Immunotherapy for Infectious Diseases Conference

November 12-14, 2018
Hotel Galvez, Galveston, TX, USA
### Agenda

**NOVEMBER 12, 2018**

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<th>Time</th>
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<tr>
<td>7:30–8:30 AM</td>
<td><strong>Registration and Breakfast</strong>—Room: West Promenade</td>
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<tr>
<td>8:15–8:30 AM</td>
<td><strong>Welcome Remarks</strong></td>
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<td></td>
<td>Magnus Hook and Zhiqiang An</td>
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<td></td>
<td><strong>SESSION 1</strong> ANTIBODY BASED DRUG DEVELOPMENT—Room: Music Hall</td>
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<td>Moderator: Livia Visai</td>
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<td>8:30–9:20 AM</td>
<td><strong>Therapeutic Antibodies: Past, Present and Future</strong></td>
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<td><strong>Keynote Speaker:</strong> John McCafferty, Iontas Ltd.</td>
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<td>9:20–9:55 AM</td>
<td><strong>Antibody Phage Display: Generating Antibodies for Diagnostic</strong></td>
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<td>and Treatment of Infectious Diseases</td>
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<td>Michael Hust, Institute for Biochemistry, Biotechnology and Bioinformatics</td>
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<td>9:55–10:30 AM</td>
<td><strong>Antibody Engineering: Humanization, Affinity Maturation and Selection Techniques</strong></td>
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<td>Zhiqiang An, University of Texas Health Science Center</td>
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<td>10:30–10:50 AM</td>
<td><strong>Break</strong>—Room: West Promenade</td>
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<td>10:50–11:25 AM</td>
<td><strong>Immunobiology and Pathogenesis of Severe Scrub Typhus: Implications in Treatment</strong></td>
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<td>Lynn Soong, The University of Texas Medical Branch</td>
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<td>11:25 AM–12:00 PM</td>
<td><strong>Regulatory Considerations in Development of Biologic Products</strong></td>
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<td>Sumathi Nambiar, U.S. Food Drug and Administration</td>
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<td>12:00–2:00 PM</td>
<td><strong>Lunch</strong>—Room: West Promenade</td>
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<td><strong>Poster Session</strong>—Room: Music Hall</td>
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<td><strong>SESSION 2</strong> IMMUNOTHERAPY AGAINST VIRAL INFECTIONS—Room: Music Hall</td>
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<td>Moderator: Zhiqiang An</td>
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<td>2:00–2:35 PM</td>
<td><strong>A Replication Defective Human Cytomegalovirus as a Vaccine to Prevent</strong></td>
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<td>Congenital Infection and Disease</td>
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<td>Tong-Ming Fu, Merck</td>
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<td>2:35–3:10 PM</td>
<td><strong>Vaccine-like Effects of Antiviral Monoclonal Antibodies: Converting Immune Therapies from Passive to Active</strong></td>
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<td>Mireia Pelegrin, Institut de Génétique Moléculaire de Montpellier</td>
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<td>3:10–3:45 PM</td>
<td><strong>T-cell Therapy for Viruses</strong></td>
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<td>Ann Leen, Texas Children's Hospital</td>
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<td>3:45–4:15 PM</td>
<td><strong>Break</strong>—Room: West Promenade</td>
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<td>4:15–4:50 PM</td>
<td><strong>mAb Monotherapy Against Ebola Infection: Structure and Molecular Basis of Potent Protection</strong></td>
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<td>Anna Honko, National Institutes of Health</td>
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<td>6:00–7:00 PM</td>
<td><strong>Reception</strong>—Room: West Promenade</td>
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<td>7:30 PM</td>
<td><strong>Dinner</strong>—Room: West Promenade</td>
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NOVEMBER 13, 2018

7:30–8:30 AM  Breakfast—Room: West Promenade

SESSION 3  IMMUNOTHERAPY AGAINST EMERGING AND NEGLECTED INFECTIOUS DISEASE
   —Room: Music Hall
   Moderator: Michael Hust

8:30–9:20 AM  The Assent Of mAbs Therapies Against Infectious Diseases
   Keynote Speaker: Gary Kobinger, Université Laval

9:20–9:55 AM  Protective Antibodies Against Zika and Their Molecular Determinants
   Qihui Wang, Chinese Academy of Sciences

9:55–10:30 AM  Structure Based Antibody Engineering, Bispecifics Against Infectious Diseases
   Luca Varani, Institute for Research in Biomedicine

10:30–10:50 AM  Break—Room: West Promenade

10:50–11:25 AM  The Promise of RNA Vaccines Against Tropical and Emerging Infectious Diseases
   Jeroen Pollet, Baylor College of Medicine

SESSION 4  IMMUNOTHERAPY AGAINST BACTERIAL INFECTIONS—Room: Music Hall
   Moderator: David Walker

11:25 AM–12:00 PM  Synthetic Nucleic Acid Technology for Prevention and Therapy of Infectious Diseases
   David Weiner, The Wistar Institute

12:00–1:30 PM  Lunch—Room: West Promenade

1:30–2:05 PM  Antibody-antibiotic Conjugate: Mechanism and Modulation of Activity
   Wouter Hazenbos, Genentech

2:05–2:40 PM  Bispecific Antibacterial Antibodies: A Tale of Two Molecules
   Bret Sellman, Medimmune

2:40–3:15 PM  Synthetic Agents that Remodel Bacterial Cell Surface for Antibody Recruitment
   Marcos Pires, Lehigh University

3:15–3:50 PM  Break—Room: West Promenade

3:50–4:25 PM  Development Of Antibodies For Biodefense: The Example Of Anti-Botulinum Neurotoxins Antibodies
   Arnaud Avril, Institute of Biomedical Research of the Armed Forces

4:25–4:55 PM  Panel Discussion: Challenges of Immunotherapy for Infectious Diseases
   Lead: Steve Projan, Anti-infective Drug Discovery and Development Consultant
   Panel: Steve Projan, Mark Benedyk, Burton Dickey

6:30 PM  Dinner—Room: West Promenade
7:30–8:30 AM  Breakfast—Room: West Promenade

SESSION 5  EMERGING NOVEL THERAPEUTICS SHOWCASE—Room: Music Hall
Moderator: Tong-Ming Fu

8:30–9:05 AM  Repurposing FDA-Approved Drugs To Sensitize MDR Pathogens to Innate Immune Clearance
Victor Nizet, University of California

9:05–9:40 AM  Inducible Innate Airway Epithelial Resistance to Infection
Burton Dickey, The University of Texas MD Anderson Cancer Center

SESSION 6  SELECTED POSTER TALKS—Room: Music Hall
Moderator: Magnus Hook

9:40–10:00 AM  Speaker 1

10:00–10:20 AM  Speaker 2

10:20–10:35 AM  Break—Room: West Promenade

10:35–10:55 AM  Speaker 3

SESSION 6  CURRENT STATUS OF IMMUNOTHERAPY AGAINST INFECTIOUS DISEASES—Room: Music Hall
Moderator: Magnus Hook

Keynote Speaker: Janice Reichert, The Antibody Society

NOVEMBER 14, 2018
ZHIQIANG AN, PHD
Professor of Molecular Medicine,
The Robert A. Welch Distinguished University Chair in Chemistry
Director of the Texas Therapeutics Institute (TTI)
Brown Foundation Institute of Molecular Medicine,
University of Texas Health Science Center, USA

Dr. Zhiqiang An is Professor of Molecular Medicine, the Robert A. Welch Distinguished University Chair in Chemistry, and Director of the Texas Therapeutics Institute at the University of Texas Health Science Center at Houston. His laboratory focuses on cancer antibody drug resistance mechanisms, biomarkers for cancer therapeutic antibodies, and antibody drug discovery targeting cancer and infectious diseases. He also directs the Therapeutic Monoclonal Antibody Lead Optimization and Development Core Facility funded by the Cancer Prevention and Research Institute of Texas (CPRIT). Previously, Dr. An served as Chief Scientific Officer at Epitomics, Inc. and was Director of Biologics Research at Merck Research Laboratories. He is a fellow of Society for Industrial Microbiology and Biotechnology and a fellow of the American Academy Microbiology. Dr. An is well published in the field of antibody drug discovery including the award-winning book “Therapeutic Monoclonal Antibodies: from Bench to Clinic”. He started his biotech career at Millennium Pharmaceuticals after receiving his PhD degree from the University of Kentucky and his postdoctoral training at the University of Wisconsin-Madison.

ARNAUD AVRIL, PHD
Project Manager in Biotechnologies-Immunology
Department on Infectious Diseases
Anti-Infective Biotherapies and Immunity Unit
French Armed Forces Biomedical Research Institute, France

Dr. Arnaud Avril works as a project manager for the French ministry of defense. He has a PhD in biotechnology applied to antibodies from the Grenoble University. He works in the department “immunity and biotherapies for infectious diseases”, which developed prophylaxis, therapy, detection and diagnostic tools. He is the head of a team specialized in the research, development and engineering of recombinant antibodies against rare diseases for biodefense. He contributed to the development of several antibodies neutralizing botulinum neurotoxins, anthrax, ricin and orthopoxvirus. He also contributed to the development of immuno-diagnostic assays for the rapid, convenient and cheap detection of biological agents, for armed forces, first responders and medical staff. He is a member of the board for the clinical development of an antibody neutralizing anthrax.

BURTON F. DICKEY, MD
Professor and Chair, Department of Pulmonary Medicine, Division of Internal Medicine,
The University of Texas M. D. Anderson Cancer Center, USA
Adjunct Professor, Escuela de Medicina, Tecnologico de Monterrey, Mexico
Adjunct Faculty, The University of Texas Graduate School of Biomedical Sciences, USA
Adjunct Professor, Center for Infectious and Inflammatory Diseases, Institute of Biosciences and Technology, Texas A&M Health Science Center, USA
Cofounder, Pulmotect, Inc.

Dr. Dickey is a Professor and Chair of the Department of Pulmonary Medicine at the University of Texas MD Anderson Cancer Center. He has studied vesicle traffic since fellowship training more than thirty years ago, and for the past eighteen years his principal focus has been airway mucin secretion. His laboratory uses a mouse genetic approach, knocking out or overexpressing genes in airway secretory cells to study their function. This approach also allows the use of these genetically modified mice in models of pathologic challenge. Together, this provides fundamental insight into the mechanism of mucin secretion and how its dysregulation contributes to pathophysiology. He has also contributed to related work on inducible epithelial resistance to infection, promotion of lung carcinogenesis by inflammation, and modulation of inflammation by β2-agonists. As a clinician, Dr. Dickey focuses on diseases of the airways to promote the transfer of knowledge between laboratory and clinic. He has founded two biotechnology companies, Pulmotect and Exotect, to develop therapeutics to treat respiratory infections and muco-obstructive lung diseases, respectively.
TONG-MING FU, PHD  
Senior Investigator, Merck, USA

Dr. Tong-Ming Fu obtained his medical doctor degree at Peking University Health Science Center, formerly Beijing Medical University, in China, and PhD at Pennsylvania State University, Hershey Medical Center. He is a member of the council of 100 of VACCINE editorial board, and an editorial member of npj Vaccines. He has co-authored more than 90 manuscripts in vaccine research.

During his 20 plus years at Merck, he initially worked on understanding antigen processing and presentation mechanisms following DNA vaccination, and viral vector or DNA vaccine modalities for eliciting T-cell responses as novel vaccines for targets such as pandemic flu and HIV-1. He established Merck internal capacity for quantitatively measuring T cell responses in humans and nonhuman primates which ultimately led to a Phase 2 evaluation of Merck Ad5 HIV-1 vaccines (the STEP study). He later worked on protection mechanisms for Merck influenza M2 peptide conjugate vaccines, and also initiated an internal mAb discovery program to develop PD-1 blockade antibodies for chronic viral infection and diseases. He started Merck CMV vaccine program in 2006 and led discovery and early clinical development of a novel candidate V160, which is currently in Phase 2 evaluation for prevention of CMV acquisition in women.

WOUTER HAZENBOS, PHD  
Scientist, Department of Infectious Diseases, Genentech, USA

Wouter Hazenbos started his scientific career by studying interactions between bacteria and phagocytes, leading to a PhD at Leiden University (The Netherlands). Subsequently he specialized further in the field of immunology and inflammation as postdoc and later as immunologist at UCSF.

In 2007, he joined Genentech, which was a good opportunity to perform translational research in the field of infectious diseases. At Genentech, he has primarily been focusing on the biology of Staphylococcus aureus, including in vivo gene regulation and antibiotic resistance mechanisms.

Recently, he has been performing research on the antibody-antibiotic conjugate (AAC). His combined experience in infection and immunity provides a good match to this work. The AAC is a relatively new approach in the treatment of infectious diseases. While it was initially developed against S. aureus, this platform has potential applications to other organisms. The AAC concept will be the topic of his talk.

ANNA HONKO, PHD  
Staff Scientist, Vaccine Research Center, NIAID, National Institutes of Health, USA  
Scientific Advisor, Medical Science and Computing, LLC, USA

Anna Honko received her doctorate in Microbiology and Immunology in 2005 from Wake Forest University School of Medicine, developing vaccine adjuvants for Yersinia pestis.

She continued her biodefense career at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), where she directed a program focused on development of animal models for viral hemorrhagic fever pathogenesis, as well as the evaluation of potential vaccines and therapeutics in these models. These biocontainment level 4 (BSL4) agents include Ebola and Marburg viruses, Lassa fever virus, Junin virus, Machupo virus, and Nipah virus. Subsequently, as a staff scientist at NIAID's Integrated Research Facility, Dr. Honko was the lead scientist for usage of radiotelemetry in animal models of high consequence pathogens and was responsible for establishing the standardized virus materials and nonhuman primate challenge model systems.

Dr. Honko has recently joined the Biodefense Research Section of the NIAID Vaccine Research Center, a team she'd collaborated with during her tenue as an investigator at USAMRIID. In addition to success with Ebola and Marburg vaccine development, the laboratory has recently discovered and characterized a human-derived monoclonal antibody for Ebola virus disease that is currently undergoing clinical trials.
MICHAEL HUST, PHD
Professor, Department of Biotechnology
Institute for Biochemistry, Biotechnology and Bioinformatics
Technische Universität Braunschweig, Germany

Michael studied biology at the Carl von Ossietzky Universität in Oldenburg, Germany, from 1993-1999. He received his PhD from the Leibniz Universität in Hannover, Germany, in 2002. Since end of 2002 he is working as group leader at the Technische Universität Braunschweig, Germany. In 2011, he finished his professorial dissertation (Habilitation, venia legendi for Biotechnology) and was appointed as Privatdozent (PD). In 2014 he was appointed as professor for biotechnology.

He published more than 120 articles and filed five patents in the field of antibody engineering and phage display. He is working on the development of human and human-like antibodies for proteome research, diagnostics and therapy with a focus on pathogens and toxins. Another field of work is the identification of biomarkers of pathogens using ORFeome phage display. He co-founded two biotech companies, the mAb-Factory GmbH in 2007 and the YUMAB GmbH (www.yumab.com) in 2012.

GARY KOBINGER, PHD
Professor and Director, Infectious Disease Research Centre at the Université Laval, Canada
Associate professor, University of Manitoba, Canada
Adjunct professor, University of Pennsylvania, USA

Gary Kobinger obtained his PhD from the University of Montreal in 1998 before completing a post-doctoral fellowship at the University of Pennsylvania. In March 2005, Gary was the Chief of the Special Pathogens Biosafety Level 4 program at the National Microbiology Laboratory where he worked for 11 years. He is now professor and the Director of the Infectious Disease Research Centre at the Université Laval and has an appointment of associate professor at the University of Manitoba and adjunct professor at the University of Pennsylvania.

Gary was granted several awards including scientist of the year award from Radio Canada (CBC), the Order of Manitoba in 2016, the Meritorious Service Cross (civil division) of the Governor General of Canada also in 2016 and the Ernest C. Manning Principal Award in 2017. Gary co-authored around 200 peer-reviewed scientific manuscripts, and gave numerous invited seminars in Universities, national and international funding agencies, departments of national defenses, the White House, Singapore NEA and the World Health Organization (WHO) concerning research on high consequence pathogens and the development of new public health policies and recommendations.

In 2013-2017, 60 minutes, National Geographic, BBC Horizon, NOVA, France 2, PBS, CBC, RC and others featured the leading work on successful treatment of Ebola infection that was developed by Gary and his team and the VSV-based Ebola vaccine to which he also contributed to bring to clinical trials including a Phase III efficacy study in Guinea.

ANN LEEN, PHD
Associate Professor, Department of Pediatrics, Section of Hematology-oncology, Baylor College of Medicine, USA

Dr. Ann Leen is an Associate Professor in the Center for Cell and Gene Therapy at Baylor College of Medicine and an immunologist with over 15 years of experience in developing and testing novel T cell therapies for the treatment of cancer and viral infections in immunocompromised patients. She has characterized the immune response to a range of viruses that cause morbidity and mortality in allogeneic hematopoietic stem cell transplant recipients. She devised and clinically implemented immunotherapeutic strategies to treat patients with Adenovirus, BK virus, cytomegalovirus, Epstein Barr virus and Human Herpesvirus 6 infections. She serves as a principle investigator on numerous clinical trials performed under investigator-initiated Investigational New Drug (IND) applications and in 2013 was awarded an Outstanding New Investigator Award from the ASCCGT for her work in developing novel cell therapies.
JOHN MCCAFFERTY, PHD  
Founder, Chief Executive Officer, Iontas Ltd., England

John McCafferty was one of the founders of Cambridge Antibody Technology (now Medimmune, Cambridge) in 1990 and published the first paper/patent describing antibody phage display. Work during this time included the discovery of the antibody which became Humira, the world's biggest selling drug.

After 12 years at CAT he returned to academia at the Sanger Institute and the University of Cambridge. In 2012 John formed IONTAS, an innovative biotechnology company using phage display to develop novel antibody therapeutics. In this period John has developed a novel technology allowing the construction of very large mammalian display libraries permitting the direct discovery of high affinity antibodies with optimal biophysical properties. Finally John has led the development of a novel molecular fusion format wherein naturally occurring cysteine-rich peptides (eg venom derived blockers of Kv1.3 or ASIC1a channels) are inserted into peripheral CDR loops of an antibody while retaining the folding and function of both molecules.

SUMATHI NAMBIAR, MD, MPH  
Director, Division of Anti-Infective Products, Office of Antimicrobial Products, FDA, USA

Dr. Sumathi Nambiar is Director of the Division of Anti-Infective Products, Office of Antimicrobial Products, since July 2013. Dr. Nambiar joined the Division of Anti-Infective Products in 2002. In her current role, Dr. Nambiar provides regulatory oversight for anti-infective products, including antibacterial, antifungal, and antiparasitic drugs.

Dr. Nambiar is board-certified in pediatrics and pediatric infectious diseases. She completed her pediatric residency at the Inova Fairfax Hospital for Children, VA and her fellowship in pediatric infectious diseases at Children's National Medical Center, Washington DC. She received her MPH from The George Washington University School of Public Health.

VICTOR NIZET, MD  
Professor & Vice Chair for Basic Research, Department of Pediatrics  
Chief, Division of Host-Microbe Systems & Therapeutics, School of Medicine  
Professor, Skaggs School of Pharmacy & Pharmaceutical Sciences  
University of California San Diego, USA

Victor Nizet is a Professor and Vice Chair for Basic Research and Chief of the Division of Host-Microbe Systems & Therapeutics at the University of California, San Diego (UCSD), School of Medicine as well as Professor at UCSD Skaggs School of Pharmacy & Pharmaceutical Sciences. Dr. Nizet received his medical training at Stanford University School of Medicine, completed a Residency and Chief Residency in Pediatrics at Harvard University's Children's Hospital in Boston, Massachusetts, and a Fellowship in Pediatric Infectious Diseases at the University of Washington's Children's Hospital in Seattle. Dr. Nizet leads a large basic and translational research laboratory focused on discovering virulence factors of invasive bacterial pathogens, elucidating mechanisms of host innate immunity, and novel approaches to infectious disease therapy. Dr. Nizet has authored over 400 peer-reviewed publications and has collaborated with several biotechnology interests in developing new antibiotic and immune-based therapies against drug-resistant pathogens. Dr. Nizet's work has been recognized by an AHA Established Investigator Award, ALA Career Investigator Award, AAF Senior Investigator Award, and the E. Mead Johnson Award for Research in Pediatrics. Dr. Nizet has been elected to the ASCI, AAP, and the American Academy of Microbiology. Details of his research program can be found on the lab website: http://nizetlab.ucsd.edu.
MIREIA PELEGRIN, PHD  
Senior Researcher, Montpellier Institute of Molecular Genetics  
National Center for Scientific Research, France

Dr. Mireia Pelegrin was born in Barcelona and obtained her Veterinary degree in this city. She next did a PhD at the Autonomous University of Barcelona focused on the development of transgenic mice as models of diabetes. In 1996, she moved to France for a post-doctoral training at the Institute of Molecular Genetics of Montpellier, in the laboratory of Marc Piechaczyk to work in the development of gene and cell therapy approaches for in vivo production of therapeutic monoclonal antibodies, project that led to two international patents. In 2000, Dr. Pelegrin became Senior Researcher at the CNRS in the same institute. Since then, she has been a Project leader of a research program on antiviral immunotherapies. By using mouse models of persistent viral infections, her group has pioneered the proof-of-concept that antiviral antibodies can induce long-term protective immunity (vaccine-like effects). The current work aims at identifying the main mechanisms underlying such mAb-induced antiviral vaccine-like effects. Addressing these issues might have important implications for the improvement of immunotherapies based on antiviral mAbs.

MARCOS PIRES, PHD  
Associate Professor, Department of Chemistry  
Advisor to Undergraduate Biochemistry Majors  
Lehigh University, USA

Marcos Pires earned a doctorate in chemistry at Purdue University, and a bachelor’s in chemistry at Ithaca College. Before joining Lehigh’s faculty, Pires was an NRSA post-doctoral fellow at the University of Pennsylvania. His research focuses on bacteriology and biochemistry, specifically, he works on immunotherapy and bacterial cell sensing and remodeling. He has presented his work widely and published in ACS Chemical Biology, Cell Chemical Biology, and ACS Infectious Diseases. His work has been highlighted by The Guardian, Smithonian, and various other news outlets.

JEROEN POLLET, PHD  
Assistant Professor  
Pediatrics-Tropical Medicine Baylor College of Medicine, USA

Jeroen Pollet, PhD is an Assistant Professor at the Section of Tropical Medicine, at Baylor College of Medicine (BCM) in Houston Texas and he is the Director of the Formulation Unit of the Texas Children’s Hospital Center for Vaccine Development. Dr. Pollet received his PhD in Biochemical Engineering from the Catholic University of Leuven, Belgium in 2010. In 2011, he came to the USA after being granted a Fulbright fellowship from the U.S. Department of State. Working at the University of Houston, Dr. Pollet developed innovative molecular diagnostics for tropical diseases. In 2012, he joined Baylor College of Medicine, where he has been involved in over a dozen vaccine projects and (co-)authored 35 peer-reviewed publications.

JANICE M. REICHERT, PHD  
Executive Director, The Antibody Society, USA  
Editor-in-Chief, mAbs

Janice M. Reichert, PhD, is Executive Director of The Antibody Society, a non-profit business association representing individuals and organizations involved in antibody research or development. Dr. Reichert is also the founder and Editor-in-Chief of mAbs, a peer-reviewed, PubMed-indexed biomedical journal that focuses on topics relevant to antibody research and development, and co-editor of the Handbook of Therapeutic Antibodies. She has published extensively on development trends for antibody therapeutics, and she has presented her research results as an invited speaker at conferences held worldwide. Dr. Reichert received her PhD in Chemistry from the University of Pennsylvania and did her post-doctoral training at Harvard Medical School.
BRET SELLMAN PHD
Director, Medimmune, USA

Bret Sellman, PhD is a Director in the Microbial Sciences Department at MedImmune, LLC and has over 17 yrs of industry experience in vaccines and antibacterial research and development. He has worked at MedImmune for over 10 years where he has led various antibacterial monoclonal antibody programs from discovery thru IND and into clinical development. Prior to MedImmune he worked at Wyeth Vaccine Research for 7 years in early vaccine discovery. He earned his B.S. in microbiology from New Mexico State University and his PhD in microbiology and immunology from the University of Oklahoma Health Sciences Center before completing his post-doctoral training at Harvard Medical School studying bacterial toxin biochemistry.

LYNN SOONG, MD, PHD, FASTMH
Professor and Vice Chair for Research, Department of Microbiology & Immunology
Director, Microbiology & Immunology Graduate Program
Director, NIAID T32 Emerging and Tropical Infectious Diseases Training Program
Director, NIAID T35 Infectious Diseases & Inflammatory Disorder Training Program
The University of Texas Medical Branch, USA

Dr. Lynn Soong received her medical and MS training at Shanghai Medical College Fudan University in China, and her PhD in immunoparasitology at the University of Georgia in Athens. She worked as a postdoctoral fellow and research associate at Yale School of Medicine. In March 1998, she joined the University of Texas Medical Branch (UTMB) as an assistant professor. Currently, she is a professor and vice chair for research in the Department of Microbiology & Immunology, director for the Microbiology & Immunology Graduate Program, as well as director for the NIAID-funded T32 and T35 training programs at UTMB. Dr. Soong's research is focused on host immunity and immunopathogenesis during infections with intracellular parasites and bacteria. Recently, her group has established lethal and sublethal Orientia tsutsugamushi infection models in mice, which mimic clinical/pathologic features of human scrub typhus. Using gene knockouts, immunological tools, and the state-of-art BSL3/ABSL3 facilities, her group has revealed, for the first time, molecular details underlying immune dysregulation and pathogenesis of severe scrub typhus, highlighting Th1-skewed, but Th2-impared, immune responses as the hallmark of lethal infection. Defining infection- versus immune-mediated dysregulation and prognostic biomarkers will help efficient control of scrub typhus, a neglected tropical disease.

LUCA VARANI, PHD
Group leader, Structural Biology, Institute for Research in Biomedicine, Switzerland

Luca Varani graduated in chemistry in Milan (Italy) and obtained a PhD at the prestigious MRC-Laboratory of Molecular Biology (Cambridge, UK) using molecular and structural biology to study RNA-protein interactions and their impact on gene expression. High caliber publications, culminated in the determination of the largest NMR structure available at the time, allowed him to move to Stanford with a “long term EMBO fellowship”, reserved to the best young molecular biologists in Europe. In California, Luca Varani completed the first magnetic resonance study on TCR/pMHC complexes.

Since 2007, he leads the Structural Biology group of the Institute for Research in Biomedicine (Bellinzona, CH), investigating the interactions between pathogens and antibodies in rare and neglected diseases such as Dengue or Zika virus, Prion or rare form of Leukemias. The NMR approach developed at Stanford was pushed forward at the IRB, where experimentally guided computational simulations yield the atomic structure of antibody/pathogen complexes. The approach allowed rationally modifying an antibody increasing its ability to neutralize Dengue virus by 50 fold utilizing, for the first time, only computational tools. More recently, the strategy allowed designing a bispecific antibody that prevents Zika virus escape mechanisms. Recent high impact publications appeared in journals such as Cell, Science, Nature Cell Biology and PNAS.

The group uses a highly multidisciplinary approach, varying from structure determination to cellular experiments, computational biology, biophysics, protein and antibody production and engineering, nanoparticles and confocal microscopy.
QIHUI WANG, PHD
Associate Professor, Institute of Microbiology
Chinese Academy of Sciences, China

Dr. Qihui Wang has completed her PhD training in Institute of Biophysics, Chinese Academy of Sciences (CAS) in 2012. She was promoted to be Associate Professor in 2015 in Institute of Microbiology, CAS. In 2017, she won the scholarship supported by China Scholarship Council as a visiting scholar in University of Texas Health Science Center at Houston. She was honorably elected National Committee member of the 9th National Committee of Chinese Association for Science and Technology (CAST). She won Young Elite Scientists Sponsorship program by CAST (2015-2017) and is Principal Investigator for the State Key Research Development Program of China.

Her research focuses on 1) Interaction between viral ligands and host receptors and 2) Isolation of therapeutic mAbs targeting virus infection and tumor. Her previous work uncovered the entry mechanism and interspecies transmission of Middle East respiratory syndrome coronavirus (MERS-CoV). She has set up a platform combining the isolation of antigen-specific memory B cells and sequencing the single cell. Applying this platform, she isolated several neutralizing monoclonal antibodies (mAbs) against Zika with high potency from a Zika patient. Her related work were published in reputed journals, including Nature, Cell Host & Microbe, Science Translational Medicine (Cover) and Journal of Virology.

DAVID B. WEINER, PHD
Executive Vice President
Director, Vaccine & Immunotherapy Center
Professor & WW Smith Chair in Cancer Research
The Wistar Institute, USA
Professor Emeritus, University of Pennsylvania, USA

Dr. Weiner directs a translational research laboratory within the area of Molecular Immunology. His group is one of the pioneering research teams establishing the field of DNA Vaccines & Immune Therapies. His laboratories & collaborators accomplishments include the first clinical studies of DNA vaccines, clinically important advances in gene optimization and in DNA delivery. His group developed the first clinically efficacious DNA vaccine (HPV immune therapy) and has moved synthetic DNA MERS, HIV, Ebola and Zika vaccines through development into clinical studies. His laboratory published over 400 papers/chapters & reviews. Dr. Weiner received multiple awards/honors, including the NIH Director's Translational Research Award (2011), W.W. Smith Family Chair in Cancer Research – 2016, Top 20 Translational Research Laboratories of the Year (Nature Biotechnology 2016 & 2017), Fellow of the American Association for the Advancement of Science 2011. Fellow of the International Society for Vaccines 2014, President International Society for Vaccines (2018-2020). Dr. Weiner has been an avid trainer and advisor for students and fellows and is highly committed to the development of young scientist's careers.
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<tr>
<td>Ansar</td>
<td>Maria</td>
<td>Protective Effect of Antibody-Mediated Interferon Blockade During Respiratory Syncytial Virus Infection</td>
<td>University of Texas Medical Branch</td>
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<tr>
<td>Bertoglio</td>
<td>Federico</td>
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PROTECTIVE EFFECT OF ANTIBODY-MEDIATED INTERFERON BLOCKADE DURING RESPIRATORY SYNCYTIAL VIRUS INFECTION

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Respiratory syncytial virus (RSV) is an enveloped RNA virus in the family pneumoviridae, and the leading cause of lower respiratory tract infections in infants. RSV is known to be resistant to the canonical antiviral activity of type I interferon (IFN I) and some studies have suggested that IFN may be associated with enhanced severity of disease in infected infants. Compared to wild type controls, mice that are genetically deficient in IFN I receptor (IFNR -/-) show a reduction in pro-inflammatory cytokines/chemokines in the lung, no significant difference in lung pathology, but increased peak lung viral titers. The goal of this study therefore was to determine the role of IFN I in antiviral responses and disease severity in a murine model of RSV infection with transient blocking of IFN I signaling using a single intranasal dose of IFN I receptor neutralizing antibody (IFNAR abx) 24 h prior to viral inoculation. RSV-infected mice treated with IFNAR abx showed a significant reduction in body weight loss and clinical disease severity (p<.001), along with significant improvement in epithelial cell integrity and airway obstruction measured by total protein content in bronchoalveolar lavage fluid (BALF) and whole body plethysmography respectively. IFNAR abx-treated mice also showed a significant reduction in pro-inflammatory cytokines and chemokines in BALF, including IL-1α/β, IL-6, IL-12(p40), TNF-α, CCL2-5, and CXCL1. Overall, blocking IFN signaling by abx did not result in a significant increase in viral titer or immune cell populations (macrophages, lymphocytes, etc.), but demonstrated a trend for reduction in neutrophil cell counts. In conclusion, this study has determined the role of transient antibody-mediated IFN I blockade, a model which has not been previously used in experimental RSV infection, and presented a potential new therapeutic approach to ameliorate airway disease severity.

RECOMBINANT HUMAN ANTIBODIES AGAINST STAPHYLOCOCCUS AUREUS SURFACE PROTEINS

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Staphylococcus aureus (SA) is still a major health problem, since antibiotic-resistant strains are widespread both in hospital-associated as well as in community-acquired infections. New antibiotic development is a long, time-demanding process and does not prevent antibiotic resistance development. Therefore, new or complementary therapies urge to be developed.

Here, we report the generation and initial characterization of fully human recombinant antibodies against CNA, SA cell wall-anchored collagen adhesin, and Coagulase, a secreted prothrombin- and fibrinogen-binding protein. These fully human antibodies have been selected by antibody phage display technology, that allows a total in vitro selection process. HAL 9 and 10 naïve antibody gene libraries were used as source for scFv (single chain Fragment variable) selection. A total of 21 specific α-CNA and 29 α-Coagulase scFs with unique DNA sequence were isolated and selected. 10 antibodies per each antigen were re-cloned in IgG-like format (scFv-Fc), recombinantly produced in HEK293.6E cells and initially characterized. All of them showed good apparent Kd towards their antigen. Furthermore, since Coagulase and Efb (Extracellular fibrinogen binding protein from SA) have sequence and functional homology, cross-reactivity of α-Coagulase antibodies was tested, showing that 8 out of 10 could efficiently bind also to Efb.

These preliminary data confirm that antibody phage display is a reliable platform for selection of antibodies and is able to provide suitable drug candidates. Owing their fully human origin and their in vitro inhibiting and displacing activity, these antibodies hold potential for successful anti-SA therapies.
AN EFFECTIVE SCREENING APPROACH TO DEVELOPING ANTI-EEEV NEUTRALIZING ANTIBODIES

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The three encephalitic alphaviruses, Venezuelan, western, and eastern equine encephalitis viruses (VEEV, WEEV, and EEEV) are classified as biothreat agents. However, the licensed medical countermeasures (MedCMs) against these viruses for humans are still not available. Neutralizing antibodies (NAbs) are fast-acting and highly effective MedCMs against biothreat agents for use in both pre- and post-exposure settings. While anti-VEEV and anti-WEEV NAbs have been successively developed and reported, anti-EEEV NAbs are lacking. As compared to VEEV and WEEV, EEEV is much more virulent and its mortality rate in humans could be up to 50%. It is imperative to develop anti-EEEV NAbs. The conventional screening approach to developing NAbs from immunized mice is to identify antigen-binding hybridoma clones first by an immunoassay and then determine neutralizing clones by an in vitro neutralization assay from these antigen-binding clones. Since EEEV is a containment level (CL)-3 agent, its use in an immunoassay is prohibited in CL-2 laboratories. Instead, either inactivated virus or recombinant antigens are used for the immunoassay. However, the conformation of inactivated virus or recombinant antigens might not be identical to authentic virus. Any change might affect neutralizing epitopes recognized by NAbs. As such, these NAb clones would be missed by the immunoassay. In order to overcome this hurdle, a rapid and feasible neutralization screening approach using live virus was developed and applied at CL3 laboratories in this study to screen for anti-EEEV NAbs directly from 2,500 hybridoma clones generated from the immunized mice. As a result, three anti-EEEV NAbs have been successfully identified and developed.

IDENTIFICATION OF RHESUS MACAQUE NEUTRALIZING ANTIBODIES TARGETING DIVERSE EPITOPES ON DENGUE VIRUS

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Dengue virus (DENV) is a leading cause of human illness in the tropics and subtropics, with more than 30% of the world's population living in areas with high risk for infection. However, a safe and effective vaccine to dengue virus is still lacking.

This study investigated monoclonal antibody (mAb) responses to an experimental dengue vaccine in rhesus macaques. Seven days after immunization boost, the variable region of antibody gene was cloned from single antibody-secreting cell. A total of 780 mAbs were expressed and analyzed. Results showed that the experimental vaccine-induced mAbs with different germline sequences and a wide range of binding affinities. Six potent neutralizing antibodies were identified. The epitopes of the neutralizing mAbs are previously reported for dengue antibodies isolated from human or mice, including antibodies binding to the hinge region, lateral ridge, bc loop, and β-strands of DI. Significantly, one broadly neutralizing antibody binds to a novel epitope at the interface of envelope and membrane protein.

In summary, this study provides an essential validation of the design for the experimental dengue vaccine. Further, the study sheds light on a potential vaccine evaluation strategy using monoclonal antibody in the non-human primate model.
AAV-MEDIATED EXPRESSION OF MONOCLONAL ANTIBODIES PREVENTS FILOVIRUS INFECTION

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AAV-mediated monoclonal antibody (mAb) expression is able to generate protective and sustained concentrations of therapeutic mAbs in animal models for various infectious diseases, including Ebola and Marburg virus. We have developed a novel AAV6 triple mutant capsid, AAV6.2FF, which facilitates rapid and robust mAb expression following intramuscular administration. We previously published data demonstrating 100% protection against Ebola virus challenge using AAV6.2FF-mediated expression of murine IgG2A mAbs 2G4 and 5D2 in mice. We have now re-engineered our expression platform to produce human IgG1 mAbs 100 and MR191, antibodies against the glycoproteins of Ebola and Marburg virus respectively. Intramuscular injection of 1x10^{10} vector genomes (vg) of AAV6.2FF-100 in mice resulted in serum concentrations of over 200µg/mL of human IgG and 6x10^{10}vg of AAV6.2FF-MR191 produced over 300µg/mL of human IgG for sustained periods (22-32 weeks). Mice that received 1x10^{11}vg of AAV6.2FF-100 were 100% protected from lethal Ebola virus challenge and lower doses resulted in partial protection (>50%). Both 1x10^{11}vg (high) and 1x10^{10}vg (low) doses of AAV6.2FF-MR191 resulted in 100% survival against lethal Marburg virus challenge. Serum human IgG concentrations immediately prior to challenge ranged from 24-137µg/mL for the low dose and 383-525µg/mL for the high dose group. Furthermore, mice receiving AAV-mAb vectors were able to generate an equivalent humoral immune response against a non-lethal challenge of influenza A virus (strain PR8) as their non-AAV treated counterparts, suggesting high concentrations of systemic mAbs do not interfere with the endogenous immune response. This method of antibody transfer prolongs the therapeutic effect of recombinant mAb administration, while also offering advantages as a potential "vaccination" strategy in individuals with compromised immune systems or in outbreak response scenario. A new class of mAbs with pan-Ebola virus specificity have recently been characterized and these represent the future direction for our AAV6.2FF-mAb platform for filovirus prevention.

MULTIDIMENSIONAL PROFILING AND OPTIMIZATION OF CSF1R INHIBITORS AS SMALL-MOLECULE IMMUNOMODULATOR

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Colony-Stimulating Factor 1 Receptor (CSF1R) is a receptor tyrosine kinase which plays critical function in regulating tumor-associated macrophages (TAMs), and consequently mediates tumor immune escape. Specifically, activated CSF1R promotes the transformation of TAMs from tumoricidal to immuno-suppressive state; while the blockade of CSF1R has been shown effective to control tumor growth and even more profound in combination with antibody based immunotherapy. Here the authors present the pre-clinical screening funnel to optimize the preliminary CSF1R inhibitors and ultimately nominate candidate for clinical evaluations. The assessment of the compound properties includes competitive binding, enzymatic assays, binding kinetics, selectivity against homologous tyrosine kinases, cellular activity, monocyte based target engagement assay, as well as PD assays with mouse plasma/tumor. The work has enabled the identification of a selective CSF1R inhibitor-IACS14359 which exhibits preclinical efficacy in combination with anti-PD1. The screening pipeline has provided valuable tool box to study CSF1R function/inhibition as well as analogous receptor kinase pathways.
SILVER NANOPARTICLES PROVIDE ANTIVIRAL AND IMMUNOMODULATORY EFFECTS DURING RSV INFECTION

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Respiratory syncytial virus (RSV) is an important etiological agent of respiratory infection in children and has no effective treatment option currently available. Recently, several studies have highlighted silver nanoparticles as having broad-spectrum antiviral activities in several viral infection models including HIV-1, hepatitis B, parainfluenza and influenza virus. Silver nanoparticles function to block entry into the host cell by attaching to viral glycoproteins as well as providing anti-inflammatory protection in many infectious models. Therefore, the objective of this study was to evaluate the antiviral and immunomodulatory effects of silver nanoparticles during RSV infection utilizing both in vitro and in vivo models. During in vitro studies, A549 and HEp-2 cells demonstrated a consistent dose dependent reduction in viral titer as well as significant dose dependent reductions in RANTES, IL-8 and INF-β. In vivo, BALB/c mice had significant dose dependent reductions in viral titer as well as with many pro-inflammatory cytokines (i.e. IL-6, TNF-α, IFN-α, and IFN-β), and pro-inflammatory chemokines (i.e. RANTES, and MCP-1). Conversely, KC, G-CSF, and GM-CSF were significantly increased. This was consistent with the dose dependent increase in total cell count, more specifically neutrophils. No significant changes in clinical parameters such as body weight or illness score were observed. In conclusion, silver nanoparticles elicit antiviral effects on RSV and alter the early innate immune response. Our study demonstrates the potential for the use of silver nanoparticles as antiviral therapeutics against RSV. Future research is focused on investigating the effects of silver nanoparticles on the adaptive immune response as well as the potential for the use of silver nanoparticles in a vaccine platform.

MONOCLONAL ANTIBODIES TO ROTAVIRUS NONSTRUCTURAL PROTEIN 4 (NSP4) NEUTRALIZE ITS CALCIUM SIGNALING ACTIVITY

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Rotavirus (RV) is a leading cause of childhood gastroenteritis and causes significant mortality in children under five years of age. Current live-attenuated oral rotavirus vaccines are highly effective in children in developed countries but they are less efficacious in developing countries where mortality remains high. Hence, continued research efforts are required to develop effective alternate vaccines. Nonstructural protein 4 (NSP4) is a novel rotavirus protein that is implicated in multiple functions critical for RV replication, morphogenesis, and pathogenesis (diarrhea induction). The mechanisms of rotavirus-induced diarrhea are multifactorial and include pathophysiologic responses to the NSP4 protein alone which binds to integrins, induces signaling pathways that elevate intra cellular calcium that results in perturbation of ionic balance, and causes diarrhea. In the absence of a crystal structure of full-length NSP4, biochemical and crystallographic studies of a coiled-coil domain (CCD, residues 95-146) of NSP4 have provided valuable structural information on the possible oligomeric states of NSP4 and its functions. Our recent studies indicate that the NSP4 CCD exhibits structural plasticity and can adopt both Ca2+-bound tetrameric and Ca2+-free pentameric states. We are seeking to understand the functional differences between the different oligomeric states of the NSP4 CCD using monoclonal antibodies (mAbs) and their possible inhibitory functions. We immunized mice with a pentameric form of NSP4 and produced clonal hybridoma cells, which were tested for specific antigenic reactivity to tetramer and pentamer forms of NSP4 CCD. One monoclonal antibody (mAb1096) detects only the pentameric NSP4 by western blot and a subset of intracellular NSP4 by immunofluorescence of rotavirus-infected cells, and also inhibit the calcium induction of NSP4-CCD proteins (along with other mAbs which detect both tetramer and pentamer form of NSP4-CCD). We are currently evaluating these mAbs for other inhibitory activities of NSP4 and possible application for passive immunotherapy.
Periprosthetic joint infection (PJI) remains a devastating complication following total joint arthroplasty. Current animal models of PJI do not effectively recreate the clinical condition. We developed the first clinically representative mouse model of PJI involving a 3-dimensionally printed Ti-6Al-4V implant and a mouse-sized cement spacer that elutes vancomycin.

Custom-made polymethylmethacrylate (PMMA) spacers containing vancomycin were prepared. Twenty C57BL/6 mice received a proximal tibial implant and an intra-articular injection of 3 x 10^5 colony-forming units of Staphylococcus aureus. At 2 weeks, mice underwent the clinically-relevant process of irrigation and debridement of the leg and insertion of an articulating vancomycin-loaded PMMA spacer. Postoperatively, mice underwent radiography and serum inflammatory-marker measurements. Following euthanasia of the mice at 6 weeks, bone and soft tissues were assayed to quantify bacteria within periprosthetic tissues.

Vancomycin-loaded PMMA spacers eluted vancomycin for 144 hours and retained antimicrobial activity. Control mice had elevated levels of inflammatory markers, radiographic evidence of septic loosening of the implant, and osseous destruction. Mice treated with a vancomycin-loaded PMMA spacer had significantly lower levels of inflammatory markers (p < 0.01), preserved tibial bone, and had no intra-articular purulence. Retrieved vancomycin-loaded spacers exhibited significantly lower bacterial counts compared with implants (p < 0.001). However, bacterial counts in periprosthetic tissue did not significantly differ between the groups.

Conclusions: The results suggest that the antimicrobial effects of PMMA spacers are tightly confined to the articular space and require additional strategies for efficient prevention of PJI.

**MTBHSP70 AS AN IMMUNOSTIMULATORY ADJUVANT FOR PROPHYLACTIC VACCINES AND TARGETED IMMUNOTHERAPIES**

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Induction of appropriate immune responses is required for effective vaccination against infective pathogens and for (re)activation of immune defenses in the context of ongoing chronic infections. *Mycobacterium tuberculosis* heat shock protein 70 (MtbHSP70) has stimulatory effects on multiple aspects of immune system function, ranging from dendritic cell maturation and lymphocyte recruitment to cytotoxic activity of natural killer cells and T cell priming. We have tested the hypothesis that MtbHSP70 can function as an immunostimulatory adjuvant in preclinical models of vaccination and targeted immunotherapy. MtbHSP70 enhanced T cell responses against influenza and Lassa fever virus targets when included as a component of self-assembling epitope-based vaccines. Successful demonstration of a corresponding enhancement of protective vaccine efficacy in planned experiments will provide a foundation for further development of a MtbHSP70-based vaccine platform for rapid development of vaccines against emerging infectious diseases. A fusion of MtbHSP70 and the small chain variable fragment (scFv) of a tumor antigen-specific monoclonal antibody stimulates anti-tumor immune responses as a targeted monotherapy in preclinical models of mesothelioma and ovarian cancer. When used in combination with other immunotherapies, the MtbHSP70-scFv fusion significantly prolongs survival in these models of terminal cancer. These results provide proof-of-concept for future design and testing of MtbHSP70-scFv immunotherapies targeting chronic infections and virally-mediated cancers.
TARGETING INTRACELLULAR *Burkholderia* BY ANTIBODY BASED COMBINATION THERAPIES AND DEVELOPMENT OF AN ANTIBODY-ANTIBIOTIC CONJUGATE

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The ability of *Burkholderia pseudomallei* to survive intracellularly, avoiding traditional antibiotic therapy, highlights the importance of investigating novel anti-microbial therapies. This project aims to use a number of approaches to target *B. pseudomallei* intracellularly including 1) antibody and antibiotic combinations, 2) autophagy inducing compounds and 3) an antibody-antibiotic conjugate.

We have developed and utilised *in vitro* macrophage infection assays to demonstrate monoclonal antibody opsonisation of *Burkholderia*. Autophagy promoting compounds have additionally been investigated for ability to reduce intracellular *Burkholderia* within *in vitro* macrophage assays. Imaging flow cytometry and confocal microscopy are being used to visualise and quantify bacterial infection within macrophages with *Burkholderia* strains expressing fluorescent protein.

We have shown that monoclonal antibodies directed against the capsule of *Burkholderia* can significantly increase macrophage bacterial uptake by over a log fold when compared to control antibody. Imaging flow cytometry has shown an increase in the percentage of infected macrophages containing intracellular *Burkholderia* from a control level of 20% up to 80% when opsonised. Autophagy inducing compounds have shown ability to reduce intracellular *B. thailandensis* within infected macrophages *in vitro*.

This data has been used to select antibody and antibiotic combinations for incorporation into an antibody-antibiotic conjugate currently under development. Autophagy inducing compounds are being further investigated for suitability as a combinational therapy. This represents the first steps towards developing a novel antibody combination therapy for *Burkholderia* infection.

NEUTROPHILS AND M1 MACROPHAGES CONTRIBUTE TO VASCULAR INJURY AND LUNG PATHOGENESIS DURING *ORIENTIA TSUTSUGAMUSHI* INFECTION

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Acute lung injury (ALI) leading to acute respiratory distress syndrome is a prevailing pathologic manifestation during *O. tsutsugamushi*-induced severe scrub typhus in humans. In this study, we tested a hypothesis that lung pathology in scrub typhus is due in part to dysregulated activation of inflammatory responses, leading to vascular malfunction and in severe cases, ALI.

Following infection with a lethal dose of *O. tsutsugamushi* in mice, lung tissues had a significant increase in ICAM1, VEGFR2, and angiopoietin-2 (Ang2), as measured by flow cytometry and immunofluorescence. Several unique features were also observed. First, a progressive decrease or loss of endothelial functional markers (Ang1 and Tie2) and CD41+ platelets, even after the peak of bacterial replication (around day 6), implying continued endothelial cell stress and tissue damage. Second, a sustained neutrophil influx and activation as disease progressed, and lung-recruited neutrophils became highly activated in releasing azurophilic granules or myeloperoxidase around day 10 (prior to host death). Finally, lung-derived macrophages were highly polarized to an M1 phenotype (CD80+CD64+CD11b+Ly6G-) at D6-D10, with no signs of M2 activation (CD206+CD64+CD11b+Ly6G-). This study reveals specific biomarkers for vascular stress/dysfunction and uncovers a type 1-skewed, but type 2-suppressed, immune responses in the lungs of lethally-infected mice. More importantly, it furthers findings from human patients and cells, implying an immunopathogenic role in ALI development during severe scrub typhus. Understanding of leukocyte effector molecules and endothelial stress pathways triggered by bacterial vs. host factors will help control this neglected tropical disease.
High-risk human papillomavirus (HPV) types, especially HPV-16 can cause a subset of head and neck cancers, in particular, oropharyngeal squamous cell carcinomas (OPSCC). Cancer stem cells have stem cell like properties and contribute to disease recurrence and metastasis. Since high risk E6 protein expression is a predictor for distant metastasis and poor survival in HPV positive OPSCC, we investigated the role of HPV-16 E6 in OPSCC development, specifically, the ability of HPV-16 E6 to confer stem cell like properties onto keratinocyte cells. Sphere forming assay, ALDEFLUOR assay as well as the expression level of stem cell marker Oct4, were used to evaluate the effects of expression of E6 proteins from high-risk type HPV-16 and low-risk HPV type 6 on inducing stem cell like properties in normal human keratinocytes. The expression of interleukin-6 (IL-6) in HPV E6 expressing cells and control cells were determined by real-time PCR and western blot. Real-time PCR was used to determine the level of Oct4 in HPV-16 E6 expressing cells upon neutralization of IL-6 using monoclonal antibody. We observe that expression of HPV-16 E6 in normal keratinocytes increases stem cell like properties within the cells: increased tumoursphere formation, elevated aldehyde dehydrogenase activity as well as expression of Oct4. These properties are specific to E6 protein from high-risk HPV type 16, but not low-risk HPV type 6. Concomitantly, a significant increase of IL-6 expression is also observed in E6 expressing cells, compared to control cells. Interestingly, the neutralization of IL-6 using neutralizing antibodies reverses the increase of Oct4 in HPV-16 E6 expressing cells. Our present study demonstrates that high-risk HPV-16 E6 expression in keratinocytes upregulates IL-6, which contributes to the expansion of cancer stem cell like cells. This information makes E6 protein and IL-6 suitable candidates for development of novel prognostic biomarkers and targeted therapies.

**IDENTIFICATION OF ADIPOCYTE PLASMA MEMBRANE-ASSOCIATED PROTEIN AS A NOVEL MODULATOR OF HUMAN CYTOMEGALOVIRUS INFECTION**

**HPV-16 E6 PROTEIN UPREGULATES IL-6 EXPRESSION TO PROMOTE STEM CELL LIKE PROPERTIES IN KERATINOCYTES**

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High-risk human papillomavirus (HPV) types, especially HPV-16 can cause a subset of head and neck cancers, in particular, oropharyngeal squamous cell carcinomas (OPSCC). Cancer stem cells have stem cell like properties and contribute to disease recurrence and metastasis. Since high risk E6 protein expression is a predictor for distant metastasis and poor survival in HPV positive OPSCC, we investigated the role of HPV-16 E6 in OPSCC development, specifically, the ability of HPV-16 E6 to confer stem cell like properties onto keratinocyte cells. Sphere forming assay, ALDEFLUOR assay as well as the expression level of stem cell marker Oct4, were used to evaluate the effects of expression of E6 proteins from high-risk type HPV-16 and low-risk HPV type 6 on inducing stem cell like properties in normal human keratinocytes. The expression of interleukin-6 (IL-6) in HPV E6 expressing cells and control cells were determined by real-time PCR and western blot. Real-time PCR was used to determine the level of Oct4 in HPV-16 E6 expressing cells upon neutralization of IL-6 using monoclonal antibody. We observe that expression of HPV-16 E6 in normal keratinocytes increases stem cell like properties within the cells: increased tumoursphere formation, elevated aldehyde dehydrogenase activity as well as expression of Oct4. These properties are specific to E6 protein from high-risk HPV type 16, but not low-risk HPV type 6. Concomitantly, a significant increase of IL-6 expression is also observed in E6 expressing cells, compared to control cells. Interestingly, the neutralization of IL-6 using neutralizing antibodies reverses the increase of Oct4 in HPV-16 E6 expressing cells. Our present study demonstrates that high-risk HPV-16 E6 expression in keratinocytes upregulates IL-6, which contributes to the expansion of cancer stem cell like cells. This information makes E6 protein and IL-6 suitable candidates for development of novel prognostic biomarkers and targeted therapies.

**IDENTIFICATION OF ADIPOCYTE PLASMA MEMBRANE-ASSOCIATED PROTEIN AS A NOVEL MODULATOR OF HUMAN CYTOMEGALOVIRUS INFECTION**

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Human cytomegalovirus (HCMV) is a ubiquitous pathogen that can cause disability in newborns and serious clinical diseases in immunocompromised patients. HCMV has a large genome with enormous coding potential; its viral particles are equipped with complicated glycoprotein complexes and can infect a wide range of human cells. Although multiple host cellular receptors interacting with viral glycoproteins have been reported, the mechanism of HCMV infection remains a mystery. Here we report identification of adipocyte plasma membrane-associated protein (APMAP) as a novel modulator active in the early stage of HCMV infection. APMAP is necessary for HCMV infection in both epithelial cells and fibroblasts; knockdown of APMAP expression significantly reduced HCMV entry into and infection of these cells. Interestingly, ectopic expression of human APMAP in cells refractory to HCMV infection, such as canine MDCK and murine NIH/3T3 cells, promoted HCMV entry independent of the viral gH/gL/pUL128-131 pentameric complex. Furthermore, viral immediate early (IE) gene expression was lower and nuclear translocation of tegument pp65 was occurred later in APMAP-deficient cells than in parental cells. These results suggest that APMAP plays a role in the early stage of HCMV infection. Results from biochemical studies of APMAP and HCMV proteins suggest that APMAP could participate in HCMV infection through interaction with gH/gL containing glycoprotein complexes in low-pH endosomes and mediate nucleus translocation of tegument pp65. Taken together, our results suggest that APMAP functions as a modulator of HCMV infection in multiple cell types and is an important player in the complex HCMV infection mechanism.

**DEVELOPMENT OF NEXT-GENERATION ANTIBODY-BASED THERAPEUTICS FOR THE TREATMENT OF INFECTIOUS DISEASES**

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Therapeutic antibodies have shown clinical success in the treatment of many diseases. By using extraordinarily large human antibody libraries, we have identified a number of potent monoclonal antibodies against emerging and chronic infectious diseases, including MERS, H7N9 influenza, Zika, HBV, HIV, etc. We have also been working on the development of novel antibody constructs (from 14 kDa to 180 kDa) as the next-generation safer, cheaper, and more potent antibody-based therapeutics.
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