Pharmacology Animal Models in Drug Development:
Fundamentals, Applications and Case Studies Related to Oncology
Metabolic diseases, Inflammation and Immunology

Date/Time: May 31, 2016; 12:45 - 5:30 pm
Venue: San Francisco Bay Area (Crowne Plaza Hotel, Foster City, CA)
Speakers: Dirk Mendel (E-Scape Bio), Stephen Gould (Genentech), Rana Samadfam (Charles River Laboratories)
Peter Havel (UC Davis), Leon Hall (Mousera)
Fees: Regular - $125; Academic - $75; Students & Unemployed - $25; Vendor Show: $375
Registration: www.PBSS.org

Workshop Description:

Preclinical research and clinical research are two major components in the process of drug development. In preclinical research, one of the most important considerations is the use of animal models to study efficacy, mechanism of action and establish the pharmacokinetic/pharmacodynamic (PK/PD) relationship. Together with toxicology studies, these efficacy-related studies are essential for any new drug candidate to advance to clinical development and eventually reach the market. Questions are routinely asked and debated such as “how to select relevant animal models”, “how to optimize rodent models for reliability and predictability”, “what are the pros and cons of different models”, and “how to translate the animal results to clinical studies”. We have assembled an experienced team of speakers from academia, the biotech/pharma industry and contract research organizations to discuss these critical questions.

The workshop is designed for both pharmacologists and non-pharmacologists. Non-pharmacologists will benefit as they will gain a better technical understanding of the process and challenges, while experienced pharmacologists can see the best practices used by their colleagues at other companies.

The following topics will be covered at the workshop:

- Animal models in translational research: Fundamentals and Applications (Dirk Mendel, E-Scape Bio)
- Oncology: animal models and case studies (Stephen Gould, Genentech)
- Autoimmune Disorders/Inflammation: In vivo models and case studies (Rana Samadfam, Charles River Laboratories)
- Metabolic diseases: Fundamentals of Animal Models of Metabolic Disease (Peter Havel, UC Davis)
- Improving the predictability of rodent models (Leon Hall, Mousera)

Detailed Presentation Outlines:

Oncology (Dr. Dirk Mandel, E-Scape Bio and Dr. Stephen Gould, Genentech)
An overview of how to approach a new project from a translational perspective; how to start identifying the key questions for a given project

- A historical perspective to the use of preclinical mouse models in oncology research
- An understanding of the pros and cons of various preclinical oncology models and a working knowledge of how to select the most appropriate model or models
- Familiarity with best practices for the preclinical evaluation of oncology drugs in mouse models
• A full understanding of PK/PD/efficacy relationships and how to apply these to set robust clinical gates
• An understanding of exposure-response relationships and how these may impact decision making in the clinic
• An appreciation of how to approach multi-targeted vs specific compounds
• How to use reverse clinical translation to help set preclinical bars for advancing molecules
• What to expect in terms of animal modeling in the era of immune-based therapies
• An understanding of the potential of using client-owned animals (eg, dogs with cancer) for translational studies; when does it make sense?
• Examples of how these concepts have been reduced to practice to enhance the translatability of preclinical work and influence clinical development of compounds that have made it to market

Autoimmune diseases/inflammation (Dr. Rana Samadfam, Charles River Laboratories)
• Overview of in in vivo models used to characterize anti-inflammatory and immune modulatory drugs
• Overview and measurement of commonly studied mediators of immune and inflammatory responses.
• Therapeutic models of common interest for immune based diseases, including rheumatoid arthritis, psoriasis, asthma, inflammatory bowel disease/Crohn's disease.
• Discussion of best practices for use of these models for evaluation of efficacy and mechanistic investigations
• Use of cell-based and molecular assays to characterize therapeutic responses.
• New and emerging technologies useful in characterization of immune and inflammatory responses.
• Strategic approaches for progression from early drug discovery screening to preclinical development, including use of biomarkers

Preclinical animal models (Dr. Leon Hall, Mousera)
• Limitations of current practices in preclinical research
• Developing more predictive models to address existing limitations
• Humanized mice in immuno-oncology applications
• Using humanized mice for other applications (safety/toxicity)

Metabolic Diseases (Diabetes/hyperlipidemia) (Dr. Peter Havel, UC-Davis)
• Review of established rodent models which have been used to study metabolic disease (obesity, insulin resistance and diabetes)
• Discuss limitations of monogenic rodent models which poorly represent the pathophysiology of these diseases
• Features of diet-induced obese rodent models of insulin resistance, which typically do not develop overt hyperglycemia sufficient to be classified as type-2 diabetes.
• Discussion of important differences between rodents in and primates with respect to metabolic physiology
• Characterization and advantages of the f UCD-T2DM rat model for studying type-2 diabetes, which combines polygenic obesity and insulin resistance with islet/ß-cell dysfunction leading to marked hyperglycemia and many of the typical features of type-2 diabetes in humans.
• Potential use of nonhuman primate models in drug development, such as the diet-induced rhesus monkey model of metabolic syndrome which exhibits insulin resistance, dyslipidemia and hepatic steatosis.

About the Speakers:

Dirk Mendel, Ph.D
Dr. Dirk Mendel is currently VP, Translational Biology, at E-Scape Bio, a local startup company focused on neurodegenerative diseases. He has almost 25 years of industry experience in preclinical research and early clinical development in several therapeutic areas. Dr. Mendel has held positions at a variety of companies including Gilead, SUGEN, Chiron, KAI Pharmaceuticals and MedImmune, the biologics arm of AstraZeneca, where he was VP and Global Head of Translational Medicine for all therapeutic areas. Dr. Mendel has extensive experience developing and successfully applying PK/PD and other translational approaches to facilitate preclinical and clinical development of targeted therapeutics in a variety of therapeutic areas. He has played a major role in progressing and/or leading multiple projects through research and early clinical development phases, including six compounds that have made it to market and a seventh that is currently under review in the US and Europe. His 2003 paper describing the PK/PD approach to understanding the activity of Sutent®, a multitargeted RTK inhibitor approved for the treatment of a variety of cancers, was recently highlighted by the senior editors of Clinical Cancer Research as one of the most important seminal articles they have published over the course of their 20-year history. Dr. Mendel received his Ph.D. in Physiology from Dartmouth Medical School and a B.S. in Engineering with a focus in Control Systems and Control Theory from Stanford University.
Stephen Gould, Ph.D  
Dr. Stephen Gould is Director of Translational Oncology at Genentech, Inc. where he has overseen the preclinical pharmacology of their oncology pipeline for the past 9 years including four marketed drugs, Erivedge, Kadcyla, Pertuzumab and Venclexta. He obtained his B.S. degree at the University of Massachusetts, North Dartmouth in 1986 and his Ph.D. in biomedical science from the University of Connecticut, Farmington in 1993 where he discovered and characterized the role of a novel transmembrane heparin sulfate proteoglycan, Synecan-3, during limb bud development. Following his graduate work he joined the Laboratory of Robert Grainger at the University of Virginia as a postdoctoral fellow studying anteroposterior patterning of the central nervous system and how signals are passed through the plane of the tissue to establish polarity. He then moved to the West Coast for a additional postdoctoral training in the Orthopedic Surgery Department at UCSF in 1996 where he investigated the cellular contribution of autologous graft to bone fusion and characterized the proliferative response of osteoblasts to mechanical force in vivo using a novel small animal model of distraction osteogenesis. With a strong background in developmental biology and a renewed appreciation for translational science he then began his career in Biotechnology at Creative Biotechnologies, Inc. in Hopkinson, MA in 1998 where he researched clinical applications of Bone Morphogenic Proteins including a previously unappreciated role in reducing renal fibrosis following acute or chronic injury. Dr. Gould rose through the scientific ranks at Creative Biomolecules which became Curis in 2000 through a corporate merger, and led a collaboration with Genentech to develop small molecule Hedgehog pathway inhibitors for the treatment of cancer. At the termination of the research collaboration with Genentech, Dr. Gould followed the molecule that would eventually become Erivedge to Genentech where he played a pivotal role in its preclinical and clinical development. In 2012, Dr. Gould along with two of his Genentech colleagues shared a “Drug Discovery of the Year Award” presented by the British Pharmacological Society for their work on the pharmacology of vismodegib (Erivedge).

Rana Samadfam, Ph.D, DABT  
Dr. Rana Samadfam is a Scientific Director of the In Vivo Pharmacology department at Charles River. She is also a principal scientist in Musculoskeletal Research department. She is a diplomat of ABT. She received her MSc and PhD degrees from the University of Sherbrook in Quebec Canada with focus on arthritis and pharmacology. Following her PhD, she accepted a post-doctoral scholar position at the University of McGill, Montreal Canada with focus on bone and endocrinology. She joined Charles River 10 years ago, accepting a position in musculoskeletal group. She is winner of several awards including the ASBMR Young Investigator Award and author of numerous peer-reviewed publications (over 80). Her areas of expertise include inflammation, early in vivo pharmacology, toxicology, bone, diabetes and the endocrine system.

Leon Hall, Ph.D  
Dr. Leon Hall is Global Head of Preclinical Operations at Mousera, a technology driven preclinical contract research organization in the Bay Area. He received his Bachelors degree from the University of Guelph in Ontario Canada, before returning to his home country of England where he obtained his Master’s degree and Ph.D. in Molecular Pathology and Toxicology from the University of Leicester. Leon moved to the US in 1999, accepting a post-doctoral scholar position at the University of California at Davis, specializing in characterizing cholinergic receptors in rodent models of dermatological disorders, and soon after he began providing core support to investigators in anesthesiology and neurodegenerative disorders research, transferring to a faculty appointment in 2003 and starting UD Davis’ spinal cord injury program. In 2005 Leon accepted a position as Study Director at The Jackson Laboratory where he helped build that program’s focus from metabolic disorders to include immunology, oncology, regenerative medicine, and neuromuscular and neurodegenerative disorders. While at JAX Leon headed up the program to commercially develop their humanized mouse immune system portfolio, and as Director of Scientific Operations he provided scientific and operations oversight to JAX’s preclinical contract research service. Leon left JAX in 2013 to lead the development of Taconic Biosciences humanized mouse and patient derived xenograft programs, and as Sr. Director of Global R&D he was also responsible for leading their GEMs and microbiome research programs. Leon joined Mousera’s senior leadership team in 2015.

Peter Havel, DVM, Ph.D  
Dr. Peter Havel received his DVM and a PhD in Endocrinology from the University of California at Davis. He is a Professor with joint appointments in the Departments of Molecular Biosciences and Nutrition. Dr. Havel and his team investigate the regulation energy and carbohydrate/lipid metabolism, and the involvement of endocrine systems in the pathophysiology of obesity, diabetes, and cardiovascular disease. His laboratory is studying the mechanisms regulating the secretion of pancreatic, gastrointestinal, and adipocyte hormones. The role of endocrine, metabolic, and dietary factors in regulating energy balance, insulin action, and lipid/carbohydrate metabolism is examined in animal models and in clinical studies in humans. A major focus of the research is the interaction of diet composition (such as dietary fats and sugars) in the development and progression of obesity, diabetes, and dyslipidemia/atherosclerosis. His research team conducts studies on the prevention and treatment of diabetes in a rat model of type-2 diabetes (UCD-T2DM Rats) that is more similar to the pathophysiology of type-2 diabetes in humans and in a diet-induced rhesus monkey model of metabolic syndrome that exhibits insulin resistance, dyslipidemia, and fatty liver disease. Dr. Havel's laboratory also studies the endocrine effects of bariatric/gastrointestinal surgery and how hormones are involved in the improvements of carbohydrate and lipid metabolism observed post-surgery. He has published more 190 original peer-reviewed articles and 35 reviews and textbook chapters on his work in these areas.