



NorCal SOT Spring Symposium
Preclinical Drug Development, Biothreats, and Biomarkers of Toxicity
 April 23, 2015
 Venue: South San Francisco Conference Center, 255 South Airport
 Boulevard, South San Francisco, CA 94080

Morning Session	
7:45 am – 8:30 am	Registration
8:30 am – 8:45 am	Opening message from The NorCal Vice President <i>Eric Harstad, PhD, DABT, Senior Scientist and Therapeutic Area Leader, Genentech Inc.</i>
8:45 am – 9:35 am	Biomarker Development and Validation for Drug Discovery and Development <i>Jon Mirsalis, PhD, DABT, Managing Director of Biosciences, SRI International</i>
9:35 am – 10:25 am	Development of Passive Immunity for Ebola Virus Infections Through Convergence of Science & Technology: Mice, Primates and Plants <i>Gene G. Olinger, Jr., PhD, MBA, Principal Advisor Science, MRI Global Inc.</i>
10:25 am – 11:00 am	Coffee Break, Posters
11:00 am – 11:20 am	Arsenic and innate immunity: macrophage function upon arsenic exposure <i>Postdoctoral Award Winner: Fenna C.M. Sille, UC Berkeley</i>
11:20 am – 12:10 pm	Development of New Therapeutics for Radionuclide Decorporations: From Discovery to IND <i>Rebecca Abergel, PhD, Chair of Radioactive Drug Research Committee, Lawrence Berkeley National Laboratory.</i>
12:10 pm – 1:30 pm	Lunch Break, Lunch with Experts, Posters
Afternoon Session	
1:30 pm – 1:45 pm	Chapter announcements and acknowledgements
1:45 pm – 2:35 pm	Using a One Health Approach to Reduce Pandemic Risk and Promote Global Health: PREDICT, A Project of USAID's Emerging Threats Program <i>Tracy Goldstein, PhD, Associate Director and Professor, UC Davis, One Health Institute</i>
2:35 pm – 2:55 pm	Effects of Organophosphorus Pesticides (OPs) on Airway Physiology <i>Graduate Student Award Winner: Frances Shaffo, UC Davis</i>
2:55 pm – 3:20 pm	Coffee Break
3:20 pm – 4:10 pm	Nonclinical Development of Neurotoxicity Biomarkers Using MRI <i>Serguei Liachenko, MD, PhD, Director of Bioimaging, Division of Neurotoxicology, FDA/NCTR, Jefferson, AR</i>
4:10 pm – 5:00 pm	Biosimilar Products: Scientific and Regulatory Challenges for Global Applications <i>Barbara Mounho-Zamora, PhD, DABT, Fellow, ATS, ToxStrategies, Inc.</i>
5:00 pm – 5:15 pm	Closing Remarks
5:15 pm – 6:15 pm	Drinks and Networking

[DIRECTIONS TO SSF CONFERENCE CENTER](#)

ABSTRACTS

Biomarker Development and Validation for Drug Discovery and Development

Jon Mirsalis, PhD, DABT

Executive Director of Preclinical Development and Managing Director of Biosciences Division
SRI International, Menlo Park, CA

Development of new biomarkers is a rapidly growing major focus of the pharmaceutical industry and regulatory agencies. Biomarkers have been traditionally used to identify disease progression, pharmacologic effect of treatments, and safety of pharmaceutical products. There has recently been an increased effort related to development of safety biomarkers that can provide better prediction of potential adverse effects of drugs in both preclinical and clinical research. This talk will give several examples of biomarker development programs that cover both pharmacologic and safety biomarkers, and will describe ongoing efforts to qualify biomarkers for regulatory applications.

Development of passive immunity for Ebola Virus Infections through convergence of science & technology: mice, primates, and plants.

Gene Olinger Jr., PhD, MBA

Principal Advisor Science

MRIGlobal, Frederick Maryland

Director of Maximum Containment Training and Adjunct Professor at Boston University, Medical Center, Department of Medicine, Section of Infectious Disease, National Emerging Infectious Diseases Laboratories (NEIDL), Environmental Health & Safety Core, Boston Massachusetts

MB-003 is a cocktail of 3 monoclonal antibodies (mAbs), originally developed for the treatment of Ebola Virus Disease (EVD). These mAbs bind to non-overlapping epitopes on Ebola virus glycoprotein, and one of the mAbs is also reactive with Sudan, Reston, and Taï Forest virus. The mAbs have been chimerized with a human constant region and expressed using a Rapid Antibody Manufacturing Platform (RAMP) in *Nicotiana benthamiana*. Individually the mAbs protect mice from lethal challenge prophylactically and two days post-exposure (p.e.) at doses \leq 5 mg/kg. When cocktailed, MB-003 protects Rhesus macaques from lethal IM challenge (1000 pfu), with 100% protection demonstrated when treatment was initiated 1 hour p.e., 67%-100% protection when initiated 1 or 2 days p.e., and 43% protection when administered after detection of virus by both RT-PCR and a sustained fever (triggers met 100-120 hours p.e.). The majority of treated survivors display minimal morbidity and no side effects were observed from the treatment regimen in any animals. To improve on efficacy, various combinations of antibodies developed by Public Health Agency of Canada (ZMAb) were used to optimize protection in rodents and primates. The resulting combination of antibodies ZMapp™ demonstrated improved efficacy over Zmab or MB-003. It is the result of an unusual partnership involving Mapp Biopharmaceutical, Inc. (San Diego, CA) and Kentucky BioProcessing (Owensboro, KY) working with the U.S. government, and Defyrus, Inc. (Ontario, Canada) working with the Canadian government. Data to date indicate ZMapp™ can provide therapeutic efficacy in non-

human primates at least 5 days after infection.

Arsenic and innate immunity: macrophage function upon arsenic exposure.

Fenna C.M. Sillé, PhD

Postdoctoral Trainee

Division of Environmental Health Sciences, School of Public Health, 375 Li Ka Shing Center, University of California, Berkeley, CA

In a unique study area in Chile, our research group has reported that *in utero* and early-life arsenic exposures were associated with *the* greatest increases in young adult mortality ever associated with an early-life environmental exposure: i.e. a 7-fold increase in lung cancer and an 18-fold increase in both bladder cancer and bronchiectasis. The risks of disease and mortality remain high up to 40 years after arsenic exposures have ended. However, the mechanisms for this prolonged effect remain unknown. We hypothesize that arsenic ingestion permanently impacts immune development and increases the risks of various immune-related diseases later in life. Here we focus on macrophages, innate immune cells known to influence tumor progression and TB pathogenesis. We performed multiplex cytokine/chemokine profiling analysis on supernatant from *in vitro* monomethylarsonous acid (MMA3)-treated mouse bone-marrow-derived macrophages (BMDM). Our results revealed significant downregulation of various pro-inflammatory cytokines and chemokines involved in the nucleotide-binding oligomerization domain (NOD)-Like receptor, Toll-Like-receptor and peroxisome proliferator-activated receptor (PPAR) pathways, all critical in the innate immunity against TB. Lipid metabolomics experiments on these same BMDMs showed that arsenic treatment led to elevations in several pro-inflammatory and tumor-promoting signaling lipids known to play a role in tumor progression as well as the immunopathogenesis of TB. We are currently validating our findings in human macrophages and investigating how arsenic-induced immunogenic and metabolic alterations in macrophages influence TB and tumor cell pathogenicity *in vitro* and *in vivo*.

This work was supported by grant # P42ES004705 from NIEHS Superfund Research Program (M.T.S.)

Development of New Therapeutics for Radionuclide Decorporation: From Discovery to IND

Rebecca J. Abergel, PhD

Chair of Radioactive Drug Research Committee

Lawrence Berkeley National Laboratory, Berkeley, CA

The threat of a major radiological contamination presents a danger of not only large-scale external radiation exposure of the population but also internal contamination with radionuclides. While major components of such contamination are likely to be actinides and lanthanide fission products, current therapies for the treatment of f-element internalization are still limited. Over the past three decades, the Lawrence Berkeley National Laboratory has dedicated a research program to the discovery of oral therapeutics for actinide decorporation, leading to the emergence of the active pharmaceutical ingredient (API) 3,4,3-LI(1,2-HOPO) as an exceptional candidate for actinide sequestration.

This synthetic hydroxypyridinonate chelator is currently undergoing advanced development for the treatment of individuals with known or suspected internal contamination with actinides such

as plutonium (Pu), americium (Am), curium (Cm), uranium (U) or neptunium (Np) to increase the rates of elimination of these radionuclides. Following the submission of an Investigational New Drug (IND) application, the U.S. Food and Drug Administration (FDA) approved the first clinical study for the decorporation agent 3,4,3-LI(1,2-HOPO) in August 2014.

In order to seek regulatory approval for this new agent, a number of efficacy and safety studies must respond to the selective criteria of the Animal Efficacy Rule from the FDA. The IND submission was the result of a large number of studies performed to optimize the drug candidate, demonstrate its safety, activity and efficacy, and establish a mechanism of action. A summary of these studies will be presented, together with an overview of the regulatory approach taken for the successful development of such new decorporation therapeutic option.

This work was supported by the Medical Countermeasures Against Radiological Threats (MCART) Consortium of the National Institute of Allergy and Infectious Diseases (NIAID, Contract #HHSN272201000046C) and the Biomedical Advanced Research and Development Authority (BARDA, Contract #PIAA12OS99609), through the U.S. DoE under Contract #DE-AC02-05CH11231

Using a One Health Approach to Reduce Pandemic Risk and Promote Global Health: PREDICT, A Project of USAID's Emerging Threats Program

Tracey Goldstein PhD

Associate Director and Professor

One Health Institute, University of California-Davis School of Veterinary Medicine, Davis, CA.

Most emerging infectious diseases (EIDs) in people originate in wildlife and have arisen in the developing world. Population growth and environmental change bring people into contact with wildlife in unprecedented ways and increasing frequency, yet many nations lack the resources and infrastructure necessary to detect and respond to EIDs in a timely, effective manner. The USAID Emerging Pandemic Threats PREDICT project, led by the UC Davis One Health Institute and the PREDICT consortium (EcoHealth Alliance, Metabiota, Wildlife Conservation Society, and Smithsonian Institution), is advancing global capacity for EID detection and control.

Launched in 2009, to date the PREDICT consortium has humanely sampled more than 56,000 wild animals (primarily primates, bats and rodents) with human contact, and has detected 815 novel mammalian viruses in addition to 169 known ones, including dozens closely related to known causes of human disease. As well, PREDICT has played a key role in investigating the cause of human and wildlife disease outbreaks, including several caused by Ebolavirus and Yellow Fever. In the second 5 yr phase of the project (2014-2019), the focus is now on further elucidating potential EID transmission pathways and spillover risk. Sampling of people and livestock is being conducted concurrently with wildlife sampling at high-risk interfaces involving wildlife value chains, animal agriculture intensification, and landscape conversion for commercialization, in order to document pathogen sharing and spillover mechanisms. As well human behaviors that increase risk for exposure to EIDs are being documented, in order to inform recommendations for reducing the potential for disease emergence and pandemics. While core PREDICT objectives center on protecting human health, wildlife conservation benefits include improved diagnostic laboratory capacity and great governmental awareness and investment in wildlife population management.

Effects of Organophosphorus Pesticides (OPs) on Airway Physiology

Frances Shaffo

Graduate Student, Departments of Molecular Bioscience

University of California-Davis School of Veterinary Medicine, Davis, CA.

OPs are well known neurotoxicants that cause toxicity via acetylcholinesterase (AChE) inhibition. OPs are also implicated in human asthma, and we previously demonstrated that the OP parathion causes airway hyperreactivity in guinea pigs independent of AChE activity. In non-sensitized guinea pigs, OP-induced airway hyperreactivity is mediated by TNF- α . In this study, we determined whether a single s.c. administration of parathion similarly influenced airway physiology as well as local and systemic immune responses of male Brown Norway rats. Pulmonary function was measured through controlled methacholine ventilation challenge by Flexivent 24 h after subcutaneous injection of 0.1, 1, or 10 mg/kg parathion. After mechanical ventilation studies were completed, lungs, cerebellum, and peripheral blood were collected and assayed for AChE activity, while peritoneal and bronchoalveolar lavage (BAL) samples were collected for cytokine expression profiles by ELISA and mast cell count. Parathion caused a dose-dependent increase in airway resistance. AChE activity was significantly decreased only at the highest dose of 10 mg/kg of parathion. IL-1 β , IFN γ , TNF- α and TGF- β were not altered in BAL or peritoneal lavage of parathion-treated animals relative to vehicle controls. The number of mast cells increased significantly at 0.1 mg/kg of parathion and decreased significantly at 10 mg/kg of parathion, indicating recruitment of mast cells at low doses and possibly degranulation at the highest dose of parathion tested. Increased β -hexosaminidase release at 10 mg/kg corroborates this explanation, suggesting mast cell degranulation after parathion exposure. In summary, our data suggests that parathion causes airway hyperreactivity in Brown Norway rats possibly via mast cell degranulation.

Work supported by NIH (grants R01 ES017592 and T32 HL07013).

Nonclinical Development of Neurotoxicity Biomarkers Using MRI

Serguei Liachenko, MD, PhD

Director of Bioimaging

Division of Neurotoxicology, FDA/NCTR, Jefferson, AR

Modern in vivo imaging technologies like magnetic resonance imaging (MRI) have attained an important role in medical research due to low invasiveness and ability to provide functional information about biological systems. Such information could be obtained from the same subject repeatedly and with the least possible interference, which makes in vivo imaging a unique and indispensable tool to support drug safety evaluation and other toxicological research. MRI was used in non-clinical settings to probe the changes in living rat brain following exposure to one of ten classical neurotoxicants. The specific response (change in T2 relaxation) was identified and the investigation of its specificity and sensitivity against current gold standard (histopathology) is initiated. This approach may lead to the development of the sensitive non-invasive early biomarker of neurotoxicity, which can significantly improve the quality of the drug safety research.

Biosimilar Products: Scientific and Regulatory Challenges for Global Applications

Barbara Mounho-Zamora, Ph.D., DABT, Fellow, ATS
Biopharmaceutical and Pharmaceutical Practice Leader
ToxStrategies, Inc.

A biosimilar is a biological product that claims to be similar to an innovative biological protein therapeutic product (reference product) that is already licensed and marketed.

The approaching expiry of patents of various innovative biological products, combined with the enactment of legislation for the approval of biosimilar products and revisions to existing biosimilar guidelines in major regions, has led to a substantial increase in the pharmaceutical industry's interest in developing biosimilar products. The European Union (EU) has served as the leader in establishing a dedicated regulatory pathway for the approval of biosimilars. Subsequent to the EU, other regions around that world (e.g., Australia, Canada, Japan, and the United States) have developed regulatory guidelines for the development of biosimilar products. While the regulatory and scientific requirements across regions have similar principles and concepts, differences in certain topics and regulatory standards exist across different regions. Biosimilar applicants seeking registration for their biosimilar product in major regions, such as Europe and the United States, are often faced with different responses and requirements from the regulatory authorities regarding their approach for the demonstration of biosimilarity in the analytical, nonclinical, and clinical studies. Due to the lack of harmonization among the regulatory authorities, the spectrum of differing regulator expectations can vary, ranging from minor to major differences. In addition, with the advancement in the analytical technology, and as more data is becoming available, the current thinking and expectations of the regulatory authorities has evolved over the years. Thus, understanding the current expectations of the regulatory authorities is critical as a sponsor develops their biosimilarity strategy and package. This presentation will provide a general review of the regulatory pathways and expectations of the European Medicines Agency (EMA) and Food and Drug Agency (FDA), as well as review how the expectations of the FDA and EMA regarding the comparative nonclinical studies required have changed over the years.

BIOGRAPHIES

Jon C. Mirsalis, PhD, DABT, Executive Director of Preclinical Development and Managing Director of SRI's Biosciences Division is an established leader in the assessment of safety of pharmaceutical products. As Executive Director of Translational Development at SRI, Dr. Mirsalis supervises all preclinical and clinical testing at SRI. As Managing Director of SRI's Biosciences Division, Dr. Mirsalis also has overall responsibility for operational management of a Division with approximately 300 staff members. Dr. Mirsalis received his PhD in toxicology and genetics from North Carolina State University in 1979. He has been certified by the American Board of Toxicology since 1983. He guest lectures regularly at Stanford University and the University of California, Santa Cruz. Dr. Mirsalis is one of the founding members of both the Critical Path Institute and the Predictive Safety Testing Consortium, a consortium of pharmaceutical industry, the US FDA and the EMA that is developing and validating new safety biomarkers. He currently serves on the Advisory Committee of the PSTC and is on the Board of Directors of the California Biomedical Research Association. He has previously served as an expert reviewer on the FDA over-the-counter medication review panel, and as a member of the Board of Scientific Councilors for the National Toxicology Program within the National Institute of Environmental Health Sciences (NIEHS).

Gene Garrard Olinger, Jr., PhD, MBA, Principal Advisor Science for MRI Global Inc. and is the high containment coordinator at the NIH NIAID Integrated Research Facility (IRF) in Frederic MD. In this role, he oversees the contract personnel and manages the coordination of research focused on high consequence pathogens utilizing state of the art medical imaging technology. Dr. Olinger is an international recognized expert in virology and immunology, especially for high consequence viral pathogens. His research interests includes two main missions within countermeasure development; 1) the development of filovirus vaccines, and 2) the development of therapeutic drug countermeasures for viral threats, including highly lethal viral hemorrhagic fever viruses (VHFV) and alphaviruses. Dr. Olinger was nominated and accepted as a full member of the American Association of Immunologist and American Society for Virology in 2006. Dr. Olinger is active in multiple national level professional organizations, journal Editorial Boards, and serves as a subject matter expert panels for HIV and VHFV. Since 2010, Dr. Olinger has maintained an adjunct associate Professor of Medicine in the Department of Infectious Disease appointment at the Boston University School of Medicine and a joint appointment to the National Emerging Infectious Diseases Laboratory (NEIDL) as the Associate Director for High Containment Training and an investigator with the Collaborative Core of the NEIDL. Dr. Olinger holds a Masters in Business Administration from Mount Saint Mary's University in Emmittsburg, MD, has completed executive training at Massachusetts Institute of Technology, Boston, MA, and completed Department of Defense Acquisition and Executive Leadership training. He is the recipient of the Achievement Medal for Civilian Service Medals in 2005 and 2010 and a Commander's Award for Civilian Service in 2013. Dr. Olinger is active in multiple STEM programs and mentors high school, undergraduate graduate students and post-doctoral fellows.

Rebecca Abergel, PhD, Staff Scientist in the chemical Sciences Division at Lawrence Berkeley National Laboratory. Dr. Abergel's research program is dedicated to investigating the coordination biochemistry of heavy and f-elements, with therapeutic and environmental applications such as chelation and bioremediation of toxic metals released in industrial processes, engineering of antimicrobial strategies targeting metal-acquisition systems, and design of advanced alpha-immuno theranostic agents. She leads a large collaborative effort on the development of new drug products for the treatment of populations contaminated with radionuclides. One of these products was granted an Investigational New Drug status from the

U.S. Food and Drug Administration in 2014. In addition, she has been actively involved in the new Lawrence Berkeley National Laboratory Initiative for Resilient Communities, the radiological component of which was sparked by the aftermath of the 2011 Fukushima Daiichi accident. Dr. Abergel currently serves as the chair of the Radioactive Drug Research Committee at the Lawrence Berkeley National Laboratory. She is an associate editor for the International Journal of Radiation Biology and a corresponding member (USA) for Radioprotection. In 2014, Dr. Abergel received an Early Career Award from the U.S. Department of Energy and was selected as an Innovator under 35 – France by the MIT Technology Review. She is also the recipient of a Director's Award for Exceptional Scientific Achievement (2013) from the Lawrence Berkeley National Laboratory, a Junior Faculty NCRP award (2013) from the Radiation Research Society, and a Young Investigator Research Fellowship (2010) from the Cooley's Anemia Foundation.

Tracey Goldstein, PhD, Associate Director and Professor at the University of California Davis, One Health Institute, where she developed and oversees the One Health Institute Laboratory and the Marine Ecosystem Health Diagnostic and Surveillance Laboratory. She is also the Co-PI and Pathogen Diagnostics Co-Lead for the viral emergence early warning project PREDICT, developed with the US Agency for International Development's Emerging Pandemic Threats (EPT) Program. Her background is in Wildlife Molecular Epidemiology and in developing disease diagnostics to detect novel pathogens. She focuses on solving global health problems using research, training, and capacity building.

Serguei M. Liachenko, MD, PhD, Director of Bioimaging in the Division of Neurotoxicology at FDA/NCTR. Dr. Liachenko's research interest is to use modern in vivo imaging technologies such as MRI to determine biomarkers of toxicity associated with neurotoxicants. Dr. Liachenko received his Medical Doctorate from Russian State medical University in Moscow in 1988 and his PhD in pharmacology from Russian Center for Safety Testing of Biologically Active Substances, in Moscow. He has served as the Sr. Principal Scientist at Pfizer Global Research and Development, in Groton, CT for nearly 7 years before he moved on to his current position. Dr. Liachenko has been a member of the International Society of Magnetic Resonance in Medicine since 1998 and a member of Society of Toxicology since 2010. For the past 10 years Dr. Leachenko has served as the Ad hoc member of CDER Neurotoxicology Committee.

Barbara Mounho-Zamora, PhD, DABT, Biopharmaceutical and Pharmaceutical Practice Leader with ToxStrategies, Inc. Dr. Mounho-Zamora has extensive experience in developing and overseeing comprehensive toxicology programs to support the development and ultimately approval of drug candidates in various therapeutic areas including oncology and inflammation (autoimmune indications). Dr. Mounho-Zamora is recognized in the biopharmaceutical industry for her strong working knowledge of biological/biosimilar products, and has been involved in developing biosimilar products. She has participated in the development of industry and trade-association comments in response to concept papers and draft guidance for biosimilar products issued by global authorities worldwide. Prior to joining ToxStrategies, Inc., Dr. Mounho-Zamora was at Amgen, Inc. (Director, Regulatory Affairs Biosimilars Policy and Strategy; Scientific Director, Toxicology Department) and Genentech, Inc. (Scientist, Toxicology Department). She is a Diplomate of the American Board of Toxicology for the past 14 years, and a member of the American College of Toxicology (Council member, 2005-2008; Continuing Education Committee, 2003-2005) and the Society of Toxicology (Continuing Education Committee, 2006 – 2009; President of the Biotechnology Specialty Section, 2010-2011).