Society of Toxicology
Specialty Section Communication
Drug Discovery Toxicology

Summer 2010

President's Message

As incoming President, I am pleased to note that 2010 marks the sixth year of the Drug Discovery Toxicology Specialty Section, and I would like to reflect a bit on our past history and future directions. The committee is on solid footing with membership, that is over 300, and with our funding. I would like to highlight our Emil A. Pfitzer endowment fund that has allowed us to make generous awards for postdocs and students who have impactful abstracts each year at the annual meeting.

Moving forward this year we would like to highlight and expand our membership to add our academic and environmental research colleagues to this specialty section. While the topic of Drug Discovery naturally draws membership from the pharmaceutical and biotechnology industries, I would like to encourage those researchers with basic research interests supporting pharmacology, molecular toxicology, bioinformatics, and physiology, as examples, to join the specialty section. Early drug discovery efforts focus on fundamental properties of molecular targets and high throughput screening assessments and there are many areas of academic research that are developing future discoveries to support these areas. We would like to round out our membership to ensure representation of this research.

We will also work this year on our outreach and integration with the regional SOT chapters. John Wisler, our newly elected Vice-President elect, will head up this effort. This should help ensure that the SOT regional members, who may not always travel to the annual meeting, are aware of the interest of our specialty section and can contribute to program proposal submissions, our newsletter, or enter our student and postdoctoral award competitions. As students and postdocs are our future toxicologists, we feel development of a strong networking program for this group is important to our overall health. We would like to appeal to all members to help us with this outreach.

In closing, I would like to welcome the new council members, John Wisler (Vice-President elect) and Mike Breider (Councilor). I would also like to recognize and sincerely thank our exiting council member, Mike Lawton. We retain our past-President, John Davis on our council for the current year, but I would like to extend special gratitude and recognition for his leadership in the President role in the past year.

by Cindy Afshari

Thanks for service as councilor, Mike Lawton (on knees because he is so tall) and Cindy Afshari. *Photo credit to SOT*

Thanks for service as President, John Davis and Cindy Afshari. *Photo credit to SOT.*

2010—2011 Officers

President:
Cynthia A. Afshari cafshari@amgen.com

Vice President:
Craig E. Thomas cthomas@lilly.com

Vice President-Elect:
John A. Wisler - Newly elected
jwisler@amgen.com

Secretary/Treasurer:
Melissa C. Rhodes melissa.c.rhodes@gsk.com

Councilor:
John W. Davis, II John.W1.Davis@pfizer.com
Past President

Councilor:
Daniel C. Kemp daniel.c.kemp@gsk.com

Councilor:
Michael A. Breider – Newly elected
mbreider@celgene.com

Post-Doctoral Representative
Kimberly A. Henderson hndkim@ucla.edu

Student Representative:
Arunkumar Asaithambi akarun@iastate.edu

Emil Pfitzer fund

We want to be sure that all of our members and prospective members are aware of the Emil A. Pfitzer Endowment fund that serves as the DDTSS source for funding our student and postdoctoral awards. The Award fund provides awards for outstanding abstracts that demonstrate application of modern toxicology science in the field of drug discovery and are presented at the annual meeting.

This award was created to honor the legacy of Dr. Pfitzer. Dr. Pfitzer worked at Hoffman-LaRoche for 22 years serving as Vice President of Toxicology and Pathology where he championed the use of mechanistic toxicology. After retiring from Roche, he served 5 years as President of RIFM. Dr. Pfitzer also served as President of the Society of Toxicology in 1985-1986. The endowment was initially created by the initial generous contributions from Hoffman-LaRoche, the Research Institute for Fragrance Materials (RIFM).

2010 Meeting Highlights

Our DDTSS reception at the SOT annual meeting was well attended by our members despite competition with many other specialty section receptions held on the same evening. John Davis, our 2009-2010 President presided over the meeting and gave opening and closing remarks with plenty of humor along the way. Craig Thomas presented an overview of the SOT program process and encouraged all members to submit ideas for the 2011 SOT program. Cindy Afshari presented plaques and thanks to our outgoing officers: John Davis, outgoing president, and Mike Lawton, outgoing councilor. Finally, Mike Lawton and Craig Thomas presented the top three student and postdoc Emil Pfitzer Student Awards. GeneGo contributed a complementary year subscription to the top winner in each category.

Excellent attendance at reception at annual 2010 meeting. *Photo credit to SOT*

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2010 Emil A. Pfitzer Drug Discovery Student and Postdoctoral Fellow Competition Results

The following awards were made at the Annual 2010 meeting. The funding for these awards came from the Emil A. Pfitzer endowment fund. The first place winners in each category also received a complementary year subscription to Gene Go.

Student Awards:

First Place ($1,000 + GeneGo subscription):
Arun Asaithambi, Iowa State University
"Positive modulation of the novel anti-apoptotic kinase PKD1 can protect dopaminergic neurons against oxidative damage in Parkinson's disease models"

Second Place ($600)
Christina Powers, Duke University
"Developmental neurotoxicity of silver nanoparticles modeled in PC12 cells"

Third Place ($300)
Sumitra Sengupta, Oregon State University
"The cryptic story of glucocorticoids"

Postdoctoral Awards:

First Place ($1,000 + GeneGo subscription)
David Castro, Burnham Institute for Medical Research
"Chemical genetic approaches to elucidate key signaling pathways for the differentiation of a mouse mammary cancer stem cell"

Second Place ($600)
Peter Bui, UCLA
"Human cytochrome P450 2S1 is able to utilize fatty acid hydroperoxides to support benzo(a)pyrene 7, 8 dihydrodiol's bioactivation"

Third Place ($300)
Harriet Kamendi, Astra Zeneca - Wilmington
"Multi-compartmental PK-PD modeling of baclofen"

All photos in this section were obtained via SOT

Requests for Newsletter Submissions

We are looking for ideas and contributions for future newsletters, especially our upcoming Fall 2010 edition. Ideally we would like to begin to expand the content of this newsletter to provide a forum for members to discuss opinions and information associated with topics related to our specialty interest. We are interested in content relating to the latest developments in research and technologies that could impact efforts in early safety assessment.

We are also looking for highlights of recently published papers with significant impact potential to our specialty area. We have started this in this edition with our submission by Michael Breider. If you are interested in making a contribution or have an idea, please email Melissa Rhodes by September 1, 2010 (Melissa.c.rhodes@gsk.com).

Current Officers (left to right): Arun Asaithambi, John Wisler, Cindy Afshari, Craig Thomas, John Davis, Dan Kemp, Michael Breider. Not pictured, Kim Henderson and Melissa Rhodes. *Photo credit to SOT*

Safety Risk Assessment of New Targets in a Research Portfolio

Michael Breider, Dale Baker, and Dinah Misner; Exploratory Toxicology, Celgene Corporation, San Diego, CA

As toxicologists in the pharmaceutical industry, our most critical contribution to human health is to predict human safety risk based on animal toxicity data. In a conventional setting this is accomplished using standard animal toxicology testing paradigms, however, as we are all aware this is a very time-, resource-, and test article-consuming activity. For those of us involved in supporting early research portfolios, we are asked to assess safety risk of pharmaceutical targets with very limited or no actual toxicology or clinical data. Fortunately, newly assembled data sources provide us with the ability to initially understand the biology of the pharmaceutical target and then the toxicology. To accurately predict relevant safety risk, we must also be aware of the pharmaceutical end-game, namely identifying the patient population to be treated, understanding the targeted disease process, and tolerance of this population to possible drug side-effects. As an example, if the project is targeting hepatic fibrosis as a primary indication, there would be a very low threshold for hepatic toxicity or associated hepatocellular functional modulation.

To meet the challenge of early safety assessment of target inhibition with limited data, many research toxicology groups have developed an in silico method of predicting safety based on more fully understanding the target biology. This activity precedes the usual early toxicology testing schema such as in silico structure-activity-relationship assessment, screening genotoxicity, hERG, cytotoxicity assays, and exploratory in vivo tolerability studies. It is possible now with access to government web-based data bases and referenced literature to obtain understanding of the target biology and probable consequences of target inhibition, despite a vacuum of toxicology data.

To accurately predict safety risk for a target, one must truly understand the biology of the target and subsequent pharmacological action of target modulation. This would include the species homology of the target, tissue distribution within those species, and genetic disease related to target deficiency from experimental oblation or spontaneous disease. Detailed below is a list of accessible data sources to assist in understanding target biology:

- Sources of general, genomic, and proteomic data for target on the NIH web page http://www.ncbi.nlm.nih.gov/sites/entrez
    - For general information select OMIM (Online Mendelian Inheritance in Man) in Search pull down menu
    - For gene sequence and selected protein similarities select Unigene in Search pull down menu
    - For gene homology information select HomoloGene in Search pull down menu
    - For protein information select Proteins in Search pull down menu
    - For published bioassays select Pubchem Bioassay in Search pull down menu
    - For compounds that have activity against the target select Pubchem Substance in Search pull down menu
    - For published bioassays select Pubchem Bioassay in pull down menu

- For additional general target information and reference sources - http://www.ihop-net.org (information hyperlinked over proteins)
- Proprietary data sources and search engines are available from regulatory agencies and competitor intelligence including:
    - Pharmapendium – regulatory agency based data
    - Integrity – competitor intelligence
    - Thomson Pharma – competitor intelligence

The examination of information from these various data sources and referenced literature can provide a fairly complete understanding of the pharmacological action of the target. Further examination of the cellular signaling pathways that the target contributes to, can provide additional insight into function and presumed consequence if the target function is inhibited. Unfortunately as a complication for accurate risk prediction, our understanding of the biological consequences of pathway component inhibition is incomplete and the role of positive or negative feedback regulation is not well defined.

The effect of target deficiency can be illustrated in in vivo models such as target-specific homozygous/heterozygous knock out mice or models using small interfering RNA (siRNA)-based modulation of the target. Additionally, spontaneous genetic deficiency has been observed for many targets in animals and/or humans, and the description of these disease syndromes can provide understanding of the consequence for target inhibition or abnormal activation.

It is important to also utilize any available information from compounds currently or previously in development, that had modulatory effects on the selected target, such as in vitro, preclinical, and clinical data. However, the selectivity of the compound must be defined and considered in order to differentiate primary from off-target related effects.

Utilization of these various data sources can provide an initial prediction of safety risk for the target and as actual data is generated with target-specific compounds, the assessment can be expanded to enable a more accurate prediction of safety risk in human patients.