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Conference Overview

The remarkable pace of biotechnology discovery is continuing unabated. New cytokines are identified, immune regulatory pathways are unraveled, promising adjuvants are reported, and investigational products are revealed to have high degrees of protection for humans against viral diseases not yet vaccine preventable. The tools of vaccination are also being applied therapeutically for various cancers and chronic conditions.

The Annual Conference on Vaccine Research provides high-quality, current reports of scientific progress featured in invited presentations, submitted posters, and oral abstracts. The disparate fields covered in both human and veterinary vaccinology encourage valuable cross-fertilization of ideas and approaches among researchers otherwise focused on specific diseases or methods.

The Conference has become the largest scientific meeting devoted exclusively to research on vaccines and associated technologies for disease prevention and treatment through immunization. The Eleventh Annual Conference promises to maintain this tradition as the premier venue for cutting edge topics and issues. International experts will lead seminars and panel discussions on topical areas of basic immunology, product development, clinical testing, regulation, and other aspects of vaccine research. Opportunities for networking and scientific collaboration critical to advancing vaccine science and development will be available through audience discussions, meet the experts breakfast sessions, poster presentations, sponsored exhibits, evening ceremonies, and receptions.

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

Symposium Objectives

Keynote Address

- Describe the link between vaccination, health, and economic well-being

Innate Immunity, Lymph Nodes in a Tube and Genomics: What They May be Doing for Vaccine Development

- Review information on the adjuvanting properties of CpG ODN
- Discuss methods to evaluate formulations before clinical trials
- Review how comparative genomics of pathogens can be used to inform with respect to the identification of targets for vaccine development
- Discuss the elimination of colonization as a goal of vaccination and the technology that makes colonization an attractive target for vaccine development

Mary Lou Clements-Mann Memorial Lecture in Vaccine Sciences

- Recognize the roadblocks to development of an HIV vaccine and review the plans for studies to attempt to overcome those roadblocks

Cutaneous Vaccination and the Global Challenge

- Explain the different (human) dendritic cell subsets in the skin (their localization, phenotype and functions) and how this knowledge may be employed in the design of novel vaccination strategies
- Describe the history, clinical effect, and range of vaccines delivered by classical intradermal vaccination using traditional devices, as well as newer devices
- Review different ways of delivering vaccines across the skin
- Explain how cutaneous immunization could facilitate vaccination, particularly in developing countries, and the scientific and technical challenges associated with this approach

Adjuvants: Past, Present, and Future

- Discuss the types of adjuvants that are used for vaccines, the clinical safety experience with vaccine adjuvants, and the preclinical safety requirements for clinical testing of vaccines containing adjuvants
- Review molecular and cellular events associated with the intramuscular administration of different classes of vaccine adjuvants
- Describe the modern state-of-the-art approaches to vaccine development

- Review how activation of the immune system through Toll-like receptors, such as TLR9 with CpG DNA, can lead to enhanced humoral and cell-mediated immune responses to vaccines
- Discuss members of the novel class of saponin based adjuvants focusing on those which are advancing through clinical development

Universal Vaccination Against Influenza

- Review current literature regarding the "downstream" impact of preventing influenza infections in young children
- Discuss concepts of herd immunity and how to model and measure indicators of such
- Review existing economic evidence regarding the cost-effectiveness of influenza vaccination of various population subgroups and consider this evidence in the context of a policy for universal vaccination
- Review immunization delivery issues under a scenario of universal influenza immunization, including the challenges and benefits of expanding influenza immunization in primary care offices
- Discuss cross-reactive immune response to influenza

Recently Licensed Vaccines

- Describe the epidemiology of genital HPV infections and the potential for prevention of HPV-related cancers and genital warts through vaccination
- Discuss the rationale for immunizing children against rotavirus and the basis upon which current vaccine recommendation vaccines have been formulated
- Review meningococcal conjugate vaccines, focusing on issues surround recent licensure and use of these vaccines in the U.S.
- Describe the epidemiology, pathogenesis, and current thinking and practice regarding the treatment of herpes zoster and postherpetic neuralgia and review of the Shingles Prevention Study and the current recommendations for the use of a varicella-zoster virus vaccine

Acknowledgments (as of April 10, 2008)

This conference is supported, in part, through unrestricted educational grants from:

- Acambis
- Aeras Global TB Vaccine Foundation
- Becton Dickinson
- DynPort Vaccine Company
- EpiVax, Inc.
- Fondation Mèrieux
- GlaxoSmithKline
- LigoCyte Pharmaceuticals, Inc.
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- Wyeth Pharamceuticals

Eleventh Annual Conference

NFID recognizes the following individuals for their support and contributions in planning this event

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**Speakers and presentations subject to change*

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The intent of this disclosure is not to prevent a speaker or Scientific Program Committee member with a significant 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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Steitz, Julia
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De Gregorio, Ennio	Novartis Vaccines	A, C
De Groot, Anne	EpiVax	A, D
De Serres, Gaston	GSK, Merck	B
dela Cruz, Tracy	Dynavax Technologies	A, C
Drane, Debbie P.	CSL Limited	C

(continued)

Disclosure Index

*(Remaining **Presenters** continued)*

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Gaglani, Manjusha	MedImmune, Novartis, GSK, sanofi pasteur	B, E
Gorse, Geoffrey	sanofi pasteur	E
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Hartikka, Jukka	Vical Incorporated	A, C
Haynes, Barton F.	Becton Dickinson	B
Higgins, Debbie	Dynavax Technologies	A, C
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Koutsky, Laura A.	Merck	B
Krieg, Arthur	Coley, GSK, Merck, Novartis, Dynavax	A, C, G
Livengood, Jill	Inviragen	C
McNeil, Shelly	GSK, Merck Frosst, sanofi pasteur	B, E
Moise, Leonard	EpiVax, Inc.	A, C
Ottinger, Elizabeth	Merck	C
Otuonye, Ngozi	Nigerian Institute of Medical Research	C, E
Oxman, Michael N.	Merck, GSK	A, B
Pancari, Greg	Merck	A, C
Patel, Shital	GSK	B
Piedra, Pedro	MedImmune, sanofi pasteur, Novartis, Merck, Roche	B, E
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Swoyer, Ryan	Merck	A, C
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Taylor, Kimberly	Nabi Biopharmaceuticals	A, C
Tobin, Gregory	Biological Mimetics, Inc.	C
van Alphen, Loek	ImSaVac technologies	A
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Warren, William	VaxDesign Corp.	A, C, E
Weniger, Bruce G.	Pfizer, Vaxgen	A
Weiser, Jeffrey N.	Merck, GSK	E, G
Weniger, Bruce A.	Pfizer, Vaxgen	A
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Siber, George R.	Wyeth, Genocea BioSciences, MedImmune	A, C, G
Weniger, Bruce G.	Pfizer, Vaxgen	A

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Label	Relationship
A	I have stocks, stock options, and/or bond holdings in this company
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C	I am employed by this company, or it employs a member of my immediate family
D	I or a member of my immediate family own or is a partner in this company
E	I or a member of my immediate family receive consulting fees, honoraria, paid meeting registration fees, paid travel, speaking fees, or other financial compensation from this company
F	I or a member of my immediate family hold a nonrenumerative position of influence with this company such as officer, board member, trustee, or public spokesperson.
G	I or a member of my immediate hold a patent for and/or receive royalties from this company's product

General Information

Americans with Disabilities Act

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 **Grand 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
Baltimore, Maryland 21202
(410) 385-3000

Continuing Education

Continuing Medical Education Accreditation

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 17 *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 a maximum of 17 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, please note the following:

1. Complete and return the Continuing Education and Evaluation form to conference staff at the Conference Information Desk, or mail to:

   NFID, Office of CME
   4733 Bethesda Avenue, Suite 750
   Bethesda, MD 20814

2. **FOR NURSES ONLY**: you must also sign in daily in order to receive credit for attendance.

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Exhibit Hall

Visit the Exhibit Hall (Grand Ballroom, Salons 1 - 4) to meet with representatives from companies displaying the latest technologies in vaccine-related products and services. The exhibit hall hours are Monday, May 5, 5:00pm – 7:00pm, and Tuesday, May 6, 7:30am – 1:00pm. A prize drawing will be held on Tuesday, May 6, at 1:15pm. Be sure to get your exhibitor passport stamped by each of the exhibitors and return to the conference registration desk by 1:00pm, Tuesday, May 6, 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 Grand 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 sleeping rooms, session rooms, coffee break area, or in the foyer adjoining the session rooms.

Poster Sessions

Posters will be on display from 10:00am on Monday, May 5 – 10:00am on Wednesday, May 7. Presenters will be at their boards to answer questions and discuss their research during the official poster session on Monday, May 5, 10:00am-11:00am and during the poster reception that day at 5:00p.m. Posters will be located in the Grand Ballroom Foyer.

Press Room

NFID will have a Press Room located in the Bristol Room. 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 Final Program and Abstract Book as part of his/her registration fee. Additional copies, if available, can be purchased for $25. Orders for additional copies will be taken at the Conference Information Desk starting Tuesday, May 6, 2008, 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.**

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, May 4	6:00 p.m. - 8:00 p.m.
Monday, May 5	7:00 a.m. - 5:00 p.m.
Tuesday, May 6	7:00 a.m. - 5:00 p.m.
Wednesday, May 7	7:30 a.m. - noon

Speaker Ready Room and Audiovisual Equipment

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.

Standard session room setup includes a PC, LCD projector, laser pointer, podium microphone, lavaliere microphone, and aisle microphones.

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

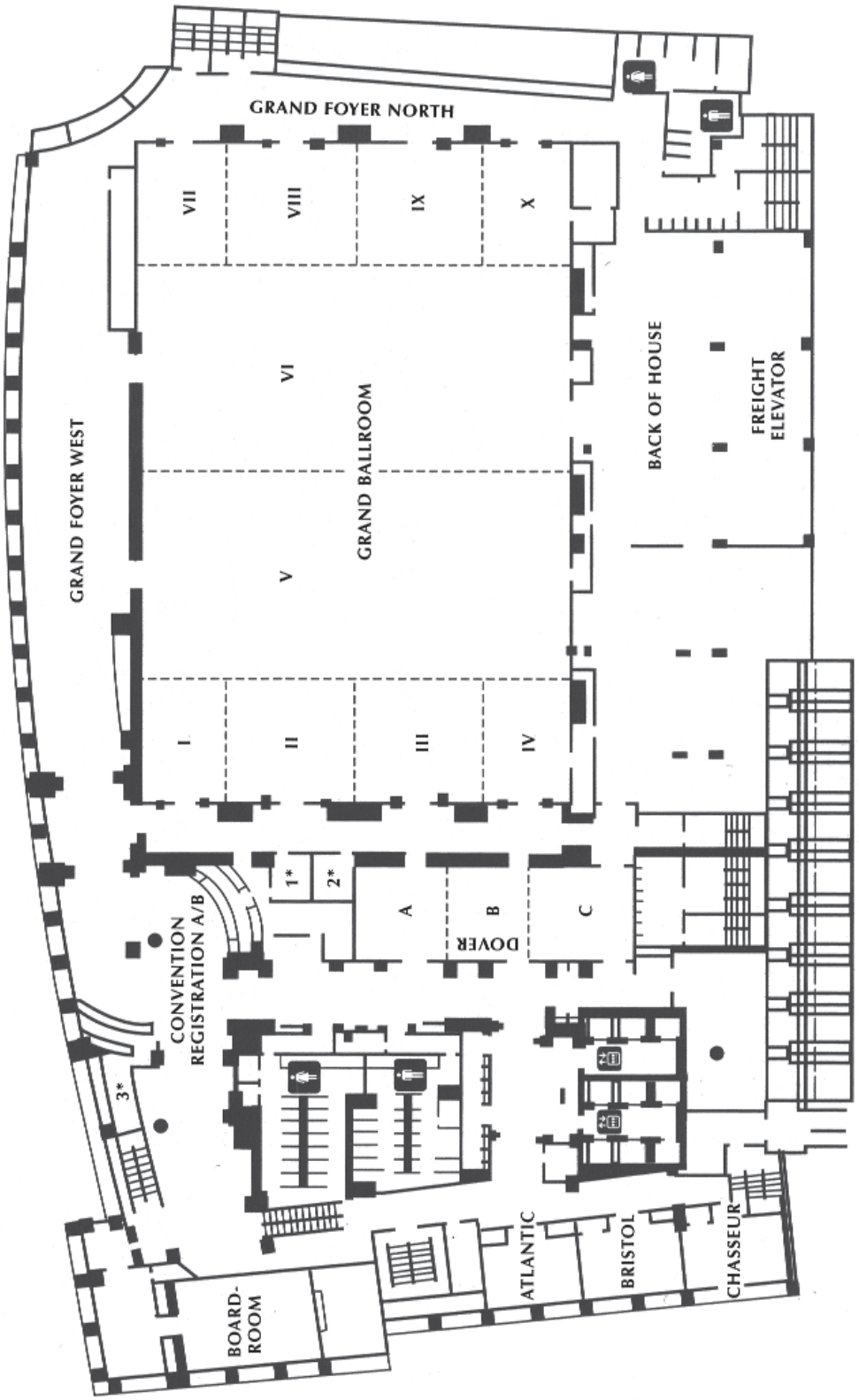
Monday, May 5, 2008

Conference on Vaccine Research Organizing and Scientific Program Committees Meeting
(Closed meeting)
6:00 p.m. – 9:00 p.m., Laurel A & B

Tuesday, May 6, 2008

Albert B. Sabin Vaccine Institute Gold Medal Award Ceremony and Reception
5:00 p.m. – 6:00 p.m., Grand Ballroom Foyer
6:00 p.m. – 7:00 p.m., Grand Ballroom, Salon V

Hotel Floor Plan



Eleventh Annual Conference

Program-at-a-Glance

	Sunday, May 4	Monday, May 5	Tuesday, May 6	Wednesday, May 7
7:00 am		Registration	Registration **Meet the Experts Breakfast Session**	Registration **Meet the Experts Breakfast Session**
7:30 am		Poster Set-up	Continental Breakfast/Exhibits	Continental Breakfast
8:00 am		Continental Breakfast	**Mary Lou Clements-Mann Memorial Lecture**	**Symposium 4:** *Universal Vaccination Against Influenza*
8:30 am		**Welcome and Introductions**		
8:35 am		**Keynote Address**		
9:00 am			Coffee Break/Exhibits	
9:30 am		Coffee Break	**Symposium 2:** *Cutaneous Vaccination and the Global Challenge*	
10:00 am		**Poster Session**		Coffee Break
10:30 am				**Submitted Presentations 5&6**
11:00 am		**Charles Mérieux Award Luncheon**		
11:30 am			***Robert Austrian Memorial Lecture and Luncheon***	
12:00 pm				Lunch (on your own)
1:00 pm		**Symposium 1:** *Innate Immunity, Lymph Nodes in a Tube and Genomics: What They May Be Doing for Vaccine Development*	**Symposium 3:** *Adjuvants: Past, Present, and Future*	**Symposium 5:** *Recently Licensed Vaccines*
3:00 pm		Coffee Break	Coffee Break	***Maurice R. Hilleman Early-stage Career Investigator Award***
3:30 pm		**Submitted Presentations 1&2**	**Submitted Presentations 3&4**	
4:00 pm				Adjournment/Participant Evaluation
5:00 pm		Adjournment **Poster Reception** **Exhibit Hall Opens**	Adjournment **Albert B. Sabin Vaccine Institute Reception**	
6:00 pm	Early Registration		**Presentation of the Albert B. Sabin Gold Medal**	

Final Program

Sunday, May 4, 2008

6:00 p.m. – 8:00 p.m.	Early Registration	*Grand Ballroom Foyer*

Monday, May 5, 2008

7:00 a.m. - 5:00 p.m.	Registration	*Grand Ballroom Foyer*
8:00 a.m.	Poster Set-Up	*Grand Ballroom Foyer*
8:00 a.m.	Continental Breakfast	*Grand Ballroom Foyer*
8:30 a.m.	**Welcome and Introductions** Susan J. Rehm, M.D. *National Foundation for Infectious Diseases* *Bethesda, MD*	*Grand Ballroom Salon V*

Keynote Address CE

Grand Ballroom Salon V

Moderator: Walter A. Orenstein, M.D.
Emory Vaccine Center, Emory University

8:35 a.m.	**1.**	**The Value of Vaccination** David E. Bloom, Ph.D. *Harvard School of Public Health* *Boston, MA*
9:10 a.m.		Questions and Answers
9:30 a.m.		**Coffee Break** *Grand Ballroom Foyer*
10:00 a.m.		**Poster Session** *Grand Ballroom Foyer*
11:00 a.m.		Charles Mérieux Award Luncheon* *Grand Ballroom Salon V* Roger I. Glass, M.D., Ph.D. *National Institutes of Health* *Bethesda, MD*

*This luncheon is made possible through a grant provided by sanofi pasteur

MONDAY, MAY 5, 2008 *(CONTINUED)*

Symposium 1: **Innate Immunity, Lymph Nodes in a Tube and Genomics: What They May Be Doing for Vaccine Development** CE — *Grand Ballroom Salon V*

Moderator: Peter L. Nara, D.V.M., Ph.D.
Biological Mimetics, Inc.

1:00 p.m. **2. Enhancement of AVA Immunogenicity by CpG Oligonucleotides**
Dennis M. Klinman, M.D.
National Institutes of Health
Bethesda, MD

1:25 p.m. Questions and Answers

1:30 p.m. **3. In Vitro Mimicking of the Human Immune System**
William Warren, Ph.D.
VaxDesign Corporation
Orlando, FL

1:55 p.m. Questions and Answers

2:00 p.m. **4. Bacterial Supragenomes and the Distributed Genome Hypothesis: How They Inform with Respect to Vaccine Development**
Garth D. Ehrlich, Ph.D.
Center for Genomic Sciences, Allegheny Singer Research Institute
Drexel University College of Medicine, Allegheny Campus
Pittsburgh, PA

2:25 p.m. Questions and Answers

2:30 p.m. **5. Colonization as a Vaccine Target: Lessons from *Streptococcus pneumoniae***
Jeffrey N. Weiser, M.D.
University of Pennsylvania
Philadelphia, PA

2:55 p.m. Questions and Answers

3:00 p.m. **Coffee Break** — *Grand Ballroom Foyer*

Submitted Presentations 1: (Concurrent Session)

Avian and Pandemic Influenza CE

Grand Ballroom Salon V

Moderator: Georges Peter, M.D.
Warren Alpert Medical School of Brown University

3:30 p.m. **S1** **A Phase I/II, Randomized, Double-blinded Placebo-controlled Trial to the Safety, Reactogenicity, and Immunogenicity of Immunization with Inactivated Subvirion Influenza A/H5N1 Vaccine Administered by the Intradermal or the Intramuscular Route among Healthy Adults**

S. M. Patel, R. L. Atmar, H. El Sahly, T. R. Cate, W. A. Keitel
Baylor College of Medicine, Houston, TX

3:45 p.m. **S2** **A Phase I, Randomized, Double-blind, Placebo-controlled Dose Ranging Clinical Trial of the Safety, Reactogenicity and Immunogenicity of Immunization with Inactivated Vero Cell Culture-derived Influenza A/H5N1 Vaccine Given Alone or with Aluminum Hydroxide to Healthy Young Adults**

W. A. Keitel[1], C. Dekker[2], C. Mink[3], J. Campbell[4], K. Edwards[5], S. Patel[1]
[1]*Baylor College of Medicine, Houston, TX,* [2]*Stanford University, Palo Alto, CA,* [3]*UCLA, Los Angeles, CA,* [4]*University of Maryland, Baltimore, MD,* [5]*Vanderbilt University, Nashville, TN*

4:00 p.m. **S3** **Pandemic Influenza Preparedness: Identification of Serological Epitopes for Use in the Evaluation and Development of Broadly Protective Vaccines**

H. Golding[1], S. Khurana[1], K. Subbarao[2], J. Beigel[2], J. Metcalf[2], A. Lanzavecchia[3]
[1]*CBER, FDA, Bethesda, MD,* [2]*NIAID, NIH, Bethesda, MD,* [3]*Institute for Research in Biomedicine, Bellinzona, Switzerland*

4:15 p.m. **S4** **Immunogenicity and Cross Protective Antibody Responses Among HA Antigens from Different Clades of Highly Pathogenic Avian Influenza H5N1 Viruses**

S. Wang[1], A. Hackett[1], C. Zhang[2], L. Zhang[2], C. Parker[1], A. Zhou[1], J. Li[2], Z. Huang[2], Y. Li[3], S. Lu[1]
[1]*U. Mass. Med. School, Worcester, MA,* [2]*Nanjing Medical University, Nanjing, China,* [3]*National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB, Canada*

4:30 p.m. **S5** **Effective and Inexpensive Influenza Vaccine in Poultry: Dose Escalation and Route of Administration Studies of an Adenovirus-based Influenza A (H5N1) Vaccine in Chicken**

J. Steitz[1], R. Wagner[2], T. Bristol[1], R. Donis[3], A. Gambotto[1]
[1]*Departments of Surgery, Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pittsburgh, PA,* [2]*Division of Laboratory Animal Resources, University of Pittsburgh, Pittsburgh, PA,* [3]*Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA*

4:45 p.m. **S6** **Protective Immune Responses by Multivalent Influenza Virus-like Particles**

S. Kang[1], F. Quan[1], D. Steinhauer[1], C. Huang[1], T. M. Ross[2], R. W. Compans[1]
[1]*Emory University, Atlanta, GA,* [2]*University of Pittsburgh, Pittsburgh, PA*

MONDAY, MAY 5, 2008 *(CONTINUED)*

Submitted Presentations 2: (Concurrent Session)

Novel Vaccines and Vaccine Design CE — *Dover A, B, C*

Moderator: David T. Durack, M.B., D. Phil.
Becton Dickinson Technologies

3:30 p.m. **S7** **Design of a Broadly Protective Influenza Vaccine**
G. J. Tobin, G. Lin, R. V. Bushnell, J. Long, P. L. Nara
Biological Mimetics, Inc., Frederick, MD

3:45 p.m. **S8** **NicVAX®, a Nicotine Conjugate Vaccine, Aids Smokers to Quit Smoking and Stay Quit: Animal and Human Data in Support of a Proposed Mechanism of Action**
A. I. Fattom, M. Hohenboken, M. Kalnik
Nabi Biopharmaceuticals, Rockville, MD

4:00 p.m. **S9** **Improved Immune Responses Following Intradermal Vaccination of a Consensus Influenza DNA Vaccine Using Electroporation in Non-human Primates**
R. Draghia-Akli
VGX Pharmaceuticals, The Woodlands, TX

4:15 p.m. **S10** **Discovery of Naturally Processed Class I HLA Vaccinia Virus T-Cell Epitopes Using Mass Spectrometry: Rational Design of a Multiepitope Smallpox Vaccine**
I. G. Ovsyannikova, K. L. Johnson, C. J. Mason, H. R. Bergen, III, G. A. Poland
Mayo Clinic and Foundation, Rochester, MN

4:30 p.m. **S11** **Epitope-based Immunome-derived Vaccines: A Strategy for Improved Design and Safety**
A. S. De Groot [1], S. Hai [2], L. Moise [3], B. Wu [3], R. W. Malone [3], J. A. McMurry [3], P. Knopf [2], W. Martin [3]
[1] *Institute for Immunology and Informatics, Providence, RI,* [2] *Brown University, Providence, RI,* [3] *EpiVax, Providence, RI*

4:45 p.m. **S12** **Preclinical Evaluation of a Multivalent Powder Vaccine against Anthrax, Botulism, Plague and Staphylococcal Toxic Shock**
J. B. Alarcon [1], J. Huang [1], A. M. D'Souza [1], B. Ford [1], M. Ferriter [1], V. Sullivan [1], *R. Ulrich* [2], *L. A. Smith* [2], *T. J. Smith* [2], *K. Amemiya* [2], *B. K. Dyas* [2], *J. A. Mikszta* [1]
[1] *BD Technologies, RTP, NC,* [2] *USAMRIID, Fort Detrick, MD*

5:00 p.m. **Adjournment and Poster Reception** — *Grand Ballroom Foyer*

5:00 p.m. **Exhibits** — *Grand Ballroom, Salons I-IV*

FINAL PROGRAM

TUESDAY, MAY 6, 2008

7:00 a.m. - 5:00 p.m. Registration — *Grand Ballroom Foyer*

7:00 a.m. - 7:45 a.m. **Meet the Experts Breakfast Session*** — *Falkland Room*

What Comparative Genomics Can Tell Us with Regards to Identifying Vaccine Targets
Garth D. Ehrlich, Ph.D.
Center for Genomic Sciences, Allegheny Singer Research Institute
Drexel University College of Medicine, Allegheny Campus

Which Vaccine Delivery Systems Could Really Improve Vaccine Coverage in Developing Countries?
Martin Friede, Ph.D.
World Health Organization

Pandemic Influenza Preparedness: How to Evaluate and License Novel Vaccines?
Hana Golding, M.D.
U.S. Food and Drug Administration

Vaccine Research and Academic Publishing
Gregory A. Poland, M.D.
Mayo Clinic and Foundation

7:30 a.m. Continental Breakfast/Exhibits — *Grand Ballroom Salon I-IV*

Mary Lou Clements-Mann Memorial Lecture in Vaccine Sciences CE — *Grand Ballroom Salon V*
Moderator: Susan J. Rehm, M.D.
National Foundation for Infectious Diseases

8:00 a.m. **6.** **Finding a Path to HIV-1 Vaccine Development**
Barton F. Haynes, M.D.
Duke Human Vaccine Institute
Duke University Medical Center
Durham, NC

8:40 a.m. Questions and Answers

9:00 a.m. **Coffee Break/Exhibits** — *Grand Ballroom Salons I-IV*

* This session is supported by a grant from Wyeth Pharmaceuticals

TUESDAY, MAY 6, 2008 *(CONTINUED)*

Symposium 2: **Cutaneous Vaccination and the Global Challenge** CE *Grand Ballroom Salon V*

Moderator: Paul-Henri Lambert, M.D.
Centre Medical Universitaire de Genève

9:30 a.m. **7.** **Update on Histology and Immunology of the Skin, for Vaccinologists**
Tanja de Gruijl, Ph.D.
Vrije Universiteit Medical Center
Amsterdam, The Netherlands

9:55 a.m. Questions and Answers

10:00 a.m. **8.** **Past, Present, and Future of Cutaneous Vaccination**
Bruce G. Weniger, M.D., M.P.H.
Centers for Disease Control and Prevention
Atlanta, GA

10:25 a.m. Questions and Answers

10:30 a.m. **9.** **Novel Ways to Breach the Stratum Corneum to Deliver Antigen For Cutaneous Vaccination**
Samir Mitragotri, M.D.
University of California, Santa Barbara
Santa Barbara, CA

10:55 a.m. Questions and Answers

11:00 a.m. **10.** **Meeting the Challenges of Global Immunization with Cutaneous Vaccination**
Martin Friede, Ph.D.
World Health Organization
Geneva, Switzerland

11:25 a.m. Questions and Answers

11:30 a.m. **Robert Austrian Memorial Lecture and Luncheon*** *Grand Ballroom Salon V*
Presentation by: Orin S. Levin, Ph.D.

*This luncheon is supported by a grant from Merck & Co., Inc.

Symposium 3: **Adjuvants: Past, Present, and Future** CE — *Grand Ballroom Salon V*

Moderator: George R. Siber, M.D.
Genocea Biosciences, Inc.

1:00 p.m. **11. Introduction to Adjuvants and Safety**
Carl R. Alving, M.D.
Walter Reed Army Institute of Research
Rockville, MD

1:15 p.m. **12. Innate Immune Response to Vaccine Adjuvants**
Ennio De Gregorio, Ph.D.
Novartis Vaccines and Diagnostics
Siena, Italy

1:25 p.m. Questions and Answers

1:30 p.m. **13. Rational Adjuvants Based Upon the Innate Immune System**
Richard Flavell, Ph.D.
Yale University School of Medicine
New Haven, CT

1:55 p.m. Questions and Answers

2:00 p.m. **14. Toll-Like Receptor 9 Activation with CpG DNA for Enhancing Prophylactic and Therapeutic Vaccines**
Heather L. Davis, Ph.D.
Pfizer Global R&D
Ottawa, Canada

2:25 p.m. Questions and Answers

2:30 p.m. **15. Saponin Based Adjuvants**
Debbie Drane, B.Sc.
CSL Limited
Parkville, Australia

2:55 p.m. Questions and Answers

3:00 p.m. **Coffee Break** — *Grand Ballroom Salon I-IV*

TUESDAY, MAY 6, 2008 *(CONTINUED)*

Submitted Presentations 3: (Concurrent Session)

Immune Response to Influenza Vaccine CE — *Grand Ballroom Salon V*

Moderator: Connie Schmaljohn, Ph.D.
U.S. Army Medical Research Institute of Infectious Diseases

3:30 p.m. **S13 Component Specific Estimates of Influenza Vaccine Effectiveness Based on a Sentinel Physician Network, 2006-07 Season**
D. M. Skowronski [1], T. L. Kwindt [1], G. De Serres [2], J. Dickinson [3], M. Petric [1], K. Fonseca [4], H. Charest [2], N. Bastien [5], Y. Li [5]
[1] *BC Centre for Disease Control, Vancouver, BC, Canada,* [2] *Quebec National Institute of Public Health, Quebec City, QC, Canada,* [3] *University of Calgary, Calgary, AB, Canada,* [4] *Alberta Provincial Laboratory, Edmonton, AB, Canada,* [5] *National Microbiology Laboratory, Winnipeg, MB, Canada*

3:45 p.m. **S14 Cellular and Humoral Immune Responses of Elderly Adults Who Received a High-dose or Standard-dose Influenza Vaccine**
W. H. Chen, S. Bowen, A. S. Cross, R. Edelman, M. Hayes, Y. Lim, M. Reymann, S. Wu, M. B. Sztein, M. F. Pasetti
University of Maryland, Baltimore, MD

4:00 p.m. **S15 Superior Immunogenicity of High Dose Influenza Vaccine in Demographic Subgroups of Elderly Subjects**
G. Gorse [1], A. Falsey [2], E. Yau [3], P. Geoffroy [3]
[1] *Veterans Affairs Medical Center and Saint Louis University, Saint Louis, MO,* [2] *University of Rochester, Rochester, NY,* [3] *sanofi pasteur, Swiftwater, PA*

4:15 p.m. **S16 Effect of Salmeterol on T cell Responses to Influenza Vaccine in Heart Failure Patients**
O. Vardeny [1], N. K. Sweitzer [2], M. R. Johnson [2], W. G. Kao [2], E. M. Winkel [2], J. Moran [1], **M. S. Hayney** [1]
[1] *University of Wisconsin School of Pharmacy, Madison, WI,* [2] *University of Wisconsin School of Medicine and Public Health, Madison, WI*

4:30 p.m. **S17 Distinct HLA, Cytokine, and Cytokine-Receptor Genotypes Influence the Human Antiviral H1- and H3-Specific Antibody Responses to Seasonal Influenza Vaccination**
I. G. Ovsyannikova, R. M. Jacobson, I. H. Haralambieva, N. Dhiman, D. A. Watson, R. A. Vierkant, G. A. Poland
Mayo Clinic College of Medicine, Rochester, MN

4:45 p.m. **S18** **Persistence of Herd Protection to Influenza One Year after Completing the Community-based Vaccination Program in School-age Children in Central Texas**
P. A. Piedra, Sr. [1], M. Gaglani [2], C. A. Kozinetz [1], G. Herschler [2], C. Fewlass [2], D. Harvey [2], W. P. Glezen [1]
[1]*Baylor College of Medicine, Houston, TX,* [2]*Scott & White Memorial Hospital and Clinic, Temple, TX*

Submitted Presentations 4: (Concurrent Session)

Adjuvants and Immunomodulators CE

Dover A, B, C

Moderator: Harriet L. Robinson, Ph.D.
Emory University

3:30 p.m. **S19** **Improvement of Vaccines Against *Bordetella pertussis* by LPS Modifications**
P. van der Ley[1], J. Geurtsen[1], R. Vandebriel[2], G. Akkerman[1], H. J. Hamstra[1], L. Steeghs3, **L. van Alphen**[1], J. Tommassen[3]
[1]*Netherlands Vaccine Institute, Bilthoven, The Netherlands, Netherlands Antilles,* [2]*National Institute for Public Health and Environment, Bilthoven, The Netherlands, Netherlands Antilles,* [3]*University of Utrecht, Utrecht, The Netherlands, Netherlands Antilles*

3:45 p.m. **S20** **Insights into the Mucosal Adjuvant Mechanism of a Soybean Oil Nanoemulsion (SO-NE): Participation of GM1 Ganglioside**
L. P. Blanco, P. E. Makidon, W. L. Hovan, A. Kuchipudi, M. R. Beer, Z. Cao, J. R. Baker, Jr
University of Michigan, Ann Arbor, MI

4:00 p.m. **S21** **A Novel Dose-Sparing Adjuvant for Protein- and Plasmid DNA-Based Influenza Vaccines**
J. Hartikka, V. Bozoukova, C. K. Yang, D. Rusalov, M. Komai, A. Rolland, L. R. Smith
Vical Incorporated, San Diego, CA

4:15 p.m. **S22** **Novel Low Toxicity Plant Adjuvants GG-6 and AH-6 for Assembling Highly Immunogenic Complexes Containing Natural or Recombinant Coccidia (*Eimeria*) Antigens for Vaccine Use**
V. E. Berezin [1], A. P. Bogoyavlenskiy [1], V. P. Tolmacheva [1], S. S. Khudiakova [1], P. G. Alexuk [1], E. S. Omirtaeva [1], G. B. Tustikbaeva [1], I. S. Korotetskiy [1], I. A. Zaitseva [1], R. H. Fetterer [2], R. C. Barfield [2], K. B. Miska [2], M. C. Jenkins [2]
[1]*Institute of Microbiology and Virology, Almaty, Kazakhstan,* [2]*Animal Parasitic Diseases Laboratory USDA-ARS, Beltsville, MD*

4:30 p.m. **S23** **Evaluation of Immune Response and Protective Efficacy of Single Dose Poly (D,L-lactic-co-glycolic acid) Microspheres Based Vaccine Against Experimental Hamster Leptospirosis**
S. M. Faisal, Y. Chang
Cornell University, Ithaca, NY

TUESDAY, MAY 6, 2008 *(CONTINUED)*

4:45 p.m. **S24** **A Novel Nanoemulsion Adjuvant Enhancing the Immune Response from Intranasal Influenza Vaccine in Mice**
T. Hamouda [1], A. Chepurnov [2], N. Mank [2], J. Knowlton [2], T. Chepurnova [2], **J. Sutcliffe** [1], J. R. Baker, Jr. [3]
[1] *NanoBio Corporation, Ann Arbor, MI,* [2] *University of Michigan, Ann Arbor, MI,* [3] *University of Michigan; NanoBio Corporation, Ann Arbor, MI*

5:00 p.m. **Adjournment**

5:00 p.m. **Albert B. Sabin Vaccine Institute Reception** *Grand Ballroom Foyer*

6:00 p.m. **Presentation of the Albert B. Sabin Gold Medal** *Grand Ballroom Salon V*

WEDNESDAY, MAY 7, 2008

7:00 a.m. -12:00 p.m. Registration *Grand Ballroom Foyer*

7:00 a.m. - 7:45 a.m. **Meet the Experts Breakfast Session*** *Falkland Room*

Adjuvants
Carl R. Alving, M.D.
Walter Reed Army Institute of Research

Meningococcal Vaccines
Nancy E. Messonnier, M.D.
Centers for Disease Control and Prevention

Challenges Faced in Implementing Current Recommendations for the Use of Zoster Vaccine
Michael N. Oxman, M.D.
University of California, San Diego

Measuring the Cost-Effectiveness of Immunizations
Lisa A. Prosser, Ph.D.
Henry Ford Health System

7:30 a.m. **Continental Breakfast** *Grand Ballroom Salons I-IV*

*This is session is supported by a grant from Wyeth Pharmaceuticals

Symposium 4: **Universal Vaccination Against Influenza** CE *Grand Ballroom Salon V*

Moderator: Anthony Fiore, M.D., M.P.H.
Centers for Disease Control and Prevention

8:00 a.m. **16. Influenza Vaccination of Children: Benefits to their Families and Communities**
James King, M.D.
University of Maryland
Baltimore, MD

8:20 a.m. **17. Herd Immunity to Influenza: Models and Measurement**
M. Elizabeth Halloran, Ph.D.
University of Washington
Seattle, WA

8:40 a.m. Questions and Answers

8:50 a.m. **18. Cost Effectiveness of Universal Vaccination**
Lisa A. Prosser, Ph.D.
Henry Ford Health System
Detroit, MI

9:05 a.m. **19. Logistics of Universal Vaccination**
Matthew F. Daley, M.D.
University of Colorado, Denver
Health Sciences Center
Denver, CO

9:20 a.m. Questions and Answers

9:30 a.m. **20. Universal Influenza Virus Vaccines**
Hildegund C.J. Ertl, M.D.
The Wistar Institute
Philadelphia, PA

9:50 a.m. Questions and Answers

10:00 a.m. **Coffee Break** *Grand Ballroom Foyer*

WEDNESDAY, MAY 7, 2008 *(CONTINUED)*

Submitted Presentations 5: (Concurrent Session)

Immunization Systems and Vaccine Policy CE

Grand Ballroom Salon V

Moderator: George Curlin, M.D.
National Institute of Allergy and Infectious Diseases

10:30 a.m. **S25 Improving Health Care Worker Influenza Vaccination Rates in a Large Health System**
R. Zimmerman, P. Nowalk, C. Lin, D. Fox, M. Raymund, J. Harper, M. Tanis
University of Pittsburgh, Pittsburgh, PA

10:45 a.m. **S26 A Decade of Pediatric Immunisation Coverage in Australia**
B. P. Hull, **S. L. Deeks**, P. B. McIntyre
National Centre for Immunisation Research and Surveillance, Sydney, New South Wales, Australia

11:00 a.m. **S27 Effective Implementation of a School-based Influenza Vaccination and Herd Protection Trial in Central Texas – VIPS: Vaccines for Influenza Prevention in Schools**
M. Gaglani[1], P. Piedra[2], G. Herschler[1], C. Fewlass[1], D. Harvey[1], L. Newman[1], W. P. Glezen[2]
[1]*Scott & White Memorial Hospital and Clinic, Texas A&M HSC COM, Temple, TX,* [2]*Baylor College of Medicine, Houston, TX*

11:15 a.m. **S28 Number Needed to Treat and Cost to Prevent Human Cases of Bat Rabies**
G. De Serres[1], P. Mimault[1], I. Rouleau[1], B. Duval[1], R. Maranda Aubut[2], M. Côte[1], D. M. Skowronski[3]
[1]*Institut National de Santé Publique du Québec, Quebec, QC, Canada,* [2]*Agence de santé et des Services Sociaux de la Capitale Nationale, Québec, QC, Canada,* [3]*BC Center for Disease Control, Vancouver, BC, Canada*

11:30 a.m. **S29 Economic Impact of Influenza Vaccination of Pregnant Women (PW) in Nova Scotia (NS): Net Cost, Cost-Effectiveness and Budget Impact**
C. Skedgel[1], J. Scott[2], J. Langley[2], N. MacDonald[2], S. McNeil[2]
[1]*Department of Medicine, Dalhousie University, Halifax, NS, Canada,* [2]*Canadian Center for Vaccinology, Dalhousie University, Halifax, NS, Canada*

11:45 a.m. **S30 The Value of Vaccinating U.S. Elderly against Herpes Zoster: A Review of Cost-Effectiveness Analyses**
I. R. Ortega-Sanchez
Centers for Disease Control and Prevention, Atlanta, GA

Submitted Presentations 6: (Concurrent Session)

Assessment of Vaccine Response: Laboratory and Clinical Parameters CE

Dover A, B, C

Moderator: Peter L. Nara, D.V.M., Ph.D.
Biological Mimetics, Inc.

10:30 a.m. **S31** **Acute Phase Immune Gene Profiling of Spleen and Peyer's Patch in Naïve and Vaccinated Chickens Following Avian Influenza A (H5N1) Virus Infection**
C. H. Kim [1], H. S. Lillehoj [1], D. Kapczynski [2], C. L. Keeler, Jr [3], Y. H. Hong [1], D. K. Kim [1]
[1] *US Department of Agriculture Animal Parasitic Diseases Laboratory, Animal and Natural Resources Institute, Agricultural Research Service, US Department of Agriculture, Beltsville, MD,* [2] *Exotic & Emerging Avian Viral Diseases, Southeast Poultry Research Laboratory, Agricultural Research Service, US Department of Agriculture, Athens, GA,* [3] *Department of Animal and Food Sciences, College of Agriculture and Natural Resources, University of Delaware, Newark, DE*

10:45 a.m. **S32** **Associations between Cytokine/Cytokine Receptor SNPs and Humoral Immunity to Measles, Mumps and Rubella in a Somali Population**
N. Dhiman, I. G. Ovsyannikova, R. A. Vierkant, S. V. Pankratz, R.M. Jacobson, G.A. Poland
Mayo Clinic Collelge of Medicine, Rochester, MN

11:00 a.m. **S33** **Characterization of Novel Anti-microbial Peptide is Produced Locally in the Gut of *Eimeria*-infected Host**
Y. Hong [1], H. S. Lillehoj [1], G. R. Siragusa [2], D. D. Bannerman [1]
[1] *USDA Agricultural Research Service, Beltsville, MD,* [2] *Agtech Products Inc, Waukesha, WI*

11:15 a.m. **S34** **Vaccinated Children among Hospitalized Meningococcal Cases Across Canada, IMPACT 2002-2006**
J. Bettinger [1], N. Le Saux [2], D. W. Scheifele [1], S. Halperin [3], W. Vaudry [4], R. Tsang [5]
[1] *University of British Columbia, Vancouver, BC, Canada,* [2] *Children's Hospital of Eastern Ontario, Ottawa, ON, Canada,* [3] *IWK Health Centre, Halifax, NS, Canada,* [4] *Stollery Children's Hospital, Edmonton, AB, Canada,* [5] *National Microbiology Laboratory, Winnipeg, MB, Canada*

11:30 a.m. **S35** **Fine Aerosol Adenovirus Vaccination against Tuberculosis in Rhesus Macaque**
D. Bolton, S. Rao, M. Roederer
VRC, NIAID, NIH, Bethesda, MD

11:45 a.m. **S36** **Positive Prediction of Immunogenic Vaccine Candidate Epitopes and Progress on the Development of an IDV Vaccine for *H. pylori***
L. Moise [1], B. Wu [1], J. A. McMurry [1], D. Lee [2], V. Ruiz [2], S. F. Moss [2], W. D. Martin [1], A. S. De Groot [1]
[1] *EpiVax, Inc., Providence, RI,* [2] *Brown Medical School, Providence, RI*

12:00 p.m. Lunch (on your own)

WEDNESDAY, MAY 7, 2008 *(CONTINUED)*

Symposium 5: **Recently Licensed Vaccines** CE *Grand Ballroom Salon V*

Moderator: Myron M. Levine, M.D., D.T.P.H.
University of Maryland School of Medicine

1:00 p.m. **21. Prophylactic HPV Vaccines**
Laura. A. Koutsky, Ph.D.
University of Washington
Seattle, WA

1:25 p.m. Questions and Answers

1:30 p.m. **22. Rotavirus Vaccines for the Developing World: Future Concerns and Future Options**
Roger I. Glass, M.D., Ph.D.
National Institutes of Health
Bethesda, MD

1:55 p.m. Questions and Answers

2:00 p.m. **23. Quadrivalent Meningococcal Conjugate Vaccine**
Nancy E. Messonnier, M.D.
Centers for Disease Control and Prevention
Atlanta, GA

2:25 p.m. Questions and Answers

2:30 p.m. **24. Vaccination Against Herpes Zoster and Postherpetic Neuralgia**
Michael N. Oxman, M.D.
University of California, San Diego
La Jolla, CA

2:55 p.m. Questions and Answers

3:00 p.m. **Maurice R. Hilleman Early-Stage Career Investigator Award***
This session will feature oral presentations by the Early-stage Career Investigator Awardees

4:00 p.m. **Adjournment/Participant Evaluation**

*Supported by a grant from Merck & Co., Inc.

Poster Session (Monday, May 5, 2008, 10:00 a.m. – 11:00 a.m., Grand Ballroom Foyer)

Travel Grant Posters (P1-P15), Grand Ballroom Foyer

P1 Kolaviron, a Novel and Potentially Potent Vaccine Adjuvant
C. S. Nworu [1], P. A. Akah [1], E. C. Nwanegbo [2], C. O. Esimone [2]
[1] *University of Nigeria, Nsukka, Nigeria,* [2] *University of Pittsburgh, Pittsburgh, PA*

P2 Immunotherapy of Autoimmune Ovarian Disease by Co-Immunization of mZP3 Protein and DNA Vaccines
J. Li, H. Jin, B. Wang
China Agricultural University, Beijing, China

P3 Evaluation of a Cationic Liposome as Adjuvant for Newcastle Disease Vaccine
E. B. Onuigbo, III
University of Nigeria, Nsukka, Nigeria

P4 Serotype-specific Efficacy and Immunogenicity of a 9-valent Pneumococcal Conjugate Vaccine (PCV-9) Determined during an Efficacy Trial in Gambia
B. J. Okoko[1], M. Saaka [1], R. C. Kohberger[2]
[1] *Medical Research Council, Fajara, Gambia,* [2] *Blair and Company, Greenwich, MD*

P5 Incorporating the Private Demand for Vaccines into a Cost-Benefit Analysis on the Introduction of a Universal Hib Vaccination Program in a Suspected Low Disease Burden Country: Thailand 2006
C. Muangchana
National Vaccine Committee Office, Muang Nonthaburi, Thailand

P6 Youths' Attitude in HIV Vaccine Trials
N. M. Otuonye, IV
Nigerian Institute of Medical Research, Yaba, Lagos, Nigeria

P7 Pretreatment with Sulfadoxine-Pyrimethamine or Artémether-Lumefantrine During the High Transmission Season: Consequences on *Plasmodium falciparum* Malaria Infection and Clinical Episodes in Under-five Children in Burkina Faso
A. Ouedraogo, T. B. Alfred, I. Nebie, A. Diarra, A. T. Konate, I. Soulama, G. Adama, B. C. Edith, S. B. Sodiomon
Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Ouagadougou, Burkina Faso

P8 Knowledge of Human Papillomavirus (HPV) and Acceptability of HPV Vaccine in Lagos State, Nigeria
O. O. Olaogun [1], A. Adeyemi [2]
[1] *Healthmatch International, Lagos, Nigeria,* [2] *Glory Medical Center, Lagos, Nigeria*

P9 Need for Vaccine Development as a Preventive Strategy Against *Helicobacter pylori* Infection in Western Nigeria

K. S. Oyedeji [1], S. I. Smith[1], A. O. Coker [2], A. O. Arigbabu [3]
[1] *Nigerian Institute of Medical Research, Lagos, Nigeria,* [2] *College of Medicine, University of Lagos, Lagos, Nigeria,* [3] *Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria*

P10 Immunogenicity of MSP3 Long Synthetic Peptides (MSP3-LSP) and its Four Overlapping Peptides Following Immunization of Adult Volunteers in a Phase 1 Trial with MSP3-LSP in a Malaria Endemic Area

I. Nebie, Sr.[1], A. Ouedraogo, Jr [1], A. B. Tiono, Jr [1], A. T. Konate, Sr [1], A. Gansane, Jr [1], A. I. Derme, Jr [1], A. Diarra, Jr [1], I. Soulama, Jr [1], N. Cuzin-Ouattara, Sr [1], S. Cousens, Sr [2], O. Leroy, Sr [3], S. B. Sirima, Sr [1]
[1] *Centre National de Recherche et de Formation sur le Paludisme, Ouagadougou, Burkina Faso,* [2] *London School of Hygiene and Tropical Medicine, London, United Kingdom,* [3] *European Malaria Vaccine Initiative, Copenhagen, Denmark*

P11 Search for Novel Antigens Commonly Expressed among Different *Helicobacter pylori* Strains by Proteomics Technology

I. Vitoriano[1], J. Moura[1], O. Jacinto[1], F. Vale[1], J. Vitor[2], C. Calado[1], **M. Roxo-Rosa**[1]
[1] *Engineering Faculty, Catholic University of Portugal, Rio de Mouro, Portugal,*
[2] *Faculdade de Farmácia,*
University of Lisbon, Lisbon, Portugal

P12 Relationship between Antibodies against Four Malaria Vaccine Candidates' Antigens and Clinical Outcome in Children Living in a Seasonal Malaria Transmission Setting of Burkina Faso

A. Diarra[1], I. Nebie[1], A. Ouedraogo[1], I. Soulama[1], E. Bougouma[1], A. Konate[1], R. Chilengi [2], M. Theisen [3], D. Dodoo [4], R. Ed [5], S. Bosomphora [4], P. Milligan [6], S. Sirima [1]
[1] *Centre National de Recherche et de Formation sur le Paludisme, Ouagadougou, Burkina Faso,* [2] *Amanet, Dar es Salam, Tanzania,* [3] *Statens Serum Denmark,* [4] *National Malaria Institute for Malaria Research, Accra, Ghana,* [5] *Primate Research Centre, Netherlands, Antilles,* [6] *London School of Hygiene, United Kingdom*

P13 Trends in Human Papilloma Virus Infection among Women Attending a Sexually Transmitted Diseases Clinic in Ibadan

O. O. Onigbogi, O. Akinyemi
University College Hospital, Ibadan, Nigeria

P14 Immunosuppressant as Adjuvant for Tolerogenic Immunization

Y. Kang [1], B. Wang [1], A. Chen [2], G. Zheng [2]
[1] *China Agricultural University, Beijing, China,* [2] *University of Illinois, Rockford, IL*

P15 Cimetidine Enhances Immune Response on HBV DNA Vaccination through Down-regulation of TGF-beta/IL-10 Without Altering the Frequency of Natural Treg Cells
J. Wang [1], B. Su [2], Z. Ding [2], B. Wang [2]
[1] *China Agricultural University, Beijing, China,* [2] *State Key Laboratories of Agro-biotechnology, College of Biological Science, China Agricultural University, Beijing, China*

General Posters (P16 – P68), Grand Ballroom Foyer

P16 Safety and Immunogenicity of a Diphtheria-Tetanus-Acellular Pertussis-Inactivated Poliovirus-Hib Conjugate-Hepatitis B Vaccine at 2, 3, 4, and 12-14 Months of Age
S. A. Halperin [1], B. F. Tapiéro [2], F. J. Diaz-Mitoma [3], B. J. Law [4], A. Hoffenbach [5], P. Zappacosta [6], D. Radley [6], B. McCarson [6], J. Martin [6], L. Brackett [6], J. Boslego [6], T. M. Hesley [6], P. Bhuyan [6], J. Silber [6]
[1] *Canadian Center for Vaccinology, Dalhousie University, Halifax, NS, Canada,* [2] *CHU Sainte Justine, University of Montreal,, Montreal, QC, Canada,* [3] *Children's Hospital of Eastern Ontario, Ottawa, ON, Canada,* [4] *Unversity of Manitoba, Winnipeg, MB, Canada,* [5] *sanofi pasteur, Marcy L'Etoile, France,* [6] *Merck Research Laboratories, Upper Gwynedd, PA*

P17 HIV-1 Infection Impairs Measles Virus-specific IgG Avidity Maturation in Zambian Children Following Infection and Vaccination
N. Nair
Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

P18 Possible RNA Agonist for RIG-I/MDA-5 as Molecular Adjuvants for Protein Vaccines
C. K. Yang, L. R. Smith, A. Vilalta, J. Hartikka
Vical, Inc., San Diego, CA

P19 Immunization with *Shigella sonnei* Carbohydrate Biopolymers Protects Mice against Polymicrobial Septic Infection and Downregulates Proinflammatory Cytokines Production *in vivo* under Experimental Endotoxic Shock Model
A. A. Markina, V. L. L'vov, I. U. Kurbatova, V. I. Shmigol, M. E. Golovina, P. G. Aparin
National Research Center Institute of Immunology, Moscow, Russian Federation

P20 Antigen-specific B Memory Cell Responses to Lipopolysaccharide (LPS) and Invasion plasmid antigen (Ipa) B among Volunteers Vaccinated with Live-attenuated Shigella flexneri 2a Vaccine Candidates
J. K. Simon, R. Wahid, M. Maciel, Jr., K. L. Kotloff, M. M. Levine, M. B. Sztein
University of Maryland, Baltimore, MD

P21 Residual Rubella in São Paulo State, Brazil, 15 Years After the Introduction of Vaccination
R. S. Azevedo [1], A. L. F. Yu [2], M. Amaku [1]
[1] *University of São Paulo, São Paulo, Brazil,* [2] *São Paulo State Center for Epidemiological Surveillance, São Paulo, Brazil*

P22 Dose-finding, Safety, and Immunogenicity Phase 1 Trial of an Intranasal *Shigella flexneri* 2a Invaplex 50® Vaccine in North American Adult Volunteers
R. W. Kaminski [1], M. S. Riddle [2], C. WIlliams [2], J. Lapa [2], S. Baqar [2], A. A. Kordis [1], T. Gilliland [2], C. Porter [2], M. Coughlin [1], C. Soltis [3], E. Jones [2], J. Saunders [1], P. B. Keiser [1], R. T. Ranallo [1], R. Gormley [2], M. Nelson [3], K. R. Turbyfill [1], D. Tribble [4], E. V. Oaks [1]
[1] *Walter Reed Army Institute of Research, Silver Spring, MD,* [2] *Naval Medical Research Center, Silver Spring, MD,* [3] *Walter Reed Army Medical Center, Washington DC,* [4] *Uniformed Services University of the Health Sciences, Bethesda, MD*

P23 Live Attenuated *virG*(*icsA*)-based Second Generation *Shigella* Vaccines: Construction and Testing in Animal Models
R. T. Ranallo, S. BarNoy, S. Thakkar, M. M. Venkatesan
Walter Reed Army Institute of Research, Silver Spring, MD

P24 Induction of Protective Immune Responses to Pathogenic Influenza Using Electroporation & Consensus DNA Immunogens
D. J. Laddy [1], J. Yan [1], A. S. Khan [2], R. Draghia-Akli [2], G. P. Kobinger, Ph.D. [3], D. Kobasa [3], J. Greenhouse [4], N. Sardesai [5], D. B. Weiner [1]
[1] *University of Pennsylvania, Philadelphia, PA,* [2] *VGX Pharmaceuticals, The Woodlands, TX,* [3] *National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB, CANADA,* [4] *Bioqual, Inc, Rockville, MD,* [5] *VGX Pharmaceuticals, Blue Bell, PA*

P25 Phase I Safety Data from a Still-blinded Trial of Reduced-dose, Intradermal Influenza Vaccination by Needle-free Jet Injector in the Dominican Republic
V. Gomez [1], **P. L. Moro** [2], G. Guzmán [1], J. Feris [1], J. Fernandez [1], C. Bridges [3], M. Friede [4], J. K. Iskander [2], B. G. Weniger [2]
[1] *Hospital Infantil Dr. Robert Reid Cabral, Santo Domingo, Dominican Republic,* [2] *Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA,* [3] *National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA,* [4] *Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland*

P26 A Prospective, Comparative Study of the Immune Response to Inactivated Influenza Vaccine in Pediatric Liver Transplant Recipients and their Healthy Siblings
R. P. Madan, M. Tan, A. Fernandez-Sesma, T. Moran, S. Emre, A. Campbell, B. C. Herold
Mount Sinai School of Medicine, New York, NY.

P27 Hepatitis A and Travel Amongst Nova Scotia Post-Secondary Students: Evidence for a Targeted versus Universal Immunization Strategy

K. Matheson, B. A. Halperin, S. McNeil, D. MacKinnon-Cameron, S. A. Halperin
Canadian Center for Vaccinology, Dalhousie University, IWK Health Centre, Capital Health, Halifax, NS, Canada

P28 A Universal Influenza Vaccine - Conjugation of Immunostimulatory DNA to Conserved Viral Antigens Generates Broad Immunity

T. B. dela Cruz, B. Milley, M. Urban, G. Ott, B. Livingston, G. Van Nest, D. Higgins
Dynavax Technologies, Berkeley, CA

P29 Follicular Targeting of Vaccines: From Skin Explant to Transcutaneous Vaccination Trials in Humans

B. Combadière[1], A. Vogt [2], B. Mahe[1], D. Costagliola[3], C. Katlama[4], B. Autran[1], U. Blume-Peytavi [5]
[1] *INSERM U543, Paris, France,* [2] *Charité Hospital, Berlin, Germany,* [3] *INSERM U720, Paris, France,* [4] *Pitié Salpétrière Hospital, Paris, France,* [5] *Charité Hospital, Paris, France*

P30 Long-term Residual IFNÁ+TNF·+ effector/memory CD4 Lymphocytes Control Skin Vaccinia Virus Vesicle Formation

B. Combadière[1], D. Garin[2], J. Crance[2], B. Puissant[1], O. Bonduelle[1], F. Gay[3], P. Bossi[3], B. Autran[1]
[1] *INSERM U543, Paris, France,* [2] *CRESSA, Grenoble, France,* [3] *Pitié Salpétrière Hospital, Paris, France*

P31 Human Antibody Responses Against Virulent Orthopoxvirus Proteins Elicited by Vaccinia Virus Vaccines

S. J. Lawrence [1], K. R. Lottenbach [2], M. K. Liszewski [1], C. Empig [3], F. K. Newman [2], M. Gurwith [3], H. Yokote [4], S. Lu [5], J. P. Atkinson [1], R. B. Belshe [2], S. L. Stanley, Jr [1], S. E. Frey [2]
[1] *Washington University School of Medicine, St. Louis, MO,* [2] *Saint Louis University School of Medicine, St. Louis, MO,* [3] *VaxGen, San Francisco, CA,* [4] *Kaketsuken, Kumamoto, Japan,* [5] *University of Massachusetts, Worcester, MA*

P32 A Unique Canadian Model of Investigators and Industry Research Sponsors Working Together to Improve Vaccine Research Culture and Opportunities

D. W. Scheifele, B. Duval, S. Halperin, B. Ward, G. Bjornson
Canadian Association for Immunization Research and Evaluation (CAIRE), Vancouver, BC, Canada

P33 A Nationwide Survey of Past Hepatitis A Infections among Canadian Adults
J. J. Ochnio [1], **D. W. Scheifele** [1], B. Duval [2], G. De Serres [2], V. Gilca [2], M. Ho [1], R. Milner [1]
[1] *University of British Columbia, Vancouver, BC, Canada,* [2] *Institut National de Santé Publique du Québec, Québec, QC, Canada*

P34 Evaluation of Genetic Drift of *S. aureus isd* B Gene in Immunized Mice
G. D. Pancari
Merck and Co., Inc, West Point, PA

P35 Kinetics of the IgG and IgA Antibody Response in Post-Partum Women after Immunization with Tdap
B. A. Halperin, S. McNeil, J. M. Langley, J. Mutch, D. MacKinnon-Cameron, V. Allen, S. A. Halperin
Canadian Center for Vaccinology, Dalhousie University, IWK Health Centre, Capital Health, Halifax, NS, Canada

P36 Protection from Influenza Virus by Recombinant Nucleoprotein Requires Antibody
D. A. Kaminski, D. Carragher, A. Moquin, L. Hartson, T. D. Randall
Trudeau Institute, Saranac Lake, NY

P37 Development of a DEN-2 PDK-53-based Chimeric Tetravalent Vaccine
J. A. Livengood [1], R. M. Kinney [1], C. Y. H. Huang [2], O. Wiggan [1], S. J. Silengo [1], A. P. Kalanidhi [3], J. E. Osorio [4], D. T. Stinchcomb [1]
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P38 Host Responses to *M.tuberculosis* PE_PGRS Antigens
P. P. Singh, M. Parra, N. Cadieux, M. J. Brennan
Center for Biologics Evaluation and Research Food and Drug Administration, Bethesda, MD

P39 Genetic and Clinical Evaluation of MP-12 as a Live Attenuated Vaccine for Rift Valley Fever Virus (RVFV)
C. Peters [1], P. Pittman [2], J. C. Morrill [1], **G. E. Bettinger** [1], N. Lokugamage [1], M. Ranadive [2], L. Korman [2]
[1] *University of Texas Medical Branch, Galveston, TX,* [2] *The United States Army Medical Research Institute for Infectious Diseases, Ft. Detrick, MD*

P40 Incidence and Severity Dual Modeling in Vaccine Evaluation
Y. Qiang, L. H. Moulton
Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

P41 Molecular Vaccine Development: Perceived Barriers and Potential Solutions

T. L. Richie [1], K. Anderson [2], D. Brake [3], M. Brennan [4], D. Dalrymple [5], C. G. Gay [6], H. Golding [4], D. Klinman [7], P. Lalor[8], R. Tiernan [4], D. Weiner[9]
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P42 Pathogen-mimicking Nanoparticles as West Nile Virus Vaccine Delivery Systems

S. L. Demento, H. G. Foellmer, M. Ledizet, E. Fikrig, T. M. Fahmy
Yale University, New Haven, CT

P43 Efficacy of a New Generation of DNA-vaccine Encoding Retrovirus-based Virus-like Particles to Induce Both Cellular and Humoral Immune Responses and its HCV-vaccine Development

D. Desjardins [1], C. Huret [1], B. Clerc [1], l. Torrieri [1], P. Garrone [2], P. Dupeyrot [2], X. Dervillez [1], M. Miyalou [1], C. Dalba [2], D. Klatzmann[1], **B. Bellier**[1]
[1] *Université Pierre et Marie Curie, Paris, France,* [2] *EPIXIS, Paris, France*

P44 Rational Design and Standardized Evaluation of Novel Genetic Vaccines

B. Bellier [1], T. Brocker [2], S. Kochanek [3], T. Dalianis [4], D. Pinschewer [5], J. Blazewicz [6], P. Mavromara [7], R. Zinkernagel [8], F. Tangy [9], F. Cosset [10], A. Williamson [11], M. Bachmann [12], A. Epstein [13], A. Sharipo [14], P. Pumpens [15], K. Sasnauskas [16], A. Osterhaus [17], C. Dalba [18], D. Klatzmann[1]
[1] *Université Pierre et Marie Curie, Paris, France,* [2] *Universitat Munchen, Munchen, Germany,* [3] *Universitatsklinikum Ulm, Ulm, Germany,* [4] *Karolinska Institute, Stockohlm, Sweden,* [5] *Université de Genéve, Genéve, Switzerland,* [6] *Poznan University of Technology, Poznan, Poland,* [7] *Hellenic Pasteur Institute, Athens, Greece,* [8] *University of Zurich, Zurich, Switzerland,* [9] *Institut Pasteur, Paris, France,* [10] *INSERM, Lyon, France,* [11] *University of Cape Town, Cape Town, South Africa,* [12] *Cytos Biotechnology AG, Schlieren, Switzerland,* [13] *Université Claude Bernard Lyon, Lyon, France,* [14] *ASLA Biotech Ltd, Riga, Latvia,* [15] *BioMedical Research and Study Center, Riga, Latvia,* [16] *Institute of Biotechnology, Vilnius, Lithuania,* [17] *Erasmus MC Rotterdam, Rotterdam, The Netherlands,* [18] *EPIXIS SA, Paris, France*

P45 A Versatile Technology Conferring Thermostability and Allowing Extended Ambient Storage of Viral Vaccines

J. Drew, H. M. Porter, J. A. Bainbridge
Stabilitech Ltd., London, United Kingdom

P46 Development of Multi-Antigenic Peptide Antigens as the Basis for a Novel Vaccine Approach to Alzheimer's Disease
E. A. Ottinger, C. Wu, V. M. Garsky, M. Citron, X. Liang, K. Grimm, D. D. Nahas, R. W. Hepler, Z. Zhang, G. Kinney, J. Shiver, J. Joyce
Merck Research Laboratories, West Point, PA

P47 HSV-2 Immunization Enhanced by Estrogen Results in Improved Efficacy
J. W. Pennock, R. Stegall, G. N. Milligan, N. Bourne
Sealy Center for Vaccine Development, University of Texas Medical Branch, Galveston, TX

P48 Immunohistological Analysis of Nanoencapsulated DNA Vaccine for RSV
S. Boyoglu [1], K. Vig [1], V. Rangari [2], S. Pillai [1], V. Dennis [3], S. R. Singh [1]
[1] *Alabama State University, Montgomery, AL,* [2] *Tuskegee University, Tuskegee, AL,* [3] *Tulane University Health Sciences Center, Covington, LA*

P49 An Efficacious Rattlesnake Vaccine for Horses
J. M. Taylor, P. A. Ibsen, H. J. Pollock, D. M. Wallis, J. L. Wallis
Hygieia Biological Laboratories, Woodland, CA

P50 The Role of CFA/I Fimbrial Proteins in Enterotoxigenic *E. coli* Strain H10407
K. Baker, E. Barry, M. M. Levine
Center for Vaccine Development, University of Maryland, Baltimore, MD

P51 Characterization of A Cross-protective, Multivalent Subunit Vaccine Against Salmonella
D. Catron [1], L. Herron-Olson [1], D. McMurray [1], J. Santiago [1], D. Emery [2]
[1] *Syntiron, Saint Paul, MN,* [2] *Epitopix, Willmar, MN*

P52 Development of a Novel Nanoemulsion-based Hepatitis B Mucosal Vaccine
P. E. Makidon, A. U. Bielinska, S. S. Nigavekar, N. J. Mank, K. W. Janczak, J. Knowlton, A. J. Scott, Z. Cao, S. Rathinavelu, M. R. Beer, L. Blanco, E. J. Wilkinson, J. J. Landers, J. J. R. Baker, Jr.
University of Michigan, Ann Arbor, MI

P53 Influenza Vaccine Antibody Responses by Lung Transplant Patients in Three Seasons
M. S. Hayney [1], J. Moran [1], M. L. Francois [2], K. L. Radford [2], H. Thomas [2], D. S. Hawes [2], K. C. Meyer [3]
[1] *University of Wisconsin School of Pharmacy, Madison, WI,* [2] *University of Wisconsin Hospital and Clinics, Madison, WI,* [3] *University of Wisconsin School of Medicine and Public Health, Madison, WI*

P54 The Brighton Collaboration Standardized Case Definitions: Tools for Use in Vaccine Safety Research and Surveillance
J. Gidudu, A. Compingbutra, J. Iskander
Centers for Disease Control and Prevention, Atlanta, GA

P55 Burden of Acute Gastroenteritis Hospitalizations and Emergency Department Visits in US Children that is Potentially Preventable by Rotavirus Vaccination - A Probe Study Using the Now Withdrawn RotaShield® Vaccine

J. E. Tate, A. T. Curns, M. M. Cortese, E. S. Weintraub, J. M. Baggs, U. D. Parashar
Centers for Disease Control and Prevention, Atlanta, GA

P56 Transcutaneous Delivery of Tetanus Toxin Hc Fragment Induces Superior Tetauns Toxin Neutralizing Antibody Response Compared to Tetanus Toxoid

F. Mawas, L. Johnston, R. Tierney, O. Qazi, N. Fairweather, D. Sesardic
National Institute for Biological Standards & Control, Potters Bar, United Kingdom

P57 Evaluation of the Immunopotentiation by TLR4 Agonists Combined with Aluminum-containing Adjuvants

A. Sokolovska, H. HogenEsch
Purdue University, West Lafayette, IN

P58 26-Valent Group A Streptococcus (GrAS) Vaccine In Healthy Adults: Summary of Immunogenicity and Extended Cardiac Safety

S. McNeil [1], A. Warren [2], J. Sharratt [2], S. Halperin [1], J. Langley [1], B. Smith [1], L. L. Fries [3], P. Vink [3], J. B. Dale [4]
[1] *Canadian Centre for Vaccinology, IWK Health Centre, Dalhousie University, Halifax, NS, Canada,* [2] *IWK Health Centre, Dalhousie University, Halifax, NS, Canada,* [3] *GSK Biologicals, North America, Baltimore, MD,* [4] *University of Tennessee and VA Medical Centre, Memphis, TN*

P59 Development of a Robust GLP-Compliant Flow Cytometric Potency Assay for Hantavirus DNA Vaccines

C. V. Badger, J. D. Richardson, J. E. Brown, J. W. Hooper, C. S. Schmaljohn
USAMRIID, Fort Detrick, MD

P60 Beyond the LAL: A Human Whole Blood Cytokine Release Assay to Estimate the Endotoxin Activity of Vaccines Containing Variant LPS Molecules

M. B. Stoddard, V. B. Pinto, W. D. Zollinger
Walter Reed Army Institute of Research, Silver Spring, MD

P61 Toxin Neutralizing Antibodies (NEUT-Abs) and Polysaccharide (PS) Opsonic Antibodies (OP-Abs) Protect against a Highly Virulent Toxin-Producing *Staphylococcus aureus* (SA): A Rationale for a Multi-Target SA Vaccine

K. L. Taylor, J. Sarwar, S. Stewart, A. I. Fattom
Nabi Biopharmaceuticals, Rockville, MD

P62 Development of a Polyvalent Lyme Disease Vaccine that Induces Antibodies that Recognize all Incorporated OspC Type-specific Sequences
C. G. Earnhart, R. T. Marconi
Virginia Commonwealth University, Richmond, VA

P63 Immunological Evaluation of a Synthetic Oligosaccharide-based Vaccine Targeting the HIV-1 2G12 Epitope
J. G. Joyce
Merck and Company, West Point, PA

P64 A Novel Approach to Produce Glycoconjugated Vaccines Using Recombinant Bacterial Cells that Directly Produce Immunogenic Bioconjugates
F. Fernandez [1], M. Wetter [1], M. Kowarik [1], J. Ihssen [2], C. Tanner [1], S. Dilettoso [2], S. Balada [1], G. Corradin [3], L. Thoeny-Meyer [2], **M. Wacker** [1]
[1] *GlycoVaxyn, Schlieren, Switzerland,* [2] *EMPA, St. Gallen, Switzerland,* [3] *University of Lausanne, Lausanne, Switzerland*

P65 Cervical Challenge with HPV Virus-like Particles (VLPs) Can Evoke an Anamnestic Anti-HPV Immune Response in HPV VLP Vaccinated Non-human Primates
R. Swoyer, M. Brownlow, E. Garner, J. Bryan
Merck, West Point, PA

P66 Immunogenicity In Vivo: Proof-of-concept Study of an Immunome-derived Smallpox Vaccine
L. Moise [1], J. A. McMurry [2], J. Lee [3], M. Buller [4], S. Frey [4], W. Martin [2], **A. S. De Groot** [1]
[1] *Institute for Immunology and Informatics, Providence, RI,* [2] *EpiVax, Providence, RI,* [3] *U. Mass Medical School, Worcester, MA,* [4] *Saint Louis University, Saint Louis, MO*

P67 Updated Results from Ongoing Work on the GAIA HIV Vaccine: Broad Recognition of Class I and II-restricted Epitopes and In Vivo Studies
J. McMurry [1], K. Coulibaly [2], L. Moise [3], O. A. Koita [2], W. Martin [1], **A. S. De Groot** [3]
[1] *EpiVax, Providence, RI,* [2] *Faculte de Sciences Technologie, Bamako, Mali,* [3] *Institute for Immunology and Informatics, Providence, RI*

P68 Rabies Post-Exposure Prophylaxis after Bat Exposure in Quebec, Canada
C. Huot[1], **G. De Serres**[2], I. Rouleau[2], B. Duval[2], R. Maranda Aubut[3], M. Côte[2], M. Ouakki[2], D. M. Skowronski[4]
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MEET THE EXPERT PRESENTERS

Meet the Expert Presenters

Garth D. Ehrlich, Ph.D.
Tuesday, May 6, 2008
7:00 am – 7:45 am

Dr. Garth Ehrlich is Executive Director of the Center for Genomic Sciences at Allegheny Singer Research Institute, and Professor of Microbiology and Immunology at Drexel University School of Medicine, Allegheny Campus, Pittsburgh, PA. Dr. Ehrlich is one of the founders of the Association for Molecular Pathology and served as the first Chair of its Infectious Disease Section. He has served on the editorial boards of *Clinical Diagnostics and Laboratory Immunology*, and *Molecular Diagnosis*. He has organized numerous sessions and symposia at various American Society of Microbiology meetings and has also organized numerous free-standing international meetings in human genetics and bacterial pathogenesis.

Dr. Ehrlich received his Ph.D. from Syracuse University in Molecular Biology, and did post-doctoral studies in human retrovirology with Dr. Bernard Poiesz at Upstate Medical Center in Syracuse, NY. He has authored one of the first books in molecular diagnostics, *PCR-based Diagnostics in Infectious Disease*, and has authored or coauthored nearly 200 research papers, reviews, perspectives, commentaries and book chapters in myriad molecular biological disciplines.

Martin Friede, Ph.D.
Tuesday, May 6, 2008
7:00 am – 7:45 am

Dr. Martin Friede is the Scientific Officer responsible for vaccine delivery systems within the Initiative for Vaccine Research (IVR) at the World Health Organization (WHO) in Geneva, Switzerland. In this position, he is the focal point for matters related to the development of technologies to improve vaccines including needle-free vaccine delivery systems, adjuvants, and vaccine stabilization methods.

Prior to joining WHO, Dr. Friede held several positions in the vaccine industry. He was Vice President of Development for Apovia, Inc., and was responsible for adjuvant and vaccine delivery research at Smithkline Beecham Biologicals (GlaxoSmithKline) in Belgium. Dr. Friede received his Ph.D. in Biochemistry from the University of Cape Town in South Africa.

Hana Golding, Ph.D.
Tuesday, May 6, 2008
7:00 am – 7:45 am

Dr. Hana Golding is Chief of the Laboratory of Retrovirus Research in the Division of Viral Products at the Center for Biologics Evaluation and Research of the Food and Drug Administration. She also serves as a member of the American Association of Immunologists and the American Association of Microbiologists. She has published over 80 articles in peer-reviewed scientific journals and contributed 13 chapters in scientific books on immunology, virology, and infectious disease topics.

Gregory A. Poland, M.D.
Tuesday, May 6, 2008
7:00 am – 7:45 am

Dr. Gregory 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 was

Meet the Expert Presenters

awarded the Secretary of Defense Medal for Outstanding Public Service. 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. 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, Annals 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.

Carl R. Alving, M.D.
Wednesday, May 7, 2008
7:00 am – 7:45 am

Dr. Carl Alving is a research investigator at the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, Maryland. He received his medical degree from the University of Miami Miller School of Medicine, and completed his internship and residency in medicine and a fellowship in pharmacology at Barnes Hospital and Washington University in St. Louis. He served on active duty in the U.S. Army Medical Corps from 1970-2000, and retired as a colonel. He was Chief of the Department of Membrane Biochemistry at WRAIR from 1978-2004. As a civil service employee, he is currently Chief of the Department of Adjuvant and Antigen Research in the Division of Retrovirology at WRAIR. Dr. Alving is also an adjunct professor of microbiology and immunology at the Uniformed Services University of Health Sciences in Bethesda, MD.

Nancy E. Messonnier, M.D.
Wednesday, May 7, 2008
7:00 am – 7:45 am

Dr. Nancy Messonnier is Chief of Meningitis and Vaccine Preventable Diseases (MVPD) in the Division of Bacterial Diseases, National Center for Respiratory Diseases, Coordinating Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC). She is a world expert on bacterial meningitis and has served as a consultant for CDC, World Health Organization (WHO), Africa Regional Office for World Health Organization (AFRO), Pan American Health Organization (PAHO), and Southeast Asia Regional Office for World Health Organization (SEARO) on this topic.

Dr. Messonnier is board certified in Internal Medicine, and has received training as an Epidemic Intelligence Service Officer. She is a member of the American Medical Association, Infectious Diseases Society of America, Commissioned Officers Association, and Reserve Officer Association. She is the primary author of 80 publications including journal articles, government publications, and book chapters. Dr. Messonnier is on the editorial board for *Emerging Infectious Diseases Journal*, and is an ad hoc reviewer for numerous other publications.

Dr. Messonier's research has focused on bacterial meningitis and other vaccine preventable diseases (including *Neisseria meningitidis*, *Haemophilus influenzae* and *Bordatella pertussis*) and bacterial zoonoses in the United States and internationally, evaluation and development of vaccines, and surveillance for infectious diseases. She has more than 45 publications in peer-reviewed journals and 35 chapters, editorials and invited reviews.

Meet the Expert Presenters

Michael N. Oxman, M.D.
Wednesday, May 7, 2008
7:00 am – 7:45 am

Dr. Michael Oxman is Professor of Medicine and Pathology at the University of California, San Diego and a Staff Physician in the Infectious Diseases Section at the Veterans Administration Medical Center in San Diego. He is National Chairman of VA Cooperative Study #403 - The Shingles Prevention Study.

Dr. Oxman's major research interests have been the mechanism of action of Interferon, the control of SV40 and Adenovirus-SV40 hybrid virus gene expression, and the pathogenesis, diagnosis, treatment and prevention of viral diseases, especially diseases caused by members of the Herpes virus family. He has played a significant role in training and mentoring physician-scientists at Harvard and the University of California, and in the use of double-blind placebo-controlled clinical trials to evaluate the treatment of herpes simplex and varicella-zoster virus infections. He has authored more than 130 book chapters and articles in peer-reviewed scientific journals.

He is a Fellow of the Infectious Diseases Society of America and a member of the American Society for Virology, the American Society for Microbiology, the Society for General Microbiology, the American Society for Clinical Investigation, and the Defense Health Board.

Lisa A. Prosser, Ph.D.
Wednesday, May 7, 2008
7:00 am – 7:45 am

Dr. Lisa Prosser is a Research Scientist at the Center for Health Services Research, at the Henry Ford Health System. Dr. Prosser's research focuses on applications and methods for valuing children's health and economic studies of vaccination and screening programs. She has published several studies on the cost-effectiveness of influenza vaccination in collaboration with the Centers for Disease Control and Prevention. Dr. Prosser also holds faculty appointments in the Department of Ambulatory Care and Prevention at Harvard Medical School and the Program for Health Decision Science at the Harvard School of Public Health. Dr. Prosser received her Ph.D. in Health Policy from Harvard University. She also holds a Master of Science in Management from the MIT Sloan School as well as a Master of Science in Technology and Policy from MIT.

ABSTRACTS OF INVITED PRESENTATIONS

Abstracts of Invited Presentations

1 The Value of Vaccination

David E. Bloom
Harvard School of Public Health, Boston, MA

Objective: Describe the link between vaccination, health, and economic well-being

Summary: Previous attempts to estimate the benefits of vaccination have been incomplete insofar as they fail to account for the fact that children who avoid, by virtue of vaccination, certain diseases (and their physical and mental sequelae) grow up to be more productive adults who earn and save more. Previous research efforts have also given short shrift to benefits associated with the contribution of vaccination to herd immunity.

The links from vaccination to health and economic well-being are the subject of two recent studies. The first is an analysis of GAVI's program to extend the use of underused, basic, and new vaccines.[1] It estimates that vaccine-mediated increases in child health will result in a more productive workforce that can earn greater wages, equating to an enviable rate of return of 12-18% for spending on the program. The second study focuses on the effect of childhood vaccination on cognitive ability and labor earnings in the Philippines. It demonstrates that vaccination is associated with significantly improved scores on IQ, language, and mathematics tests and – considering the higher earnings that accompany greater education – estimates a rate of return on vaccine spending of 21%.[2]

These findings highlight the potential net benefits of new vaccines as a means to strengthen both the health and wealth of nations.

References:

1. Bloom DE, Canning D, Weston M. The value of vaccination. World Economics. 2005;6(3):15-39.
2. Bloom DE, Canning D, Seiguer E. Childhood immunization as human capital. 2008, submitted for publication.

2 Enhancement of AVA Immunogenicity by CpG Oligonucleotides

Dennis Klinman
National Institutes of Health, Bethesda, MD

Objective: Review information on the adjuvanting properties of CpG ODN

Summary: Vaccination remains the single most effective method for preventing infectious diseases. Improved vaccines and vaccine adjuvants are being developed to reduce the threat posed by a terrorist. Synthetic oligodeoxynucleotides (ODN) containing unmethylated CpG motifs represent a novel class of immune adjuvant. CpG ODN trigger cells via toll-like receptor 9, thereby improving the functional activity of professional APCs and triggering the production of cytokines and chemokines that support the development of adaptive (antigen-specific) immune responses.

Combining CpG ODN with Anthrax Vaccine Adsorbed (AVA, the licensed human vaccine) increases the speed, magnitude and avidity of the resultant anti-anthrax response in mice, rhesus macaques and humans. Adsorbing CpG ODN onto cationic poly (actide-co-glycolides) microparticles further boosts immunity to co-administered AVA. The Ab response induced by CpG ODN plus AVA confers protection against systemic anthrax challenge. The role of systemic versus mucosal immunity was then evaluated by challenging mice with aerosolized anthrax spores. Results indicate that protection from inhalational anthrax correlates with the induction of a strong systemic rather than mucosal immune response. As above, protection was improved and accelerated by the addition of CpG ODN. Long term studies evaluated the duration of protective immunity. Mice immunized with CpG adjuvanted AVA maintained protective Ab titers for >15 months, while animals immunized with AVA alone lost protection in <6 months. These findings suggest that CpG ODN may represent useful adjuvants for vaccines against biothreat pathogens.

References:

1. Klinman DM, Xie H, Little SF, Currie D, Ivins B. CpG oligodeoxynucleotides improve the protective immune response induced by anthrax vaccination of rhesus macaques. Vaccine. 2004;22(21-22):2881-2886.
2. Xie H, Gursel I, Ivins BE, Singh M, O'Hagan DT, Ulmer JB, Klinman DM. CpG oligodeoxynucleotides absorbed onto PLG microparticles improve the immunogenicity and protective activity of the licensed anthrax vaccine. Infect Immunity. 2005;73(2):828-833.
3. Klinman DM, Currie D, Lee G, Grippe V, Merkel T. Systemic but not mucosal immunity induced by AVA prevents inhalational anthrax. Microbes Infect. 2007;9(12-13):1478-1483.

3 In Vitro Mimicking of the Human Immune System

William Warren
VaxDesign Corporation, Orlando, FL

Objective: Discuss methods to evaluate formulations before clinical trials

Summary: Despite the promise of high-throughput screening, genomics, and proteomics, the number of new drugs reaching the market has not increased. A challenge is the translation from test systems (animal or cell culture) to human immunology. The successful transfer between human biology and traditional test systems requires an intricate understanding of disease pathogenesis and immunological responses at all levels; innate, adaptive and functional. This talk will provide data on the development of *in vitro* systems to assess vaccine candidates using tissue engineered constructs to mimic human immunophysiology.

The *in vitro* system is modular; the first module simulates the innate responses via antigen presentation and inflammatory responses; the second simulates the adaptive responses of antigen specific T and B cells; and a third module is a functional assay or disease model that uses the products of the other two modules together with a pathogen to measure the effect of the immune response on the disease, e.g., neutralizing antibody responses. These *in vitro* modules reproduce the conditions that exist in a human body, such as the spatial segregation of immune cells and the temporal dynamics that bring different immune cells together in a sequential order that accurately reflects interactions in a lymph node.

Reference:

1. Schanen BS, Drake DR. A novel approach for generating human dendritic cells from blood monocytes in the absence of exogenous factors. J. Immunol Methods. 2008, in press.

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4 Bacterial Supragenomes and the Distributed Genome Hypothesis: How They Inform with Respect to Vaccine Development

Garth D. Ehrlich
West Penn Allegheny Health System, Pittsburgh, PA

Objective: Review new approaches to study immune memory after hepatitis B vaccination and discuss the implications for vaccination strategies

Summary: Whole genome sequencing of large numbers of independent clinical isolates of several major bacterial pathogens has revealed that each strain contains only a small subset of the genes of the species as a whole. Therefore, at the population level there exists a supragenome that is much larger than the genome of any of the component strains. Comparative genomic analyses among the strains of a species can then be used to identify the species core genome, which is composed of all genes that all strains of a species possess, and its distributed genome, those genes that are found in only a subset of strains. Thus, each individual strain's genome is composed of the species' core genome and a unique set of distributed genes. Comparative genomic analyses can then be used to aid in the identification of vaccine targets. If a broadly efficacious vaccine is desired one should focus first on the set of core genes, and then using a number of gene parsing techniques identify those genes whose products are most likely surface exposed. Next these putative surface-exposed genes should be comparatively analyzed to identify those that have signatures of being under immune surveillance. In general genes showing significantly higher numbers of allelic variants that result in amino acid substitutions, insertions, and deletions (compared with the genome as a whole) are excellent candidates for being under selective pressure. A broad-based vaccine that targets all strains of a species, however, may not always be the best choice, particularly if the species is also a part of a commensal microbiome, as is often the case with mucosal species that contain both pathogenic and nonpathogenic (or less pathogenic) strains. In these cases it may be more efficacious to specifically target virulent strains, as wanton disruption of the resident microbiome could lead to colonization of the body site by an even more highly pathogenic species, such appears to be occurring with increased MRSA recovery from the nasopharynx following the introduction of highly polyvalent pneumococcal vaccines. To identify genes associated with specific virulence profiles a distributed genome chip is constructed that contains all nonrare ($\mu \geq .05$) distributed genes from the species supragenome. This chip is then interrogated in a manner analogous to a CGH chip using the genomic DNA of large numbers of phenotypically-characterized (with respect to disease) clinical strains to find the set of distributed genes that are statistically associated with a specific disease phenotype. These disease-associated genes then serve as the targets for focused vaccine development.

References:

1. Hogg JS, Hu FZ, Janto B. Characterization and modeling of the Haemophilus influenzae core and supra-genome based on the complete genomic sequences of Rd and 12 clinical nontypeable16 strains. Genome Biol. 2007;8(6):R103.
2. Hiller NL, Janto B, Hogg JS, et al. Comparative genomic analyses of seventeen Streptococcus pneumoniae strains: insights into the pneumococcal supragenome. J Bacteriol. 2007;189(22):8186-8195.

5 Colonization as a Vaccine Target: Lessons from *Streptococcus pneumoniae*

Jeffrey N. Weiser
University of Pennsylvania, Philadelphia, PA

Objective: Review recent data on B-cell mediated immune responses after influenza vaccination

Summary: For many leading bacterial pathogens colonization of host mucosal surfaces is a first and necessary step in the infectious process. Elimination of the carrier state, therefore, may have the greatest overall impact on the subsequent burden of disease. Reduction of the carrier state, moreover, has been shown to have the added benefit of conferring herd immunity.

In contrast to the more thoroughly studied mechanisms of the disease process, the differing requirements of colonization offer unexplored strategies for therapy and prevention. In addition, events during colonization can be modeled in ways that may be more representative and tractable than those in enduring disease. This lecture will use *Streptococcus pneumoniae* as an example of an important mucosal pathogen to examine the biology of its colonization of the mucosal surface of the airway. The focus will be on how an understanding of the colonization process can be exploited for novel approaches to treatment and vaccination.

Reference:

1. Roche AM, King SJ, Weiser JN. Live-attenuated Streptococcus pneumoniae induce serotype-independent mucosal and systemic protection in mice. Infect Immun. 2007;75(5):2469-2475.

6 Finding a Path to HIV-1Vaccine Development

Barton F. Haynes
Duke Human Vaccine Institute
Duke University Medical Center, Durham, NC

Objective: Recognize the roadblocks to development of an HIV vaccine and review the plans for studies to attempt to overcome those roadblocks

Summary: HIV vaccine development is a major global scientific priority. However, to date, development of an HIV vaccine has been thwarted by HIV integration into the host genome, HIV quasispecies diversity, the immunosuppression caused by HIV, and the poor immunogenicity of the HIV envelope. In addition, the recent failure of a recombinant adenovirus-based HIV vaccine candidate in the STEP Phase IIb vaccine trial was compounded by a trend in possible vaccine-induced enhancement of HIV acquisition in the trial. In this talk, requirements for what a successful HIV vaccine will need to accomplish in order to extinguish transmitted HIV will be discussed, and basic and translational research strategies for new vaccine design will be reviewed.

Reference:

1. Haynes BF, Shattock RJ. Critical issues in mucosal immunity for HIV-1 vaccine development. J Allergy Clin Immunol. May 2008; in press.
2. Haynes BF, Alam SM. HIV-1 hides an achilles' heel in virion lipids. Immunity 2008;28:10-12.

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7 Update on Histology and Immunology of the Skin, for Vaccinologists

Tanja de Gruijl
Vrije Universiteit Medical Center, Amsterdam, The Netherlands

Objective: Explain the different (human) dendritic cell subsets in the skin (their localization, phenotype and functions) and how this knowledge may be employed in the design of novel vaccination strategies

Summary: A dense network of cutaneous dendritic cells (DC) may account for the reported efficacy of vaccination through the skin. Two phenotypically distinct subsets are discerned: epidermal Langerhans cells (LC) and dermal DC (DDC). Upon appropriate activation both subsets can efficiently migrate to draining lymph nodes (LN) to prime T and/or B cell mediated responses.

More and more information is emerging on the relative contribution of LC and DDC to the preferential priming of cell-mediated or humoral responses. Many of these findings derive from studies involving the selective ablation of LC in mouse models. Although these studies have yielded vital information on the ontogeny and functions of the different DC subsets in skin, similar information on their human counterparts has been lagging.

We and others have therefore employed human skin explant models and skin-draining LN to study the biology of human LC and DDC. These studies have yielded vital information on 1) their cytokine- and TLR-L dependent maturation, 2) their migration to LN and the involved chemokines and receptors, 3) their ability to produce immunostimulatory cytokines, and 4) their ability to activate both memory and naïve T cells. This information should facilitate the rational design of novel skin DC-based vaccination strategies.

Reference:

1. Mathers AR, Lareggina AT. Professional antigen-presenting cells of the skin. Immunol Res. 2006;36(1-3):127-136.

8 Past, Present, and Future of Cutaneous Vaccination

Bruce G. Weniger
Centers for Disease Control and Prevention, Atlanta, GA

Objective: Describe the history, clinical effect, and range of vaccines delivered by classical intradermal vaccination using traditional devices, as well as newer devices

Summary: Vaccination into or onto the skin offers potential advantages over other routes, including minimal invasiveness, certain delivery, unnecessary patient cooperation, needle-free delivery, wide separation of competing simultaneous antigens, and dose-sparing. This route was reported as early as the 16th Century for variolation, and it remains today the primary route for smallpox vaccination, as well as BCG for tuberculosis. To clarify the nomenclature, *cutaneous* vaccination here encompasses all prefixes and adjectives used for this route. The term classical *intradermal* (ID) is reserved for deposition of a liquid bolus under the basement membrane to create a bleb, as in the Mantoux technique and easier ID methods that use microneedles and jet injectors.

A large literature documents the alternative ID route for over a dozen vaccine types. Excellent results for rabies justify widespread use in developing countries to economize on post-exposure prophylaxis. Generally good results for influenza since 1937 suggest a strategy for dose-sparing in case of vaccine shortage. Salk's original polio vaccine (IPV) was delivered ID, a route adopted throughout Denmark in the 1950s. Studies of modern IPV suggest a dose-sparing strategy for the necessary conversion from oral vaccine (OPV) after eradication. Mixed to poor results were reported for ID hepatitis B, hepatitis A, cholera, and measles vaccines.

A variety of novel methods for cutaneous vaccination use abrasion, kinetics, heat, electricity, light, sound, and chemicals to breach the formidable barrier of the stratum corneum to deliver antigen. Clinical studies included seasonal and avian influenza, HIV, non-small-cell lung cancer, and travelers' (enterotoxigenic *E. coli*) diarrhea. Animal models evaluated adenovirus, Eurasian encephalitic virus, hantavirus, *Helicobacter pylori*, hepatitis B, herpes simplex 2, SARS coronavirus, smallpox, seasonal and avian influenza, malaria, melanoma, and tetanus.

Reference:

1. Weniger BG, Papania MJ. *Alternative Vaccine Delivery Methods,* Chapter 61 in: Plotkin SA, Orenstein WA, Offit PA, eds: *Vaccines,* 5th ed. Philadelphia, PA: Saunders (Elsevier), 2008, pp1357-1392.

9 Novel Ways to Breach the Stratum Corneum to Deliver Antigen for Cutaneous Vaccination

Samir Mitragotri
University of California, Santa Barbara, Santa Barbara, CA

Objective: Review different ways of delivering vaccines across the skin

Summary: Needles and syringes are the most commonly used method for administering vaccines and protein therapeutics, such as insulin, into humans. About 12 billion injections are given annually, 5% of which account for immunizations. Despite their common use, needle-based immunizations have several limitations. Hence, the development of needle-free immunization methods has now been identified as a major goal in global healthcare. Needle-free immunizations made their first prominent appearance almost 50 years ago as the oral polio vaccine (OPV) which is still used in developing countries but has been discontinued in the United States since 2000. However, administration of most vaccines without using needles, especially non-living vaccines which offer several advantages, has proved challenging. The past decade, however, has witnessed a strong step forward in addressing the technological challenges associated with immunization without needles. In this context, skin offers an advantageous route of vaccination due to the presence of Langerhans cells. A simple topical application of a vaccine, however, does not typically yield an adequate immune response. Vaccine delivery into skin is limited by low permeability of the stratum corneum, the outermost 15-20 micron-thick layer of skin which consists of cornified keratinocytes embedded in a lipid-rich matrix. The lipids of the stratum corneum are organized into an ordered bilayer structure and consequently exhibit a strong barrier to molecular transport. Increasing the permeability of the stratum corneum without irritating underneath keratinocytes has been a prominent challenge in the field. Several innovative methodologies are being developed to facilitate antigen delivery into the skin. I will present an overview of these methodologies

Reference:

1. Mitragotri S. Immunization without needles. Nat Rev Immunol. 2005;5(12):905-916.

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10 Meeting the Challenges of Global Immunization with Cutaneous Vaccination

Martin Friede
World Health Organization, Geneva, Switzerland

Objective: Explain how cutaneous immunization could facilitate vaccination, particularly in developing countries, and the scientific and technical challenges associated with this approach

Summary: Vaccines have had a tremendous global impact in curbing the problems of infectious diseases, yet 1.4 million children still die each year from diseases against which vaccines have been available for many years, and an even greater number from infectious diseases against which we do not yet have vaccines. It is therefore urgent that technologies are developed that facilitate broader coverage with existing vaccines, and also that novel vaccines against killer diseases such as TB, HIV and malaria are developed.

Numerous delivery technologies have been proposed as being able to improve vaccine coverage through simplifying vaccine administration, facilitating the logistics of immunization, improving the efficacy of vaccines or reducing the cost and complexity of production. These include oral, nasal, pulmonary, and cutaneous delivery, but also include thermostable vaccine formulations, 'single-shot' formulations, and means of enhancing the immunity of vaccines through the use of adjuvants etc.

Cutaneous vaccine delivery, particularly with appropriate reliable administration devices may be the most promising of the delivery systems to facilitate immunization, particularly in developing countries. This route offers the promises of: easy administration, particularly with patch-type devices; improved immunization safety if the device is 'needle-free'; increased capacity if dose-reduction can be achieved; and potential induction of immune responses that are not readily achieved via other routes.

There are, however, also many unknowns that need to be addressed before the real potential of this route can be accurately assessed: will all vaccines work via this route? Which cutaneous delivery method is the most applicable? Which formulations are the most effective and will the cost of re-formulating, re-packaging and re-licensing existing vaccines for cutaneous delivery be prohibitive? In addition, variables such as skin-types, site of administration, exposure to UV radiation, etc need to be taken into consideration.

The presentation will highlight the potential of cutaneous delivery to address the challenges of broad vaccination coverage in developing countries, and discuss the pros and cons that each of the cutaneous delivery approaches present.

References:

1. Weniger BG, Papania MJ. *Alternative Vaccine Delivery Methods* [Chapter 61]. In: Plotkin SA, Orenstein WA, Offit PA, eds. **Vaccines**, 5th ed. Philadelphia, PA: Saunders (Elsevier); 2008;1357-1392.

11 Introduction to Adjuvants and Safety

Carl R. Alving
Walter Reed Army Institute of Research, Rockville, MD

Objective: Discuss the types of adjuvants that are used for vaccines; the clinical safety experience with vaccine adjuvants, and the preclinical safety requirements for clinical testing of vaccines containing adjuvants

Summary: Aluminum salts, often referred to generically as alum, are adsorbent adjuvants that exhibit complex interactions with antigens. Although they are still included in many vaccines, they are relatively weak adjuvants and they sometimes cause local reactions at the site of injection, particularly when administered subcutaneously. New adjuvants, and new adjuvant combinations (including combinations with alum), have been developed to: increase the potency of relatively weak antigens; reduce cost and promote antigen sparing; reduce the number of injections required; improve the efficacies of new types of antigen carriers (such as liposomes); allow new methods of immunization (such as DNA immunization); or enhance effectiveness of new routes of immunization (such as transcutaneous immunization). Combinations of adjuvants, sometimes referred to as adjuvant systems, are being considered for numerous vaccines. The safety issues of adjuvants in humans usually involve variable local effects of pain, erythema, induration, or swelling that are often subjective, and that are generally not predicted by preclinical studies. However, pyrogenicity is frequently an important effect in which the rabbit model is quite predictive for endotoxin toxicity. Animal models are sometimes effective and sometimes not effective as predictors of other types of toxicity, or of potency, of novel adjuvants in humans.

References:

1. Fries LF, Gordon DM, Richards RL, et al. Liposomal malaria vaccine in humans: a safe and potent adjuvant strategy. Proc Natl Acad Sci USA. 1992;89(1):358-362.
2. Glenn GM, Taylor DN, Li X, Frankel S, Montemarano A, Alving CR. Transcutaneous immunization: A human vaccine delivery strategy using a patch. Nature Med. 2000;6(12):1403-1406.
3. Güereña-Burgueño F, Hall ER, Taylor DN, et al. Safety and immunogenicity of a prototype enterotoxigenic Escherichia coli vaccine administered transcutaneously. Infect Immun. 2002;70(4):1874-1880.
4. Alving CR. Design and selection of vaccine adjuvants: animal models and human trials. Vaccine. 2002;20(Suppl 3):S56-S64.
5. Alving CR, Rao M. Lipid A and liposomes containing lipid A as antigens and adjuvants. Vaccine. 2007 Dec 26; [Epub ahead of print]
6. Alving, CR. Vaccine adjuvants, in Barrett A, Stanberry L, eds: *Vaccines for Biodefense and Emerging and Neglected Diseases.* New York: Elsevier, 2008, in press.

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12 Innate Immune Response to Vaccine Adjuvants

Ennio De Gregorio
Novartis Vaccines and Diagnostics, Siena, Italy

Objective: Review molecular and cellular events associated with the intramuscular administration of different classes of vaccine adjuvants.

Summary: Oil in water emulsions are the most potent human vaccine adjuvants. Recently they have been instrumental for the development of effective, dose sparing pandemic influenza vaccines. To understand the molecular mechanisms of oil in water emulsions, we performed microarray analysis of the whole mouse muscle injected with MF59 and other two adjuvants, CpG and alum. MF59 induced a time dependent change in expression of 890 genes, while CpG and alum modulated 387 and 312 genes respectively. At early time points, MF59 activated the expression of the transcription factor JunB and the innate immunity sensor Ptx3 in muscle fibers, and the local expression of chemokine and proinflammatory cytokine genes. Subsequently, MF59 induced cytokine receptors, genes involved in leukocyte migration and ultimately antigen presentation genes. All adjuvants modulated the expression of a common set of 168 genes and promoted the recruitment of antigen presenting cells in the muscle; however, MF59 triggered a faster influx of blood cells. We propose that oil in water emulsions are the most efficient human vaccine adjuvants because they induce a rapid and strong immunocompetent environment at injection site.

Reference:

1. O'Hagan DT. MF59 is a safe and potent vaccine adjuvant that enhances protection against influenza virus infection. *Expert Rev Vaccines 2007;* 6:699-710.

13 Rational Adjuvants Based Upon the Innate Immune System

Richard Flavell
Yale University School of Medicine, New Haven, CT

Objective: Review molecular and cellular events associated with the intramuscular administration of different classes of vaccine adjuvants

Summary: Traditionally, adjuvants have been developed empirically and based upon the experience of decades of practical undertaking; a limited number of safe and effective adjuvants have been found. Still, very few adjuvants are available for use in humans, despite a great deal of effort.

The innate immune system provides immediate protection against infection, but is also required to potentiate the adaptive immune response which provides memory and hence, enhanced resistance to subsequent infection. Recent studies have shown that many components of the innate immune response contribute to the "adjuvant" function of various systems. Thus, stimulation of Toll-like receptors which mediate innate immune response through transmembrane receptors, potentiates adaptive immunity in a highly effective fashion. I will discuss the various ways in which this has been achieved. Recent work has shown that stimulation of other arms of the innate immune response is also effective, and shows that even traditional adjuvants function through these other innate pathways.

Reference:

1. Huleatt JW, Jacobs AR, Tang J, et al. Vaccination with recombinant fusion proteins incorporating Toll-like receptor ligands induces rapid cellular and humoral immunity. Vaccine. 2007;25(4):763-775.

14 Toll-Like Receptor 9 Activation with CpG DNA for Enhancing Prophylactic and Therapeutic Vaccines

Heather L. Davis
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Objective: Review how activation of the immune system through Toll-like receptors, such as TLR9 with CpG DNA, can lead to enhanced humoral and cell-mediated immune responses to vaccines

Summary: CpG motifs are a pathogen-associated molecular pattern found in viral and bacterial DNA. These activate innate immunity through Toll-like receptor 9 (TLR9), which is found in the endosomal compartment of human B cells and plasmacytoid dendritic (pDC) cells. Synthetic oligodeoxynucleotides containing CpG motifs (CpG ODN) may also be used for TLR9 activation and are under development as drug candidates. CpG ODN can be combined with antigens and used as vaccine adjuvants since direct activation of the innate immune system through TLR9 leads to subsequent activation of adaptive immunity. Animal studies show CpG ODN can augment the kinetics and strength of both antibody and cell-mediated responses to virtually all types of antigens. As well, CpG adjuvants are effective in hyporesponsive populations and at mucosal routes, and permit antigen dose sparing and earlier boosting. In human clinical studies, CPG 7909 (a B Class CpG) induced faster and higher titers of higher avidity antibodies to a commercial hepatitis B vaccine (Engerix-B®, GlaxoSmithKline) in normal volunteers. Similar results were found in a subsequent trial conducted in HIV infected subjects who failed to respond to previous vaccination, and the proportion of subjects remaining seroprotected up was significantly greater for the CpG than the control group, even 5 years later. The CpG group also had significantly stronger, long lasting lymphoproliferative responses. In other Phase I clinical studies, enhancement of the strength and kinetics of antibody responses were found with addition of CPG 7909 to either the BioThrax™ whole killed AVA anthrax vaccine (Emergent), or recombinant malaria vaccines containing either *Plasmodium falciparum* AMA1 or MSP1 adsorbed to alum (Malaria Vaccine Development Branch, NIAID).

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15 Saponin Based Adjuvants

Debbie Drane
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Objective: Discuss members of the novel class of saponin based adjuvants focusing on those which are advancing through clinical development

Summary: The adjuvant properties of saponin were first reported in the 1920's and its ability to increase antibody titres was subsequently studied in more detail in the 1930' and 40's leading to its use in veterinary vaccines in the 1950s. Although saponin is available from

a number of diverse sources the only effective source for adjuvant properties was found to be the bark of the *Quillaia saponaria* tree.

The use of saponin as an adjuvant for human vaccines was hindered by their complexity and concerns about toxicity. This led to the development of more purified saponin fractions and enhanced formulation methods. Saponin based adjuvants currently in clinical development include QS21, AS02, AS15, GPI0100 and ISCOMATRIX™ adjuvant. QS21 is fraction 21 of a HPLC elution of crude quillaia. AS02 and AS15 contain QS21 along with other immunomodulatory agents. GPI0100 is a chemical derivative of natural quillaia saponin. ISCOMATRIX™ adjuvant is a complex of ISCOPREP™ saponin with cholesterol and phospholipids which is then formulated with antigens to produce ISCOMATRIX™ vaccines. ISCOPREP™ saponin is a well defined multi-component fraction of crude quillaia.

ISCOMATRIX™ adjuvant combines the immunomodulatory power of saponin with antigen delivery capabilities to provide enhanced and accelerated antibody and T cell immune responses. Furthermore the ISCOMATRIX™ adjuvant can be reproducibly manufactured at large scale and has been extensively characterized. A range of ISCOMATRIX™ vaccines have been evaluated in clinical trials showing the adjuvant is safe and generally well tolerated and increases the vaccine immune responses.

Reference:

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16 Vaccination of Children: Benefits to their Families and Communities

James King
University of Maryland, Baltimore, MD

Objective: Review current literature regarding the "downstream" impact of preventing influenza infections in young children

Summary: There is increasing evidence that children are very important for the spread of influenza to their families and communities. A number of biological and behavioral factors are likely responsible for children to have increased transmission of influenza to others compared to adults. Epidemiologic data suggest that children are indeed amplifiers not just transmitters of influenza to the rest of the general population. Therefore, large-scale influenza vaccination of children should result in both direct and indirect reduction of the impact of influenza in the children's families and communities. This concept of 'downstream' protection resulting from large-scale influenza vaccination of children is supported by a number of retrospective and prospective studies. Data from these studies suggest a reduction of influenza related outcomes in family members and communities of children involved in these vaccination programs. In communities, these outcomes included reduced acute respiratory illnesses in adults and reduced mortality in the elderly. In families, these outcomes included reduced influenza related days of school and work lost, physician visits, medication purchases and doctor visits. Large-scale influenza vaccination of children should benefit not only themselves, but also their communities. This approach should be incorporated in public health responses to epidemic and pandemic influenza outbreaks.

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Abstracts of Invited Presentations

17 Herd Immunity to Influenza: Models and Measurement

M. Elizabeth Halloran
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Objective: Discuss concepts of herd immunity and how to model and measure indicators of such

Summary: Researchers have long believed that vaccinating schoolchildren annually would greatly curtail seasonal influenza in the general population. Recently, influenza vaccination of schoolchildren was recommended. Computer simulation results suggest that vaccination of schoolchildren would substantially reduce spread of influenza in the community. We present results of such models and discuss their relation to field studies. Some field studies have provided some evidence, though the results are open to criticism. We discuss a possible large-scale intervention study of influenza vaccination in which units such as school districts, cities, counties, or states introduce the vaccination campaign in a staggered fashion. We present field study designs to evaluate direct, indirect, total and overall effects of vaccination. Currently, influenza incidence is generally measured using non-specific case definitions, such as pneumonia and influenza-like illness. We show how virologic confirmation of a random sample of influenza-like cases can be used to estimate the proportion of the non-specific influenza-like cases that were in fact truly influenza.

Reference:

1. Halloran ME, Longini IM. Public health. Community studies for vaccinating schoolchildren against influenza. Science. 2006;311(5761):615-616.

18 Cost Effectiveness of Universal Vaccination

Lisa A. Prosser
Henry Ford Health System
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Objective: Review existing economic evidence regarding the cost-effectiveness of influenza vaccination of various population subgroups and consider this evidence in the context of a policy for universal vaccination

Summary: Current recommendations from the Centers for Disease Control and Prevention for routine annual influenza vaccination have been expanded in recent years to include most segments of the population except for healthy working-age adults. Cost-effectiveness evidence is one type of evidence considered during the policy decisions for influenza vaccination and can incorporate information on projected costs, risks, and health benefits of vaccination. Existing studies of the cost-effectiveness of influenza vaccination are mostly consistent with current recommendations for influenza vaccination. Cost-effectiveness ratios are most dependent on vaccination costs, vaccine effectiveness, and herd immunity. Vaccination is cost-saving under a wide range of assumptions for elderly populations. Favorable cost-effectiveness for healthy working-age adults will likely require more efficient vaccination delivery settings and consideration of benefits of herd immunity.

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3. Prosser LA, O'Brien MA, Molinari NA, et al. Cost-effectiveness of delivering adult influenza vaccination in non-traditional settings. Pharmacoeconomics. 2008;26(2):163-178.

19 Logistics of Universal Vaccination

Matthew Daley
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Denver, CO

Objective: Review immunization delivery issues under a scenario of universal influenza immunization, including the challenges and benefits of expanding influenza immunization in primary care offices

Summary: Because universal influenza immunization of children 6 months to 18 years of age substantially increases the number of children needing vaccination, increased capacity for immunization delivery will be needed. Most influenza vaccination currently occurs in physician offices, but little is known about the potential capacity of offices, including primary care offices, to meet increased demand. Within primary care offices, possible means of increasing capacity include using nurse-only visits during normal clinic hours, expanding clinic hours, or conducting dedicated influenza clinics. The opportunity costs of various approaches are important to consider, as absorbing additional clinic visits may lead to the deferral of other tasks.

Vaccine delivery in settings outside of primary care offices, such as in schools, emergency departments, and pharmacies, also represent a means to expand capacity. Influenza vaccination in these non-traditional settings has potential advantages, including increased convenience for parents and families and reduced burden of universal vaccination on primary care practices. Potential disadvantages of vaccination in these settings include the "scattering" of immunization records across multiple providers, the likelihood that non-traditional settings will not be aware of chronic medical conditions that children may have, and a lack of experience some settings may have with vaccinating younger children.

References:

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Abstracts of Invited Presentations

20 Universal Influenza Virus Vaccines

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Objective: Discuss cross-reactive immune response to influenza

Summary: Vaccines for influenza virus are seasonal vaccines which are updated annually in spring to incorporate the latest circulating viruses, and then produced and delivered before the peak influenza season starts in late fall and winter. The efficacy of seasonal vaccines is linked to their ability to induce virus-neutralizing antibodies, which provide subtype-specific protection to influenza A viruses. Influenza viruses due to antigenic drift can evade vaccine induced protection and the vaccines thus need to be given annually. Furthermore, through more pronounced mutations such as antigenic shifts, influenza viruses periodically evolve and cause global pandemics. Universal vaccines to influenza virus that induce broadly cross-reactive immune responses to all types of influenza A virus would not require annual vaccination and they could prevent outbreak of influenza virus pandemics. This lecture will discuss potential strategies to develop a universal vaccine to influenza A virus.

References:

1. Gerhard W, Mozdzanowska K, Zharikova D. Prospects for universal influenza virus vaccine. Emerg Infect Dis. 2006;12(4):569-574.
2. Lawson CM, Bennink JR, Restifo NP, Yewdell JW, Murphy BR. Primary pulmonary cytotoxic T lymphocytes induced by immunization with a vaccinia virus recombinant expressing influenza A virus nucleoprotein peptide do not protect mice against challenge. J Virol. 1994;68(6):3505-3511.

21 Prophylactic HPV Vaccines

Laura. A. Koutsky
University of Washington, Seattle, WA

Objective: Describe the epidemiology of genital HPV infections and the potential for prevention of HPV-related cancers and genital warts through vaccination

Summary: Of the over 100 HPV types identified to date, at least 37 are primarily transmitted through sexual activity. In rare instances such infections cause cellular changes that will progress to cancer if left untreated. Most cases of cervical cancer are caused by an HPV infection that was acquired in late adolescence or early adulthood. In fact, HPV is so common and communicable that many young women are infected with HPV by their first and only sex partner. With the recent development of prophylactic HPV vaccines, it is now possible to prevent infection with four HPV types that cause a large percentage of HPV-related cancers and genital warts. The quadrivalent HPV6/11/16/18 vaccine has been licensed for use among females, 9 to 26 years of age in the US, and in many other countries. The bivalent HPV16/18 vaccine has been licensed for use in females in Europe and in other countries, and is currently under review in the US. Both vaccines have acceptable safety profiles, and have the potential to substantially reduce HPV-related morbidity and mortality. Now that prevention of many HPV-related cancers and intraepithelial lesions has become a possibility, the challenge is to implement immunization programs that are based on knowledge of optimal ages and genders for routine and "catch-up vaccination," barriers to access, and impact on participation in cervical cancer screening programs.

Reference:

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22 Rotavirus Vaccines for the Developing World: Future Concerns and Future Options

Roger I. Glass
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Objective: Discuss the rationale for immunizing children against rotavirus and the basis upon which current vaccine recommendation have been formulated

Summary: Rotavirus vaccines currently licensed in more than 90 countries hold the promise of preventing more than 600,000 diarrhea deaths and many hospitalizations and doctor visits worldwide. While the positive impact of vaccination programs is just becoming evident in US and middle income countries of Latin America, vaccine efficacy in poor developing countries remains to be determined, and some ominous signs are appearing that are cause for concern. Live oral vaccines against polio and cholera have been problematic for populations living in the developing world, and rotavirus is no exception. The immune response to the GlaxoSmithKline vaccine in infants in S. Africa and Bangladesh has been substantially less than that measured in studies in Latin America, the US and Finland. This lower immune response may reflect lower efficacy and trials ongoing should determine the efficacy in two populations in Sub-Saharan Africa. The reasons for this impaired immune response are numerous-high titers of maternal antibody, breast feeding practices, and interfering gut flora, micronutrient deficiency-to name a few; ways to address these issues will be key to either improving these vaccines or to rejecting them should the results of ongoing field trials prove disappointing. Research is needed today to identify the cause of the low immune responses and to identify strategies to improve this problem. Insurance policies to consider new vaccines should be considered as well so that alternative vaccine candidates are in the wings should they be needed.

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Abstracts of Invited Presentations

23 Quadrivalent Meningococcal Conjugate Vaccine

Nancy E. Messonnier
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Objective: Review meningococcal conjugate vaccines, focusing on issues surround recent licensure and use of these vaccines in the U.S.

Summary: Meningococcal disease, caused by the bacteria *Neisseria meningitidis*, is a leading cause of bacterial meningitis and sepsis in the United States and globally, with one out of four cases leading to death or long term disability. Although rates of disease are highest among children aged <2 years, more than half of meningococcal disease in the U.S. occurs among persons aged ≥11 years. The proportion of cases caused by each serogroup varies by age group. Among infants aged <1 year, 50% of cases are caused by serogroup B, for which no vaccine is licensed or available in the U.S. Of all cases of meningococcal disease among persons aged ≥11 years, approximately ¾ are caused by serogroups (C, Y, or W-135) which are included in vaccines available in the U.S.

In January 2005, a tetravalent meningococcal polysaccharide-protein conjugate vaccine ([MCV4] Menactra™, manufacturered by sanofi pasteur, Inc., Swiftwater, Pennsylvania) was licensed for use among persons aged 11-55 years. In October 2007, MCV4 was approved for use among 2-10 year olds.

CDC's Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with 1 dose of MCV4 for persons aged 11-12 years, persons entering high school (i.e., at approximately age 15 years) if not previously vaccinated with MCV4, and other persons at increased risk for meningococcal disease, including college freshmen living in dormitories. ACIP recommends routine vaccination of children aged 2–10 years who are at increased risk for meningococcal disease; MCV4 is preferred to meningococcal polysaccharide vaccine ([MPSV4], Menomune®, sanofi pasteur). ACIP does not recommend routine vaccination against meningococcal disease in children aged 2-10 years at this time, except for children at increased risk of disease.

Reference:

1. Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2005;54(RR7):1-21.

24 Vaccination Against Herpes Zoster and Postherpetic Neuralgia

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Objective: Describe the epidemiology and pathogenesis of herpes zoster and postherpetic neuralgia

Summary: The frequency and severity of herpes zoster (HZ) and its most common debilitating complication, postherpetic neuralgia (PHN), increase with increasing age in association with a progressive age-related decline in cell-mediated immunity (CMI) to varicella-zoster virus (VZV). The Shingles Prevention Study (VA Cooperative Study #403) demonstrated that a high-potency live attenuated VZV vaccine (zoster vaccine), which stimulates VZV-specific CMI, protected immunocompetent adults age 60 years and older from HZ and PHN. The Shingles Prevention Study was a double-blind placebo-controlled trial in which 38,546 subjects ≥60 years of age were stratified by age (60-69; ≥70 years) and randomized to receive a single dose of zoster vaccine or placebo. They were then actively followed for HZ and PHN.

Zoster vaccine reduced the *burden of illness due to HZ*, a severity-by-duration measure of the total pain and discomfort caused by HZ, by 61.1% - by 65.5% in 60-69 year-olds and by 55.4% in subjects ≥70 years of age. Zoster vaccine reduced the *incidence of PHN* by 66.5% - by 65.7% in 60-69 year-olds and by 66.8% in subjects ≥70 years of age. Zoster vaccine also reduced the *incidence of HZ* by 51.3% - by 63.9% in 60-69 year-olds, but by only 37.6% in subjects ≥70 years of age. Zoster vaccine was well tolerated and neither induced nor caused HZ in this population.

The FDA licensed zoster vaccine (ZOSTAVAX™; Merck & Co., Inc.) for the prevention of herpes zoster on the basis of these results on May 25, 2006. On October 25, 2006 the Center for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) made a provisional recommendation to administer a single dose of zoster vaccine to adults 60 years of age and older for the prevention of herpes zoster (shingles) and postherpetic neuralgia, regardless of a prior history of HZ. In October 2007, zoster vaccine was added to the CDC's list of recommended adult immunizations.

A number of questions regarding the appropriate use of the zoster vaccine will be discussed, including the differences between the FDA's "Product Approval Information" (the "Package Insert") and the ACIP's recommendation; the rationale for vaccinating persons with a history of HZ; the potential use of zoster vaccine in persons younger than 60 years of age; the duration of vaccine efficacy and the possible need for and timing of a "booster" dose; vaccine safety and efficacy in persons ≥80 years of age; the need to keep the lyophilized vaccine frozen; and coverage by Part D of Medicare.

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1. Oxman MN, Levin MJ, Johnson GR, et al. Prevention of herpes zoster and postherpetic neuralgia in older adults with a live attenuated varicella-zoster virus vaccine: results of Department of Veterans Affairs Cooperative Study #403 - the Shingles Prevention Study. New Engl J Med. 2005;352(22):2271-2284.
2. Oxman MN: Vaccination to prevent herpes zoster and postherpetic neuralgia. Human Vaccin. 2007;3(2):64-68.

ABSTRACTS OF ORAL SUBMITTED PRESENTATIONS

Abstracts of Oral Submitted Presentations

S1 A Phase I/II, Randomized, Double-blinded Placebo-controlled Trial to the Safety, Reactogenicity, and Immunogenicity of Immunization with Inactivated Subvirion Influenza A/H5N1 Vaccine Administered by the Intradermal or the Intramuscular Route among Healthy Adults

S. M. Patel, R. L. Atmar, H. El Sahly, T. R. Cate, W. A. Keitel
Baylor College of Medicine, Houston, TX

Background: Intradermal (ID) immunization has been proposed as a potential dosage-sparing strategy for immunization against influenza. Results of previous studies of ID immunization have been inconsistent, and in most studies direct comparisons of similar dosages given by the intramuscular (IM) or the ID route have not been made. **Methods:** 226 healthy 18-49 year old adults were randomized to receive 2 doses one month apart of either placebo or a subvirion inactivated influenza A/H5N1 vaccine containing 30µg of H5N1 hemagglutinin (HA) by the IM or ID route. Serum samples for antibody assays were collected before and one month after each immunization. The study was powered to detect a 20% absolute increase in seroresponse frequency in the ID vaccine group, assuming a 30% seroresponse frequency in the IM vaccine group. **Results:** Immunization by both routes was safe and well tolerated. Seroresponse frequencies and the geometric mean titer (GMT) of serum hemagglutination-inhibition (HAI) and neutralizing (Neut) antibodies one month after receipt of two doses of vaccine are shown in the table.

Vaccine	HAI Antibody Response			Neut Antibody Response		
Group	≥4-fold rise*	≥40 Titer	GMT	≥4-fold rise	≥40 Titer	GMT
IM	35% (27-45)†	35% (27-45)	18.1 (13.6-24.1)	51% (42-61)	51% (42-61)	33.1 (26.5-41.3)
ID	42% (32-51)	42% (33-52)	25.2 (18.3-34.5)	57% (47-66)	60% (51-69)	42.7 (34.3-53.0)

* % with ≥4-fold increase in titer (increase from<10 pre to ≥40 after immunization)
† 95% confidence interval

Conclusions: Immunization with this inactivated influenza A/H5N1 vaccine by the IM and ID routes was well tolerated. Immune responses after two doses containing ~30µg of influenza A/H5N1 HA were not significantly different when given by the ID or IM route.

References:

1. Belshe RB, Newman FK, Cannon J, et al. Serum antibody responses after intradermal vaccination against influenza. N Engl J Med. 2004;351:2286-2294.
2. Patel SM, Atmar RL, El Sahly H, Cate TR, Keitel WA. A randomized, open-label, phase I clinical trial comparing the safety, reactogenicity, and immunogenicity of booster immunization with inactivated influenza A/H5N1 vaccine administered by the intradermal (ID) or the intramuscular (IM) route among healthy adults. Abstract LB-5, 44th Annual Meeting of the IDSA, Toronto, Ontario; October 2006.

S2 A Phase I, Randomized, Double-blind, Placebo-controlled Dose Ranging Clinical Trial of the Safety, Reactogenicity and Immunogenicity of Immunization with Inactivated Vero Cell Culture-derived Influenza A/H5N1 Vaccine Given Alone or with Aluminum Hydroxide to Healthy Young Adults

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Background: Dosage-sparing strategies are being explored for the development of vaccines against potential pandemic influenza viruses. We evaluated whether aluminum hydroxide (AlOH) could enhance immune responses to an influenza A/H5N1 vaccine. **Methods**: 306 healthy 18-40 year old subjects were enrolled in a multicenter trial of several formulations of a Vero cell culture-grown, inactivated whole virus H5N1 vaccine (*wt* A/VN/1203/2004). Subjects were randomized to receive 2 doses 1 month apart of vaccine containing either 7.5 or 15µg of H5N1 hemagglutinin (HA) +/- 350µg/dose AlOH; 45µg of H5N1 HA without AlOH; or placebo (~50/group). Subjects were followed for adverse events; sera for antibody assays were obtained before and 1 month after each dose. **Results**: No serious clinical or laboratory adverse events related to vaccine were reported. Dose-related increases in injection site discomfort were noted; most reactions were mild. Antibody responses 1 month after each dose are shown.

Vaccine Group (µg HA)	HAI Antibody (Dose1, Dose2)		Neutralizing Antibody (Dose1, Dose2)	
	% with ≥4-fold rise†	GMT†*	% with ≥4-fold rise†	GMT†*
7.5	8, 19	6+, 11	10+, 17	7+, 13+
7.5 + AlOH	0, 8	5+, 7	0+, 6	5+, 8+
15	12, 18	8, 9	10, 27	9+, 20+
15 + AlOH	2, 8	6, 8	0, 17	6+, 13+
45	17, 40	10, 18	19, 44	11, 32
Placebo	0, 0	5, 5	0, 0	5, 5

+ $p<0.05$; 7.5- vs.7.5+ and 15- vs. 15+
† $p<0.05$; nonadjuvanted groups after dose 2
*$p<0.05$; adjuvanted groups after dose 1 (HAI) and dose 2 (Neut)

Conclusions: All formulations were well tolerated. Increasing HA dosage increased antibody responses. Addition of AlOH reduced the immunogenicity.

References:

1. Keitel WA, Atmar RL. Preparing for a possible pandemic: influenza A/H5N1 vaccine development. Curr Opin Pharmacol. 2007;7(5):484-490. 17.

Abstracts of Oral Submitted Presentations

S3 Pandemic Influenza Preparedness: Identification of Serological Epitopes for Use in the Evaluation and Development of Broadly Protective Vaccines

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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-phage display libraries (GPDL) expressing all the open reading frames of avian influenza H5N1 (A/Vietnam/1203/2004 & A/Indonesia/5/05) viruses were constructed. Each GPDL contains 10^9-10^{10} 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 monoclonal antibodies derived from B cells of H5N1 exposed individuals; b) serum antibodies from H5N1 survivors; c) immune sera from unadjuvanted and adjuvanted pandemic influenza vaccinees. **Results**: Binding of broadly neutralizing H5 human monoclonal antibodies require large sequences in the n-terminal half of HA1, encompassing the receptor binding site, to form their conformational epitopes. Critical contact residues, which could explain the cross-clade neutralization of some of the mAbs, were identified. In convalescence sera from H5N1 survivors, a very broad epitope profile was observed. Several novel potentially protective epitopes were identified both in HA and NA. First generation inactivated H5N1 vaccine elicited limited repertoire of anti-H5N1 antibodies. Sera from adjuvanted vaccine recipients are under investigation. **Conclusions**: The FLU-GPDL 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.

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S4 Immunogenicity and Cross Protective Antibody Responses Among HA Antigens from Different Clades of Highly Pathogenic Avian Influenza H5N1 Viruses

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Background: Avian influenza A (H5N1) viruses have caused concern over their ability to cause pandemic influenza. Studies have indicated that there are at least 9 clades of H5N1 viruses. Therefore, it is important to determine whether H5N1 vaccines using antigens from one clade can elicit protection against other H5N1 clades. The current study investigated the immunogenicity and cross antibody responses using HA antigens from several H5N1 clades. **Methods:** Rabbits received DNA vaccines constructed to express codon optimized HA antigens from key vaccine strains of H5N1 with diverse genetic backgrounds. Sera were collected for binding and functional antibody responses. **Results:** H5N1 HA DNA vaccines are highly immunogenic as measured by antigen-specific IgG binding antibodies. The HA antigens used in our studies are the original viral HA antigens without any deletion/mutation at the HA cleavage site. Although high titer haemaglutination inhibition and microneutralization antibodies are detected against autologous and heterologous H5N1 viruses, levels of cross reactivity are highly strain-specific. Some HA antigens are more capable in eliciting higher levels of protective antibodies against heterologous viruses. **Conclusions:** Not every H5N1 HA antigen elicits similar breadth of protective antibodies against heterologous H5 viruses. HA DNA vaccines offer unique technology advantages to screen/optimize the selection of vaccine strains with broad protection.

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S5 Effective and Inexpensive Influenza Vaccine in Poultry: Dose Escalation and Route of Administration Studies of an Adenovirus-based Influenza A (H5N1) Vaccine in Chicken

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The emergence and recurrent outbreaks of highly pathogenic influenza virus (H5N1) in poultry and the multiple cases of transmission to humans stimulated the development of avian influenza vaccines in the last few years. Recently, we demonstrated that immunization with recombinant adenovirus encoding the hemagglutinin protein of the influenza A virus was able to induce humoral and cellular immune responses against HA in addition to providing complete protection against H5N1 influenza virus in mouse and chicken challenge models. To examine the protective efficacy of Ad-HA vaccine in poultry, we first investigated different routes of administration in the chicken including: intratracheal, conjunctival, *in ovo*, and subcutaneous application. We performed dose escalation studies to address the minimal dosage to induce HA-specific immune responses. The Ad-HA vaccine induced HI-titre in sera of immunized chickens; in particular, subcutaneous immunization with 10^7 Ad-HA particles/chicken was sufficient to induce high HI-titre and substantial cross-reactivity against an H5N1 strain from a different clade (clade 2). These data indicate that the Ad-HA vaccine is an excellent candidate to immunize poultry in an efficient, easy, and cost-effective manner, which would reduce the environmental load of H5N1 and its transmission to humans.

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Abstracts of Oral Submitted Presentations

S6 Protective Immune Responses by Multivalent Influenza Virus-like Particles

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Background: Conventional egg-grown influenza vaccines are trivalent and intramuscularly administered. Although influenza virus-like particles (VLPs) have been demonstrated to be a promising alternative vaccine, multivalent influenza VLPs have not been investigated. In this study, we tested the bivalent influenza VLPs to provide a proof-of-concept to parallel the influenza vaccines. **Methods**: We developed cell-derived influenza VLPs containing the hemagglutinin (HA) of the H1 subtype virus A/PR/8/34 or the H3 subtype virus A/Aichi/2/68. Mice were immunized intramuscularly with bivalent influenza VLPs containing H1 and H3 HAs, and neutralizing antibodies and protective efficacies were determined. **Results**: Mice that immunized with bivalent VLPs induced neutralizing activities against the homologous and closely related H1N1 strains A/PR/8/34 and A/WSN/33 as well as the H3N2 strains A/Aichi/2/68 and A/Hong Kong/68, but not the A/Philippines/2/82 strain isolated 14 years later. HA sequence and structure analysis indicated that antigenic distance could be a major factor in predicting cross-protection by VLP vaccines. The bivalent influenza VLP vaccine demonstrated broader protective immunity after challenge infections when compared to a monovalent influenza VLP vaccine as expected. Immunization of mice with influenza VLPs induced memory B cell responses and long-term protective immunity even after 14-months post-immunization. **Conclusion**: Multivalent influenza VLP vaccines are an effective strategy for developing safe and alternative vaccine to control the spread of influenza viruses.

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S7 Design of a Broadly Protective Influenza Vaccine

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Current influenza vaccines provide little, if any, protection from divergent drifted circulating virus strains. Thus, the H3N2 Wisconsin in the 2007-8 trivalent vaccine has failed to induce robust protective immunity against infection by the dominant seasonal subtype, A/Brisbane. The Deceptive Imprinting Hypothesis suggests that the immune system overreacts to strain-specific immunodominant epitopes while failing to develop antibody responses to more highly conserved epitopes that overlap functional domains such as receptors. We hypothesized that masking the immunodominant epitopes would allow the immune system to target more broadly protective epitopes. To test this hypothesis, we designed a panel of immune refocused hemagglutinin (HA) subunit antigens with mutations in the defined immunodominant epitopes. Mice were immunized with a DNA prime and recombinant HA protein boost and the sera tested for hemagglutination inhibition (HA-I) activities against homologous (Wyoming) and heterologous H3N2 viruses. Although the sera from each of the animal groups contained similar levels of anti-HA antibodies as measured by HA ELISA (1:300,000), the HA-I activities against different H3 subtypes varied widely. Sera from some of the novel vaccine candidates had heterologous HA-I titers that were 8-fold higher than sera from unmodified HA immunizations when tested against viruses such as Wellington and Panama subtypes (1:10,240 vs. 1:1280 and 1:1920 vs. 1:226, respectively). The data suggest that immune refocusing technology can lead to the design of vaccines with pronounced improvements in cross-protection. The presentation will discuss the data generated in the course of this study, outline future directions, and request input from the audience.

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1. Nara PL. Deceptive imprinting: insights into mechanisms of immune evasion and vaccine development. Adv Vet Med. 1999;41:115-134.

S8 NicVAX®, a Nicotine Conjugate Vaccine, Aids Smokers to Quit Smoking and Stay Quit: Animal and Human Data in Support of a Proposed Mechanism of Action

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Background: About 42 million Americans smoke cigarettes, with 440,000 annual deaths related to smoking tobacco. Available therapies yield moderate results (20-40% quit rates, but the vast majority relapse to smoking by 1 year. NicVAX® induces specific antibodies that block nicotine from reaching the brain, thus prevent its reinforcing action. **Methods**: NicVAX® was evaluated in animals for preventing nicotine addiction and withdrawal and in humans for safety, immunogenicity and efficacy in aiding smoking cessation. **Results**: 1) robust animal models show NicVAX® antibodies significantly extend the half life of nicotine, prevent acquisition of self administration, and attenuate withdrawal symptoms in nicotine-addicted animals; 2) NicVAX® in human trials safely induced high antibody levels resulting in 24% smoking cessation at six months compared to placebo ($P<0.05$) without increased craving and withdrawal symptoms. These quitters were able to stay quit for 12 months (odds ratio 3.84, $p=0.014$); and 3) high-antibody vaccinees who continued to smoke not only did not increase their cigarette consumption, but actually smoked significantly less ($p=0.002$). **Conclusion**: We hypothesize that NicVAX® antibodies work through capture release mechanism and prevent nicotine from reaching the brain thus interrupting drug reinforcement and resulting in smoking cessation. Antibodies work through capture release mechanism to interrupt drug reinforcement resulting in acute quit. Persisting antibody levels capture nicotine from voluntary or involuntary exposure (slips or second hand smoke) and prevent recalling past experiences and pleasures from cigarette smoking that lead to restarting the cycle of addiction.

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Abstracts of Oral Submitted Presentations

S9 Improved Immune Responses Following Intradermal Vaccination of a Consensus Influenza DNA Vaccine Using Electroporation in Non-human Primates

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This presentation highlights our comprehensive development of novel methodologies for a universal influenza DNA vaccine using constant current electroporation. First, we developed consensus antigens that can offer cross protection against a series of influenza viruses. Second, we designed a skin-specific electroporator that minimizes the discomfort usually associated with an intramuscular (IM) vaccination procedure while maximizing the immunogenicity by using an intradermal (ID) electroporation (EP) delivery. Finally, we have developed a novel formulation that maximizes the plasmid concentration (more than 10 mg/mL) allowing delivery of a required plasmid dose in the smaller volume of a regular ID injection. We have tested the delivery of an avian influenza H5 antigen to groups of non-human primates (n=5/group) using the following routes: IM, ID+EP, IM+EP. One group was not vaccinated and served as negative control. The EP was performed using CELLECTRA^{TM} adaptive constant-current EP device. Animals were immunized at three-week intervals for a total of three immunizations and HI titers were measured. Results were analyzed using ANOVA and post-hoc t-tests. The ID+EP group yielded the highest titers after one vaccination (120±25, $p<0.05$ compared to IM+EP and controls), which was maintained to four weeks post-third vaccination (352±78). Both EP approaches yielded enhanced levels of protective HAI titers (>1:40) compared to the IM alone or the control animals. Significant HI titers persisted in IM+EP animals to 14 weeks post-third vaccination (116±52). Overall these findings demonstrate that delivery of influenza antigens using ID+EP could be an important vaccination strategy and has important advantages over current influenza vaccine approaches.

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2. Hirao LA, Wu L, Khan AS, Satishchandran A, Draghia-Akli R, Weiner DB. Intradermal/subcutaneous immunization by electroporation improves plasmid vaccine delivery and potency in pigs and rhesus macaques. Vaccine. 2008;26(3):440-448.

S10 Discovery of Naturally Processed Class I HLA Vaccinia Virus T-Cell Epitopes Using Mass Spectrometry: Rational Design of a Multiepitope Smallpox Vaccine

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Background: To date, the majority of known T-cell epitopes from vaccinia virus have been discovered using predictive computer algorithms. While algorithms have become increasingly successful at predicting peptides that bind to HLA, there still exists a gap in predicting which peptides are naturally produced by the proteasome and transported to the HLA molecules. **Methods:** Using 2-dimensional liquid chromatography coupled to mass spectrometry (MS), we isolated a spectrum of class I HLA-presented (A*0201, B*1501, and C*03) vaccinia peptides derived from the NYCBOH vaccine strain. **Results:** A total of 120 peptides encoded by 63 vaccinia open reading frames (ORFs) were identified. Importantly, 69 (58%) of these peptides are highly conserved in distinct proteins of vaccinia and variola major viruses. Of these 69 naturally processed peptides, 9 peptides were 12 amino acids long or longer, and another 12 were 11 amino acids long. These 21 peptides were outside of the range of predictive algorithms. Seven of the peptides have been previously reported to have immunogenic properties, including ILDDNLYKV (ORF G5R), which has been classified as an immunodominant vaccinia epitope. The other immunogenic peptides are: KLFTHDIML, ILSDENYLL, KIDYYIPYV, FLTSVINRV, NLFDIPLLTV, and GLLDRLYDL. Predictive computer algorithms were insufficient in predicting the full repertoire of naturally presented vaccinia peptides, failing to predict approximately 22% of the peptides identified by MS. **Conclusions:** These data provide the first evidence that multiple naturally processed vaccinia peptides can be efficiently identified in the context of several class I HLA (A, B, and C) alleles and are missed by predictive algorithms. Direct identification of vaccinia-derived peptides from the peptide binding groove of HLA molecules is important for understanding both poxvirus immunity and future multiepitope-based vaccine development.

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S11 Epitope-based Immunome-derived Vaccines: A Strategy for Improved Design and Safety

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Background: Vaccine science has extended beyond genomics to proteomics and has come to also encompass "immunomics," the study of the universe of pathogen-derived or neoplasm-derived peptides that interface with B and T cells of the host immune system. It has been theorized that effective vaccines can be developed using the minimum essential subset of T and B-cell epitopes that comprise the "immunome." **Methods:** Our research group has been using bioinformatics sequence analysis tools, epitope-mapping tools, micro arrays and high-throughput immunology assays to discover the minimal essential components of the immunome so as to develop a range of vaccines, including HIV, TB, Tularemia, *H.Pylori,* HPV and EBV. We use EpiMatrix and Conservatrix to identify minimal components, or epitopes, from genome data. We then align and package these epitopes in string-of-beads DNA constructs and/or liposomes with adjuvants, using EpiAssembler and VaccineCAD (computer-driven algorithms) to find the best alignment of the sequences, the complete package comprises an epitope-based immunome-derived vaccine. **Results:** Epitope driven, immunome-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. This presentation will review the pre-clinical and anticipated clinical

(continued)

development of computer-driven vaccine design and the validation of epitope-based immunome-derived vaccines in animal models. It will also include an overview of heterologous immunity and other emerging issues that will need to be addressed by vaccines of all types in the future.

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S12 Preclinical Evaluation of a Multivalent Powder Vaccine against Anthrax, Botulism, Plague and Staphylococcal Toxic Shock

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Background: A solution containing the combination of four recombinantly-derived subunit antigens; Protective Antigen (PA) of *Bacillus anthracis*, botulinum neurotoxin A, C-fragment (BoNT-A), F1-V fusion protein of *Yersinia pestis* (plague) and Staphylococcal Enterotoxin B (SEB), was formulated with excipients prior to spray freeze dried (SFD) into a Multivalent Powder Vaccine (MPV). The antigens were adsorbed to aluminum hydroxide adjuvant upon reconstitution. **Methods:** Mice were immunized with reconstituted MPV by intradermal (ID) injection using a minimally-invasive microneedle device, then challenged with a lethal dose of either *B. anthracis, Y. pestis*, BoNT-A or SEB. For comparison, mice were challenged following immunization with reconstituted monovalent powder vaccines or with multivalent or monovalent liquid formulations of each of the four subunit proteins adsorbed to aluminum hydroxide. **Results:** Mice immunized with reconstituted MPV generated antibody responses against all four antigens at levels similar to those elicited by the liquid version of the multivalent vaccine. In addition, the multivalent vaccine formulations induced antibody titres against all four antigens that were comparable to those induced by the monovalent liquid and powder controls. Upon challenge, mice immunized with MPV, exhibited levels of protection of up to 100%, comparable to, and in some cases greater than from liquid and monovalent controls. **Conclusion:** These results demonstrate the successful combination of multiple antigens into a single MPV and show the viability of an alternate route of delivery. Adoption of this technology could potentially reduce the number of vaccinations required to protect against multiple bioterrorism agents by combining several antigens into one easily administered and effective vaccine.

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S13 Component Specific Estimates of Influenza Vaccine Effectiveness Based on a Sentinel Physician Network, 2006-07 Season

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Background: Trivalent inactivated influenza vaccine (TIV) is reformulated annually to contain two influenza A subtypes (H1N1 *and* H3N2) and one B lineage (Yamagata *or* Victoria). We describe a case-control approach to derive component-specific vaccine effectiveness (VE) against laboratory-confirmed influenza using a sentinel physician network. **Methods:** TIV components for 2006-07 included A/NewCaledonia/20/99(H1N1)-like, A/Wisconsin/67/2005(H3N2)-like and B/Malaysia/2506/2004-like(Victoria lineage). Participants presented with influenza-like illness (ILI) to a sentinel physician in British Columbia, Alberta or Quebec, Canada between November, 2006-April, 2007. Cases were participants in whom influenza was identified; controls tested negative by PCR and culture. Isolates were characterized by hemagglutination-inhibition (HI) and gene sequencing. Odds ratios (OR) for influenza in vaccinated versus non-vaccinated persons were derived. VE was estimated as 1-OR. **Results:** 841 participants were included: 20% received TIV ≥2weeks prior to ILI onset, 14% had a chronic condition, 10% were ≥65years old. 337(40%) were positive for influenza: 242(72%) A/H3N2, 55(16%) A/H1N1, 4(1%) non-subtyped A and 36(11%) influenza B. All but one of the A/H1N1 isolates characterized were well-matched to vaccine (one A/SolomonIslands/3/2006-like). More than one-third of A/H3N2 isolates characterized showed four-fold-reduced HI titres to the vaccine component with clustering around A/Brisbane/9/2006 (H3N2)-like or A/Nepal/921/2006(H3N2)-like variants on sequencing. All influenza B isolates characterized were mismatched to vaccine as B/Shanghai/361/2002-like(Yamagata lineage). Age-adjusted VE for the A/H1N1, A/H3N2 and B components was: 92% (95%CI 42%-99%), 41% (95%CI 5%-63%) and 19% (95%CI 0-69%) with overall VE of 47% (95%CI 18%-65%). **Conclusions:** VE varies with vaccine component and the proportionate mix of circulating influenza subtypes, strains and drift variants. Overall VE estimates are not generalizable to communities with different profiles of circulating viruses. Component-specific estimates should be derived where possible. Despite relative vaccine mismatch, cross-protection is found.

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S14 Cellular and Humoral Immune Responses of Elderly Adults Who Received a High-dose or Standard-dose Influenza Vaccine

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Background: The elderly respond poorly to vaccination. In fact, it is even controversial whether influenza vaccination is effective in the elderly population. A higher dosage influenza vaccine has been shown to improve vaccine responses, but it is not known how these responses might compare to those of young adults. **Methods:** Healthy elderly adults (age≥65) received a standard-dose, Fluzone®, (ES, n=26) or a high-dose influenza vaccine (EH, n=23). For comparison, young adults (age 18-40) received standard-dose (YS, n=14) vaccine. The high-dose vaccine contained four times greater hemagglutinin than the standard-dose. Samples were obtained on days 0 and 28; we measured: hemagglutination inhibition (HAI), viral microneutralization (VN), total ELISA IgG and IgA antibodies, IgG subclasses, and IFN-Á production.

Results

		HAI			VN			ELISA IgG		ELISA IgA		IFN-γ ELISpot*	
		%≥1:32	%4x^	GMT	%≥1:32	%4x^	GMT	%4x^	ΔGMT	%4x^	ΔGMT	SFC	Fold^
H1N1	YS	100	64	380	100	57	580	44	107214	50	1681	145	4.1
	ES	42	15	69	100	12	193	0	6541	0	27	50	2.5
	EH	83	52	68	96	52	292	0	10929	0	71	55	2.8
H3N2	YS	100	40	312	100	64	780	71	80645	14	236		
	ES	85	12	81	96	15	220	8	8413	0	11		
	EH	87	39	95	96	26	244	13	11325	0	26		
B	YS	79	79	82	93	79	168	11	8902	14	114		
	ES	47	19	27	96	31	123	0	624	0	35		
	EH	74	61	64	100	70	237	13	1593	4	31		

* response to preservative-free Fluzone

Discussion: Influenza is a leading cause of morbidity and mortality in the elderly and vaccination is the primary means of prevention. We show that humoral and cellular immune responses of the elderly fared poorly in comparison to the young adult in response to a currently FDA-approved seasonal influenza vaccine. A higher dose improves the immune response of the elderly but still falls short of those of the young, particularly for IFN-Á production. We are performing further studies to examine T cell proliferation, cytokine-producing subpopulations and ex vivo frequency of influenza specific T cells by MHC-peptide multimer staining and flow cytometry.

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S15 Superior Immunogenicity of High Dose Influenza Vaccine in Demographic Subgroups of Elderly Subjects

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Background: Since the very elderly and those with chronic medical conditions may be most at risk of severe influenza and a suboptimal response to standard dose influenza vaccine (SD), we explored the effects of age, gender and underlying cardiopulmonary disease on the immune response to a high dose trivalent inactivated split-virion influenza vaccine (HD) (60µg hemagglutinin (HA)/strain). **Methods:** In a multicenter randomized phase 3 study (2006/07 strains), post-hoc analyses evaluated the immunogenicity 28 days post-vaccination of HD versus a licensed SD vaccine (15µg HA/strain), each given as one 0.5ml IM injection, in subgroups of non-institutionalized, medically stable adults aged ≥65 years. **Results:** Of 2576 subjects who received HD and 1275 SD, 35.4% and 36.0% were aged ≥75 years, 51.3% and 54.6% were women, and 71.0% and 72.6% had cardiopulmonary disease. Immunogenicity results met the pre-defined criteria for overall superiority of HD vaccine (superiority for ≥2 strains and non-inferiority for 3 strains). Within each age group (<75 or ≥75 years) responses were significantly greater with HD than SD: the ratio of hemagglutination inhibition (HAI) antibody GMT between groups (HD/SD) for each strain ranged between 1.35-1.95 among those <75, and 1.27-1.68 among those ≥75 years. Seroprotection rates (HAI ≥1:40) were significantly higher for HD than SD in both age groups and genders for all three strains. Both vaccines elicited significantly greater responses in women than men, but HD/SD GMT ratios (women: 1.30-1.80; men: 1.34-1.91) and seroprotection rates were comparable between genders. Underlying cardiopulmonary disease did not affect immune response to either vaccine. **Conclusions:** Overall superior immunogenicity observed with HD versus SD was maintained irrespective of gender, age group or underlying cardiopulmonary disease.

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S16 Effect of Salmeterol on T cell Responses to Influenza Vaccine in Heart Failure Patients

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Background: The beta-2 adrenergic receptor (β2AR) has increased importance in heart failure (HF) due to β1 receptor downregulation. Catecholamines may decrease T-cell immune responses through the β2AR. HF patients are at high risk for influenza complications and mount less vigorous T-cell immune responses to influenza vaccine. We hypothesized that beta blocker therapy with carvedilol in HF patients would influence in vitro response to salmeterol, a beta-2 agonist that affects T-cell mediated vaccine responses. **Methods:** We studied 21 HF patients on target doses of non-selective beta blocker therapy and 17 healthy controls. Participants received the inactivated influenza vaccine, and underwent phlebotomy before and 2-4 weeks after vaccination. Influenza-specific T-cell responses (via IFNγ and IL-10 production) were measured in isolated peripheral blood mononuclear cells (PBMCs) using ELISA. β2AR effects were studied by culturing cells with and without salmeterol for 96 hours prior to ELISA. **Results:** HF patients showed similar T-cell responses to influenza vaccine compared with healthy controls. (91 ± 35.7 vs. 113.2 ± 53.8 pg/ml; p= 0.139, t-test) Salmeterol blunted IFNγ production more completely in carvedilol-treated HF patients compared to healthy controls (21/21 vs. 11/17; p<0.005, chi-square). No intergroup differences in IL-10 production

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were found. All participants achieved influenza antibody responses at least 40 hemagglutination inhibition units. **Conclusions:** B2AR-mediated IFNγ production in response to influenza antigens appears to be well preserved in HF pts on carvedilol, suggesting that nonspecific beta blockade with agents active at the B2AR may be important to preserve T-cell immune responsiveness in HF and reversing influenza vaccine nonresponsiveness.

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S17 Distinct HLA, Cytokine, and Cytokine-Receptor Genotypes Influence the Human Antiviral H1- and H3-Specific Antibody Responses to Seasonal Influenza Vaccination

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Background: The immunogenetic basis for heterogeneity in humoral immune response to influenza vaccine is largely unknown. **Methods:** To assess associations between immune response genes and both influenza A/H1N1- and A/H3N2-induced humoral vaccine response, we genotyped healthy subjects (n=185; 18-40 year old Caucasian males) for HLA class I and II alleles, and a panel of 586 cytokine and cytokine receptor SNPs using PCR-SSP and the Illumina platform. Subjects received trivalent influenza vaccine containing the H1N1 New Caledonia/20/99 and H3N2 Panama/2007/99 strains and were enrolled from 12/2005 to 03/2006. Sera were tested for H1/H3 antibodies (Ab) by a hemagglutination inhibition (HAI) assay using a starting dilution of 1:10 and 0.65% guinea pig erythrocytes (protective Ab titer ≥1:40). **Results:** The median value for H1/H3-specific Ab titer for the 2005-2006 season was 1:160 and 1:80, respectively. The HLA-A locus was significantly associated with H1 post-vaccination Ab titer (global p-value 0.005). Specifically, A*1101 (median Ab titer of 1:640; p=0.0001) allele was associated with higher median levels of influenza H1 vaccine-induced Abs, whereas DRB1*1303 (median Ab titer of 1:30; p=0.03) was associated with lower HAI. Significant associations (p-values 0.002 to 0.04) were found between SNPs belonging to cytokine (IL6, IL18, IL12A, IL12B, IFNG) and cytokine receptor (IL1R, IL2RG, IL4R, IL10RB, IL12RB, IFNAR2, TNFRSF1A) genes and variations in HAI Abs to influenza H1 and H3 antigens. SNPs in IL6 (rs1800796; 1:640/1:320/1:160; p=0.004), IL12B (rs3212227; 1:160/1:120/1:80; p=0.03) and IL1R1 (rs3732131; 1:160/1:80/1:60; p=0.04) genes demonstrated significant allele dose-related H1-specific immune response. **Conclusions:** Our data suggest that HLA, cytokine and cytokine receptor genes may have important immunogenetic associations with circulating H1/H3 Ab titers following seasonal influenza vaccine and provide new knowledge for understanding influenza immunity.

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S18 Persistence of Herd Protection to Influenza One Year after Completing the Community-based Vaccination Program in School-age Children in Central Texas

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Background: In 2003-04, 2004-05 and 2005-06, we conducted a field trial in central Texas to determine the vaccination coverage in children necessary to affect spread of influenza. **Methods:** In the intervention cities in 2003-04, 2004-05 and 2005-06, healthy children 5 to 18 years received attenuated influenza vaccine and those with at-risk conditions received the inactivated influenza vaccine. Study vaccines were not provided in the comparison cities and in 2006-07. Scott & White Health Plan provided defined populations for analyses. Age-specific rates for medically-attended acute respiratory illness (MAARI) were calculated prior, during and after the epidemic. To assess effectiveness, point estimates and 95% confidence intervals for the incidence rate ratios were calculated. Influenza surveillance of medically attended febrile respiratory illness was used to define the influenza outbreak. **Results:** In 2003-04, 2004-05 and 2005-06 influenza seasons, approximately 50% of school-age children who received care at Scott & White clinics in the intervention cities were vaccinated compared to approximately 18% in the comparison cities. In 2006-07 the vaccination coverage in school-age children and all other age groups was approximately 17% and 21% in the intervention cities and approximately 20% and 22% in the comparison cities. During the epidemic period, MAARI was reduced by 9% (4-14%) in children <5 years and by 13% (10-17%) in adults ≥35 years in the intervention cites relative to their age-specific groups in the comparison cities. **Conclusion:** Persistence of herd protection to influenza was observed one year after completing our community-based influenza vaccination program in school-age children.

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Abstracts of Oral Submitted Presentations

S19 Improvement of Vaccines Against *Bordetella pertussis* by LPS Modifications

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Background: LPS, a major constituent of the outer membrane of gram-negative bacteria, can have a role as both immunogen and adjuvant. However, its endotoxic activity also causes significant reactogenicity, which limits widespread acceptance of bacterial vaccines containing it. Both the endotoxic and adjuvant activity of LPS are largely determined by the structure of its membrane-anchoring part, the lipid A moiety. Modification of the lipid A biosynthetic pathway might provide a means to improve LPS-containing vaccines. **Methods:** B. pertussis LPS was modified in the following ways: (i) altered fatty acid composition (altered expression of lpxL homologues); (ii) expression of the normally silent deacylation and acylation pagL and pagP genes; (iii) up/down regulation of a novel hexosamine modification of the 4'P of lipid A; and (iv) truncation of oligosaccharide chain to affect targeting to antigen-presenting cells. We have investigated the effect of these modifications on the biological activity (i.e. TLR-mediated cytokine induction and DC activation) and immunogenicity (protection in a mouse intranasal infection model) of both purified B. pertussis LPS and whole cells. **Results:** Expression of PagL significantly increased vaccine efficacy without altering vaccine reactogenicity in a mouse model, while PagP expression increased both. Most lipid A modifications increased LPS activity, but elimination of the previously unidentified hexosamine modification in a transferase knockout mutant resulted in whole cells and purified LPS with approximately 10-fold lower cytokine-inducing capacity. **Conclusions:** We conclude that genetically engineered B. pertussis LPS modifications can lead to improved whole cell pertussis vaccines. Several of these modified LPS compounds have additional potential as safe adjuvant in other vaccines.

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S20 Insights into the Mucosal Adjuvant Mechanism of a Soybean Oil Nanoemulsion (SO-NE): Participation of GM1 Ganglioside

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Background: We have developed a mucosal adjuvant that induces protective immunity against influenza and smallpox. The molecular mechanisms involved are not elucidated and this research gathers insights into early events involved. Bacterial enterotoxins which are well-known mucosal adjuvants require recognition of ubiquitous ganglioside GM1 (a lipid raft marker) to induce immune responses. Based on its membrane-active nature and absence of acute inflammation, we propose that SO-NE bridges antigens to membranes in innate immune cells with GM1/lipid rafts participation. **Methods and results:** We studied SO-NE's ability to recognize GM1 in vitro using a GM1-based ELISA and glioma C6 cells. These cells lack complex gangliosides but can acquire them after overnight incubation with exogenously added ganglioside. Our results suggest that SO-NE facilitates interaction of antigens with immobilized GM1 and that C6 cells internalize hepatitis B antigen (HBAg) by a SO-NE and exogenous GM1 dependent mechanism. In vivo, GM1 added exogenously to intranasal inoculums inhibits dissemination of quantum dots in whole mice and enhances immune response (serum IgG and s-IgA) against HBAg compared to immunization with just HBAg. Using TEM we detect nasal epithelium cells loaded with vesicle-like material in SO-NE size range after 24 h of nasal inoculation. After 24 h of nasal delivery SO-NE also promotes E-GFP trafficking to submandibular lymphoid nodes and thymus where it co-localizes with dendritic cells. **Conclusions:** Our data suggest that SO-NE adjuvant in vitro promotes direct interaction between antigens and GM1, enhances antigen trafficking to lymphoid tissues and co-localization with dendritic cells. The ability of SO-NE adjuvant to enhance the antigen interactions with GM1 may promote antigen internalization, processing and presentation phenomena that subsequently determine the development of specific immune response.

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S21 A Novel Dose-Sparing Adjuvant for Protein- and Plasmid DNA-Based Influenza Vaccines

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Background: New adjuvants are needed to increase the potency of vaccines that are poorly immunogenic in humans, such as pandemic influenza virus vaccines. Vaxfectin®, a cationic lipid-based adjuvant, was initially designed to enhance humoral and cellular immune responses generated by plasmid DNA (pDNA) vaccines, and has been tested in several infectious disease animal models[1,2]. A Vaxfectin®-formulated pandemic H5N1 pDNA vaccine is currently being evaluated in clinical trials. Additionally, we have recently evaluated Vaxfectin® with protein-based trivalent inactivated (TIV) and pandemic H5N1 influenza vaccines. **Methods:** TIV (Fluzone®) was obtained from sanofi pasteur, and pandemic H5N1 vaccine from BEI Resources. On Days 0 and 21, mice were injected i.m. with TIV (0.1-9.0 µg total HA/mouse/injection) ± Vaxfectin® (10-900 µg total lipid/mouse/injection). On Day 42, mice were bled and hemagglutination-inhibition (HI) titers were determined for H1N1 and H3N2. Anti-TIV titers were determined by ELISA. A 1 µg-dose of H5N1 vaccine was injected in mice with or without 300 µg of Vaxfectin®. Wilcoxon Rank Sum test was used for statistical analysis. **Results:** With 1 µg TIV, Vaxfectin® increased HI and anti-TIV titers by 23- to 79-fold ($p<0.001$), and these responses were up to 8-fold higher than obtained with 9 µg TIV without adjuvant. With 0.1 µg TIV, Vaxfectin® increased HI and anti-TIV titers by 20- to 28-fold

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(p<0.001), and these responses were up to 28-fold higher than obtained with 1 µg TIV without adjuvant. With pandemic influenza vaccine, Vaxfectin® produced a 9-fold increase in anti-H5 ELISA titers (p<0.001). **Conclusions:** Vaxfectin® improved the immunogenicity of seasonal and pandemic influenza vaccines, and elicited >10-fold dose-sparing effect with TIV. Vaxfectin® may be a useful adjuvant for other protein-based conventional and emerging vaccines.

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S22 Novel Low Toxicity Plant Adjuvants GG-6 and AH-6 for Assembling Highly Immunogenic Complexes Containing Natural or Recombinant Coccidia (Eimeria) Antigens for Vaccine Use

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Avian coccidiosis, an intestinal disease caused by intracellular coccidian protozoan parasites (Genus; *Eimeria*), is estimated to cost the world-wide poultry industry over $1 billion annually. Many studies on control of poultry coccidiosis have centered on elicitation of protective immune response to parasite infection by development, delivery and effective use of parasite vaccines. In the present research, novel adjuvant-active saponins GG-6 and AH-6 were isolated from *Glycyrrhiza glabra* and *Aesculus hippocastanum,* plants indigenous to Kazakhstan, by HPLC fractionation. Purified saponins GG-6 and AH-6 which were previously demonstrated to have low toxicity in various animal models (chickens, chicken embryos, mice) were used for assembling immunostimulating complexes (ISCOMS) containing either natural coccidia antigens or SO7 recombinant antigen. Two routes of immunization were used: 18-day old chicken embryos were immunized in ovo; 1-day old chickens were immunized intranasally with ISCOM preparations. A single immunization with an antigen dose of 6ug per animal was used for both routes of immunizations. The results of the study indicate that ISCOMS containing GG-6/AH-6 saponins stimulated high levels of humoral immune responses against natural or recombinant coccidia antigens, prevented increases in serum nitrate-nitrite levels, reduced oocyst output and prevented reduction in weight gain. Activity of immune responses and protection against challenge was much higher when coccidia antigens were assembled with GG-6/AH-6 saponins into ISCOMS in comparison with coccidian antigens alone. It was concluded that ISCOMS containing novel adjuvant active saponins GG-6 and AH-6 could be used for production of a highly immunogenic coccidia vaccine for intranasal and in ovo immunization.

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S23 Evaluation of Immune Response and Protective Efficacy of Single Dose Poly (D,L-lactic-co-glycolic acid) Microspheres Based Vaccine Against Experimental Hamster Leptospirosis

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Subunit vaccine is a potential intervention strategy against leptospirosis, an important zoonotic disease afflicting both humans and live stock. However, the success of subunit vaccine has been hampered by weak or short term immunity and unavailability of nontoxic and potent adjuvants. Microparticles have proved to be an ideal adjuvant and have been widely used against various infectious diseases. In our earlier studies we have demonstrated the protective efficacy of *Leptospira* immunoglobulin like protein A (LigA) both as recombinant protein and DNA vaccine in a hamster model of leptospirosis. In the present study we have demonstrated that single dose of PLGA microsphere incorporating variable region of LigA(MS-LigAvar) produced robust immune response that induced significant protection against virulent *L. interrogans* serovar Pomona challenge in hamsters. Four-week-old hamsters were immunized subcutaneously with single dose (20µg) of MS-LigAvar or LigVar with alum adjuvant (two doses of 10 µg each at three week interval). All animals were challenged intraperitoneally six weeks after primary immunization with a lethal dose (2.5 X LD_{50}) of virulent *L. interrogans* serovar Pomona. Animals were bled at various time points to evaluate antibody response, sacrificed, and splenocytes were isolated and assayed for lymphocyte proliferation and cytokine profiles in response to recall antigen. Our results indicate that microsphere has proved to be a better adjuvant as compared to alum as revealed by long term antibody response, enhanced lymphoproliferation and significant enhancement in level of both Th1(IL-12, IFN-g) and Th2 (IL-4,IL-10) cytokines. Moreover, they provided better protection than alum as revealed by enhanced survival and reduced histopathological lesions in vital organs. The study suggests that LigAvar incorporated PLGA microsphere is promising candidate for controlled delivery of vaccine against leptospirosis.

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Abstracts of Oral Submitted Presentations

S24 A Novel Nanoemulsion Adjuvant Enhancing the Immune Response from Intranasal Influenza Vaccine in Mice

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Background: Approved commercial trivalent influenza vaccines in the US protect 60-90% of vaccinated individuals and do not contain adjuvants. Adjuvanted vaccines that provide improved immunity could extend vaccine protection. **Methods:** Mice were immunized intranasally with either nanoemulsion-inactivated influenza A/Puerto Rico/8/34 (H1N1) virus or with β-propiolactone-inactivated influenza virus mixed with the nanoemulsion. Mice received either freshly made vaccine or preparations stored up to 3 months; two doses 4 weeks apart were administered intranasally. Sera were collected prior to each vaccination and 3 weeks following boost to test for the presence of specific antibodies using hemagglutination inhibition (HAI) titer and ELISA assays. Protection was monitored following challenge with a lethal dose of virus. **Results:** Mice vaccinated with 2 doses of nanoemulsion-inactivated influenza virus showed HAI titers (and consistent ELISA results) that ranged between 10,000 and 45,000 for freshly prepared vaccine or vaccines stored up to 1 month at 4°C or 25°C. HAI titers of 6,400 were attained when stored for 3 months at either temperature, equivalent to titers in mice surviving infection with live virus. Vaccines prepared from β-propiolactone-inactivated virus had HAI titers of 160 even after 3 months of storage. All mice receiving vaccination were protected against challenge with 100xLD_{50} while 8/10 mice died in the nonvaccinated group. **Conclusions:** The nanoemulsion-inactivated viral vaccine provided a robust immune response and protection against a lethal influenza challenge while nanoemulsion mixed with β-propiolactone-inactivated virus resulted in a more modest protective response. In addition to adjuvant activity, the route of immunization and the stability of the nanoemulsion-based vaccines provide advantages not equaled in current vaccines.

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S25 Improving Health Care Worker Influenza Vaccination Rates in a Large Health System

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Background: Influenza vaccination rates for health care personnel (HCP) remain low nationally. As HCP influenza vaccination becomes a quality indicator for health care facilities, effective interventions are needed. **Methods:** In a large, multi-facility health system (UPMC), education, publicity, free and easily accessible influenza vaccines were used to encourage vaccination of all employees. Additionally, a factorial design was used to determine the effect of mobile vaccination carts and incentives on vaccination rates of HCP divided into three groups based on their level of patient contact (business/administrative, indirect and direct patient contact). **Results:** Among >26,000 employees, influenza vaccination rates increased significantly in most facilities and system-wide from 32.4% to 39.6% (P<.001). In the baseline year, business unit employee vaccination rates were significantly higher than among HCP with patient contact; rates did not differ significantly across groups in the intervention year. In logistic regression analyses that accounted for demographics, intervention year and other factors, mobile carts that provided access to vaccine at the work unit significantly increased the likelihood of vaccination among HCP with direct patient contact, while incentives were more effective for HCP with indirect patient contact compared with controls. **Conclusion:** Interventions to improve vaccination rates are differentially effective among HCP with varying levels of patient contact. Mobile carts remove access barriers for those involved in direct patient care, while incentives may motivate those with less patient contact to be vaccinated. Education and publicity may be sufficient for increasing rates among business or administrative staff.

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S26 A Decade of Pediatric Immunisation Coverage in Australia

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Background: The Australian Childhood Immunisation Register (ACIR) is a uniquely comprehensive national vaccination registry. Established in 1996, it now holds records for 5.8 million children from 21,000 immunisation providers. Aspects of the system and its use as a tool for program planning and epidemiologic analysis will be reviewed. **Results:** A range of payments and financial incentives for parents and immunisation providers are operated through the ACIR. Total annual payments to providers include $8 million for notifications, payable to GP and non-GP providers, $35 million in annual payments to GPs and a parental payment of AU$ 233 in 2007 when children reach 18-24 months of age if all immunisations due at or before 18 months of age are received or a medical/philosophical exemption applies. In 2006, overall national coverage for full immunisation at 12 and 24 months of age was at least 92% and has exceeded 90% at both ages since 2003. Comparison with prior household survey estimates of immunisation coverage in the 1980s and 1995 suggest that coverage is not just an artefact of improved reporting. As expected, timeliness of receipt of vaccines decreased by dose; 94.2% of children were on time for the first dose of DTP, declining to 75.6% by the third dose. Rates of conscientious objection can also be assessed; in New South Wales the average proportion of conscientious objection to immunisation was 0.4% (range 0 to 4.2%). **Conclusion:** ACIR data reveal that Australia has achieved high levels of immunisation coverage in the paediatric population. The ACIR also provides data critical for assessment of vaccine safety and effectiveness. Lessons learned over the past 10 years are applicable to other countries.

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S27 Effective Implementation of a School-based Influenza Vaccination and Herd Protection Trial in Central Texas – VIPS: Vaccines for Influenza Prevention in Schools

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Background: Our community-based influenza immunization field trial achieved influenza vaccine coverage of 15-30% in school-age children from 1998-2006. A school-based trial was implemented in 2007-2008 to increase influenza immunization coverage in school-age children. **Methods:** For 25 intervention area elementary schools from seven school districts and three parochial schools, a study information packet in English or Spanish was sent home with each school child by their teacher. Approximately two weeks before the scheduled influenza vaccination day, informed consent and assent was obtained from the parent and capable children seven years of age or older, respectively. Influenza Vaccine Permission forms containing child's demographic and health information were completed, signed and dated by parent and child, and collected by the teachers. School staff organized student flow and research staff triaged students for live or killed influenza vaccine based on the child's health information. Research, public health and student nurses and investigators administered influenza vaccines during morning hours. Second doses for eligible children are scheduled in the pediatric clinic. **Results:** Study information packets were sent to 11,380 students. From 10/26/07 to 12/19/07, one immunization day was conducted at 22 schools, and two days each at six schools. School-based influenza immunization coverage was 45% (25-66%) in the 28 elementary schools. A single dose of live nasal spray influenza vaccine was administered to 85% of 5,144 students vaccinated at schools, and 15% received killed vaccine. We also vaccinated 887 school staff. An additional 996 students were vaccinated during nine weekend clinics and five community events. Ninety-four other students reported receiving influenza vaccine elsewhere. **Conclusion:** It is feasible to implement an efficient school-based research trial to increase influenza immunization coverage in elementary schools.

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S28 Number Needed to Treat and Cost to Prevent Human Cases of Bat Rabies

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Background: Rabies post-exposure prophylaxis (RPEP) consisting of immunoglobulin and five spaced doses of vaccine is recommended for persons with direct contacts with bats or who have been asleep in a room where a bat was found. The objective of this study was to estimate the number needed to vaccinate (NNV) and the cost to prevent one human case of bat rabies. **Methods:** A survey was done in randomly selected households in the province of Quebec, Canada. Participants were queried about any possible RPEP-eligible bat exposure during the calendar year 2006. NNV was derived by multiplying the rate of RPEP-eligible bat exposures by the incidence of human bat rabies observed in Canada and the United States between 1990 and 2007, assuming 100% RPEP efficacy. **Results:** Among the 36,445 persons belonging to 14,453 households included in the survey,0.01% reported direct physical contact with a bat without evidence of bite and 0.09% reported the presence of a bat in the room where they were sleeping. To prevent one human case of bat rabies in individuals with direct contact with a bat without evidence of bite, RPEP would have to be administered to 66,000 individuals whereas the NNV for bedroom exposure varied between 668,000 and 2.5 million people. At ~$1000US per RPEP course, the purchase cost of RPEP per case prevented for bedroom exposures would vary between $350 million US and $1 billion US. **Conclusions:** The NNV and cost of RPEP to prevent human rabies following bedroom exposure to bats is in order of magnitude higher than any other public health interventions. Current RPEP recommendation for that type of exposure should be reconsidered.

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S29 Economic Impact of Influenza Vaccination of Pregnant Women (PW) in Nova Scotia (NS): Net Cost, Cost-Effectiveness and Budget Impact

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Background: Pregnancy increases influenza hospitalizations and physician visits (events) in women with and without comorbidities (COM). In 2006/2007 the National Advisory Committee on Immunization expanded its influenza immunization recommendation to include all pregnant women (PW). We developed an economic model to estimate net cost, cost-effectiveness and budget impact of implementing a publicly-funded universal influenza immunization program for PW in Nova Scotia (NS) and explored cost implications of different vaccine delivery strategies. **Methods:** A decision tree characterized the 1-year costs/consequences of vaccination/no vaccination in a hypothetical cohort of PW. Event probabilities and quality-of-life weights were

derived from the literature and event costs from administrative databases. Vaccine acquisition and administration costs were provided by NS Department of Health. Three delivery strategies were considered: public health nurse (PHN), family physician (FP) incorporated into routine prenatal care visit (FP+0) and FP requiring an extra visit (FP+1). **Results:** The number needed to vaccinate to prevent 1 hospitalization was 376. The net cost of vaccination (vaccination cost - event costs avoided) was $0.44 (PHN), $4.70 (FP+0) and $33.43 (FP+1). Cost/QALY gained was $761, $8,195 and $58,330 with PHN, FP+0 and FP+1, respectively. Projected net program costs were $4,500, $48,450 and $345,000/year, respectively. Targeting women with COM was cost-saving with all delivery strategies except FP+1. **Conclusion:** Universal immunization of PW by FP is very cost-effective if incorporated into routine prenatal care. Programs utilizing PHN vaccination could be extremely cost-effective, bordering on cost-saving. Targeting only PW with COM is cost-saving but risks reducing coverage rates and overall health benefit of the immunization program.

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S30 The Value of Vaccinating U.S. Elderly against Herpes Zoster: A Review of Cost-Effectiveness Analyses

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Background: In October 2006 the Advisory Committee on Immunization Practices recommended vaccinating immunocompetent people aged ≥ 60 years with herpes zoster vaccine (HZV). HZV is expected to prevent much of the substantial burden of zoster including the quality-of-life reduction from persistent and severe pain. However, estimates of HZV cost-effectiveness vary widely. **Objective:** To examine cost-effectiveness studies of the recently recommended HZV in the United States (US). **Method:** A systematic review of economic studies on HZV was conducted. Studies were identified by searching Medline, Embase, and Econlit databases and included unpublished studies. Each study was reviewed for appropriateness of model design, base-case setup, sensitivity analyses and input variables (i.e., epidemiological, clinical, costs and quality-of-life scores). **Results:** Five economic studies were identified for the US. All five studies used a Markov cohort model and quality-adjusted life-year (QALY) scores to assess gains in quality of life with a one-dose routine vaccination program. Studies' assumptions varied regarding the duration of vaccine protection, the HZV efficacy for preventing post-herpetic neuralgia (PHN) among vaccinees developing zoster, HZV-associated adverse events, and losses in work productivity. Per-person benefits from a routine vaccination program range from 0.0016 QALYs (0.6 days) to 0.0087 QALYs (3 days) gained. At a cost of $150 per dose, the societal costs range from $27,000 to $112,000 per QALY gained. Vaccine costs, duration of vaccine efficacy, PHN risk and QALY scores strongly influence outcomes. **Conclusion:** Cost-effectiveness estimates range widely, due mainly to differing assumptions regarding vaccine impact, duration and adverse events. Although costly, the use of HZV would provide sizable health benefits to the elderly and society.

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S31 Acute Phase Immune Gene Profiling of Spleen and Peyer's Patch in Naïve and Vaccinated Chickens Following Avian Influenza A (H5N1) Virus Infection

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Recent advances in immunogenomic and proteomic tools are facilitating the characterization of complex host-pathogen immunobiology. In this study, we applied functional genomics tools to investigate the early immunological response of chickens to highly pathogenic (HP) avian influenza virus (AIV). Infection with HPAIV usually results in the rapid death of poultry and has been implicated as a pandemic threat to both avian and animal populations because of their high mortality and morbidity. The aim of this study was to identify host immune genes which are associated with local immune response to HPAIV H5N1 isolated from Southeast Asia. Gene mRNA expression profiles isolated from spleen and Peyer's patch, from naïve and vaccinated chickens, were examined after infection with HPAI using a newly developed 10K chicken intestinal-intraepithelial lymphocyte cDNA microarray. Two groups (naïve or H5N9-vaccinated) of 4 week-old chickens were infected with H5N1 viruses. Comparative gene expression in the spleen and Peyer's patches were compared to that of mock challenged birds at 24 hr following AI infection using Volcano plot methods with $p<0.05$ false discovery rate. Differential expression analysis revealed that the immune response genes, especially those associated with inflammation and apoptosis including *Ah221, CCL4, CXCR4, FCGBP1, DDX47, IL1R1, TNFSF10, TFNSF15*, and *XCL1* were significantly downregulated in the Peyer's patches of vaccinated chickens challenged with H5N1, compared to naïve-challenged birds. In spleen, *Ah221, CCL4, CXCR4, IGHMBP2, IL1B, IL7R, IL18, MMP1*, and *TNFRSF1B* genes were suppressed after H5N1 infection in H5N9-vaccinated group. These results suggest that the vaccination reduces the viral pathogenicity induced by highly pathogenic H5N1 mostly via the dampening of "cytokine storm" phenomenon.

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Abstracts of Oral Submitted Presentations

S32 Associations between Cytokine/Cytokine Receptor SNPs and Humoral Immunity to Measles, Mumps and Rubella in a Somali Population

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Background: Cytokines and their receptors are the key mediators of innate and adaptive immunity to viruses. Genetic variations in their corresponding genes that modulate the cytokine level or activity may influence the immune response to vaccination/disease. **Methods:** We genotyped a Somali population (n=85; median-age in years=10.4; inter-quartile range=6.7-18.5, 55% males) for 618 cytokine/cytokine receptor SNPs using Illumina GoldenGate genotyping post one-dose MMR vaccination. Associations between SNP genotypes and measles-mumps-rubella-specific IgG levels (Dade Behring, Germany) were determined using ANOVA. **Results:** Sixty-two significant associations ($p \leq 0.01$) were found between SNPs in genes regulating Th1 (IL12RB2, IL2RA, B and RG), Th2 (IL4R, IL10RB) and innate (IL1B, TNFA, IL1RA, IL6, IFNB1, IFNAR2, IL18R1, TNFRSF1A and B) immunity, and variations in antibody levels to measles-mumps-rubella. SNPs within two major inflammatory cytokine genes, TNFA and IL6, demonstrated associations with measles-specific antibodies. Specifically, the minor allele variant of rs1799964 located in the 5' intergenic region of the TNFA gene was associated with seronegative values (median EIA index values ≤ 0.87; $p \leq 0.002$) in response to measles vaccination and/or disease. A heterozygous variant GA for synonymous SNP (rs2069849; Phe201Phe) located in the IL6 gene was also associated with seronegative values and a lower median level of antibody response to measles vaccination and/or disease (p=0.004) or measles vaccination alone (p=0.008). Several SNPs in the coding and regulatory regions of cytokine/cytokine receptor genes demonstrated significant associations with mumps and rubella antibody. **Conclusions:** Our study identifies specific SNP associations between cytokine/cytokine receptor genes and humoral immune responses to measles-mumps-rubella vaccination/infection in Somalis, which may inform race/ethnicity-specific considerations for newer vaccine designs.

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S33 Characterization of Novel Anti-microbial Peptide is Produced Locally in the Gut of Eimeria-infected Host

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NK-lysin is an anti-microbial and anti-tumor protein produced by NK cells and T lymphocytes in mammals and is considered to be an important component of the local innate immune response to pathogens. Chicken NK-lysin consists of an 868 bp DNA sequence with an ORF of 140 amino acids with a predicted molecular mass of 15.2 kDa. Comparison of its deduced amino acid sequence showed less than 20% identity to the mammalian NK-lysin. Chicken NK-lysin also is a member of the saposin-like protein family with potent antimicrobial activity. To evaluate the biological role of chicken NK-lysin, we expressed biologically active recombinant NK-lysin and examined its antimicrobial activity against various bacterial strains, tumor cell lines and three major *Eimeria* spp. in chickens. Recombinant chicken NK-lysin expressed in COS7 cells and purified as His-tagged NK-lysin exhibited potent anti-tumor cell activity against LSCC-RP9, retrovirus-transformed B-cell line and direct cytotoxicity against *E. acervulina and E. maxima* sporozoites. Interestingly, unlike mammalian NK-lysins, the chicken counterpart did not show cytotoxic activity against a number of bacteria strains. Further studies using synthetic peptides of chicken NK-lysin will lead to better insights on the mechanism of anti-microbial activity of NK-lysin and a potential application of this protein in the pharmaceutical agricultural industry.

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S34 Vaccinated Children among Hospitalized Meningococcal Cases Across Canada, IMPACT 2002-2006

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Background: Meningococcal infections rank second in Canada among life-threatening bacterial infections in children and adolescents. Canada was among the first countries to use MenC conjugate vaccines routinely. All provinces implemented routine infant and/or adolescent vaccination programs with MenC conjugate vaccines in 2002-2005. **Methods**: Active metropolitan area surveillance was conducted across Canada by the 12 centers of the Immunization Monitoring Program, Active (IMPACT) for all hospital admissions related to *Neisseria meningitidis* invasive infections from January 2002 - December 2006. MenC vaccine failure was defined as serogroup C disease in a completely immunized healthy child. **Results:** A total of 225 cases were reported in children <20 years over five years: 47 in 2002, 53 in 2003, 41 in 2004, 42 in 2005 and 42 in 2006. Serogroups B (64%), C (16%) and Y (12%) caused most infections. Five children < 5 years of age had serogroup C disease despite vaccination with MenC conjugate. Among the five, one case appears to be a MenC conjugate failure, while three were

incompletely immunized. The one apparent vaccine failure occurred in a healthy 2 year old who had received one dose of MenC at 12 months of age. Two children were immunized with 2 doses of MenC vaccine before 1 year of age and did not receive a booster dose after 12 months, and one child developed disease < 5 days after receiving MenC vaccine. For one case the vaccination date information is insufficient.
Conclusion: While loss of vaccine effectiveness (VE) over time remains a concern for meningococcal conjugate vaccines administered in infancy, our surveillance data indicate incomplete vaccine administration rather than loss of VE is a larger problem.

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S35 Fine Aerosol Adenovirus Vaccination against Tuberculosis in Rhesus Macaque

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Lung mucosal tissue is the primary site of exposure and replication for respiratory pathogens. Since immunity in the lung may prevent disease, we aimed to induce strong immune responses in the respiratory tract mucosa using fine aerosol droplets of recombinant adenovirus encoding tuberculosis and influenza proteins. Indian rhesus macaque were immunized (n=4) either intramuscularly or via aerosols generated by the PARI eFlow® nebulizer with rAd35 encoding TB Ag85A at 10^9, 10^10, or 10^11 PU. Droplet size diameters of 4 µm and 12 µm were also compared using rAd5 encoding SIV proteins. In an ongoing influenza immunogenicity study, ferrets were immunized with 10^8-10^10 PU of rAd5-HA. Systemic and mucosal immune responses were measured by ELISPOT, intracellular cytokine staining, and ELISAs. All comparisons between vaccine groups used a two-tailed Student's t-test. The aerosol route induced stronger cellular responses in the lung than intramuscular immunization ($p<0.001$), with up to 60% of T-lymphocytes specific for the immunogen. Higher doses of aerosolized vaccine generated more antigen-specific lung cells ($p<0.001$ and $p<0.035$), while the proportion of polyfunctional cells was greater at the lowest dose ($p<0.003$). In addition, decreasing droplet size markedly enhanced systemic humoral and cellular responses. Moreover, antigen-specific T cells in the lung persisted for over one year. Neither previous exposure to adenovirus nor systemic adenovirus neutralizing antibodies prevented responses to subsequent aerosolized adenovirus immunization. Thus aerosolized adenovirus vaccines generate strong and persistent lung cellular immune responses and thus may represent a powerful immunization vehicle for respiratory pathogens such as influenza, respiratory syncytial virus, and tuberculosis.

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S36 Positive Prediction of Immunogenic Vaccine Candidate Epitopes and Progress on the Development of an IDV Vaccine for H. pylori

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Background: Chronic infections may induce suppressive or regulatory T cell responses that may make the development of effective vaccines more difficult. An epitope-driven approach is one possible solution. **Methods:** Using EpiMatrix, open reading frames (ORFs) highly conserved between human HP strains J99 and 26695 were analyzed for T cell epitope clusters with motifs for HLA Class II and mouse I-Ab alleles. 50 epitopes were incorporated into "HelicoVax," a DNA-prime/peptide-boost vaccine. HelicoVax was tested in p27 -/- mice pre-infected with murine-adapted HP SS1 strain, a novel model for HP-associated gastric carcinogenesis. Immunogenicity and modulation of immune response were measured 45 weeks post-immunization. **Results:** 1,152 epitope clusters were identified from 1,107 conserved ORFs. From the top 150 epitopes, 50 were selected for vaccine formulation based on their high affinity for HLA DR1, defined by >50% inhibition of reference peptide at 10 µM in a competition assay. Interferon-gamma ELISpot assays of epitope-stimulated splenocytes demonstrated that 47/50 peptides (94%) were immunogenic following IN or IM DNA immunization with the multi-epitope vaccine as compared with only 4/50 epitopes were recognized in SS1 lysate-immunized animals. Pathology results and culture results are pending. In addition, mice immunized with HelicoVax displayed reduced regulatory T cell populations ($CD4^+$ $CD25^+$ double positive cells) among both splenocytes (41% reduction, p=0.098) and mesenteric lymph node cells (35% reduction, p=0.026) compared to non-immunized mice. Similar reductions in numbers of Tregs were seen among mice immunized with SS1 (splenocytes: 48% reduction p=0.02; lymph node cells: 28% reduction p=0.036). **Conclusion:** HelicoVax generates long-lived antigen-specific T cell clones that may prevent gastric adenocarcinoma pathogenesis.

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ABSTRACTS OF SUBMITTED POSTER PRESENTATIONS

Abstracts of Submitted Poster Presentations

P1 Kolaviron, a Novel and Potentially Potent Vaccine Adjuvant

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Background: Formulation of vaccines with potent adjuvants is an attractive approach for enhancing immune responses to subunit antigens. Immunostimulatory compounds of natural sources are often preferred and have demonstrated good potentials as vaccine adjuvant in previous studies (Khajuria *et al*, 2007; Gautam *et al*, 2004). In this study, the immunostimulatory properties of Kolaviron (KV), a mixture of three related biflavonoids of the seeds of *Garcinia kola* Heckel (Clusiaceae) were investigated for use as a vaccine adjuvant. **Methods:** The effect of 14 day oral supplementation of KV (100 and 250mg/kg/day) on primary and secondary antibody synthesis in albino rats immunized with sheep red blood cell was investigated by serial antibody titer determination. The effects of KV on cell mediated delayed type hypersensitivity (DTH) and on the rate of leucopoiesis, lymphocytes proliferation as well as on impaired wound repair processes in immunocompromised rats were also investigated. Data obtained were analyzed by one way ANOVA and significant differences between means taken at $P < 0.01$. **Results:** KV caused a significant ($P<0.01$) and dose-related increase in both primary (47.62% and 57.14%) and secondary (32.14% and 35.71 %) antibody synthesis in rats immunized with sheep erythrocytes. Supplementation with KV increased leucopoiesis, lymphocyte proliferation and the rate of excision wound repair significantly ($P< 0.01$) in immunocompromised rats. Oral administration of KV (100 and 250mg/kg) also caused a dose-dependent and significant ($P< 0.01$) inhibition of DTH in rats. **Conclusion:** The potent effect of KV on antibody synthesis and cellular immune responses makes it a potential candidate for use as a vaccine adjuvant.

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P2 Immunotherapy of Autoimmune Ovarian Disease by Co-Immunization of mZP3 Protein and DNA Vaccines

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Autoimmune ovarian disease (AOD) caused by auto-reactive T cells is considered a major reason for human premature ovarian failure that affects 5% of women worldwide. To develop an effective treatment for AOD, we showed that the co-immunization of mouse zona pellucida protein 3 (mZP3) protein and DNA vaccine encoding the mZP3 was able to ameliorate the AOD in an AOD murine model induced by the mZP3. We observed that established AOD in mice reverted to a normal ovarian morphology without notable T cell infiltration in the co-immunized group; whereas mice immunized with DNA vaccine, protein vaccine alone or immunized with mismatched combinations induced rather severe AOD with profound T cell infiltrations and aberrant structures of ovaries. The amelioration was antigen specific because other co-immunization combinations failed to reverse AOD and correlated with significant reductions of pathogenic T cell responses and productions of TNF-α and IFN-γ. Furthermore, the amelioration was apparently associated with the induction of mZP3 specific regulatory T (Tr) cells that exhibited a phenotypic $CD4^+CD25^-FoxP3^+IL\text{-}10^+$ in the co-immunized group, which can be transferred to reverse AOD in vivo. Thus, co-immunization of mZP3 DNA and protein vaccines can be used to treat established AOD, and may provide a novel immunotherapy strategy to treat other autoimmune diseases.

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P3 Evaluation of a Cationic Liposome as Adjuvant for Newcastle Disease Vaccine

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Background: Although liposomal adjuvants have been shown to boost the immune response of diverse bacterial, viral and protozoal antigens with virtually no side-effects, liposomal composition could markedly affect their adjuvanicity. In the present study, we evaluate the effect of a cationic surfactant (cetrimide)-based liposome on the immunogenicity of a Newcastle disease vaccine (NDV) in chickens. **Methods:** The La Sota strain of NDV was formulated in cetrimide+ phosphatidylcholine (Group I), phosphatidylcholine (Group II) or water (Group III). The negative control contained cetrimide+phosphatidylcholine without vaccine (Group IV). The above treatments were administered orally to four groups of birds (two weeks old) on a weekly basis for three weeks and the immune response monitored by hemagglutination inhibition (HI) assay. By the 5th week post-vaccination, the birds were challenged orally with velogenic strain of NDV and the degree of protection monitored clinically. **Results:** Both Group I and II-treated birds exhibited identical increment in HI titre after the 1st (275%) and 4th (400%) week post vaccination. However, the positive control (Group III) exhibited a lower HI titre increment by the 1st week (50%) but a considerably higher titre by the 4th week (500%). Clinical signs observed between days 2 to 7 postinfection include depression, reduced appetite and slight turning of the neck in the unvaccinated bird (Group IV). **Conclusion:** Liposomal formulation of NDV results in a rapid onset of the immune response. Cetrimide confers no advantage to the liposome in terms of adjuvanicity but might enhance overall liposomal stability.

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Abstracts of Submitted Poster Presentations

P4 Serotype-specific Efficacy and Immunogenicity of a 9-valent Pneumococcal Conjugate Vaccine (PCV-9) Determined during an Efficacy Trial in Gambia

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Background: A large placebo-controlled vaccine trial in Gambia showed that a 9-valent pneumococcal conjugate vaccine (PCV-9) had high efficacy against radiological pneumonia. The objective of this study was to determine the serotype specific vaccine efficacy and immunogenicity of a 9-valent pneumococcal conjugate vaccine (PCV-9) in African children. **Method:** A single 2-4 ml venous blood specimen was collected from 213 Gambian children 4 - 6 weeks after the third dose of vaccine or placebo. IgG antibodies to pneumococcal serotype 1, 4, 5, 6B 9V 14 18C, 19F and 23F polysaccharides were measured by ELISA. Per-protocol and intention-to-treat analyses of serotype specific vaccine efficacy were undertaken and the results compared with serological findings. **Results:** Geometric mean concentrations (GMCs) of anti-pneumococcal polysaccharide antibodies were significantly higher for each serotype in children who received three doses of PCV-9 than those in the placebo group. Among PCV-9 recipients, GMCs ranged between 2.61 and 11.09 mcg/ml with the highest being against serotype 14 and the lowest against 9V polysaccharide. The proportions of infants with antibody concentrations above 0.15 mcg/ml, 0.35 mcg/ml and 1.0 mcg/ml were also higher in the vaccinated than in the control infants. The estimated overall protective level for all 9 serotypes, based on the vaccine efficacy against type specific invasive pneumococcal disease of 77% (95% CI: 51, 90) observed in the trial, was 2.3 mcg/ml (95% CI: 1.0, 5.0). **Conclusion:** The 9-valent pneumococcal conjugate vaccine studied was immunogenic in a Gambian population where it was also found to be efficacious.

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P5 Incorporating the Private Demand for Vaccines into a Cost-Benefit Analysis on the Introduction of a Universal Hib Vaccination Program in a Suspected Low Disease Burden Country: Thailand 2006

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Background: *Haemophilus influenzae* type b (Hib) is the most common cause of meningitis in Thai infants. **Objective:** To evaluate the economic impact of universal Hib vaccination in Thailand. **Methods:** Decision-tree-based analysis was conducted on a birth cohort of 740,109 infants using the current vaccination coverage and disease incidence data. All costs and benefits were estimated from the direct cost (medical and non-medical) and the indirect cost from both providers and clients. The intangible benefit was estimated by a willingness-to-pay survey. The net present value (NPV) and the benefit-cost ratio (BC-ratio) of the program were evaluated. **Results:** The results of these analyses showed that the universal vaccination program using the Hib conjugate vaccine in Thailand in 2006 was not cost-beneficial unless the intangible benefit was taken into account in the analysis model. In the analysis model with the intangible benefit included, the BC-ratio for the Hib vaccination program was 8.06. In the analysis model with the intangible benefit excluded, the Hib vaccination program would be cost-beneficial when the cost per dose of vaccine was cheaper than 29 THB (0.8 USD), or annual Hib meningitis incidence was greater than 9 per 100,000 children under five years of age (or 2.5 times of the current incidence). **Conclusions:** When analyzing the economical rationale to introduce Hib conjugate vaccine into the Thai universal vaccination program, the intangible benefit plays an important role.

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P6 Youths' Attitude in HIV Vaccine Trials

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HIV vaccine trials require proxy consent in addition to their assent, making the inclusion of youths in future trials of HIV vaccine a challenging and controversial issue. This study evaluated youths' attitude towards HIV vaccine trials in Nigeria. **Methods:** Three hundred and eighty six youths were randomly recruited. Data were derived from FGD and individual interviews. A structured questionnaire covered socio-demographic data, knowledge of HIV status, willingness to participate in the HIV clinical trial, obtaining parental approval, willingness to participate if approval is refused, letting friends know and inviting them to join, believing that participation in the clinical trial will not expose them to HIV infection and predisposition to stigmatization from friends and families. **Results:** Of the 386 respondents, 96.2% were single, with 59.3% female and 40.7% male. Age range was 14-22 years. 83.9% were Christians and 14.3% Moslems. 83.0% were in secondary school and 14.5% were in tertiary institutions. 31.3% knew their HIV status. 72.7% ($X^2_{P0.05}$=0000) indicated willingness to participate in the clinical trial. 66.2% ($X^2_{P0.005}$=0000) wanted parental consent, and 36.7% would participate if parents refused consent. 74.1% wanted their friends to know and 73.7% wanted friends to participate. 66.2% believed they would not be predisposed to HIV infection. 74.4% believed they would not be stigmatized. **Conclusion:** A significant number of youths wanted to participate; however, parental consent significantly affected the willingness of the majority of them. There is urgent need to educate parents about current information on HIV research. In the planning and designing of HIV vaccine trials, efforts should be made to integrate parents into the program to achieve the successful implementation of HIV vaccine trials in Nigeria.

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P7 Pretreatment with Sulfadoxine-Pyrimethamine or Artémether-Lumefantrine During the High Transmission Season: Consequences on *Plasmodium falciparum* Malaria Infection and Clinical Episodes in Under-five Children in Burkina Faso

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Objective: To assess the effects of radical cure of malaria parasites with sulfadoxine-ppyrimethamine (SP) or artémether-lumefantrine (AL), on subsequent malaria infection and clinical malaria episodes in a future malaria vaccine candidate trials site. **Methods**: 197 children received supervised curative therapy with SP, 88 received AL; a third group of 295 children were not pre-treated. Active detection of infection and malaria episodes was performed through home visits twice a week. Survival analysis methods were used. **Results**: The mean time to the first malaria infection was 27 days (IC95% [24-30]) and 22 days (IC95%[19.6-24.4]) in the SP and AL arms respectively (P= 0.008). The incidence density of malaria infection was higher in the AL group than the SP group; however the difference was not statistically significant (9.1% IC95% [7.7-10.5] versus 7.4% IC95% [5.6-8.3]). The mean time to the first clinical malaria episode was 27.4 days (IC95% [24.5-29.5]) and 27.3 days in the SP and AL arms respectively. (P= 0.4). The incidence density of clinical malaria episode was significantly higher in the pretreated group with AL than no treatment group (7% IC95% [5.7-8.2] versus 5.1% with IC95% [4.4-5.6]). No significant difference was found when comparing the AL and the SP groups. **Conclusions**: Our findings suggest that the radical elimination of malaria parasites with ACT drugs may increase the susceptibility to subsequent malaria infection and therefore clinical malaria episode. This aspect must be considered when designing malaria vaccines trials where endpoints are assessed following initial cure with effective antimalarial drugs.

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P8 Knowledge of Human Papillomavirus (HPV) and Acceptability of HPV Vaccine in Lagos State, Nigeria

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Background: Knowledge of HPV is important for its vaccine uptake. HPV virus is a known risk factor for cervical neoplasia.[1] There are many types of HPV; however, the Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine is effective against the carcinogenic types 6, 11, 16, 18. Education is needed for its awareness and acceptability. **Method:** A cross sectional survey of 320 female participants in Lagos State was done with questionnaires administered from August -October 2007. The age range was 15-45 years. **Results:** Mean age: 23.5 years; median age of first sexual intercourse: 17.5 years; knowledge of HPV 10%; knowledge of the HPV vaccine: 4%; sexually active: 78% and 18% had more than one male sexual partner; condom use: 72% regularly; 22% sometimes and 6% never; knowledge about Pap smear: 54% and only 24% have ever had Pap smear. 36% of the 204 urban dwellers would accept HPV vaccine compared to 22% of the 116 rural dwellers (p=0.009). 90 out of the 156 with tertiary education were 2 times more likely to accept HPV compared to 98 participants with secondary education and below (OR=2.1, 95% CI (1.3-3.2). Challenges to participation: fear of the vaccine 38%; adverse effect 32%; stigma 28%; mistrust 24%; support from partner/parent 22%. 82% would take the vaccine if it is nationally recommended by Ministry of Health. **Conclusion:** Success of the HPV vaccine depends on knowledge, acceptability and implementation. It is important to promote Pap smear screening.[2] Public health policy should be put in place to ensure availability and accessibility. Health education is a key to convincing stakeholders about HPV vaccination.

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P9 Need for Vaccine Development as a Preventive Strategy Against *Helicobacter pylori* Infection in Western Nigeria

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Background: *Helicobacter pylori* is known to be responsible for the development of gastritis, peptic ulcer and gastric malignancy.[1] Effective vaccination is needed to provide long-term solutions for high risk individuals despite limited resources. **Method:** Stomach mucosal biopsy samples were taken from 532 dyspepsia patients who underwent gastroscopy in three hospitals in Western Nigeria to detect *Helicobacter pylori* with relevance to its vaccine development in 2007. Culture and other detection techniques such as urease test, gram reaction, serology and polymerase chain reactions (PCR) were used to screen for the presence of the organism. **Results:** Age range: 12- 78 years; 276 males; 256 females. The most common diagnosis was antral gastritis, 287 (54%) with 97 (34%) *H. pylori* positive. 123 patients had peptic ulcer of which 36 (29.3%) were *H. pylori* positive. In the 37 patients with no abnormalities, 25 (67.6%) were positive for *H. pylori*. Seven (46.7%) out of 15 patients diagnosed as having gastric carcinoma were positive for *H. pylori*. Of the 532 samples, 453 (85.1%) were positive using serology, 327 (61.5%), 245 (46.1%). 224 (42.1%) and 186 (35.0%) using Gram stain, PCR, CLO tests and culture respectively. However, the best detection methods could be Gram reaction, serology and PCR, which detected *H. pylori* in 133 (25.0%) of the 532 patients. All the isolates were resistant to amoxicillin, metronidazole, and tetracycline but were all sensitive to norfloxacin and ciprofloxacin. **Conclusion:** Discovery of safe, effective and acceptable vaccine is important given the prevalence.

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Also, the challenges of drug resistance call for vaccine development[2], and Nigeria will provide opportunity for future *H. pylori* vaccine trials.

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P10 Immunogenicity of MSP3 Long Synthetic Peptides (MSP3-LSP) and its Four Overlapping Peptides Following Immunization of Adult Volunteers in a Phase 1 Trial with MSP3-LSP in a Malaria Endemic Area

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Background: Merozoites surface protein 3 (MSP3) is a malaria blood stage vaccine candidate which has been shown to be safe and immunogenic in naïve volunteers. **Objective:** We performed a Phase I trial of MSP3-LSP in adults living an area of stable and seasonal malaria transmission in Burkina Faso to assess the safety and immunogenicity of this vaccine formulation. **Methods:** Thirty eligible volunteers received three doses of 30µg of MSP3-LSP or of tetanus toxoid on days 0, 28 and 112. Humoral and cell-mediated immune responses against MSP3-LSP and its four overlapping peptides were assessed at different time-points. **Results:** IgG, IgG subclasses and IgM responses to MSP3-LSP and IgG responses to four peptides were similar in both vaccine groups. At days 56 and 140, 73.3% (11/15) of the volunteers in the MSP3-LSP vaccine group had stimulation indices (SI) to MSP3-LSP at least the double of those obtained at D0. At the same time-points, only 13.3% (2/15) of volunteers belonging to the tetanus toxoid group had a SI that was at least the double of that measured at D0. At days 56 and 140, 53.3% of volunteers in MSP3-LSP vaccine group had IFN-γ levels at least the double of those obtained at D0. A similar pattern was observed for the four peptides fragments in both groups. **Conclusion:** These data demonstrate that MSP3-LSP can boost cellular immune responses of semi-immune adults living in malaria endemic area where they are annually exposed to more than 200 infected bites.

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P11 Search for Novel Antigens Commonly Expressed among Different *Helicobacter pylori* Strains by Proteomics Technology

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Background: Infecting half of the world's population, *Helicobacter pylori* is the unique known bacterium that persistently infects human stomach, causing different gastric diseases. Because of genomic variability among strains, the development of an efficient large scale vaccine requires identification of protein targets commonly expressed among *H. pylori* isolated from individuals with distinct gastric mucosa phenotypes. Included in this study are strains clinically isolated from colonized patients with normal mucosa and those with peptic ulcers, gastritis and gastric cancer. Bacterial total protein extracts were analyzed by two-dimensional gel electrophoresis (2DE) being isoelectric focused onto non-linear pH 3-11 gradient strips (GE-Healthcare) and then separated according to their molecular weight, on a 7-16% (w/v) SDS-PAGE. Proteins were visualized by coomassie and silver-staining. 2DE-gels digitalized images are being analysed using ImageMaster™ 2D Platinum software (Geneva-Bioinformatics, SA) in order to evaluate commonly expressed proteins (with statistical significance) among all strains. The majority of the proteome seem quite similar, moving us to the next step, identification of equally expressed immunoreactive proteins, by immunobloting those 2DE-gels with a pool of antibodies against *H. pylori* (commercially available). Relevant proteins were identified by mass spectrometry (MS). These are good candidates for the construction of an efficient bi-, tri-valent antigen vaccine. Furthermore, preliminary results indicate proteins specifically expressed on *H. pylori* strains recovered from each patients group might be implicated in their pathogenesis. MS identification of such proteins will contribute to understanding the mechanisms underlining virulence of this organism.

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P12 Relationship Between Antibodies against Four Malaria Vaccine Candidates' Antigens and Clinical Outcome in Children Living in a Seasonal Malaria Transmission Setting of Burkina Faso

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Introduction: Protective immunity to *Plasmodium falciparum* malaria is acquired over several years with numerous disease episodes. Antibodies against malaria vaccine candidates were challenged to play a protective role against clinical malaria. Study aims to 1) characterize profile of IgG, IgG isotype and IgM responses to selected antigens and 2) examine the relationship between natural antibody isotypes responses to mentioned

antigens and protection against clinical malaria. **Methodology**: Target population was children aged 0.5 to 15 years homozygote for haemoglobin AA. Cross-sectional survey was carried out and 5 ml venous blood taken from each child and plasma used for antibodies (IgG, IgM and IgG subclasses) measurement. Active case detection for malaria episodes was then conducted from July to October. Each child was visited daily. If febrile, presumptive treatment with chloroquine and paracetamol was given, according to the national guidelines applied at the time of the study. Thick and thin blood films prepared for parasites check. **Results**: Malaria incidence was 2.4 episodes per child year at risk. After adjusting for confounding effects of age, total IgG to GLURP was strongly associated with reduced malaria incidence rate ratio associated with a doubling of total IgG (IRR 0.79 ((95%CI 0.66-0.94), *P=0.009.)*; there was a weak association for total IgG to MSP3. No evidence of an association for total IgG to AMA1 or to MSP1-19. Of IgG subclass responses studied, only IgG3 and IgG4 against GLURP and IgG1 against AMA1 were associated with protection against clinical malaria. **Conclusion**: AMA1 and GLURP offer good prospects for malaria vaccine development.

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P13 Trends in Human Papillomavirus Infection among Women Attending a Sexually Transmitted Diseases Clinic in Ibadan

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Background: The prevalence of Human Papillomavirus (HPV) infection has been on the increase in Nigerian women in recent times with concurrent increase in incidence of cervical malignancies. HPV vaccines have been advocated in some parts of the world to curtail the spread of this disease. **Methods**: A seven year retrospective review of 212 case notes of female patients attending the clinic was carried out. The case notes of patients presenting with cervical cancers were reviewed for presentation with other sexually transmitted diseases (STDs), age at initiation of sex, present number of sexual partners and overall sexual behavioral pattern. The results of laboratory tests taken by the patients were also reviewed. Data was analyzed with the use of the SPSS (version 10) data editor. Chi square tests were used to determine associations. **Results:** Thirty-two cases of patients presenting with cervical cancers were reviewed (15.1%).The mean age at sexual initiation was 18.7 years (SD=1.6, SEM=0.375). A total of nineteen cases had other sexually transmitted diseases (59.4%). None of the patients with cervical carcinoma had taken the HPV vaccine. A history of cervical cancer had a significant association with the presence of other sexually transmitted diseases (p=0.005). **Conclusions:** The presence of HPV infection is associated with cervical cancer. HPV vaccine administration with aggressive management of STDs will need to be carried out to reduce the incidence of cervical cancers.

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P14 Immunosuppressant as Adjuvant for Tolerogenic Immunization

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Background: Vaccination for auto- and allo-immune diseases has long been an attractive idea; yet there is still a lack of suitable adjuvant to forcefully steer immune responses toward tolerance. **Methods:** BALB/c mice with pre-established delayed-type hypersensitivity(DTH) to hen ovalbumin(OVA) were suppressive immunized with $OVA_{323-339}$ in the presence of dexamethasone (DEX).Blood Treg were counted by flow cytometry, using tail blood. Antigen specificity of the Treg was confirmed by in vitro restimulation with immunizing peptide and suppression assays. DC and T cells in draining lymph nodes were analyzed by flow cytometry. Antigen specific expansion of Treg in vivo was analyzed by adoptive transfer of CFSE-labeled DO11.10 TCR-transgenic CD4+ T cells into DEX-pretreated BALB/c mice. Female NOD mice of 6 weeks of age were treated with DEX and B:9-23 and diabetic was checked weekly using Diastix strips. **Results**: The suppressed immunization caused longterm desensitization to the recall antigen, via a dexamethasone-dependent tolerogenic mechanism that blocks dendritic cell maturation and expands OVA323-339-specific $CD4^+CD25^+Foxp3^+$ regulatory T cells. Similar treatment of NOD mice using dexamethasone and an insulin-derived, MHC II-restricted peptide (B:9-23) prevented predisposed spontaneous diabetes. **Conclusion**: This study reveals for the first time the potential usefulness of immunosuppressants as tolerogenic adjuvant.

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P15 Cimetidine Enhances Immune Response on HBV DNA Vaccination through Down-regulation of TGF-beta/IL-10 Without Altering the Frequency of Natural Treg Cells

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Background: Increasing the efficacy of DNA vaccination by the use of adjuvant is an attractive strategy. Cimetidne (CIM), a histamine 2-receptor antagonist, is proposed to enhance immune responses owing to its inhibitory effects on suppressor T cells. Therefore, we proposed that CIM at certain concentration can be used as a potent chemical adjuvant to enhance the immunogenecity of DNA vaccine. **Methods:** Hepatitis B

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virus (HBV) DNA vaccine, pcD-S2, encoding the hepatitis B surface antigen (HBsAg), plus CIM were intramuscularly injected into mice. The effects of CIM as adjuvant on humoral or cellular responses were determined by quantitated ELISA or T cell proliferation and DTH. The effects of CIM as adjuvant on *in vivo* cytotoxic responses and expression of cytokines were detected by FACS and RT-PCR. The data was analyzed with Student's t-test. **Results:** Compared to pcD-S2 alone, immunization of pcD-S2 plus 0.5%CIM enhanced both humoral and cellular responses. Importantly, from the therapeutic view, 0.5% CIM on HBV DNA vaccine could produce the most amounts of IFN-γ and augmented *in vivo* cytotoxic responses. Interestingly, we demonstrated that 0.5% CIM as adjuvant might be through down-regulating expressions of anti-inflammatory cytokines, IL-10 and TGF-, without altering the frequency of natural Treg cells, and reciprocally increase the level of IL-2 and IL-12 productions. **Conclusions:** Cimetidine as a potent adjuvant may be used in an effective DNA therapeutic vaccine for chronic hepatitis B virus infection.

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P16 Safety and Immunogenicity of a Diphtheria-Tetanus-Acellular Pertussis-Inactivated Poliovirus-Hib Conjugate-Hepatitis B Vaccine at 2, 3, 4, and 12-14 Months of Age

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Objective: To assess the safety and immunogenicity of an investigational, fully liquid, hexavalent pediatric vaccine at 2, 3, 4 and 12-14 months of age. **Methods:** In this double-blind, multi-center study, 708 infants were randomized in approximately equal numbers to receive 0.5mL intramuscular doses of 1 of 4 vaccine formulations differing in the contents of *Haemophilus influenzae* type b (Hib) polyribosylribitol-phosphate (PRP) conjugate component (tetanus-toxoid [PRP-T, 12µg] or *Neisseria meningitidis* outer-membrane-protein-complex [PRP-OMPC, 3 or 6µg]), and in hepatitis B surface antigen (HBsAg, 10 or 15µg). A minimum acceptable postdose-3 antibody response rate was defined by the lower limit of the 95%-confidence-interval exceeding a prespecified target. **Results:** Rates of adverse-experiences (AEs) were similar among groups, with a trend for increased solicited injection-site reactions (pain, redness, swelling) with increasing PRP-OMPC and HBsAg. Serious AEs reported by eight subjects were not considered to be vaccine-related.

SUMMARY OF IMMUNOGENICITY AT POSTDOSE-3, 4 FOR PRP AND HBsAg ANTIGENS

Antigen	Observed seroresponse rate % (95% CI) † and Geometric mean titers of formulations			
Seroprotective threshold	PRP-T (12,10) †† N=178	PRP-OMPC (3,10) †† N=176	PRP-OMPC (6,10) †† N=178	PRP-OMPC (6,15) †† N=176
Postdose-3				
PRP (% >1 µg/mL)	69% (61, 76); 2.1 µg/mL	94% (89, 97); 8.1 µg/mL	96% (91, 99); 8.9 µg/mL	93% (87, 96); 10.6 µg/mL
HBsAg (% >=10 mIU/mL)	95% (90, 98); 133.4 mIU/mL	91% (86, 95); 108.3 mIU/mL	90% (84, 95); 92.6 mIU/mL	92% (87, 96); 123.5 mIU/mL
Postdose-4				
PRP (% >1 µg/mL)	97 (93, 99); 27.4 µg/mL	98 (94, 100); 10.5 µg/mL	99 (96, 100); 13.2 µg/mL	99 (96, 100); 13.1 µg/mL
HBsAg (%>=10 mIU/mL)	98% (94, 100); 911.6 mIU/mL	98% (94, 100); 913.0 mIU/mL	99% (95, 100); 1077.1 mIU/mL	96% (92, 99); 1266.6 mIU/mL

† postdose-3 target response rate [lower bound of 95%CI] for PRP=85% [70%] and HBsAg=95% [80%]
†† concentration of PRP, HBsAg

All PRP-OMPC formulations met prespecified acceptability criteria for postdose-3 immunogenicity for all antigens: PRP, HBsAg, pertussis, diphtheria, tetanus and polio. Apart from the Hib response, the postdose-3 responses obtained with the PRP-T formulation met the acceptability criterion for each antigen. Postdose-4 responses were acceptable for all antigens in all formulations. **Conclusion:** All vaccine formulations were well-tolerated. The three PRP-OMPC formulations met pre-specified immunogenicity criteria, and were selected for further optimization of immunogenicity.

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P17 HIV-1 Infection Impairs Measles Virus-specific IgG Avidity Maturation in Zambian Children Following Infection and Vaccination

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Objective: To characterize the impact of HIV-1 infection on qualitative features of the antibody response to wild-type and vaccine strains of measles virus (MV) in Zambian children. **Background:** Most MV transmission occurs in Sub-Saharan Africa where HIV-1 prevalence is high. HIV-1 infection is associated with severe measles, higher measles vaccine failure and measles mortality, and lower MV-specific (sp) transplacental antibody in infants of HIV-1 infected mothers. **Methods:** Blood samples were obtained longitudinally from children enrolled in a prospective study of measles (n=57) or measles vaccination (n=44). HIV-1 infection was confirmed by plasma HIV-1 RNA measurement using reverse-transcriptase PCR assay. CD4+ T-lymphocyte counts were determined by FACS. MV-sp IgG and IgG isotypes were measured by EIA. MV-sp IgG avidity was determined by dissociation of MV-sp IgG from MV lysate by NH_4SCN titration. Plaque reduction neutralization (PRNT) was performed using Vero cells. **Results:** HIV-1 infection significantly impaired development of MV-specific IgG measured by EIA, but did not impair the development of neutralizing antibody measured by PRNT. Avidity maturation was impaired in HIV-infected children 1-month following wild-type infection (P=0.01) and 3-months following vaccination (P=0.03). MV-specific IgG1 developed in response to wild-type infection and vaccination. MV-specific IgG3 developed solely in response to wild-type infection. Avidity was not correlated to PRNT or to CD4+ T-lymphocyte counts. **Conclusions:** These findings show that the responses of HIV-1 infected children to wild-type and vaccine strains of MV are impaired, indicating the importance of understanding the effect of HIV on immune responses to MV.

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P18 Possible RNA Agonist for RIG-I/MDA-5 as Molecular Adjuvants for Protein Vaccines

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Background: The RIG-I/MDA-5 pathway has been shown to function as a cellular defense mechanism to detect RNA viruses. During viral infection, viral RNA and dsRNA generated from replication intermediates or transcription binds to cytoplasmic proteins RIG-I/MDA-5. This activates IRF3 and NFkB-dependent cytokine and chemokine expression, resulting in the release of type I IFN and other pro-inflammatory cytokines. Since type I IFN has been shown to enhance T- and B-cell responses, we hypothesized that RIG-I/MDA-5 agonists may function as molecular vaccine adjuvants and enhance antigen-specific immune responses. **Methods:** Mouse fibroblasts were transfected with several *in vitro* transcribed RNAs, and cytokine production was measured by ELISA. The strongest activator of cytokine production was tested in a mouse model for the ability to enhance immune responses of a protein-based vaccine. **Results:** Out of the six RNA species tested, measles virus leader (ML) RNA was identified as the most potent enhancer of IFN-beta and IP-10 expression in transfected cells by greater than 400-fold. When ML RNA in PBS was injected into mouse muscle, IFN-beta and other pro-inflammatory cytokine levels in muscle and serum were elevated by 3 to 15-fold. To assess whether ML RNA can enhance antigen-specific antibody responses, ML RNA was coinjected with trivalent influenza vaccine Fluzone® into mouse muscle. At 20 days after initial injection, serum antibody titers in mice injected with 1µg Fluzone® + 100µg ML RNA were up to 3-fold higher than in mice vaccinated with Fluzone® alone ($p<0.05$; Wilcoxon rank sum test). The enhancement was sustained through 2 weeks after boost. **Conclusions:** These results suggest that ML RNA may be used as an adjuvant for protein vaccines.

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P19 Immunization with *Shigella sonnei* Carbohydrate Biopolymers Protects Mice against Polymicrobial Septic Infection and Downregulates Proinflammatory Cytokines Production *in vivo* under Experimental Endotoxic Shock Model

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Background: Original approach to prophylaxis (correction) septic (endotoxic) shock based on preliminary immunization with carbohydrate biopolymers (CBP) from *Sh.sonnei* under present development. Clinically applicable CBP: low-endotoxic lipopolysaccharide (LPS) and O-specific glycolipid, represented compounds used in licensed *Shigella* vaccine Shigellvac®, protected mice against cecal ligation and puncture (CLP)-induced lethality and reduced the levels of TNF-α and IL-1β following endotoxin *E. coli* 0.55 challenge. **Methods:** To induce polymicrobial sepsis we used CLP as a model which reproduces many pathophysiologic features of septic shock. Mice were intraperitoneally (i.p.) injected with 400 µg of CBP from *Sh. sonnei* or Shigellvac® several days before induction of experimental peritonitis. For endotoxic shock correction mice were i.p. injected with 50 µg of the same preparations 72 hours before challenge with 3 mg LPS *E. coli* 0.55. TNF-α and IL-1β sera concentrations were assayed 1.5 h and 5.5 h after challenge. **Results:** Immunization with *Sh. sonnei* CBP combinations and Shigellvac® significantly improved survival rates of mice under polymicrobial sepsis. 3-4-fold increase (60-90 hours) of mean survival time was registered in groups of immunized mice. After immunization with *Sh. sonnei* CBP and Shigellvac® under endotoxin challenge TNF-α and IL-1β sera concentration reduced from 4000 pg/ml to 0 pg/ml and from 1000 pg/ml to 170 pg/m, respectively. **Conclusions:** Immunization with Shigellvac® and *Sh. sonnei* CBP provides a suppressive effect on experimental peritonitis development at

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early stages after CLP. Downregulation, caused by immunization with Shigellvac® and *Sh. sonnei* CBP, of TNF-α and IL-1β release under mouse endotoxic shock is associated with improved protection against LPS (*E. coli*)-mediated death.

Reference:
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P20 Antigen-specific B Memory Cell Responses to Lipopolysaccharide (LPS) and Invasion Plasmid Antigen (Ipa) B Among Volunteers Vaccinated with Live-attenuated *Shigella flexneri* 2a Vaccine Candidates

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Background: Shigella causes an estimated 600,000 deaths per year among children less than 5 years old. A well-tolerated vaccine that induces durable immunity is highly desirable. We evaluated the induction of antigen-specific memory B cells and avidity of antibody responses in volunteers who received live-attenuated *Shigella flexneri* 2a vaccine strains which induce vigorous serologic and antibody secreting cell (ASC) responses. **Methods:** Healthy adult volunteers received 10^7, 10^8, or 10^9 cfu of deletion guaBA *S. flexneri* 2a (CVD 1204) or deletion guaBA, sen, and set *S. flexneri* 2a (CVD 1208) and then treatment with antibiotics 5 days later. Antibody avidity of type-specific humoral immune responses to LPS and Ipa B were measured by ELISA on days 0, 7, 14, 28, and 42. B memory cells specific to LPS, Ipa, as well as total IgG were assessed by ELISPOT on days 0 and 28. **Results:** Avidity maturation was not seen up to 42 days after vaccination with either vaccine strain. LPS-specific memory B cells increased from a median of 0 spot forming cells (SFC)/10^6 expanded cells pre-vaccination to a median of 20 SFC/10^6 expanded cells 28 days post-vaccination for LPS seroresponders (p=0.008 by Wilcoxon signed rank test). The correlation coefficient comparing LPS-specific SFC/10^6 expanded cells to maximum seroresponse was 0.95 (p=0.0001 by Spearman rho). IpaB memory B cell responses were also observed. **Conclusion:** Oral vaccination with live-attenuated *S. flexneri* 2a elicits detectable memory B cells to LPS and IpaB. A strong correlation was found between anti-LPS B memory cells and the antibody seroresponse.

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P21 Residual Rubella in São Paulo State, Brazil, 15 Years After the Introduction of Vaccination

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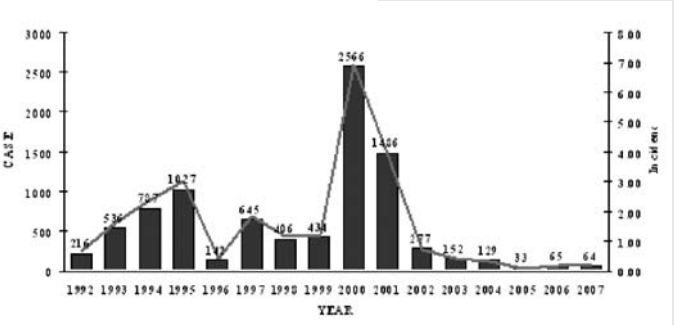
Rubella vaccine was introduced in the official immunization calendar of São Paulo State in 1992. At that time, the estimated incidence of the disease in the State was above 40 cases per 100,000 inhabitants, with an estimated annual number of Congenital Rubella Syndrome (CRS) above 3 cases per 100,000 live births. Based on previous experience with rubella epidemiology and mathematical modeling, a mixed strategy was proposed consisting of a mass pulse vaccination against measles, rubella and mumps, targeting all children between 1 and 10 years of age and the introduction of this triple vaccine at 15 months of age in the immunization calendar. The impact of the proposed strategy was outstanding, and rubella seemed to be almost eliminated in the State of São Paulo; however, analyzing the incidence after 15 years of continuous immunization and high coverage rates, rubella cases are still occurring. This presentation aims to show the incidence profile during those 15 years and to discuss possible interventions on the vaccination strategy to achieve rubella elimination.



*FROM: IAL/SINAN/D.D.T.RESPIRATÓRIA/ CVE (*data updated on 18/06/07)*

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P22 Dose-finding, Safety, and Immunogenicity Phase 1 Trial of an Intranasal *Shigella flexneri* 2a Invaplex 50® Vaccine in North American Adult Volunteers

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Background: *Shigella* Invaplex 50® is a mucosal subunit vaccine consisting of LPS in a complex with IpaB and IpaC. In an initial phase 1 trial *Shigella* Invaplex 50® demonstrated safety and moderate immunogenicity after nasal administration with a pipette at doses ranging from 10-480 µg. The current study examined the safety and immunogenicity of the vaccine delivered with a nasal spray device at doses ranging from 240 µg to 690 µg. **Methods:** A randomized, double-blind, phase 1 trial was conducted in which a total of 36 subjects received one of three Invaplex 50® vaccine doses (240, 480 and 690 µg) by an intranasal spray device on days 0, 14 and 28. Vaccine safety was actively monitored by physical exams and symptom diaries during vaccination and for 28 days post-dosing for local and systemic adverse events. Serum and mucosal antibody responses and antibody-secreting cells (ASC) levels were determined throughout the study. **Results:** The *Shigella* Invaplex 50® vaccine was safe and well-tolerated with no serious adverse events. The majority (98%) of the solicited adverse events were coded as mild, predominantly rhinitic in nature, with no significant differences in the frequency of adverse events between the vaccine groups. Significant ASC (≥ 10 ASC/10^6 PBMC), serum, and mucosal (≥ 4-fold increase over baseline) antigen-specific antibodies were detected in volunteers from each dose group with the 690 µg dose inducing responses of the highest magnitude and in the greatest percentage of volunteers. **Conclusions:** The *Shigella* Invaplex 50® vaccine was safe, well-tolerated and induced robust levels of antigen-specific intestinal IgA and ASC responses. Future studies to investigate dose amount, schedule, and efficacy of the Invaplex® vaccine are warranted.

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P23 Live Attenuated *virG*(*icsA*)-based Second Generation *Shigella* Vaccines: Construction and Testing in Animal Models

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Background: Bacillary dysentery caused by *Shigella* continues to be one of the most common infectious diseases facing travelers abroad and deployed military personnel. Three different live attenuated *Shigella* vaccines based on deletion of the *virG*(*icsA*) gene, WRSS1, SC602, and WRSd1, have been tested in healthy adults for safety, immunogenicity and in one case protective efficacy [1, 2]. The findings from these trials indicate that although safe, immunogenic and efficacious, the vaccines could be improved through further attenuation. **Methods:** New, *virG*(*icsA*)-based *S. flexneri* 2a vaccine candidates, WRSf2G12 and WRSf2G15, with additional deletions in enterotoxin genes (*set, senA, and senB*) and a lipid A acyl-transferase gene (*msbB2*) have been constructed from the *S. flexneri* 2a human challenge strain 2457T. Each strain was assayed using both *in vitro* cell culture and animal models of infection. **Results:** Both WRSf2G12 (Δ*virG*(*icsA*), Δ*set*, Δ*senA*, Δ*senB*) and WRSf2G15 (Δ*virG*(*icsA*), Δ*set*, Δ*senA*, Δ*senB*, Δ*msbB2*) are invasive in cultured epithelial cells, but negative in the Sereny test. Each strain is equally cytotoxic to macrophages, but induces differential levels of pro-inflammatory cytokines in epithelial cells. Guinea pigs immunized ocularly with SC602, WRSf2G12 or WRSf2G15 and challenged with 2457T are protected from disease and show comparable levels of serum and mucosal humoral immunity. **Conclusions:** These data indicate that deletion of the *set*, *senA*, *senB* and the plasmid-borne *msbB2* genes do not appear to alter the protective immune responses induced with vaccine strains carrying a *virG*(*icsA*) mutation. Nonhuman primate studies and future clinical trials will attempt to validate the increased safety of enterotoxin negative *virG*-based live *Shigella* vaccines with modified lipid A.

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P24 Induction of Protective Immune Responses to Pathogenic Influenza Using Electroporation and Consensus DNA Immunogens

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There is a pressing need to develop novel technologies for immunizing against emerging viral threats, including emerging influenza viruses to which no prior herd immunity exists. Consensus DNA immunogens have the potential to induce highly cross-reactive immune responses. Using pathogenic influenza as a model, we have developed four consensus constructs: pH5HA (a consensus of 16 clade1 H5N1 hemagglutinin sequences); pM2eNP (fusion of the N-terminal domain

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of the M2 ion channel with the nucleoprotein antigen, designed from 40 influenza A sequences); pN1NA (designed from over 40 N1-neuraminidase sequences) and pM1 (from over 40 influenza A sequences). We show here, using electroporation (CELLECTRATM constant-current device), that these immunogens can induce robust and protective immune responses against highly pathogenic avian and human influenza viruses. Murine challenge studies show efficacy of both antibody- and cell-mediated immunity against pathogenic H5N1 influenza (100% and 80% survival from vaccination with pH5HA and pM2eNP, respectively), in addition to T-cell depletions to understand correlates of immunity in the presence of an H5N1-induced cytokine storm. Four groups of ferrets were also immunized and electroporated with pVax (controls); pH5HA; pM2eNP; or pH5HA, pM2eNP, and pN1NA. Following H5N1 challenge, 100% survival was observed in each challenge group (0% in the control). By day 5 post-infection, there was a minimum of 90% reduction in viral load ($p < .01$), in addition to protection from weight loss. These studies were extended into a primate model of vaccination, showing in rhesus macaques the ability of our consensus sequences to induce cellular immune responses in addition to protective titers of antibody (HI > 1:40) following two immunizations.

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1. Laddy DJ, Yan J, Corbitt N, Kobasa D, Kobinger GP, Weiner DB. Immunogenicity of novel consensus-based DNA vaccines against avian influenza. Vaccine. 2007;25(16):2984-2989.

P25 Phase I Safety Data from a Still-blinded Trial of Reduced-dose, Intradermal Influenza Vaccination by Needle-free Jet Injector in the Dominican Republic

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Objective: Describe adverse events (AEs) following vaccination from a phase I trial comparing reduced-dose and intradermal vaccination for influenza. **Background:** Intradermal (ID) delivery of influenza vaccine by disposable-cartridge jet injector (DCJI) may reduce antigen quantity needed for seasonal and pandemic protection and avoid drawbacks of ID vaccination by needle-syringe (N-S). **Study Design**: In a still-blinded trial, 48 children from 6.9-22.8 months of age (mean 13.9) received two doses 4 weeks apart of trivalent, inactivated Vaxigrip® (sanofi-pasteur) in 3 randomly-assigned groups: 0.1 mL ID by investigational spacer on Biojector® 2000 DCJI; 0.1 mL intramuscularly (IM) by N-S; or 0.25 mL IM by N-S (control). AEs were assessed by investigators on days 0, 2, 7, and 28 after each dose and by parents in recorded diaries for prompted symptoms on days 0-7 and open-ended reports for days 8-28. **Results:** After either dose, local mild pain ("light reaction") on touching injection site occurred in 8 (17%) participants, and moderate pain ("cries or protests") in 1 (2%). Mild local AEs of ≥ 10-<25 mm occurred for erythema (7, 15%), swelling (3, 6%), and hematoma (1, 2%). None had induration or nodules. All local AEs occurred within 2 days after a dose. Systemic AEs noted were diarrhea (20, 42%), loss of appetite (18, 38%), vomiting (14, 29%), fever ≥ 38.0°C (12, 25%), irritability (8, 17%), unusual crying (8, 17%), and sleepiness (7, 15%). None clustered temporally after doses. One febrile convulsion on day 24 after dose 1 was the only serious AE reported. **Conclusion:** Local AEs were mild. Most systemic AEs are likely unrelated to vaccination dose and route, but can only be determined after unblinding of phases I and II.

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P26 A Prospective, Comparative Study of the Immune Response to Inactivated Influenza Vaccine in Pediatric Liver Transplant Recipients and their Healthy Siblings

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Background: Solid organ transplant recipients are highly susceptible to severe influenza disease, and annual influenza vaccination is routinely recommended for these individuals. However few studies have evaluated the immune response to the inactivated vaccine in this population. This prospective study compared the humoral and cell mediated immune (CMI) response to the trivalent subvirion influenza vaccine in pediatric liver transplant recipients to that of their healthy siblings. **Methods:** All subjects received inactivated influenza vaccine (two doses for children ≤ 9 yrs and for all transplant recipients), with hemagglutination inhibition (HI) assays and interferon-gamma (IFNγ) ELISPOTS for New Caledonia (NC) and Shanghai (SH) strains performed at baseline and at one month after each vaccine dose. Seroconversion was defined as a four-fold rise in antibody titers; seroprotection was defined as an antibody titer of ≥1:40. An increase in the number of T cells secreting IFNγ was considered a positive ELISPOT response. **Results:** Following one dose of vaccine and for both viral strains, transplant recipients achieved rates of antibody seroprotection (NC p=0.3, SH p=0.3) and seroconversion (NC p=0.1, SH=1) similar to that of their healthy siblings. In contrast, ELISPOT IFNγ responses to both viral strains were significantly attenuated in transplant recipients following two doses of vaccine (NC p=0.01, SH p=0.02). No cases of influenza or vaccine-related serious adverse events were documented in the study. **Conclusions:** The diminished CMI response to influenza immunization observed in pediatric liver transplant recipients suggests that the current vaccine strategy may not provide optimal protection. Further studies are necessary to determine the clinical parameters predictive of vaccine immunogenicity, as well as the optimal immunization strategy, for this high risk population.

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P27 Hepatitis A and Travel Amongst Nova Scotia Post-Secondary Students: Evidence for a Targeted versus Universal Immunization Strategy

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Background: Current Canadian guidelines indicate hepatitis A virus (HAV) vaccination for groups at high risk of contracting the infection, such as travelers to HAV-endemic areas. However, the Centers for Disease Control in the United States advocates a universal approach to HAV vaccination that calls for the immunization of all children. **Objectives:** Our objective was to determine whether the Canadian guidelines that indicate HAV vaccination for high risk groups such as travelers are being followed within the post-secondary student population. We planned to use this data to help determine whether or not a universal immunization strategy for HAV rather than the current targeted approach is justified. **Methods:** We designed and distributed an electronic survey to four groups of post-secondary students. The survey was constructed to elicit HAV risk factors, HAV immunization history, and known disease status to determine whether the Canadian guidelines for HAV vaccination are being followed. Questions were included to help determine the factors that predisposed to or prevented vaccination when indicated under the current guidelines. **Results:** We received 2279 completed surveys (10.6% response rate). Our data showed that 1380 (60.6%) participants had traveled to HAV-endemic regions in the past and that 1851 (81.2%) respondents were planning to do so within the next 5 years. Less than half of the students who traveled to HAV-endemic areas reported a history of HAV vaccination (662 or 48.0%). The vast majority (93.9%) of unvaccinated students surveyed indicated a willingness to receive the immunization if it were provided free of charge. **Conclusions**: The current Canadian guidelines for HAV vaccination are not being followed within the post-secondary student population. A universal approach to HAV vaccination may be warranted.

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P28 A Universal Influenza Vaccine - Conjugation of Immunostimulatory DNA to Conserved Viral Antigens Generates Broad Immunity

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Background: Standard influenza vaccines rely on generating strain-specific neutralizing antibody responses to prevent viral infection. Frequent viral mutations of the envelope hemagglutinin proteins result in a yearly race to select appropriate strains and produce vaccine to meet public health needs. These annual efforts to produce standard flu vaccine do not address the threat of emerging pandemic strains. **Methods:** To address the deficiencies of standard vaccines, we have conjugated the conserved influenza antigens nucleoprotein (NP) and matrix protein 2, extracellular domain (M2e) to immunostimulatory DNA sequences (ISS) to generate highly immunogenic conserved antigens that can be used alone or in combination with the standard vaccine to induce potent, broadly reactive immunity. **Results:** NP-ISS induces strong Th1 and CTL responses that reduce viral titers and provide protection against shift and drift strains in mouse challenge systems. Co-delivery of NP-ISS with standard vaccine enhances the antibody responses to HA in both mouse and primate models. Polymeric presentation of M2e-ISS induces strong antibody responses in mice. Similar to NP-ISS, co-delivery of M2e-ISS with standard vaccine enhances the antibody response to HA in mice. **Conclusion:** ISS-linked NP and M2e represent unique vaccine components that can provide strong, cross-strain protective immunity and may be used in conjunction with standard vaccines to enhance their immunogenicity. The NP-ISS/M2e-ISS vaccine represents a promising approach to a broadly reactive, universal influenza vaccine. Research funding supported by NIAID grant 1U01AI074578-01.

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P29 Follicular Targeting of Vaccines: From Skin Explant to Transcutaneous Vaccination Trials in Humans

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Background: Induction of T-cell responses has become one of the major goals in therapeutic vaccination against viral diseases and cancer. The use of the skin as target organ for vaccine has been spurred by recent implication of epithelial dendritic cells (DC) in CD8 cell cross-priming suggesting its relevance in the induction of cellular immune responses. **Methods:** We have set up a standard operating procedure (SOP) allowing the application of vaccine compounds on cyanoacrylate treated skin that would allow the penetration of vaccines via the hair duct. We have investigated safety and immune responses against an inactivated influenza protein-based vaccine by transcutaneous (TC) and intramuscular (IM) vaccination in 11 volunteers (Pilot study) followed by a Phase I study on 24 healthy volunteers. Mann-Whitney tests were used to compare continuous variables between the groups. Statistical significance was set at $p < 0.05$. **Results:** We found that application of an inactivated-influenza virus vaccine by TC route vaccination is safe and demonstrated that solely TC vaccination selectively induced a significant increased in antigen-specific CD8 (IFNg, TNFa, IL2)-producing cells and not IM vaccination. **Conclusion:** This study proposes new perspectives for the development of vaccination strategies that trigger T cell immune responses in humans.

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P30 Long-term Residual IFNγ+TNFα Effector/Memory CD4 Lymphocytes Control Skin Vaccinia Virus Vesicle Formation

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Background: Historically, efficacy of vaccinia virus (VV) vaccination was estimated with the inspection of the cutaneous pustule formation at the vaccination site. Antibody responses have been widely proposed as correlates of efficacy and protection without direct evidence in the control of pustule formation; however, the role of components of cellular and humoral immunity in vesicle formation remained uncertain. **Methods:** We have studied in a large cohort of 184 vaccinated individuals correlates of immune responses in skin lesion formation, in previously vaccinated individuals and after recent re-vaccination. Mann-Whitney tests were used to compare continuous variables between the groups. Statistical significance was set at $p < 0.05$. **Results:** We showed that solely residual effector/memory T cell response as defined by IFNγ+TNFα-producing CD4 lymphocytes but neither humoral nor proliferative T cell nor CD8 effector T cell responses control the size of the cutaneous vesicle formation. In addition, large skin vesicle at the site of vaccination strongly correlates with strong induction of neutralizing anti-VV Abs production after re-vaccination. **Conclusion:** This finding remains essential for further progress in measurement of viral vaccination efficacy in future clinical trials.

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P31 Human Antibody Responses Against Virulent Orthopoxvirus Proteins Elicited by Vaccinia Virus Vaccines

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Background: NYBOH vaccinia virus protects versus variola (smallpox) and monkeypox viruses but has serious adverse effects. Highly-attenuated MVA and LC16m8 vaccinia vaccines appear safe and immunogenic, and subunit vaccines derived from vaccinia proteins appear promising in animals; efficacy cannot be measured against these eradicated/rare diseases. One potential immune surrogate might be elicitation of antibodies targeting variola and monkeypox proteins, compared to responses elicited by NYBOH. Subunit vaccines derived from variola membrane proteins A30, B7 and F8 are immunogenic in mice and protect versus lethal vaccinia challenge. LC16m8 elicits antibody responses against vaccinia virus proteins similarly to NYBOH. **Methods**: Baseline and 30 day post-vaccination sera from vaccinia-naïve subjects in an LC16m8 vaccine trial (N=20; 15 LC16m8, 5 NYBOH) were analyzed by ELISA for antibodies against monkeypox (MOPICE) and variola (SPICE) inhibitors of complement enzymes, and F8. Responses were assessed by detection of antibody at Day 30 and by seroconversion (4-fold titer rise). **Results:** Overall, 14 (70%), 9 (45%), and 6 (30%) subjects had detectable antibodies to MOPICE, SPICE and F8, respectively. LC16m8 recipients showed trends toward better anti-MOPICE response with higher proportion of detectable antibodies (80% vs. 40% for NYBOH, p=0.13) and higher titer fold-increase (2.6- vs. 0.4-fold increase for NYBOH, p=0.05). All subjects with anti-SPICE antibodies also had anti-MOPICE antibodies. Aggregate seroconversions were 20%, 5%, and 10% for MOPICE, SPICE and F8, with no significant differences between the vaccine groups. **Conclusions:** This preliminary study is the first to confirm that vaccinia virus-based smallpox vaccines variably elicit antibodies targeting variola and monkeypox virus proteins in humans. Further characterization of responses to other homologous proteins may help to assess newer generation smallpox vaccines.

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P32 A Unique Canadian Model of Investigators and Industry Research Sponsors Working Together to Improve Vaccine Research Culture and Opportunities

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Objective: Demonstrate an innovative approach to improving vaccine research culture and opportunities. **Background:** The Canadian Association for Immunization Research and Evaluation (CAIRE) is a unique professional organization formed in 2000. Its 130 members are dedicated to building the scientific foundation of optimal immunization programs. Creating a 'corporate voice' for researchers permitted high-level interactions with industry to seek improvements in sponsored research. **Methods:** A Research Sponsors' Advisory (RSA) Board was established in 2002, bringing together senior representatives of 5 vaccine companies and CAIRE leaders from academic and public health settings. Twice-yearly meetings are a forum to discuss generic issues. Each agenda considers new opportunities, potential collaborations and mutual concerns in the areas of research education, advocacy and practice. Any member can propose agenda items and lead a discussion. **Results:** Board meetings have led to numerous positive outcomes. Education advances include an annual vaccinology course for residents in training, multidisciplinary workshops and greater research emphasis in the national immunization conference. Research advocacy has focused on increasing sponsored projects in Canada including research prioritization workshops, enhanced disease surveillance and timely evaluations of newly established programs. Research practice advances include improvements in study planning, agreed means of investigator participation in data analysis and practical strategies to reduce study costs. Greater consideration is being given to integrating product and program related research and the respective academic and public health researchers. Two joint publications and a new model for multi-partner project funding have resulted. **Conclusions:** CAIRE's RSA Board provides a unique, neutral venue to discuss means to improve interactions between researchers and companies that sponsor research.

Abstracts of Submitted Poster Presentations

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P33 A Nationwide Survey of Past Hepatitis A Infections among Canadian Adults

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Objective: To assess the burden of hepatitis A virus (HAV) past infections among Canadian adults. **Background:** HAV infection rates in Canada are low and declining. Our recent survey confirmed that HAV infection is uncommon in children but the burden in adults remains unclear. The true incidence might be substantially underestimated and the observed decline may also reflect changing patterns in reporting. More accurate, population-based sero-epidemiological estimates would better guide use of hepatitis A vaccines in Canada. **Methods:** A country-wide survey of prior exposure to HAV and of selected risk factors was conducted among 18-70 year-olds identified by random digit dialing. Volunteers were sent study materials and returned oral fluid and completed questionnaires by mail. An ultra-sensitive assay was used to detect HAV antibody in oral fluid. Multiple logistic regression was used for risk factor assessment. **Results:** Of 2104 potential study participants, 1552 (74%) returned an adequate oral fluid specimen and questionnaire. Anti-HAV was detected in 509 individuals (33%) and was associated with birth in HAV endemic areas, self-reported prior hepatitis A vaccination, prior travel to developing countries, and increasing age. Among Canadian-born, non-vaccinated participants, anti-HAV was present in 30% individuals from Quebec, 22% from Maritimes, 18% from Western Canada and 14% from Ontario. Age-specific positivity rates were: 18-29 years 2.6% (3/115); 30-39 years 6.1% (9/148); 40-49 years 11.4% (22/193); 50-59 years 26.4% (47/178) and 60-70 years 46.5% (85/184). **Conclusions:** Past HAV infection rates among Canadian-born non-vaccinated individuals are low in young adults and increase by two fold per age decade. Travel to developing countries is a significant risk factor for Canadians. Interregional differences in anti-HAV prevalence are also present, reflecting population differences.

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P34 Evaluation of Genetic Drift of *S. aureus isdB* Gene in Immunized Mice

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Bacteria are experts at escaping selective environmental pressure. A vaccine composed of a single antigen could produce strong selective pressure on the targeted bacterial antigen, not unlike that of an antibiotic. We wanted to examine whether immune selective pressure would induce vaccine resistance. Vaccination with the *S. aureus* protein IsdB (iron-regulated surface determinant B) enhances survival in a murine lethal challenge model. With immune pressure in IsdB-vaccinated mice, there exists a possibility for selection of *isdB* mutants. We investigated the occurrence of IsdB antigenic drift in response to immune pressure. ICR mice were immunized with IsdB on adjuvant or adjuvant alone to induce a high titered antibody response. Mice were challenged i.v. with a lethal dose (1-2 X 10^9 CFU) of *S. aureus* Becker. Post challenge (D3), mice were sacrificed and bacteria harvested from the kidneys. Two separate inocula were created from this material, one from the IsdB immunized mice and one from the adjuvant alone mice. These inocula were used to challenge mice in the same immunization group respectively. The passage process was repeated 10X. These passage stocks were saved and compared to the original Becker strain. RFLP and DNA sequence analysis of the *isdB* gene from these stocks confirmed that the sequence continued to be highly conserved for both groups and continued to display similar levels of IsdB protein on the surface.

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P35 Kinetics of the IgG and IgA Antibody Response in Post-Partum Women after Immunization with Tdap

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Background: Pertussis is a life-threatening disease in the first six months of life, but completion of the primary vaccine series does not occur until the end of this period. Passive immunization via transfer of maternal antibodies could potentially protect the infant until immunity has developed. We sought to determine if immunization to Tdap in the immediate post-partum period would result in a rapid rise of maternal serum levels sufficient to achieve the transfer of anti-pertussis antibodies into breast milk. **Methods**: Within 24 hours of delivery, 50 postpartum women were randomized in a 4:1 ratio to receive either Tdap or no vaccine. Serum, salivary and breast-milk antibodies against pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN) and fimbriae-2/3 (FIM) were measured on days 0, 7, 10, 14, and 28 post-immunization. **Results:** Maternal serum IgG antibody levels for all antigens approached peak levels by day 10 and remained at these levels through day 28 (Table).

(continued)

	Pertussis Antibody (ELISA Units/mL)			
Day	PT	FHA	PRN	FIM
0	5.1	7.6	6.8	13.8
7	13.2	25.6	26.5	400.4
10	32.9	130.5	140.8	1511.1
14	42.3	156.9	193.7	1943.1
28	40.1	132.3	177.9	1941.6
2-fold rise (%)	97.4	100	100	97.4
4-fold rise (%)	87.2	100	100	97.4

Serum IgA antibody-response followed a similar pattern approaching peak response by day 10; however, IgA antibodies to all antigens began to noticeably decline between days 14 and 28. **Conclusions:** Although the serum antibody-response to Tdap in post-partum women is suggestive of an anamnestic immune response, it may not be sufficiently rapid to result in transfer of humoral immunity to the infant via breast-milk, particularly in the first 10 days of life.

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P36 Protection from Influenza Virus by Recombinant Nucleoprotein Requires Antibody

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Objective: To understand how nucleoprotein vaccination protects C57BL/6 mice from sublethal influenza virus infection. **Background**: Anti-hemagglutinin antibodies neutralize influenza virus and prevent infection in naive mice. Due to hemagglutinin variability, these antibodies are primarily effective against viruses of the same subtype used for vaccination, and may be inadequate for protecting against new strains, such as H5N1 isolates that could cause pandemic influenza. However, immunizing mice with the highly conserved nucleoprotein (NP) protects against multiple influenza serotypes. Although CD8 T cells may participate in this cross-protection, a role for the non-neutralizing antibody that is generated against NP cannot be excluded. **Methods:** Mice were immunized intraperitoneally with recombinant influenza NP (rNP) at days 0 and 10. On day 40, rNP-immune mice were challenged intranasally with 0.25 LD50 influenza PR8 virus. Separately, rNP-immune serum was transferred to B cell-deficient uMT mice prior to challenge. Morbidity and viral titers were monitored thereafter. NP-specific CD8 T cell responses were monitored by flow cytometry. **Results:** rNP immunization reduced morbidity and reduced lung viral titers by 100-fold on day 8 post-infection in C57BL/6 mice, but not in antibody-deficient mice. NP-specific T cell responses correlated poorly with this protection. rNP-immune serum from C57BL/6, but not from antibody-deficient mice, transferred these protective effects to uMT recipients. **Conclusions:** These unexpected results strongly suggest that non-neutralizing antibody to a conserved influenza protein can contribute to protection from virus challenge. Thus, eliciting humoral immune responses to non-neutralizing epitopes could significantly improve current vaccine strategies to confer greater cross-protective immunity against unexpected viral strains.

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P37 Development of a DEN-2 PDK-53-based Chimeric Tetravalent Vaccine

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Dengue fever is a worldwide public health threat caused by infection with one of four different RNA viruses: DEN-1, DEN-2, DEN-3 or DEN-4. No dengue vaccine is currently available nor is there an antiviral therapy for dengue virus infection. DENVax® tetravalent vaccine is based on the live-attenuated candidate dengue type 2 (D2) PDK-53 vaccine which has been shown to be safe and immunogenic, generating long-lasting neutralizing antibodies in human clinical trials. We are using D2 PDK-53 as the genetic backbone to engineer candidate chimeric vaccine viruses that express the structural genes of D1, D3 and D4. To complete development and clinical testing of these vaccine viruses, we have formed an international consortium consisting of scientists at Inviragen, the CDC, the University of Wisconsin and Shantha Biotechnics. GMP-quality seed stocks for each of the four vaccine viruses were rederived via transfection of certified Vero cells with viral genomic RNA transcribed from the original infectious cDNA clones. Following amplification of these seeds, all four re-derived viruses contained the expected genomic sequences. The seed viruses were sequentially plaque-purified, and 24 isolates were spot sequenced to ensure retention of the three D2 PDK-53-specific attenuating mutations, and a single premaster seed virus for each dengue serotype was chosen based on genome sequence analysis. The final, formulated D2-based tetravalent vaccine is being produced and tested for toxicity and efficacy in animal models. Human clinical testing of the D2-based vaccine will assess its safety, its ability to generate neutralizing antibody responses and ultimately its ability to protect against dengue fever. Development of an affordable, safe, and effective dengue vaccine will protect those most at risk of dengue, dengue shock syndrome, and dengue hemorrhagic fever.

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P38 Host Responses to *M. tuberculosis* PE_PGRS Antigens

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Background: We have previously shown that PEPGRS33 has a role in mediating mycobacteria interactions with host cells. Since *Mycobacterium tuberculosis* (*Mtb*) express numerous PEPGRS proteins, we chose three members of this family, PE_PGRS 16, 26 and 33, to determine if they elicit different biological responses. **Methods**: Recombinant *M. smegmatis* (*MS*) strains expressing *Mtb* PE_PGRS proteins under a BCG *hsp*60 promoter were constructed to study the host response following *in vitro* and *in vivo* infection. For protection studies, mice were immunized with DNA vaccines constructed from the three PEPGRS genes, challenged with *Mtb* and lung CFUs determined after 30 days. **Results**: Ten days after intraperitoneal injection of 10^7 CFU into mice, *MS* PE_PGRS 33 and 26 persisted significantly better in the spleen (3.5 and 3.2 log cfu) and liver (3 and 2.6 log cfu) compared with *MS* PEP_PGRS 16 (1 log cfu) or the vector control (2 log cfu). Similarly, infection of mouse macrophages with *MS* PE_PGRS 33 and 26 resulted in significant increases (~ 1 log CFU at day 6) in survival of the recombinant mycobacteria compared with *MS* PE_PGRS 16. **Conclusions**: The increased survival of MS PE_PGRS 33 and 26 in macrophages is associated with increased host cell death as indicated by the release of significant levels of LDH while expression of PE_PGRS 16 is associated with higher levels of NO and more effective killing of mycobacteria by host cells. None of the PEPGRS vaccines demonstrated protection but colonization of lungs was more pronounced in mice immunized with PEPGRS 26 and 33 compared with PEPGRS 16 and the naïve control. These studies indicate that different PEPGRS proteins can elicit variable host responses.

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P39 Genetic and Clinical Evaluation of MP-12 as a Live Attenuated Vaccine for Rift Valley Fever Virus (RVFV)

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New data about the safety and immunogenicity of MP-12, an experimental live attenuated vaccine for Rift Valley Fever Virus (RVFV), a zoonotic virus capable of causing hemorrhagic fever in humans, will be discussed. RVFV has the potential to invade the USA, and the only present countermeasure is an investigational formalin killed Army vaccine requiring 3 doses over 28 days. MP-12 was developed at the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), and evaluated in animals and a human trial performed in the 1990s. We determined the genetic sequence of MP-12 virus taken directly from the vaccine vial and found that *in-vitro* serial passage at low moi (0.001) in Vero E6, MRC-5 and fetal Rhesus lung cells gave rise to low numbers of point mutations, none of which affected the attenuating sites. Passage in interferon incompetent Vero cells resulted in a spontaneous deletion of the NSs gene. We gave 19 volunteers a single injection of 10^5 pfu MP-12 vaccine (made in 1988 and retaining full potency during frozen storage). Eighteen responded with $PRNT_{80}$ titers above the 1:40 target by 14 dpi and all were ≥1:40 after one year. By contrast, only 28/540 unboosted volunteers given the killed vaccine retained antibodies with a GMT of 1:18 after one year (unpublished). We cultured the plasma from all subjects daily for 14 dpi by double blind passage on Vero cells and recovered virus from 5 vaccinees. The RNA sequence showed a low mutation frequency and no reversions in the attenuating sites of vaccine virus. These data support the continued development of MP-12 as a countermeasure for RVFV to be used by responders and people living in affected areas. This work supported by NIAID Grant AI-062636 to C.J. Peters.

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P40 Incidence and Severity Dual Modeling in Vaccine Evaluation

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Background: Vaccine efficacy, defined as the proportion of disease incidence reduction attributable to the vaccine under ideal conditions, may not reflect the multiple aspects a vaccine's intrinsic property. We developed a dual model to jointly evaluate vaccine effects on incidence and severity of infectious disease. **Methods:** Through instructive scenarios, large sample simulation studies, and practical examples, the dual model is compared with individual modeling, ordinal logic model, sieve analysis, and a two-part model. The bias and true parameter coverage of 95% confidence intervals were used to compare the model estimates. For model performance in hypothesis testing on significance of coefficients, the type I error and power were compared between the dual model and a two-part model. **Results:** Compared to other models, the dual model estimates were more robust to sensitivity of disease definition. The dual estimates had the smallest mean bias and the highest true parameter coverage of the 95% confidence intervals when the vaccine efficacy was at a low to medium level. The dual model worked the best when a vaccine is efficacious on both incidence and severity or on severity only. In situations when a disease definition has low sensitivity to infection, or when a subclinical infection is of great public health importance, the incidence and severity dual model provides the closest estimates of vaccine parameters. With a reasonable sample size for vaccine trials, the dual model was comparable to the two-part model in having small type I error and maintaining high statistical power. **Conclusion:** The incidence and severity dual model can provide more information about different modes of action of a vaccine, and thus merits serious consideration in vaccine evaluation.

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P41 Molecular Vaccine Development: Perceived Barriers and Potential Solutions

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Background: The Molecular Vaccines Interagency Working Group hosted 75 vaccine development professionals representing pharmaceutical industries, biotechnology companies, academic institutions and the Federal government in a symposium and workshop to identify and prioritize barriers slowing development of safe and effective molecular vaccines. The premise of the meeting was that if solutions to barriers could be identified to facilitate successful movement of new technologies to licensure, molecular vaccines could address many public health priorities, including "difficult" infectious diseases like HIV, TB and malaria, emerging pathogens and agents of biological warfare requiring agile technologies, and needs outside of infectious diseases such as cancer and autoimmune diseases where vaccines could improve prevention and treatment. **Methods:** To better understand the barriers, speakers explored case histories of failed vaccines and reviewed challenges to the advancement of promising novel technologies. In four workshops, spanning basic research, preclinical development, early clinical testing and post phase 1 testing, participants attempted to devise solutions to the many barriers identified. **Results:** Prominent themes emerged: (1) Low immunogenicity in humans (particularly with 1st generation technologies); (2) lack of validated surrogate markers of protection (even when protection has been achieved in animal models); and (3) insufficient market potential to justify increasing development costs, at least for some targets like West Nile Virus and Ebola. Additional challenges identified included lack of predictive animal models and concerns over safety, funding, intellectual property, advanced development partnerships, manufacturing costs, scale-up, liability and public perception. **Conclusions**: Participants concluded that the development of molecular vaccines could be accelerated by greater focus on vaccine-related basic research, restructuring funding priorities and processes, increasing market incentives for vaccine development, and improving public perception regarding the value of vaccines.

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P42 Pathogen-mimicking Nanoparticles as West Nile Virus Vaccine Delivery Systems

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Background: We have devised a method to modify the surface of poly(lactic-co-glycolic acid) (PLGA) nanoparticles with immune potentiators. Previously we have shown that dendritic cells preferentially internalize and present antigen encapsulated in LPS-modified nanoparticles compared to unmodified particles. In this study, we test our delivery system for vaccination efficacy with a West Nile (WN) antigen. There is currently no vaccine or specific treatment for WN. **Methods**: Particles were loaded with WN envelope protein (E) made in Drosophila S2 cells. Mice (n=10) were subcutaneously or nasally administered LPS-modified or unmodified particles. A control group was given PBS. Mice vaccinated nasally received a booster dose at 14 days. Mice were subcutaneously challenged with an LD70 of WN 2741 at 15 days or 30 days post - subcutaneous and oral vaccination, respectively. Serum was sampled every 14 days and screened for E-specific IgG by ELISA. **Results**: At 21 days post-challenge, we observed 90 percent and 80 percent survival after single-dose subcutaneous vaccination with LPS-modified and unmodified, E-loaded nanoparticles, respectively. High titers of E-specific IgG were detected in the serum. Nasal administration of LPS-modified nanoparticles and unmodified nanoparticles yielded 80 percent and 60 percent survival. The nasally vaccinated mice had significantly lower IgG titers than mice vaccinated subcutaneously. Thirty percent survival was observed in the control group. **Conclusion**: Modified nanoparticles loaded with WN envelope protein are effective subcutaneous vaccine delivery vehicles leading to protection against viral infection. Nasal administration of modified particles with some optimization could be a feasible alternative to systemic injection. This route of administration, coupled with the stability of the vaccine at room temperature, would allow for application to diseases in developing countries.

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P43 Efficacy of a New Generation of DNA-vaccine Encoding Retrovirus-based Virus-like Particles to Induce Both Cellular and Humoral Immune Responses and its HCV-vaccine Development

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Objective: We engineered and investigated the immunogenicity of DNA-vaccines expressing recombinant retrovirus-based virus-like particles (VLPs) (plasmo-retroVLPs). **Background:** The expression of the Moloney murine leukemia virus (Mo-MLV) gag and envelope proteins is sufficient to generate retroVLPs that can be used as antigen platforms after epitope insertion in structural constituents. We already demonstrated that plasmo-retroVLPs forming recombinant retroVLPs that harbor a CTL epitope in Mo-MLV envelope induce significantly better antigen-specific responses than control plasmid preventing retroVLP assembly (Bellier B. et al, Vaccine 2006). Moreover, surface

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glycoproteins from heterologous enveloped viruses, including E1E2 from hepatitis C virus (HCV), can be efficiently incorporated onto retroVLPs that open new possibilities for vaccine applications.[2] **Methods:** We designed HCV-specific plasmo-retroVLPs expressing Mo-MLV gag and HCV-E1E2 proteins able to form pseudotyped retroVLPs. Formation of such pseudo-particles has been tested in vitro by western-blot analysis and infectious assays. In vivo vaccine immunogenicity was determined after needle-free injection of DNA in BALB/C and HLA-A2+ transgenic mice by measuring E1E2-specific IFNg response and neutralizing antibodies. Prime-boost experiences were also performed using adenovector expressing HCV-E1E2 for priming. **Results:** We demonstrated that HCV-specific plasmo-retroVLPs induce efficient primary and memory T-cell immune responses that can be also enhanced by association with genetic adjuvants (pIL-12, pGM-CSF). In addition, we observed that plasmo-retroVLPs significantly boosted the HCV-specific CTL and humoral immune responses induced in mice previously primed with HCV-E1E2 recombinant adenovirus. In contrast, control plasmids preventing HCV-pseudotyped retroVLP formation had no boosting effect. **Conclusions:** Taken together, DNA vaccines encoding HCV-pseudotyped retroVLPs represent efficient immunogens. Their capacity to induce significantly better CTL and antibody responses than the same antigens presented as nonVLPs make them excellent vaccine candidates.

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P44 Rational Design and Standardized Evaluation of Novel Genetic Vaccines

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CompuVac™ is a project financed by the European Commission, which involved 18 partners worldwide. The main objectives of CompuVac™ are to setup a standardized approach for the rational development of genetic vaccines and to apply this methodology to the development of vaccines against the hepatitis C virus. The process comprises the development of: (i) a large panel of vaccine vectors representing various vector platforms and all expressing the same model antigens; (ii) standardized methodologies for the evaluation of T- and B-cell responses and of molecular signatures relevant to safety and efficacy; (iii) a database for data storage and analysis of large data sets; (iv) intelligent algorithms for the rational development of prime boost vaccination. One of our final goals is to generate and make available to the scientific community a tool box and an interactive database allowing the comparative assessment of future vaccines. We also aim to validate these tools by the rational development of preventive and/or therapeutic vaccines against HCV. We have now assembled a unique set of 142 vaccines of different classes, from viral vector derived vaccines to inert VLPs, analyzed their efficacy with standardized methodologies, and compared them with an intelligent database. This has already allowed us to make significant comparisons between different vaccine types and to initiate novel vaccine design and vaccination regimen. We are now evaluating prime-boost immunization regimen with these vectors. We believe that this should have a significant impact on vaccine development, notably for those vaccines requiring prime/boost immunizations.

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P45 A Versatile Technology Conferring Thermostability and Allowing Extended Ambient Storage of Viral Vaccines

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Vaccine formulations usually require refrigeration during storage and distribution to avoid loss of potency due to lability at ambient temperature. Maintaining correct storage requirements can be logistically challenging and expensive. Our group has overcome vaccine thermo-instability using its proprietary stabilizing formulations. Stability has been demonstrated using several thermolabile, model "live" viruses including: measles, adenovirus and foot-and-mouth Disease virus (A and O). Our approach was based on events occurring during seed maturation, whereby seeds are rendered desiccation and thermo-tolerant. The process involves deposition of sugars at various ratios and, importantly, a class of proteins only present when the seed is desiccation/thermally tolerant. By identifying a functional analogue of these proteins, histone 2A, and careful selection of excipient sugars, We were able to duplicate this phenomenon and apply it to stabilization of viral vaccines. **Method:** 50ul of virus/vaccine solution was mixed with 250ul of stabilizer (a solution comprising sucrose, stachyose and histone 2A, in PBS). The mixture was frozen and lyophilised over the course of 2 days. Accelerated thermal challenge studies were performed by holding the samples at 37 degrees C for up to 7 days. At the end of this period virus potency assays were carried out. **Results:** FMDV, adenovirus and measles were rendered thermally stable. Potency losses observed during processing were negligible (consistently less than 1 log10). In the absence of excipients, or removal of any one excipient component, a significant loss of potency occurred. **Conclusions:** Our technology has overcome a major hurdle affecting vaccine storage and distribution. Histone 2A has been subsequently used as a basis to identify proprietary, non-biological excipients mimicking histone 2A and capable of conferring vaccine stability.

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Abstracts of Submitted Poster Presentations

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P46 Development of Multi-Antigenic Peptide Antigens as the Basis for a Novel Vaccine Approach to Alzheimer's Disease

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Background: Alzheimer's Disease (AD) is characterized by the deposition in the brain of amyloid beta peptide (Aβ 1-42) into insoluble plaques. A therapeutic approach for treatment of AD is, therefore, to prevent the formation of the Aβ plaques by developing vaccines directed against the Aβ (1-42) peptide. Various studies have shown that it is possible to utilize Aβ (1-42) peptide as an antigen to induce an immune response in mice and non-human primates that reduces brain Aβ deposits and slows AD progression. A human vaccine directed against the full-length Aβ (1-42) peptide went into clinical trials but had serious safety issues linked to the activation of T-cell responses to the autoantigenic part of the peptide.[1,2] **Methods:** We initially synthesized linear Aβ (1-42) peptide-derived antigens that would avoid a T-cell proliferative response by limiting the peptide size to ≤ 8 amino acids. Based on immunogenicity data from these small linear peptides, we synthesized multivalent linear and branched antigenic peptides (MAPs) that were conjugated to carrier proteins. These peptide antigens were evaluated for their ability to elicit immune responses and change plasma Aβ levels or reduce Aβ plaques. **Results:** Linear peptide epitopes based on Aβ (1-42) peptide containing ≤ 8 amino acids were determined to be immunogenic and cross reactive with human AD brain tissue. A second generation branched MAP construct was then developed that was found to be highly immunogenic and to significantly increase plasma Aβ1-40 level, which may indicate clearance of Aβ peptides from the CNS. **Conclusions:** A novel MAP approach has been pursued to design an efficacious and well-tolerated anti-Aβ active vaccine construct, using a ≤ 8-amino acid epitope strategy.

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P47 HSV-2 Immunization Enhanced by Estrogen Results in Improved Efficacy

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The objective was to explore the effects of estrogen on vaccine efficacy. It was our hypothesis that adding estrogen to an immunization can significantly enhance the immunity engendered. We used an ovariectomized mouse model for studying Herpes Simplex Virus 2 (HSV-2) infection; a glycoprotein-D subunit vaccine from GlaxoSmithKline for immunization (currently undergoing Phase III clinical trials); prescription delestrogen as the estrogen source, administered one week prior to an immunization regimen; ELISA for the detection of HSV-specific IgG in serum; ELISPOT for the detection of gD-specific IL-4 producing T-cells; and Fisher's Exact and Student's Unpaired T Tests for measurements of statistical significance ($P<0.05$ for all "significant" results). We observed that adding estrogen to an immunization regimen resulted in significant protection against infection both across a range and even at very high HSV-2 challenge doses, whereas immunization alone does not. We also saw an increase in the threshold HSV-2 dose required to infect 50% of mice when estrogen is added, compared to immunization alone. Similarly, we observed that adding estrogen to an immunization regimen significantly increases the protection against disease at very high challenge doses and increases the threshold required to cause disease in half of the mice, compared to immunization alone. Mice who are resistant to infection due to an estrogen-enhanced immunization regimen have twice as much HSV-2-specific IgG in serum and almost three-times as many gD-specific IL-4-producing T-cells in draining lymph nodes prior to challenge, when compared to mice immunized alone. Therefore, we concluded that estrogen enhances vaccine efficacy by increasing the quantity of antigen-specific T-cells and antibody, resulting in improved protection against infection and disease.

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P48 Immunohistological Analysis of Nanoencapsulated DNA Vaccine for Respiratory Synctical Virus

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Human respiratory synctical virus (RSV) causes severe lower respiratory tract infection in infants and result in pneumonia. In the present study, antigenic regions of RSV F, M2 and G genes were cloned into a DNA vaccine vector, phCMV1, resulting in development of a vector named DR-FM2G. The DNA vaccine vector was also used to formulate a DNA-nanoparticles complex using chitosan. Stability of the nanoparticles was investigated at different pH values by enzymatic degradation and subsequent gel retardation assay. Temperature stability was evaluated using DSC. DSC results suggest that chitosan microparticles were stable until 80°C. The effect of DNA concentration on release rate from chitosan microparticles was examined using similar intestinal fluid (SIF) and similar gastro fluid (SGF). When incubated with SIF, after a

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release of about 10% of DNA in the first 60 minutes, DNA release occurred at a higher (60%) rate during the following week. However, when incubated with SGF (similar gastro fluid), the microparticles released a small burst of DNA (10%) in the first 60 minutes, followed by slow release of DNA (45%) during the following week. Cytotoxicity of chitosan microparticles was measured using MTT dye reduction assay in two cell line. The characteristics of microparticles were evaluated by SEM (scanning electron microscopy), TEM (transmission electron microscopy), and light microscopy. The characterized DR-FM2G vector and DNA+ nanoparticles were used to vaccinate BALB/c mice. Vaccinated mice were challenged with live RSV to assess the protection capabilities of the DNA vaccine vector. On each respective day, major organs (heart, kidney, liver, spleen, and lungs) were collected and used for immunohistochemical analysis. RSV was detected using PCR (polymerase chain reaction) & RT-PCR.

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P49 An Efficacious Rattlesnake Vaccine for Horses

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In the United States, the estimated mortality rate for horses bitten by venomous snakes is 10-30%. Therefore, a vaccine to protect horses against western diamondback rattlesnake (Crotalus atrox) venom is being developed along the lines of the commercially available canine vaccine, Crotalus Atrox Toxoid. Efficacy of this vaccine was evaluated using two groups of horses that were immunized either subcutaneously or intramuscularly with three doses, one month apart. The vaccine elicited serum IgG antibody responses in all animals specific to several native Crotalus atrox antigens. Additionally, serum from vaccinated animals was shown to neutralize whole Crotalus atrox venom in a mouse survival assay at a rate of 1 ml of sera per 57 µg venom - a level which is believed to represent a significant degree of protection against rattlesnake envenomation in horses.

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P50 The Role of CFA/I Fimbrial Proteins in Enterotoxigenic *E. coli* Strain H10407

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The participant will discuss fimbriae proteins critical for attachment of enterotoxigenic *E. coli* (ETEC) to the human host, and their potential as vaccine antigens. The role of ETEC fimbriae in colonization of the human gut and in generation of protective immunity has been previously established; however, the contribution of the individual components of the fimbriae to intestinal binding remains incompletely defined. The epidemiologically relevant ETEC strain H10407 expresses CFA/I fimbriae, which are composed of multiple CfaB structural subunits and a CfaE tip subunit. To identify the role in attachment for the CfaE tip protein, an R181A single amino acid substitution was introduced by recombination into the CFA/I operon of the H10407 background. The substitution of R181A eliminated in vitro human cell binding, without loss of CFA/I fimbriae expression, as confirmed by agglutination with anti-CFA/I sera and by electron microscopy. The binding phenotype was restored when the wild type cfaE gene was supplied on a plasmid in trans. In contrast, in trans expression of cfaE containing amino acid 181 substitutions with biochemically, spatially, or functionally related amino acids did not restore the binding phenotype. Thus the R181A single amino acid mutation in cfaE did not disrupt translation of CFA/I proteins or biogenesis of fimbriae, indicating that the loss of binding behavior was due to localized areas of epitope disruption. R181 appears to have a unique and irreplaceable role in the formation of a receptor-binding feature on CFA/I fimbriae. The data also confirms that the CfaE tip protein is a required binding factor in CFA/I-mediated ETEC colonization and could be a target antigen for vaccine inclusion.

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P51 Characterization of a Cross-protective, Multivalent Subunit Vaccine Against Salmonella

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Salmonella enterica is a leading cause of bacterial foodborne illness worldwide. As with many bacterial pathogens, an important requirement for salmonella pathogenesis is the acquisition of iron during the invasion of host tissues. To mimic the host environment, we have grown salmonella under iron restriction to produce a multivalent vaccine consisting of outer membrane proteins. The predominant protein components of the vaccine were identified as porins (OmpA, OmpC, and NmpC), and receptors for iron-bound siderophores (IroN, CirA, FepA). Western blot analysis with antisera from vaccinated mice revealed cross-reactivity with multiple serovars of *S. enterica* that are relevant to human disease, indicating the high degree of conservation among these proteins. Mouse memory CD4 T cells from vaccinated mice produced a wide array of cytokines upon re-stimulation with the vaccine proteins, including IFN-gamma, a cytokine known to be important for Salmonella immunity. In addition, vaccination of mice provided protection against lethal salmonella infection. Current work is aimed at identifying which of the proteins in the composition

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stimulate protective immunity. These studies will help establish immune correlates of protection for the development of a cross-protective vaccine for use in humans.

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P52 Development of a Novel Nanoemulsion-based Hepatitis B Mucosal Vaccine

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Background: Hepatitis B Virus (HBV) infection remains an important global health concern despite the availability of prophylactic vaccines that require three intramuscular injections. A mucosal vaccine requiring fewer immunizations could improve protection. **Methods:** Physical characterization included laser particle sizing, zeta potential measurement, isothermal titration calorimetry, and gel electrophoresis. Mice, rats and guinea pigs were intranasally vaccinated with HBsAg-NE. Humoral and mucosal immune responses were evaluated by IgG and IgA ELISA. Cellular immunity was evaluated by cytokine expression in splenocytes. Vaccine safety was assessed by physical examination and tissue histopathology and biochemical analysis of serum. **Results:** The vaccine consists of uniform lipid droplets (<350 nm) that are associated with HBsAg by electrostatic and hydrophobic interactions. The vaccine is immunogenic in various concentrations and also retains immunogenicity at normal, stressed and accelerated (40^{o}C) temperatures for up to 3 months. Intranasal immunization of mice produces serum IgG responses comparable to intramuscular vaccination with an alum-adjuvanted vaccine. Normalization with a standardized human anti-HBV serum shows that intranasal vaccination correlates with a protective immunity equivalent or greater than 1000 IU/ml. HBsAg-NE also induced CTL with Th1 polarization. Results from toxicology studies in rodents and in dogs indicate normal histopathology and blood chemistry. **Conclusions:** HBsAg-NE is an efficacious vaccine for protection against HBV infection via intranasal administration. This vaccine may not require cold-chain storage and could be administered without the use of needles; this possibly overcomes critical problems in immunizing populations in developing countries.

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P53 Influenza Vaccine Antibody Responses by Lung Transplant Patients in Three Seasons

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Background: Lung transplant (LTX) patients are at high risk of morbidity and mortality from influenza infection because of altered lung physiology and immunosuppression. Annual influenza immunization is recommended. Because vaccine antibody responses may be limited by immunosuppression, we hypothesized that LTX patients would mount poorer antibody responses to new influenza vaccine viruses in comparison to healthy individuals or non-immunosuppressed individuals awaiting lung transplantation. **Methods:** Twenty-six healthy individuals, 71 LTX patients and 35 patients awaiting lung transplantation participated in the 2004-05, 2005-06, and 2006-07 influenza seasons. Pre-transplant patients were reallocated to the post-transplant group over time. Serum for influenza antibodies measured by hemagglutination inhibition assay were collected prior to and 2-4 weeks after immunization. A four-fold increase in antibody concentration (seroconversion) for the three different seasons was considered an adequate vaccine response, and response rates were compared using chi square tests. **Results:** The A/H3N2 vaccine viruses were different in each of the three seasons while the H1N1 vaccine viruses remained the same in all three seasons, and the type B virus changed in 2006. Seroconversion rates to A/H3N2 viruses were lower in lung transplant patients than healthy subjects or those awaiting LTX. (2004-05 30% vs. 46% vs. 58%; p=0.04; 2005-06 31% vs. 70% vs. 54%; p=0.005; 2006-07 26% vs. 72% vs. 25%; p=0.001, chi test) Patterns for pre and post-immunization antibody concentrations tracked in parallel fashion with the seroconversion rates. **Conclusion:** The seroconversion rate to the new influenza vaccine viral determinants is lower in lung transplant patients than in healthy subjects and patients awaiting lung transplantation. Alternate immunization strategies may be required to achieve adequate conversion rates for this high-risk population.

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P54 The Brighton Collaboration Standardized Case Definitions: Tools for Use in Vaccine Safety Research and Surveillance

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Background: The Brighton Collaboration is an international effort to develop standardized case definitions and guidelines for collecting and reporting vaccine safety data for pre and post-licensure vaccine safety studies. The goal is developing international consensus on a "common language" or "vocabulary" for vaccine safety. **Methods:** Definitions were developed by working group experts from 328 volunteer scientists from 44 countries with various backgrounds including public health,

regulatory, clinical, academic, and industry backgrounds. Evaluations have been performed for sensitivity, specificity reliability and applicability in post-marketing surveillance studies using different approaches. Twenty-two case definitions have been published. **Results:** Examples include: for intussusception definition, a high sensitivity (98%) and inter-rater reliability (k=0.95) among clinician reviewers was obtained. Fever and persistent crying definitions had sensitivity of 88%, and 75% respectively. Other definitions evaluated included: hyptonic-hyporesponsive episode, seizure, nodule, aseptic meningitis, and anaphylaxis and were found to have a high specificity (above 98%) in identifying the cases. **Conclusion:** Evaluated standardized case definitions are sensitive, reliable and specific within surveillance systems. These tools may facilitate comparability and communication of vaccine safety data.

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P55 Burden of Acute Gastroenteritis Hospitalizations and Emergency Department Visits in US Children that is Potentially Preventable by Rotavirus Vaccination - A Probe Study Using the Now Withdrawn RotaShield® Vaccine

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Background: With the implementation of a new rotavirus immunization program in the United States in 2006, determining the potential health impact of vaccination is important. **Methods:** We conducted a retrospective cohort analysis of children who were eligible to receive the now withdrawn RotaShield® vaccine and were continuously enrolled in one of six managed care organizations (MCOs) in the Vaccine Safety Datalink (VSD). Vaccine effectiveness estimates against hospitalizations and emergency department (ED) visits for gastroenteritis (using ICD-9-CM codes for all causes of gastroenteritis) adjusted for month of birth, gender, and MCO were calculated as one minus the risk ratio of outcomes among children in different dose groups. The burden of gastroenteritis prevented by vaccination was compared with the rotavirus burden estimated by two different indirect methods. **Results:** The effectiveness of three doses of RotaShield® over a one year follow-up period was 83% (95% confidence interval (CI):45%-94%)) against all-cause gastroenteritis hospitalizations and 45% (95%CI:17%-64%) against all-cause gastroenteritis ED visits in children aged 2 to 15 months at study initiation. An increasing number of doses improved the effectiveness in preventing gastroenteritis hospitalizations but no clear trend was observed between number of doses and effectiveness in preventing gastroenteritis ED visits. The proportion of gastroenteritis hospitalizations and ED visits prevented by vaccination was substantially greater than the 44-53% of year-round hospitalizations and 25% of ED visits estimated due to rotavirus by indirect methods. **Conclusions:** RotaShield® was highly effective in preventing gastroenteritis hospitalizations and ED visits. Health benefits of the new US rotavirus vaccine program may be greater than previously estimated and the VSD should provide an excellent platform to assess impact of vaccination.

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P56 Transcutaneous Delivery of Tetanus Toxin Hc Fragment Induces Superior Tetanus Toxin Neutralizing Antibody Response Compared to Tetanus Toxoid

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Transcutaneous immunization is a promising vaccination delivery strategy, which targets potent immune cells residing in the outer layer of the skin. In this study the immunogenicity and neutralizing potency of the non-toxic Hc fragment of tetanus toxin (HcWT) and a mutant of Hc lacking ganglioside binding activity were compared with that of tetanus toxoid (TTxd) following transcutaneous immunization (TCI) of mice. Mice immunized with HcWT in the absence of an adjuvant induced highest anti-toxoid and anti-Hc antibody titres with a significant increase in toxin neutralizing potency compared with TTxd. These results are in contrast to previous studies employing subcutaneous delivery, where TTxd was found to be a more potent immunogen than the Hc fragment of the toxin. We conclude that the HcWT protein is more immunogenic than TTxd when given via the transcutaneous route. Our results suggest that TCI may provide an opportunity for effective delivery of toxin-like vaccine antigens which harbour protective epitopes but which may suffer from poor immunogenicity when delivered subcutaneously. We conclude that the underlying mechanisms of induction of a protective antibody response by TCI differ from those involved in subcutaneous immunization and that traditional toxoid proteins may not be optimal antigens for skin immunization.

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P57 Evaluation of the Immunopotentiation by TLR4 Agonists Combined with Aluminum-containing Adjuvants

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Background: Aluminum-containing adjuvants are the only adjuvants approved by the U.S. Food and Drug Administration for use in licensed human vaccines. However, these adjuvants predominantly enhance a T_H2 immune response, whereas a T_H1 immune response would be more desirable for some candidate vaccines. In this study, we investigated the effect of LPS and MPL in combination with two aluminum-containing adjuvants on the immune response. **Methods:** Cytokine production by BALB/c bone marrow-derived mouse dendritic cells (DCs) *in vitro,* and antibody production *in vivo* were measured by ELISA. Comparisons were made using ANOVA and paired T test. **Results:** In combination with LPS

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or MPL, the aluminum adjuvants significantly inhibited IL-12p70 and TNF-α production by DCs when compared to LPS or MPL alone. The addition of MPL and LPS to aluminum phosphate but not aluminum hydroxide adjuvant increased IL-1β production. Immunization of BALB/c mice with OVA (10 μg/dose) and aluminum adjuvants (150 μg Al/dose) with LPS (1.5 μg/dose) or MPL (7.5 μg/dose), increased OVA-specific IgG1 production when compared to either adjuvants alone. However, OVA-specific IgG2a antibody was only detected following immunization with LPS and with aluminum phosphate and MPL as adjuvants. **Conclusion:** The data demonstrate that LPS and MPL in combination with aluminum-containing adjuvants predominantly enhance a T_H2 but not a T_H1 immune response.

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P58 26-Valent Group A Streptococcus (GrAS) Vaccine In Healthy Adults: Summary of Immunogenicity and Extended Cardiac Safety

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Background: GrAS is an important human pathogen. We summarize immunogenicity and long-term safety of 26-valent GrAS vaccine. **Methods:** We performed Phase I/II trials of 26-valent GrAS vaccine comprising 4 recombinant proteins containing N-terminal peptides from 26 M proteins. Subjects had baseline cardiac exam, echo, ECG, and screening for tissue cross-reacting antibodies (XrAb). 100 subjects received GrAS vaccine and 20 subjects were randomized to receive control (Havrix™) at 0, 1, 6 months with clinical and laboratory follow-up for safety and assay of type-specific M Ab by quantitative ELISA. To assess long-term cardiac safety, 86 subjects who received GrAS vaccine (n=75) or Havrix™ (n=11) underwent ECG, echo, and comprehensive exam by a cardiologist ≥ 1 year after last dose. **Results:** No vaccine-associated serious adverse events occurred. Injection site reactions were most common adverse events (AEs); most were mild and self-limited. Systemic AEs were uncommon and were similar in both groups. No clinical or lab evidence of nephritogenicity or rheumatogenicity or XrAb developed. Cardiac safety follow-up revealed new ECG findings (asymptomatic supraventricular tachycardia, non-specific t-wave flattening, and asymptomatic sinus bradycardia) and new echo findings (small pericardial effusion, increased septal thickness, and physiologic mitral regurgitation) in 3 GrAS vaccine recipients. The examining cardiologist felt all were not clinically significant or related to GrAS vaccine. GrAS vaccine evoked a ≥ 4-fold rise in geometric mean Ab titres to 24/27 antigenic peptides with a mean increase in serum Ab level to all 27 antigens of 9.05- fold (95% CI 8.47-9.67). **Conclusions:** 26-valent GrAS vaccine is well-tolerated and immunogenic in adults. Safety evaluation ≥ 1 year after GrAS vaccine revealed no cardiac safety concerns. Studies in adolescents and children are warranted.

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P59 Development of a Robust GLP-Compliant Flow Cytometric Potency Assay for Hantavirus DNA Vaccines

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Background: Hantaviruses causing hemorrhagic fever with renal syndrome (HFRS) remain public health problems in Asia and Europe. U.S. FDA-licensed vaccines are currently unavailable. We developed plasmid DNA vaccines expressing the envelope glycoprotein genes of two HFRS-causing hantaviruses, Hantaan and Puumala viruses. We plan to test these vaccines in a Phase 1 clinical study during 2008. Volunteers will be vaccinated with DNA-coated microscopic gold beads delivered by hand-held disposable delivery devices (gene gun). To support that study, we developed rapid, reliable, and sensitive qualitative and quantitative assays for measuring the potency of the vaccines. **Methods:** For the qualitative assay, devices are actuated over a cell monolayer to directly deliver DNA-coated gold into cells. For the quantitative assay, devices are actuated into ethanol, the DNA is eluted from the discharged gold, and then transfected into cell monolayers. Expression is measured relative to a standard curve. For both assays, transfected cells are trypsinized, fixed, and permeabilized and then probed with a virus glycoprotein-specific mouse monoclonal antibody followed by a fluorescently-tagged anti-mouse antibody. Flow cytometry is used to detect expression and quantify the amount of DNA recovered. Results: We have used these assays over a 9 month period for measuring the potency and stability of cGMP-manufactured vaccines. Standard curve readings at the various time points are highly reproducible, and signal to noise ratios are low. **Conclusion:** We have developed an in vitro potency assay that is easy to perform, reliable, and compliant with Good Laboratory Practice (GLP) guidelines. Moreover, the flow cytometry and data analysis can be completed within a day. Lastly, this GLP assay can be readily adapted to other DNA vaccines, including those delivered by other methods.

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P60 Beyond the Limulus Amebocyte Lysate (LAL) Test: A Human Whole Blood Cytokine Release Assay to Estimate the Endotoxin Activity of Vaccines Containing Variant Lipopolysaccharide (LPS) Molecules

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Background: Many vaccines, including those under development against group B *Neisseria meningitidis*, include LPS. Products may contain LPS contaminants or may utilize LPS as an adjuvant or immune modulator. Stimulation of human whole blood with antigens and quantification of pro-inflammatory cytokine release is a sensitive assay that may be more relevant for determining toxicity and changes in toxicity stemming from genetic or chemical modifications to bacterial

LPS than the LAL or rabbit pyrogen tests. **Methods**: Whole blood was incubated with serial dilutions of vaccines or other antigens for 4 hours at 37°C and 5% CO_2. Serum was assayed for IL-6 and TNF-α with the LINCOplex™ HCYTO-60K kit. The effectiveness of the assay at detecting minute quantities of LPS was determined by comparing unstimulated blanks with samples containing LPS standards. Endotoxin activity was expressed in units of pg of cytokine released per ng of stimulatory antigen and was determined using points in a roughly linear range of the response curves (100 to 8000 pg/ml and 50 to 2500 pg/ml of IL-6 and TNF-α released respectively). In each case, significance was determined using *t*-tests. **Results:** A significant increase of cytokine release was observed upon stimulation with 4-40 pg/mL of LPS standards. Wild type, hexacyl LPS was found to be a far more potent inducer of pro-inflammatory cytokines than pentacyl LPS, tetraacyl LPS or MPLA. **Conclusion:** The assay appears to be an effective and relevant *in vitro* method for measuring endotoxin activity in products intended for human use.

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P61 Toxin Neutralizing Antibodies (NEUT-Abs) and Polysaccharide (PS) Opsonic Antibodies (OP-Abs) Protect Against a Highly Virulent Toxin-Producing *Staphylococcus aureus* (SA): A Rationale for a Multi-Target SA Vaccine

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Background: *Staphylococcus aureus* (SA) is a major pathogen that causes severe outbreaks in hospitals and the community. Toxin production has enhanced SA virulence, leading to severe skin/soft tissue infections (SSTI) and invasive infections including necrotizing pneumonia, organ abscesses and sepsis in otherwise healthy individuals. We hypothesize that antibodies that neutralize major cytolytic toxins, alpha-toxin (AT) and PVL may enhance the efficacy of OP-Abs generated by PS-conjugate vaccines [1]. **Methods:** Non-toxic recombinant AT and PVL antigens, and capsular (CP) type 5-, CP type 8- and 336PS-conjugates were used to generate NEUT-Abs (AT/PVL) and OP-Abs (5/8/336), respectively. Mice were administered OP-Abs and/or NEUT-Abs. Mice were challenged i.d. with USA300-0114, the most common CA-MRSA clone, which harbors PVL and AT [2]. Mice were observed for 72 h for signs of dermonecrosis (DN). Thereafter, mice were sacrificed and bacterial organ colonization (BOC) was determined. **Results:** Mice treated with NEUT-Abs alone were protected from DN (70%) and showed 50% reduction in BOC compared to no protection in the control animals. OP-Abs alone were marginally protective against DN (25%), however protected against BOC (70%). Mice treated with both OP-Abs and NEUT-Abs demonstrated enhanced protection against DN (90%) and BOC (70%). **Conclusions:** Data demonstrates that a combination of PS specific OP-Abs and NEUT-Abs act synergistically to protect animal against SSTI and systemic infections. A multi-target approach that combines opsonic and toxin neutralizing activities should significantly improve the chance for development of an efficacious vaccine against SA infections.

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P62 Development of a Polyvalent Lyme Disease Vaccine that Induces Antibodies that Recognize all Incorporated OspC Type-specific Sequences

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Lyme disease is the most common vector-borne (*Ixodes* ticks) disease in North America and Europe, and is caused by *Borrelia burgdorferi* and related species. Untreated disease is associated with serious cardiac, neurological, dermatological, and arthritic sequelae. There is no vaccine commercially available for human use. The participant will discuss significant advances in the development of a second generation vaccine based on outer surface protein C (OspC). OspC is a critical determinant of *Borrelia* pathogenesis, is expressed at high levels during early infection, and is highly immunogenic. OspC is variable in sequence at surface-exposed regions, forming 29 stable major OspC phyletic types. The anti-OspC response is type-specific, as is protection conferred by immunization. Mapping has delineated two regions that contain linear B-cell epitopes which define the type-specificity of the anti-OspC immune response. Based on these maps, a tetravalent vaccinogen was constructed that, in mice, elicited IgG that labels intact cells, and is bactericidal against *Borrelia* expressing each of the incorporated OspC types. This vaccine construct has been expanded to incorporate epitopes from eight OspC types. Immune responsiveness to the initial construct was found to induce a suboptimal response to some epitopes. Minor changes have greatly improved the immune response, and this construct is now being tested for *in vivo* protective efficacy. To broaden the coverage of the vaccine, outer surface protein A, used in previous vaccines, has been mapped for linear epitopes. Two previously undescribed epitopes were localized and have the potential to be valuable additions to a chimeric vaccine. This presentation describes the development of a novel chimeric, epitope-based Lyme disease vaccine with the potential to provide broad protection against this emerging infectious disease.

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Abstracts of Submitted Poster Presentations

P63 Immunological Evaluation of a Synthetic Oligosaccharide-based Vaccine Targeting the HIV-1 2G12 Epitope

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The conserved carbohydrate epitope recognized by monoclonal antibody 2G12 is an attractive prophylactic vaccine candidate for prevention of HIV-1 infection[1]. We recently reported the synthesis of mono-, di-, and trivalent glycopeptides which mimic the gp120 carbohydrate structure recognized by 2G12[2]. We prepared a covalent conjugate of the divalent mimetic to outer membrane protein complex of *N. meningitidis* and evaluated immunogenicity in guinea pigs and rhesus macaques. A series of differential immunoassays was employed to dissect the serum response to specific vaccine components. A multiplexed immunoassay was developed to assess the ability of the synthetic immunogens to compete with recombinant gp120 protein binding to 2G12. To ascertain whether antibodies produced during natural HIV-1 infection could recognize the synthetic epitope mimetics, we screened a panel of HIV^+ and HIV^- human sera using this multiplex format for binding to gp120 and the synthetic 2G12 epitope-like antigens. Immunization with conjugate led to induction of high levels of carbohydrate-specific antibodies. However, these antibodies were poor competitors of 2G12 binding to gp120 and failed to neutralize a clade B isolate in an entry-based neutralization assay. Multiplex results confirmed the ability of 2G12 to bind divalent carbohydrate epitopes, but no recognition of synthetic mimetics by donor sera was observed. Certain HIV^+ donor sera contained antibodies that could compete with 2G12 for binding to recombinant gp120. Synthetic 2G12 epitope mimetics induced carbohydrate-specific antibody responses when presented in the format of a conjugate vaccine platform, but these antibodies do not compete with 2G12 for binding to gp120 and do not neutralize virus. The most likely explanation is that a high degree of conformational flexibility results in elicitation of a largely irrelevant immune response.

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P64 A Novel Approach to Produce Glycoconjugated Vaccines Using Recombinant Bacterial Cells that Directly Produce Immunogenic Bioconjugates

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Chemically synthesized complexes of polysaccharides and proteins have been successfully used as conjugated vaccines to protect against a number of bacterial infections. This report describes a novel bioengineering approach to produce immunogenic conjugated vaccines that provides advantages over classical chemical conjugation methods. This has been first applied to the development of a *Shigella dysenteriae* O1 glycoconjugate vaccine, using genetically engineered *E. coli* with simple fermentation and purification methods. The proprietary technology is based on the discovery that *Campylobacter jejuni* contains a general N-linked protein glycosylation system that can be functionally expressed in *Escherichia coli*. Various proteins of *C. jejuni* have been shown to be modified by a heptasaccharide that is pre-assembled on the carrier lipid, undecaprenyl pyrophosphate and transferred to asparagine (Asn) residues of a specific consensus sequence by the oligosaccharyltransferase PglB. Since the specificity of PglB for the lipid-linked sugar substrate is low, the enzyme is capable of transferring different antigenic polysaccharides from undecaprenyl pyrophosphate to a protein carrier. Using this technology, the antigenic polysaccharide of *S. dysenteriae* O1 was expressed in *E. coli* and conjugated to two different protein carriers *in vivo*. Both bioconjugates elicited a specific IgG response against the polysaccharide in mice. A highly efficient production process has now been developed that can be used for industrial scale preparations in a cost-efficient process. This novel cost-efficient bioengineering approach to produce glycoconjugates can now be applied to other conjugates. It may considerably simplify the production of several bacterial vaccines with high reproducibility and a potentially reduced risk of lot failures.

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P65 Cervical Challenge With HPV Virus-like Particles (VLPs) Can Evoke an Anamnestic Anti-HPV Immune Response in HPV VLP Vaccinated Non-human Primates

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Background: Questions regarding duration of protection and the potential of natural HPV exposure, post vaccination, to boost antibody titers have arisen following the presentation of the Gardasil® human clinical trial data. Non-human primates have been immunized with various HPV L1 VLP combinations to demonstrate immunogenicity. Full length L1 VLPs mimic the HPV virion structure remarkably well. Therefore, a study was designed to utilize VLPs as a substitute for live virus, in a VLP cervical challenge model. **Methods:** Non-human primate animals were identified as having completed a 2 or 3 dose HPV L1 VLP vaccine regimen greater than 1 yr prior. Yeast expressed full length L1 protein assembled into VLPs and highly purified was applied to the cervix on days 0, 3, 7 and 10. Serum was collected on days 0, 3, 7, 10, 17, 24, 31 and 38. HPV type-specific neutralizing antibody titers were evaluated by competitive Luminex immunoassay (cLIA). **Results:** At the higher doses of applied HPV VLPs, a ~2 fold rise in HPV cLIA antibody titers was observed. This increase was first observed at the 17 day time interval. The titers continued to increase generally through day 24, after which they generally leveled off, but remained elevated. **Conclusions:** This *in vivo* HPV VLP cervical challenge model provides evidence to suggest that natural exposure to HPV may serve to boost antibody HPV VLP immune response post HPV L1 VLP vaccination.

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P66 Immunogenicity In Vivo: Proof-of-concept Study of an Immunome-derived Smallpox Vaccine

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Background: We used an immunoinformatics approach to examine three variola genomes and four vaccinia genomes for conserved, immunogenic vaccine candidate peptides.[1] Vaccine 2005]. **Methods**: 908,040 9-10mer peptides from 1,472 non-redundant genes were examined with our Conservatrix and EpiMatrix tools and 10,147 (6%) were found to be conserved in all strains and potentially immunogenic. Ninety-one percent of the variola/vaccinia epitopes identified were confirmed in ELISpot assays. Here we report on the immunogenicity of a DNA prime, peptide boost IDV vaccine containing the validated epitopes. Epitopes were engineered into string-of-beads multi-epitope genes using VaccineCAD and subcloned into pVAX1. DRB1*0101 transgenic mice were immunized intramuscularly with a single DNA construct and boosted subcutaneously with the corresponding peptides. Two groups of DRB1*0301 transgenic mice were intramuscularly immunized each with a different DNA vaccine and boosted intranasally with peptides formulated in liposomes with CpG oligodeoxynucleotide. Immunogenicity was measured by IFNg ELISpot. **Results**: Variola/vaccinia epitopes that stimulated >20 SFC/106 splenocytes in comparison with non-immunized mice ($p<0.01$) were considered immunogenic. In a previous report[3], immunization of DRB1*0101 transgenic mice stimulated significant T cell responses to 6 of 25 epitopes (24%). In comparison, DRB1*0301 mice immunized with the same 25-epitope set responded to 10 (40%) of epitopes, of which two were also reactive in DRB1*0101 mice. A vaccine encoding a second set of 25 epitopes stimulated significant responses for 8 (32%) epitopes in DRB1*0301 mice. **Conclusion**: We confirmed more variola/vaccinia epitopes for less cost and demonstrated immunogenicity in less time than two previously published studies (Moutaftsi et al, [2006] and Jing et al, [2007]). The IDV approach is an efficient method of developing vaccines for biodefense.

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P67 Updated Results from Ongoing Work on the GAIA HIV Vaccine: Broad Recognition of Class I and II-restricted Epitopes and In vivo Studies

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Background: We set out to develop an epitope-driven, DNA-prime, pseudoprotein-boost HIV vaccine (GAIA vaccine) composed of both CTL and T helper cell epitopes that are highly conserved and immunogenic over a broad range of HLA backgrounds. The advantages of an epitope-based approach have become more apparent due to recent vaccine trial failures. **Methods:** As previously described, 10,199 HIV protein sequences were searched for conserved 9-10-mer segments. 5,494 of the most highly (>5%) conserved 9-mer sequences were analyzed by EpiMatrix for affinity to HLA and used to create immunogenic consensus sequence (ICS) class II epitopes. Initial evaluations of these epitopes have been performed in Mali, Thailand and in Providence. DNA-prime/peptide-boost vaccine studies including these epitopes were performed in HLA transgenic mice. **Results:** Individual epitopes selected for study are more broadly conserved than those chosen for other epitope-based vaccines (>70%, compared to Epimmune's 40%). ELISpots confirmed the immunogenicity of 98% of the ICS epitopes and Class I epitopes (85% A2, 29% A3, 67% B7, 20% A24). Fifteen of the ICS peptides were also confirmed in Mali. Two HLA transgenic mouse studies have been performed this year, confirming the immunogenicity of selected epitopes in this model. **Conclusion:** HIV sequences exhibiting broad coverage over time, HIV strains, and geographic regions were discovered for well-represented class I and II alleles in the general population. DNA vaccine prototypes encoding these epitopes are immunogenic in HLA transgenic mice. We anticipate that the epitope-rich GAIA vaccine will be equally or more immunogenic in human volunteers as other DNA/viral vector prime-boost vaccines.

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P68 Rabies Post-Exposure Prophylaxis after Bat Exposure in Quebec, Canada

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Background: Rabies post-exposure prophylaxis (RPEP) is broadly recommended for bat exposure in North America. In Quebec, Canada RPEP investigation and administration is managed by nurses and physicians in public health units. The objective of this study was to describe the profile of bat exposures reported to public health and the RPEP recommendations made in response. **Methods**: All investigations conducted by public health units in Quebec (pop. 7.6M) following report of human exposure to a bat between October 1, 2004 and September 30, 2006 were included. **Results:** There were 957 notifications of bat exposures among 1933 persons. The rate of notification was 1/100,000 for exposures involving direct bat contact with bite, 0.7/100,000 for direct contact where bite could not be ruled out and 9/100,000 for household exposure without direct bat contact. Among bats tested, 5% overall were rabies positive. When an implicated bat was not available for testing, RPEP was virtually always recommended. Of all RPEP recommended, 12% was for scenarios involving direct bat contact and bite, 7% was for direct bat contact where bite could not be ruled out and 81% was for household exposure without bat contact identified. Only 3-5% of household exposures and 7% of direct contacts without evidence of bite were notified to public health when compared to the expected number estimated in another study. **Conclusion**: Bat exposure without direct contact has become the most frequent reason for RPEP administration. Only a small fraction of persons with RPEP-eligible bat exposures notify public health. In that context, the impact/utility of current "non-bite" RPEP recommendations may be questionable. Bat exposures of concern requiring RPEP intervention should be clarified, better communicated or reconsidered.

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