March 2014

Northern California

President's Message

Dear NorCal SOT regional chapter members,
It has been an exciting year so far! We continue to provide a variety of opportunities for the member ship and hopefully you have enjoyed participating in them. We extend a warm welcome to all our new members and congratulations to all of our newly elected board members of 2014-2015.
Our Fall symposium, which was held on October 24th, 2013 at the SSF Conference Center, focused on ADME and its role in toxicology. Invited speakers from Bay Area institutions and industry detailed current and cutting edge scientific progress in the field of metabolism. You can read about the meeting on page 2. We are hosting the Spring Symposium on April 29th at the David Brower Center in Berkeley.
NorCal SOT congratulates the winners of the student and postdoctoral awards (page 2). Thanks to Caroline English and the Past President Awards Committee for all their contributions. We continue to provide various mentoring opportunities for students and post-doctoral students. The ever popular speed mentoring event was held at Sudwerk, Davis on October 1st, 2013. Stay tuned for announcements for upcoming mentoring sessions: Toxicology Career Day at UC Davis campus in April and Lunch with the Experts at the Spring Symposium. The K-12 event is also being planned for the Spring of 2014. We encourage you to volunteer for these events!
Many thanks to all of our Sponsors! Your sponsorship goes a long way in funding all the chapter activities. The next Sponsorship drive will occur March - April 2014 prior to the Spring symposium. If you are interested in becoming a sponsor please contact Toufan Parman to learn more about how your sponsorship can contribute to the continued growth and success of the chapter.
We regret to inform you that Donna Dambach resigned from the NorCal Board for personal reasons. As per our bylaws, Pamela Lein resumed the position of Vice President as of December 1st 2013. Many thanks to all of our Board members for their continued support, hard work, and dedication.
We look forward to seeing you at the NorCal reception at SOT on Tuesday March 25th.

Best Regards

Sushmita M. Chanda, PhD DABT

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Preclinical Drug Safety Group
Dan Ness

NorCal SOT Reception
Tuesday March 25th, 7-9 PM
Arrogant Butcher, 2 E Jefferson St, Ste 150
Phoenix AZ 85004
For directions Click Here

SAVE THE DATE!!
April 29th, 2014
NORCAL SOT Spring SYMPOSIUM

Venue: David Brower Center, 2150 Allston Way, Berkeley, CA 94704

Preliminary Program:

- Screening for drug abuse liability: Dinah Misner, PhD, Sr. Scientist, Genentech
- The Changing Role of EEG in the Assessment of Preclinical Seizure Risk: Joe Arezzo PhD, Albert Einstein College of Medicine, NY
- Organs on a chip: Luke Lee, PhD, Arnold and Barbara Silverman Distinguished Professor of Bioengineering, University of California, Berkeley
- Zebrafish as a screening model and nanoparticles: Robert Tanguay PhD, Distinguished Professor and Director of NIEHS toxicology Training grant, Sinnhuber Aquatic Research Laboratory, Oregon State University, Corvallis, OR
- ToxCast and Screening for neurotoxicity: Kevin Crofton PhD, Acting deputy director with EPA National Center for Computational Toxicology, USEPA, RTP, NC
- In vitro safety profiling for small molecules in drug discovery: Jacques Mignon PhD, Principal Scientist, CEREP

We hope that you will join us!

Student Award Winners-Congratulations!

NorCal SOT Post-doctoral Achievement Award

Hua Shen, UC Berkeley, "Functional Genetic Screen in Human Haploid Cells to Identify Genes Involved in Susceptibility to Chemical Exposure."
Abstract Number 920 Poster Board -319
Abstract Title: Functional Genetic Screen in Human Haploid Cells to Identify Genes Involved in Susceptibility to Chemical Exposure.
Presenting Author: Hua Shen
Session Title: Gene Regulation and Signal Transduction I
Presentation Date & Time: March 25, 2014 from 9:00 AM to 12:30 PM
Presentation Location: CC Exhibit Hall

Student Award Winners-continued

NorCal SOT Graduate Student Achievement Award

Chris Barnhart, UC Davis, "Dioxin-Like and Non-Dioxin-Like Polychlorinated Biphenyls (PCBs) Modulate Basal and Activity-Dependent Dendritic Arborization in Primary Neuronal Cell Cultures."
Abstract Number/Poster Board number: 351 Poster Board -608
Abstract Title: Dioxin-Like and Non-Dioxin-Like Polychlorinated Biphenyls (PCBs) Modulate Basal and Activity-Dependent Dendritic Arborization in Primary Neuronal Cell Cultures
Presenting Author: Christopher Barnhart
Session Title: Neurotoxicity: General
Presentation Date & Time: March 24, 2014 from 9:30 AM to 12:30 PM
Presentation Location: CC Exhibit Hall

NorCal SOT Undergraduate Student Travel Award to Annual SOT Meeting

- **Hiroko Irimagawa, UC Berkeley,** "Genetic Variation of Iron Metabolism in Mice."
  Abstract Number: 1281 Poster Board -452
  Abstract Title: Genetic Variation of Iron Metabolism in Mice
  Presentation: March 25, 2014 from 1:00PM to 4:30PM
  Presentation Location: CC Exhibit Hall

- **Michele Lin, UC Berkeley,** "Computational Analysis of the Combined Therapeutic Effects of Traditional Chinese Medicines and Western Therapeutics in Breast Cancer."
  Abstract Number 436 Poster Board -163
  Abstract Title: Computational Analysis of the Combined Therapeutic Effects of Traditional Chinese Medicines and Western Therapeutics in Breast Cancer
  Presenting Author: Annette Chu, Michele Lin
  Session Title: Computational Toxicology and Data Integration I
  Presentation Date & Time: March 24, 2014 from 1:00 PM to 4:30 PM
  Presentation Location: CC Exhibit Hall

High School Student Travel Award to Annual SOT Meeting (CRL-sponsored)

Isabel Arnould, Oak Ridge HS, El Dorado Hills and ToxiSan, "Prevalence of molds in residential indoor and outdoor environments in Northern California and its implication in health risk assessment."

Abstract Number/Poster Board number: 1831m Poster Board -180
Abstract Title: Prevalence of Molds in Residential Indoor and Outdoor Environments in Northern California and Its Implication in Health Risk Assessment
Presenting Author: Isabel Arnould
Session Title: Risk Assessment II
Presentation Date & Time: March 26, 2014 from 1:00 PM to 4:30 PM
Presentation Location: CC Exhibit Hall

Many thanks to the Past Presidents George Clemens, Linval DePass, Tao Wang, and Sanjay Chanda for serving as our judges. Thanks also to Charles River Laboratories who made possible the special HS Student Travel Award this year.

New NorCal SOT Members

Christopher Gibson	Rutgers University
Patricia Weidman	Genentech Inc
Mindy Lew	ChemRisk Inc
Michael Dong	California EPA
Jonathan Maher	Genentech
Taylor Choi	Lawrence Berkeley National Laboratory
Patrick Elias	Clorox Company
Amber Goetz	Syngenta Crop Protection Inc
Nicola Stagg	Genentech
Peter Korytko	Preclinical GPS - Global Preclinical Services
Carolyn Moyer	Amgen Inc
Ronald Shank	University of California Irvine
Timothy Patterson	Chevron
Christopher Murphy	OSOD LLC
Ana Cristina Dragomir	Mount Sinai School of Medicine
Grace Anderson	Cardno ChemRisk
Doris Zane	Genentech Inc
William Mitchell	
Eloy del Toro	Huntingdon Life Sciences
Kevin Donnelly	Theravance

A Review of the 2013 Fall NorCal SOT Symposium

On 24 October 2013, NorCal SOT hosted the 2013 Fall Symposium at the South San Francisco Convention Center. The NorCal SOT President, Dr. Sushmita Chanda, along with Board of Directors greeted approximately 110 attendees from regional business, government and academia. Our featured speakers and their topics are listed below:

- **Mitochondrial Toxicity of Nucleoside Analogs:** Joy Feng PhD, Sr. Scientist, Gilead Sciences
- **Role of Metabolism in Respiratory Toxicity:** Alan Buckpitt PhD, Professor Dept of Molecular Biosciences, UC Davis School of Veterinary Medicine
- **Role of Ceruloplasmin in Manganese Distribution and Toxicity:** Donald Smith PhD, Professor Dept of Chemistry and Biochemistry, UC Santa Cruz
- **Key Note: Chemoproteomic and Metabolomic Strategies for Drug Discovery and Toxicology:** Dan Nomura, PhD, Assistant Professor, Department of Nutritional Sciences and Toxicology, UC Berkeley
- **Transporters in Metabolism and Toxicity:** Joe Ware PhD, Sr. Scientist, Genentech, Inc.

- **How Drugs Get into the Brain & Assessment of Brain Levels:** Carol Green PhD, DABT, Sr. Director, SRI International

Speakers and attendees engaged in lively discussions about the symposium topics over breakfast, lunch, and a wine and cheese reception provided by our Sponsors. A special wine tasting event hosted by Andy Standeven, provided a wonderful opportunity for members to taste some of the fine local wines of California. The always popular Lunch with an Expert event attracted graduate and undergraduate student and mentors.

Above all, we would like to appreciate and thank our Sponsors for making this event a success:

- Silver Sponsors: Genentech, Gilead, Huntingdon Life Sciences, MPI Research, SRI International, WIL Research, WuXi AppTec,
- Bronze Sponsors: BioReliance, Biotox Sciences, Charles River, ChanTest, CiTox Lab, Covance, Cyprotex, ITR Laboratories, Pacific BioLabs, Ricercaand Toxikon

Newly Elected NorCal SOT Board Members for 2014-2015

It is with great pleasure that we can now announce next year's NorCal regional chapter executive committee:

- Pamela Lein, UC Davis – President (2 year remaining)
- Eric Harstad, Genentech – Vice President (3 yr term)
- Toufan Parman, SRI International – Vice President Elect (4 yr term)
- Doris Tham Zane, Genentech – Secretary (2 yr term)
- Caroline English, NSF – Treasurer (1 year remaining)
- Joanne Birkebak, Gilead – Councilor (2 yr term)
- Lolita Boyd, Charles River Laboratories – Councilor (2 yr term)
- Sushmita Chanda, Alios – Past-President (1 year remaining)

We have not identified the Student and Post Doctoral Representative at this time. If you know of an interested student/post-doc please have them send their resume to Jeff Tepper.
Thanks to members who sought positions and to everyone who participated in the voting process

Preclinical Drug Safety Group

By Jeff Tepper, PhD, DABT, Past President

Seventeen NorCal members with experience in the safety assessment of pharmaceuticals met for dinner at Sapore Italiano in Burlingame on December 4th. On top of informal networking, group discussions covered diverse topics ranging from strategies for species selection; the role of clinical pathology in short-term bioassays; evaluation of effector function for monoclonal antibodies; use of in vitro micronucleus for genotoxicity; and strategies for combining cardiovascular/pulmonary/CNS endpoints in a single safety pharmacology study. There was

very active participation by the attending members that represented large pharma, small biotech, CROs, consultants, and academia; all of whom brought a wealth of knowledge to the discussion. Additionally, the food was excellent. NorCal was happy to support appetizers and wine for the event.

Postdoc / Student Updates

News, events and updates from your NorCal SOT student and postdoc representatives.
Here is the Nor Cal SOT info you need to get the most out of your student or postdoc membership…

Want to get more involved in SOT?

We are currently looking for a new postdoc rep and grad student rep for NorCal SOT. Kathryn Page (your current post doc rep) and Sandra Chang (your current grad student rep) have enjoyed their time and are sad to go, but are excited for the next steps in their careers! Please contact Sushmita Chanda if you are interested in participating as a postdoc or student rep for NorCal SOT. It's a wonderful opportunity to get involved!

Past events

On October 1st NorCal SOT successfully hosted another Speed Mentoring Event! The event at University of California, Davis featured multiple individual mentoring sessions with students paired up with professionals (in the format of speed dating) followed by a networking event. UC Davis students were able to connect and receive mentorship with professionals from all over the Bay Area to learn about the diverse career opportunities in government, academia, industry and consulting.
Thank you mentors and mentees for making this Speed Mentoring event a great experience for everyone that attended!

Upcoming events

UC Davis will be hosting the event Careers in Toxicology: Panel Discussion and Mixer with Professionals on April 2nd. The event will feature a panel of professionals with government, academic, or industry careers discussing their jobs and their path in gaining their position. Students are encouraged to ask questions and raise concerns they may have about their careers. The panel discussion will be followed by a networking event for further discussion and mentorship. This is a great opportunity for students in toxicology to network and learn more about what options they have after graduation in the field of toxicology. Students from all related majors (and universities!) are encouraged to attend to help understand what goes on between being a student and having a successful career in field of toxicology. Register here! If you have any questions or are interested in attending as a panelist, mentor or student please contact Sandra Chang sndchang@ucdavis.edu.
There are many student & postdoc events at the Annual meeting in Phoenix, including The *Student/Postdoc mixer*, *Chat with an Expert*, *Poster Tours for Trainees*, the *PDA luncheon*, and more! Don't miss out, sign up when you register, or online. Visit the SOT 2014 Student & Postdoctoral Scholars Events page for more information.

Also, the NorCal Spring Symposium is fast approaching, including the *lunch with an expert*, *short talks from 2014 NorCal Student & Postdoc Award winners*, and the opportunity to *present a poster*. Register online on the NorCal SOT website Events Page.
Thanks for your time, and we look forward to meeting you at the NorCal SOT mixer in Phoenix.
Don't forget to sign up for mentor match!!
Reps out!

Sandra & Kathryn
Your Student & Postdoc Rep

Scientific Articles

PCB 95 Enhances Dendritic Spine Density through the Upregulation of miR132

Hao Chen, B.S. and Karin Streifel, PhD
Department of Molecular Biosciences, University of California, Davis, CA 95616

The prevalence of mental disorders in children has increased substantially in recent years. In 2013, the Centers for Disease Control and Prevention estimated that up to 1 in 5 children are diagnosed with a mental disorder each year. While changes in diagnostic criteria explain a proportion of the increasing prevalence, the interplay between genetic and environmental factors is likely a critical contributor to the rise. In particular, because of the vulnerability of the developing brain, children are particularly susceptible to adverse neurodevelopmental outcomes as a result of exposure to environmental contaminants. Among them, the ubiquitous polychlorinated biphenyls (PCBs) are recognized developmental neurotoxicants that can negatively impact cognitive function.

PCBs are organic pollutants that, though banned in the 1970s, persist in soil and food. PCBs are chemically stable, lipophilic, and resistant to biodegradation, and as a result of these characteristics, they bioamplify up the food chain. Non-dioxin-like (NDL) PCBs, a class of PCBs that act through different pathways than dioxin, are associated with developmental neurotoxicity. NDL-PCBs have been shown to interact with the ryanodine receptor (RyR), an intracellular calcium channel, to stabilize its open conformation, which results in an aberrant increase of intracellular calcium. Since calcium is a universal signaling molecule, disruption of calcium homeostasis can inappropriately activate downstream signaling pathways, including those important for neuronal growth and development. A collaborative research effort between the laboratories of Pamela Lein (UC Davis) and Gary Wayman (Washington State University) discovered that neurons exposed to PCB 95, a NDL-PCB congener, exhibit larger dendritic arbors as a result of activation of the calcium-dependent CamKI-CREB-Wnt2 signaling pathway.[1,2]The size of the dendritic arbor determines how many synaptic inputs a neuron can

accommodate and influences processing of signals. Therefore abnormal size and shape of dendritic branches could alter synaptic connectivity, and altered patterns of synaptic connectivity are thought to mediate many of the clinical features of developmental brain disorders.

More recent studies by the Lein and Wayman research team demonstrate that PCB 95 affects an activity-dependent microRNA (miRNA)-dependent signaling pathway associated with activity-dependent synapse formation to increase the number of dendritic spines and synapses.[3] Dendritic spines are the primary excitatory synaptic input for neurons, and alterations in dendritic spines are linked to a number of neurodevelopmental disorders. miRNAs are negative regulators of gene expression and can dynamically regulate the synaptic transcriptome in the brain. miR132 is a CREB-regulated miRNA involved in spine morphogenesis. Upregulation of miR132 suppresses translation of GTPase activating protein p250GAP, a signaling molecule that negatively regulates Rac1-PAK-mediated spinogenesis. PCB 95 activates CREB via RyR-dependent mechanisms that in turn upregulates expression of miR132. PCB 95-mediated increases in miR132, and the subsequent de-repression of Rac1 through p250GAP suppression, manifests in an increase in dendritic spines and synapse formation. Functionally, PCB 95-induced spine formation manifests as an increase in excitatory currents. Excitatory/inhibitory synaptic imbalance and the dysregulation of miR132 have been associated with cognitive impairment and mental disorders such as Rett syndrome and schizophrenia. Postmortem analyses of children with syndromic autism were found to have significantly higher levels of PCB 95 in brain tissue compared to neurotypical controls.[4] These data further implicate PCB 95 exposure as a neurodevelopmental risk factor, especially amongst genetically susceptible populations. The widespread exposure of child-bearing women to PCBs through diet and reports documenting the detection of PCBs in the paint, light fixtures, and caulk in schools, warrants public health focus to minimize childhood exposure thereby potentially reducing the prevalence of mental health disorders.[5,6,7]

References

[1]Wayman GA, Yang D, Bose DD, Lesiak A, Ledoux V, Bruun D, Pessah IN, Lein PJ. PCB-95 promotes dendritic growth via ryanodine receptor-dependent mechanisms. Environ Health Perspect. 2012 Jul;120(7):997-1002.

[2]Wayman GA, Bose DD, Yang D, Lesiak A, Bruun D, Impey S, Ledoux V, Pessah IN, Lein PJ. PCB-95 modulates the calcium-dependent signaling pathway responsible for activity-dependent dendritic growth. Environ Health Perspect. 2012 Jul;120(7):1003-9.

[3]Lesiak A, Zhu M, Chen H, Appleyard SM, Impey S, Lein PJ, Wayman GA. The Environmental Neurotoxicant PCB 95 Promotes Synaptogenesis via Ryanodine Receptor-Dependent miR132 Upregulation. J Neurosci. 2014 Jan 15;34(3):717-25.

[4]Mitchell MM, Woods R, Chi LH, Schmidt RJ, Pessah IN, Kostyniak PJ, LaSalle JM. Levels of select PCB and PBDE congeners in human postmortem brain reveal possible environmental involvement in 15q11-q13 duplication autism spectrum disorder. Environ Mol Mutagen. 2012 Oct;53(8):589-98.

[5]Hu D, Martinez A, Hornbuckle KC. Discovery of non-aroclor PCB (3,3'-dichlorobiphenyl) in Chicago air. Environ Sci Technol. 2008 Nov 1;42(21):7873-7.

[6]Hu D, Hornbuckle KC. Inadvertent polychlorinated biphenyls in commercial paint pigments. Environ Sci Technol. 2010 Apr 15;44(8):2822-7.

[7]Thompson MR, Boekelheide K. Multiple environmental chemical exposures to lead, mercury and polychlorinated biphenyls among childbearing-aged women (NHANES 1999-2004): Body burden and risk factors. Environ Res. 2013 Feb;121:23-30.

The global epidemic nature of microcystins and the need to monitor and manage it locally in Northern California's rivers, lakes and ground water

Caroline Moore, PhD candidate and Birgit Puschner, DVM, PhD
University of California, Davis School of Veterinary Medicine

Harmful algal blooms expose humans and animals to microcystins (MCs) through contaminated drinking water, seafood and blue green algae supplements (like spirulina). MCs are known to cause acute liver toxicity at high concentrations, but at low concentrations their impact on other organs, such as the nervous system, is not well understood. We developed a novel statistical approach using a generalized linear model and the quasibinomial family to analyze how MCs alter specific neurons in the adult worms *Caenorhabiditis elegans* (*C. elegans*). *C. elegans* were exposed to two MC variants, MC-LR and MC-LF, for 24 hours and then the worm's ability to be attracted to two different odors, diacetyl and benzaldehyde, was determined using a chemotaxis assay. The two neurons analyzed were the AWA and AWC sensory neurons: the AWA senses diacetyl, and the AWC senses benzaldehyde. Both MCs impaired AWA but not AWC function, and MC-LF was a more potent neurotoxin than MC-LR. In the liver, MCs main mechanism of toxicity is through the inhibition of protein phosphatases (PPs) 1 and 2A. To probe a potential role for PP1 and 2A in MC neurotoxicity, we evaluated the chemotactic response in worms exposed to the PP1 inhibitor tautomycin or the PP2A inhibitor okadaic acid for 24 hours. Okadaic acid impaired both AWA and AWC function, while tautomycin had no effect on function of either neuronal cell type at the concentrations tested. These findings suggest that MCs selectively impair the AWA neuron at concentrations that do not cause general systemic toxicity via mechanisms other than PP inhibition. As water levels drop, temperatures increase and nutrient pollution continues to pollute Northern California's lakes, rivers and oceans, there is a great risk of MC contamination in our water and locally grown blue green algae for health supplements. Regulations need to be established in California to determine levels of MCs in drinking water and consumable products to prevent potential neurotoxicity.

Innovative in-vitro model to predict Thrombocytopenia

Preeti Dhawan, Hirdesh Uppal, Dinah Misner and Donna Dambach
Genentech Inc., SSF, CA

Discovery toxicology faces a persistent challenge of identifying in vitro assays that can predict in-vivo bone marrow toxicity. The development of in-vitro toxicity testing that is predictive of hematopoietic toxicity seen in-vivo, is necessary to optimize the drug candidate selection process. Our Safety Assessment lab at Genentech understands the importance of in-vitro model systems and is constantly working towards building new and innovative predictive in-vitro models that can mimic the in-vivo conditions.

In recent years, great progress has been made in elucidating the progenitor cell hierarchy of the myeloid and lymphoid lineages. Transcription factors and cytokine signaling pathways have been shown to be key determinants in the orchestration of myeloid identity and differentiation fates. Most signaling pathways and transcription factors show cell-lineage-restricted and stage-restricted expression patterns, indicating the requirement for tight regulation of their activities. In addition, kinases have shown to be major determinants at the lymphoid-myeloid junctures as they play a key role in the regulation of developmental cytokine signaling pathways and functioning of transcription factors in the lymphoid and myeloid lineages, which helps to establish and maintain their fate. Furthermore, dysregulation or inhibition of kinase activity has an important role in bone marrow toxicity, implicating kinases as potential targets for bone marrow toxicity. Thus a major concern with development of kinase inhibitors as drug targets is the identification of kinases crucial to the hematopoietic function; inhibition of which would lead to bone marrow toxicities.

The hematopoietic system represents a continuum of cells with changing phenotype and properties as they progress from stem to differentiated cells. Thus, one could expect that in a steady-state situation, variations detected in the more mature compartments will faithfully reflect those occurring in stem cells. Unfortunately, both compartments are controlled by different factors and may vary independently from each other. This warrants the need for assays that evaluate each compartment independently. This means identifying separately the various classes of hematopoietic progenitors that are produced sequentially during the progression from stem cells to differentiated functional cells.

We devised an in-vitro model to assess thrombocytopenia risk associated with candidate molecules (small and large molecules), both in the pre-clinical and clinical phases. We utilize an innovative approach that involves assessment of thrombocytopenia by differentiation of hematopoietic stem cell (HSCs) obtained from healthy human donors to megakaryocytes. HSCs, which are CD34+/CD133+, are supplemented with megakaryocyte specific growth factors that support the proliferation and differentiation into mature megakaryocytes. Depending upon the experimental setup, the megakaryocyte differentiation is carried out in well-plates or tissue culture flasks where the compound dose is added as three replicates in each dose. The compound is incubated at concentrations that are determined from in vivo exposure data. Endpoints are evaluated at different time points to perform a kinetic analysis of the compound's effects on the early progenitor population, the differentiating population, and on

mature megakaryocytes. For each compound tested, three controls are included: spontaneous control which contained cells without growth factors or drug/compound addition, growth factor control, and a growth factor plus vehicle control. During the differentiation process cells are evaluated for cell viability and proliferation. The former is measured by the proportion of the intracellular ATP concentration compared to control and the latter is evaluated by cell number. Decreased ATP levels and cell number are indicative of toxicity of a compound on a specific bone marrow population. The effects of the compounds on megakaryocyte production are also evaluated by FACS using Direct Immunofluorescence Multi-color staining for markers that are common to platelets and megakaryocytes e.g. CD41, CD42a and CD61. The decrease in marker specific to megakaryocytes is indicative of decreased production of megakaryocytes leading to decrease production of platelets. During the differentiation process cells are also evaluated for DNA nucleoploidy; any significant effect leads to impaired megakaryocyte and platelet production leading to thrombocytopenia. The model has been utilized by many projects to help guide decision-making during the early and late stage development of a molecule exhibiting bone marrow toxicity or thrombocytopenia. One of the examples where we have successfully implemented this model is during the development of trastuzumab emtansine (T-DM1). Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate (ADC) comprising trastuzumab, a stable thioether linker, and the maytansine derivative DM1, a microtubule polymerization inhibitor. T-DM1 has been evaluated for the treatment of HER2-positive metastatic breast cancer (MBC) in several phase I/II clinical trials. Thrombocytopenia was observed as dose limiting toxicity in patients treated with T-DM1 although Her2 was not expressed in platelets. Our goal was to determine the mechanism of T-DM1-induced thrombocytopenia by evaluating the effect of T-DM1 on formation of mature megakaryocytes from hematopoietic stem cells in-vitro. As described above we utilized human CD34+cells and differentiated those into megakaryocytes, during which cells were collected for cytotoxicity, cell number CD41/CD61 expression and nucleoploidy of differentiating megakaryocytes. We also evaluated the effect of T-DM1 on mature megakaryocytes and platelets. The data showed that T-DM1did not act directly on the production of platelets but acted by reducing the number and maturation of megakaryocytes formed from HSCs. Treatment of differentiating megakaryocytes with T-DM1 also showed a significant effect on DNA nucleoploidy.

Use of primary cells either HSCs, megakaryocytes or platelets separately would not have allowed us to uncover this mechanism, demonstrating how stem cell differentiation has opened up new opportunities to evaluate the potential of a drug candidate to cause thrombocytopenia or bone marrow toxicity.

Collectively, the work in hematopoietic stem cell is expected to decrease the risk of late-stage failure of new chemical entities and large molecule drugs, reduce R&D costs, and increase the likelihood and rate of genuine drug discovery – primary objectives for the pharmaceutical industry.

Our goal for hematopoietic toxicity testing is to include all available crucial information about a test compound, such as its physical and chemical properties, structural similarities to compounds with known biological activity. This approach will entail estimating how a compound interacts with molecular targets that are important for hematopoietic toxicity in

humans. The main challenge is to identify chemical properties of bone marrow toxicity alerts and to compose a test strategy with relevant end points.

Reference

Mahapatra, K, Darbonne, WC, Bumbaca, D, Shen, B, Du, X, Tibbitts, J, Olsen, S, Sliwkowski, MX, Girish, S, Hartley, D, Dambach, D, Ramakrishnan, V, Uppal, H. T-DM1–induced thrombocytopenia results from impaired platelet production in a HER2-independent manner. European Organization for Research and Treatment of Cancer Meeting, 2011.

Job Announcement

Theravance, South San Francisco, CA is seeking an associate director in Safety Assessment. Position is responsible for designing and conducting programs for the safety evaluation of drug development candidates and preparation of nonclinical sections of regulatory submissions. Job Requirements: Doctoral level (Ph.D., D.V.M. or M.D.) or equivalent, and a minimum of 7 years of experience in pharmaceutical development in a specific discipline (e.g. toxicology, pathology). Management experience desired. http://www.theravance.com/openings/view/13_022

Upcoming Chapter Events

UC Davis Careers in Toxicology Event: 2 April 2014

The Careers in Toxicology Event will be held at UC Davis ***April 2nd***! **Northern California Society of Toxicology regional chapter** will host the event featuring a panel discussion with professionals with government, academic, or industry careers. Panelists discuss their jobs, their path in gaining their position with students, answering questions and concerns about careers in toxicology. There will be a networking event following the panel discussion to allow for further discussion and mentorship. If you have any questions or are interested in attending as a panelist, mentor or student please contact Sandra Chang sndchang@ucdavis.edu

K-12 Event Report: 6 April 2014

By Toufan Parman, PhD, DABT, Chair of NorCAL SOT K-12 Outreach Program

We are planning another K-12 education event in collaboration with Berkeley Toxicology Student Association (ToxSA) and Girl Scouts. This event will be catered to 6-8th grade students. The event will be held At Audubon Middle school in Foster City, CA on ***Sunday April 6, 2014***. The event is from 1-6pm. I need toxicology volunteers to help with various activities. This is a fun event and last year not only the students but also the volunteers enjoyed it. If you are interested in volunteering for this event please contact me at parmant@hotmail.com.