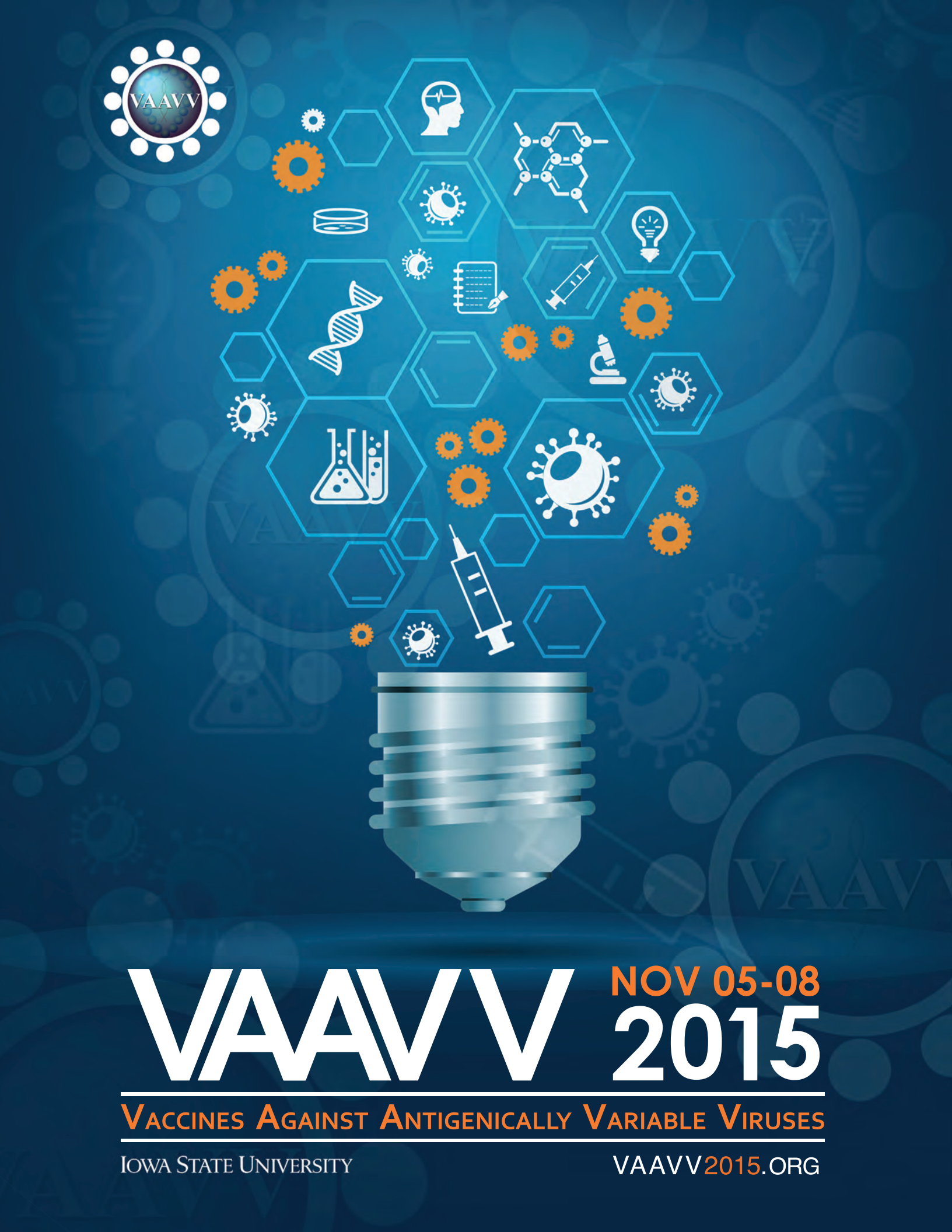

VAAVV 2015

NOV 05-08

Vaccines Against Antigenically Variable Viruses

Iowa State University

VAAVV2015.ORG

Welcome and thank you for your participation in the 2nd annual ***Vaccines Against Antigenically Variable Viruses Symposium***. The VAAVV 2015 symposium is designed to bring scientists, researchers and students from human and veterinary medical research arenas together to explore advancements, ideas, and opportunities for innovative vaccines against antigenically variable viruses.

A special ***thank you*** to our generous sponsors and educational partners for providing financial support for this important symposium.

VAAVV 2015 Symposium provides a great opportunity to learn, grow, collaborate, and network with fellow researchers, students, and mentors. We are glad you could join us!

~ **Michael Cho**, VAAVV 2015 Director

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NOVEMBER 05 - 08

VAAVV 2015

SYMPOSIUM PROGRAM

Vaccines Against Antigenically Variable Viruses

Gateway Hotel & Conference Center . 2100 Green Hills Drive . Ames . Iowa . 50014 . Iowa State University

FEATURED GUEST SPEAKERS

Nancy Haigwood
Oregon Health Sciences University
Keynote Speaker

Jim Mullins
University of Washington

Gary McLean
Imperial College London

Kyoung-Jin Yoon
Iowa State University

Richard Webby
St. Jude's Children's Hospital

Kevin Legge
University of Iowa

Bob Rowland
Kansas State University

Malcolm Martin
National Institutes of Health, NIAID

Adrian Shepherd
University of London, Birkbeck

Thomas Kepler
Boston University

Michael Katze
University of Washington

Nancy Haigwood
Oregon Health Sciences University

Federico Zuckermann
University of Illinois,
Urbana-Champaign

Shan Lu
University of Massachusetts

Laurent Verkoczy
Duke University

Nicole Baumgarth
University of California, Davis

James Binley
SD Biomedical Research Institute

Elizabeth Rieder
USDA ARS, Plum Island

Sudhir Paul
University of Texas Health

David Verhoeven
Iowa State University

Xiangpeng Kong
New York University

Roland Strong
Fred Hutchinson Cancer Research Center

Kelly Lee
University of Washington

Adolfo Garcia-Sastre
Icahn School of Medicine, Mount Sinai

PROGRAM COMMITTEE

Kay Faaberg
NADC, USDA, ARS, Ames

Deborah Fuller
University of Washington

Shiu-Lok Hu
University of Washington

Kevin Legge
University of Iowa

Daniel Perez
University of Georgia

Adrian Shepherd
University of London, Birkbeck

Jamie Scott
Simon Fraser University

PLANNING COMMITTEE

Michael Cho
Iowa State University

James Roth
Iowa State University

Kyoung-Jin Yoon
Iowa State University

David Verhoeven
Iowa State University

THURSDAY, NOVEMBER 5

4:00 REGISTRATION Gallery Lobby

6:00 **WELCOME RECEPTION** Garden Room

7:00 **DINNER** Garden Room

NANCY HAIGWOOD
KEYNOTE SPEAKER

Nancy L. Haigwood, Ph.D., is a Senior Scientist, Professor of Molecular Microbiology and Immunology, and Director of the Oregon National Primate Research Center at Oregon Health & Science University. The primary focus of her research is the role of neutralizing antibodies in mother-to-child transmission of HIV-1 and the development of novel vaccines designed to elicit these antibodies. Dr. Haigwood is a board member of Cascade AIDS Project in Portland OR, and of the National Association for Biomedical Research in Washington, DC. At NIH she serves on the Council of Councils, which advises NIH Director Dr. Francis Collins, and the Vaccine Research Center Board of Scientific Counselors. Dr. Haigwood was elected a Fellow of the American Society for Microbiology in 2014.

FRIDAY, NOVEMBER 6

7:00 REGISTRATION / BREAKFAST Garden Room

SESSION I: ANTIGENIC VARIATION IN VIRUSES

CHAIR: JIM ROTH, IOWA STATE UNIVERSITY North Prairie
CHAIR: KYOUNG-JIN YOON, IOWA STATE UNIVERSITY

8:00 HIV Genetic Variation and Vaccine Immunogen Design
Jim Mullins, University of Washington

8:30 Genetic and Antigenic Variability of Foot-and-Mouth Disease Virus: a Practical Problem
Elizabeth Rieder, USDA ARS, Plum Island

9:00 Molecular Evolution of PRRSV under Experimental and Field Conditions
Kyoung-Jin Yoon, Iowa State University

9:30 Antigenic Variation and Human Immune Responses
Richard Webby, St. Jude's Children's Hospital

2 ABSTRACT PRESENTERS:

10:00 Founder Virus Signatures in SIV Rectal Transmission
Zhe Yuan, University of Nebraska, Lincoln

10:15 Immunization with Heterogeneous Mosaic Array of Influenza HA Receptor-Binding Domains Induces Broadly Neutralizing H1N1 Antibody Responses
Masaru Kanekiyo, National Institutes of Health, NIAID

10:30 REFRESHMENTS

SESSION II: IMMUNE CORRELATES OF PROTECTION

CHAIR: KEVIN LEGGE, UNIVERSITY OF IOWA
CHAIR: DEBORAH FULLER, UNIVERSITY OF WASHINGTON

11:00 Dendritic Cell Regulation of Influenza Virus Immunity
Kevin Legge, University of Iowa

11:30 The Role of Host Genetics in the Design of PRRS Vaccines
Bob Rowland, Kansas State University

12:00 Studies of Broad and Potent anti-HIV-1 Neutralizing Antibodies in SHIV Infected Rhesus Macaques
Malcolm Martin, National Institutes of Health, NIAID

2 ABSTRACT PRESENTERS:

12:30 Quantitation of anti-Ebola Virus Immunoglobulins Serves as a Good Immune Correlate of Protection against Lethal Ebola Virus Challenge
Rachel Brouillette, University of Iowa

12:45 IRF3 Deficiency Contributes to Impaired Memory T Cell Function in Response to Influenza Infection
Alexander Vogel, University of Nebraska, Lincoln

1:00 LUNCH Garden Room

SESSION III: INSIGHTS FROM BIOINFORMATICS AND COMPUTATIONAL/SYSTEMS BIOLOGY

CHAIR: DRENA DOBBS, IOWA STATE UNIVERSITY
CHAIR: ADRIAN SHEPHERD, UNIVERSITY OF LONDON, BIRKBECK

2:00 Informing HIV Immunogen design by Characterizing Clonally Related Sequence Sets with NGS
Adrian Shepherd, University of London, Birkbeck

2:30 B Cell Lineage Dynamics during Serial Immunizations
Thomas Kepler, Boston University

3:00 Systems Biology of Infection and Immunity-Deadly Virus Infections in the 21st Century: Successes, Challenges, Ebola, and Networks to Nowhere?
Michael Katze, University of Washington

2 ABSTRACT PRESENTERS:

3:30 High Throughput Analysis of B-Cell Clonal Lineages
William Lees, University of London, Birkbeck

3:45 Transcriptome Profiling of SIV Gag-Specific CD8+ T Cells to Understand the Time-Dependent Protection Elicited by SIV-Δnef Live Attenuated Vaccine
Wuxun Lu, University of Nebraska, Lincoln

4:00 **POSTER PRESENTATIONS**
REFRESHMENTS Central Prairie

6:00 DINNER BUFFET / SOCIAL NETWORKING Garden Room

PROGRAM SCHEDULE

SATURDAY, NOVEMBER 7

7:00 BREAKFAST Garden Room

SESSION IV: B CELL IMMUNITY ISSUES FOR VACCINE DESIGNS North Prairie

CHAIR: JAMIE SCOTT, SIMON FRASER UNIVERSITY, CANADA
CHAIR: NANCY HAIGWOOD, OREGON HEALTH SCIENCES UNIVERSITY

8:00 Clues to Generating Highly Cross-Reactive and Neutralizing Antibody Responses in Primates using Natural HIV Envelopes
Nancy Haigwood, Oregon Health Sciences University

8:30 Polyvalent HIV Vaccines
Shan Lu, University of Massachusetts

9:00 Knock-in Models for Studying the Development of Immunization Guided HIV-1 Broadly Neutralizing Responses
Laurent Verkoczy, Duke University

9:30 Local and Systemic B cell Responses to Influenza Virus Infections
Nicole Baumgarth, University of California, Davis

2 ABSTRACT PRESENTERS:

10:00 Porcine Circovirus as a Potential Delivery Virus Vector to Express Antigenic Determinants of Porcine Reproductive and Respiratory Syndrome Virus
Pablo Pineyro, Iowa State University

10:15 Delta Inulin Adjuvant Enhances Plasmablast Generation, Expression of Activation-Induced Cytidine Deaminase and B-Cell Affinity Maturation in Human Subjects Receiving Seasonal Influenza Vaccine
Nikolai Petrovsky, Flinders Medical Centre, Australia

10:30 REFRESHMENTS

SESSION V: STRATEGIES TO ENHANCE IMMUNE RESPONSES AND VACCINE EFFICACY

CHAIR: KAY FAABERG, ARS, USDA, AMES
CHAIR: DANIEL PEREZ, UNIVERSITY OF GEORGIA

11:00 Linking Innate Immunity to the Protective Efficacy of PRRSV Vaccines
Federico Zuckermann, University of Illinois, Urbana-Champaign

11:30 Induction of anti-HIV-1 Neutralizing Antibodies using Native Trimer Immunogens
James Binley, San Diego Biomedical Research Institute

12:00 Developing a Vaccine for Human Rhinoviruses
Gary McLean, Imperial College of London

12:30 A Universal Influenza Virus Vaccine Approach based on Chimeric Hemagglutinins
Adolfo Garcia-Sastre, Icahn School of Medicine, Mount Sinai

1:00 LUNCH Garden Room

2:00 Electrophilic Immunization against HIV
Sudhir Paul, University of Texas Health

3 ABSTRACT PRESENTERS:

2:30 Signaling Molecules of the Innate Immune System as Genetic Adjuvants in DNA Immunizations against Influenza A Viruses
Dennis Lapuente, Ruhr University-Bochum, Germany

2:45 Development of a Prophylactic Vaccine for Hepatitis C Virus
Heidi Drummer, Burnet Institute-Melbourne, Australia

3:00 Eliciting Antibodies Targeting Key Neutralizing Sites of the Membrane Proximal External Region of HIV-1 gp41 using DNA and Liposome Vaccines and Alternative Immunization Strategies
Naveed Gulzar, Simon Fraser University, Canada

SESSION VI: HOT TOPICS / LATE BREAKERS

CHAIR: MICHAEL CHO, IOWA STATE UNIVERSITY

3:15 Equine Influenza HA3 Antigen Induces Immunological Responses against Multiple Strains of Flu
David Verhoeven, Iowa State University

1 ABSTRACT PRESENTER:

3:45 Design and Evaluation of gp41 MPER-based Vaccine Candidates against HIV-1
Saikat Banerjee, Iowa State University

4:00 **SCIENTIFIC SPECIALTY NETWORKING**
POSTER VIEWING / REFRESHMENTS Central Prairie

6:00 DINNER BUFFET / SOCIAL NETWORKING Garden Room

SUNDAY, NOVEMBER 8

7:00 BREAKFAST Garden Room

SESSION VII: INSIGHTS FROM STRUCTURAL BIOLOGY

CHAIR: BRIAN LEE, IOWA STATE UNIVERSITY North Prairie
CHAIR: ROLAND STRONG, UNIVERSITY OF WASHINGTON

8:00 Antibody Gene Usage, Maturation, and HIV Vaccine
Xiangpeng Kong, New York University

8:30 Reverse-Engineering HIV bnAbs: How Hard it is To Get Antibodies To Do What You Want Them To
Roland Strong, Fred Hutchinson Cancer Research Ctr

9:00 Novel Approaches to Map Structural Determinants of Antigenicity in Viral Glycoproteins
Kelly Lee, University of Washington

2 ABSTRACT PRESENTERS:

9:30 HLA-F and MHC Open Conformers in a Novel HIV-1 Immunization Strategy
Daniel Geraghty, Fred Hutchison Cancer Research Ctr

9:45 The Structure of Newcastle Disease Virus Fusion Protein Bound to Chicken Protein Disulfide Isomerase A3 Suggests a Molecular Target for New Therapies
John Hsieh, Iowa State University

10:00 **AWARDS & CLOSING REMARKS**

POSTER PRESENTERS

FRIDAY, NOVEMBER 6

4:00 POSTER PRESENTATIONS & REFRESHMENTS Central Prairie

P001 Identification of Immune Factors Contributing to Influenza Vaccine Failures in Young Children
David Verhoeven, Iowa State University

P002 Differential Response of Resistant and Susceptible ChickenLines to a Newcastle Disease Virus Vaccine Strain
Melissa Herrmann, Iowa State University

P003 Separable Functions for the Membrane Proximal Ecto-domain Region (MPER) of HIV-1 gp41 in Cell-Free Versus Cell-to-Cell Viral Transmission: Implications for Neutralization
Andy Poumbourios, Monash University

P004 Immunogenic Properties of a Trimeric gp41-based Immunogen Containing an Exposed Membrane-Proximal External Region
Saikat Banerjee, Iowa State University

P005 Identifying Host Genes and Genetic Markers for Antibody Production to Newcastle Disease Virus (NDV) Vaccine Strain in Commercial Layer Chickens
Kaylee Rowland, Iowa State University

P006 Identification of a Region in the N-Terminus of HIV-1 gp41 that Confers Resistance to MPER Broadly Neutralizing Antibodies
Marisa Banasik, Iowa State University

P007 A Fungal Quorum Sensing Molecule Acts as an Adjuvant to Promote Innate Inflammatory Responses and anti-Influenza A Viirus Antibodies
Jessica Hargarten, University of Nebraska, Lincoln

P008 Comparison of Antigen Delivery Platforms to Reinforce Efficacy of Universal H5N1 Influenza Vaccine
Jie-Yeun Park, Iowa State University

P009 Isolation and Characterization of Novel Monoclonal Antibodies that Recognize the gp41 MPER Domain of HIV-1
Hojin Moon, Iowa State University

P010 Design and Evaluation of Gene Gun Based DNA Immunization
Kari Rohl, Iowa State University

P011 Natural Antibodies to SIV Antigens in Mauritian Cynomolgus Macaques
Hongzhao Li, University of Manitoba, Canada

P012 Strategies for High-Level Antigenic Protein Expression from a Mammalian Orthoreovirus Vector
Promisree Choudhury, Iowa State University

P013 Focusing the Immune Response Towards Critical Neutralizing Epitopes on HIV-1 through Immune Complex Vaccination in Rabbits
Aditi Agrawal, Iowa State University

P014 Adaptive Immune Responses Elicited by RV144-like Vaccination in Humanized BLT Mice
Wenjin Fan, University of Nebraska, Lincoln

P015 Immunological Characterization of gp41 Mutants Mimicking the Prehairpin Fusion Intermediate Form of HIV-1
Heliang Shi, Iowa State University

P016 Utilizing Organ-on-Chip Method to Build a Drug Testing Model on Human Placenta
Rajeendra Pemathilaka, Iowa State University

P017 Application of αGal HyperAcute Technology to Viral Vaccines
Wenlan Alex Chen, New Link Genetics Corporation

P018 Investigation of Endothelial and Epithelial Cell Lines Concerning a 3D Microfluidic Drug Testing Model for the Placenta
Jeremy Caplin, Iowa State University

P019 Mx1 is Overexpressed in Activated HIV-1-Specific CD8+ T Cells
Weidong Xu, Iowa State University

SCIENTIFIC SPECIALTY NETWORKING

SATURDAY, NOVEMBER 7

4:00 NETWORKING & REFRESHMENTS Central Prairie

"Scientific Specialty Networking is an informal gathering for all VAAVV 2015 participants. This is an excellent time for students to visit with professionals in their field of study, meet the symposium speakers, or network with colleagues from around the world. This will be your final opportunity to view the symposium poster presentations or just relax with new friends and have some refreshments.

We hope to see you there!"

FEATURED SPEAKERS

THURSDAY, NOVEMBER 5

KEYNOTE SPEAKER Garden Room

Nancy Haigwood
Oregon Health & Science University

KEYNOTE SPEAKER

Nancy L. Haigwood, Ph.D., is a Senior Scientist, Professor of Molecular Microbiology and Immunology, and Director of the Oregon National Primate Research Center at Oregon Health & Science University. She led the preclinical development of one of the first HIV vaccines at Chiron Corporation and was founding director of the Viral Vaccines Program at the Seattle Biomedical Research Institute. The primary focus of her research is the role of neutralizing antibodies in mother-to-child transmission of HIV-1 and the development of novel vaccines designed to elicit these antibodies. She has published over 100 peer-reviewed articles, in addition to many commentaries and book chapters. Dr. Haigwood is a board member of Cascade AIDS Project in Portland OR, and of the National Association for Biomedical Research in Washington, DC. At NIH she serves on the Council of Councils, which advises NIH Director Dr. Francis Collins, and the Vaccine Research Center Board of Scientific Counselors. Dr. Haigwood was elected a Fellow of the American Society for Microbiology in 2014.

FRIDAY, NOVEMBER 6

Jim Mullins
University of Washington

Jim Mullins, Ph.D. is a Professor of Microbiology and Medicine at the University of Washington. Dr. Mullins obtained his Ph.D. in Cell Biology and Biochemistry from the University of Minnesota in 1978. He did postdoctoral work at the California Institute of Technology before becoming Assistant then Associate Professor at the Harvard University School of Public Health. In 1989 he moved to Stanford University as Professor and was Chairman of the Department of Microbiology and Immunology from 1991 until his move to the University of Washington in 1994 where he is on the faculty of the Departments of Microbiology, Medicine, and Laboratory Medicine. He served as Chair of Microbiology from 1997-2002. Dr. Mullins has published more than 360 original articles, reviews and book chapters on the topics of retroviruses and AIDS and has delivered more than 320 invited seminars and symposium presentations.

The Mullins lab uses the techniques of molecular, computational and virus biology to provide basic insights into the HIV-human host relationship in an effort to assist the fight to stop the AIDS pandemic. They use a variety of techniques to understand the implications of HIV's extraordinary genetic diversity for the pathogenesis of AIDS, with the intention of applying this information to the development of more effective therapies and vaccines. These techniques include virology, molecular biological and statistical analysis of nucleotide sequences.

Elizabeth Rieder
USDA, ARS, Plum Island ADC

Elizabeth Rieder received her M. Sc. Degree in Biochemistry (1986) and a Ph.D. in Virology and Genetic (1991) from the University of Buenos Aires in Argentina. Her doctoral studies involved the molecular mechanism of Foot-and-Mouth Disease Virus (FMDV)-escape mutant generation, isolated under selective immune pressure. Following receipt of her Ph.D., Dr. Rieder was a Research Scientist (1991-1997) at PIADC, USDA, ARS and studied FMDV pathogenesis and developed experimental FMDV vaccines through the generation of an infectious cDNA clone for this virus. From 1997 through 2002, Dr. Rieder was a Senior Scientist/Instructor for the Department of Molecular Genetics and Microbiology at the State University of New York, Stony Brook, NY. Her research work at Stony Brook focused on the analysis of replication signals in the genome of plus strand RNA viruses including poliovirus and rhinovirus. She also assembled and characterized infectious cDNA clones of important human pathogens of the enteroviruses including those that causes upper respiratory disease in humans or have been implicated in the induction of type I diabetes, and characterized their biological, antigenic and genetic properties. Since 2003, Dr. Rieder is leading a Molecular Biology Laboratory within the Foreign Animal Research Unit, Plum Island Animal Diseases Center as a Senior Scientist. She has a long-standing and active research interest in the processes that lead to replication of RNA viruses. She has conducted research on foot-and-mouth disease virus for more than 20 years, and made important contributions to the understanding of the mechanism contributing to virus replication and virus-host cell interaction at the molecular levels. The primary interest in her laboratory concerns the role of both viral factors (proteins and genetic elements), and host factors, that might influence how the virus causes disease.

VAAVV 2015 SYMPOSIUM

FRIDAY, NOVEMBER 6

Kyoung-Jin Yoon
Iowa State University

Kyoung-Jin Yoon, DVM, MS, PhD, Diplomate ACVM is a Professor in the Department of Veterinary Diagnostic & Production Animal Medicine at the College of Veterinary Medicine, Iowa State University and is also serving as Section Leader of Virology and Molecular R & D at the Veterinary Diagnostic Laboratory in the College. Dr. Yoon's main areas of expertise and research include Viral Diseases of Animals particularly swine, such as PRRSV, Influenza, PEDV, rotaviruses, PCV2, and the development of diagnostic tools.

Bob Rowland
Kansas State University

Raymond "Bob" Rowland, Ph.D., is a Professor in the Diagnostic Medicine and Pathobiology department of Kansas State University's College of Veterinary Medicine. Dr. Rowland's current research interests center on addressing fundamental problems in infectious diseases caused by emerging pig viruses. The current focus is on molecular mechanisms of diseases caused by porcine reproductive and respiratory syndrome virus (PRRSV) and porcine circovirus type 2 (PCV2). Related research includes the design and development of novel detection and vaccine approaches, as well as the control of PRRS in the field. This research has contributed to several publications and review articles. Dr. Rowland's research is supported by funding from United States Department of Agriculture (USDA), National Institutes of Health (NIH), Department of Homeland Security (DHS), the National Pork Board (NPB) and various other entities. Besides research, Dr. Rowland is actively involved in the training of graduate, undergraduate and DVM students. He teaches introductory lectures in veterinary virology for DVM students and is the coordinator of the DVM/PhD dual degree program in the College of Veterinary Medicine.

Dr. Rowland is co-director of the PRRS Host Genetics Consortium (PHGC), a multi-year project devoted to understanding the genetics of the interaction between PRRSV and the pig host. Other research-related activities include executive director of the PRRS Symposium.

Dr. Rowland received a Ph.D. in microbiology in 1989 from the University of New Mexico School of Medicine in Albuquerque. He was a postdoctoral fellow from 1989 to 1994 at the University of Minnesota, Minneapolis, in the laboratory of arteriviologist, Peter Plagemann. He then joined the faculty at South Dakota State University in Brookings. He joined Kansas State University in 2001. Dr. Rowland can be reached via e-mail at browland@vet.k-state.edu

Richard Webby
St. Jude's Children's Hospital

Richard Webby, PhD. obtained his undergraduate and graduate degree from the University of Otago New Zealand. His Postdoctoral studies were conducted at St Jude Children's Research Hospital where he remains as a faulty and Member of the Department of Infectious Diseases. He is Director of the World Health Organization (WHO) Collaborating Center for Studies on the Ecology of Influenza and the NIAID/NIH-funded St Jude Center of Excellence in Influenza Research and Surveillance. His research interests lie in understanding the virologic properties of influenza virus transmission and pathogenicity through dissecting the human-animal interface. Data gathered through these activity are used to inform WHO recommendations for influenza vaccine compositions.

Kevin Legge
University of Iowa

Kevin Legge, Ph.D. is an Associate Professor of Pathology at the University of Iowa. He received his B.S. in Microbiology from the University of Tennessee in 1994 and a Ph.D. from the University of Tennessee in 2000. He completed his postdoctoral work at University of Virginia. Dr. Legge's research is focused on the induction and regulation of the adaptive immune response to pulmonary pathogens. His current research focuses on the areas of peripheral control of pathogen specific CD8 T cells responses by dendritic cells in the lungs, dendritic cell regulation of the developing CD8 T cell response in the regional lymph nodes following influenza virus infections, immunity following vaccination against influenza vaccination, and the effects of chronic alcohol on pulmonary adaptive immunity. Dr. Legge is also a collaborating research member of the Nanovaccine Initiative consortium originating at Iowa State University.

Malcolm Martin
National Institutes of Health, NIAID

Malcolm Martin, M.D. is currently Chief of the Laboratory of Molecular Microbiology and Chief of the Viral Pathogenesis and Vaccine Section at the National Institutes of Health, NIAID. Studies of primate and murine retroviral biology and genetics in cell culture systems and animal models is one of Dr. Martin's major areas of research.

FEATURED SPEAKERS

FRIDAY, NOVEMBER 6

Adrian Shepherd
University of London, Birkbeck

Adrian Shepherd, Ph.D. is a Reader in Computational Biology in the Department of Biological Sciences at the University of London, Birkbeck. He arrived at his current academic position via an unusually circuitous route. With a first degree in History of Art and having spent six years working outside academia (as Information Officer for a welfare rights charity and as a journalist), he started a Masters in Computer Science at UCL in 1991. This included a module on neural computing, from which began a continuing interest in machine learning. A PhD in Neural Computing at UCL followed, after which he joined Prof. Janet Thornton's group to work on protein structure prediction. After a further spell at UCL working on the CATH database for Prof. Christine Orengo, Adrian joined Birkbeck as a Lecturer in Bioinformatics in 2002. He became a Senior Lecturer in Computational Biology in the Department of Biological Sciences in 2009 and a Reader in Computational Biology in 2014. Since 2006, when he became a founding member of the ImmunoGrid Consortium, a major focus for his research has been immunoinformatics. He was a "named expert" contributing to the development of the Virtual Physiological Human Roadmap (see Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human). Currently his research group is working on immune responses to several viruses that have a major global impact on human health (influenza A, HIV, hepatitis B virus, herpes simplex virus) and immune responses to protein therapeutics (notably replacement factor VIII used in the treatment of haemophilia A). He also retains an interest in more general computational methods relevant to the field (notably biomedical text mining and data visualization).

Thomas B. Kepler
Boston University

Thomas B. Kepler, Ph.D., is Professor of Microbiology at Boston University School of Medicine and of Mathematics and Statistics at Boston University. The Kepler laboratory develops computational tools and applies them in the context of systems-level experimentation to address outstanding questions in immunology and vaccine development. Much of their work is centered on antibodies and the population dynamics of the B cells that produce them.

Michael Katze
University of Washington

Michael G. Katze, PhD, is Professor of Microbiology at the University of Washington and Associate Director for Molecular Sciences at the Washington National Primate Research Center. He is also the Director of the Nonhuman Primate Core Functional Genomics Laboratory for AIDS Vaccine Research and Development, funded by the Division of AIDS, National Institute of Allergy and Infectious Diseases. He has studied virus-host interactions for more than 35 years and is a leader in the use of systems biology approaches to define and model virus-host interactions, innate immune signaling, and the varied strategies used by viruses to evade cellular defense mechanisms. His research covers a wide range of viral pathogens, including Ebola virus, pandemic influenza virus, MERS coronavirus, and human and simian immunodeficiency viruses. He is also spearheading efforts to develop genomic resources for nonhuman primate, ferret, and Syrian hamster models of human virus infection. Dr. Katze has published over 300 scientific articles and was recently elected to Fellowship in the American Academy of Microbiology.

SATURDAY, NOVEMBER 7

Nancy Haigwood
Oregon Health & Sciences University

Nancy L. Haigwood, Ph.D., is a Senior Scientist, Professor of Molecular Microbiology and Immunology, and Director of the Oregon National Primate Research Center at Oregon Health & Science University. She led the preclinical development of one of the first HIV vaccines at Chiron Corporation and was founding director of the Viral Vaccines Program at the Seattle Biomedical Research Institute. The primary focus of her research is the role of neutralizing antibodies in mother-to-child transmission of HIV-1 and the development of novel vaccines designed to elicit these antibodies. She has published over 100 peer-reviewed articles, in addition to many commentaries and book chapters. Dr. Haigwood is a board member of Cascade AIDS Project in Portland OR, and of the National Association for Biomedical Research in Washington, DC. At NIH she serves on the Council of Councils, which advises NIH Director Dr. Francis Collins, and the Vaccine Research Center Board of Scientific Counselors. Dr. Haigwood was elected a Fellow of the American Society for Microbiology in 2014.

VAAVV 2015 SYMPOSIUM

SATURDAY, NOVEMBER 7

Shan Lu
University of Massachusetts

Shan Lu, MD, PhD, MHA, is a professor at the Department of Medicine, University of Massachusetts Medical School and a pioneer in gene-based vaccines. In the last two decades, he has used the DNA vaccination approach to develop and optimize vaccines against HIV-1, bioterrorism (plague, smallpox, anthrax and botulinum) and emerging pathogens (SARS, seasonal and pandemic influenza), pathogens causing chronic infectious diseases (hepatitis viruses and h-CMV) and pathogens causing neglected infectious diseases, including diarrhea (cholera and EV71). His research has focused on the design and delivery of immunogens to elicit long lasting and highly functional antibody responses. His group developed and tested the first polyvalent DNA prime-protein boost HIV vaccine in humans, which elicited robust and balanced T cell and antibody responses, including cross-subtype neutralizing antibodies against HIV-1 of different subtypes. He has published over 170 research articles. He is a current member on the editorial boards of Journal of Virology, Vaccine, Human Vaccines and Immunotherapeutics, and Current Opinion of Virology. He is a deputy editor-in-chief for Emerging Microbes and Infections, which is published by Nature Publishing Group. He is the immediate past president of International Society for Vaccines (ISV). He is a fellow of American College of Physicians (FACP) and a fellow of ISV (FISV).

Laurent Verkoczy
Duke University

Laurent Verkoczy, Ph.D., is Assistant Professor of Medicine and Pathology at Duke University Medical Center and directs the Laboratory of B-cell Immunoregulation at the Duke Human Vaccine Institute. Dr. Verkoczy also serves as a B-cell Focus Investigator in Duke's Center for HIV/AIDS Vaccine Immunology & Immunogen Discovery (CHAVI-ID) consortium. He obtained his Ph.D. in Immunology from the University of Toronto in 2000 and completed post-doctoral studies at The Scripps Research Institute in 2005. His lab seeks to identify impediments limiting protective antibody responses against variable pathogens like HIV-1 and aims to test novel immunogens/vaccine strategies to overcome such roadblocks. Recently, to develop a more focused setting to evaluate the ability of vaccine candidates to generate HIV-1 broadly neutralizing antibody (bnAb) responses, his group has engineered mouse strains carrying individual unmutated precursors of several rare, but well-characterized B-cell lineages capable of eventually producing bnAbs during HIV-1 infection.

Nicole Baumgarth
University of California, Davis

Nicole Baumgarth, Ph.D. is a Professor in the Pathology, Microbiology & Immunology Center for Comparative Medicine, at the University of California, Davis, School of Veterinary Medicine. The Baumgarth Lab investigates the basic immunological mechanisms that regulate and control immunity to pathogens. They aim to reveal the signals that drive a protective B cell response and to determine how these responses might be disregulated by certain pathogens. They are also interested in understanding the development and the role and function of a small innate-like B cellsubset, termed B-1 cells.

Federico Zuckermann
University of Illinois, Urbana-Champaign

Federico Zuckermann, Ph.D. is a Professor of Immunology in the Pathobiology department of the College of Veterinary Medicine at the University of Illinois, Urbana-Champaign. He is the Founder and Chief Scientific Officer for Aptimmune Biologics, Inc. Dr. Zuckermann obtained his Ph.D. in 1986 at the University of Texas Southewestern Graduate School of Biomedical Science.

James Binley
San Diego Biomedical Research Center

James Binley, Ph.D. is a Professor at San Diego Biomedical Research Institute, SDBRI. Dr. Binley earned his Ph.D. in Immunology/HIV in 1995 from The Scripps Research Institute and the University of Sheffield, UK. He completed a post-doctoral fellowship at Aaron Diamond AIDS Research Center in New York in 1999. He was an Instructor at the Weill Medical College of Cornell University. In 2001, he returned to The Scripps Research Institute as Staff Scientist. In 2004, he established his laboratory at Torrey Pines Institute for Molecular Studies. In 2014, he became a founding member of SDBRI.

FEATURED SPEAKERS

SATURDAY, NOVEMBER 7

Gary McLean
Imperial College of London

Gary McLean, Ph.D. completed his Ph.D in pathology at the University of Otago in New Zealand and performed postdoctoral studies at the University of British Columbia (Canada) and Albert Einstein College of Medicine (USA). He then joined the Faculty at the University of Texas Health Science Centre Houston (USA) before relocating to London, UK where he is now a Reader in Molecular Immunology at London Metropolitan University. He also holds an honorary research position at Imperial College London in the Airways Disease Infection Section of the National Heart and Lung Institute. His current research investigates the adaptive immune response to rhinovirus infections – the aim of his research is to generate novel therapeutic interventions or a protective vaccine to rhinovirus. He has published 25 papers in peer-reviewed scientific journals in serves as an editorial board member and reviewer of numerous reputed journals in immunology.

Adolfo Garcia-Sastre
Mount Sinai School of Medicine

Adolfo Garcia-Sastre, Ph.D. is a Professor in the Department of Microbiology and the Director of the Global Health & Emerging Pathogens Institute at Mount Sinai School of Medicine in New York. He is also Principal Investigator for the Center for Research on Influenza Pathogenesis (CRIP), one of five NIAID Centers of Excellence for Influenza Research and Surveillance (CEIRS). Together with Charlie Rice, he is the leader of the basic research component on Viral Therapeutics and Pathogenesis of the North East Biodefense Center proposal, which was funded by NIAID and involves the collaboration of more than 20 academic institutions in New York, Connecticut and New Jersey. For the past 20 years, Dr. Garcia-Sastre's research interest has been focused on the molecular biology of influenza viruses and several other negative strand RNA viruses. His research has resulted in more than 100 scientific publications and reviews. He was among the first members of the Vaccine Study Section of the NIHve strand RNA viruses. In addition, he is an editor for Journal of Experimental Medicine and PLoS Pathogens and a member of the Editorial Board of Journal of Virology, Virology, Journal of General Virology and Virus Research.

Sudhir Paul
University of Texas Health

Sudhir Paul, Ph.D. is Professor of Pathology and Director, Chemical Immunology Research Center at the Univ of Texas Houston Health Sciences Center. After his Ph.D. in Biochemistry from the All-India Institute of Medical Sciences in 1981, Dr. Paul was a Humboldt Fellow until 1983 at Christian Albrechts Univ, Gemany. He served as Asst Professor at Univ of Oklahoma until 1987 and then moved to Univ of Nebraska Medical Center, where he was Assoc Professor and then Professor of Pharmacology, Pathology and Anesthesiology until 1998. Dr. Paul has published more than 190 original articles, reviews and book chapters, and he has edited several books and conference proceedings on catalytic antibodies, HIV vaccination, amyloid disease and autoimmunity. He has delivered over 250 invited seminars and symposium presentations.
The Paul lab discovered proteolytic antibodies and identified them as transitional molecules bridging the innate and adaptive features of humoral immunity. A single catalytic antibody molecule is reused to cleave thousands of antigen molecules, and the Paul lab is developing catalytic antibodies as a platform for treating intractable diseases. While developing immunogens for inducing catalytic antibody synthesis, they serendipitously identified an electrophilic immunogen that bound B cells covalently and corrected the immunological defect precluding synthesis of mature antibodies directed to the vulnerable, superantigenic CD4 binding site of HIV. This immunogen induced antibodies that neutralized HIV strains found world-wide. They are now exploring the potential of electrophilic immunization for vaccination against HIV.

David Verhoeven
CAHDIT, Iowa State University

David Verhoeven, PhD, is a Research Assistant Professor in the Department of Biomedical Sciences and Center for Advanced Host Immunobiotics and Translational Comparative Medicine at the College of Veterinary Medicine, Iowa State University. Dr. Verhoeven's main areas of expertise and research include Respiratory Pathogen Diseases of children, such as Influenza, RSV, Streptococcus pneumoniae, nontypeable Haemophilus influenzae, CD4 memory T-cell activity, and HIV vaccine research/pathogenesis.

VAAVV 2015 SYMPOSIUM

SUNDAY, NOVEMBER 8

Xiangpeng Kong
New York University

Xiangpeng Kong, Ph.D., is an Associate Professor in the Department of Biochemistry and Molecular Pharmacology at New York University. Structural Biology of Urothelial Membranes Structure-based immunogen design in HIV/AIDS vaccine discovery is Dr. Kong's area of research interest.

Roland Strong
Fred Hutcinson Cancer Research Center

Roland Strong, Ph.D. is a biophysicist by training and a fundamental scientist by vocation. Strong has dedicated three decades to determining the structures and interactions of some of the most important molecules of life, from the antibodies involved in fighting disease to the markers on viruses that trigger an immune response. Dr. Strong received his B.S. in Biophysics in 1984 from the University of Michigan and his Ph.D. in Biophysics from Harvard University in 1990. He is now an Affiliate Professor in the Department of Immunology and a Joint Affiliate Associate Professor in the Department of Biochemistry at the University of Washington. He is a Member, Division of Basic Sciences, Fred Hutchinson Cancer Research Center (primary appointment) as well as an External Joint Member, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center.

Kelly Lee
University of Washingoton

Kelly Lee, Ph.D. is an Assistant Professor in the Department of Medicinal Chemistry, University of Washington, as well as an Adjunct Assistant Professor in the department of Microbiology, University of Washington. The Lee Lab's research in the Department of Medicinal Chemistry, University of Washington focuses on the structure and dynamics of membrane fusion proteins in influenza and HIV, with the goals of understanding how the specialized glycoprotein machinery from each virus mediates membrane remodeling during cell invasion and determining how they interact with cellular receptors and antibodies. By analyzing structural order of viral the proteins and protein complexes in solution, one gains insight into isolate-specific differences in epitope order and presentation that can be correlated with antigenicity and potentially vaccine immunogenicity.

SELECTED SPEAKERS

Zhe Yuan
University of Nebraska, Lincoln

Masaru Kanekiyo
National Institutes of Health, NIAID

Rachel Brouillette
University of Iowa

Alexander Vogel
University of Nebraska, Lincoln

William Lees
University of London, Birkbeck

Wuxun Lu
University of Nebraska, Lincoln

Pablo Pineyro
Iowa State University

Nikolai Petrovsky
Flinders Medical Centre, Australia

Dennis Lapuente
Ruhr University-Bochem, Germany

Heidi Drummer
Burnet Institute-Melbourne, Australia

Naveed Gulzar
Simon Fraser University

Saikat Banerjee
Iowa State University

Daniel Geraghty
Fred Hutchinson Cancer Research Center

John Hsieh
Iowa State University

S102 Elizabeth Rieder

GENETIC AND ANTIGENIC VARIABILITY OF FOOT-AND-MOUTH DISEASE VIRUS: A PRACTICAL PROBLEM

Elizabeth Rieder

USDA-ARS Plum Island Animal Disease Center, Greenport NY, USA

Abstract: Foot-and-mouth disease viruses (FMDV) exhibit high antigenic diversity manifested by the existence of seven serotypes and more than 65 subtypes. In order to understand the genetic basis of these antigenic phenotypes, we have determined the full capsid sequence of field FMDVs and analyzed these data in context of antigenic relationship (*r*) values generated using type-specific antisera. Comparisons of capsid sequences have identified substitutions in neutralizing antigenic sites, which either individually or together contributes to these observed antigenic phenotypes. The results are discussed in relation to the practical challenges to control FMD by vaccination and what strategies we are undertaking to develop novel vaccine platform to countermeasure the disease.

S104 Richard Webby

INFLUENZA VIRUS ANTIGENIC VARIATION AND HUMAN RESPONSES

Richard Webby

Department of Infectious Diseases, St. Jude's Children's Research Hospital

Abstract: The influenza virus is the poster child for an antigenically variable virus for which a vaccine is available. The antigenic diversity of the virus stems from drift in response to immunologic pressure and also from the spectrum of viral subtypes present in animal reservoirs. Although an effective vaccine is available, the requirement for a close match between the circulating and vaccine strains requires constant monitoring of viruses in the context of seasonal influenza and rapid production of a matching vaccine in the context of pandemic influenza. Developed specifically to monitor the nature of circulating influenza viruses, the World Health Organization Global Influenza Surveillance and Response System comprises over 140 global laboratories that collect and characterize specimens and viruses during influenza seasons. Antigenic, genetic, and serologic data derived from these specimens are used to inform decisions about the most appropriate strains to be used in seasonal influenza vaccines. As will be discussed by others throughout this symposium, making substantial improvements to the current systems will rely on identifying aspects of the immune response against the influenza virus that target more conserved epitopes. Such activities have identified the hemagglutinin stalk as one candidate target and accumulating data from clinical studies have identified broadly reactive immune responses generated during acute infections. Understanding how best to stimulate these immune signatures through vaccination remains so far elusive.

S201 Kevin L. Legge

DENDRITIC CELL REGULATION OF INFLUENZA VIRUS IMMUNITY

Emma Hornick, Emily Hemann, Jodi McGill, and Kevin L. Legge
University of Iowa, Iowa City, IA 52242

Abstract: Both CD8 and CD4 T cells contribute to the protection against influenza virus (IAV) infections via production of pro- and anti-inflammatory cytokines and direct lysis of infected cells. The mechanistic and cellular requirements regulating this multi-faceted IAV-specific T cell response within the lungs remain unclear. Our studies have established that the effector IAV-specific CD8 T cell response in the lungs requires a local interaction with dendritic cells (DC). These DC provide a critical survival signal to the CD8 T cells, without which there are not sufficient numbers to control the infection. Recently we have sought to determine whether a similar interaction is required for the IAV-specific CD4 T cell response. Using a surrogate marker approach to identify all effector T cells recruited into the response our results demonstrate that the IAV-specific CD4 T cell response peaks at 10dpi and is predominantly composed of T-bet cells. Further our studies demonstrate that effector CD4 T cell in the lungs are, like the CD8 T cell response, under local DC regulation as in the absence of pulmonary APC the IAV-specific CD4 T cells are substantially decreased across all Th subsets. This reduced pulmonary CD4 T cell response in the absence of APC is due to increased apoptosis of IAV-specific CD4 T cells in the lungs. Therefore all together, our results suggest that both the pulmonary IAV-specific CD4 and CD8 T cell responses require a local interaction with pulmonary APC within the lungs to promote their survival and allow for viral control.

S301 Adrian J. Shepherd

INFORMING HIV IMMUNOGEN DESIGN BY CHARACTERISING SEQUENCE SETS WITH NGS

Adrian J. Shepherd
Institute of Structural and Molecular Biology, Birkbeck College, University of London Malet Street, London WC1E 7HX

Abstract: NGS anSbody repertoire sequencing is a powerful approach that is transforming our understanding of how repertoires evolve in response to infecSon and vaccinaSon. PotenSal insights relevant to immunogen design range from the broad (helping us characterise the degree of repertoire similarity between individuals, including individuals from different species) to the specific (including the detailed characterisaSon ofspecific affinity maturaSon pathways). This talk will present some recent results from our work, including evidence for an unexpected degrees of parallel anSbody evoluSon between individuals with HIV, and an assessment of the potenSal role of structural modelling as a means of idenSfying anSgenic targets and/or criScal subsStuSons that make a dominant contribuSon to affinity maturaSon.

S402 Shan Lu

POLYVALENT DNA VACCINES AGAINST ANTIGENICALLY VARIABLE PATHOGENS

Shan Lu, MD, PhD, MHA
University of Massachusetts Medical School, Worcester, MA

Abstract: DNA vaccination was formally accepted as a new technology in early 1990s. Its applications to human vaccine development was stalled for low immunogenicity when it was tested alone in human studies. With persistency and serendipity, we now learned that DNA immunization is a very powerful tool to reveal the secret of inducing high quality antibody response which is the central component of almost any successful vaccines. DNA immunization can effectively link the innate and acquired arms of immune responses to achieve the maximum benefits of vaccines. More significantly DNA vaccine is an ideal technology platform to develop polyvalent vaccines against antigenically variable pathogens including HIV-1.

S303 Michael G. Katze

SYSTEMS BIOLOGY OF INFECTION AND IMMUNITY-DEADLY VIRUS INFECTIONS IN THE 21ST CENTURY: SUCCESSES, CHALLENGES, EBOLA AND NETWORKS TO NOWHERE

Michale G. Katze

Department of Microbiology and Washington National Primate Research Center, University of Washington, Seattle, WA 98195-8070

Abstract: My laboratory is using systems biology and novel computational methods to understand and model the host response to highly pathogenic viruses, including Ebola virus; H5N1, H7N9, and pandemic influenza viruses; MERS coronavirus; and human and simian immunodeficiency viruses. We are also using these methods to study the early innate response to vaccination and to illuminate the events that lead to protective immune outcomes. Our approaches take particular advantage of next-generation RNA-sequencing and innovative experimental systems, such as the Collaborative Cross mouse genetics platform, to examine global patterns of host gene expression and the role of host genetic variation on infection outcome. Our studies using the Collaborative Cross have recently resulted in the development of a first-of-its-kind mouse model of Ebola hemorrhagic fever. We have shown that different recombinant inbred mouse lines exhibit distinct disease phenotypes after mouse-adapted Ebola virus infection. Phenotypes range from complete resistance to lethal disease to severe hemorrhagic fever and 100% mortality. RNA-seq is also expanding our views to encompass the uncharted territory of noncoding RNAs, where we have observed changes in the expression of diverse classes of small and long noncoding RNAs in response to virus infection. These findings suggest that a detailed knowledge of noncoding RNA regulation and function will be necessary for a full understanding of transcriptional control and viral pathogenesis. Our goal is to exploit these systems to provide molecular signatures for diagnostic or prognostic assays and a rational basis for antiviral drug and vaccine development.

S403 Laurent Verockzy

KNOCK-IN MODELS FOR STUDYING THE DEVELOPMENT OF IMMUNIZATION-GUIDED HIV-1 BROADLY NEUTRALIZING RESPONSES

Laurent Verockzy

Duke Human Vaccine Institute, Durham, NC 27710

Abstract: An effective HIV vaccine will likely require inducing broadly neutralizing antibodies (bnAbs). However, a key immunologic conundrum impeding this goal is that bnAb traits required for their function, i.e. poly-/autoreactivity, long HCDR3s, and high somatic mutation levels, also invoke B-cell tolerance controls and/or necessitate extensive maturation pathways. Furthermore, Env immunogens may express multiple epitopes that preferentially activate B-cell precursors lacking neutralization potential. Animal models for more iteratively testing the ability of novel immunogens and vaccine strategies to overcome such hurdles would be highly beneficial. This talk will overview various humanized Ig mice we and others have generated and present our recent results in knock-in models expressing unmutated precursors of three, well-characterized bnAbs targeting distinct Env regions, in order to illustrate how insights from each provide a starting point for re-engineering immunogens and/or modifying vaccine regimens. Identifying hurdles preventing optimal vaccine-guided activation/maturation in models expressing individually knocked-in bnAb precursors should collectively help inform which candidate Env sites are most feasible to target by immunization.

S502 James M. Binley

INDUCTION OF ANTI-HIV-1 NEUTRALIZING ANTIBODIES USING NATIVE TRIMER IMMUNOGENS

Ema T. Crooks[1], Tommy Tong[1], Bimal Chakrabarti[2¶], Kristin Narayan[3#], Ivelin S. Georgiev[4], Sergey Menis[2,5], Xiaoxing Huang[6], Daniel Kulp[2,5], Keiko Osawa[1], Janelle Muranaka[3], Guillaume Stewart-Jones[4,7], Joanne Destefano[8], Sijy O'Dell[4], Celia LaBranche[9], James E. Robinson[10], David C. Montefiori[9], Krisha McKee[4], Sean X. Du[3], Nicole Doria-Rose[4], Peter D. Kwong[4], John R. Mascola[4], Ping Zhu[6], William R. Schief[2,5,11], Richard T. Wyatt[2,5], Robert G. Whalen[3], James M. Binley[1]

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Abstract: Eliciting broadly neutralizing antibodies (nAbs) is a major goal in HIV-1 vaccine research. Here we investigated the ability of native, membrane-expressed JR-FL Env trimers to elicit nAbs. Unusually potent nAbs developed in 2/8 rabbits immunized with virus-like particles (VLPs) expressing trimers (trimer VLP sera) and in 1/20 rabbits immunized with DNA expressing native Env trimer, followed by a protein boost (DNA trimer sera). All 3 sera neutralized via quaternary epitopes and exploited natural gaps in the glycan defenses of the C2 region of JR-FL gp120. Specifically, 'trimer VLP sera' took advantage of the unusual absence of a glycan at residue 197 (present in 98.7% of Envs). Intriguingly, removing the N197 glycan rendered up to 50% of clade B tier 2 isolates sensitive to trimer VLP sera, indicating broad neutralization via the surface masked by the N197 glycan. Neutralizing sera targeted epitopes that overlap with the CD4 binding site, consistent with the role of the N197 glycan in a "glycan fence" that limits access to this region. The neutralizing 'DNA trimer' serum took advantage of the absence of a glycan at residue 230, perhaps with a similar epitope to monoclonal antibody 8ANC195. Taken together, our data show that strain-specific holes in the glycan fence can allow the development of tier 2 nAbs to native spikes and that cross-neutralization can occur in the absence of protecting glycan. These observations provide new insights for strategies aimed at improving the frequency and breadth of tier 2 nAb responses. These ongoing studies will be discussed.

S601 David Verhoeven

EQUINE INFLUENZA HA3 ANTIGEN INDUCES IMMUNOLOGICAL RESPONSES AGAINST MULTIPLE STRAINS OF FLU

David Verhoeven, Brett Sponseller, Jessie Trujillo

Iowa State University, Ames IA

Abstract: Antigenic shift/drift necessitate yearly updates to influenza vaccines for which mismatches between circulating and vaccine strains offer little protection. A long sought goal of the influenza vaccine field is the development of a universal vaccine that offers protection across the multiple strains that circulate. Investigation of equine serum responses to live attenuated H3N8 vaccine demonstrated significant cross-strain reactivity with a strong hemagglutinin inhibition (HAI) response against the recurring circulating H1N1 pnd2009 as well as H3N2 viruses. Further qualification in mice, with Ig diversity more similar to humans, demonstrates even higher levels of cross-protective HAI responses and strong IgG responses. Vaccinated mice were also better protected from challenge with H3N2 and H1N1 pnd-2009 challenge. IgG responses appeared to target potential cross-strain HA head epitopes (conformational) rather than HA stem epitopes. Thus, the equine H3 antigen may represent a unique potential vaccine candidate for the long-sought universal influenza vaccine.

S503 Gary McLean

DEVELOPING A VACCINE FOR HUMAN RHINOVIRUSES

Gary McLean

Airways Disease Infection Section, National Heart and Lung Institute, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, Centre for Respiratory Infections, Imperial College London, UK

Abstract: Human rhinovirus (RV) infections are the principle cause of common colds and precipitate asthma and chronic obstructive pulmonary disease exacerbations. Currently there is no vaccine for RV which is largely due to the existence of ~150 serotypes/strains. The hypothesis was that highly conserved regions of the RV polyprotein, when used as an immunogen, would generate broadly cross-reactive protective immunity to RV. A bioinformatic approach defined highly conserved areas of the RV proteome, recombinant proteins were produced and tested as candidate immunogens for a broadly cross-reactive vaccine using a mouse infection model. C57/BL6 mice were immunized subcutaneously with the RV immunogen prior to intranasal challenge with RV. At specific time points following live RV challenge, specific humoral and cellular immune responses as well as parameters of RV-induced inflammation were determined. Regions of the VP0 (VP4+VP2) capsid protein were identified as having high homology across RVs. Immunization with a recombinant VP0 combined with a Th1 promoting adjuvant induced systemic, antigen specific, cross-serotype, humoral and T cell immune responses. Similar cross-reactive responses were observed in the lungs of immunized mice after infection with heterologous RV strains. Immunization enhanced the generation of heterosubtypic neutralizing antibodies and caused more rapid virus clearance. In conclusion, conserved domains of the RV capsid are immunogenic in mice and induce cross-reactive immune responses that neutralize RV in vitro and are protective in vivo. This approach has identified candidates for the continued development of a broadly reactive subunit RV vaccine.

S505 Sudhir Paul

ELECTROPHILIC IMMUNOGENS (E-IMMUNOGENS) FOR AMPLIFYING BROADLY NEUTRALIZING ANTIBODIES (BNABS) TO HIV

Sudhir Paul[1,2], Stephanie A. Planque[1,2], Richard J. Massey[2]

[1]Chemical Immunology Research Center, Univ Texas Houston Medical School Dept of Pathology, Houston, TX; [2]Covalent Biosciences, New York, New York

Abstract: The linear, mostly-conserved gp120 residues 421-433 (C^{421}) are essential for HIV-1 binding to CD4 receptors, and C^{421} is one of few epitopes vulnerable to bNAbs. Non-infected humans innately produce nucleophilic IgM+ B cell receptors (BCRs) and secreted IgM subsets with framework regions (FRs) that bound C^{421} peptides reversibly or proceeded to degrade purified gp120 catalytically. The innate variable (V)-domains of C^{421}-directed Abs displayed intact HIV binding and broad HIV neutralization in the IgG/IgA but not IgM scaffold, indicating that IgM→IgG/IgA class-switching (CS) is necessary for protection against HIV. We identified an epitope-selective defect in IgM→IgG CS or post-CS survival of B-cells directed to C^{421} but not other gp120 regions in HIV infected patients and gp120 immunized mice, consistent with the ability of superantigen epitopes to downregulate B cells by noncovalent binding at the BCR FRs. Murine immunization with C^{421}-containing E-immunogens that bind covalently to nucleophilic BCRs corrected the selective CS defect. The resultant C^{421}-directed monoclonal IgGs neutralized infection of cultured human peripheral blood mononuclear cells by subtype A/B/C/D/AE strains and suppressed HIV infection of PBMCs in immunodeficient mice. Mechanistic studies suggested upregulated C^{421}-directed bNAb synthesis due to high energy covalent BCR—E-immunogen binding, together with CDR binding by an immunogen epitope neighboring the FR-C^{421} interaction. Adaptive-strengthening of IgG nucleophilicity resulted in irreversible binding and hydrolysis of gp120, effector functions that improve IgG neutralization potency. The E-gp120 immunogen also reproducibly induced ~1:100 serum titers of C^{421}-directed neutralizing IgGs in macaques. The E-immunogen approach is suitable for advancement to vaccine trials.

S702 Roland K. Strong

REVERSE ENGINEERING HIV BNABS: HOW HARD IT IS TO GET ANTIBODIES TO DO WHAT YOU WANT THEM TO DO

Roland K. Strong

Fred Hutchinson Cancer Research Center, Seattle WA 98109

Abstract: The list of antibodies that broadly neutralize HIV continues to grow, along with the list of susceptible epitopes targeted by such antibodies on the Env glycoprotein. Engineering of potential vaccine immunogens has (finally) begun to yield results for eliciting some of these antibodies in uninfected individuals. However, it remains true that many, if not most, broadly-neutralizing antibodies are the products of multiple rounds of extensive somatic hypermutation during chronic HIV infection. The pathway followed by many important families of, for instance, anti-CD4 binding antibodies during ontogeny is likely reproducibly achievable by immunization. But the pathways for many antibodies, including some of the archetypical broadly neutralizing antibodies, like 4E10 and b12, are much more convoluted. Extensive biochemical and biophysical analysis of 4E10 and b12 ontogeny reveal that reeliciting these antibodies by design is likely not achievable by conventional immunization regimens. The lessons bear on current efforts to rationally engineer subunit vaccine immunogens, and the ofttimes remarkably tortuous path of antibody ontogeny.

S105 Zhe Yuan

FOUNDER VIRUS SIGNATURES IN SIV RECTAL TRANSMISSION

Zhe Yuan[1,2]; Fangrui Ma[1]; Andrew J. Demers[1, 2]; Dong Wang[3]; Jianqing Xu[4, 5]; Mark G. Lewis[6]; Brandon F. Keele[7]; Qingsheng Li[1,2]

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Abstract: HIV-1 is typically transmitted through mucosal routes, through which a swarm of viruses in exposure are restricted into a single virus or a few founder viruses by a genetic bottleneck. To prevention transmission, protective immunity elicited by HIV-1 vaccine needs to target and block founder virus transmission. To better understand the mechanism governing virus transmission, we studied transmitted/founder viruses in the samples of blood, distal lymph nodes and rectum of Indian rhesus macaques at 6 (n=3) and 10 (n=3) days post intrarectal inoculation with SIVmac251 (3.4 x 10^4 TCID50) using single genome amplification (SGA) of full-length env. We found that there is no tissue compartmentalization of founder viruses across rectum, lymph node and blood samples and the dominant founder viruses were recurrently derived from low abundance or even undetected variants in the inoculum. Importantly, there is an animal-specific founder virus signature (ASFVS) shared within dominant founder virus group but not in rare transmitted viruses or untransmitted viruses in the inoculum. It is also noteworthy that defective transmitted viruses are most likely derived from functional funder viruses after transmission through a yet unidentified mechanism, since defective transmitted viruses are phylogenetically more related to functional variants than defective variants in the inoculum. The findings in this study support that genetic bottleneck mainly works through an animal-specific selection and the identified ASFVS may inform HIV-1 vaccine design for preventing HIV-1 mucosal transmission.

S106 Masaru Kanekiyo

IMMUNIZATION WITH HETEROGENEOUS MOSAIC ARRAY OF INFLUENZA HA RECEPTOR-BINDING DOMAINS INDUCES BROADLY NEUTRALIZING H1N1 ANTIBODY RESPONSES

Masaru Kanekiyo[1]; Hadi M Yassine[1,2]; Adam K Wheatley[1,3]; Rebecca A Gillespie[1]; Madhu S. Prabhakaran[1]; Sarah F Andrews[1]; Adrian B McDermott[1]; Richard A Koup[1]; John R Mascola[1]; Barney S Graham[1]

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Abstract: Continuous antigenic drift of hemagglutinin (HA) enables influenza viruses to evade host immunity developed from prior years. Particularly, substitutions in the receptor-binding domains (RBDs) are responsible for the antigenic transition and neutralization resistance, limiting the breadth of current vaccines, and creating the need for annual vaccination. To address the problem of antigenic diversity, we created a synthetic array of antigenically distinct HA RBDs on a single self-assembled nanoparticle (np) to co-localize diverse antigenic clusters and preferentially stimulate B cells with cross-reactivity. Immunization of mice with co-assembled, heterogeneous RBD-np resulted in broader antibody responses compared to a cocktail of single np encompassing the same set of RBDs and maintained responses as each specific antigen was diluted. Further, a monoclonal antibody isolated from a mouse immunized with co-assembled RBD-np exhibited neutralization to all tested H1N1 strains spanning >90 years. Interestingly, this antibody, 441D6, did not compete with viral hemagglutination or binding of CH65, a broadly neutralizing H1N1 antibody that recognizes the HA sialic acid-binding site, indicating 441D6 recognizes a conserved epitope distinct from the sialic acid-binding site within the RBD. Together, mosaic arrangement of heterogeneous RBDs on a single np may select for B cell receptors (BCRs) capable of heteroligation by adjacent RBDs, providing an avidity advantage for cross-reactive interactions over strain-specific BCRs. This may provide a mechanism to circumvent antigenic competition by limiting the immunodominant strain-specificity and allow the development of influenza vaccines with more breadth. The concept could potentially be extended to other targets that escape immunity through antigenic diversity.

S204 Rachel Brouillette

QUANTITATION OF ANTI-EBOLA VIRUS IMMUNOGLOBULINS SERVES AS A GOOD IMMUNE CORRELATE OF PROTECTION AGAINST LETHAL EBOLA VIRUS CHALLENGE

Rachel Brouillette[1], Nicholas J. Lennemann[1], Andrew Herbert[2], Bethany Rhein[1], Katherine Perschbacher[1], Julia Biggins[2], Gene Olinger[2], John M. Dye[2], and Wendy Maury[1]

[1]University of Iowa , Iowa City

Abstract: Filoviruses cause sporadic hemorrhagic fever outbreaks in Africa. The current outbreak is ongoing in West Africa and is now responsible for more than 11,000 deaths. This novel West Africa outbreak presents a significant public health burden, highlighting the need for preventative measures to combat this infection. Yet no filovirus vaccine is currently FDA approved. Here, we assessed the efficacy of non-infectious VSV pseudovirions bearing EBOV glycoprotein (GP) to protect against lethal challenge with mouse-adapted Ebola virus (MA-EBOV) as well as cross protect against Sudan virus challenge. We found that a prime/boost vaccination regime protected against challenge with MA-EBOV in a dose-dependent manner, with doses as low as 2 x 10^5 transducing units protecting 100% of mice. Surprisingly, pseudovirions bearing EBOV GPs that were partially or fully denuded of N-linked glycans offered less protection than virions containing wild-type GP. Deglycosylated EBOV GP mutants also did not provide better cross protection to Sudan virus than did wild-type EBOV GP. Assessment of immune correlates revealed that protection did not correlate with the presence of neutralizing antibodies, but strongly correlated with the quantity of anti-EBOV GP antibodies produced in response to the immunogen. Our findings suggest that these non-infectious pseudovirions are a safe and highly efficacious vaccine candidate. Further, assessment of anti-EBOV GP IgG levels may serve as a simple surrogate marker for immune efficacy.

S205 Alexander Vogel

IRF3 DEFICIENCY CONTRIBUTES TO IMPAIRED MEMORY T CELL FUNCTION IN RESPONSE TO INFLUENZA INFECTION

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Abstract: The role of IRF3 in initiating antiviral responses in innate immune cells has been well studied in the context of viral infection. However, it remains unclear the role that IRF3 plays in modulating the adaptive immune response. To address this, IRF3 deficient (IRF3 KO) mice were infected with influenza A virus (IAV) and T cell responses measured. During the primary effector response, the frequency of IFN-γ and Granzyme B (GrB) positive T cells in the lung were similar between IRF3 KO and wildtype mice. Interestingly, 30 days after the initial infection, IRF3 KO mice exhibited significant defects in antigen-specific recall memory T cell responses to IAV. Because IRF3 has been implicated in the expression of key cytokines that influence effector and memory T cell responses, cytokine supplementation studies were performed. While supplementation with IL-12 rescued IFN-γ deficiencies in IRF3 KO cells, maximal GrB expression was not restored, particularly in CD8 cells. Similarly, upon secondary challenge with a heterosubtypic IAV, GrB responses were impaired in the lungs suggesting that IRF3 deficiency has a substantial impact on the cytotoxic potential of memory T cells and secondary recall responses. Together, this work suggests a role for IRF3 in the molecular regulation of memory T cell responses to viral infection and may serve to inform future vaccine strategies that require the development of robust memory T cells.

S304 William Lees

HIGH THROUGHPUT ANALYSIS OF B-CELL CLONAL LINEAGES

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Abstract: Next-Generation Sequencing has enabled representative sampling of the B cell repertoire and has already provided fascinating insights into the immune response. Few published tools exist, however, to assist with the downstream analysis of clonal lineages. Here we present a set of tools for phylogenetic analysis and annotation, which facilitate both large scale automated analysis and the presentation of results for high-quality publication. We present insights from their analysis of the immune response to vaccination. The tools are publicly available on our website, and are also freely available for download.

S305 Wuxun Lu

TRANSCRIPTOME PROFILING OF SIV GAG-SPECIFIC CD8+ T CELLS TO UNDERSTAND THE TIME-DEPENDENT PROTECTION ELICITED BY SIV-ΔNEF LIVE ATTENUATED VACCINE

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Abstract: SIVmac239Δnef live attenuated vaccine (LAV) elicits the best protection among all the vaccine modalities tested in the rhesus macaque model of HIV-1 infection. There is a unique time-dependent protection induced by this vaccine, wherein macaques are protected between 15 and 20 weeks post vaccination (WPV), but not at 5 WPV. However, the correlatives of protection of this vaccine, specifically the mechanism of the time-dependent protection, remain poorly understood. To better understand the potential contribution of SIV-specific cellular immunity to this time-dependent protection induced by SIV-Δnef LAV, adult female Indian rhesus macaques (Macaca mulatta) of Mamu-A*01+ were vaccinated with SIVmac239Δnef (supplied by Dr. Ronald Desrosiers) intravenously. At 3 (n=5) and 20 WPV (n=3), SIV Gag-specific CD8+ T cells were isolated from peripheral blood samples using tetramer staining and flow cytometry. Genome-wide transcriptome profiles of the Gag-specific CD8+ T cells at 3 and 20 WPV were detected using GeneChip Rhesus Macaque Genome Array (Affymetrix). We found that transcriptional profiles in SIV Gag-specific CD8+ cells at 20 WPV qualitatively differ from cells at 3 WPV. Gag-specific CD8+ T cells at 20 WPV showed an expression pattern of central memory T cells, with higher expression of CCR7, TCRA, TCRB, CD28, and lower expression negative factor CTLA4. Consistent with the central memory-like gene expression pattern, these cells have lower expression levels of IFN-γ, Rantes, CD226, and granzyme A and B as compared with 3 WPV. Taken together, our data suggest that SIV-specific CD8+ T cells are functionally more y mature at 20 than 3 WPV, which may contribute to the observed time-dependent protection.

S405 Pablo Pineyro

PORCINE CIRCOVIRUS AS A POTENTIAL DELIVERY VIRUS VECTOR TO EXPRESS ANTIGENIC DETERMINANTS OF PORCINE REPRODUCTIVE AND RESPIRATORY SYNDROME VIRUS

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Abstract: One of the most common co-infections in the swine industry is PCV2 and PRRSV. PCV2 is pathogenic causing an economically-important porcine circovirus-associated disease (PCVAD) in swine worldwide which may be exacerbated via co-infection with PRRSV. Two types of PCV, PCV1 and PCV2, have been identified thus far. Whereas PCV2 is widespread and causes disease, PCV1 is non-pathogenic in pigs. Previously, it has been demonstrated that a genetically modified infectious PCV1-2a can tolerate up to a 27 aa insertion in the C-terminus of ORF2 without affecting infectivity. The aim of this study is to use a PCV1 wild type (wt) and PCV1-2a vaccine strain (vs) to express four known B-cell epitopes of PRRSV. Peptide epitopes of PRRSV-VR2385, including GP2II (aa 40–51, ASPSHVGWWSFA), GP3I (aa 61–72, QAAAEAYEPGRS), GP5I (aa 35–46, SSSNLQLIYNLT), and GP5IV (aa 187–200, TPVTRVSAEQWGRP) were inserted in frame into the C-terminus of the ORF2 of PCV1wt and PCV1-2avs. Four PCV1-PRRSEPI and PCV1-2a-PRRSVEPI chimeric viruses were infectious in vitro and co-expressed PCV1cap or PCV2cap with each specific PRRSV epitope. Two independent animal studies showed that three PCV1-PRRSVEPI and two PCV1-2a-PRRSVEPI chimeric viruses were infectious in vivo. PCV1-PRRSVEPI and PCV1-2a-PRRSVEPI chimeric viruses not only induced specific PCV1 or PCV2 IgG but also specific anti-PRRSV epitope antibody response. Regardless of the PCV backbone the PCV-PRRSV chimeric viruses elicited neutralizing antibodies against PRRSV-VR2385. These results provided a proof of concept for further exploring the use of the non-pathogenic PCV1 and PCV1-2a as delivery system to generate immunity against PRRSV.

S406 Nikolai Petrovsky

DELTA INULIN ADJUVANT ENHANCES PLASMABLAST GENERATION, EXPRESSION OF ACTIVATION-INDUCED CYTIDINE DEAMINASE AND B-CELL AFFINITY MATURATION IN HUMAN SUBJECTS RECEIVING SEASONAL INFLUENZA VACCINE

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Abstract: There is a major need for new adjuvants to improve the efficacy of seasonal and pandemic influenza vaccines. Advax™ is a novel polysaccharide adjuvant based on delta inulin that has been shown to enhance the immunogenicity of influenza vaccine in animal models and human clinical trials. To understand the mechanism we assessed the effectof Advax on the post-immunization plasmablast response in day 7 post-vaccination (7dpv) peripheral blood mononuclear cell samples from 26 adult human subjects who had been immunized intramuscularly with a standard dose of 2012 trivalent inactivated influenza vaccine (TIV) alone or combined with 5mg or 10mg of Advax adjuvant. Subjects receiving adjuvant had increased 7dpv plasmablasts, which in turn exhibited a 2-3 fold higher rate of non-silent mutations in the B-cell receptor CDR3 region associated with higher expression of activation-induced cytidine deaminase (AID), the major enzyme controlling BCR affinity maturation. Hence Advax adjuvant enhanced influenza immunity in immunized subjects via multiple mechanisms including increased plasmablast generation, AID expression and CDR3 mutagenesis resulting in enhanced BCR affinity maturation and increased production of high avidity antibody.

S506 Dennis Lapuente

SIGNALING MOLECULES OF THE INNATE IMMUNE SYSTEM AS GENETIC ADJUVANTS IN DNA IMMUNIZATIONS AGAINST INFLUENZA A VIRUSES

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Abstract: Introduction: Influenza A viruses (IAV) are the main pathogens associated with severe respiratory infections. Nevertheless, licensed trivalent inactivated Influenza vaccines (TIV) protect only against the vaccine strains by antibodies specific for the surface proteins hemagglutinin (HA) and neuraminidase (NA). Due to constant evolutional changes, vaccinations are required annually for continuous protection. In this regard, DNA vaccines are promising alternatives. They induce additionally cytotoxic T cells (CTL) specific to conserved viral epitopes, e.g. in the nucleoprotein (NP), conferring immunity against a broad range of IAV strains.

Objectives: Signaling molecules involved in the initiation of immune responses to natural IAV infections (IPS1, IL1β or IL18) should be exploited as genetic adjuvants in DNA immunizations to enhance the strength and breadth of the vaccine-induced immune responses.

Methods: Plasmids encoding HA, NP and the respective adjuvant were delivered into mice via i.m. electroporation. Immunogenicity and efficacy of the adjuvanted DNA vaccines were evaluated.

Results: All immunizations induced robust humoral and cellular responses resulting in protection against the homologous and a divergent IAV strain. Co-administration of IPS1 increased T cell responses, whereas both Interleukins revealed an influence on humoral responses. Furthermore, IL1β and IL18 treated mice tended to loose less weight during a heterologous infection.

Conclusion: Our DNA vaccines mediate protection against heterosubtypic IAV, which is not observed for the recent TIVs. Refinement of adjuvant/antigen dose might potentiate the adjuvant effects and further improve the efficacy of these alternative IAV vaccines.

S507 Heidi Drummer

DEVELOPMENT OF A PROPHYLACTIC VACCINE FOR HEPATITIS C VIRUS

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Abstract: Hepatitis C Virus (HCV) is classified into 7 genotypes that differ by up to 30% at the nucleotide level affecting 200 million people world-wide for which there is no vaccine. The major surface glycoprotein E2 attaches virions to host cell receptor CD81 and antibodies that block this interaction are protective. However, preclinical evaluation of vaccines using intact forms of E2 have shown limited capacity to elicit cross-genotype neutralizing antibodies (bNAbs). This vaccine failure is partly due to the immune-dominance of the N-terminal hypervariable region 1 (HVR1) that elicits type specific NAbs that drive immune escape. Using monoclonal antibodies, we show that HVR1, and two additional variable regions HVR2 and the igVR, allosterically modulate neutralization providing an additional mechanism of immune evasion. To further examine how the three variable regions modulate the immune response to E2, HVR1, HVR2 and the igVR were deleted (Δ123). Our results show that Δ123 retains the ability to bind CD81, is recognized by panels of conformation dependent antibodies and elicits significantly higher titres of bNAbs than intact forms of E2. The most potent form of Δ123 is a high molecular species as this elicits bNAbs that are able to block infectivity of all 7 HCV genotypes in cell culture and the immune response is focused on multiple conserved epitopes located within the E2 core domain. We show that Δ123 has an altered antigenic structure that accounts for its unique immunogenicity. These studies provide a pathway for the development of a prophylactic vaccine against HCV.

S508 Naveed Gulzar

ELICITING ANTIBODIES TARGETING KEY NEUTRALIZING SITES OF THE MEMBRANE PROXIMAL EXTERNAL REGION OF HIV-1 GP41 USING DNA AND LIPOSOME VACCINES AND ALTERNATIVE IMMUNIZATION STRATEGIES

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Abstract: The induction of neutralizing (Nt) antibody (Ab) responses against the membrane proximal external region of HIV-1 gp41 (MPER), a target of a number of broadly NtAbs, is rarely observed in HIV+ individuals or through MPER-based vaccine strategies. Impediments include our incomplete understanding of the MPER structure, and restricted/transient exposure of key Nt sites. Here, we engineered liposome and DNA vaccines, and compared DNA-prime/liposome-boost and co-immunization strategies in rabbits and guinea pig models in eliciting Abs targeting Nt sites of the MPER. Immunization with a MPER-based DNA vaccine encoding a non-native transmembrane domain (TMD) elicited marginal Ab responses against the MPER in rabbits; boosting with MPER-peptide liposome vaccines (PLVs) moderately increased titres. Serum responses only mapped to the 2F5 region of the MPER and affinity-purified Abs neutralized a Tier 2 HIV-1 envelope, but were not durable and of low titre. Co-immunization with DNA and PLVs improved durability of MPER-specific titers but remained low; stronger anti-MPER responses were observed in guinea pigs, but sera had high background and did not exhibit significant neutralizing activity. To aid 4E10 exposure, we further engineered our MPER DNA vaccine to support a trimeric helical structure and to better expose key Nt sites. Serum responses mapped to both the 2F5 and 4E10 sites of the MPER and were of moderate titres; analysis of the neutralization breadth of the immune sera is currently ongoing. Our results suggest MPER activity and durability are augmented by co-immunization, and the nature of the TMD affects MPER immunogenicity at the 4E10/10E8 site.

S602 Saikat Banerjee

DESIGN AND EVALUATION OF GP41 MPER-BASED VACCINE CANDIDATES AGAINST HIV-1

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Abstract: An effective vaccine against HIV-1 must be able to induce antibodies capable of neutralizing a large number of antigenically distinct viruses from diferent clades. A number of broadly neutralizing antibodies (bnAbs) against gp120 and gp41 have been isolated from virus-infected patients, indicating that it is not impossible to induce such bnAbs. One of the attractive vaccine targets is the membrane-proximal external region (MPER) of gp41, a functionally critical, highly conserved linear epitope that is recognized by bnAbs 4E10 and 10E8. In our attempts to induce similar bnAbs, we have designed and evaluated immunogenic properties of multiple antigens that might represent different stages of fusion intermediates in rabbits. Our findings demonstrate that the immunogenicity of the MPER is strongly influenced by the presence or the absence of neighboring domains. Although we have not yet succeeded in inducing 4E10-/10E8-like antibodies, we have made significant progress towards targeting 4E10/10E8 epitopes. Results from a number of vaccine strategies we have been pursuing will be presented.

S704 Daniel Geraghty

HLA-F AND MHC OPEN CONFORMERS IN A NOVEL HIV-1 IMMUNIZATION STRATEGY

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Abstract: HLA-F is expressed as a protein independent of bound peptide or β2-microglobulin and surface expression is upregulated in dendritic cells, monocytes and most lymphocyte subsets upon activation. Classical MHC class I (MHCI) is also expressed on proliferating lymphoid cells as so-called 'open conformers (OCs)', in addition to the ubiquitously expressed form complexed with peptide and β2-microglobulin. Previous studies showed that HLA-F binds most MHCI proteins as open conformers without peptide but not as peptide bound complex. These studies were extended to show that both HLA-F and MHCI OC are ligands for a specific subset of killer Ig-like receptors (KIRs), defining a new paradigm for MHCI function and communication between the innate and acquired immune responses. The HLA-F/MHCI physical interaction was further implicated in the function of HLA-F and MHCI open conformers in a general mode of exogenous MHCI antigen uptake and antigen presentation by activated immune cells that differs from the canonical MHCI endogenous antigen presentation. A long-term extension is to dissect the HLA-F/MHC-I OC pathway to uncover the requirements for antigens to access the pathway. We are currently testing the hypothesis that antigen entry is governed by a synergy between specific structural characteristics of the exogenous antigen and the MHC-I allele types of target cells. New evidence is presented using HIV-1 p24 gag derived long polypeptides suggesting a requirement for HLA class I peptide epitope specificity in antigen uptake, upstream of antigen presentation, which subsequently can be presented by either or both of MHCI and MHCII. These experiments suggested that the physical proximity of HIV-1 class I and class II peptide epitopes within a p24 polypeptide can govern antigen presentation of epitopes through either MHCI or MHCII or both. A goal is to manipulate these features in designing effective immunogens for directed stimulation of antigen-specific host responses.

S705 John Hsieh

THE STRUCTURE OF NEWCASTLE DISEASE VIRUS FUSION PROTEIN BOUND TO CHICKEN PROTEIN DISULFIDE ISOMERASE A3 SUGGESTS A MOLECULAR TARGET FOR NEW THERAPIES

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Abstract: Newcastle disease (ND) is an avian disease with high impact on animal health and global food security. Newcastle disease virus (NDV) belongs to the family Paramyxoviridae. NDV is a single-stranded, non-segmented, negative sense RNA virus with 6 known genes. Chicken protein disulfide isomerase A3 (PDIA3) was previously reported to be a binding partner for the NDV fusion (F) protein based upon a two-dimensional virus overlay protein binding assay.

In this study, we modeled the chicken PDIA3 protein using sequence homology based on a human PDIA3 protein structure from the protein databank (PDB) with SWISS-MODEL. The model shows sequence identity of 84% and the predicted chicken PDIA3 structure has an RMSD of 0.07Å with the human PDIA3 structure. We proceeded to dock the NDV F protein (pdb:1G5G) with the human PDIA3 protein (pdb:3F8U) using ClusPro2.0. We found that the NDV F protein forms a binding pocket for the PDIA3 thioredoxin 2 domain. This structure implies that a disulfide reaction takes place during the activation of the NDV F protein, and this interaction could serve as a molecular target for drug development.

Future studies involving knockout of PDIA3 and the response to NDV may provide evidence for the importance of PDIA3 in ND. The human PDIA3 structure has been co-crystallized with a tapasin molecule suggesting that the predicted binding structure interacts with the host immune system. Determining whether host variability in response to NDV is associated with PDIA3 or tapasin variants could also contribute to development of other anti-viral strategies.

P001 David Verhoeven

IDENTIFICATION OF IMMUNE FACTORS CONTRIBUTING TO INFLUENZA VACCINE FAILURES IN YOUNG CHILDREN

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Abstract: Influenza vaccination is imperfect as only 40-68% of individuals are protected from infection year to year with children representing a population at higher risk for infection and lower vaccine compliance rates. In the young children, lower quality (neutralizing) antibody responses stem from lower levels of B-cell Ig rearrangements, lower hypersomatic mutation rates, and low CD4 T-cell follicular numbers. In the young children that do receive their influenza vaccines, fewer are protected from trivalent inactivated vaccine (TIV) as compared to live attenuated vaccine (LAIV). To further qualify the limitations to better efficacy rates of TIV in young children aged 6 months to 2 years of age, we examined their adaptive immune responses from years 2009-2011 after vaccination. We found that 10% of this population of children had higher vaccine failure rates that also correlated with increased frequency of recurrent otitis media (ear infections). Further qualification of the adaptive immune responses demonstrated lower CD8 T-cell responses to influenza, lower proliferative CD4 T-cell responses to HA antigen, and lower hemagglutinin inhibition titers despite similar total influenza-specific antibody responses as compared to their peers. Thus, otitis prone children represent a sub-group of children that significantly contribute to the rates of TIV failure in children and a group for which other vaccine strategies might prove more efficacious.

P002 Melissa Herrmann

DIFFERENTIAL RESPONSE OF RESISTANT AND SUSCEPTIBLE CHICKEN LINES TO A NEWCASTLE DISEASE VIRUS VACCINE STRAIN

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Abstract: Newcastle Disease Virus (NDV) threatens poultry health. In developed countries, the disease is managed with live virus vaccines, which are not feasible in undeveloped regions. This study aims to characterize differential responses to the vaccine strain by studying two genetic lines of chickens, Fayoumi and Leghorn, which have been previously demonstrated as relatively resistant and susceptible to NDV, respectively. Chicks were challenged with LaSota NDV or given PBS as a control. Viral RNA was isolated from tears and the viral titer was quantified by qRT-PCR. NDV specific antibody titers were measured by ELISA. At 2dpi, challenged birds of both genetic lines had similar viral titers. At 6dpi, however, the NDV-challenged Fayoumis had significantly less virus than the challenged Leghorns, suggesting that Fayoumis are able to eliminate the virus more quickly. The challenged birds' antibody titer did not differ between genetic lines at 10dpi. RNA sequencing was performed on tracheal epithelial cells. Results showed a large impact of time post-challenge and genetic line on NDV response. GO analysis suggests that cell-mediated immunity is important in NDV response in the tracheal epithelium. The two genetic lines differ in the expression of MHC and antigen processing genes after challenge. This study will identify gene families and pathways associated with response and resistance to NDV, which can aid in control of NDV-induced infection by gaining a better understanding of the host genetic response to the live virus vaccine.

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P003 Andy Poumbourios

SEPARABLE FUNCTIONS FOR THE MEMBRANE PROXIMAL ECTODOMAIN REGION (MPER) OF HIV-1 GP41 IN CELL-FREE VERSUS CELL-TO-CELL VIRAL TRANSMISSION: IMPLICATIONS FOR NEUTRALIZATION

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Abstract: The gp41 transmembrane/membrane fusion glycoprotein of HIV-1 anchors the gp120 receptor-binding glycoprotein to the viral envelope. The ectodomain of gp41 is linked to the membrane-spanning sequence via the MPER, a conserved 22–residue Trp-rich helix that is embedded in the interfacial region of the envelope. The MPER is the only target within gp41 of broadly reactive neutralizing antibodies (bNAbs). Here, we used mutagenesis to examine the importance of the MPER for cell-free and cell-to-cell virus transmission. Whereas cell free viral infection of U87.CD4.CCR5 cells and PBMCs was blocked by W666A and I675A mutations, spreading infection was observed when cultures were initiated with cell-associated virus. The block to cell-free virus infectivity was overcome by mutations in the cytoplasmic domain of gp41 that disrupt interactions between gp41 and the matrix protein. W666A in 2 transmitted/founder (T/F) isolates caused contrasting effects: blockade of cell-free virus infectivity for SC45, whereas infectivity was retained by PRB958-W666A; both strains retained the ability to mediate cell-cell spread with W666A. A chimerization approach revealed that complex determinants within gp120 conferred the disparate W666A phenotypes of SC45 and PRB958. MPER-directed bNAbs such as 2F5, 4E10, and 10E8 neutralized cell-free infection by SC45 and PRB958, however cell-cell viral spread was not neutralized. Our data indicate separable functions for the MPER in cell-free versus cell-associated HIV-1 infectivity that are modulated by the cytoplasmic domain and determinants within gp120. These separable functions appear to be related to the differential sensitivities of cell-free and cell-associated viruses to MPER-directed bNAbs.

P004 Saikat Banerjee

IMMUNOGENIC PROPERTIES OF A TRIMERIC GP41-BASED IMMUNOGEN CONTAINING AN EXPOSED MEMBRANE-PROXIMAL EXTERNAL REGION

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Abstract: The membrane-proximal external region (MPER) of HIV-1 gp41 is an attractive target for vaccine development as it harbors the epitopes for broadly neutralizing antibodies (bnAbs) like 2F5, 4E10, Z13e1 and 10E8. Thus, better understanding of its immunogenic properties in various structural contexts is important. We previously described the crystal structure of a trimeric protein complex named gp41-HR1-54Q, which consists of the heptad repeat regions 1 and 2 (HR1 and HR2) and the MPER. The protein was efficiently recognized by bnAbs. Here, we describe its immunogenic properties in rabbits. The protein was highly immunogenic. Although antibodies exhibited strong competition activity against 4E10 and 10E8, neutralizing activity was not detected. PepScan analyses showed that 671NWFDITNWLW680 was highly immunogenic and critical binding residues were N671, F673, D674, T676 and N677. These residues reside on the face of the alpha helix opposite to the epitopes recognized by 4E10 and 10E8, which explains the lack of neutralizing activity despite recognition of the same peptide. These results provide critical information for designing the next generation of MPER-based immunogens.

P005 Kaylee Rowland

IDENTIFYING HOST GENES AND GENETIC MARKERS FOR ANTIBODY PRODUCTION TO NEWCASTLE DISEASE VIRUS (NDV) VACCINE STRAIN IN COMMERCIAL LAYER CHICKENS

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Abstract: Identifying birds with genetic variants for enhanced antibody response to NDV vaccination may improve vaccine efficacy and increase security of the food supply in underdeveloped regions where the virus is endemic. Birds of a commercial egg-laying line, Hy-Line Brown, were inoculated with the B1 type, LaSota strain, live virus, NDV vaccine to provide a wide range of disease phenotypes in the experimental population. The experiment was replicated across three hatches from the same set of 150 dams. In total, control N=60; challenge N=540. Birds were inoculated with NDV, La Sota strain, on day 21 in both nares and ocular conjunctiva. Body weights were recorded, and blood and tears were collected throughout the study. Analyses of viral RNA and antibody levels confirmed response of challenge groups and lack of response in control groups. Dams, which had been vaccinated, had a significant ($p<0.0001$) effect on maternal antibody levels in the chicks (pre-infection). However, maternal antibody levels in chicks did not differ with time post-vaccination of the dams. Genomic DNA was genotyped on the Affymetrix 600k chicken SNP array and MHC haplotypes were determined. Genome-wide association study will be performed using GenSel to determine associations between single-nucleotide polymorphisms (SNPs) and NDV antibody levels. ASREML will be used to measure heritabilities and genetic correlations. This study will identify host genes and genomic regions controlling response to NDV vaccine strain virus and will also characterize correlations between vaccine response and production traits such as growth, thus enabling sustainable genetic improvement in NDV response in chickens.

P006 Marisa Banasik

IDENTIFICATION OF A REGION IN THE N-TERMINUS OF HIV-1 GP41 THAT CONFERS RESISTANCE TO MPER BROADLY NEUTRALIZING ANTIBODIES

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Abstract: HIV-1 affects over 34 million people worldwide. Although there is no vaccine, some patients develop broadly neutralizing antibodies (bnAbs) after years of infection. However, these antibodies are unable to neutralizing all HIV-1 strains. Understanding the mechanisms behind neutralization resistance is crucial for creating an effective vaccine. Differences in the exposed envelope glycoprotein may explain why certain strains are neutralization sensitive while others, particularly those circulating in patients, are resistant. By understanding how regions external to the bnAb epitope prevents these antibodies from binding, we may be able to produce improved immunogens to guide the immune system to overcome resistance-inducing changes.

We focused our efforts on determining factors that prevented bnAb binding to the highly conserved membrane proximal external region (MPER) of the envelope glycoprotein gp41 subunit. We generated several chimeric viruses merging portions of a representative neutralization sensitive env (MN.3, Clade B, Tier 1A) and neutralization resistant env (6535.3, Clade B, Tier 1B). Through this work, we have identified that an N-terminal region in gp41, stretching from the furin cleavage site to the heptad 2 repeat, affects the sensitivity or resistance to several MPER bnAbs (2F5, 4e10, 10e8). Furthermore, we have identified that there are at least two amino acid differences acting in concert to exert this affect. While the exact differences involved have not been identified, analysis of the recent BG505 SOSIP gp140 structure has identified candidate residues that may be involved. Further work will focus on generating envs with these specific changes and analyzing their sensitivity to neutralization.

P007 Jessica Hargarten

A FUNGAL QUORUM SENSING MOLECULE ACTS AS AN ADJUVANT TO PROMOTE INNATE INFLAMMATORY RESPONSES AND ANTI-INFLUENZA A VIRUS ANTIBODIES

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Abstract: The mechanisms through which adjuvants act to enhance anti-viral immune responses are not well understood, but are critical for the development of effective universal vaccines that offer long-term cross protection against diverse viral strains, including Influenza A virus (IAV). Historically, fungal- and bacterial-produced small molecules have been successfully used as vaccine adjuvants to stimulate protective immune responses. In ongoing experiments, we have found that the fungal-secreted molecule, farnesol, may act as an adjuvant by promoting innate inflammatory responses to IAV infection. Following intraperitoneal (ip) injection, farnesol stimulates the recruitment of temporally distinct innate immune cells to the peritoneum of mice. Kinetic analysis of the transcriptional profile of these migratory cells from farnesol treated mice reveal an increase in chemokines consistent with macrophage recruitment and activation. Additionally, macrophages and dendritic cells entering the peritoneal cavity in response to farnesol demonstrate hallmarks of innate immune activation through higher surface expression of class II and co-stimulatory molecules compared to thioglycollate, suggesting farnesol may prime antigen presenting cells for T cell activation. Following ip vaccination with inactivated IAV, farnesol induces high titer anti-ovalbumin and anti-IAV antibody responses similar to the known adjuvant, AddaVax, and greater than UV inactivated virus alone. Defining the immunostimulatory properties of farnesol, will improve strategies for vaccine design that promote both cell mediated and humoral immunity against a variety of infectious diseases.

P008 Jie-yeun Park

COMPARISON OF ANTIGEN DELIVERY PLATFORMS TO REINFORCE EFFICACY OF UNIVERSAL H5N1 INFLUENZA VACCINE

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Abstract: While the development of an effective influenza vaccine antigen for the highly pathogenic and potentially pandemic H5N1 influenza virus is important, the development of appropriate vaccine delivery platforms is also necessary to elicit proper and efficacious immune responses targeting the various subtypes. Previously, Du et al. demonstrated the efficacy of a H5N1 HA1-Fc vaccine antigen in the presence of sigma adjuvant system (SAS). In this study, to find a better delivery regimen to improve the efficacy of the vaccine, we analyzed additional delivery platforms in mice, such as gold nanoparticles (GNP) and Zinc-Chitosan (ZCH). Mice immunized with HA1-Fc formulated with GNP or ZCH could elicit a sufficiently high titer of of antigen-specific immune responses as compared to antigen alone. However, GNP showed lesser immune stimulatory efficacy and no clade-cross neutralizing activity as compared to ZCH. Unlike GNP, HA1-Fc/ZCH induced the strongest immune responses among the comparison groups and elicited clade-cross neutralization. The immunogenic properties of the antibodies induced by HA1-Fc/ZCH were similar to what was observed previously with HA1-Fc/SAS. Of the three delivery platforms, the original SAS was the most effective adjuvant system in mouse, but it is not permitted for human applications. However, ZCH could be approved for clinical applications because both Zinc and Chitosan are not harmful substances to human. Therefore, this new vaccine formula, HA1-Fc/ZCH, can be a potent candidate for a universal H5N1 influenza vaccine.

P009 Hojin Moon

ISOLATION AND CHARACTERIZATION OF NOVEL MONOCLONAL ANTIBODIES THAT RECOGNIZE THE GP41 MPER DOMAIN OF HIV-1

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Abstract: Generation of broad neutralizing antibodies (bnAbs) is a key feature for designing an effective vaccine against HIV-1. The gp41 envelope protein harbors a ~ 22 amino acid long, linear domain called the membrane proximal external region (MPER), that is targeted by multiple bnAbs- 2F5, 4E10, Z13e1 an 10E8, all of which are isolated from infected patients. Attempts to elicit similar bnAbs in animals through immunization have largely failed. However, it is critical to study such antibody response at a monoclonal level because it can provide valuable insights for future vaccine design. In one such study, we have characterized the antibody response in a rabbit immunized with multiple gp41-based immunogens. We describe the isolation of two novel monoclonal antibodies (mAbs)- 21B5 and 9F6 that bind the C terminus end of MPER also recognized by 4E10 and 10E8 bnAbs. We further performed a fine epitope mapping for both antibodies. Our results show that 21B5 recognizes a slightly different face of the same peptide bound by 4E10 and 10E8. Interestingly, 9F6 recognizes several of the residues critical for 4E10 and 10E8 binding. Future neutralization assays and structural characterization with whole antibodies and Fab fragments will reveal important differences between these mAbs and bnAbs. To our knowledge, this is the first report to isolate and characterize monoclonal antibodies that share binding epitopes with 4E10 and 10E8 bnAbs.

P010 Kari Rohl

DESIGN AND EVALUATION OF GENE GUN BASED DNA IMMUNIZATION

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Abstract: HIV-1 is a global pandemic, and this virus possesses a highly variable sequence. Thus far, the search for a vaccine that induces broadly neutralizing antibodies (bnAbs) capable of targeting multiple HIV-1 strains has been unsuccessful. Based on previous research elsewhere, we decided to immunize mice with a diverse group of HIV-1 env genes that are a representative sample of the global epidemic. We hypothesized that even though this strategy may not elicit true bnAbs, it could lead to the generation of type-specific neutralizing Abs that cover many different clades of HIV-1, therefore protecting the host against infection. Mice were immunized with 12 different virus envelopes from several different clades representing the potential breath of infection. Immunizations were performed with submixtures of envelope DNA using particle mediated epidermal delivery (PMED, gene gun). There were four immunizations using DNA, followed by two protein boosts with gp140. Results to date indicate that after the fourth DNA immunization, antigen specific antibody titers reached 1x10^4. The mouse serum did not result in any neutralizing activity against highly sensitive tier 1 viruses (five tested). The second protein boost (sixth immunization) resulted in antibody titers of >1x10^5.

P011 Hongzhao Li

NATURAL ANTIBODIES TO SIV ANTIGENS IN MAURITIAN CYNOMOLGUS MACAQUES

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Abstract: Cynomolgus macaques are an increasingly used non-human primate (NHP) model in biomedical research including HIV vaccine development. However, natural immunity to SIV or related retroviruses pre-existing in these animals, as described in this report, needs to be taken into consideration in vaccine projects, including animal selection, experimental design and result interpretation. In this study, we screened 108 female Mauritian Cynomolgus macaques (14 capture bred and 94 colony bred) for natural antibodies to SIV antigens using a Bio-Plex multiplex system. The SIV antigens included twelve 20mer peptides overlapping the twelve protease cleavage sites (-10/+10), respectively (PCS peptides), and three non-PCS Gag or Env peptides, derived from SIVmac239 and conserved among multiple SIV strains. The screening revealed various levels of natural antibodies to these SIV antigens with a subset of monkeys showing extremely high antibody levels to some of the peptides, although the monkeys were not infected by SIV or other known retroviruses. Interestingly, vaccination of monkeys with rVSV-PCS peptides induced antibody responses to all three non-PCS peptides, despite that these two peptide groups share no sequence homology. Possibly the PCS vaccination activated the expression of dormant proviral genes of SIV-like retrovirus(es) and subsequent host immune responses to the resulting viral antigens. Our observations are consistent with the recent findings in human that HIV infection triggers the expression of several classes of human endogenous retroviral genes. We speculate that activation of dormant SIV-like proviruses in Cynomolgus macaques by yet-to-be-identified stimuli may be a potential cause of the natural antibodies.

P012 Promisree Choudhury

STRATEGIES FOR HIGH-LEVEL ANTIGENIC PROTEIN EXPRESSION FROM A MAMMALIAN ORTHOREOVIRUS VECTOR

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Abstract: Discovering innovative strategies to deliver foreign genetic material into target cells is a key step towards vaccine development and viral vectors have been shown to be effective for this purpose. Mammalian orthoreoviruses (MRV) are non-enveloped, dsRNA viruses with a segmented genome that bind Microfold (M) cells of the respiratory and gastrointestinal mucosa, making this virus a potential candidate to be used as an effective gene delivery vehicle to trigger a robust mucosal immune response. However, in order to utilize MRV as a mucosal gene delivery vector, it is essential to understand how these viruses package their genetic information, as well as devising methods for MRV-derived expression of foreign genetic material in target cells. We have recently developed strategies to manipulate the MRV genome that enable the virus to incorporate exogenous genetic material into the virion while maintaining replication competence. The presented work is focused on utilizing these strategies to test methods for driving high-level expression of antigenic protein to create first generation gene delivery vectors. Each approach appropriates existing cellular protein expression strategies from which two proteins are produced from a single mRNA. We have created MRV gene segments that are modified such that the MRV protein and a second protein are expressed from internal ribosome entry sites (IRES), or termination-reinitiation stop/start strategies. We have demonstrated dual protein expression from the modified gene segments in transfected cells. Current and future studies include extending these studies to additional gene segments and exploring additional dual protein expression strategies.

P013 Aditi Agrawal

FOCUSING THE IMMUNE RESPONSE TOWARDS CRITICAL NEUTRALIZING EPITOPES ON HIV-1 THROUGH IMMUNE COMPLEX VACCINATION IN RABBITS

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Abstract: There have been many attempts at designing HIV-1 vaccines based on subunit protein immunogens using gp120 for eliciting broad and potent neutralizing antibodies. Unfortunately, immunization with subunit protein antigens alone has resulted in low antibody titers displaying limited neutralization breadth and potency due to the targeting of type-specific neutralizing epitopes (e.g. V3 loop). In light of this information, vaccination using immune complexes has particularly drawn attention due to its known capacity to reduce immune system access to less desired epitopes and to augment the host immune response. Augmentation of host immune response by immune complexes has been mainly attributed to the interaction of antibody and antigen mediated via Fc receptors. Other groups have used immune complex vaccination to direct antibody response towards some neutralizing epitopes on gp120. We propose that blocking both non-neutralizing and lesser neutralizing epitopes may increase response towards the more highly desired broadly neutralizing epitopes (e.g. CD4 binding site). Four rabbits were immunized with immune complexes made of gp120 and recently reported anti-V3 loop mAb 10A37. We are hoping to induce high antibody titers while simultaneously suppressing V3 loop specific antibodies. In the near future, antibody responses will be evaluated for antigen-specific antibody titer, linear epitope mapping and neutralization ability.

P014 Wenjin Fan

ADAPTIVE IMMUNE RESPONSES ELICITED BY RV144-LIKE VACCINATION IN HUMANIZED BLT MICE

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Abstract: A safe and effective HIV-1 vaccine is urgently needed to curtail HIV-1 pandemic, however its development had been disappointing prior to RV144 Thai HIV-1 vaccine trial, which revealed a 31.2% efficacy against HIV-1 acquisition. To date, the protective immune responses to this vaccine were only studied in peripheral blood samples, but not in lymphatic and mucosal tissues. Therefore, the current understanding of protective mechanism of this vaccine remains limited. To evaluate the utility of humanized-BLT (Hu-BLT) mice in vaccine study, seven Hu-BLT mice were primed with vCP2427 4 times and boosted with gp120 at 2-week intervals. The immunized mice were sacrificed between 4 and 12 weeks following last immunization. To study adaptive immune responses in HIV-1 natural infection, Hu-BLT mice were inoculated with HIV-1 (SUMA.c/2821) and sacrificed at 8, 12, and 16 weeks post infection for analysis. We found RV144-like vaccine elicited lower HIV-1 specific CD4 and CD8 T cells responses as compared with HIV-1 infection using intracellular cytokine staining (ICCS) assay. RV144-like vaccine elicited only gp41 antibody, but not other virus-specific antibodies including gp120 antibody assessed using western blot. In contrast, HIV-1 infection induced multiple HIV-1 specific antibodies, such as gp160, p55, p40, and p24, but emerged late at 8 weeks post infection. We conclude Hu-BLT mice cannot fully recapitulate human immune response upon vaccination yet.

P015 Heliang Shi

IMMUNOLOGICAL CHARACTERIZATION OF GP41 MUTANTS MIMICKING THE PREHAIRPIN FUSION INTERMEDIATE FORM OF HIV-1

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Abstract: The envelope glycoproteins of HIV-1, comprised of gp120 and gp41, are the major targets of the humoral immune response. Of the two subunits, gp41 is more highly conserved and contains the epitopes of four broadly neutralizing antibodies (bNAbs) in the relatively small membrane proximal external region (MPER). However, eliciting bNAbs towards gp41 remains an elusive goal. During infection, gp41 undergoes extensive conformational changes that ultimately form a six helix bundle that mediates fusion of virus and cellular membranes. As all gp41 crystal structures represent this post fusion conformation, antibodies elicited towards these structures may not halt infection. Several groups have suggested the generation of a gp41 prefusion or fusion intermediate form would be a better vaccine candidate.

Our previous work detailed a stable, post fusion gp41 structure. We introduced various amino acid mutations and deletions to disrupt interactions between domains responsible for the six helix bundle formation. We demonstrated that these putative fusion intermediate mutants are structurally distinct from the post fusion construct. They are also recognized by MPER bNAbs indicating that they are antigenically intact. Four candidates were chosen for immunological studies in rabbits. We observed strong humoral responses against these mutants. Linear epitope mapping revealed that antibodies target significantly different regions from those raised against the post fusion form. No neutralization activity was detected. As antigens representing fusion intermediates were not sufficient for eliciting bNAbs against HIV-1 gp41, future studies could focus on developing antigens representing a more stable prefusion conformation as seen on the native virus.

P016 Rajeendra Pemathilaka

UTILIZING ORGAN-ON-CHIP METHOD TO BUILD A DRUG TESTING MODEL ON HUMAN PLACENTA

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Abstract: An Organ-on a-chip technology is becoming a popular method for drug testing. Microfluidic Organ-on-a-chip eliminates the need of live objects like animals to do drug testing. Although the Organ-on-a-chip devices are becoming popular, creating a microfluidic device to represent human placenta is more challenging than other organs. Current drug testing methods are considered unethical and unreliable due to drug testing on animals and cost. Human placenta is a temporary organ that creates during pregnancy to connect fetus and mother to allow nutrient supply, gas exchange, waste elimination and avoid internal infections. Researches wanted to study how the two-way traffic reacts when it's blocking by bacteria/viruses, while it transfers the nutrient/ oxygen, since the lack of transportation can effects the health of mother and fetus. When animal organs are used for testing on the human placenta, inconsistent results have been found due to the differences among species in placental permeability, transport activity, blood flow patterns, and even metabolic activities. Our "Placenta-on-a-chip" device is designed to represent a working placenta organ using human cells in order to mimic the nutrient/waste transfer between the maternal blood and fetal blood that occurs in the cotyledon section of the placenta. HUVEC cells (endothelial) and BeWo cells (trophoblast) are used to represent the placental barrier with a gelatin coated collagen membrane. Objective here is to analyze the glucose transport between the endothelial-trophoblast barrier through the membrane. In the future, researchers will have the opportunity to use the placenta-on-a-chip model for additional research in drug testing.

P017 Wenlan Alex Chen

APPLICATION OF αGAL HYPERACUTE TECHNOLOGY TO VIRAL VACCINES

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Abstract: The αGal HyperAcute® Technology exploits a robust zoonotic blockade to enhance potency of vaccines. Due to strong, pre-existing immunity against the αGal epitope (galactose-alpha(1,3)-galactose-beta(1,4)-N-acetylglucosamine) in humans, any viral vaccine presenting this epitope is immediately recognized as foreign, leading to induction of naturally-acquired αGal immune pathway in humans and activation of strong protection against virus infection. Based on this theory, we introduced αGal epitopes to vaccine candidates against multiple viruses, including seasonal and pandemic influenza viruses. These vaccine candidates were produced in the forms of virus-like particle (VLP) and recombinant protein, and modified with αGal epitopes by either biological or chemical means. Animal experiments were performed in the α(1,3)-galactosyltransferase (αGT) knockout mice that were primed with abundant αGal. Our studies repeatedly showed that addition of the αGal epitope to viral vaccine candidates against different types of viruses significantly increased their immunogenicity at doses that were at least 10 times lower than other studies used, without addition of any adjuvants. Our data successfully demonstrated that αGal-modification of vaccines against infectious diseases lead to highly effective immunization, and strongly support the potentially broad application of αGal HyperAcute technology for vaccines against viral infections.

P018 Jeremy Caplin

INVESTIGATION OF ENDOTHELIAL AND EPITHELIAL CELL LINES CONCERNING A 3D MICROFLUIDIC DRUG TESTING MODEL FOR THE PLACENTA

Jeremy Caplin[1], Rajeendra Pemathilaka[1], Marta Sucur[1], Norma Granados[1], Catherine Meis[1], Lindsey Matheney[2], Nastaran Hashemi[1]
[1]Iowa State University; [2]University of California, Riverside

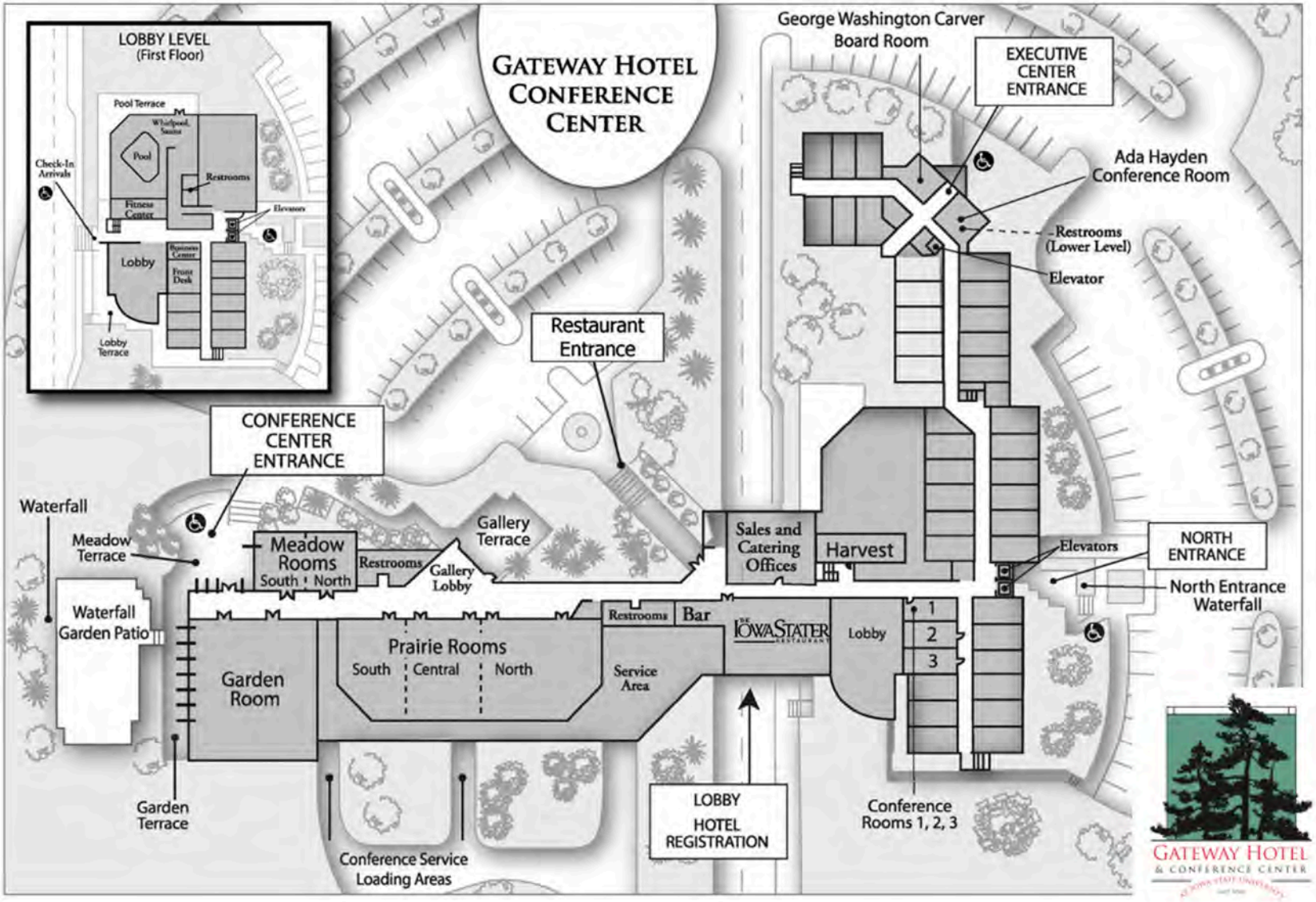
Abstract: Currently, the technology surrounding replicating organ functions on a microfluidic chip, or "organ-on-a-chip" devices, has seen a vast increase in popularity, as the understanding of utilizing the properties of microfluidics has become more prevalent. Additionally, they are cost effective, use minimal product to create, and dodge the ethical dilemma of using in vivo animal models. While organ-on-a-chip designs are becoming the future of drug testing, functional designs for a 'placenta-on-a-chip' are few and far between. Using microfluidic technology to produce in vitro results that can replicate drug administration for patients involved in complications during pregnancy is an important next step. In fact, the ethics involving in vivo patients in pregnancy are even more convoluted, and as a result, we must rely on these other methods. This chip will consist of two PMMA layers containing a channel network designed to mimic both the maternal bloodstream and the fetal bloodstream. To better replicate placental functions, a membrane is positioned between the layers to represent the boundary between these two streams, with syncytiotrophoblast cells grown on the maternal side and vascular endothelial cells grown on the fetal side. In this project, proper cell lines to represent the endothelial and epithelial layers of the placenta are investigated to replicate the surface functions on both the endothelial and epithelial layers of the cotyledon. The final result will be a working "placenta-on-a-chip" capable of representing in vivo situations involving drug reactions occurring in the placenta.

P019 Weidong Xu

MX1 IS OVEREXPRESSED IN ACTIVATED HIV-1-SPECIFIC CD8+ T CELLS

Elsa Obando, Feng Jiao, Weidong Xu

Abstract: The Mx proteins are key components of the antiviral protein family induced by interferons in many species. They inhibit several different viruses by blocking early steps of the viral replication cycle. Human Mx1 provides a safeguard against introduction of avian influenza A viruses into the human population. The related human Mx2 is a restriction factor for HIV-1 and other lentiviruses. Using microarray, we found Mx1 was significantly upregulated in activated HLA-B*57-restricted HIV-specific CD8+ T cells as compared to their non-B*57-counterparts. Overexpression of Mx1 in activated HIV-specific CD8+ T cells were confirmed by real time quantitative PCR. Our finding indicates that Mx1 may also have anti-HIV function through regulating the cytolytic activities of CD8+ T cells.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CENTER
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Pool Terrace
Whirlpool, Sauna
Pool
Restrooms
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Restrooms
(Lower Level)
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