I am pleased to take over the responsibility as President of the Regulatory Safety Evaluation Specialty Section (RSESS) after such an excellent year under Frank Sistare’s leadership. Frank and the Council have done a great job and I appreciate the foundation that they have laid for the 2009-2010 year.

The Section is in outstanding shape with many talented members. We have strong finances and we use the Section’s resources to encourage innovative scientific programs and student and post-doctoral travel to the SOT meeting each year. The RSESS has an excellent history of professional contributions to the Society of Toxicology’s Scientific Program. Our members are found on SOT committees and on SOT Council. There are a number of important issues that need to be discussed and addressed in the coming year. I strongly encourage each of you to consider how we are using our time and money to improve the value of toxicology to society.

If you need suggestions on how you can contribute, I have a list:

Facility advisors should encourage their students to compete for travel money distributed by the RSESS.

Encourage students and other colleagues to attend the RSESS meeting at the SOT.

All RSESS members should make suggestions for program sessions and for the 2010 RSESS Great Debate.

SOT has a great system to support Current Concepts in Toxicology and we have not taken full advantage of it yet. Please consider whether you are working in an area that should be the subject of such a focused meeting.

We have started an Endowment Fund, I encourage you to consider this fund in your contributions. All the money is earmarked for student and postdoctoral travel grants.

Make suggestions to the Council members on issues that affect your career. We have been elected to help you succeed. We need to hear from you as the year proceeds.

Thank you for the opportunity to serve as your section’s President.

Jim Lamb, IV, PhD, DABT
"Can clinical trials be run safely without data from dog studies?"

The prime non-rodent species for toxicology testing is the dog. The emerging awareness of the 3Rs of Russell (reduction, refinement and replacement) and wider acceptance of biomarkers as toxicity predictors has spurred a debate regarding non-rodent animal testing. To obtain an insight on public opinion on this issue, the RSESS conducted the annual great debate at the SOT meeting in Baltimore titled “Can Clinical trials be run safely without data from dog studies?” The speakers included Dr. Thomas Monticello (Pro Position) and Dr. Harry Olson (Con position).

Dr. Monticello advocated limiting the use of non-rodents in toxicity testing. He began by providing a brief history of toxicity testing. In brief, the seeds of multiple species toxicity testing were sown in 1927 with J. Trevan (inventor of LD50), emphasizing the need for acute testing to be conducted in several species. However, it was not until 1965, that the necessity to conduct two species testing, a rodent and a non-rodent, became well established. Subsequently, in 1977, the Beagle Dog was identified as the defacto non-rodent species. Citing data from a multinational pharmaceutical company survey he further stated that non-rodent testing provided 63% concordance with human toxicity test compared to 43% concordance using rodent species and that the combination provided approximately 70% concordance. Furthermore, Dr. Monticello felt that the use of dog testing for safety pharmacology studies allowed for a detailed analysis of various cardiovascular parameters. Elaborating on the prospects for refining the use of non-rodents in regulatory testing of pharmaceuticals, he emphasized the expanded adoption of exploratory IND, incorporation of novel technologies and tissue biomarkers into toxicity testing and also embracing the 3Rs. Specifically, in the realm of exploratory IND, he suggested the use of short-term rodent testing allowing for NOAEL determination allowed reduced use of non-rodents. This non-rodent study could employ fewer animals and also single gender, if no gender differences were observed in previously conducted rodent study. He strongly supported the incorporation of techniques such as magnetic resonance imaging with biomarkers to monitor non-rodent target organ toxicity. This approach, Dr. Monticello said, would not only minimize the read out time, but also allow for “real time” longitudinal toxicity assessment. Finally, he also suggested revisions in certain regulatory guidelines such as the necessity to achieve an MTD in subchronic and chronic studies.

Human safety is the prime consideration of a clinical trial. Emphasizing this point, Dr. Olson, argued against changing the use of non-rodent species to enable clinical
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He felt that extensive understanding of cross-species pharmacologic properties of new chemical entities (NCEs) and biologicals was essential. In this context, he advised extreme caution when translating their pharmacologic properties to human subjects. Not only is the manifestation of NCEs pharmacological activity incompletely understood, single species (rat) testing may also falsely predict the toxicity. Supporting the use of non-rodents for enabling clinical trials, he stated that animal toxicity testing has obvious advantages such as exploring high dose effects, defining toxicologic properties and also providing safety margins for NCEs. On a different note, considering the removal of the dog from testing trial and relying only on the rat data, Dr. Olson felt would be extremely detrimental to toxicity prediction. The rat predicts only 40% of known human toxicities and is not entirely accurate for several organ systems such as the liver, GI and the kidney. Learning from our past experience, he stressed that the use of two species was more appropriate to define human toxicity. In this context, he suggested the use of both rats and dogs to initially identify the sensitive species and subsequently reducing the requirement for two species chronic testing.

The traditional audience poll at the end of the debate revealed greater public support for the continued use of dog testing to enable clinical trials.

Jaishree Bankoti

The IVGT Project Committee: Formulating a Comprehensive Decision Tree

The ILSI Health and Environmental Sciences Institute’s (HESI) Project Committee on the “Relevance and Follow-up of Positive Results in In Vitro Genetic Toxicity (IVGT) Testing” is wrapping up a busy and productive 2009. The IVGT was formed in 2006 with the mission of improving the scientific basis of the interpretation of results from in vitro genetic toxicology tests for purposes of more accurate human risk assessment; developing follow-up strategies for determining the relevance of in vitro test results to human health; and providing a framework for integration of in vitro testing results into a risk-based assessment of the effects of chemical exposures on human health.

To address this mission, the IVGT formed three Subgroups: Review, Quantitative, and New/Emerging Technologies, all composed of international genetic toxicology experts from academia, government and industry. The Review Subgroup is tasked with evaluating existing tests and guidelines. Towards this end, the Review Subgroup has classified the existing genotoxicity assays in four categories based on their strengths and weaknesses, and their ability to contribute to data interpretation. This Subgroup is developing a flow chart to be considered in case of positive findings in the in vitro assays of the standard genotoxicity battery. This flow chart attempts to describe how the intended chemical use, the data obtained in the initial genotoxicity battery, the potential confounding factors, and the already available data other than genotoxicity data could be used to define the most appropriate follow-up strategies that could include additional in vitro genotoxicity assays, mechanistic studies (e.g. DNA reactive versus non-DNA reactive) and in vivo genotoxicity tests, if any, in order to better
The IVGT Project Committee: Formulating a Comprehensive Decision Tree—(con’t)

evaluate the level of concern for human in the intended usage.

The Quantitative Subgroup is attempting to address a long-lasting need to move away from the current regulatory paradigm for genotoxicity testing that relies on qualitative interpretation of the outcome of in vitro and limited in vivo testing. The need for quantitative analysis of the relationship between exposure and health risk of genotoxic damage in vivo was recognized when regulatory genetic toxicology testing began in the 1970s. The Quantitative Subgroup is developing a database of in vitro and in vivo exposure-response relationships in test systems used for genotoxicity testing to use as a basis for analysis of exposure-response relationships, development of recommendations for extrapolation of results across test systems, and approaches to improved exposure-based estimates of in vivo risk.

The New/Emerging Technologies Subgroup is tasked with identifying and reviewing promising approaches that could be used to replace or improve existing models, and to identify useful follow-up tests in case of in vitro positive results in the initial battery of genotoxicity assays. As part of this initiative, a workshop was convened in May 2008 to discuss mature, maturing and emerging technologies in genetic toxicology. This workshop provided a forum to solicit informal feedback on assay strengths, weaknesses and lessons learned from previous validation efforts.

The overarching theme of these three Subgroups is to provide separate pieces of information to elucidate the logic behind the decision tree/flow chart. The IVGT will be presenting the work of these Subgroups at the upcoming International Conference on Environmental Mutagens (August 20-25) in Florence, Italy. These efforts will be published in an upcoming special issue of Environmental and Molecular Mutagenesis.

Past President’s Letter

As I reflect back over the past year I remember most vividly our specialty section's most noteworthy accomplishments to be: 1) RSESS efforts to stimulate, to review, and to selectively endorse the best scientific programs for our 2009 and 2010 SOT Annual Meetings, 2) a stimulating reception at our SOT 2009 Annual Meeting that opened debate on the increasingly important topic of developing creative approaches to reduce nonrodent testing while ensuring patient safety in clinical drug trials, 3) our timely and always stimulating newsletters, 4) our SOT Annual Meeting travel support awards and reach out to our students to stimulate them to realize the vital importance of product regulatory and safety evaluations to their chosen profession, 5) our executive officer succession planning efforts, and 6) a fully updated RSESS website.

No year like the past one happens without a lot of hard work from a great team behind the scenes. Again, this year RSESS had more total session endorsement plus sponsorship requests than any single other specialty section. This year's RSESS Scientific Program Review Committee was chaired for the first time by Susan Hart and included returning committee members Bob Ostberg, Denise Robinson, Vicki Dellarco, and Harry Olson. Susan quickly organized the group to provide a rigorous and fair assessment of each proposal's merits and shortcomings and delivered prioritized recommendations for the Executive Committee. Sincere thanks to all and especially to Susan for an outstanding job! This year's Great Debate at the RSESS Annual Meeting reception was lively, entertaining, and provocative. While the extreme positions are always debated in this forum, there certainly seems to be desire for some evolution from our current state expressed by many in the large audience in attendance. Kudos to David Jacobson-Kram for organizing this very provocative session and to Harry Olson and Tom Monticello for their superb presentations! For those who had to miss the debate you can review the slides on our website and read the very nice summary in
Past President’s Letter—(con’t)

this issue from our past Student Representative, Jaishree Bankoti. Sadly for us, Jaishree graduates and leaves behind some tough shoes to fill for her successor, Tom Simones our new Student Rep from the University of Montana. Congratulations, thank you, and best wishes for a strong career hopefully in regulatory and safety sciences, Jaishree. When you check out that website, note how complete and up to date everything is, thanks to your Vice President Brian Short's untiring efforts to seize every opportunity to track a lot of loose ends and missing pieces down over the year. This newsletter will also be the last production from Vicki Delarco. While Vicki leaves our Executive Committee and passes on the Secretary/Treasurer/Newsletter Editor baton to David, happily we will continue to benefit from Vicki's continued participation on the RSESS Scientific Program Review Committee. Thanks for your gentle ways Vicki of drawing out so many excellent articles from our many contributors over this past year. Our two newly elected officers were announced and introduced to the membership at our reception. Congratulations to our Vice-President Elect Tim Pastoor and to Nancy Beck, our new Councillor for agreeing to all the work ahead of them and then getting elected, in that order. RSESS Executive Committee has a solid succession team coming over the next 3 years. With the coming of the new Officers, it means it's time to say good bye, though, and to extend a sincere thank you as well to our Past President Jim Green for his guidance, encouragement, and strong leadership over the past 4 years. Now comes my final reference to the SOT 2009 Annual Meeting and RSESS Reception. Again, the competition for the RSESS Student Travel Awards was strong this year, and the selection process and award preparations coordinated by our new President Jim Lamb brought to our reception five very polished and poised summaries of elegant research from Susan Tilton, Gabriel Knudsen, Binu Philip, Xianglu Han, and Emily McClure. Congratulations all, and please keep up the great work!

In our last couple of newsletters and at the beginning of my term I had stated an RSESS Executive Council objective of seeking to sponsor in the Washington, DC area a timely scientific workshop aligned with our mission. The topic of strong mutual interest that Executive Council had selected was to foster efforts to review and revisit the current conduct of rodent carcinogenicity testing. Well we failed, sort of, maybe, but maybe not exactly. Let me explain. On May 27 leadership form PhRMA's Safety Leadership Committee, and members of their Ad Hoc Carcinogenicity Working Group met with leadership from the Pharm-Tox review scientists of FDA's Center for Drug Evaluation and Research in Silver Spring, Maryland to present and share a database of close to 200 compounds representing the results of an 18
month data mining effort to evaluate the relationship between chronic toxicology outcomes and 2 year carcinogenicity outcomes in rats. The PhRMA conclusions were that while positive findings in a chronic study are poor predictors of tumor outcome due to a high false positive rate, the low false negative prediction rate taken together with the low significance evaluation of the few false negatives was very supportive of further investigation. The discussions were lively and the audience was very engaged. At the end of a very full day, FDA and PhRMA reached agreement to commit to taking the initiative to the next level. Because the compound identities are blinded between PhRMA companies this means that only FDA who has been given the identity of each compound can complete a thorough quality assurance check on the accuracy of the data in the database. If everything checks out, then a mutually agreed upon strategy to assess an independent and prospective data set would be launched. Because of the timing of events, David Jacobson-Kram and I therefore proposed to bring this developing story integrated with other exciting developments in carcinogenicity prediction tools to the SOT Annual Meeting next March in Salt Lake City. Now we don't know if our proposed workshop will be accepted and approved by the SOT Program Committee, but if it is, we might have missed our precise objective by only about 2000 miles…

Finally, congratulations to our New RSESS Logo Competition winners, the team of RSESS members Louis Radulovic, Brian Walker, and Nelson Wilson who will soon be receiving their well earned gift certificates in the mail in recognition of their very creative symbolism and artistry, and in appreciation for allowing us to now adorn our newsletters for all eternity (or at least until computers eliminate the need for the toxicologists that read our newsletter).

Frank D. Sistare, PhD
Past President, RSESS

ToxCast™ Data Analysis Summit

The EPA ToxCast™ Program is developing new approaches to predict chemical toxicity using high-throughput and high content in vitro assays. On May 14-15, EPA’s National Center for Computational Toxicology, hosted the ToxCast™ Data Analysis Summit at Research Triangle Park NC, May 14-15\textsuperscript{th}. More than 200 scientists from around the world attended this summit to discuss new ways of predicting the potential hazards of environmental chemicals.

To date, EPA’s ToxCast™ research program has generated data on 320 chemicals from over 500 in vitro assays. In addition, about 75 in vivo endpoints have been mined from available laboratory animal toxicity studies. Prior to the May summit, EPA made the in vitro ToxCast™ and the animal toxicity data available to “analysis partners” who signed a Materials Transfer Agreement, and invited these partners to apply their best analysis strategies and present their findings at this summit.

Research needs identified at the summit included the need to identify well characterized and robust endpoints in standard toxicological tests for use as benchmarks, the need to develop approaches for predicting the role of metabolism in chemical toxicity, and the need to put results from the many high throughput biological assays into the context of toxicity pathways and human disease pathways. Participants also discussed what additional biological assays are needed, the chemicals that should be studied next to verify the utility of this approach, and various statistical and machine learning methods for analyzing such large data sets and building predictive models of toxicity.

Based upon input from the summit, EPA researchers are now preparing to launch a second phase of the ToxCast™ program that will expand on and verify the ability of this approach to predict potential human toxicity. One important component of this next phase will come through an agreement between EPA and Pfizer, Inc. that is providing more than 100 drugs that showed adverse effects in clinical human testing. Pfizer will make public this clinical data, and EPA will run these compounds through the ToxCast™ assays, providing a critical and direct link to human toxicity outcomes. EPA expects to complete this second phase of ToxCast™ over the next several years, and at that time be ready to deliver an innovative computational method for evaluating potential...
ToxCast™ Data Analysis Summit—(con’t)

health impacts of environmental chemicals.

The ToxCast Summit presentations are available at http://epa.gov/nct/toxcast/summit.html

For More Information Contact: Dr. Richard Judson, 919 541-3085; judson.richard@epa.gov.

David Dix, PhD
Vicki Dellarco, PhD

Best Practices for Use of Historical Control Data of Proliferative Rodent Lesions

The Historical Control Data Working Group under the direction of the Scientific and Regulatory Policy Committee (SRPC) of the Society of Toxicologic Pathology (STP) was tasked with reviewing the current scientific practices, regulatory guidance and relevant literature pertaining to rodent microscopic historical control data (HCD) of proliferative lesions in order to provide best practice recommendations for locating, generating and applying such data. The Working Group focused exclusively on HCD of proliferative lesions from non-clinical rodent carcinogenicity studies. The HCD Working Group recommends the following consensus principles to guide the use of HCD of proliferative lesions from chronic rodent (rats/mice) bioassays:

• The concurrent control group is the most relevant comparator for determining treatment related effects in a study.

• HCD may be useful in the interpretation of rare tumors, marginally greater incidences and/or severity of proliferative changes in treated animals compared to controls, and unexpected increases or decreases of tumor incidences in study control animals. HCD can be used as a tool to provide scientific perspective of disparate findings in dual concurrent control groups and review trends in tumor biology and behavior which may evolve over time in these rodent models

• Study design related parameters such as laboratory, species/strain, route of administration, vehicle, feed, feeding practices, study duration, and housing have a potential to impact study outcomes and control findings. These parameters should be considered when selecting the appropriate studies for the HCD.

• Pathology practices including necropsy and trimming procedures and application of diagnostic criteria can impact study data and HCD. HCD is best if these factors are standardized.

• HCD from the laboratory that conducted the study under review will likely be more comparable than HCD from several laboratories.

• Similarly, HCD that underwent a peer review process are generally more reliable than those that did not.

• Published HCD should be evaluated carefully. It may provide guidance in evaluating data associated with particular effects but difficulties in assessing the quality of published data should be taken into context with the “weight of evidence” for determining its relevance to study findings.

• HCD may be presented as a range of incidences or percentages, mean, and standard deviation for a given change. Reporting of incidences per study will allow both presentation and use of a broad range of observations and provide transparency of potential influences and outlier populations

• Although a limited time span of two to seven years for collection of HCD is proposed in the guidance documents of several agencies, wider intervals may be appropriate if tumor types are stable over a longer period. HCD should be considered as one of many sources of information that add to the “weight of evidence” approach when assessing the potential carcinogenic effect of a compound.

Brian Short, DVM, PhD, DACVP