NorCal SOT newsletter
April 2010

Spring Symposium

Drug development: from small molecules to biologics

Time: Thursday, 5/6/2010
Location: SRI International, 333 Ravenswood Avenue, Menlo Park, CA94025

AM

Case Files of the FDA – How Not to Develop a Cancer Drug
William David McGuinn, Jr., MS, Ph D, DABT, Division of Drug Oncology Products, CDER, FDA

Nonclinical evaluation of oral antiviral agents
GrushenkaH. I. Wolfgang, Ph.D, DABT, Vice President, Drug Safety Evaluation, Gilead Sciences, Inc.

Toxicological Considerations for Oligonucelotide Therapeutics
Page Bouchard, DVM, DACVP, Global Head of Preclinical Safety, Novartis

PM

FDA and Nanotechnology for Medical Products
Richard A. Canady Senior Advisor, McKenna Long & Aldridge, LLP

Assessment of Genotoxic Impurities in Small Molecule Drug Candidates
Kurt Black, PhD, DABT, Comparative Biology and Safety Science, Amgen.

Safety Evaluation of Antibody Drug Conjugates
Kelly Flagella, Ph.D, DABT, Safety Assessment, Genentech

Incorporation of Fertility Endpoints in Non-Human Primate Chronic Toxicology Studies for Monoclonal Antibodies
Anu Vaidyanathan, Ph.D., DABT, Safety Assessment, Genentech

Table of Contents

Editor Tao Wang
Associate Editor Susanne Brander

NorCal SOT newsletter April 2010

SOT Annual Meeting in Salt Lake City

by Heather Bolstad

NorCal SOT members had a great time learning and networking in beautiful Salt Lake City. Members had a chance to connect during the NorCal SOT reception at Squatter's Pub and Brewery, where Young Investigator Awards (YIAs) were presented to UC Davis Ph.D. students Thomas Hill and Laurel Plummer and the Past President-Emeritus plaque was presented to George Clemens. We are already looking forward to next year's meeting in Washington D.C.!

"The 2010 Young Investigator Award was a great honor and a high point in my trip to the Society of Toxicology Conference in Salt Lake City. This was my first chance to attend an SoT conference, and it did not disappoint. The opportunity to present my work at SoT has been a goal throughout my pre-doctoral training here at UC Davis, and having this milestone completed at this point in my life and training was particularly sweet. I was very determined to go to this conference, and the honorarium from the 2010 Young Investigator Award as well as the SoT travel award went a long way to make this dream a financial reality for me this year. It also bore unexpected fruit in my inclusion in the Committee on Diversity Initiatives program for the undergraduates and a subsequent request by Dr. Jorge Davila to participate again next year. I fully intend to do so. I should like to once again express my deep gratitude to the Northern California Chapter of the Society of Toxicology for honoring me with this award and helping me realize a long awaited milestone in my scientific odyssey. It has been said that "a man's reach should exceed his grasp, or what's a Heaven for?" -- I was able to hold it in my grasp and experience an unforgettable moment with your help. Thank you." - Tom Hill

NorCal SOT President Steve DiZio (left) with YIA winner Thomas Hill of UC Davis (right)

Steve DiZio (right) presents George Clemens (left) with the Past President-Emeritus plaque

(left to right) Former NorCal SOT Presidents Sanjay Chanda, George Clemens, Susan Rice, and Bob Howd at the NorCal SOT reception

Amy Kim (right), NorCal SOT Councilor and chair of the Awards Committee, presents a YIA to Laurel Plummer of UC Davis (left)

A Conversation with Jon Cook, Vice President of SOT

by Tao Wang & Susanne Brander

Q: Clearly increasing the membership seems to be a goal for the society, but as the membership grows the group becomes more impersonal. What are your plans for maintaining the cohesiveness and camaraderie of the society?

Jon: A few of SOT's strategic goals are to strengthen scientific programs and deepen member engagement while increasing membership is really an outcome of the former. The SS and RC are SOT's principle mechanisms to maintain cohesiveness and camaraderie of the Society. SOT always tries to balance the scientific program. More than 90% programs are offered by Specialty Sections. It is really a grass root effort, and these grass root efforts provide the growth of the scientific society as expanding SS has led to an increase in overall SS membership. The SS and RC provide the opportunity for networking and leadership development. Regional chapters can also propose courses or symposia. Over the next few years, SOT Council will be implementing recommendations from the Global Strategy Task Force (Chaired by Ruth Roberts, Astra Zeneca). A primary goal is to make SOT a more welcoming society for toxicologists from outside US. For instance, the Global Strategy Task Force will provide recommendations to Council on helping toxicologists from developing countries to become active in SOT. For example, reducing fee structure for members from developing countries is one tangible recommendaton. One of the key goals of the Global Strategy is to provide tools and resources to the toxicologists in developing countries so they can improve public health within their country.

Q: Industry has started to send fewer toxicologists to attend the SOT annual meetings, and the excuse is that there are not many programs for industrial toxicologists. What does SOT want to do about it?

Jon: While this may be true at some companies, I have not personally seen this trend at Pfizer. This year actually many programs are offered to industrial toxicologists through continuing education courses, symposia, roundtable discussions, and workshop sessions. We also created at least one new SS focused on Biotherapeutics. The topics cover from small molecule to biologics, from drug discovery to development, and so on. For example, combination toxicology studies for drug development, genotoxic impurities in drug products, latest ICH directions on doing preclinical safety evaluation, etc. If more industrial programing is needed, I would encourage industrial toxicologists to propose sessions through their SS or RC.

Q: Many SOT presidents are from academia. But the two major tox communities are from academic and industry. It seems that industry representation has not been that strong. What does SOT do to balance these two communities? Do you have any advice for students in toxicology field?

Jon: SOT Nominating Committee, which is an elected committee, strives to maintain diversity and gender balance. The 2010-2011 Presidential chain has the broadest diversity in recent memory; the Past-President is from academia, the President is from a NGO (Non-governmental organization), the Vice President is from industry, and the Vice President-Elect is from government. Hence, we currently represent all of the major sectors of employment. For early career scientists, the SS, SIGs, and RC provide leadership opportunities to get involved in SOT.
In order to be nominated for the SOT presidential chain, one must have served on Council previously. I was a member of several committees, specialty sections, task forces and regional chapters before becoming the Vice President –Elect for the SOT.

Q: What kind of changes would you like to implement as President?

Jon: Each SOT President has a theme to define their Presidency. My Presidential Theme will focus on making SOT a more welcoming society for members outside of the United States. The Global Strategy Task Force is developing recommendations for Council and this task force has a two year remit. In terms of the scientific program, we would like to highlight global issues. We exploring ways to increase our partnership with IUTOX and key universities in developing countries to improve toxicology trainings around the globe. SOT has formed a Global Strategy Task Force to focus on this issue. Currently, our non-US based membership is about 15% of the total SOT membership. Among 6000-7000 attendees at the annual SOT meeting about 20% are from outside the US. We will continue to encourage non-US-based membership and actively engage a diversity of perspectives to help evolve our global role. Revising the fee structure for membership and attending the annual meeting will be one of the first tangible steps toward making the SOT more welcoming to SOT members from developing countries.

Q: SOT has grown too large and over time the science is evolving and touching too many different aspects of our world. Where is the area going? Is tox being submerged as a distinct field as more and more biological research becomes multidisciplinary?

Jon: I can understand this perspective, but toxicology is broadening, and science is evolving. As a consequence, we have made conscious efforts to have the Scientific Program bring in disciplines from outside of SOT. This strategy is designed to ensure that SOT does maintain its relevance. There are many challenges for toxicology. For example, the testing paradigms have not radically changed since the 1970s, with the advent of omics and pathway analysis it is now possibleto apply systems biology approach to risk assessment yet this is not occurring as frequently as it should, and how do address population diversity in response (i.e., pharmacogenomics) in our risk assessments. These are some of the opportunities that toxicology needs to address to maintain it relevance as a Society.

Q: Do you see a need for an EcoTox Specialty Section?

Jon: I think that it is a terrific idea to provide a home for those members who also belong to SETAC. It is easy to start a Specialty Section. You only need 50 members to sign on and write by-laws. SOT provides start up funds for a few years and thereafter the SS needs to be self sufficient. The challenge is the sustainability which can be facilitated by actively submitting ideas for sessions at the annual meeting.

Editor's Choice for *Environmental and Molecular Mutagenesis*

Recently, an article by Dr. Luoping Zhang and others was selected by The Environmental Mutagen Society as the Editor's Choice, to be highlighted in an upcoming edition of *Environmental and Molecular Mutagenesis*. The article "Formaldehyde and Leukemia: Epidemiology, Potential Mechanisms, and Implications for Risk Assessment" provides a multidisciplinary review of the state of the science regarding the health effects of formaldehyde and assessment of formaldehyde risk. Below is a link to the article on the *Environmental and Molecular Mutagenesis* website: http://www3.interscience.wiley.com/journal/122612710/abstract

This review by Dr. Zhang *et al.* communicates the content of a Symposium held as part of the 2008 Annual Meeting of the Environmental Mutagen Society, and broadly covers different areas of formaldehyde risk assessment. The review article includes a new meta-analysis of studies assessment the association between leukemia and formaldehyde exposure. Potential mechanisms through which formaldehyde affects human health are described, including formaldehyde's effects on DNA damage response pathways. In addition, the state of the science in terms of the measurement of formaldehyde-DNA adducts is presented. Finally, information from these different areas is integrated, implications for formaldehyde risk assessment are discussed, and areas where additional research is needed are identified.

Dr. Zhang is an Associate Professor from School of Public Health at the University of California, Berkeley, CA. She is a member of NorCal SOT Regional Chapter, and national SOT. She has been a very active supporter to NorCal SOT by promoting her students and postdoctoral fellows to participate in chapter meetings and other activities. Her students have presented their research work at meetings, representing their group research projects and writing assignments. Dr. Zhang created a graduate/undergraduate course called "**Practical Toxicology**" at *Cal* a few years ago and applied different teaching methods both inside and outside the classroom. She invites various NorCal SOT members to give lectures in her class, so that students can garner practical toxicology knowledge, and also make connections with speakers and build useful networks. Dr. Zhang has also taken her motivated and creative students on fieldtrips to the spring meetings at NorCal SOT.

Dr. Zhang's current research focuses on understanding the mechanisms underlying blood cancers induced by chemical exposures to benzene, formaldehyde and trichloroethylene. Her recent studies in formaldehyde and leukemia have gained much attention from government agencies (EPA & NTP) and industries. In fact, one of her publications (Zhang *et al.*, CEBP 19:80-8, 2010) reported the results generated from their biomarker study in China, which provided evidence that formaldehyde exposure may have caused damage to hematopoietic cells that originated in the bone marrow of Chinese workers. This provides support for the biologic plausibility that formaldehyde causes myeloid leukemia, and formed the evidence for the conclusion reached by the IARC Working Group 100F (Baan *et al.*, The Lancet Oncology 10:1143-4, 2009). The Environmental Mutagen Society specially contacted NorCal SOT and asked us to highlight this important accomplishment as part of our public relations activities.

Besides working and teaching, Luoping also enjoys hiking and bicycling with her husband Philip, son Eugene, and her friends. Additionally, she is a passionate international folk dancer and is actively involved with the Berkeley Folk Dance group.

Dr. Luoping Zhang

News/Notes from Graduate Students in Toxicology

Vanessa De La Rosa and Brandon Gaytán, graduate students in the *Molecular Toxicology Program* at the University of California, Berkeley, recently participated in the 2010 National SOT meeting held in Salt Lake City. They share their unique experiences mentoring undergraduates in toxicology here:

With funding from the NIH MARC (Minority Access to Research Careers) program, the National Society of Toxicology Committee on Diversity Initiatives (CDI) sponsored the 22nd annual Undergraduate Education Program at the 2010 SOT meeting. SOT provided fifty outstanding undergraduate students of underrepresented backgrounds with the opportunity to attend the annual meeting. As graduate students, we participated in the program as peer mentors-
groups of 4-5 undergraduate students were paired with 1-2 graduate students as well as 2 experts from academia, government, or industry. The three day program, designed to cultivate passion for higher education and careers in toxicology, was filled with informative lectures, workshops, and social events that stimulated candid and insightful discussions amongst the students and their mentors.

The heart and soul of the Undergraduate Education Program is the mentorship opportunity that undergraduate students received from current graduate students and field toxicologists. The close-knit atmosphere allowed students the opportunity to learn how a graduate education could ultimately lead to an exciting and fulfilling career in the field of toxicology. For example, we led an informal workshop entitled "How to Go to Graduate School" that provided students with advice on applying as well as a snapshot of life at graduate school. We also attended the *In Vitro* student luncheon as a group, where we formed opinions on the merits and disadvantages of *in vitro* methods. At the student/postdoc reception, students attempted to master the nuances of networking through creative icebreakers and learned about other aspects of SOT, such as regional chapters and specialty sections. In addition, students were able to attend a Nobel Laureate lecture and also received program information at a "graduate school fair". Throughout the program, students verbally expressed their excitement and thank yous and were visibly inspired by the meeting proceedings.

As past undergraduate participants, we returned to participate as graduate mentors, and many other program alumni also returned to the program as mentors, speakers, and organizers. Serving as a mentor was a rewarding experience that went beyond just volunteering. Our experience allowed us to form friendships, collaborations, and most importantly, offer guidance to others by sharing our experiences as entering graduate students. By partaking in the Undergraduate Education Program, we helped reach out to the toxicologists of tomorrow and provided a stepping-stone for students to become successful and active members of SOT.

Those who are interested in participating in the program can contact Adrian Nanez at ananez@amgen.com

Vanessa De La Rosa & Brandon Gaytán
Molecular Toxicology Graduate Group, University of California, Berkeley


Dr. Martin Ronis

Is Soy Estrogenic?

Sitting at the cross-roads of Toxicology and Nutrition research, Dr. Martin Ronis is the Associate Director for Basic Research at the Arkansas Children's Nutrition Center (ACNC). The ACNC is one of 6 Human Nutrition Research Centers funded by the USDA –ARS and one of only two working in the area of childhood nutrition. Although a toxicologist by training, Dr. Ronis has learned a lot about nutrition since helping Dr. Thomas Badger, Professor of Pediatrics at the University of Arkansas for Medical Sciences, establish the ACNC in 1995. The mission of the center which employs 14 senior level scientists, nearly 100 staff and has funding of $6 million/year, is to explore the long term health consequences of early nutrition.

One of the focuses of the center is on the consequences of breast vs. formula feeding of infants. Approximately 20% of all formula-fed infants (1 million/year in the U.S.) are fed formulas made with soy protein as compared to cow's milk-based formula and since soy contains "phytoestrogens" (isoflavone phytochemicals which have weakly estrogenic properties), nutritionists have been dragged into the ongoing Endocrine Disruptor debate in the toxicology community. The question we are asking is "Is soy estrogenic?" says Dr. Ronis. There is plenty of data in the literature on the estrogenic effects of purified isoflavones, but can this reductive approach be successfully applied to complex mixtures such as foods? Dr. Ronis is conducting a series of basic studies in rodents and neonatal piglets to ask this question at the whole genome level in different estrogen target tissues during different developmental windows (neonate, pre- and post-puberty) where endogenous estrogen levels are very different. In a multi-disciplinary collaboration, the investigators at the ACNC, are also translating this research clinically and are in a middle of conducting the largest longitudinal study of breast, milk-based and soy-based formula feeding of infants in the world.

When completed, data will be obtained for 200 infants in each cohort, monitored from age 3 months to 6 years for multiple parameters including body composition, reproductive organ development, cognitive and immune development. In addition to answering questions regarding potential safety issues/ reproductive toxicity associated with soy exposure during early development, these studies will also shed light on molecular mechanisms underlying potential health beneficial properties of soy including cancer protection, reduced risks of diabetes and cardiovascular disease and anabolic effects on bone. The latter studies dovetail with Dr. Ronis NIH funded research program on the toxic effects of alcohol on the skeleton. "Sometimes it is difficult to juggle NIH and USDA funded programs, but my alcohol work involves similar skeletal endpoints to our ACNC studies and in many ways alcohol is just another foodstuff since alcoholic beverages are a major source of calories in many people's diet".

NorCal SOT 2010-11 Board of Directors

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Career Opportunities

Genentech, Inc

For more than 30 years, Genentech has been at the forefront of the biotechnology industry, using human genetic information to develop novel medicines for serious and life-threatening diseases. Today, Genentech is among the world's leading biotech companies, with multiple therapies on the market for cancer and other serious medical conditions. Please take this opportunity to learn about Genentech, where we believe that our employees are our most important asset.

The following opportunity exists in our South San Francisco, CA, headquarters:

Senior Research Associate - Investigative Toxicology

Responsibilities:
The Senior Research Associate will be responsible for conducting and overseeing investigative and screening toxicology activities to support discovery and development projects. He/she will develop new cutting-edge molecular science capabilities to support safety assessment in early drug discovery. This includes developing higher throughput/content molecular expression-based safety assays to differentiate chemical series/targets and guide project direction and drug design quality. The candidate will also apply molecular-based safety assays to guide structure-activity relationships, differentiate chemotype from target/off-target safety and utilize chemical and systems biology approaches to evaluate mechanism of action or identify toxic pathways for end organ effects.

Requirements:
This position requires a Master's degree or equivalent in a biological science field. In addition, the candidate should have at least 3-6 years of relevant industrial or academic research experience in molecular toxicology and experience in designing and developing novel higher throughput/content molecular-based predictive toxicity assays. He/she will have the proven ability to independently design, execute and interpret experiments and proactively apply, qualify and troubleshoot new technologies or assay platforms as needed. Strong communications, organizational and collaboration skills are essential. Experience with stem cell work is highly desirable. A background in cellular biology and research experience in systems biology or chemical genomics is advantageous.

Genentech is dedicated to fostering an environment that is inclusive and encourages diversity of thought, style, skills and perspective. To learn more about our current opportunities, please visit: http://careers.gene.com and reference Req. #1000031061. Please use "Web – Society of Toxicology" when a source is requested. Genentech is an equal opportunity employer.

Scientist - Toxicology

Responsibilities:
The Scientist - Toxicology will provide scientific leadership and play an active role in the process of drug development from late-stage discovery through marketed products. Working in a collaborative team environment, he/she will lead the safety assessment of Genentech therapeutics by creating a best-evidence synthesis of existing knowledge and comprehensive investigations of toxicological activity. The candidate will design and supervise in vitro and in vivo toxicology studies to support the goals of small molecule project teams. He/she will also be accountable for interdisciplinary project team membership, preparation and review of regulatory documentation, study reports and manuscripts and participation in toxicology and pharmacology initiatives.

Requirements:
This position requires a PhD and post doctorate or equivalent experience in toxicology or a relevant field. In addition, the candidate should have 7-10 years of toxicology experience in the pharmaceutical/biotechnology/CRO industry. Strong decision-making, problem-solving and analytical skills are essential, as are excellent communications and collaboration skills. Candidates with experience in small molecule drug development or supporting various therapeutic areas are preferred. Board certification in toxicology is desirable.

Genentech is dedicated to fostering an environment that is inclusive and encourages diversity of thought, style, skills and perspective. To learn more about our current opportunities, please visit: http://careers.gene.com and reference Req. #1000031242. Please use "Web – Society of Toxicology" when a source is requested. Genentech is an equal opportunity employer.

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March 29, 2010

Dear Colleague:

Because of your track record and relevant research experience, I am writing to seek your help in identifying potential candidates for our faculty search. The University of Kentucky Sanders-Brown Center on Aging is seeking qualified applications for two tenure-track faculty positions at the Assistant or Associate Professor level in the area of translational neuroscience.

Attached is a job description that I would appreciate you sharing with your organization and any relevant professional contacts. The Center on Aging wants to identify outstanding candidates and provide them the resources and environment that they need to succeed. We would very much appreciate receiving any recommendations you are willing to forward regarding potential candidates, as well as your help in alerting those who may be interested in a faculty position.

Please send your nominations, including names, institutions and email addresses if you have them to me directly or to SBCoAFacultySearch@uky.edu.

Thank you for your help.

Sincerely,

Linda J. Van Eldik

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