CDC's Immunization Safety Office (ISO) developed a draft 5-year Scientific Agenda (Agenda) and asked the National Vaccine Advisory Committee (NVAC) to review it. The goal of the Agenda is to identify and prioritize future ISO vaccine safety studies. Methods: During 2007-2008, ISO reached out to 45 scientists in academia, government, and industry at three meetings and conducted a selected literature review to identify vaccine safety science gaps that ISO could address. Criteria for including topics in an initial list were an ability to frame a vaccine safety hypothesis that was consistent with ISO's mission, where a study could be initiated within five years. ISO grouped topics into specific questions or thematic areas and reviewed this second list with ISO-sponsored researchers and CDC scientists to define possible research needs. Results: The initial list included 351 topics; 129 met inclusion criteria. The second list identified 18 specific questions and 42 thematic areas. Reviews yielded 30 possible research needs for the draft Agenda. Seven were specific vaccine safety questions (e.g., risk for neurological deterioration after vaccination in children with mitochondrial dysfunction and wheezing after live attenuated influenza vaccine). Twenty-three were thematic areas around vaccines/vaccination practices (e.g., simultaneous vaccination, non-antigen vaccine components), special populations (e.g., pregnant women, premature infants, immunodeficient persons), and clinical outcomes (e.g., encephalitis/encephalopathy, neurodevelopmental disorders, postimmunization fever). Conclusions: Though a deliberative process, ISO defined 30 possible vaccine safety research needs. Further work will focus on defining specific questions in the thematic areas and prioritizing research topics. CDC will finalize this first comprehensive vaccine safety Agenda after receiving input from NVAC, stakeholders, and the public.

References:

S30 Maintenance of T Cell Memory in Airway Lumen following Mucosal Immunization Requires Both de novo Antigen Presentation and Cell Proliferation

M. Jeyanathan, S. McCormick, C. Small, Z. Xing
McMaster University, Hamilton, CANADA

Objective: Review the mechanism of long-term maintenance of memory T cells at the site of infection under the scenario of intranasal immunization of TB vaccine and consider this knowledge in the context of effective vaccination routes

Background: Mucosal vaccination is considered superior to parenteral vaccination in protecting against mucosal infections because of persistence of memory T cells at the site of infection long after immunization. We have previously shown that persisting memory T cells in the airway lumen following intranasal adenovirus vectored TB vaccination (AdAg85a) play an important role in protection against secondary infection. However, it is not clear how these populations are maintained under steady-state conditions in lung airways. Methods: Underlying mechanisms of long-term maintenance of antigen-specific memory T cells in the airway lumen of Balb/c mice immunized via intranasal route with AdAg85a were studied. Results: The majority of Ag85a-specific CD8 T cells residing in the airway lumen 3 months after vaccination displayed an activated phenotype (CD44+ CD127-), indicating recent antigen stimulation. Comparison of degree of incorporation of BrdU administered intranasally and intraperitoneally by Ag-specific T cells in the airway lumen and spleen one month after immunization suggests de novo proliferation of these cells in airway luminal space. In vivo CFSE labeling residential airway luminal cells, we obtained further evidence of de novo proliferative
expansion of these cells long after vaccination, but exhibiting different levels of proliferation. Such de novo proliferation was found to be antigen dependent as adoptive transferred Ag-specific T cells proliferated only in antigen specific microenvironment. Furthermore, adoptively transferred Ag-specific T cells underwent proliferative expansion in the airway luminal space of mice immunized 45 and 90 days ago, suggesting the presence of antigens long after the clearance of viral vaccine. Conclusion: Continuous antigen presentation long after vaccination and de novo proliferation of Ag-specific T cells underpin the maintenance of long-term protective T cell memory.

References:

S31 Plasmid-Based IL-12 Used in Combination with in vivo Electroporation and a Heterologous pDNA Prime, rVSV Vector Boost Vaccination Regimen Preferentially Improves the Induction of Antigen-Specific T cell with a Polyfunctional Effector Memory Phenotype in Rhesus Macaques

M. A. Egan
Protocells Bioscience, Tarrytown, NY

Objective: Describe recent developments being made in three key areas of vaccine research and development: (i) development and use of plasmid-based cytokine adjuvants, (ii) use of in vivo electroporation to enhance pDNA vaccine delivery, (iii) development and use of novel replication competent recombinant vesicular stomatitis virus based viral vectors

Background: DNA vaccines by themselves are poor inducers of Ag-specific immunity in humans and non-human primates (NHPs). We have shown that plasmid IL-12 functions as a potent pDNA vaccine adjuvant and the combined use with live viral vectors improves the induction of cellular immune responses in NHPs. Methods: A series of NHP studies were carried out to define the immunological consequences of (i) using plasmid IL-12 as a vaccine adjuvant and (ii) to determine whether a prime/boost vaccination regimen consisting of a pDNA vaccine delivered by in vivo electroporation (EP) followed by a recombinant Vesicular stomatitis virus (rVSV) vectored vaccination resulted in improved immune responses relative to a homologous pDNA vaccine only immunization regimen.

Results: Following immunization with a pDNA delivered via EP, total peak IFN-gamma ELISpot responses in macaques immunized with the pDNA vaccine in combination with IL-12 pDNA were significantly higher (p<0.05) compared to the responses seen in macaques immunized in the absence of plasmid IL-12. More importantly, pDNA immunization in combination with IL-12 also resulted in a 3-fold increase in the number of Ag-specific CD4+ or CD8+ T cells with a polyfunctional effector memory (EM) phenotype. In a separate study, vaccine-specific responses as measured by IFN-γ ELISpot assay were similar in macaques receiving the homologous pDNA prime/boost relative to macaques receiving a heterologous pDNA/rVSV prime/boost. However, macaques immunized by the heterologous vaccination regimen had an increased proportion of antigen-specific EM CD8+ or CM CD8+ T cells with a polyfunctional phenotype. Conclusion: Collectively, these data provide strong justification for the continued development of a cytokine enhanced plasmid DNA prime, rVSV vector boost immunization regimen for the prevention and or treatment of infectious disease and cancer.

References:

S32 Mucosal Vaccination with a Recombinant H5 Antigen and Nanoemulsion Adjuvant Potentiates Immune Response against Pandemic Avian Influenza

1University of Michigan Medical School, Ann Arbor, MI, 2NanoBio Corporation, Ann Arbor, MI

Objective: Discuss the ability of a nanoemulsion adjuvant to induce a humoral immune response to a recombinant influenza H5 antigen

Background: Avian influenza remains a high concern for global health due to the high mortality rate associated with infection and the possibility for human to human transmission [1]. In this study, a recombinant influenza hemagglutinin antigen (rH5), type A/Indonesia/05/05 H5N1, was mixed with an oil-in-water nanoemulsion adjuvant to produce a mucosal vaccine. Nanoemulsion has previously been used as an adjuvant for Hepatitis B, Anthrax Protective Antigen, and a traditional influenza vaccine [2]. The rH5 antigen has been shown to protect ferrets against a lethal challenge. Methods: naïve CD-1 Mice were immunized with 1, 5, or 15 µg of rH5 in 10 µL of either 5 or 10% w/w W805EC nanoemulsion or the antigen alone diluted in phosphate buffered saline (PBS). The mice were given 2 doses 4 weeks apart and bled at 2 and 6 weeks after the second dose. IgG specificity to rH5 and end titer was measured by ELISA. Results: The response was found to be dependent on both the nanoemulsion and antigen concentration. The highest immune response was in the group which was given 15 µg of rH5 mixed with 10% nanoemulsion with an antibody titer of 8.8x10^5 and 4/4 seroconversion. Lower antigen doses in 10% nanoemulsion produced lower specific IgG titers, but still provided 100% seroconversion. 5% nanoemulsion produced lower titers and not all animals seroverted. The antigen alone gave only low antibody titers and many of the animals failed to seroconvert. Conclusion: Recombinant H5 antigen mixed with W805EC was able to induce a robust humoral immune response in mice. This vaccine strategy has the potential for rapid production of influenza vaccine in the event of a pandemic.

References:
Validation of the Vaccine Population Studies: Consistent Associations of HLA Genotypes with Rubella Vaccine Humoral Immunity

I. G. Ovsyannikova, R. M. Jacobson, R. A. Vierkant, M. M. O’Byrne, V. S. Pankratz, G. A. Poland
Mayo Clinic and Foundation, Rochester, MN

Objective: Discuss the validation of HLA gene polymorphism associations with humoral immune response following rubella vaccine

Background: Validation of population studies based on genetic associations are important for determining mechanisms by which polymorphisms influence immune responses to vaccines. Methods: We previously reported rubella vaccine-induced immune responses and HLA associations in 342 children, age 12-18 years (1st cohort) following two-doses of rubella vaccine. We sought to replicate the associations discovered in that work by verifying these associations in a new cohort of 396 subjects, age 11-19 years (2nd cohort) after two-doses of rubella vaccine. Rubella-specific IgG antibody (Ab) titer is determined using linear regression models. Results: Median rubella-specific Ab levels for the cohorts were 32.75 IU/ml and 26.20 IU/ml, p=0.128; 2nd cohort 26.15 IU/ml, p=0.057) alleles were associated with lower rubella-specific Abs. The association of DRB1*04-DQB1*03-DPB1*03 (mean 1st cohort 25.17 IU/ml, p=0.011; 2nd cohort 21.37 IU/ml, p=0.032) and DRB1*15/16-DQB1*06-DPB1*03 (1st cohort 16.27 IU/ml, p=0.043; 2nd cohort 19.10 IU/ml, p=0.023) haplotypes with lower rubella-specific Abs were observed in both studies (global p=0.006 and 0.004, respectively). Conclusions: This study provides further evidence for an association between specific HLA markers and rubella vaccine-induced humoral responses and lends further weight to the validity of these observations.

References:

The Decennial Administration of a Reduced Antigen Content Diphtheria, Tetanus, Acellular Pertussis Vaccine (Boostrix™) in Young Adults

J. Mertsola1, O. Van Der Meeren2, Q. He1, A. Linko-Parvinen1, G. Ramakrishnan1, L. Mannermaa1, M. Soini1, M. Pulkkinen1, J. Jacquet2
1University of Turku and National Public Health Institute, Turku, FINLAND, 2GlaxoSmithKline Biologicals, Rixensart, BELGIUM, 3GlaxoSmithKline Biologicals, Bangalore, INDIA, 4GlaxoSmithKline Biologicals, Espoo, FINLAND

Objective: Describe the purpose of repeated administration of a reduced antigen content diphtheria, tetanus, acellular pertussis (dTpa) vaccine 10 years after a previous dose

Background: Booster vaccination against tetanus (T) and diphtheria (D) at 10-year intervals is commonly recommended (Kretsinger et al, 2006). Reduced-antigen-content dTpa vaccines have been specifically developed for booster vaccination of adolescents and adults (Frampton and Keating, 2006); however, they are mainly only licensed for once-in-a-lifetime use. This is the first study to evaluate the decennial administration of a dTpa vaccine (NCT00610168). Methods: Young adults (mean age 21.1 years) who had received a single dose of either dTpa or Td + pa in the 263855/004 trial 10 years previously, all received one dose of dTpa (Boostrix™, GSK) in this open, phase IV trial. Blood samples were taken before and one-month post-vaccination. Antibody concentrations against D, T, pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) were determined. Solicited local and general symptoms, unsolicited symptoms and SAEs were recorded. Results: 82 subjects received the dTpa booster. Before this decennial booster, the percentage of subjects seroprotected/seropositive was: 98.8% (D); 97.5% (T); 64.6% (PT); 100% (FHA); 96.3% (PRN). One-month post-booster, all subjects were seroprotected/seropositive against all vaccine antigens. Booster responses were observed in 85.0% (PT), 96.3% (FHA) and 93.8% (PRN) of subjects. Antibody concentrations increased by a similar magnitude after this second booster than after the previous one 10 years earlier. During the 4-day follow-up, 9.9% subjects recorded grade 3 pain; 16.0% recorded redness or swelling ≥50mm. Fever (≥37.5°C) was reported by 8.6% subjects. One SAE (hyperventilation) was recorded, that was not considered causally related to the vaccine. Conclusions: A second dTpa booster was highly immunogenic and well tolerated in this population of young adults. This study supports the use of a second dTpa as a decennial booster.

References:
ABSTRACTS OF SUBMITTED POSTER PRESENTATIONS
Selected prfA* Mutations in Recombinant Attenuated Listeria monocytogenes Strains Augment Expression of Foreign Immunogens and Enhance Vaccine-Elicited Humoral and Cellular Immune Responses

L. Yan
University of Illinois at Chicago, Chicago, IL

Objective: Describe the recent process of vaccine vector development, especially in Listeria monocytogenes vaccine vectors

Background: While recombinant Listeria monocytogenes strains can be explored as promising intracellular live vaccine vectors for delivering immunogens into host cells, it is important to develop attenuated but highly immunogenic L. monocytogenes vaccine candidates. Taking advantage of the deletion of a L. monocytogenes virulence gene, actA, and the up-regulating mutant of a major transcriptional activator, PrfA, in this study we creatively developed recombinant attenuated L. monocytogenes ΔactA prfA* vaccine strains expressing immunogens, and investigated the safety and immunogenecity of these novel vaccine candidates in mice.

Methods: A total of 63 recombinant L. monocytogenes vaccine vectors expressing seven individual viral or bacterial immunogens each in nine different L. monocytogenes strains carrying wild-type prfA or having prfA* mutations were constructed and investigated. Results: Western Blot analysis indicated that the mutations selected on the basis of increased PrfA activation in recombinant L. monocytogenes prfA* vaccine vectors augmented expression of seven individual protein immunogens remarkably. Consistently, prime and boost vaccination studies with mice indicated that the prfA (G155S) mutation in recombinant L. monocytogenes ΔactA prfA* strains enhanced vaccine-elicited cellular immune responses. Surprisingly, the prfA (G155S) mutation was found to enhance vaccine-elicited humoral immune responses as well. The highly immunogenic recombinant L. monocytogenes ΔactA prfA* vaccine strains were as attenuated as the recombinant parent L. monocytogenes ΔactA vaccine vector. Conclusions: This study demonstrated that the recombinant attenuated L. monocytogenes ΔactA prfA* vaccine vector may be a superior candidate for further clinical development of both therapeutic and prophylactic vaccines against infections or cancers.

References:
P4 Rotavirus Diarrhoeal Disease Vaccine Coverage in Nigeria: Perceived Barriers and Potential Solutions

N. Idika, P. Anochie, A. Adesanmi, A. Adeiga
Nigerian Institute of Medical Research, Lagos, NIGERIA

Objective: Describe the efforts in Nigeria to increase rotavirus diarrhoeal vaccine utilization

Introduction: Rotavirus is the leading single cause of severe diarrhoea among infants and young children1. There are seven species of this virus (A-G) and it is transmitted by the faecal-oral route. Globally, about 500,000 children under 5 die each year from rotavirus infection2 and almost another million get severely ill.3. In Nigeria, the prevalence is 20-40% in children under five years yet the diarrhoeal vaccine coverage in Nigeria is low. In view of the public health importance in children under five, the elderly and the immunocompromised, this study investigated the perceived barriers and potential solutions of diarrhoeal vaccine development, coverage and utilization in Nigeria. Method: In-depth interviews were conducted with selected relevant authorities in research laboratories, government and private hospitals, pharmaceutical industries, immunization programmes and caregivers of children less than five years of age. Results: Only a few research laboratories have the electron microscope and PCR machines required for sero-typing the rotavirus isolates from the locality for effective vaccine production. There are few experts on vaccinology in Nigeria hence diarrhoeal vaccine production is not yet in place. One pharmaceutical industry is currently supplying hospitals with Rotarix® vaccine costing 8,000 Naira (about 70 USD) for the 2 doses required for each child. This high cost affects the utilization especially the poor in the rural areas with poor potable water supply and inadequate sanitation, thus the low coverage in Nigeria. Conclusion: Adequate funding is required for equipping the research laboratories, capacity building and setting up vaccine production plants in Nigeria to attain the required coverage to reduce diarrhoeal infections especially in children under five years of age in Nigeria.

References:

P5 Evaluation of the Immunogenicity and Efficacy of Inactivated Venezuelan Equine Encephalitis Virus (VEEV) Vaccine Candidates in BALB/c Mice

S. Martin, M. Parker, P. Glass, R. Bakken, C. Lind, P. Garcia, E. Jenkins, M. Hart
DynPort Vaccine Company, Frederick, MD, United States Army Medical Research Institute of Infectious Diseases, Frederick, MD

Objective: Discuss why the route of vaccination is an important parameter to consider in vaccine development

Background: Historically, inactivated VEE vaccines have proven effective in protecting humans and animals against infectious disease. C84, a formalin inactivated vaccine, used to protect at risk personnel against VEEV, is no longer manufactured. To fulfill this continued need, a formalin inactivated VEEV vaccine (IV3526) is under development. Methods: In this study the immunogenicity and efficacy of IV3526 when administered intramuscularly (IM) or subcutaneously (SC) were evaluated in the presence or absence of adjuvant. Mice were vaccinated either IM or SC on Days 0 and 28 with IV3526 formulated with or without Viprovex®, CpG ODN 2395 (CpG), Alhydrogel™ (CpG+Alh) or CpG plus Alhydrogel™ (CpG+Alh). Sera were collected on Days 21 and 49 for evaluation of ELISA and plaque reduction neutralization (PRN) titers and the mice then challenged on Day 56 by either aerosol or SC route with a lethal dosage of VEE IAB Trinidad Donkey strain (TbD). Results: Three of the four adjuvant-containing vaccine formulations administered SC or IM protected 100% of the mice against SC challenge. All IV3526 formulations, regardless of route of administration, performed as well as, if not better than, C84 in protecting mice against SC challenge. IV3526 formulated with CpG+Alh administered SC or IM protected 100% of mice against aerosol challenge. IV3526 formulated with CpG+Alh or CpG alone, when administered IM provided better protection than C84 against aerosol challenge. Conclusion: Both SC and IM vaccinations with IV3526 formulated with CpG + Alh provide complete protection against aerosol challenge. Because the IM route uses significantly less viral protein to achieve high level protection and is the clinically preferred route of vaccination, it will be the route of vaccination for future studies with IV3526.

References:
P6 Validation of a Mouse Assay for Evaluation of Recombinant Botulinum Vaccine Potency

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1DynPort Vaccine Company LLC, a CSC company, Frederick, MD, 2Battelle Biomedical Research Center, West Jefferson, OH

Objective: Describe a successful approach for validating a mouse bioassay for assessment of vaccine potency.

Background: A recombinant botulinum vaccine (rBV A/B) is being developed to protect humans against inhalational intoxication with botulinum neurotoxin complex serotype A, subtype A1 (BoNT/A1) and serotype B, subtype B1 (BoNT/B1). A mouse vaccine potency assay (VPA) which measures resistance to challenge in vaccinated mice has historically been used to assess the potency of the individual antigens (antigen A and antigen B) in the rBV A/B vaccine. The VPA was originally developed at the United States Army Medical Research Institute of Infectious Diseases. A validation study was conducted to evaluate the acceptability of the VPA for assessing rBV A/B quality at various stages of manufacture and storage.

Methods: Pre-validation studies were performed to verify vaccine dilution accuracy and examine the timing for challenge. For validation, precision of the VPA was assessed by performing assays across three different days using three different dilution technicians, three different animal dosing technicians and four different BoNT challenge levels. In addition, specificity was assessed by evaluating the ability of the individual antigens in rBV A/B to protect against a non-cognate BoNT challenge. Results: The coefficient of variation (%CV) for total assay precision was approximately 40%. Total assay precision was most impacted by uncontrolled residual error which was used to estimate repeatability. The %CV was below 40% for the main variables of test date, dilution technician and dosing technician. Upper and lower specifications for BoNT/A1 and BoNT/B1 challenge levels were established for the VPA. The ability of rBV A/B to provide specific protection against cognate botulinum neurotoxin challenge was confirmed.

Conclusion: The mouse VPA was successfully validated for evaluation of rBV A/B manufacturing consistency, stability and potential clinical efficacy.

References:

P7 A Five Year Follow up of Antibody Response in Children Vaccinated with a Single Dose of Live Attenuated SA-14-14-2 Japanese Encephalitis Vaccine: Immunogenicity and Anamnestic Response

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1Japanese Encephalitis Support Group, Kathmandu, NEPAL, 2Yonsei University, Seoul, REPUBLIC OF KOREA

Objective: Describe how a single dose of live Japanese Encephalitis (JE) vaccine could be effective in providing a long-term protection in JE endemic area.

Out of 98 subjects who had participated in the 2000 Japanese encephalitis (JE) vaccination campaign, 69 people were enrolled in the tests of 2004 and 2005 for the evaluation of long-term immune response of a single dose SA 14-14-2 JE vaccine. 89.9% of study subjects (62/69) had maintained a high level of neutralizing antibody until 2004 as their GMT was measured as 133 (11, max. 2991). Forty-four subjects were still positive in 2005, 5 years after JE vaccination, and their neutralizing antibody positive rate was significantly higher than that of 69 age-sex matched unvaccinated control subjects: 63.8% (44/69) vs. 14.5% (10/69) (p <0.05). Twenty-four subjects (Group 1) who were sero-negative for neutralizing antibody at the 2005 test were given a second dose for revaccination in 2006. Also 49 sero-negative (Group 2) subjects who were enrolled as a control group in 2005 were given one dose of primary JE vaccine in 2006. Seven days after vaccination, the sero-positive rate and GMT was discovered to be 76.5% (13/17) and 168.52 (min. 38, max. 2173) in Group 1, while there was no sero-conversion in Group 2. On the 30th day the sero-positive rate and GMT were 82.4% (14/17) and 392.01 (min 22, max. 2197) in Group 1, while there were 75.7% (28/37) and 45.72 (min. 12, max. 2173) in Group 2. We observed the persistence of neutralizing antibody after a single dose of SA 14-14-2 JE vaccine was 89.9% after four years and 63.8% after 5 years. There was a rapid secondary immune response on the seventh day after booster dose among those who had been sero-negative after the first dose of vaccine. A single dose of live JE vaccine could effectively provide a long-term protection in JE endemic areas, where natural boosting is quite probable in the vaccinees. However, further studies should be carried out to support whether one dose of live JE vaccine is sufficient for people in JE non-endemic areas.

Reference:
expression in the germinated spore (i.e., the vegetative cell), and third, using a non-GM method of binding the antigen to spores. Using all three methods, humoral responses to MPT64 were detected. The most significant humoral and cellular responses resulted from intra-nasal delivery of MPT64 bound to spores of HU58, a human isolate of *B. subtilis*. These responses were noticeably better than when MPT64 was fused to a spore coat protein or expressed in the germinating spore. Using a challenge experiment intra-nasal delivery of HU58 spores coated with MPT64 protein conferred protection against tuberculosis following BCG priming. These results are encouraging and potentially demonstrate the potential of spores as a non-GM TB vaccine.

References:

P9

Adjuvant-Free Vaccine Potentiation Technique Demonstrated with Influenza Peptide M2e in Mice

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1Paul Simon Consulting, LLC, Wilmington, DE, 2Impact Biologicals, Inc., Wallingford, PA

Objective: Describe a novel adjuvant-free immunization method with a test influenza peptide immunogen

A strategy for augmenting the potency of immunogens without the need for immune adjuvants is being developed. It is based on a recombinant immunotargeted fusion protein comprised of (1) a single chain fragment derived from a monoclonal antibody that recognizes a surface protein on murine erythrocytes, and (2) streptavidin. Any biotinylated immunogen can easily be affixed to this fusion protein via biotin-streptavidin linkage. The immunogen is targeted to the erythrocyte surface whence it is transported to the reticuloendothelial system and presented efficiently to the immune system. The M2e peptide, the ectodomain of the M2 protein shared by influenza virus A strains, was used as a test immunogen. Mice were immunized with peptide alone, peptide combined with the fusion protein, or peptide adsorbed onto alum. Sera collected one week after primary inoculation and again after two bi-weekly boosts were analyzed for peptide-specific IgG concentration by ELISA. Free M2e peptide (30 ug) generated 0.8 ug/mL anti-M2e IgG following two boosts. Adsorption of M2e peptide onto alum did not enhance the IgG response, but immunization with 330 ng M2e coupled to the fusion protein resulted in a peak of 14 ug/Ml anti-M2e IgG, and even 37 ng M2e generated 1 ug/mL anti-M2e IgG. Taken together, the immune potency of M2e was increased more than 2,000-fold by linkage with the fusion protein. These results demonstrate the immunopotentiation of this adjuvant-free and versatile immunogen targeting strategy.

References:

P10

Safety, Tolerability and Immunogenicity of Recombinant Protective Antigen (rPA) Anthrax Vaccine Compared with Anthrax Vaccine Adsorbed (AVA) in a Healthy Population

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1PharmAthene, Annapolis, MD, 2PharmAthene UK, Billingham, UNITED KINGDOM, 3Quintiles, South Bend, IN

Objective: Review the safety and immunogenicity of anthrax vaccines

Background: This study evaluated the safety, tolerability and immunogenicity of a 3-dose priming series of SparVax™ rPA vaccine compared to AVA administered according to its package insert for general use in prophylaxis against anthrax. Methods: 226 healthy male and female volunteers, 18-55 years of age, were enrolled into 3 dose groups: 50 μg SparVax™ on Days 0, 28 and 56 (n = 91); 100 μg SparVax™ on Days 0, 28 and 56 (n = 92); 0.5 mL AVA on Days 0, 14, and 28 (n = 43). At day 182, subjects receiving SparVax™ were re-randomized to a challenge at the original dose, on either day 182 or 364. Safety and immunogenicity were assessed throughout the study. Results: The incidence of associated AEs was higher in the AVA group as compared to the SparVax™ groups, due mostly to injection site reactions. There were no notable differences between the SparVax™ groups and the AVA group regarding safety laboratory values, vital signs and ECG results. In the challenge phase, no differences in the AE profile between the SparVax™ dose groups were noted. Both vaccines were immunogenic following the 3-dose prime with response rates of approximately 90%. There were no significant differences in either TNA or ELISA geometric mean titers (GMT) between the vaccine groups 14 days after the 3rd vaccination. No differences seen between SparVax™ groups in terms of response rate or GMT measured by ELISA at the 6 or 12 month challenge. Conclusions: SparVax™ was safe, well-tolerated and produced antibody responses comparable to the licensed product. It appeared to be better tolerated than AVA with good immunologic memory demonstrated at 6 or 12 months.

Reference:
Evaluation of a Ricin Vaccine Candidate (RVEc) for Human Toxicity Using an in vitro Vascular Leak Assay
A. L. Porter, L. DeSilva
US Army Medical Research Institute for Infectious Diseases, Frederick, MD

Objective: Discuss and evaluate the in vitro testing system that has been developed at USAMRIID to test the cytotoxicity of a genetically derived ricin A chain vaccine candidate (RVEc).

Ricin (RT) is a toxin that has potential to be used as an agent of biological warfare. Inhalation of RT induces pulmonary edema that ultimately results in death. In an effort to develop preventive measures against RT intoxication, a genetically derived ricin A chain vaccine candidate (RVEc) has been developed. In the current study, the RVEc vaccine was evaluated for its interaction on human endothelial cells by using an in vitro cellular bioassay. The model consisted of primary human endothelial cells cultured on collagen-coated inserts, to which concentrations of the vaccine (0.6, 2 or 9 μM) were added. The changes in electrical resistance through the endothelial monolayer were then measured. At these concentrations, the vaccine was not toxic, as no considerable changes in electrical resistance were noticed. In contrast, cytotoxicity due to exposure to 9 μM ricin A chain was apparent as early as 2 hr. Light microscopy of endothelial cells treated for 24 hr with 0.6 and 9 μM of vaccine showed little cytotoxicity when compared to cells treated with the ricin holotoxin or the ricin A chain. Because binding of ricin to the endothelial cell surface may indicate vascular leak, we performed flow cytometry. The results indicated that the ricin A chain bound slightly to endothelial cells while RVEc did not bind to the cells. The human vascular leak model provides an in vitro testing system to evaluate cytotoxicity intrinsic to vaccines. It can also be used for pre-testing therapeutics to infectious agents. In this study, the model successfully demonstrated the reduced toxicity of the lead ricin vaccine indicating that vascular leak is not a major concern associated with the RVEc.

References:

Rift Valley Fever Virus NSs Protein Promotes Post-Transcriptional Downregulation of Protein Kinase PKR and Inhibits eIF2α Phosphorylation
The University of Texas Medical Branch, Galveston, TX

Objective: Discuss the molecular virology of Rift Valley fever MP-12 vaccine

Rift Valley fever virus (RVFV) (genus Phlebovirus, family Bunyaviridae) which is comprised of 3 genomic RNA called S, M and L, causes mosquito-borne zoonotic disease, characterized by hemorrhagic fever in humans and abortions in ruminants. Effective RVFV vaccine for humans and animals is important for preventing future introduction of RVFV from sub-Saharan African endemic countries into other countries. RVFV MP-12 is one of the promising live-attenuated vaccine candidates for humans and animals. MP-12 carries functional NSs, which is encoded in S-segment and suppresses cellular RNA synthesis, whereas MP-12 is attenuated by mutations in M and L-segments. In this study, we further characterized the NSs function to understand the pathology and vaccinology of RVFV. We generated recombinant MP-12 lacking NSs by using MP-12 reverse genetics system. Viral replication and translation in cells infected with MP-12 or MP-12 lacking NSs were analyzed in the presence of drugs to suppress cellular RNA synthesis. Upon the infection of MP-12 lacking NSs, cells treated with actinomycinD or α-amanitin, which inhibit cellular RNA synthesis, induced double-stranded RNA-dependent protein kinase (PKR)-mediated eukaryotic initiation factor (eIF)2α phosphorylation, leading to the suppression of host and viral translation, resulted in inefficient viral replication. MP-12 NSs promoted post translational downregulation of PKR early in the course of infection, suppressed the eIF2α phosphorylation, and supported efficient viral translation even in the presence of transcription inhibitors. We also confirmed that wild-type RVFV NSs induced PKR downregulation. Thus, two distinct functions of NSs: (1) the suppression of host transcription, including that of type I interferon mRNAs, and (2) the downregulation of PKR, work together to prevent host innate anti-viral functions and allow efficient RVFV replication.

References:

Nasal Administration of W805SEC-Adjuvanted Influenza Vaccine in Mice
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1NanoBio Corp, Ann Arbor, MI, 2University of Michigan, Ann Arbor, MI

Objective: Describe the specific immune response resulting from a novel nanoemulsion-adjuvanted influenza vaccine administered intranasally in mice

Background: W805SEC is an oil-in-water emulsion adjuvant composed of high-energy nanometer-sized droplets stabilized by surfactants. W805SEC kills enveloped viruses on contact via membrane destabilization, thereby inactivating the virus. Incorporation of protective epitopes into nanodroplets stabilizes them and co-delivery of the antigen-adjuvant enhances uptake of viral antigens into mucosal dendritic cells. Methods: Mice were immunized intranasally with influenza A/Puerto Rico/8/34 (H1N1) virus inactivated and adjuvanted with W805SEC. Animals received
different doses of virus inactivated with varying doses of the adjuvant on two occasions, four weeks apart. Sera from different intervals were tested for the presence of specific antibodies using hemagglutination inhibition assay and ELISA. Spleens were harvested and tested for cytokine production following stimulation with PR virus. Results: Based on antibody response, the optimal vaccine formulations were achieved using 5 x 10^6 pfu PR virus and adjuvant concentrations from 5-20%. Cytokine analysis showed that IFN-γ, IL-2, IL-17, IL-13 and GM-CSF responses were enhanced 10- to 100-fold upon virus stimulation as compared to PBS-stimulated controls. TNF-α, IL-10, IL-4, IL-6, IL-1a, IL-5, KC, and MIP-1α increased more than two-fold over baseline, but the biological significance is unclear. Conclusions: The W^5EC-adjuvanted influenza viral vaccine provided an exceedingly robust and dose-dependent immune response. Although other adjuvanted vaccines have been shown to have a Th1-bias response, W^5EC-adjuvanted influenza vaccine uniquely enhanced both Th1 and Th17 responses. W^5EC is novel in its ability to inactivate influenza virus and evoke a more balanced systemic response to the pathogen.

References:

P14 Intramuscular Delivery of a Cholera DNA Vaccine Primes Both Systemic and Mucosal Protective Antibody Responses Against Cholera

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11st Affiliated Hospital, Nanjing Medical University, Nanjing, CHINA; 2U. Mass. Med. School, Worcester, MA, 3Jiangsu CDC, Nanjing, CHINA

Objective: Describe the effectiveness of parenterally delivered DNA vaccines in eliciting mucosal protective immune responses

Cholera is a potentially lethal diarrheal disease caused by the gram-negative bacterium *Vibrio cholera*. The need for an effective cholera vaccine is clearly indicated, but the challenges of eliciting both systemic and mucosal immune responses remains a significant challenge. In the current report, we discovered that a DNA vaccine expressing a protective cholera antigen, cholera toxin B subunit (CTB), delivered parenterally can elicit both systemic and mucosal anti-CTB antibody responses in mice. The priming effect by DNA immunization was demonstrated by higher mucosal antibody responses following one boost with the inactivated cholera vaccine (KWC-B) delivered orally when compared to the twice oral administration of KWC-B alone. This finding indicates that DNA vaccines delivered parenterally are effective in eliciting mucosal protective immune responses - a unique advantage for DNA vaccination that has not yet been well realized and should bring value to the development of novel vaccination approaches against mucosally transmitted diseases.

Reference:
**P16**

*Eimeria*-Derived Macrophage Migration Inhibitory Factor (MIF)-
Mediated Immunoregulation of Host Innate Immunity

**S. I. Jang, S. H. Lee, Y. H. Hong, D. K. Kim, M. Poges, H. S. Lillehoj**

Animal and Natural Resources Institute, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, MD

**Objective:** Evaluate immunological properties of recombinant eMIF and cMIF to better understand their role in avian coccidiosis

Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine that plays an important role in host defense against many pathogens including *Toxoplasma*. However, some pathogens also express a MIF protein during infections although its role in innate host immune response is not known. In avian coccidiosis caused by intestinal protozoa, *Eimeria,* *Eimeria* MIF (eMIF) transcript was detected during the merozoite and sporozoite stages. Interestingly, strong expression of chicken MIF (cMIF) transcript was detected in the gut at 3 days post primary, but not after secondary infection with *E. tenella*. The aim of this study was to evaluate immunological properties of recombinant eMIF and cMIF to better understand their role in avian coccidiosis. Injection of 18-day-old chicken embryos with eMIF, but not cMIF significantly enhanced protective immunity against live challenge infection with *E. tenella* given at post-hatch. A macrophage cell line which was treated with eMIF and cMIF showed significant expression of pro-inflammatory cytokines including IL-6, IL-17 and TNFSF-15. These studies provide the first evidence of immunoregulatory role of *Eimeria*-derived MIF in coccidiosis and suggest a mechanism of immune evasion employed by *Eimeria*.

**References:**

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**P17**

Assess Kinetics of HDP Depot Effect and Trafficking via Distinct Routes of Administration in Mice

**T. Dybvik**

VIDO, Saskatoon, CANADA

**Objective:** Describe the development of nanocapsulated DNA vaccine for RSV

Host defense peptides (HDPs) are small, cationic molecules produced in cells found at the mucosal surfaces, in the skin and within immune cells. They have antimicrobial and immunomodulatory effects and synergize with each other. They can also alter expression of chemokines and chemokine receptors, to promote recruitment of leukocytes to the site of infection. They promote angiogenesis and modulate dendritic cell development. Despite their current use in vaccine formulations, information on the real-time distribution of these adjuvants has not been well characterized. In order to determine the kinetics of HDP trafficking via different routes of administration BMAP-27, Indolicin, HH2, and PG1 (5 mg/ml) were labeled with Near Infrared (IR) dye 700 and 800CW, as indicated and introduced to BALB/c mice by intramuscular, oral, subcutaneous, or intranasal routes. Mice were scanned at 15 min, 2 h, 6 h, 24 h, 48 h and 96 h to determine the trafficking effect of the HDPs. Serum, urine and fecal samples were obtained and tested for the presence of labeled product. HDPs were detected as early as 24 h indicating that HDPs trafficked not only to the blood but also to the intestine and kidneys. These data are in concurrence with the *in vivo* images which show rapid distribution of all labeled-products to the abdominal cavity. Labeled products were retained at the subcutaneous and intramuscular injection site for 8 weeks but the products were mostly cleared at this time when administered via oral or intranasal routes. Whether the significant presence of HDPs at the injection site after 8 wks is due to increased uptake of the adjuvant followed by increased cellular migration or simply a depot effect is under investigation.

**Reference:**

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**P18**

Chitosan Encapsulated Multivalent DNA Vaccine for RSV

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**Objective:** Describe the development of nanocapsulated DNA vaccine for RSV

Respiratory syncytial virus (RSV) has long been considered a major respiratory tract pathogen in children causing lower respiratory tract infections and pneumonia. The three major RSV proteins targeted for vaccine development include the fusion (F), attachment (G) glycoprotein and matrix protein (M2) proteins. In this study, the antigenic regions of the RSV F, M2 and G genes were cloned into the pHCMV vector resulting in the development of a multivalent DNA vaccine vector (DR-FM2G). The plasmid DNA was purified and the protein from the vaccine vector was expressed in Cos-7 cells. To increase the efficacy of the vaccine, the DNA vaccine vector was also used to formulate chitosan based DNA-nanoparticles (DCNP) using a complex coacervation process that yielded an encapsulation efficiency of 94.7%. Four groups of 10 BALB/c female mice were immunized either intramuscularly with DR-FM2G DNA, or intranasally with DCNP, PBS or RSV. Serum and saliva samples were collected on days 0, 14, 28 and 49 to assess the antibody response from 6 mice. Four mice in each group were euthanized on day 21 for histological evaluation of lung pathology. Two immunogens, DR-FM2G DNA and DCNP, yielded higher serum antibody titers as compared to the PBS group. However, the DCNP group had at least two fold higher serum IgG titers as compared to the naked DNA group. Histological studies showed that mice receiving DNA and DCNP exhibit less epithelial damage than mice treated with RSV and PBS that exhibit extensive disruption of the epithelium. Antibody isotyping, cellular immune response and immunoprotection studies are being carried out to further assess the effectiveness of the chitosan encapsulated multivalent DNA vaccine.

**Reference:**
ABSTRACTS OF SUBMITTED POSTER PRESENTATIONS

P19 Evaluation of Systemic and Mucosal B Cell Immune Response to the Oral Challenge with Shigella dysenteriae 1 in Cynomolgus Macaques

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Objective: Review new data on systemic and mucosal B cell response after the Shigella dysenteriae challenge in cynomolgus macaques

Background: The lack of data on the immune response to the Shigella infection hampers the use of monkeys as a model for vaccine development. Methods: We investigated the B cell response against Shigella antigens, namely LPS, IpaB, -C, -D, VirG and MxiH after challenge with S. dysenteriae 1 (Sd1). Three cynomolgus macaques (Macaca fascicularis) were infected with 109 CFU Sd1 strain 1617 on days 0, 82 and 450. Peripheral blood mononuclear cells (PBMCs) were obtained before and after challenges and at regular intervals. At sacrifice, day 528, cells from spleen, bone marrow, mesenteric LN as well as from ileum, cecum, proximal and distal colons were also isolated. Antigen-specific antibody-secreting cells (ASCs) were quantified by ELISPOT in fresh samples and frozen samples after in vitro expansion of memory B cells with Pokeweed mitogen, CpG and SAC (Cowan). Results: In expanded PBMCs, the number of total IgG ASCs (median 8,017/106) was higher than total IgA ASCs (median 1,367/106), causing the percentages of Ag-specific IgA ASCs to be higher than Ag-specific IgG ASCs. High percentages of IgA anti-LPS (median 1.11 and 5.25%), and IpaB (1.02 and 0.68%) ASCs were detected 7-14 days after the two first challenges in expanded PBMCs and after the last challenge in fresh PBMCs (10.0 and 3.4%). High percentages of IgA ASCs against all antigens, mainly anti-LPS, were observed in colonic cells after the third challenge. Conclusion: The B cell response after Sd1 infection is primarily IgA ASCs with fewer Ag-specific IgG ASCs present. LPS is the main target antigen but several protein antigens including IpaB are also recognized. Cynomolgus macaques are a viable model to detect systemic and mucosal anti-Shigella B cell responses.

References:
1. Levine MM, Kotloff KL, Barry EM, Pasetti MF, Sztein MB. Clinical and mucosal anti-B cell responses. Shigella recognized. Cynomolgous macaques are a viable model to detect systemic

P20 A Universal Influenza Vaccine: Generating Broad Immunity Using an M2e/NP Fusion Protein

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Objective: Discuss a novel influenza vaccine approach based on inducing responses to conserved viral antigens linked to an immunostimulatory oligodeoxynucleotides (ODN)

Background: Standard influenza vaccines generate strain-specific neutralizing antibodies to the highly variable hemagglutinin antigen and need to be annually matched with circulating strains to provide efficacy. We are developing a broadly reactive, universal flu vaccine containing the conserved influenza antigens nucleoprotein (NP) and the extracellular domain of M2 protein (M2e). These antigens induce immune responses that kill cells infected with divergent influenza A viruses and thereby provide heterosubtypic immunity that can limit virus replication, speed viral clearance, and reduce morbidity and transmission of influenza regardless of the strain encountered. Methods: A fusion protein containing both M2e and NP was made and linked to an immunostimulatory ODN (ISS). The fusion protein conjugate (M2e/NP-ISS) was evaluated in mice to ensure its ability to induce both NP-specific cell mediated immunity and M2e-specific antibody responses. Statistical significance was analyzed on log transformed data using one-way ANOVA (Kruskal-Wallis Test and Dunn’s Multiple Comparison post tests). Results: M2e/NP-ISS induces a high frequency of IFN-G producing CD8+ T cells (p<0.001 spot forming units) and high IFN-G cytokine production (p<0.01 pg/ml) compared to M2e/NP Alone or M2e/NP + ISS. M2e/NP-ISS induces not only the M2e-specific IgG1 response induced by the fusion protein, but adds an IgG2a response, as well. Conclusion: M2e/NP-ISS induces two separate immune responses that will provide broad protection against divergent influenza viruses. M2e/NP-ISS may be used in conjunction with standard hemagglutinin (HA) based influenza vaccine to enhance immunogenicity and provide dose sparing of the HA components. The use of an ISS conjugated fusion protein represents a promising approach to creating a broadly reactive, universal influenza vaccine. Research funding supported by NIAID grant 5U01 AI074578-02.

References:
The A1 Subunit of Cholera Toxin as an Adjuvant for DNA Vaccines

K. C. Bagley
Profectus Biosciences, Baltimore, MD

Objective: Demonstrate the potential of DNA vaccine adjuvants to enhance immune responses to vaccine antigens

Background: DNA vaccination remains a promising means to develop effective vaccines against infectious diseases and cancer. However, their poor performance in primates has demanded the use of genetic adjuvants or improved delivery techniques. One of our approaches to improving vaccine potency is to exploit genetic adjuvants. Although cytokine, chemokine and growth factor adjuvants have shown promise, we believe that the most potent genetic adjuvants will be those that mimic the inflammation and dendritic cell (DC) maturation caused by natural infections. One such adjuvant is the A1 domain of cholera toxin (CTA1). We and others have shown that plasmid encoded CTA1 (with or without the targeting B subunits) potently adjuvants immune responses to DNA vaccine antigens.

Methods: Immunization studies were conducted on mice and macaques to determine the adjuvant effects of CTA1 when delivered IM or by gene gun. Results: Using SIV gag and HIV gp120 as model antigens in mouse studies, we found that the adjuvanticity of CTA1 is modulated significantly by dose, route (IM vs. gene gun), frequency (1, 2, 3 doses), and type of antigen administered. Gene gun immunization of macaques showed that CTA1 enhanced antibody responses to GAG and enhanced a DNA prime for a protein boost. Conclusions: In mice, CTA1 is a potent DNA adjuvant requiring only a single dose to induce substantial T cell responses that equal or exceed those induced by IL-12 or electroporation. Future studies will determine if IM immunization of macaques with CTA1 will also dramatically enhance antigen-specific T cell responses. We also continue to evaluate CTA1 with additional immunogens and to determine if the adjuvanticity diminishes with each subsequent use.

References:

Vaccination Strategies Tailored to Regions with Different Endemicity for Hepatitis B

Netherlands Vaccine Institute, Bilthoven, NETHERLANDS

Objective: Discuss factors that influence vaccination strategies for hepatitis B

Hepatitis B is a serious public health problem, with about 600 000 fatalities worldwide each year. About 350 million people are chronically infected and have an increased risk of dying from liver cancer or cirrhosis. Worldwide three distinct geographic areas for hepatitis B endemicity (high, middle and low) can be distinguished. These areas require tailored vaccination strategies, whereby factors such as infection risk per age group, vaccination rate and duration of protection after vaccination, cost effectiveness of vaccination strategies and ease of implementation in existing national immunization schedules should be taken into account. For middle- and high endemic countries the greatest risk of infection with hepatitis B virus (HBV) is during early childhood. Therefore, it is not surprising that in these countries universal childhood vaccination strategies, which have been implemented in over 160 countries, have shown to result in an enormous drop in hepatitis B incidence in these countries. For low endemic countries, on the other hand, a risk group-based strategy seems more appropriate. In these countries, infant vaccination should be given to high risk infant groups, such as children of hepatitis B positive mothers and children with a parent originating from a middle- or high endemic country. Whereas, universal pre-adolescent vaccination is more appropriate for the remaining population, for which the greatest risk of acquiring HBV infection is through sexual activity. These persons are then optimally protected in the high risk period. The immune system is fully matured by then, and the anticipated decrease in disease incidence is reached at least 10 years sooner than with universal childhood vaccination.

Reference:

Neurovirulence and Immunogenicity of Highly Attenuated rVSV/HIV-1 Vaccine Vectors in Non-Human Primates

D. Clarke
Profectus Biosciences, Tarrytown, NY

Objective: Describe a method to attenuate vesicular stomatitis virus while preserving immunogenicity

A prototype rVSV/HIV-1 vaccine vector that protected non human primates (NHP) from disease following challenge with a pathogenic recombinant simian/human immunodeficiency virus (SHIV), appeared to be inadequately attenuated for clinical evaluation when tested in a stringent NHP neurovirulence model. To reduce virulence, the prototypic rVSV vector was attenuated by combination of specific G protein truncations and N gene translocations, incorporation of mutations affecting temperature sensitivity, ablation of expression of defined M gene products, and by generation of a G protein-dependent replicon. The resulting attenuated rVSV vectors were assessed in a series of NHP neurovirulence and immunogenicity studies, which allowed the identification of variants causing minimal neurological injury following intrathalamic inoculation, while retaining the ability to elicit robust HIV-1 gag-specific cellular immune responses that were equivalent in magnitude to those generated by the much more virulent prototypic vector. These data demonstrate the rational attenuation of rVSV neurovirulence and provide insights regarding the interaction of rVSV with the immune system. The data have also allowed identification of an optimal rVSV vector expressing HIV-1 gag for clinical evaluation.

References:

Neurovirulence and Immunogenicity of Highly Attenuated rVSV/HIV-1 Vaccine Vectors in Non-Human Primates

D. Clarke
Profectus Biosciences, Tarrytown, NY

Objective: Describe a method to attenuate vesicular stomatitis virus while preserving immunogenicity

A prototype rVSV/HIV-1 vaccine vector that protected non human primates (NHP) from disease following challenge with a pathogenic recombinant simian/human immunodeficiency virus (SHIV), appeared to be inadequately attenuated for clinical evaluation when tested in a stringent NHP neurovirulence model. To reduce virulence, the prototypic rVSV vector was attenuated by combination of specific G protein truncations and N gene translocations, incorporation of mutations affecting temperature sensitivity, ablation of expression of defined M gene products, and by generation of a G protein-dependent replicon. The resulting attenuated rVSV vectors were assessed in a series of NHP neurovirulence and immunogenicity studies, which allowed the identification of variants causing minimal neurological injury following intrathalamic inoculation, while retaining the ability to elicit robust HIV-1 gag-specific cellular immune responses that were equivalent in magnitude to those generated by the much more virulent prototypic vector. These data demonstrate the rational attenuation of rVSV neurovirulence and provide insights regarding the interaction of rVSV with the immune system. The data have also allowed identification of an optimal rVSV vector expressing HIV-1 gag for clinical evaluation.

References:
Objective: Describe novel HIV vaccine immunogens

Background: The coreceptor binding site of HIV-1 gp120 comprises some of the most conserved and functionally important residues on the viral envelope. Therefore, antibody responses to these epitopes [designated as CD4-induced (CD4i)] should be highly cross-reactive and potentially useful for HIV vaccine development. Methods: To address this question, rhesus macaques were vaccinated with the rhesus full-length single-chain (rhFLSC), a subunit immunogen designed to raise humoral responses against CD4i epitopes. The rhFLSC was formulated in saponin derived adjuvants, QS-21 or GPI-0100, for inoculation. Animals were then challenged rectally with heterologous SHIV162P3. Results: Animals vaccinated with rhFLSC exhibited accelerated clearance of plasma viremia and an absence of long-term tissue viremia compared with unvaccinated control animals. Such control correlated with stronger responses to CD4i epitopes in the rhFLSC-vaccinated animals, compared with macaques that received control immunogens. The control of infection was not associated with anti-CD4 responses, overall anti-gp120-binding titers, or neutralizing activity measured in conventional assays. Follow-on experiments were performed to delineate an optimal dose. Control animals were immunized with either saline or adjuvant alone. Surprisingly, compared to saline controls, adjuvant inoculated animals exhibited heightened viral loads and disease pathology. Compared to these animals, the protection afforded by rhFLSC vaccination was highly dose dependent with 5/6 animals receiving the highest dose resolving and maintaining the infection below detectable levels. Conclusions: Systemic inoculation with the rhFLSC immunogen can generate responses capable of controlling a SHIV challenge. This protection may be afforded by antibodies directed to CD4i epitopes along with other mechanisms of immunity. We believe this data represents the first clear demonstration that a subunit vaccine can control a mucosal infection with a pathogenic SHIV.

References:

Objective: Cytokine Production by Naive Murine Dendritic and Spleen Cells in Response to Neospora caninum Stimulation

In cattle, infection caused by the intracellular protozoan pathogen Neospora caninum is characterized primarily by abortion. The cause of abortion may be related to a biased type 1 immune response of the host in response to Neospora infection during pregnancy, which is often accompanied by production of high levels of pro-inflammatory and/or inflammatory cytokines. The goal of this study is to evaluate the profile of cytokine production by murine naïve dendritic cells and spleen cells stimulated with whole Neospora tachyzoites (live, heat-killed, and freeze-killed) and whole-cell tachyzoite lysate in the form of total (NcAg), insoluble antigen (iNcAg) and soluble antigen (sNcAg). Our results showed that whole Neospora tachyzoites and antigen preparations can elicit high levels of interleukin-12 (IL-12), TNF-alpha and IFN-gamma except for the heat-killed tachyzoites and sNcAg. Whole tachyzoites were more potent than antigen preparations in cytokine stimulation. The heat-killed tachyzoites induced less (p<0.05) IFN-gamma and IL-10 but more IL-4 in comparison to live and freeze-killed tachyzoites. sNcAg induced moderate levels of IL-12 and very low levels of TNF-alpha. Therefore, heat-killed tachyzoites and soluble antigen preparations may not be ideal vaccine candidates to induce strong type 1 immune response against Neospora infection. This study provides further understanding to the initial immune responses against Neospora caninum and may facilitate the design of vaccines against neosporosis.

References:
The PRINT® (Particle Replication in Non-wetting Templates) Platform can provide scalable delivery systems that can enhance the efficacy of different antigens.

Background: Next generation vaccine technologies will require flexible, scalable delivery systems that can enhance the efficacy of different antigens. The PRINT® (Particle Replication in Non-wetting Templates) Platform leverages the precision of micro-electronics to create molded nanoparticles with absolute control over particle size, shape, composition and surface chemistry in a uniform, controlled, and scalable manufacturing process. In developing particle technologies for vaccines, each of these variables can be optimized for a specific immunogenic response allowing for an unprecedented level of design control over other delivery systems. In addition to controlled co-delivery of antigens and adjuvants, the PRINT platform allows the exploration of the impact of non-spherical particle shapes on biological response. Methods: Particles of multiple sizes, shapes, and compositions were fabricated using the PRINT® process from Fluorocur® molds generated from silicon masters with features patterned to the desired particle form. Crosslinked poly (ethylene glycol) particles ranging from 200 x 200 nm to 1 x 1 x 10 micron cylinders were coated with the influenza hemagglutinin protein and evaluated in murine immunogenicity studies. Results and Conclusions: Data from these studies show that size and shape significantly impact immunogenicity and demonstrate that PRINT particles are a versatile platform for vaccine delivery.

References:

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The Effect of Cefpodoxime on Neisseria meningitidis Carriage

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Objective: Describe the prevalence of N. meningitidis colonization in a community with hyperendemic meningococcal disease and discuss the effectiveness of the antibiotic cefpodoxime in eliminating N. meningitidis carriage.

Background: Ciprofloxacin is the only single-dose chemoprophylaxis agent currently recommended to eliminate Neisseria meningitidis carriage in meningococcal disease contacts. Ciprofloxacin-resistant N. meningitidis strains have been identified; additional chemoprophylaxis agents are needed. The effect of cefpodoxime on N. meningitidis carriage was studied in a county with hyperendemic serogroup B meningococcal disease.

Methods: Pharyngeal swabs were collected from 593 middle school students. Modified Thayer-Martin agar plates were inoculated and observed for ≥72 hours. N. meningitidis isolates were serogrouped using PCR and slide agglutination. N. meningitidis colonized students were given a single 400 mg dose of cefpodoxime and reswabbed after 48-72 hours.

Results: 19 (3.2%) students had N. meningitidis colonization; 6 (31.6%) isolates were serogroup B, 2 (10.5%) serogroup Y, 3 (15.8%) serogroup X, 7 (36.8%) non-groupable and 1 (5.3%) was unknown. Two (33.3%) serogroup B strains matched the predominant hyperendemic strain. Students living in homes with >2 household members per bedroom were 4.2 (95% CI 1.5-11.4; p=0.005) times more likely to be colonized. Race, sex, age, household size, smoking in the household and being previously vaccinated were not significantly associated with colonization. 17 colonized students were administered cefpodoxime and reswabbed; colonization was eliminated in 12 (71%, 95% CI 49% - 92%). Of the remaining 5, 3 had serogroup X strains and two had serogroup Y. Colonization was eradicated in both carriers of the hyperendemic serogroup B strain.

Conclusions: A single 400 mg dose of cefpodoxime eliminated carriage in 71% of colonized students. Further studies are warranted to determine if cefpodoxime is an effective agent for N. meningitidis chemoprophylaxis. Although residing in a community with hyperendemic meningococcal disease, students in this study had low rates of N. meningitidis carriage.

References:

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Modeling the National Pediatric Vaccine Stockpile: Supply Shortages, Health Impacts, and Cost Consequences

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Objective: Discuss the utility of VacStockpile model in evaluating the health and budgetary impacts of policy decisions regarding the national pediatric vaccine stockpile targets.

Background: The Centers for Disease Control and Prevention (CDC) maintains the National Pediatric Vaccine Stockpile to address disruptions in vaccine supply. Increases in the number of vaccines recommended for pediatric and adolescent patients have increased the cost of stocking and maintaining the stockpile. We developed a spreadsheet-based model (VacStockpile) to evaluate the costs and potential health outcomes of maintaining vaccine stockpiles of different sizes for 14 vaccines, including combination vaccines.

Methods: To illustrate the implications of policy options, we compared “high” to “low” stockpile scenarios. The high stockpile scenario ensures a 6 month vaccine supply to vaccinate all children according to recommended schedules. The low scenario comprised of 50% of the high stockpile or existing stocks (whichever is smaller). For each vaccine, we used a weighted average of five shortage scenarios ranging from 0% to 100%, in 25% increments. Demand for each vaccine was based on current distribution or birth cohort size.
NK Cells Mediate Cytotoxicity of Parasitized Host Cells and Induce the Egression of Eimeria Sporozoites

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Objective: Evaluate whether the splenic lymphocytes can mediate cytotoxicity of parasitized host cells and induce the egression of Eimeria sporozoites

Natural killer (NK) cells are effector cells of host innate immune system. Splenic and intestinal NK cells play an important role in host defense against intestinal protozoan infections. For intracellular parasitic infections, immune mechanisms exerted by NK-cells include direct killing of infected host cells or perforin-mediated egression of intracellular parasites, e.g., Toxoplasma gondii. Innate immune mechanism mediated by NK-cells in Eimeria infections is not known. Using Eimeria tenella (ET), primary chicken kidney cells which are infected with sporozoites or loaded with ET antigen were used as target cells to evaluate splenic NK cells from naïve and Eimeria-immune chickens. Enriched NK cells were prepared by depleting T and B cells using magnetic beads. Apoptosis was evaluated using Annexin V-FITC apoptosis detection kit. Splenic lymphocytes from chickens which were immunized with ET showed significant cytotoxic activity against sporozoite-infected or ET antigen-loaded PCK target cells. This cytotoxic activity was detected at 1 h post co-culture of effectors and target cells, reaching the peak at 3 h. In contrast, effectors from unimmunized chickens showed very low level of cytotoxicity. After enriching NK cells from splenic lymphocytes, the level of cytotoxic activity increased significantly. Furthermore, upon co-culturing of ET-primed splenocytes with target cells, sporozoites showed a rapid egression from the host cells. The enriched NK cells from normal and ET-primed birds triggered the parasite egress, but the percentage of egress decreased in primed group. We demonstrated that splenic NK cells from both Eimeria-infected chickens mediate cytotoxicity against sporozoite-infected or antigen loaded target cells. Splenic lymphocytes from the prime chickens can also induce parasite egression. These studies demonstrate complex interaction between host and parasites during early stage of infection with Eimeria.

References:

References:

LEAPS Immunogens Direct the Immune Response by Promoting Development of Human Immature Dendritic Cells into IL12 Producing Dendritic Cells (DC1s)

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Objective: Describe a new approach to converting epitopes into immunogens and directing the subsequent immune response

Background: The Ligand Epitope Antigen Presentation System (L.E.A.P.™) converts an epitope as small as 8 amino acids into an immunogen. Tandem synthesis of the J peptide sequence (from beta-2-microglobulin) with an epitope creates an immunogen that promotes T helper 1 immune responses. Previous studies in our labs showed that vaccines with epitopes of 8-20 amino acids from HIV (peptide from the gag protein (H)), and M. tuberculosis conjugated to the J peptide were immunogenic and HSV-1 vaccines (e.g. peptide from glycoprotein D (gD)) elicited protection in mice from challenge. Methods: Monocytes were obtained from two donors by leukopheresis and elutriation. The cells were stored frozen in aliquots and thawed into serum free medium containing IL4 and GM-CSF for 24 hours. The cells were then treated with 5.8 umoles of JgD or JH (in 1 ml) and incubated for 3 days. Cells were analyzed and medium was evaluated for cytokines with RayBiotech protein arrays. Results: The cells from both donors treated with JgD or JH peptides, but not the untreated, J, gD, or H peptide treated cells, clustered, expressed dendrites, and increased levels of CD86 and HLA DR consistent with maturation. The JgD and JH treated cells increased production of IL12p70 by 4 fold, decreased IL10 to half without production of IL1, TNFalpha or IL6. The J peptide decreased IL10 production. Conclusions: The J-LEAPS immunogens interact with immature dendritic cells (DC) and promote their development into DC1s capable of producing IL12 without production of acute phase cytokines. This type of response suggests a unique mechanism of activation to promote DC1 and Th1 immune responses to an antigenic peptide.

References:
Objective: Describe data on serum bactericidal activity of human infant vaccinated with Hib vaccines

Background: We sought to explore whether the N. meningitidis serogroup B (MenB)-derived outer membrane protein complex (OMPC) used as the carrier for the H. influenzae type B (HIB) conjugate vaccine, PedvaxHIB®, could elicit SBA activity against MenB in human infants.

Methods: Sera from infants vaccinated at 4 time points with either PedvaxHIB® or ActHIB® (which does not contain OMPC), were tested for serum bactericidal activity (SBA) against the OMPC homologous strain (B11) and against the epidemic New Zealand strain (NZ). The assay was first performed using baby rabbit serum as the complement source; a subsequent subset was tested using serum complement from a hypogammaglobulinemic human donor. All laboratory personnel were blinded to vaccination group.

Results: Post-dose 3, ~20% of subjects had positive rSBA titers (to both B11 and NZ) and there was no difference in rSBA titers between vaccination groups. Post-dose 4, ~40% of the PedvaxHIB® group had positive rSBA to strain B11 versus ~20% in the ActHIB® group; however, there was no difference between vaccine groups in rSBA against the heterologous NZ strain. When a subset of rSBA-positive samples was tested with human serum as the complement source; 5/5 samples in the PedvaxHIB® group had positive rSBA titers against B11 versus 0/5 samples in the ActHIB® group. Conclusions: Vaccination of infants with PedvaxHIB®, but not ActHIB®, elicited SBA activity against MenB when human serum was used as the complement source. This is likely the result of a serotype-specific response to PorA or other antigens contained in OMPC, which was the carrier for the HIB polysaccharide (PRP) in PedvaxHIB®. The results suggest that limited crossprotection against meningococcal disease may result from immunization with PedvaxHIB®.

References:

Objective: Discuss the dynamics of maternal EV71 neutralizing antibody titers in young infants, which is critical to the design of vaccine trials in young infants

Background: Clinical spectrum of enterovirus 71 (EV71) infection ranges from mild hand-foot-mouth disease to severe cases with central nervous system and cardiopulmonary involvements. In 1998, Taiwan suffered a nationwide EV71 epidemic. Since then, EV71 has been endemic in Taiwan and development of EV71 vaccines has become a national priority. This cohort study was designed to understand the dynamics of maternal EV71 neutralizing antibody titers in young infants.

Methods: This is a prospective longitudinal cohort study. Sera were obtained from the participants for measuring EV71 neutralizing antibody titers in the following schedules: right before delivery for pregnant women, birth (umbilical cord blood) for neonates, and 6 months of age for infants.

Results: By June 2008, 309 longitudinal serum specimens collected from mothers, neonates, and 6-month-old babies (two mothers delivered twins) have been measured for EV71 neutralizing antibody titers. The seropositive
rates (antibody titer $\geq 1:8$) in mothers, neonates, and 6-month-old infants were 65% (200/307), 50% (154/309), and 1% (4/309), respectively. Half-life of maternal EV71 neutralizing antibody is estimated to be 42 days.

Conclusions: In Taiwan, only 50% of neonates have detectable maternal EV71 neutralizing antibodies, and these maternal antibodies have declined to an undetectable level by 6 months of age.

References:  

P34 Development of a Challenge Model to Evaluate Vaccine Candidates Against African Trypanosomiasis in Cattle  
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Objective: Discuss why suitable challenge models are a prerequisite for testing of the efficacy of vaccine candidates

African trypanosomiasis is fatal to humans and animals if left untreated. Infected ruminants serve as reservoirs for transmission of the parasite to humans. High mortality in cattle reduces milk and meat production, which are important economic commodities in sub-Saharan Africa. No effective vaccine has been developed against this disease. The trypanosome changes the dominant variable surface glycoprotein (VSG) antigen that covers nearly the entire trypanosome surface, over time. To overcome this obstacle, non-variable antigens have been identified that can generate protective immune responses. Tubulin, one such candidate, was shown to confer protection in mice, when animals were challenged with homologous or heterologous strains of Trypanosoma. The logical step forward is to test the tubulin-based vaccine candidates for their efficacy to protect cattle from challenge with trypanosomes. A prerequisite for such vaccine candidate trials in cattle is the development of a suitable challenge model. We undertook experimental cattle challenge studies under controlled indoor conditions. We found that Trypanosoma brucei brucei challenge doses in the range of 5x103 to 5x106 were ultimately lethal to Ankole longhorn breed calves. Calves challenged with 5x103 parasites survived up to 127 days post challenge, whereas those challenged with the higher dose of 5x106 survived for only 67 days post challenge. Cattle that received the low challenge dose of 5x103 had too low numbers of parasites in their bloodstream for reliable diagnosis with direct parasitological methods. In heavily challenged cattle, direct parasitological diagnostics worked reliably during early but not during later stages of infection. Packed cell volume and weight change differed in cattle that received the higher but not in cattle that received the lower challenge doses compared to healthy controls.

References:  

P35 Prophylactic HIV-1 Vaccine Candidates Based on Structured gp41 N-helical Repeat Peptides  
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Objective: Discuss whether structured gp41 NHR immunogens can be useful as the basis for a prophylactic vaccine against HIV-1 infection

Background: The identification of MAb D5 has validated the NHR as a potential vaccine target. Utilizing the crystal structure of D5 bound to 5-helix, we designed and prepared a series of chimeric peptide constructs in which gp41 epitope sequences are displayed as structured coiled coil trimers.

Methods: Chimeras were prepared from either the minimal epitope-containing sequence LLQLTVWQIKQ1ARIL (N17) or extended 36-mer (N36) and 51-mer (N51) NHR peptides coupled to leucine-zipper scaffolds. The immunogens were used to conduct a series of comparative immunogenicity studies in Guinea pigs and rabbits. Serological assessment consisted of (1) ELISA; (2) quantitation of a “D5-like” specific immune response by a D5/5-Helix competitive binding assay (DCBA); and (3) assessment of in vitro neutralization potency in a single-cycle infectivity assay.

Results: Robust immune responses were achieved and we showed that trimer structural integrity and stabilization are critical to elicitation of desired D5-like responses. Purified IgG from vaccinated animals neutralized a D5 hypersensitive mutant and wild type HXB2 viruses, and potency correlated with ELISA titer and IC50 in the DCBA. Unfractionated sera from the most potent immunogens neutralized a limited number of viral isolates. Conclusions: This is the first demonstration of the ability to elicit neutralizing responses against a highly conserved NHR epitope and confirms the importance of appropriate structural presentation. Importantly, direct comparison of covalently constrained chimeras suggests a distinct potency advantage for longer NHR peptides, suggesting that neutralizing epitopes outside of the D5 pocket may exist.

References:  
**P36 Human Complement Bactericidal Activity in a Phase 2 Safety and Immunogenicity Study Following Vaccination with a New Meningococcal A Conjugate Vaccine in Healthy West African Toddlers**

**Objective:** Describe the immunologic assessment of conjugate meningococcal vaccines and the impact that complement source has on the determination of functional bactericidal activity.

**Background:** Group A meningococci cause devastating epidemics of meningococcal disease in sub-Saharan Africa. The Meningitis Vaccine Project (MVP), a Gates Foundation funded partnership between WHO and PATH, has coordinated the development of a new conjugate vaccine, PaA-TT. Following a Phase I study in India, a pivotal Phase II, observer-blind, randomized, controlled study of PaA-TT safety and immunogenicity in Malian and Gambian toddlers 12-23 months of age is underway.

**Methods:** 601 participants received a first injection of PaA-TT, Haemophilus influenzae type b (HiB-TT) or meningococcal polysaccharide (PaACYW) vaccine followed 10 months later by PaA-TT, HiB-TT or 1/5 dose of PaACYW. Bactericidal activity in an assay using pooled human complement (hSBA) was determined for sera from a representative subset of 180 participants at 4 weeks post primary immunization, and pre- and 4 weeks post booster. **Results:** Among the subset of toddlers, four week post immunization hSBA titers ≥1:8 were detected in 75% (95% CI 61%-85%) who received PaA-TT, 30% (95% CI 18%-44%) who received PaACYW and 13% (95% CI 6%-25%) who received HiB-TT vaccines; the GMTs were 15 (95% CI 11-21), 5 (95% CI 3-6) and 3 (95% CI 3-4) respectively. A four fold rise in hSBA titer between pre- and one month post booster dose was observed in 30% (currently blinded to study arm).

**Conclusions:** Human complement SBA responses in this Phase 2 clinical trial indicate that PaA-TT vaccine induced strong functional immune responses in a target population of 12 to 23 month African children. These data are consistent with IgG ELISA and rabbit SBA results and are highly encouraging as MVP and partners continue working towards the goal of eliminating epidemic meningitis in sub-Saharan Africa.

**References:**

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**P37 A Multisystem Approach for the Evaluation of Inactivation Efficiency for Venezuelan Equine Encephalitis Virus (VEEV) Vaccine Candidates**

**Objective:** Describe the application to the development and evaluation of other inactivated viral vaccines for both human and veterinary use.

**Background:** A multisystem assay strategy was used to assess the efficiency of VEEV inactivation methods for vaccine development. **Methods:** We utilized a combination of diverse assays (plaque, *in vitro* cytopathology, mouse neurovirulence) to assess virus inactivation and vaccine safety, along with a specific ELISA to measure VEEV glycoprotein epitope retention in developing and qualifying inactivated VEEV candidate vaccine preparations. Live attenuated VEEV (V3526) production aliquots were treated with formalin at concentrations of 0.1% or 0.5% v/v for either 4 or 24 hours, or exposed to gamma radiation targeted doses ranging from 13.5 to 50 kilorad (kGy). Inactivated preparations and untreated controls were assayed for infectivity by plaque assay and for cytopathology via blind passage of supernatants from inoculated Vero or BHK cell cultures. Corresponding aliquots were tested by ELISA for binding activity to monoclonal antibodies specific for the E2 glycoprotein of VEEV, and residual neurovirulence via intracerebral inoculation of suckling BALB/c mice. **Results:** Each of the formalin treatments completely inactivated V3526 with the highest residual ELISA binding activity in the 0.1% v/v formalin-treated preparations. Radiation doses up to and including 40 kGy substantially reduced epitope binding by monoclonal antibodies, but did not render the vaccine completely inactivated. In contrast, the 50 kGy radiation dose completely inactivated the vaccine. All formalin- and gamma-irradiated V3526 formulations were negative for neurovirulence in comparison to the untreated V3526 control. **Conclusion:** The combination of the four approaches was effective in selecting formalin as the preferred method and in optimizing parameters for VEEV inactivation processes. Corroborative studies conducted with these VEEV preparations suggest that E2 epitope retention represents an indication of vaccine immunogenicity.

**References:**

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**P38 B. pertussis Transmission in Household and Duration of Protection of DTaP Immunizations**

**Objective:** Describe the duration of protective immunity conferred by DTaP vaccines.

**Background:** B. pertussis infection often goes undetected especially among adolescents and adults; therefore, estimates of vaccine effectiveness may be overestimated. In 1996, DTaP was licensed for infants and children. We sought to examine pertussis transmission among household contacts and to measure the duration of protection among children who have
ABSTRACTS OF SUBMITTED POSTER PRESENTATIONS

P39 In Vivo Immunogenicity of Mycobacterium tuberculosis T-cell Epitopes Discovered using Immunoinformatics
L. Moise
EpiVax, Inc., Providence, RI

Objective: Describe development of an epitope-based immunome-derived vaccine for treatment and prevention of tuberculosis

Background: A multi-epitope Mycobacterium tuberculosis (Mt) vaccine could be used for vaccination of latent-infected individuals or as an adjunct to TB treatment. Here, we describe proof-of-concept studies for identification of TB vaccine candidates. Methods: Published antigenic and protective Mt antigens, including non-BCG proteins, secreted proteins and proteins upregulated under hypoxic conditions, were screened by the EpiMatrix algorithm for T-cell epitope content. 67 clustered peptides containing multiple Class II HLA-binding motifs and bearing low human sequence homology were selected for screening. HLA A2/DR1 transgenic mice were immunized twice intranasally with Mt peptides formulated in liposomes with CpG oligodeoxynucleotide. Vaccine immunogenicity was measured prior to vaccinia challenge using ELISpot. Results: Immunization of A2/DR1 transgenic mice with the clustered Mt peptides stimulated significant T cell responses to 36/67 (54%) Class II HLA epitopes in ELISpot assays (the cut off for immunogenicity was >50 SFC/10^6 splenocytes, p<0.001). ELISpot culture supernatants analyzed for production of other cytokines by ELISA demonstrated elevated IL-2 production in immunized mice. Conclusions: These results illustrate breadth of vaccine immunogenicity and efficacy. Vaccination and challenge studies are underway.

References:

P40 T-cell Epitope Vaccine Protects HLA Transgenic Mice Against Lethal Vaccinia Challenge
L. Moise
EpiVax, Inc., Providence, RI

Objective: Describe an epitope-based, immunome-derived vaccine for protection against smallpox.

Background: We postulated that a vaccine based on vaccinia/variolavaccinia cross-reactive class II T-cell epitopes ("VennVax"), identified using bioinformatics and immunological methods, would protect against smallpox challenge in HLA transgenic mice. Methods: Two multi-epitope genes each containing 25 HLA class II T-cell epitopes were designed using vaccine design algorithms developed by EpiVax. Results: Immunization of DRB1*0301 transgenic mice were intramuscularly immunized twice with the DNA vaccine constructs and boosted intranasally twice with the same epitopes formulated as peptides in liposomes with CpG oligodeoxynucleotide. Vaccine immunogenicity was measured prior to vaccinia challenge using IFNγ ELISpot, multiplex cytokine bead array and thymidine incorporation in peptide-stimulated splenocyte cultures. Mice were challenged with 10X LD50 vaccinia WR and followed post-infection for weight change and survival.

Results: Immunization of DRB1*0301 mice stimulated significant T cell responses to 6/10 peptide pools by IFNγ ELISpot. Pooled epitopes that stimulated >50 SFC/10^6 splenocytes in comparison with non-immunized mice were considered immunogenic. (N=3 per group, p<0.001). Significant peptide-stimulated proliferation was observed for 8/10 pools and IFNγ, IL-2 and MIP-1β production for various pools (p<0.05). 100% of vaccinated mice (N=18) survived lethal vaccinia challenge while only 19% of control mice (N=16) recovered (p<0.001). Conclusions: VennVax provides excellent protection against lethal challenge in a humanized animal model. Protection may be due to T cell response rather than protective antibody production as the vaccine was comprised of short linear epitopes. The multi-cytokine Th1 vaccine-induced response suggests that T cells with robust effector and memory potential were generated. VennVax priming before vaccination with a licensed live attenuated such as MVA would be a dose-sparing strategy to expand the supply of smallpox vaccine.

References:
**ABSTRACTS OF SUBMITTED POSTER PRESENTATIONS**

**P41**

**A Randomized, Double-blind, Controlled Trial of the Comparative Viremic, Immunogenicity and Safety of Live, Attenuated 17D Yellow Fever Vaccine Given in Combination with Human Immune Globulin or Placebo**

S. Edupuganti
Emory University School of Medicine, Decatur, GA

**Objective:** Discuss the 17D yellow fever vaccine induced viremia and the immunological responses

**Background:** The live, attenuated 17D yellow fever virus vaccine is a highly effective vaccine in preventing yellow fever. Although the 17D vaccine has been generally safe, there have been rare serious adverse events, namely viscerotropic and neurotropic diseases. These adverse events are thought to be due to high levels of vaccine-induced viremia and other unknown viral and host factors. We evaluated whether co-administration of 17D vaccine with human immunoglobulin (Ig), which contained YFV-specific neutralizing antibodies, would reduce post-vaccination viremia without compromising immunogenicity. **Methods:** In a double-blind, controlled trial, we randomized previously unvaccinated people, 18 to 40 years of age, to receive (1) 17D vaccine and Ig; or (2) 17D vaccine and saline placebo (40 in each group). We followed them on Days 1, 2, 3, 5, 7, 9, 11, 14, 30 and 91 for safety, and evaluated viremia by RT-PCR and neutralizing antibodies by the plaque-reduction neutralization test (PRNT). We also evaluated the kinetics of CD8 T-cell responses and innate immune responses. **Results:** The 17D vaccine co-administered with Ig was well tolerated and safe. The proportion of participants that developed viremia were similar in the Ig (38/40) and the saline (40/40) groups (p=0.49). The frequency of seroconverters (40/40 in Ig vs. 40/40 in placebo group), the geometric mean log, PRNT titers (8.30 ± 2.15 in Ig vs. 8.90 ± 1.96 in placebo group), and the magnitude and kinetics of CD8 T-cell and innate immune responses were similar in both groups. **Conclusions:** The administration of 17D vaccine with human Ig did not reduce vaccine-induced viremia and did not alter neutralizing antibody titers or T-cell kinetics.

**References:**

**P42**

**Thermal Stabilisation of Influenza Haemagglutinin Using Proprietary Stabilisers**

J. Drew
Stabilitech, London, UNITED KINGDOM

**Objective:** Describe novel excipient mixes for thermal stabilisation of Influenza vaccine

**Background:** A thermally stable influenza vaccine would have a significant impact on future stockpiling plans. Currently, any such stockpile is bound by the need for strict temperature control which is essential to preserve the efficacy of the vaccine, and brings with it huge logistical implications, significant cost, and complications surrounding deployment. Stabilitech Ltd is a UK-based company which has overcome live virus thermostability issues using its proprietary stabilizing formulations, and more recently has demonstrated the utility of the technology for stabilizing isolated proteins and sub-units. We have developed a proprietary stabilizer which, when mixed with haemagglutinin suspensions enables the product to be lyophilized and prevents thermal damage when stored at elevated temperatures. Upon reconstitution it no change in protein levels as measured by ELISA and SRID assays could be detected. Stabilitech’s approach was based on mimicry of the biochemical events occurring during the maturation of seeds. During this process, seeds are rendered desiccation and thermo-tolerant. **Methods:** Protein solution was mixed at a ratio of 1:5 with stabilizer. The mixture was frozen and lyophilized over the course of 2 days. Accelerated thermal challenge studies were performed by holding the samples at 50°C for several days or 80°C for several hours. At the end of this period the remaining haemagglutinin was determined by ELISA and SRID. **Results:** Haemagglutinin was rendered thermally stable to a very high level over the timeframe examined. Protein losses observed during processing were negligible (consistently less than 10%). In the absence of excipients almost total loss occurred. **Conclusions:** Stabilitech’s technology has overcome a major hurdle affecting Influenza vaccine storage and distribution, which will significantly simplify any stockpiling plans for the vaccine.

**Reference:**

**P43**

**Papillomavirus-Based Vaginal Delivery of DNA Vaccine Plasmids Expressing Respiratory Syncytial Virus Antigens**

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1Vaccine Research Center, National Institutes of Health, Bethesda, MD; 2National Cancer Institute, Bethesda, MD

**Objective:** Discuss the advantages of papillomavirus-based vaginal delivery of DNA vaccine plasmids as a novel approach to immunization against diseases, especially those requiring the induction of mucosal antibodies

**Gene-based delivery of vaccine antigens is an important technology for developing platform approaches for emerging infectious diseases. However, delivery and potency of naked DNA immunogens in humans has been limited. Papillomavirus-based gene transfer vectors can encapsidate DNA plasmids up to 8Kb and have been shown to specifically transduce basal epithelial cells in vitro. The papillomavirus vector being evaluated in these studies, HPV-M/M2, was produced by encapsidating a plasmid encoding a fusion gene expressing RSV M and M2 proteins with HPV capsid proteins L1 and L2. A single immunization with intravaginal (IVag) HPV16-M/M2 or HPV45-M/M2 induced T cell responses comparable to a 10,000-fold higher dose of IVag naked M/M2 DNA. However, only HPV vectors induced M/M2-specific antibody responses. Next, we asked whether HPV vectors could prime for a heterologous vector boost. CB6F1/J mice were primed with HPV vectors IVag and boosted with recombinant adenovirus serotype 5 (rAd5)-M/M2. Responses were compared to primary rAd5-M/M2 and naked M/M2 DNA IM priming. Isotype-specific antibody was measured by kinetic ELISA, and T cell responses were evaluated by MHC class I tetramers, intracellular cytokine staining, and memory phenotype by multi-color flow cytometry. There was evidence that HPV vectors primed for the rAd5-M/M2 IM boost, but antibody and T-cell responses pre- and post-RSV challenge were similar to those induced by primary rAd5-M/M2. These data support the immunogenicity of HPV vectors delivered mucosally, and suggest that parenteral delivery of a potent secondary immunogen like adenovirus may redirect immune responses.
to be more systemic. Future studies will evaluate mucosal boosting of the responses induced by HPV vector mucosal priming.

References:

P44

A B Cell-Deficient Pig Model Produced By Knock-Out of the Immunoglobulin Heavy Chain Locus

M. Mendicino1, J. Ramsoondar1, C. Phelps1, T. Vaught1, S. Ball1, T. LeRoith2, J. Monahan1, S. Chen1, A. Dandro1, J. Boone1, P. Jabs1, A. Vance1, N. Wertz1, I. Polejeva1, Y. Dai1, J. Butler3, K. Wells1, D. Ayares1

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Objective: Describe the generation of pig models for studying human diseases, and production of fully human, antigen-specific, polyclonal antibodies for patient immunization leading to broad disease treatment and prevention

Currently, there are no large animal disease models proven deficient in humoral responses available to replace insufficient rodent models. Here we show the targeted deletion of the single functional porcine heavy chain (Hc) joining region in fibroblasts using a poly (A)-trap. Pigs were generated via somatic cell nuclear transfer. Production of a null phenotype in Hc knockout (-/-) pigs was confirmed by the absence of immunoglobulin production, a deficiency of B cells and lymph node follicles, and severe susceptibility to typically innocuous bacterial infections. In addition, a pig expressing fully human polyclonal antibodies (PAbs), capable of antigen-specificity, would have broad therapeutic utility for clinical treatment of infectious diseases. Therefore, the Hc -/- pig i) can be immediately utilized as a pre-clinical model to study porcine and human diseases in the absence of B cells to aid vaccine development, and ii) serves as a significant component of a broad genetic platform to enable the generation of fully-human antigen-specific PAbs in pigs.

References:

P45

Revisiting Original Antigenic Sin Response to Influenza Virus

J. Kim, I. Scountzou, R. Compans, J. Jacob
Emory University, Atlanta, GA

Objective: Discuss the significance, potential risk and outcome of the unique phenomenon of influenza virus infection

As the reigning paradigm in immunology, Burnet’s clonal selection theory dictates that antigens select specific lymphocytes from a large repertoire of T and B cells to induce their proliferation. These lymphocytes then rapidly clear antigen and upon neutralization of the pathogenic threat, persist in the host as memory lymphocytes for a lifetime. Later in life, encounter with the same antigen induces their massive proliferation and accelerates antigen clearance. While this scheme holds true for most immune responses, the phenomenon of “original antigenic sin” (OAS) to influenza virus stands out as a paradox to Burnet’s theory. Humans previously exposed to a strain of influenza virus, upon infection with a novel strain, produce antibodies primarily against the older viral strain. This occurs at the expense of responses to novel protective antigenic determinants, exacerbating the severity of the current infection. This blind spot in the immune system and the redirection of responses to the “original antigen” rather than to novel epitopes were described fifty years ago. Recent reports, however, have questioned the very existence of this phenomenon, raising uncertainty on the significance and possible outcome of OAS.

In this study, we revisited this issue to determine the extent to which OAS is induced by variant influenza viruses. Using two related strains of influenza A virus, we showed that OAS led to a significant decrease in the development of immune memory and recall responses. Furthermore, we found that sequential infection of mice with live influenza virus strains led to antibody responses almost exclusively against the first strain. These data suggest that the induction of OAS is a potential strategy by which variant influenza viruses subvert the immune system.

References:
P46 Hospitalizations Associated with Pneumonia and Influenza in the Philippines, 2004-2006: Implications for Prevention Using Vaccine and Non-vaccine Interventions

S. Kim1, P. Kilgore1, G. S. Diaz2, L. C. Bravo3, M. R. Z. Capeding4, J. A. Santos5
1International Vaccine Institute, Seoul, REPUBLIC OF KOREA, 2Philippine Health Insurance Corp., Pasig, PHILIPPINES, 3Philippine General Hospital, Manila, PHILIPPINES, 4Research Institute for Tropical Medicine, Muntinlupa, PHILIPPINES, 5Philippine Children’s Medical Center, Quezon, PHILIPPINES

Objective: Describe the disease burden of hospitalizations associated with pneumonia and influenza (P&I) in the Philippines using health insurance claims data

Background: In 2007, 73% of the total Philippines population was covered by social health insurance. To better understand the national burden of P & I, we studied hospital discharge records from the country’s largest national health insurance program. Methods: A standardized list of diagnosis for P&I was selected from the International Classification of Diseases (ICD), 10th Edition, and data from the national health insurance provider, PhilHealth, was used. We examined trends in hospitalizations and total medical costs associated with P & I from January 2004 through December 2006. Results: During the 36-month study period, 856,697 hospitalizations were associated with P & I. The annual numbers of P&I hospitalizations were 264,320 (2004), 321,473 (2005), and 270,904 (2006). The greatest proportion was accounted for by children <5 years (46.0%, n=393,674) and the elderly aged ≥65 (17.5%, n=149,536). Seventy three (73%) (n=623,188) of hospitalizations were coded using presumed infectious etiologies followed by bronchitis (22.3%, n=190,622) and influenza (3.4%, n=29,107). There were relatively few hospitalizations encoded with pathogen-specific ICD-10 codes for Mycoplasma pneumoniae (0.20%, n=1,706), other bacterial pneumonias (0.08%, n=652), Streptococcus pneumoniae (0.01%, n=123), and Haemophilus influenzae (0.005%, n=42). For all P & I hospitalizations, total medical costs (hospital room charges, drugs and medicines, radiological and laboratory services, surgical procedures and medical staff services) were US $97,362,088. Conclusions: P & I is an important cause of hospitalization among children and the elderly in the Philippines. This substantial burden suggests opportunities for improved laboratory-based surveillance of respiratory diseases, and evaluation of public health interventions that can reduce the P & I burden.

Reference:

P47 Leptosomes: Immune Response and Prophylactic Efficacy in Hamster Model of Leptospirosis

S. M. Faisal, Y. Chang
Cornell University, Ithaca, NY

Objective: Describe why a liposome based vaccine is a promising intervention strategy for leptospirosis

Leptospirosis is an important zoonotic disease that affects both animals and humans. Subunit vaccine is an attractive intervention strategy against the disease but needs potent, yet nontoxic adjuvants for effective implementation. Among the candidates for adjuvants, liposomes have garnered recent attention for their capacity as carriers of vaccines. In present study we prepared novel liposomes from total polar lipids of nonpathogenic Leptospira biflexa serovar potac (designated leptosomes) and evaluated its vaccine delivery/adjuvant potential with novel protective antigens (Lp0607, Lp1118, Lp1454) against hamster leptospirosis. The immune response induced against multiple antigens and protective efficacy was evaluated and compared to those induced by conventional liposomes and with liposomes of similar lipid profile viz. E. coli lipid liposomes (escheriosomes). Our results demonstrate that both leptosomes and escheriosomes carrying antigens have proved to be better adjuvants than conventional liposomes and alum as revealed by enhanced and long term antibody response and significant enhancement in both Th1 (IFN-γ) and Th2 (IL-4, IL-10) cytokines. Additionally, leptosomes induced memory response which was significantly higher than conventional liposomes. Above all they imparted significantly higher level of protection than those achieved with conventional liposomes and alum as revealed by enhanced survival, reduced histopathological lesions and bacterial load in vital organs. Taken together, the results of present study clearly reveals that both leptosome and escheriosomes have emerged as a promising delivery vehicle-adjuvants that can be widely exploited with newly discovered antigens in future leptospirosis vaccines.

References:

P48 Needle-Free Intranasal Immunization with P. falciparum CS Protein Conjugated to Flagellin, a Potent TLR5 Agonist, Elicits Protective Systemic Humoral Responses

D. Carapau1, R. Mitchell2, A. Price3, E. Nordin4
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Objective: Discuss how an intranasally-delivered recombinant vaccine comprised of P. falciparum CS protein and the TLR5 agonist flagellin from S. typhimurium is able to protect from malaria sporozoite challenge

Background: Intranasal immunization provides significant advantages in cost and patient compliance by eliminating the need for injections while inducing systemic IgG and cellular responses that have the potential to protect against blood-borne diseases. Methods: The bacterial expressed recombinant protein vaccine was comprised of Salmonella typhimurium flagellin B (STF2) conjugated with either full length P. falciparum circumsporozoite protein (CSP) or immunodominant epitopes. Antibody responses were followed by ELISA and cellular responses by ELISPOT. Protection in vivo and in vitro was measured by real-time PCR quantification of Plasmodium 18S ribosomal RNA in liver cells post sporozoite challenge. Results: Mice immunized I.N. with either of the flagellin-modified constructs developed systemic IgG antibodies specific for P. falciparum CSP repeats, as well as flagellin. Both IgG1 and IgG2a antibodies were induced by IN and SC immunizations, consistent with cellular cytokine responses of a mixed Th1/Th2 phenotype. Transgenic P. falciparum/P. berghei sporozoites expressing Pf CSP repeats were neutralized after incubation with sera from the IN immunized mice, as evidenced by >90% reduction in the levels of parasite rRNA in infected hepatocytes. Consistent with these in vitro findings, I.N. immunized mice challenged by the bites of PfPb-infected mosquitoes had a >90%
decrease in malaria liver stage infection (measured as parasite rRNA in liver extracts). In contrast, mice immunized SC with the flagellin modified CS construct had low levels of sporozoite-neutralizing antibodies when tested in vitro (<70%) or in vivo (61%). **Conclusion:** Using a murine model, we present the first demonstration of protective immunity elicited by a TLR5 agonist modified- P. falciparum CSP vaccine delivered intranasally. These studies support the feasibility of developing a scalable, low cost, needle-free malaria vaccine.

**Reference:**

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**P50 Bacterial Co-Infections in Canadian Children Hospitalized With Influenza, 2004 - 2008**

**L. J. Sauvé1, J. Bettinger1, W. Vaudry2, D. Moore3, S. Halperin4, R. Bartolussi5, B. Lue1**

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**Objective:** Describe the epidemiology of bacterial infections associated with seasonal influenza in children

**Background:** Bacterial co-infections are an important part of influenza-associated morbidity in children. In the 2004 - 2007 season(s), the United States saw an increasing frequency of severe *Staphylococcus aureus* (SA) related complications. We describe influenza associated bacterial co-infections in national surveillance data from Canadian children, and assess SA co-infections. **Methods:** The IMPACT active surveillance program has collected data on influenza hospital admissions since 2004 from 12 participating centres, covering >90% of Canada’s tertiary care pediatric beds. A bacterial co-infection was defined as isolation of bacteria from a sterile site or clinical signs of a bacterial infection. Bacterial pneumonia was defined as chest x-ray changes with positive blood or pleural fluid cultures. **Results:** From 2004 - 2008, 1634 children were admitted with lab-confirmed influenza; 43 (2.6%) had relevant bacterial co-infections. Children with bacterial co-infections were not significantly different from those without, in terms of age and gender. While 55% of the subjects had an underlying health condition, they were not more likely to have a bacterial co-infection. SA and *Streptococcus pneumoniae* accounted for 15% and 7% of invasive isolates, respectively. There was no change in the proportion of SA over time, although the numbers are small, and there was only one case of methicillin-resistant SA. Bacteremia (21, 43%) and pneumonia (11, 26%) occurred most often. Children with bacterial co-infections had a longer length of stay (8 vs.3 days, p<0.0001), and more frequent intensive care unit admission (34% vs. 12%, p<0.0001). No deaths occurred in those with a bacterial co-infection. **Conclusions:** A small proportion of children hospitalized with influenza have a bacterial co-infection and experience greater morbidity. We found no increase in SA infections.

**References:**
Epidemiological, Clinical, and Laboratory Features of Varicella Zoster CNS Disease 10 Years after Introduction of the Varicella Vaccine

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1Stanford University School of Medicine, Stanford, CA, 2California Department of Public Health, Richmond, CA, 3Kaiser Permanente Vaccine Study Center, Oakland, CA, 4Centers for Disease Control and Prevention, Atlanta, GA

Objective: Describe features of CNS disease associated with varicella-zoster virus and recognize that reactivated vaccine strain can be associated with clinical meningitis.

Background: Live attenuated varicella vaccine was licensed in the US in 1995. Varicella-zoster virus (VZV) can cause neurological complications after primary infection or reactivation. Methods: Specimens from 3945 cases from the California encephalitis project were tested for multiple pathogens; epidemiological, clinical and laboratory data were collected using a standardized case report form. PCR testing of CSF identified 41 cases of VZV CNS disease. Twenty-six specimens with sufficient DNA were genotyped at CDC using multi-single nucleotide polymorphism (SNP) analysis.

Results: Patients ranged in age from 12-85 years (median 46.5): seven (27%) were <18 years of age. Eight were immunocompromised (30%). Eleven (42%) had rash; 9 (35%) were described as zosteriform. Seven (27%) were <18 years of age. Eight were immunocompromised (30%). Eleven (42%) had rash; 9 (35%) were described as zosteriform. Results: Patients ranged in age from 12-85 years (median 46.5): seven (27%) were <18 years of age. Eight were immunocompromised (30%). Eleven (42%) had rash; 9 (35%) were described as zosteriform.

Conclusions: These results suggest that varicella-zoster virus continues to be associated with CNS disease, including reactivation of vaccine virus. Cases presented clinically with lymphocytic pleocytosis, and reactivation was not always accompanied by zoster rash. Sequencing data show that no one genotype predominates, and that wild type J strains are beginning to circulate in the U.S. This is the fourth reported instance of a varicella vaccine strain associated with clinical disease (meningitis and zoster) presenting 10 years after immunization.

References:

Prevalence of Rotavirus Infection in Nicaraguan Children Following a Universal Rotavirus Immunization Program

S. Becker-Dreps1, M. Paniagua2, M. G. Hudgens1, D. Morgan1, F. Espinoza2
1University of North Carolina at Chapel Hill, Chapel Hill, NC, 2University of Nicaragua, Leon, NICARAGUA

Objective: Describe the effectiveness of the pentavalent rotavirus vaccine in a field setting in the developing world.

Background: Nicaragua became one of the first developing world nations to begin universal infant rotavirus immunization (UIRI) with the pentavalent rotavirus vaccine (Rotateq®). By the end of 2007, in León, Nicaragua, coverage of the vaccine for the first, second, and third doses was 98%, 93%, and 77%, respectively. In León prior to URII, the prevalence of rotavirus infection among children presenting to health facilities with severe diarrhea was 28%. Our aim was to measure the new prevalence of rotavirus infection following URII implementation.

Methods: Stool samples were collected from all children ages 3 to 36 months presenting with severe diarrhea to 6 primary care clinics in León over the course of one year. Severe diarrhea was defined as 3 or more liquid stools in the past 24 hours. Stool samples underwent ELISA testing for rotavirus. We also recorded information on the child’s immunization status, daycare attendance, maternal education, household water source and sanitation system. Prevalence was calculated as the frequency of rotavirus among all participants. We also compared characteristics between children who tested positive for rotavirus versus those with diarrhea of another etiology.

Results: The prevalence of rotavirus infection among the children was 2.5% (8/323). Among those with rotavirus, 2 were unimmunized, one received only one dose, and 5 were completely immunized. Those with rotavirus infection were less likely to have been breastfed.

Conclusions: The prevalence of rotavirus infection among children presenting to health facilities with severe diarrhea in León, Nicaragua decreased from 28% before URII to 2.5% following URII implementation. The pentavalent rotavirus vaccine is extremely effective in this developing world setting.

Reference:
Evaluation of Combined Effects of Influenza Vaccine to Mothers and Pneumococcal Conjugate Vaccine to Infants: Results from a Randomized, Double-blind, Controlled Trial

S. B. Omer1, X. Zamar2, E. Roy3, S. E. Arifeen2, R. Raqib1, M. C. Steinhoff3
1Global Health, Emory University, Atlanta, GA, 2International Centre for Diarrhoeal Disease Research, Dhaka, BANGLADESH, 3Johns Hopkins University, Baltimore, MD

Objective: Describe the effectiveness of the combination of influenza vaccine to mother plus PCV7 in preventing respiratory illness with fever in young infants

Background: Influenza and Streptococcus pneumoniae are two important pathogens responsible for acute respiratory infections. Previous animal and human studies have indicated a biological interaction between influenza and S. pneumoniae resulting in a higher susceptibility to each other and increased severity of illness with co-infection. We assessed the biological synergy between influenza virus and pneumococcus by analyzing vaccine interventions against each organism. Methods: We describe a new 2X2 factorial analysis of a double-blind, randomized trial, 340 Bangladeshi mothers were randomized to receive either the influenza vaccine or the 23-valent pneumococcal polysaccharide vaccine (PPV23) in third trimester. Infants of these women (n=331) were again randomized to receive either the pneumococcal conjugate vaccine (PCV7) or Hib conjugate vaccine. The infants were followed weekly through 24 weeks of age. Poisson regression was used to compute incidence rate ratios (IRR) of respiratory illness with fever in infants older than 10 weeks (i.e. 4 weeks after 1st PCV7). We used the following formula to compute percent effectiveness: (1 - IRR) x 100. Results: See table.

<table>
<thead>
<tr>
<th>Vaccine Assignment</th>
<th>Effectiveness (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother PPV23; Infant Hib</td>
<td>Reference</td>
</tr>
<tr>
<td>Mother Influenza; Infant Hib</td>
<td>36.5% (57.9%-4.2%)*</td>
</tr>
<tr>
<td>Mother PPV23; Infant PCV</td>
<td>4.5% (-34.8%-32.3%)</td>
</tr>
<tr>
<td>Mother Influenza; Infant PCV</td>
<td>41.3% (62.1%-9.3%)*</td>
</tr>
</tbody>
</table>

*p<0.05

Conclusions: In this South Asian setting, the combination of influenza vaccine to mother plus PCV7 to infant takes advantage of the biological interaction between influenza virus and S. pneumoniae and may be a useful strategy in preventing clinical respiratory illness in infants 10 weeks or older.

References:
**P55** Enhancement of Mucosal and Cellular Immune Response in Mice by Vaccination with Respiratory Syncytial Virus DNA Encapsulated with Transfersome

**J. Xu**

Pediatric Institute, Children's Hospital, Fudan University, Shanghai, CHINA

**Objective:** Describe how transfersome can be utilized as a simple, non-invasive, economical and effective carrier and adjuvant for vaccination of DNA vaccine

**Background:** Respiratory syncytial virus (RSV) is one of the principal causes of bronchiolitis and pneumonia in young children. There is no safe and effective vaccine. DNA vaccines encoding RSV surface glycoproteins are one option being examined. We evaluated the topical delivery of transfersome encapsulated DNA vaccine for its ability to confer protection against RSV challenge in mice and to determine whether such delivery could induce strong and specific immunity against RSV.

**Methods:** Transfersome was prepared with DOTMA and SDC. Purified RSV-DNA vaccine pcD-F was mixed with transfersome at final concentration of 500 μg DNA/ml transfersome. Naked pcD-F was delivered to mice by intramuscular (IM) immunization, and transfersome pcD-F complex was given to mice by topical immunization. The RNA copies of RSV were determined by real-time RT-PCR. Immune sera and BAL were analyzed for anti-RSV IgG and sIgA responses using ELISA. The frequency of RSV-specific, IFN-γ-producing lymphocytes in spleens were performed with an ELISPOT assay. One-way analysis of variance was performed for statistics.

**Results:** After topical vaccination with a transfersome encapsulated RSV-F DNA, both RSV-specific mucosal antibody response and IFN-γ-producing cells were detected. Intramuscular vaccination of a naked RSV-F DNA only induced a significant anti-RSV IgG antibody response but no remarkable sIgA antibody and virus-specific cellular activity. Lungs from mice receiving topical vaccination had fewer histopathologic anomalies after RSV challenge than did mice receiving intramuscular vaccination or controls.

**Conclusions:** Immunization with transfersome encapsulated F gene encoding DNA induces mucosal and cellular immune responses in mice that appear to produce protective immunity against respiratory syncytial virus.

**References:**

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**P56** Safety and Immunogenicity of a Candidate Tuberculosis (TB) Vaccine, MVA85A, in Healthy Gambian Infants Previously Vaccinated with BCG

**M. O. Ota1, O. A. Owolabi2, O. A. Odutola2, P. K. Owiafe1, R. A. Adegbola1, H. McShane1**

1Medical Research Council Laboratories (United Kingdom), Banjul, GAMBIA, 2Department of Veterinary Parasitology & Entomology, University of Nigeria, Nsukka, NIGERIA, 3Department of Veterinary Parasitology & Entomology, University of Nigeria, Nsukka, NIGERIA, 4Department of Surgery, University of Pittsburgh, Pittsburgh, PA

**Objective:** Review the potentials of Ad5 in P. vivax vaccine development and the role of the Influenza virus hemaglutininTM in enhancing antigen surface expression

**Background:** Replication-defective adenoviral vectors based on adenovirus type 5 (Ad5) have been used in vaccine development against several diseases, including malaria, where induction of T-cell and antibody responses, as well as protective immunity have been consistently recorded. In order to harness the potentials of Ad5 as a suitable platform for malaria vaccines, we developed Ad5-based P. vivax MSP-1 (PvMSP1) vaccines using two modified MSP-1 antigens, one derived from the C-terminal region (MSP-1C) and the other from the N-terminal region (MSP-1N). Methods: Using Cre-lox recombination as previously described, five E11/E3-deleted replication-incompetent adenoviral vectors were engineered to encode codon-optimized PvMSP1 antigens. For better processing and surface expression, a signal sequence derived from the native PvmSP1 protein and/or the transmembrane region of the influenza HA protein were added. The 5 constructs of the MSP-1 protein were evaluated in vitro and in mouse model after a homologous prime-boosting regimen.

**Results:** Protein expression studies confirmed that the TM region of the Ad 19K vaccine (Ad-19KTM) enhanced surface expression and that virus Ankara encoding antigen 85A (MVA85A) is used as heterologous boost to BCG, thus combining the benefits of both. The epidemiology of TB in the endemic areas requires protection against infection as early in life as possible. This study aimed at selecting dose and providing safety and immunogenicity data of MVA85A in infants that are required for large efficacy trial.

**Methods:** An open randomised study of 4-month old infants allocated to one of three groups according to the following: group 1: MVA85A at 16/52 and EPI vaccination deferred for 1 week (group 2); and MVA85A at 16/52 and EPI vaccination deferred for 1 week (group 3). 12 infants per group were involved in the low (2.5 x 10^9 pfu), and high (5.0 x 10^9 pfu) dose studies. Safety was evaluated by clinical, renal, haematological and liver function tests, while immunogenicity was by IFN-γ response to Ag85A peptides using ELISPOT assay.

**Results:** The safety profile was similar between the vaccinees and controls and between recipients of low dose and high dose. The immunogenicity of high dose was significantly higher and more sustained than that of low dose.

**Conclusion:** MVA85A is safe and immunogenic in Gambian infants, which are essential data needed to proceed to the efficacy trial against tuberculosis.

**References:**

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**P57** Development and Preclinical Evaluation of Ad5-based Plasmodium vivax Vaccines Derived from the Blood Stage Merozoite Surface Protein 1 (MSP-1)

**C. O. Esimone1, A. Valderrama A2, D. N. Onah3, J. Steitz4, S. Herrera2, A. Gambotto5**

1Department of Pharmaceutics and Pharmaceutical Microbiology, University of Nigeria, Nsukka, NIGERIA, 2Malaria Vaccine and Drug Development Center, Coli, COLOMBIA, 3Department of Veterinary Parasitology & Entomology, University of Nigeria, Nsukka, NIGERIA, 4Department of Surgery, University of Pittsburgh, Pittsburgh, PA

**Objective:** Describe how transfersome can be utilized as a simple, non-invasive, economical and effective carrier and adjuvant for vaccination of DNA vaccine

**Background:** Transfersome was prepared with DOTMA and SDC. Purified RSV-DNA vaccine pcD-F was mixed with transfersome at final concentration of 500 μg DNA/ml transfersome. Naked pcD-F was delivered to mice by intramuscular (IM) immunization, and transfersome pcD-F complex was given to mice by topical immunization. The RNA copies of RSV were determined by real-time RT-PCR. Immune sera and BAL were analyzed for anti-RSV IgG and sIgA responses using ELISA. The frequency of RSV-specific, IFN-γ-producing lymphocytes in spleens were performed with an ELISPOT assay. One-way analysis of variance was performed for statistics.

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**Conclusions:** Immunization with transfersome encapsulated F gene encoding DNA induces mucosal and cellular immune responses in mice that appear to produce protective immunity against respiratory syncytial virus.

**References:**

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**P56** Safety and Immunogenicity of a Candidate Tuberculosis (TB) Vaccine, MVA85A, in Healthy Gambian Infants Previously Vaccinated with BCG

**M. O. Ota1, O. A. Owolabi2, O. A. Odutola2, P. K. Owiafe1, R. A. Adegbola1, H. McShane1**

1Medical Research Council Laboratories (United Kingdom), Banjul, GAMBIA, 2Department of Veterinary Parasitology & Entomology, University of Nigeria, Nsukka, NIGERIA, 4Department of Surgery, University of Pittsburgh, Pittsburgh, PA

**Objective:** Discuss the use of MVA85A vaccine in Gambian infants

**Background:** Tuberculosis kills about three million people annually, most of which are from developing countries. Unfortunately, the currently available vaccine, M. bovis BCG, is largely ineffective at protecting against disease in endemic areas, warranting an urgent need for new vaccines and strategies that improve upon BCG. A recombinant modified vaccinia virus Ankara encoding antigen 85A (MVA85A) is used as heterologous boost to BCG, thus combining the benefits of both. The epidemiology of TB in the endemic areas requires protection against infection as early in life as possible. This study aimed at selecting dose and providing safety and immunogenicity data of MVA85A in infants that are required for large efficacy trial.

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**Results:** The safety profile was similar between the vaccinees and controls and between recipients of low dose and high dose. The immunogenicity of high dose was significantly higher and more sustained than that of low dose.

**Conclusion:** MVA85A is safe and immunogenic in Gambian infants, which are essential data needed to proceed to the efficacy trial against tuberculosis.

**References:**
the signal sequence attached to the Ad-200L vaccine (Ad-200Ls) did not enhance antigen recognition. The fusion protein (Ad-19K/200L) was less immunogenic than either Ad-19K TM or Ad-200L alone. Immunogenicity studies in Balb/c mice demonstrated the specificities of the immune responses mounted by the three most effective Ad-PvMS1 vaccines (Ad-19KTM, Ad-200L and Ad-200Ls). Conclusions: Three out of five candidate vaccines were shown to be immunogenic in mice. Moreover, combinations of Ad-19KTM with either Ad-200L or Ad-200Ls have shown additive effects, mounting specific immune response against the two different antigens.

References:

Objective: Describe how the new finding of a receptor molecule of dengue virus is useful for dengue vaccine development.

Dengue viruses (DENV) infect cells by attaching to a surface receptor. However, the host cell receptor remains unknown. This study investigated the putative receptor molecules of dengue virus type 2 (DENV-2) on the surface of mosquito (AP-61) and mammalian (LLC-MK2) cell lines. Immunochemical detection by thin layer chromatography (TLC)/virus-binding and TLC-immunostaining with β-N-acetyl-hexosaminidase treatment, and structure analysis by matrix-assisted laser desorption/ionization time of flight mass spectrometer (MALDI-TOF-MS) demonstrated that neutral glycosphingolipids, L-3 (GlcNAcβ1-3Manβ1-4Glcβ1-1’Cer) and L-4 (GlcNAcβ1-4Glcβ1-1’Cer) in AP-61 cells, and asialo-GM1 (GlcNAcβ1-4Galβ1-4Glcβ1-1’Cer) and nLeβCer (Galβ1-4GlcαNacβ1-3Galβ1-4Glcβ1-1’Cer) in LLC-MK2 cells were exclusively recognized with DENV-2. In acidic lipids of AP-61 and LLC-MK2 cells, sulfatide (HO₂-S-Galβ1-1’Cer) was also significantly reacted with DENV-2. These findings strongly suggest that the neutral glycosphingolipids and sulfatide share the key determinant for binding with DENV-2. Particularly βHexNAc residue which is commonly contained in four neutral glycosphingolipids may play an important role in DENV binding to host cell surface.

References:
P61 A Complex Formation of Rhoptry Neck Protein 2 with a Microneme Protein, AMA1, in Plasmodium falciparum
J. Zuo1, O. Kaneko2, A. Thomkukancha1, M. Tachibana1, H. Otukvi1, T. Tsuboi2, M. Tsur1
1Jiangsu Institute of Parasitic Diseases, Wuxi, CHINA, 2Institute of Tropical Medicine, Nagasaki University, Nagasaki, JAPAN, 3Faculty of Science, Burapha University, Chonburi, THAILAND, 4Ehime University Graduate School of Medicine, Toon, JAPAN, 5Cell-Free Science and Technology Research Center, Ehime University, Matsuyama, JAPAN

Objective: Describe how Rhoptry neck protein RON2 forms a complex with microneme protein AMA1 in Plasmodium falciparum merozoites. Erythrocyte invasion is an essential step of the malaria parasites to establish the infection in human. Recent proteome analysis of the closely-related apicomplexa parasite, Toxoplasma gondii, revealed a panel of novel rhoptry neck proteins (RONs), and some of them have been shown to form a complex with a microneme protein, Apical Membrane Protein 1 (AMA1), at the interface of the parasite and the host cell (the moving junction) during invasion. Because most of the RONs and AMA1 are conserved among apicomplexa phylum parasites and Plasmodium AMA1 is a leading blood-stage vaccine candidate, RONs appears to have not only a fundamental role in the invasion mechanism of this parasite, but also a potential for the malaria intervention. Here we characterized PIRON2, one of RONs in Plasmodium falciparum. PIRON2 transcription peaked at the mature schizont and expressed at the neck portion of the rhoptry in the merozoite shown by immuno-electronmicroscopy. PIRON2 possesses a region harboring a strong homology with a rhoptry body protein PIRhopH1/Clag, a component of the RhopH complex, however, coimmunoprecipitation experiment indicated that PIRON2 was not a component of the RhopH complex. Coimmunoprecipitation of PIRON2 and PAM1 was observed, suggesting that co-operative function of the rhoptry and microneme proteins during erythrocyte invasion.

References:

P62 The Expression and Characterization of Cholera Toxin B Subunit—Pneumolysin Toxoid Fusion Protein
A. P. M. Arêas1, M. L. S. Oliveira2, E. N. Miyaji2, L. C. C. Leite2, P. L. Ho3
1Universidade Federal do ABC, Santo André, BRAZIL, 2Instituto Butantan, São Paulo, BRAZIL

Objective: Discuss some aspects of adjuvant science and pneumococcal infections, which represent a severe public health problem worldwide.

Background: This work presents the characterization of a fusion protein consisting of Cholera Toxin B subunit (CTB) and PdB as a vaccine candidate to pneumococcal infections. PdB is a non-toxic derivative of Pneumolysin, a pneumococcal toxin, involved in the bloodstream stage of pathogenesis. Methods: CTB-PdB was expressed in Escherichia coli as a soluble protein and purified by a Ni2+-affinity chromatography. This protein was characterized by its ability to bind GM1 receptor by a GM1-ELISA and to induce anti-PdB antibodies. BALB/C mice were immunized by intradermal route and after 3 weeks, individual blood samples were collected and analyzed by ELISA. Individual levels of antibodies were compared by Student t-test. Results: The protein was successfully produced in E. coli. A GM1-ELISA showed the specific binding of the CTB-PdB to the cellular receptor in a dose-dependent manner. Therefore, CTB-PdB was obtained in a functional form, at least the CTB moiety. Mice intradermally immunized with CTB-PdB displayed statistically significant higher levels of anti-PdB and anti-CTB IgG than control mice, which show an adjuvant effect of CTB and PdB in this preliminary experiment. This unexpected adjuvant effect of PdB seems to be related to the recognition of this protein by the Toll-like receptor 4 (TLR-4). Conclusion: The approach of conjugating adjuvant and antigens seems to be a good alternative to produce less expensive as well as more efficient vaccine formulations. According to the results, PdB may be used either as an adjuvant or an antigen to compose a multipurpose vaccine, since it presented an adjuvant effect to a non-pneumococcal protein. Other experiments will be made to better investigate these preliminary results.
References:

Objective:
Discuss newly emerging rotavirus strains and the impact on the formulation of rotavirus vaccine, i.e., monovalent vs. polyvalent vaccine

Background: Knowledge of rotavirus serotypes is important in planning vaccine strategy. Phase-II clinical trial of a monovalent rotavirus vaccine candidate 116E in India emphasizes priority of estimating rotavirus strain diversity.

Methods: 1524 fecal specimens from children admitted at AIIMS with diarrhea during year 2000-07 were tested for rotavirus by commercial ELISA kit. Rotavirus G and P types were determined by multiplex RT-PCR. Specimens that did not react with either of the primers (nt) were sequenced.

Results: 465 of 500 rotavirus-positive specimens were genotyped (G/P). RV genotypes G1, G2, and G9 were predominant (Table 1). The study demonstrated emergence of G12 strains in Northern India, with prevalence identical to that of G9 strains, while G3 and G4 strains were rare. Among the P types, P[4], P[6], and P[8] were frequently detected with high percentage of mixed infections. Significant but low frequencies of nontypeables were detected, among which majority were G1P[8] with consistent mismatches within the type specific primer. A significant contribution of the study was detection of a rare human G8 RV strain.

Conclusion: The study demonstrated a larger diversity of rotavirus strains among Indian children than previously thought with an unexpected emergence of G12 and detection of a rare G8 genotype in Delhi. These findings underscore need for continuous surveillance and for evaluation of candidate rotavirus vaccine in different geographical settings, both developed and developing.

References:
P65  Mucosal and Systemic Immune Responses to an Oral Killed Bivalent Vibrio cholerae O1/O139 Whole Cell Cholera Vaccine in Bangladeshi Adults

S. Shamsuzzaman
University of Dhaka, Dhaka, BANGLADESH

Objective: Discuss the safety and immunogenicity of an oral killed bivalent cholera vaccine

Background: Although the prevalence of diarrhea due to Vibrio cholerae O139 has recorded a decrease, efforts on vaccine development continue to formulate an oral vaccine capable of stimulating the gut mucosal system. In this study, we have analyzed the mucosal immune responses to a bivalent whole cell oral killed cholera vaccine (WC-O1/O139/CTB) among Bangladeshi study participants and compared the responses to that obtained with the licensed monovalent O1 killed cholera vaccine, Dukoral™ (WC-O1/CTB).

Methods: Thirty-one adult male study participants were given two doses of the vaccines with a two-week interval. Venous blood, intestinal lavage fluid and feces were collected from vaccinees on day 0 (preimmunization sample) and 7 days after the second dose of vaccination (day 21, postimmunization sample). Duodenal pinch biopsies were also obtained from vaccinees receiving bivalent WC-O1/O139/CTB vaccine. Direct estimation of vaccine specific mucosal responses were carried out using lymphocytes isolated from duodenal biopsies, intestinal lavage fluid and feces.

Results: The vaccine induced robust antibody-secreting cell responses in the duodenum specific to CTB as well as the O1 and O139 lipopolysaccharide (LPS). Magnitude of response was higher in the gut than in the circulation in all three antibody isotypes. The CTB and LPS specific mucosal antibody responses were also seen in intestinal lavage fluid and feces. Vibriocidal antibody responses in plasma were observed to both the V. cholerae O1 and O139 serogroups. The immune responses were comparable to that seen to the monovalent WC-O1/CTB recipients in all components studied.

Conclusions: The bivalent cholera vaccine induces strong mucosal responses and the addition of the O139 component does not interfere with the responses to the licensed monovalent cholera vaccine Dukoral™.

References:

P66  Rotavirus Vaccination in Nicaragua and Infant Mortality by Acute Diarrhea in 2007

K. J. Amador Sánchez1, S. D. Flores González2
1PATH Nicaragua, Managua, NICARAGUA, 2Monte España Hospital, Managua, NICARAGUA

Objective: Evaluate the reduction in the national mortality rate from acute diarrhea after the introduction of pentavalent rotavirus vaccine (RV5) in Nicaragua

Background: October 2006 the RV5 was introduced in Nicaragua with 78.1% coverage in 2007 for 3rd doses.

Methods: We analyzed infant diarrhea mortality in 2007 in the whole country, obtaining information from Ministry of Health and visiting hospitals and health centers. We analyzed the national coverage of RV5 and the mortality rate in children vaccinated in compare to non-vaccinated.

Results: National RV5 coverage in 2007 was 86.1% for first dose, 78.3% second doses, 78.1% third doses. The mortality rate reduction comparing 2000-2005 versus 2007 was 27% in children less than 1 year of age. Of 97 who died due to infant acute diarrhea, 71 (73.2%) did not receive any dose; 8 (8.2%) received 1 dose; 9 (9.3%) received 2 doses; 9 (9.3%) received 3 doses. The mortality rate by non-specific acute diarrhea in not-vaccinated children between 3 to 11 months of age was 12.7 x 10,000; and the mortality rate in same-age children that received at least one dose was 3.5 x 10,000, finding 72.7% reduction in mortality, RR=0.27, (95% CI 0.17-0.45) (P-value=0.0). The mortality rate by non-specific acute diarrhea in not-vaccinated children between 7 to 11 months of age was 6.1 x 10,000; and the mortality rate in vaccinated children with 3rd doses was 3.4 x 10,000, with RR=0.55, (95% CI 0.24-1.23) (P-value=0.14), and 44% reduction in mortality.

Conclusions: The mortality rate by non-specific acute diarrhea in children between 7 to 11 months vaccinated with 3 doses was reduced 44% compared with same-age not vaccinated children and the mortality rate in children between 3 to 11 months with 1-3 doses was 72.7% less than not vaccinated children at the same age.

References:
# Twelfth Annual Conference

## Author Index

*(primary authors are in bold type)*

<table>
<thead>
<tr>
<th>Author</th>
<th>Presentation Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdelnabi, G H.</td>
<td>P29</td>
</tr>
<tr>
<td>Abdillea, M H.</td>
<td>P29</td>
</tr>
<tr>
<td>Adams, William</td>
<td>S27</td>
</tr>
<tr>
<td>Adegbola, Richard A.</td>
<td>P36, P56</td>
</tr>
<tr>
<td>Adeiga, Adesina</td>
<td>P4</td>
</tr>
<tr>
<td>Adesanmi, Adeyinka</td>
<td>P4</td>
</tr>
<tr>
<td>Albertyn, Jacobus</td>
<td>P60</td>
</tr>
<tr>
<td>Amador Sanchez, Karen</td>
<td>P66</td>
</tr>
<tr>
<td>Amuel, Carsten</td>
<td>P20</td>
</tr>
<tr>
<td>Andersen, Peter</td>
<td>16</td>
</tr>
<tr>
<td>Anderson, Edwin L</td>
<td>S9</td>
</tr>
<tr>
<td>Anochie, Philip</td>
<td>P4</td>
</tr>
<tr>
<td>Aréas, Ana P. M.</td>
<td>P62</td>
</tr>
<tr>
<td>Arifeen, S E.</td>
<td>P53, S17</td>
</tr>
<tr>
<td>Ayares, David</td>
<td>P44</td>
</tr>
<tr>
<td>Babusis, Elizabeth</td>
<td>S14, S9</td>
</tr>
<tr>
<td>Baggs, James</td>
<td>S25</td>
</tr>
<tr>
<td>Bagley, Kenneth C.</td>
<td>P21</td>
</tr>
<tr>
<td>Baker, James</td>
<td>S32</td>
</tr>
<tr>
<td>Baker, James R</td>
<td>S4, P13</td>
</tr>
<tr>
<td>Bakken, Russ</td>
<td>P37</td>
</tr>
<tr>
<td>Bakken, Russell</td>
<td>P5</td>
</tr>
<tr>
<td>Balea, Gheoghe</td>
<td>P54</td>
</tr>
<tr>
<td>Ball, Suyapa</td>
<td>P44</td>
</tr>
<tr>
<td>Ballou, W. Ripley</td>
<td>19</td>
</tr>
<tr>
<td>Barnett, Elizabeth</td>
<td>S27</td>
</tr>
<tr>
<td>Bash, Margaret C.</td>
<td>P36</td>
</tr>
<tr>
<td>Bastien, Nathalie</td>
<td>S7</td>
</tr>
<tr>
<td>Bauch, Chris T.</td>
<td>P15</td>
</tr>
<tr>
<td>Baxter, Roger</td>
<td>S16, S26, S27, S28, P51</td>
</tr>
<tr>
<td>Becker-Dreps, Sylvia</td>
<td>P52</td>
</tr>
<tr>
<td>Belshe, Robert B.</td>
<td>S12, S14, S9</td>
</tr>
<tr>
<td>Benes, Oleg</td>
<td>P54</td>
</tr>
<tr>
<td>Bernstein, David I.</td>
<td>S14, S9</td>
</tr>
<tr>
<td>Bettinger, Julie</td>
<td>P50</td>
</tr>
<tr>
<td>Bhan, M K.</td>
<td>P63</td>
</tr>
<tr>
<td>Bianchi, Elisabetta</td>
<td>P35</td>
</tr>
<tr>
<td>Black, Marissa A.</td>
<td>P38</td>
</tr>
<tr>
<td>Black, Steven</td>
<td>3, S26, S27</td>
</tr>
<tr>
<td>Bontovics, Erika</td>
<td>S7</td>
</tr>
<tr>
<td>Boog, Claire J. P.</td>
<td>P22</td>
</tr>
<tr>
<td>Boone, Jeremy</td>
<td>P44</td>
</tr>
<tr>
<td>Borov, R.</td>
<td>P36</td>
</tr>
<tr>
<td>Borotolussi, Robert</td>
<td>P50</td>
</tr>
<tr>
<td>Boslego, John</td>
<td>P31</td>
</tr>
<tr>
<td>Bostik, Vanda</td>
<td>P51</td>
</tr>
<tr>
<td>Boyoglu, Seyhan</td>
<td>P18</td>
</tr>
<tr>
<td>Bragg, Robert R.</td>
<td>P60</td>
</tr>
<tr>
<td>BRAVO, LULU C.</td>
<td>P46</td>
</tr>
<tr>
<td>Bresnahan, Brian W.</td>
<td>P15</td>
</tr>
<tr>
<td>Broder, Karen</td>
<td>S25, S29</td>
</tr>
<tr>
<td>Bruder, Joe</td>
<td>S20</td>
</tr>
<tr>
<td>Buck, Christopher</td>
<td>P43</td>
</tr>
<tr>
<td>Butler, John</td>
<td>P44</td>
</tr>
<tr>
<td>Cao, Jun</td>
<td>P61</td>
</tr>
<tr>
<td>Capeding, Maria R. Z.</td>
<td>P46</td>
</tr>
<tr>
<td>Carapau, Daniel</td>
<td>P48</td>
</tr>
<tr>
<td>Carlson, Christopher</td>
<td>4</td>
</tr>
<tr>
<td>Carpenter, Diane</td>
<td>S26</td>
</tr>
<tr>
<td>Casey, Christine</td>
<td>S27</td>
</tr>
<tr>
<td>Caulfield, Michael J.</td>
<td>P31, P35</td>
</tr>
<tr>
<td>Chang, Yung-Fu</td>
<td>P47</td>
</tr>
<tr>
<td>Chao, An-Shine</td>
<td>P33</td>
</tr>
<tr>
<td>Charest, Hugues</td>
<td>S7</td>
</tr>
<tr>
<td>Chaung, Ilin</td>
<td>S20</td>
</tr>
<tr>
<td>Chen, Man</td>
<td>P43</td>
</tr>
<tr>
<td>Chen, Shu-Hung</td>
<td>P44</td>
</tr>
<tr>
<td>Chiang, Pai-Shan</td>
<td>P33</td>
</tr>
<tr>
<td>Chu, Alice</td>
<td>S19, S23</td>
</tr>
<tr>
<td>Cimpoi, Leonid</td>
<td>P54</td>
</tr>
<tr>
<td>Citron, Michael</td>
<td>P35</td>
</tr>
<tr>
<td>Clark, Thomas</td>
<td>P27</td>
</tr>
<tr>
<td>Clarke, David</td>
<td>P23</td>
</tr>
<tr>
<td>Co, Mary</td>
<td>S5</td>
</tr>
<tr>
<td>Cochi, Stephen I.</td>
<td>7</td>
</tr>
<tr>
<td>Compans, Richard</td>
<td>P45</td>
</tr>
<tr>
<td>Copp, Laura</td>
<td>P26</td>
</tr>
<tr>
<td>Corbett, Kizzmekia</td>
<td>P43</td>
</tr>
<tr>
<td>Creech, Clarence B.</td>
<td>S14, S9</td>
</tr>
<tr>
<td>Crowcroft, Natasha</td>
<td>S7</td>
</tr>
<tr>
<td>Curry, Lawrence</td>
<td>P10</td>
</tr>
<tr>
<td>Cutting, Simon</td>
<td>P8</td>
</tr>
<tr>
<td>Dai, Yifan</td>
<td>P44</td>
</tr>
<tr>
<td>Dandro, Amy</td>
<td>P44</td>
</tr>
<tr>
<td>Darga, Allyson J.</td>
<td>P32</td>
</tr>
<tr>
<td>Dargan, Jennifer</td>
<td>P31</td>
</tr>
<tr>
<td>DaSilva, Luis</td>
<td>P11</td>
</tr>
<tr>
<td>de Graaf, Truus W.</td>
<td>P22</td>
</tr>
<tr>
<td>De Groot, Annie</td>
<td>S18</td>
</tr>
<tr>
<td>De Serres, Gaston</td>
<td>S15, S7</td>
</tr>
<tr>
<td>Dekker, Cornelia</td>
<td>S27, S51</td>
</tr>
<tr>
<td>Dekleva, Michael</td>
<td>S12</td>
</tr>
<tr>
<td>dela Cruz, Tracy</td>
<td>P20</td>
</tr>
<tr>
<td>Dembele, Fanta N.</td>
<td>P2</td>
</tr>
<tr>
<td>Dennis, Vida</td>
<td>P18</td>
</tr>
<tr>
<td>DeSimone, Joseph</td>
<td>P26</td>
</tr>
<tr>
<td>DeVico, Anthony</td>
<td>P24</td>
</tr>
<tr>
<td>Diaz, Gilda S.</td>
<td>P46</td>
</tr>
<tr>
<td>Dickinson, Jim</td>
<td>S7</td>
</tr>
<tr>
<td>Diggs, Carter</td>
<td>S20</td>
</tr>
<tr>
<td>Donahue, James</td>
<td>S29</td>
</tr>
<tr>
<td>Dong, Xiaojuuan</td>
<td>P29</td>
</tr>
<tr>
<td>Doolan, Denise</td>
<td>S20</td>
</tr>
<tr>
<td>Drew, Jeffrey</td>
<td>P42</td>
</tr>
<tr>
<td>Drews, Steven J.</td>
<td>S7</td>
</tr>
<tr>
<td>Drobeniuc, Jan</td>
<td>P54</td>
</tr>
<tr>
<td>Duchars, Matthew</td>
<td>P10</td>
</tr>
</tbody>
</table>
### Author Index

(primary authors are in **bold type**)

<table>
<thead>
<tr>
<th>Author</th>
<th>Presentation Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupuy, Lesley C.</td>
<td>S22</td>
</tr>
<tr>
<td>Dybvig, Tova</td>
<td>P17</td>
</tr>
<tr>
<td>Edupuganti, Srilatha</td>
<td>P41</td>
</tr>
<tr>
<td>Edwards, Kathryn M.</td>
<td>S9, S13, S14, S27, S29</td>
</tr>
<tr>
<td>Egan, Michael A.</td>
<td>S31</td>
</tr>
<tr>
<td>Ellefsen, Barry</td>
<td>S22</td>
</tr>
<tr>
<td>Emery, Kirt</td>
<td>P27</td>
</tr>
<tr>
<td>Ennis, Francis</td>
<td>S5</td>
</tr>
<tr>
<td>Epstein, Judith E.</td>
<td>S20</td>
</tr>
<tr>
<td>Esmione, Charles O.</td>
<td>P57</td>
</tr>
<tr>
<td>Espinoza, Felix</td>
<td>P52</td>
</tr>
<tr>
<td>Evans, Barbara</td>
<td>S12</td>
</tr>
<tr>
<td>Eyanu, Samuel</td>
<td>P34</td>
</tr>
<tr>
<td>Faber, Michael J.</td>
<td>P32</td>
</tr>
<tr>
<td>Fagone, Paolo</td>
<td>S1</td>
</tr>
<tr>
<td>Fairman, Jeffery</td>
<td>S5</td>
</tr>
<tr>
<td>Faisal, Syed M.</td>
<td>P47</td>
</tr>
<tr>
<td>Fewlass, Charles</td>
<td>S8</td>
</tr>
<tr>
<td>Fine, Donald</td>
<td>P37, P5</td>
</tr>
<tr>
<td>Finotto, Marco</td>
<td>P35</td>
</tr>
<tr>
<td>Fireman, Bruce</td>
<td>S16, S26, S28</td>
</tr>
<tr>
<td>Fitzgerald, Theresa</td>
<td>S11</td>
</tr>
<tr>
<td>Flores, Rosemary</td>
<td>P34</td>
</tr>
<tr>
<td>Flores González, Saúl D.</td>
<td>P66</td>
</tr>
<tr>
<td>Foglia, Ginamarie</td>
<td>S3</td>
</tr>
<tr>
<td>Fonseca, Kevin</td>
<td>S7</td>
</tr>
<tr>
<td>Fouts, Timothy R.</td>
<td>P24</td>
</tr>
<tr>
<td>Gagliani, Manjusha</td>
<td>S8</td>
</tr>
<tr>
<td>Gaisan, Nicolai</td>
<td>P54</td>
</tr>
<tr>
<td>Galindo, Claudia</td>
<td>S26</td>
</tr>
<tr>
<td>Galloway, Ashley</td>
<td>P26</td>
</tr>
<tr>
<td>Gambotto, Andrea</td>
<td>P57</td>
</tr>
<tr>
<td>Garcia, Patricia</td>
<td>P37, P5</td>
</tr>
<tr>
<td>Garçon, Nathalie</td>
<td>S2</td>
</tr>
<tr>
<td>Gargiullo, Paul</td>
<td>S25</td>
</tr>
<tr>
<td>Garrison, Louis P.</td>
<td>P15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Presentation Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaskins, Jonathan</td>
<td>P38</td>
</tr>
<tr>
<td>Ge, Hong</td>
<td>P20</td>
</tr>
<tr>
<td>Ge, Julianne</td>
<td>S29</td>
</tr>
<tr>
<td>Gerber, Michael A.</td>
<td>S14, S9</td>
</tr>
<tr>
<td>Gidudu, Jane</td>
<td>S29</td>
</tr>
<tr>
<td>Girgenti, Douglas</td>
<td>S21</td>
</tr>
<tr>
<td>Glaser, Carol A.</td>
<td>P51</td>
</tr>
<tr>
<td>Glass, Pamela</td>
<td>P37, P5</td>
</tr>
<tr>
<td>Glezen, W. Paul</td>
<td>S8</td>
</tr>
<tr>
<td>Golding, Hana</td>
<td>S13</td>
</tr>
<tr>
<td>Graham, Barney</td>
<td>P43</td>
</tr>
<tr>
<td>Graham, Irene</td>
<td>S12, S9</td>
</tr>
<tr>
<td>Gray, Ian</td>
<td>P10</td>
</tr>
<tr>
<td>Greger, Patricia</td>
<td>S8</td>
</tr>
<tr>
<td>Grimm, Brad</td>
<td>P37</td>
</tr>
<tr>
<td>Gruber, William A.</td>
<td>S21</td>
</tr>
<tr>
<td>Gu, Ling</td>
<td>P14</td>
</tr>
<tr>
<td>Gutierrez, Don</td>
<td>S23</td>
</tr>
<tr>
<td>Hackett, Anthony</td>
<td>P14</td>
</tr>
<tr>
<td>Haidaara, F.C.</td>
<td>P36</td>
</tr>
<tr>
<td>Halperin, Scott</td>
<td>P50</td>
</tr>
<tr>
<td>Halperin, Scott A.</td>
<td>S21</td>
</tr>
<tr>
<td>Halsey, Neal A.</td>
<td>9</td>
</tr>
<tr>
<td>Hamouda, Tarek</td>
<td>P13, S32, S4</td>
</tr>
<tr>
<td>Hanekom, Willem</td>
<td>15</td>
</tr>
<tr>
<td>Hannaman, Drew</td>
<td>S22</td>
</tr>
<tr>
<td>Hansen, John</td>
<td>S26</td>
</tr>
<tr>
<td>Harriman, Kathleen</td>
<td>P27</td>
</tr>
<tr>
<td>Hart, Mary Kate</td>
<td>P5</td>
</tr>
<tr>
<td>Harvey, Dianne</td>
<td>S8</td>
</tr>
<tr>
<td>Hassan-King, M.</td>
<td>P36</td>
</tr>
<tr>
<td>Hatcher, Cynthia</td>
<td>P27</td>
</tr>
<tr>
<td>Hayne, Mary S.</td>
<td>P32</td>
</tr>
<tr>
<td>Hazlet, Thomas K.</td>
<td>P15</td>
</tr>
<tr>
<td>He, Qiushi</td>
<td>S34</td>
</tr>
<tr>
<td>Heinrichs, Jon</td>
<td>P31</td>
</tr>
<tr>
<td>Henderson, Ian</td>
<td>P6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Presentation Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepler, Robert</td>
<td>P35</td>
</tr>
<tr>
<td>Herrera, Socrates</td>
<td>P57</td>
</tr>
<tr>
<td>Hibbs, Beth</td>
<td>S29</td>
</tr>
<tr>
<td>Hiebert, Brett</td>
<td>S15</td>
</tr>
<tr>
<td>Hill, Adrian V.</td>
<td>13</td>
</tr>
<tr>
<td>Hoffman, Stephen L.</td>
<td>22</td>
</tr>
<tr>
<td>Higgins, Debbie</td>
<td>P20</td>
</tr>
<tr>
<td>Ho, Paulo L.</td>
<td>P62</td>
</tr>
<tr>
<td>Hoft, Daniel E.</td>
<td>S14</td>
</tr>
<tr>
<td>Holtzman, Douglas</td>
<td>P34</td>
</tr>
<tr>
<td>Hong, Yeong H.</td>
<td>P16</td>
</tr>
<tr>
<td>Hotte, Travis S.</td>
<td>S7, S15</td>
</tr>
<tr>
<td>Hrini, Renee</td>
<td>P35</td>
</tr>
<tr>
<td>Huang, Wan-Ting</td>
<td>S25</td>
</tr>
<tr>
<td>Huang, Zuhu</td>
<td>P14</td>
</tr>
<tr>
<td>Hubby, Boly</td>
<td>P26</td>
</tr>
<tr>
<td>Hudgens, Michael G.</td>
<td>P52</td>
</tr>
<tr>
<td>Huithui, Bao</td>
<td>S1</td>
</tr>
<tr>
<td>Huntziker, Natasha R.</td>
<td>P51</td>
</tr>
<tr>
<td>Iarovoi, Petru</td>
<td>P54</td>
</tr>
<tr>
<td>Idika, Nneoma</td>
<td>P4</td>
</tr>
<tr>
<td>Idika, Nneoma N.</td>
<td>P4</td>
</tr>
<tr>
<td>Ikegami, Tetsuro</td>
<td>P12</td>
</tr>
<tr>
<td>Indravati, Lani</td>
<td>P31</td>
</tr>
<tr>
<td>Ingallinella, Paolo</td>
<td>P35</td>
</tr>
<tr>
<td>Iskander, John</td>
<td>S25, S29</td>
</tr>
<tr>
<td>Jacob, Joshy</td>
<td>P45</td>
</tr>
<tr>
<td>Jacobson, Robert M.</td>
<td>S33</td>
</tr>
<tr>
<td>Jacquet, Jeanne-Marie</td>
<td>S34</td>
</tr>
<tr>
<td>Jakob, Kathleen</td>
<td>S27</td>
</tr>
<tr>
<td>Jang, Seung I.</td>
<td>P16</td>
</tr>
<tr>
<td>Janji, Naved Z.</td>
<td>S7, S15</td>
</tr>
<tr>
<td>Jenkins, Erin</td>
<td>P37, P5</td>
</tr>
<tr>
<td>Jeyanathan, Mangalakumari</td>
<td>S30</td>
</tr>
<tr>
<td>Jin, Hong</td>
<td>P29</td>
</tr>
<tr>
<td>Jobst, Peter</td>
<td>P44</td>
</tr>
<tr>
<td>Johnson, Casey</td>
<td>S10, S5</td>
</tr>
<tr>
<td>Author</td>
<td>Presentation Number</td>
</tr>
<tr>
<td>-------------------------</td>
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</tr>
<tr>
<td>Johnson, Teresa</td>
<td>P43</td>
</tr>
<tr>
<td>Jones, Andrew</td>
<td>10</td>
</tr>
<tr>
<td>Joyce, Joseph G.</td>
<td>P35</td>
</tr>
<tr>
<td>Kaziajik, Patricia</td>
<td>P22</td>
</tr>
<tr>
<td>Kadiyala, Srikanth</td>
<td>P15</td>
</tr>
<tr>
<td>Kamitani, Wataru</td>
<td>P12</td>
</tr>
<tr>
<td>Kaneko, Osamu</td>
<td>P61</td>
</tr>
<tr>
<td>Kanan, Senthil</td>
<td>S1</td>
</tr>
<tr>
<td>Kavita, Uma</td>
<td>S10</td>
</tr>
<tr>
<td>Kellner, James D.</td>
<td>S21</td>
</tr>
<tr>
<td>Khan, Abdul</td>
<td>P19</td>
</tr>
<tr>
<td>Khurana, Surender</td>
<td>S13</td>
</tr>
<tr>
<td>Kilgore, Paul</td>
<td>P46</td>
</tr>
<tr>
<td>Kilkarni, P.</td>
<td>P36</td>
</tr>
<tr>
<td>Kim, Duk K.</td>
<td>P16</td>
</tr>
<tr>
<td>Kim, Jin Hyang</td>
<td>P45</td>
</tr>
<tr>
<td>Kim, Peter</td>
<td>P35</td>
</tr>
<tr>
<td>Kim, Sooane</td>
<td>P46</td>
</tr>
<tr>
<td>Kindig, Jeff</td>
<td>P26</td>
</tr>
<tr>
<td>Kines, Rhonda</td>
<td>P43</td>
</tr>
<tr>
<td>King, C R.</td>
<td>S20</td>
</tr>
<tr>
<td>Klein, Jerome</td>
<td>S27</td>
</tr>
<tr>
<td>Klein, Nicola P.</td>
<td>S26, S27, S28</td>
</tr>
<tr>
<td>Knapp, Elisabeth</td>
<td>P34</td>
</tr>
<tr>
<td>Knobel, Vincent</td>
<td>S5</td>
</tr>
<tr>
<td>Knowlton, Jessica</td>
<td>S4, P13</td>
</tr>
<tr>
<td>Kondiah, Kulsum</td>
<td>P60</td>
</tr>
<tr>
<td>Koski, Gary K.</td>
<td>P30</td>
</tr>
<tr>
<td>Kotloff, Karen</td>
<td>P2</td>
</tr>
<tr>
<td>Krishnappa, Arthi</td>
<td>S10</td>
</tr>
<tr>
<td>Kwindt, Lisan T.</td>
<td>S7</td>
</tr>
<tr>
<td>LaForce, M.</td>
<td>P36</td>
</tr>
<tr>
<td>Lamprey, Helena</td>
<td>P59</td>
</tr>
<tr>
<td>Lankaraman, Karthikbabu M.</td>
<td>S1</td>
</tr>
<tr>
<td>LaForce, E. Marc</td>
<td>8</td>
</tr>
<tr>
<td>LaRussa, Phil</td>
<td>S27</td>
</tr>
<tr>
<td>La, Shao</td>
<td>P14</td>
</tr>
<tr>
<td>Law, Barbara</td>
<td>P50</td>
</tr>
<tr>
<td>Lay, Marla</td>
<td>S5</td>
</tr>
<tr>
<td>Lee, Janelle</td>
<td>S16</td>
</tr>
<tr>
<td>Lee, Min-Shi</td>
<td>P33</td>
</tr>
<tr>
<td>Lee, Sung H.</td>
<td>P16</td>
</tr>
<tr>
<td>Leite, Luciana C. C.</td>
<td>P62</td>
</tr>
<tr>
<td>Levine, Nancy</td>
<td>S29</td>
</tr>
<tr>
<td>Lewis, Edwin</td>
<td>S28</td>
</tr>
<tr>
<td>Lewis, George</td>
<td>P24</td>
</tr>
<tr>
<td>Lewis, Ned</td>
<td>S26</td>
</tr>
<tr>
<td>Li, Guangxing</td>
<td>S6</td>
</tr>
<tr>
<td>Li, Yan</td>
<td>S7</td>
</tr>
<tr>
<td>Liang, Xiaoping</td>
<td>P35, S12</td>
</tr>
<tr>
<td>Lillehoj, Hyun S</td>
<td>S6, P16, P29</td>
</tr>
<tr>
<td>Limbach, Keith</td>
<td>S20</td>
</tr>
<tr>
<td>Lin, Reyin</td>
<td>P33</td>
</tr>
<tr>
<td>Lin, Tzou-Yien</td>
<td>P33</td>
</tr>
<tr>
<td>Lind, Cathleen</td>
<td>P5</td>
</tr>
<tr>
<td>Linke-Parvinen, Anna</td>
<td>S34</td>
</tr>
<tr>
<td>Linton, Olivia</td>
<td>S10</td>
</tr>
<tr>
<td>Liou, Guan-Yuan</td>
<td>P33</td>
</tr>
<tr>
<td>Livingston, Brian</td>
<td>S22</td>
</tr>
<tr>
<td>Lockett, Anthony</td>
<td>P10</td>
</tr>
<tr>
<td>Lottenbach, Kathleen</td>
<td>S14</td>
</tr>
<tr>
<td>Loughlin, Anita M.</td>
<td>P38, S27</td>
</tr>
<tr>
<td>Lu, Shan</td>
<td>P14</td>
</tr>
<tr>
<td>Lubega, George</td>
<td>P34</td>
</tr>
<tr>
<td>Luo, Shu-Ting</td>
<td>P33</td>
</tr>
<tr>
<td>Luurtjes, Willem</td>
<td>P22</td>
</tr>
<tr>
<td>Lyon, Mandie</td>
<td>S12</td>
</tr>
<tr>
<td>Ma, Dexing</td>
<td>S6</td>
</tr>
<tr>
<td>Maciel, Milton</td>
<td>P19</td>
</tr>
<tr>
<td>Maiolatesi, Santina</td>
<td>S20</td>
</tr>
<tr>
<td>Makino, Shinji</td>
<td>P12</td>
</tr>
<tr>
<td>Manasan, Rachel</td>
<td>P38</td>
</tr>
<tr>
<td>Manger, Walter</td>
<td>S12</td>
</tr>
<tr>
<td>Mank, Nicholas J.</td>
<td>P13, S32, S4</td>
</tr>
<tr>
<td>Manermaa, Leni</td>
<td>S34</td>
</tr>
<tr>
<td>Marchant, Colin D.</td>
<td>P38, S27</td>
</tr>
<tr>
<td>Margolis, Harold S.</td>
<td>6</td>
</tr>
<tr>
<td>Marchetti, E.</td>
<td>P36</td>
</tr>
<tr>
<td>Martin, Shannon</td>
<td>P37, P5</td>
</tr>
<tr>
<td>Mast, T. Christopher</td>
<td>P31</td>
</tr>
<tr>
<td>McCormick, Sarah</td>
<td>S30</td>
</tr>
<tr>
<td>McKenna, Philip</td>
<td>P35</td>
</tr>
<tr>
<td>McShane, Helen</td>
<td>17, P56</td>
</tr>
<tr>
<td>Mehlman, Martin I.</td>
<td>P28</td>
</tr>
<tr>
<td>Mendicino, Michael</td>
<td>P44</td>
</tr>
<tr>
<td>Mendoza-Silveiras, Jose</td>
<td>S20</td>
</tr>
<tr>
<td>Mertsola, Jussi</td>
<td>S34</td>
</tr>
<tr>
<td>Mertsola, Jussi</td>
<td>S34</td>
</tr>
<tr>
<td>Messenger, Sharon L.</td>
<td>P51</td>
</tr>
<tr>
<td>Metcalfe, Karen</td>
<td>P6</td>
</tr>
<tr>
<td>Miller, Michael</td>
<td>P35</td>
</tr>
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<td>Milley, Bob</td>
<td>P20</td>
</tr>
<tr>
<td>Milstien, Julie B.</td>
<td>P2</td>
</tr>
<tr>
<td>Mitchell, Robert</td>
<td>P48</td>
</tr>
<tr>
<td>Miyaji, Eliane N.</td>
<td>P62</td>
</tr>
<tr>
<td>Mocca, Brian</td>
<td>P36</td>
</tr>
<tr>
<td>Mogg, Robin</td>
<td>S12</td>
</tr>
<tr>
<td>Moise, Leonard</td>
<td>P39, P40, S18</td>
</tr>
<tr>
<td>Monahan, Jeff</td>
<td>P44</td>
</tr>
<tr>
<td>Monath, Tom</td>
<td>S5</td>
</tr>
<tr>
<td>Moore, Dorothy</td>
<td>P50</td>
</tr>
<tr>
<td>Moran, John J. M.</td>
<td>P32</td>
</tr>
<tr>
<td>Morgan, Douglas</td>
<td>P52</td>
</tr>
<tr>
<td>Moss, Ronald</td>
<td>S19, S23</td>
</tr>
<tr>
<td>Murphy, Andrew</td>
<td>P26</td>
</tr>
<tr>
<td>Murtada, Taha</td>
<td>P18</td>
</tr>
<tr>
<td>Musey, Luwy</td>
<td>S12</td>
</tr>
<tr>
<td>Muthumani, Gowtham</td>
<td>S1</td>
</tr>
</tbody>
</table>
### Author Index

*(primary authors are in **bold** type)*

<table>
<thead>
<tr>
<th>Author</th>
<th>Presentation Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muthumani, Karuppiah</td>
<td>S1</td>
</tr>
<tr>
<td>Myc, Andrzej</td>
<td>P13, S32, S4</td>
</tr>
<tr>
<td>Mytle, Nutan</td>
<td>S4</td>
</tr>
<tr>
<td>Nahas, Debbie</td>
<td>P35</td>
</tr>
<tr>
<td>Namayananja, Monica</td>
<td>P34</td>
</tr>
<tr>
<td>Nanteza, Ann</td>
<td>P34</td>
</tr>
<tr>
<td>Narayanan, Krishna</td>
<td>P12</td>
</tr>
<tr>
<td>Nardin, Elizabeth</td>
<td>P48</td>
</tr>
<tr>
<td>Newman, Frances</td>
<td>S9</td>
</tr>
<tr>
<td>Newman, Lindsay</td>
<td>S8</td>
</tr>
<tr>
<td>Nicewonger, John</td>
<td>P43</td>
</tr>
<tr>
<td>Niemuth, Nancy</td>
<td>P6</td>
</tr>
<tr>
<td>O’Byrne, Megan M.</td>
<td>S33</td>
</tr>
<tr>
<td>Ockenhouse, Christian</td>
<td>S20</td>
</tr>
<tr>
<td>Offit, Paul A.</td>
<td>S5</td>
</tr>
<tr>
<td>Oduotola, Oluwasimi A</td>
<td>P56</td>
</tr>
<tr>
<td>Okoko, B</td>
<td>P36</td>
</tr>
<tr>
<td>Oliveira, Maria L. S.</td>
<td>P62</td>
</tr>
<tr>
<td>Omer, Saad B.</td>
<td>P53</td>
</tr>
<tr>
<td>Onah, Denis N.</td>
<td>P57</td>
</tr>
<tr>
<td>Ostrovsky, Andrey O.</td>
<td>P38</td>
</tr>
<tr>
<td>Ota, Martin O.</td>
<td>P56</td>
</tr>
<tr>
<td>Otsuki, Hitoshi</td>
<td>P61</td>
</tr>
<tr>
<td>Ortinger, Elizabeth</td>
<td>P35</td>
</tr>
<tr>
<td>Ovsyannikova, Inna G.</td>
<td>S33</td>
</tr>
<tr>
<td>Owiafe, Patrick K.</td>
<td>P56</td>
</tr>
<tr>
<td>Owolabi, Olumuyiwa A.</td>
<td>P56</td>
</tr>
<tr>
<td>Pages, M.</td>
<td>P16</td>
</tr>
<tr>
<td>Pahud, Barbara A.</td>
<td>P51</td>
</tr>
<tr>
<td>Pal, Ranajit</td>
<td>P24</td>
</tr>
<tr>
<td>Paniagua, Margarita</td>
<td>P52</td>
</tr>
<tr>
<td>Pankratz, V S.</td>
<td>S33</td>
</tr>
<tr>
<td>Parashar, Umesh</td>
<td>2</td>
</tr>
<tr>
<td>Parekh, Falgunee</td>
<td>S20</td>
</tr>
<tr>
<td>Parker, Michael</td>
<td>P37, P5</td>
</tr>
<tr>
<td>Pascal, Ecaterina</td>
<td>P54</td>
</tr>
<tr>
<td>Patel, Ekta</td>
<td>P49</td>
</tr>
<tr>
<td>Paterson, Noelle B.</td>
<td>S20</td>
</tr>
<tr>
<td>Paul, Vinod K.</td>
<td>P63</td>
</tr>
<tr>
<td>Pavia, Andrew</td>
<td>S29</td>
</tr>
<tr>
<td>Peters, Clarence J.</td>
<td>14</td>
</tr>
<tr>
<td>Payne, Angela</td>
<td>P31</td>
</tr>
<tr>
<td>Pelton, Stephen I.</td>
<td>P38</td>
</tr>
<tr>
<td>Penny, Mary</td>
<td>P31</td>
</tr>
<tr>
<td>Pessi, Antonello</td>
<td>P12</td>
</tr>
<tr>
<td>Peters, C. J.</td>
<td>S7</td>
</tr>
<tr>
<td>Petric, Martin</td>
<td>P44</td>
</tr>
<tr>
<td>Phelps, Carol</td>
<td>P44</td>
</tr>
<tr>
<td>Picking, William D.</td>
<td>P19</td>
</tr>
<tr>
<td>Piedra, Pedro</td>
<td>S8</td>
</tr>
<tr>
<td>Plowe, Christopher V.</td>
<td>S21</td>
</tr>
<tr>
<td>Pillai, Shreekumar</td>
<td>P18</td>
</tr>
<tr>
<td>Poland, Gregory A.</td>
<td>S33</td>
</tr>
<tr>
<td>Polejaeva, Irina</td>
<td>P44</td>
</tr>
<tr>
<td>Porter, Aimee I.</td>
<td>P11</td>
</tr>
<tr>
<td>Preziosi, M P.</td>
<td>S36</td>
</tr>
<tr>
<td>Price, Albert</td>
<td>P48</td>
</tr>
<tr>
<td>Pritchard, Roger</td>
<td>P34</td>
</tr>
<tr>
<td>Przysecki, Craig</td>
<td>P31</td>
</tr>
<tr>
<td>Pulkkinen, Markku</td>
<td>S34</td>
</tr>
<tr>
<td>Ramakrishnan, Guna</td>
<td>S34</td>
</tr>
<tr>
<td>Ramsoondar, Jag</td>
<td>P44</td>
</tr>
<tr>
<td>Raqib, R.</td>
<td>P53, S17</td>
</tr>
<tr>
<td>Ray, Pratima</td>
<td>P63</td>
</tr>
<tr>
<td>Ray, Paula</td>
<td>S26</td>
</tr>
<tr>
<td>Regis, David</td>
<td>S20</td>
</tr>
<tr>
<td>Ren, Xiaofeng</td>
<td>S6</td>
</tr>
<tr>
<td>Reyes, Sharina</td>
<td>S20</td>
</tr>
<tr>
<td>Ribalco, Vladimir</td>
<td>P54</td>
</tr>
<tr>
<td>Richards, Chesley</td>
<td>S29</td>
</tr>
<tr>
<td>Richards, Michelle</td>
<td>S22</td>
</tr>
<tr>
<td>Rich, Thomas L.</td>
<td>S20</td>
</tr>
<tr>
<td>Rohde, Kalynn A</td>
<td>P32</td>
</tr>
<tr>
<td>Rolland, Alain</td>
<td>S19, S23</td>
</tr>
<tr>
<td>Roos, David S</td>
<td>20</td>
</tr>
<tr>
<td>Roos, Leslie L.</td>
<td>S15</td>
</tr>
<tr>
<td>Rosenthal, Ken S</td>
<td>P30</td>
</tr>
<tr>
<td>Roth, Samantha</td>
<td>P26</td>
</tr>
<tr>
<td>Rots, Nynke Y.</td>
<td>P22</td>
</tr>
<tr>
<td>Ray, E</td>
<td>S17</td>
</tr>
<tr>
<td>Ray, E</td>
<td>S10</td>
</tr>
<tr>
<td>Sadoff, Jerald C.</td>
<td>S24</td>
</tr>
<tr>
<td>Salisbury, David M.</td>
<td>1</td>
</tr>
<tr>
<td>Salmon, Daniel</td>
<td>S29</td>
</tr>
<tr>
<td>Santos, Jaime A.</td>
<td>P46</td>
</tr>
<tr>
<td>Sauvé, Laura J.</td>
<td>S50</td>
</tr>
<tr>
<td>Schechter, Robert</td>
<td>P27</td>
</tr>
<tr>
<td>Scheifele, David</td>
<td>S21</td>
</tr>
<tr>
<td>Schiller, John</td>
<td>P43</td>
</tr>
<tr>
<td>Schmaljohn, Connie S.</td>
<td>S22</td>
</tr>
<tr>
<td>Schmid, D S</td>
<td>S51</td>
</tr>
<tr>
<td>Schmidt, Johannes</td>
<td>S26</td>
</tr>
<tr>
<td>Schmink, Susanna</td>
<td>P27</td>
</tr>
<tr>
<td>Schoedel, Florian</td>
<td>S12</td>
</tr>
<tr>
<td>Schwartz, Benjamin</td>
<td>S29</td>
</tr>
<tr>
<td>Scott, Daniel</td>
<td>S21</td>
</tr>
<tr>
<td>Scountzou, Ioanna</td>
<td>P45</td>
</tr>
<tr>
<td>Sedegah, Martha</td>
<td>S20</td>
</tr>
<tr>
<td>Selling, Bernard</td>
<td>P9</td>
</tr>
<tr>
<td>Shaikh-Lesko, Ridvana B.</td>
<td>P51</td>
</tr>
<tr>
<td>Shamsuzzaman, Sohel</td>
<td>P65</td>
</tr>
<tr>
<td>Sharma, Sumit</td>
<td>P65</td>
</tr>
<tr>
<td>Shaw, Alan</td>
<td>S10, S11</td>
</tr>
<tr>
<td>Shaw, Eric E.</td>
<td>S12</td>
</tr>
<tr>
<td>Shearer, Jeffrey</td>
<td>P6</td>
</tr>
<tr>
<td>Shellock, Devon J.</td>
<td>S1</td>
</tr>
<tr>
<td>Sheldon, Eric</td>
<td>S3, S5</td>
</tr>
</tbody>
</table>
## Author Index

*(primary authors are in **bold** type)*

<table>
<thead>
<tr>
<th>Author</th>
<th>Presentation Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiver, John</td>
<td>P35</td>
</tr>
<tr>
<td>Shrestha, Sundar S.</td>
<td>P28</td>
</tr>
<tr>
<td>Simmons, Cameron</td>
<td>S13</td>
</tr>
<tr>
<td>Simon, Jakub K.</td>
<td>P19</td>
</tr>
<tr>
<td>Simon, Paul M.</td>
<td>P9</td>
</tr>
<tr>
<td>Singh, Shree R.</td>
<td>P18</td>
</tr>
<tr>
<td>Sisti, Maggie</td>
<td>S5</td>
</tr>
<tr>
<td>Skillen, Elizabeth</td>
<td>S29</td>
</tr>
<tr>
<td>Skowrons, Danuta M.</td>
<td>S15, S7</td>
</tr>
<tr>
<td>Slade, Barbara</td>
<td>S29</td>
</tr>
<tr>
<td>Small, Cherie-Lee</td>
<td>S30</td>
</tr>
<tr>
<td>Smith, Kathryn</td>
<td>S20</td>
</tr>
<tr>
<td>Smith, Larry R.</td>
<td>S19, S23</td>
</tr>
<tr>
<td>Snider, Dixie</td>
<td>S29</td>
</tr>
<tr>
<td>Sofronicie, Vasile</td>
<td>P54</td>
</tr>
<tr>
<td>Sohn, Young M.</td>
<td>P7</td>
</tr>
<tr>
<td>Soilia, Maaria</td>
<td>S34</td>
</tr>
<tr>
<td>Soisson, Loraine</td>
<td>S20</td>
</tr>
<tr>
<td>Song, Langzhou</td>
<td>S11</td>
</tr>
<tr>
<td>Sow, S</td>
<td>P36</td>
</tr>
<tr>
<td>Sow, Samba O.</td>
<td>P2</td>
</tr>
<tr>
<td>Sparks, Robert</td>
<td>S27</td>
</tr>
<tr>
<td>Spencer, Charles</td>
<td>S14</td>
</tr>
<tr>
<td>Spiniu, Constantin</td>
<td>P54</td>
</tr>
<tr>
<td>Spring, Michelle</td>
<td>S20</td>
</tr>
<tr>
<td>Stanley, Jamie</td>
<td>S14</td>
</tr>
<tr>
<td>Steinbeiss, Victoria</td>
<td>S20</td>
</tr>
<tr>
<td>Steinhoff, Mark C.</td>
<td>P53, S17</td>
</tr>
<tr>
<td>Steitz, Julia</td>
<td>P57</td>
</tr>
<tr>
<td>Strauss, Walter</td>
<td>P31</td>
</tr>
<tr>
<td>Subbarao, Kanta</td>
<td>S13</td>
</tr>
<tr>
<td>Suo, Xun</td>
<td>P29</td>
</tr>
<tr>
<td>Sutcliffe, Joyce</td>
<td>P13, S32, S4</td>
</tr>
<tr>
<td>Sztein, Marcelo B.</td>
<td>P19</td>
</tr>
<tr>
<td>Tachibana, Mayumi</td>
<td>P61</td>
</tr>
<tr>
<td>Tamminga, Cindy</td>
<td>S20</td>
</tr>
<tr>
<td>Tandan, Jay B.</td>
<td>P7</td>
</tr>
<tr>
<td>Tapia, M</td>
<td>P36</td>
</tr>
<tr>
<td>Taylor, David N.</td>
<td>S10, S11</td>
</tr>
<tr>
<td>Taylor, Patricia R.</td>
<td>P30</td>
</tr>
<tr>
<td>Thomas, Lynn</td>
<td>S8</td>
</tr>
<tr>
<td>Thongkukiatkul, Amporn</td>
<td>P61</td>
</tr>
<tr>
<td>Tobias, Joshua</td>
<td>P3</td>
</tr>
<tr>
<td>Torii, Motomi</td>
<td>P61</td>
</tr>
<tr>
<td>Toye, Phil</td>
<td>P49</td>
</tr>
<tr>
<td>Trenor, John J.</td>
<td>S11, S12</td>
</tr>
<tr>
<td>Tsuboi, Takafuli</td>
<td>P61</td>
</tr>
<tr>
<td>Turley, Christine</td>
<td>S10</td>
</tr>
<tr>
<td>Tussey, Lynda</td>
<td>S10, S11</td>
</tr>
<tr>
<td>Valderama A, Augusto</td>
<td>P57</td>
</tr>
<tr>
<td>Van Caeselee, Paul</td>
<td>S15</td>
</tr>
<tr>
<td>Van Der Meeren, Olivier</td>
<td>S34</td>
</tr>
<tr>
<td>van der Zeijst, Ben A. M.</td>
<td>P22</td>
</tr>
<tr>
<td>Vance, Amy</td>
<td>P44</td>
</tr>
<tr>
<td>Vassar, Michelle</td>
<td>P6</td>
</tr>
<tr>
<td>Vaudry, Wendy</td>
<td>P50</td>
</tr>
<tr>
<td>Vaught, Todd</td>
<td>P44</td>
</tr>
<tr>
<td>Veenstra, David L.</td>
<td>P15</td>
</tr>
<tr>
<td>Vierkant, Robert A.</td>
<td>S33</td>
</tr>
<tr>
<td>Vig, Komal</td>
<td>P18</td>
</tr>
<tr>
<td>Viviani, S</td>
<td>P36</td>
</tr>
<tr>
<td>Vranceau-Benes, Angelia</td>
<td>P54</td>
</tr>
<tr>
<td>Wahid, Rezwan</td>
<td>P19</td>
</tr>
<tr>
<td>Wallace, Gregory S.</td>
<td>P28</td>
</tr>
<tr>
<td>Walld, Randy</td>
<td>S15</td>
</tr>
<tr>
<td>Wang, Hua</td>
<td>P14</td>
</tr>
<tr>
<td>Wang, Shixia</td>
<td>P14</td>
</tr>
<tr>
<td>Warner, John F.</td>
<td>S5</td>
</tr>
<tr>
<td>Wasson, Lucinda</td>
<td>P27</td>
</tr>
<tr>
<td>Waters, W. Ray</td>
<td>P18</td>
</tr>
<tr>
<td>Webby, Richard J</td>
<td>12</td>
</tr>
<tr>
<td>Weiner, David B.</td>
<td>S1</td>
</tr>
<tr>
<td>Weintraub, Eric</td>
<td>S25</td>
</tr>
<tr>
<td>Welebob, Carolee</td>
<td>S12</td>
</tr>
<tr>
<td>Wells, Kevin</td>
<td>P44</td>
</tr>
<tr>
<td>Wertz, Nancy</td>
<td>P44</td>
</tr>
<tr>
<td>White, Jesse</td>
<td>P26</td>
</tr>
<tr>
<td>Wichit, Sineewanlaya</td>
<td>P58</td>
</tr>
<tr>
<td>Wiedmann, Richard</td>
<td>S12</td>
</tr>
<tr>
<td>Wijmenga-Monsuur, Arienke J.</td>
<td>P22</td>
</tr>
<tr>
<td>Williams, Frank</td>
<td>S20</td>
</tr>
<tr>
<td>Winter, Anne-Luise</td>
<td>S7</td>
</tr>
<tr>
<td>Winter, Kathleen</td>
<td>P27</td>
</tr>
<tr>
<td>Winther, Birgit</td>
<td>S12</td>
</tr>
<tr>
<td>Wloch, Mary</td>
<td>S19, S23</td>
</tr>
<tr>
<td>Wolchok, Jedd D.</td>
<td>11</td>
</tr>
<tr>
<td>Won, Sungyong</td>
<td>P12</td>
</tr>
<tr>
<td>Worku, Shewangizaw</td>
<td>S14</td>
</tr>
<tr>
<td>Wu, Chengwei</td>
<td>P35</td>
</tr>
<tr>
<td>Xing, Zhou</td>
<td>S30</td>
</tr>
<tr>
<td>Xu, Guifang</td>
<td>P14</td>
</tr>
<tr>
<td>Xu, Jin</td>
<td>P55</td>
</tr>
<tr>
<td>Yalda, Dorice</td>
<td>P20</td>
</tr>
<tr>
<td>Yan, Jian</td>
<td>S1</td>
</tr>
<tr>
<td>Yan, Lin</td>
<td>P1</td>
</tr>
<tr>
<td>Yu, Lihua</td>
<td>P8</td>
</tr>
<tr>
<td>Yusibov, Vidadi</td>
<td>P34</td>
</tr>
<tr>
<td>Zaman, K</td>
<td>P53</td>
</tr>
<tr>
<td>Zaman, K</td>
<td>S17</td>
</tr>
<tr>
<td>Zhang, Chunhua</td>
<td>P14</td>
</tr>
<tr>
<td>Zhang, Lu</td>
<td>P14</td>
</tr>
<tr>
<td>Zhuang, Ling</td>
<td>P14</td>
</tr>
<tr>
<td>Zimmerman, Daniel H.</td>
<td>P30</td>
</tr>
</tbody>
</table>
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