NorCal SOT newsletter

september 2008

Welcome back after the Summer Olympics and Party Conventions (be sure to vote) to join us in our fall Safety Pharmacology Symposium on October 16th - co-hosted by Roche and held at the wonderful Roche facility in Palo Alto.

Dinah Misner and Sushmita Chanda were instrumental in developing this Symposium and arranging the venue. We will have a full day of speakers covering all aspects of Safety Pharmacology testing and will provide breakfast, lunch and dinner at a nominal cost for all - except the students – for them it is free – and yes you may win a bottle or two of wonderful California wine if you do attend.

This is a terrific opportunity to network with other Bay Area toxicologists. Steve Dizio (our vice president) attended the National SOT leadership conference with representatives from all the Regional SOT Chapters and I am proud to report that NorCal is considered one of the most dynamic chapters in SOT.

Our May 2008 Newsletter (you can find this on the SOT Regional Chapter website) developed by Tao Wang (our vice president elect) with assistance of Susanne Brander (our student/postdoc liaison) was used as a shining example of what communication tools can be used by Regional SOT Chapters to reach out and serve their membership. From programs to job postings to local toxicology assessment of national and international importance (e.g., "Safety Assessment of Fish and Shellfish Impacted by the M/V Cosco Busan Oil Spill in San Francisco Bay, California" – by S. Klasing, R. Brodberg, M. Gassel and our very own George Alexeeff (a NorCal SOT past president) – the NorCal SOT Newsletter provides the membership with useful and interesting information.

Once again we strive to reach out to students and faculty at UC's Davis, Berkeley, Santa Cruz and San Francisco as well as other local schools to attend our meetings - at no cost for travel or attendance. With the awareness that these same students will seed the SOT – we provide them with the ability to participate locally and nationally (e.g., poster presentations, travel grants, student awards) and to network (e.g., local member companies offer summer internships and possible other employment opportunities).

Please set aside October 16th for our wonderful Symposium and chance to network with Bay Area toxicologists at Roche.

Warmest regards,

George R. Clemens
President NorCal SOT

NorCal SOT

2008 Fall Symposium

Everything you wanted to know about Safety Pharmacology testing - and don't be afraid to ask

Cohosted by Roche Palo Alto
October 16, 2008

Program:

8 :15 am – 9 :00 am	Registration & Breakfast
9 :00 am – 12:15 am	Symposium
12 :15 am – 1 :30 pm	Lunch
1 :30 pm – 4 :30pm	Symposium
5 :30 pm – 7:30pm	Dinner

Roche Palo Alto, 3431 Hillview Avenue, Palo Alto, CA 94304

Student/postdoctoral members: FREE* admission
* travel reimbursement & awards available!

Regular members: $25 registration fee by October 10th 2008, and $35 for on-site registration

Non-members: $35 registration fee by October 10th 2008, and $45 for on-site registration

Special thanks to Sushmita Chanda, Dinah Misner and Stefan Platz of Roche for their help in organizing this event !!

Please send the attached Meeting Registration Form to Jeff Tepper by October 10th 2008. (teppertox@aim.com)

IN VIVO RESPIRATORY SAFETY PHARMACOLOGY AND TOXICOLOGY EVALUATION: MEASUREMENTS, METHODS AND BEYOND & RESPIRATORY SAFETY PHARMACOLOGY ASSESSMENT: CONSIDERATIONS THAT AFFECT DOSE-RESPONSE

Jeff Tepper, PhD – Consultant
Terry Sweeney, PhD – Nektar

Safety pharmacology studies of the respiratory system examine the impact of drug exposure on altering the lungs primary function; that of ensuring the body is adequately oxygenated. Respiratory safety pharmacology studies are typically used to address the occurrence of primary or secondary adverse pharmacodynamic effects when exposure is in the therapeutic range or above. These types of studies can also serve to better understand the mechanism of adverse respiratory effects observed in toxicology and/or clinical studies. Current guidelines call for the acute assessment of drug on ventilation prior to first administration in humans. Because clinical observation is insufficient to assess adequacy of ventilation in animals, the various methods used to evaluate ventilation and the interpretation of the data will be discussed. Beyond the basic core measurements of ventilation, more discriminating measurements of pulmonary function can be made. Measurements of resistance, compliance, pulmonary arterial pressure, blood gases, blood pH and even forced expiration, diffusion capacity and inhomogeneity of ventilation can be made in animals as small as mice. New technologies and better biomarkers of lung injury may improve respiratory assessment allowing easier incorporation of these techniques into long term toxicology studies.

Evaluating the safety of inhaled therapeutics poses unique challenges compared to other routes of administration. Of particular importance is the accurate determination of lung dose which is critical to assess the disposition and safety of inhalation products. When evaluating the safety pharmacology of an inhalation product it is important to understand how inhalation exposure systems, methods, and technologies/formulations (e.g., liquid vs dry powder) may affect the safety assessment. This talk will review factors that affect lung dose such as the anatomy of the respiratory tract, species differences, deposition, clearance, and particle size. Different delivery technologies either liquid or dry powder will be presented and factors that are important in evaluating each type of delivery technology will also be discussed. Finally the practical challenges for determining lung dose and the implications of inhalation dose estimates on safety assessment will be discussed.

NorCal SOT

2008 Fall Symposium Abstracts

BEYOND THE CORE BATTERY: SECOND AND THIRD TIER SAFETY PHARMACOLOGY
Mark Vezina, PhD – Charles River

The ICH S7 guidelines (a and b) for the conduct of safety pharmacology studies are specific on the core (first tier) requirements to support a first dose into humans. However, the guidelines are less specific about the next steps following a positive pharmacological response in one or more core studies; when organ systems other than cardiovascular, respiratory and CNS, should be examined; or when adverse pharmacology is encountered in the clinic. The presentation will explore these situations with descriptions of some of the "supplemental" and "follow-up" techniques available (often referred to as second or third tier) as well as some real-life examples of approaches that have been applied to investigate pharmacological activity detected in core studies.

NON-CLINICAL ASSESSMENT OF POTENTIAL CNS EFFECTS AND ABUSE LIABILITY
Dinah Misner, PhD – Roche Palo Alto

As part of the core battery of tests defined in the ICH S7A guidelines, new molecules must be assessed for potential effects in the central nervous system. In vitro and in vivo models to assess effects on the CNS will be discussed. Additionally, molecules with activity in the CNS now require assessment for abuse potential, according to recent EMEA guidelines. The basic pharmacology underlying abuse potential and study designs/data interpretation will be presented, as well as the impact of such studies on a drug development program.

THE UTILITY OF IN VIVO CARDIOVASCULAR MODELS FOR DRUG SAFETY EVALUATION
Michael Gralinski, PhD – CorDynamics

Problematic interactions with the cardiovascular system remain one of the leading causes for compound attrition and drug withdrawal. It is imperative that discovery and development testing funnels contain a rigorous interrogation of putative effects on cardiovascular function. To this end, predictive in vivo cardiovascular models will be discussed along with recommendations on strategy and timing to enable key decisions with regard to compound selection.

DEVELOPMENT AND UTILITY OF VARIOUS IN VIVO CARDIOVASCULAR SAFETY MODELS FOR SAFETY ASSEMENEMT IN EARLY-STAGE DRUG DISCOVERY

Hai Ming Tang*, Hong Wang, Justin Ly, Michael Sweeney, Ray Zhang, Alvie Bello, Chris Lawson, Bluegrass Biggs, Vicki Garcia, Sushmita Chanda, Kyle Kolaja, Stefan Platz, Christina Riordan and Dinah Misner * (*presenters)
Department of Safety Pharmacology, Non-Clinical Safety, Roche Palo Alto

The development of robust cardiovascular safety models, particularly in non-rodent animal species, for safety assessment during early-stage drug discovery process has been an area of intense focus recently. However, standard CV safety models such as conscious and “free-roaming” telemetry models in dogs and monkeys may have limited utility early on in the process. Limited API supply and lack of bioavailability information are common problems facing early-stage drug discovery programs, making standard telemetry models less attractive. We have developed and adapted several CV safety models at Roche to specifically address the above issues and have successfully screened novel, early-stage compounds using these models to prioritize compounds moving forward. Four separate CV safety models in different species were successfully developed and used in early-stage drug safety evaluations. Intravenous infusion in either step-up or continuous fashion is the desirable route of administration for the following reasons: 1), To minimize compound usage; 2). To perform extensive PK-PD analyses and 3). To allow evaluation of compounds with unknown bioavailability. These models allow multiple compounds to be screened at an early stage to prioritize compounds moving forward into conventional models that carry the least risk of cardiovascular liabilities.

DRUG-INDUCED HERG & NON-HERG CHANNEL LIABILITIES: IN VITRO AND EX VIVO METHODS OF ANALYSIS

Hugo Vargas, Ph.D.

A variety of pharmacological methods are available to assess cardiovascular safety and can be used to optimize candidate selection. Assays for specific ion channels, e.g., hERG, NaV1.5 and CaV1.2, and isolated heart preparations, e.g, rabbit Langendorff, can be used in a coordinated fashion to identify cardiovascular risk prior to execution of cardiovascular telemetry studies. This presentation will focus on ion channel and isolated heart models, their value to early screening, and how they can be used for cardiac liability testing, and risk assessment.

NONCLINICAL SAFETY PHARMACOLOGY EVALUATION OF THERAPEUTIC MONOCLONAL ANTIBODIES, GENENTECH'S APPROACH

Hong Wang, PhD

Rather than performing "stand-alone" single dose safety pharmacology studies, we routinely include cardiovascular, respiratory and central nervous system safety pharmacology assessments in repeat-dose toxicity studies. Separate, IND-enabling safety pharmacology studies have occasionally been requested by the FDA; however, we have been successful in justifying that the integrated approach is scientifically sound and sufficient for the IND submission. Since the implementation of ICH E14 guidance, additional nonclinical cardiovascular safety pharmacology studies including in vitro assays (hERG, Purkinje fiber) and stand-alone in vivo studies specifically to assess QT/QTc prolongation potential of biologics have in some cases been requested by the FDA. In response, an integrated assessment has been conducted to formulate a scientific rationale and strategy for evaluation of QT/QTc prolongation potential of monoclonal antibodies (MAbs). As MAbs are unlikely to block hERG ion channel current flow either directly or indirectly, in vitro assays are generally considered inappropriate for MAb QT/QTc risk assessment. In addition, certain formulation excipients required for MAb stability interfere in the hERG assay. Consequently, Genentech does not include an in vitro hERG assay as part of the nonclinical assessment for MAbs. Electrocardiogram (ECG) and hemodynamic measurements are routinely included in repeat-dose toxicity studies for MAbs as part of the IND-enabling nonclinical safety program. Different study designs incorporating surface ECG, surgically implanted telemetry and Jacketed External Telemetry (JET) system have been used. Our experiences with different designs will be presented. The in vivo models allow assessment of effects that could result from potential neuronal and/or hormonal perturbations. Following ECG evaluation in nonclinical studies appropriate incorporation of ECG monitoring in Phase I clinical trials supports development of an informed strategy for overall risk assessment of QT/QTc prolongation potential in later stage clinical trials. In conclusion for MAbs with highly specific target binding, it is generally sufficient to assess safety pharmacology endpoints by incorporation of these endpoints directly into multiple-dose, IND-enabling toxicology studies. This approach allows continuous evaluation of potential cumulative effects over the course of a study, and it enables an integrated assessment of potential effects within a study where standard toxicology endpoints and toxicokinetic data are collected from the same animals.

NorCal SOT

2008 Fall Symposium Biosketches

Dinah L. Misner, Ph.D.
Associate Director, Roche Palo Alto

Dinah joined Roche Palo Alto over 8 years ago in the central nervous system therapy area, developing molecules for the treatment of Alzheimer's disease and neuro-psychiatric disorders. She moved into the non-clinical safety department in 2005, where she is now head of the safety pharmacology group in Palo Alto, and a member of the discovery and investigative safety department.
Dinah earned her B.S. in Biochemistry at Worcester Polytechnic Institute and Ph.D. in Biomedical Sciences at University of California, San Diego.

Hugo M. Vargas, PhD
Scientific Director, Amgen Inc.

Dr. Vargas is a Scientific Director in the Investigative Toxicology Department and Head of the Investigative Safety Pharmacology group at Amgen, Inc. He has been conducting general and safety pharmacology studies in the pharmaceutical industy since 1991, and has worked at several companies including Aventis, DuPont Pharma, and Merck Research Laboratories. At Amgen, his group is responsible for providing early cardiovascular safety evaluation for all new chemicals entities and biologicals considered for preclinical development, and for regulatory safety pharmacology studies required to enable first-in-man testing. In addition, he serves as a core member of the Cardiovascular Safety Advisory Committee at Amgen. Dr. Vargas is a member of the Board of Directors of the Safety Pharmacology Society.

Hai Ming Tang, M.S.
Research Scientist II, Roche Palo Alto LLC

Hai Ming joined Syntex in 1990 in the Department of Cardiovascular Pharmacology upon obtaining his M.S. in Pharmacology. In 1995, Hai Ming joined the then newly-established Genitourinary group after Syntex was acquired by Roche. Since 2005, Hai Ming has been a member of the Safety Pharmacology group within Non-Clinical Safety organization at Roche Palo Alto.

As a Pharmacologist with eighteen years of industrial drug discovery experience in the areas of in vivo cardiovascular and urologic pharmacology, Hai Ming has developed numerous animal models in many species and made significant contributions towards the successes of several drug discovery programs. Since joining the Safety Pharmacology group three years ago, Hai Ming has played a key role in developing several cardiovascular animal models for safety assessment in early-stage drug discovery.

Hai Ming earned his B.S. in Pharmacy at the Shanghai Medical University and M.S. in Pharmacology at the University of Hawaii.

NorCal SOT

2008 Fall Symposium Biosketches

Jeff Tepper, PhD
Consultant

Jeff Tepper has over 25 years experience in the conduct of preclinical pharmacology and toxicology studies. He obtained his Ph.D. in Pharmacology and Toxicology from the University of Rochester and is certified by the American Board of Toxicology. He is author of numerous peer-reviewed publications and chapters, particularly in the area of respiratory pharmacology and inhalation toxicology. He has previously worked with the US EPA, for Genentech and Bayer, and helped found Aerovance Inc. He is currently working as a consultant to the biotech industry and can be reached at TepperTox@aim.com

Terry Sweeney, PhD
Director of Life Sciences, Nektar Therapeutics

Terry Sweeney is the Director of Life Sciences at Nektar Therapeutics where she leads the team responsible for evaluating the safety of drug candidate molecules. She has a PhD in Physiology and Biophysics and has more than 20 yrs of experience in pulmonary drug delivery. She has published numerous articles and book chapters and has particular expertise in the deposition and clearance of inhaled particles. Previously she worked at Genentech and in the Respiratory Biology Program at the Harvard School of Public Health.

Hong Wang, PhD, DABT
Toxicologist, Genentech Inc.

Hong Wang is a scientist/toxicologist in the Safety Assessment Department at Genentech, Inc. Hong received her M.D. from Beijing University, Medical School in 1990 and her Ph.D. in Molecular, Cellular and Developmental Biology from the University of California, Santa Cruz in 1997. She joined the Preclinical Department at PDL Biopharma in 1998 and worked on pharmacology, translational medicine and nonclinical safety evaluation of a variety of monoclonal antibody therapeutics. In 2005, she joined Celera Genomics Inc. where she was a project toxicologist overseeing a number of small-molecule programs through candidate selection and early development. Since 2006, Hong worked as a toxicologist at Genentech, Inc. and supported a number of large and small molecule programs of different development stages. Hong is a member of the Society of Toxicology and is a Diplomat of the American Board of Toxicology.

NorCal SOT

2008 Fall Symposium Biosketches

Michael R. Gralinski, Ph.D.
Chief Executive Officer, Co-Founder (CorDynamics)

Mike is the Chief Executive Officer and Co-Founder of CorDynamics, a cardiovascular contract research organization and consulting group in Chicago. Along with his partners, Mike started CorDynamics in 2002 and since then the company has grown into a leading provider of nonclinical cardiovascular services for more than 100 international biopharmaceutical clients.

Mike has extensive management experience working for several pharmaceutical organizations including Warner-Lambert/Parke-Davis, G.D. Searle, Pharmacia, and Pfizer. His past responsibilities included directing product safety and toxicology operations, leading resolution efforts for cardiovascular issues involving discovery, development, and marketed compounds including Rezulin, Celebrex, and other COX-2 inhibitors, as well as cultivating relationships with international colleagues throughout small and large biopharma. He was involved in the genesis of the Safety Pharmacology Society and has been elected to multiple positions on its Board of Directors including Treasurer, Vice-President, and President. Mike earned his B.S. in Pharmacology & Toxicology at the University of Wisconsin-Madison and Ph.D. in Pharmacology (Cardiovascular) at the

Mark Vézina, PhD
Charles River Laboratory

Mark Vézina has worked in the pharmaceutical industry for the past 20 years, 18 of which have been in contract research. With a background in electrophysiology, he has been involved with the conduct of safety pharmacology studies since the early 90's and is currently head of the Safety Pharmacology department as well as the Ocular and Neuroscience department at the Charles River preclinical site in Montreal.

NorCal SOT newsletter

september 2008

2008-2009 NorCal SOT Board of Directors

President:	**George Clemens, Rigel Pharmaceuticals, South San Francisco gclemens@rigel.com (650) 624-1377**
Vice President:	**Stephen Dizio, Department of Toxic Substances Control, Sacramento, sdizio@dtsc.ca.gov**
Vice-President Elect:	**Tao Wang, Novartis Pharmaceuticals, Emeryville tao.wang@novartis.com (510) 923-3562**
Secretary:	**Charles Barton, Xoma, Berkeley barton@xoma.com (510) 204-7553**
Treasurer:	**Jeffrey S Tepper, Consultant jtepper@catbio.com (650) 266-8673**
Councilor: (Past President)	**Sanjay Chanda, Anacor Pharmaceuticals, Palo Alto schanda@anacor.com (650) 543-7592**
Councilor:	**John A Wisler, Amgen, South San Francisco jwisler@amgen.com (805) 447-9787**
Councilor:	**Karen Steinmetz, SRI International, Menlo Park karen.steinmetz@sri.com (650) 859-4145**
Student Liaison:	**Susanne Brander, University of California at Davis smbrander@ucdavis.edu (707) 227-0384**

NorCal SOT newsletter september 2008

Northern California Regional Chapter
Society of Toxicology

2008 Meeting Registration Form
Please print clearly

Name: _____

Company: _____

Telephone: _____ Email: _____

Member of Northern California SOT: Yes No

Registration fee: free students/postdoctoral fellows
$25 full members
$35 non-members

Payment Type: Check _____ Credit Card _____

Credit Card # _____ Exp date _____

Name on Card _____

Make checks payable to Northern California Chapter, Society of Toxicology

Please submit to:

Jeffrey S. Tepper, Treasurer, NorCal SOT
197 Glasgow Lane
San Carlos, CA 94070
TepperTox@aim.com

- **Would you like to attend the dinner?** **Yes** **No**

For additional information, please contact George Clemens, NorCal SOT President at gclemens@rigel.com

NorCal SOT newsletter september 2008

Careers ...

Pharmacokinetics & Metabolism Scientist
The Toxicology and Metabolism group at SRI International seeks a highly qualified candidate to perform pharmacokinetic and toxicology studies in animal models. The candidate will assume the role of a Study Director to conduct several preclinical GLP and non-GLP studies supported by NIH and other government and commercial funds. Responsibilities include planning and management of all aspects of animal studies including preparation of study protocols, coordination with other groups (such as Formulation, Mammalian Toxicology, Bioanalysis), analysis of pharmacokinetic and other data, and preparation of study reports. The studies will include compounds of various therapeutic classes (e.g. anti-cancer, anti-infective, cardiovascular). The candidate will also participate in the planning, design and preparation of reports for *in vitro* drug metabolism and drug transport experiments. Will participate or assume lead authorship in resulting manuscripts from these studies and present abstracts in meetings/conferences. Opportunities also exist within our group to pursue independent research interests in the form of grants and contracts, as well as working closely with other research scientists/mentors in the areas of drug metabolism and pharmacogenetics.

Requirements:

Ph.D. degree in Pharmacology, Pharmacokinetics, Pharmaceutical Sciences, Toxicology or related discipline with 0 – 3 years of post-doctoral experience in academia or industry. Experience in pharmacokinetic modeling and use of appropriate software and interpretation of pharmacokinetic/pharmacodynamic data is required. Excellent skills in written and oral communication as well as time management and multi-tasking are required. Experience in preclinical GLP studies is preferred.

How to apply:
Apply via our web page at:
https://sri.ats.hrsmart.com/cgi-bin/a/highlightjob.cgi?jobid=3449

SRI International

NorCal SOT newsletter

september 2008

Stay tuned for information about NorCal SOT's

SPRING MEETING

... to be held in April 2009 at Amgen in South San Francisco !