News from the American Society for Cellular and Computational Toxicology

Following a successful 1st Annual Meeting in September, the American Society for Cellular and Computational Toxicology (ASCCT) elected a new Board of Directors. Voting was held in person at the annual meeting and through an online system, and the results were announced at a webinar-based repeat of the annual business meeting, held for those who could not attend the annual meeting in person. Members of the board are: President Rodger Curren, Treasurer Erin Hill, Secretary Kristie Sullivan, Thomas Hartung, Marianna Gaça, Jack Fowle, and Marilyn Aardema. Members are set to meet in December and will be generating ideas for further growth and collaboration of the ASCCT with other individuals and organizations.

One such collaboration continues to yield dividends: in October, ASCCT held a session at the European Society for Toxicology in Vitro (ESTIV) congress in Lisbon. The session was titled "Crossing Transatlantic Barriers" and featured presentations from four different NGO members of ASCCT and ESTIV on how to ensure that the validation and utilization of *in vitro* methods overcomes common barriers on both sides of the Atlantic.

ASCCT members participated in a member webinar held by Maureen Bunger with Cellular Dynamics International on December 11. Dr Bunger presented *Human Induced Pluripotent Stem Cell-derived Model Systems: Applications for Mechanistic and Predictive Toxicology*. Finally, the Society will have a booth at the upcoming Society of Toxicology meeting in San Antonio, March 10-14, 2013. Stop by to join or just say "Hi!"

CAAT*feed*

Joint US workshop: "Scientific roadmap for the future of animal-free systemic toxicity testing"

The scientific challenges of developing *in vitro* approaches to systemic toxicity testing are formidable. These challenges have taken on greater urgency in the context of the 2013 deadline for marketing cosmetics in Europe that are free of animal-testing, including tests for systemic and chronic endpoints. We believe the time is ripe to advance a forward-looking strategy to develop the science for the systemic, chronic toxicities for cosmetics and other products. We strongly believe that such a focused effort applies to regions outside of Europe and products and industries outside of cosmetics.

In the context of our transatlantic think tank for toxicology (t^4), we held a workshop about a year ago to develop five white papers on systemic toxicity, taking a larger perspective on how to make further progress. The outcome has been published as "A roadmap for the development of alternative (non-animal) methods for systemic toxicity testing," by Basketter et al. in *ALTEX* (see http://www.altex.ch/en/index.html?id=50&iid=129&aid=1). The roadmap was favorably reviewed and discussed at a follow-up meeting in Brussels in March, 2012, co-organized by numerous organizations and attended by some 150 experts.

We would like to hold a similar public discussion of the roadmap in the US in Spring 2013 in the Washington, DC area. We are open to organizations with US/international scope and outreach to cohost the workshop.

The workshop is meant to be a scientific process. We do not aim to make political recommendations.

For contact: Martin Stephens
(mstephen@jhsph.edu)

CAAT presentations at the European Parliament

CAAT Director Thomas Hartung presented at the 289th session of the Intergroup on the Welfare & Conservation of Animals, held December 13, 2012 in Strasbourg. This cross-party interest group of 41 Members of the European Parliament meets monthly with the secretariat organized by EuroGroup for Animals, our CAAT-Europe board member. Dr Hartung addressed *The Human Toxome project and endocrine disruption testing*. Following workshop presentations by Dr Hartung in May and Dr Leist in October, this was the third presentation in the European Parliament in 2012. On October 10, in the European Parliament, MEPs Mario Pirillo and Teresa Riera Madurell hosted "*Advancing Safety Science and Health Research under Horizon 2020 with Innovative, Non-Animal Tools*." Dr Leist spoke in Brussels about: "Mapping the Pathways of Toxicity in Humans. What are the Benefits?" This discussion will continue with an invitation to Dr Hartung by the EP Science and Technology Options Assessment (STOA) group to a workshop in January.

In the frame of the scientific event at the European Parliament in Brussels called "*EU Science: Global Challenges, Global Collaboration*," CAAT is organizing a workshop called *Worldwide implementation of the 3Rs in regulatory toxicology – What are the leadership challenges and opportunities?* The workshop will be held on March 7, 2013.

For contact: Dr Francois Busquet
(caat-eu-policy@uni-konstanz.de)

CAAT addresses "Clinical trial and error: Beauty and the Beast"

CAAT Director Thomas Hartung served as a co-organizer, as well as one of three featured speakers at the February 2013 meeting of the American Association for the Advancement of Science (AAAS) in a session on "Clinical Trial and Error: Beauty and the Beast." Dr Hartung's talk addressed "Look Back in Anger? What Clinical Trials tell us about Preclinical Research."

International Symposium on Endocrine Active Substances (EASs) December 17, 2012, Rome, Italy

CAAT-IPAM (Italian Platform for Alternative Methods)-ISS (*Institute Superiore di Sanita*) partnered for a symposium on "*Alternative in vitro methods to characterize the role of Endocrine Active Substances (EASs) in hormone-targeted tissues*" focused on the use of human cell cultures in the field of endocrine disruption with the primary goal of promoting the assessment and validation of alternative methods to animal experimentation in agreement with the requirements of Directive 2010/63/EU and REACH policy and to support various fields of investigation, including toxicology, environmental sciences, and biomedical research.

The complete program is available for viewing at: http://bit.ly/Z8ne8v

Evidence-based Toxicology Collaboration

With the creation of the EBT Collaboration in Europe as a satellite to EuroTox on June 17, the EBTC is now operational on both sides of the Atlantic. Our secretariat, led by Martin Stephens and supported by Sebastian Hoffmann in Europe, is up and running (http://www.ebtox.com) and the regular e-mail newsletter started. The proceedings of the January conference hosted by EPA in RTP are found in this ALTEX issue. The first working groups and systematic reviews are on the way. A symposium on EBT was accepted by the IUTOX 2013 meeting in Korea and a lunch session at EuroTox 2013 in Interlaken, Switzerland is under negotiation.

Alternatives for Nanoparticle Toxicity Testing

Dr Hartung became part of the advisory committee of ITS-NANO, building on the 2011 t^4 workshop, review article, and "Food for thought …" paper. The EU FP7 Project ITS-NANO was launched in March 2012. The project consists of ten partners from four European Countries (Italy, United Kingdom, Denmark, and Germany), and it will last until the summer of 2013. The main objective of ITS-NANO is the integration of key stakeholders into the decision-making process towards the definition of the Intelligent Testing Strategy and the definition of a reliable methodology for exposure assessment, hazard identification, and risk assessment applicable in future research, thereby speeding up the reliable generation of knowledge.

Start of Green Chemistry Workshop series

We have teamed up with Nick Anastas, EPA, for a first conference "*Toxicology and Sustainable Molecular Design Conference*" held at the University of Connecticut on December 11, 2012. The conference included a presentation by Dr Hartung. Drs Goldberg and Stephens are preparing a conference on the topic for later in 2013. The first sponsors have committed.

Alternatives for Medical Devices

We are preparing for a process to develop a roadmap for medical device testing by alternative methods, tailored after the 2011-2012 process for systemic toxicity for chemicals and cosmetic ingredients. Sponsors including NAMSA, Cook Medical, and Medtronic have committed their support.

Alternatives for Food Safety

Following our 2011 info day, a workshop on "*Toxicity Testing for the 21st Century Beyond Chemicals*" addressed new approaches for food (and pharmaceuticals) on June 4-6, 2012 in Ranco, Italy. The report is in preparation. A follow-up workshop on food (only) was suggested. Don Prater, FDA liaison to EFSA, became a CAAT-Europe board member.

In the US, a meeting with Dr Michael M. Landa, Director FDA Center for Food Safety & Applied Nutrition, and our FDA board member Suzanne Fitzpatrick, explored the option of establishing an academic center for food safety within Hopkins.

Lush Alternative Method Award

For two years, Dr Felix Rivera-Mariani, with Dr Patrick Breysse's group at Johns Hopkins, collaborated with CAAT on the *in vitro* pyrogen test developed by Dr Hartung. Dr Rivera-Mariani uses it for airborne pyrogens, which may play a role in childhood asthma. In a number of joint projects, he participated in the supervision of students working in the CAAT laboratories. We are pleased that his application for the Lush Alternative Method Awards was selected, and he received the £ 12,500 Young Researcher Prize (http://www.lushprize.org) this month.

3Rs Center at Australia National University (ANU) Canberra

Brett Lidbury, Medical Advances Without Animals Trust (MAWA) Fellow and Associate Professor in Alternatives to animal research, Australia National University (ANU), recently visited CAAT and met with various faculty and staff members to share ideas and information about starting an alternatives center in Canberra. Dr Lidbury reported back that, since arriving back in Canberra, he was granted approval to start an alternatives "unit" within the John Curtin School of Medical Research (JCSMR – http://jcsmr.anu.edu.au). He plans to launch the unit early in the New Year. Dr Lidbury plans to include links from the Altweb and CAAT sites in his website, and CAAT hopes to post news and updates from Canberra on Altweb. A collaboration agreement is in preparation.

YouTube video on fundraiser for CAAT by Michigan School

Holly Smith, a teacher at East Hills Middle School in Bloomfield Hills, Michigan, selected CAAT as the recipient for a "Be the Change" program to raise awareness about animal testing and alternatives. Smith's students organized a fundraising campaign, "Candygrams for Critters," and donated the proceeds to CAAT, after carefully looking at several organizations supporting alternatives. Michael Hughes spoke at the school and made a video, which you can watch here: http://www.youtube.com/watch?v=c8LgsUYeRHM

Recent publications

Krug, A. K., Kolde, R., Gaspar, J. A., et al. (2012). Human embryonic stem cell-derived test systems for developmental neurotoxicity: a transcriptomics approach. *Arch Toxicol, Nov 21*. Epub ahead of print.

Hoelting, L., Scheinhardt, B., Bondarenko, O., et al. (2012). A 3-dimensional human embryonic stem cell (hESC)-derived model to detect developmental neurotoxicity of nanoparticles. *Arch Toxicol, Dec 2*. Epub ahead of print.

News from NICEATM and ICCVAM

Fall NICEATM activities focus on international collaborations

Scientists in the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) worked with international colleagues in the fall to advance innovative new test methods and integrated testing and decision strategies for chemical safety and vaccine testing. NICEATM Director Rear Admiral William Stokes, DVM, met with colleagues in Japan in September to consider new ways to identify whether substances may cause allergic contact dermatitis. A NICEATM-sponsored September workshop then reviewed recent advances in science and technology and improved methods for *Leptospira* vaccine potency testing.

Stokes coordinates test method development activities with Japanese counterparts

Stokes joined scientists in Japan for a September workshop on "Adverse Outcome Pathways for Skin Sensitization Testing." He also participated in a meeting of the management team for a Japanese-led study of a new test method proposed to identify whether substances have the potential to cause skin allergies.

Regulatory authorities worldwide require testing of chemicals and products for skin allergy hazard potential. "Our work at NICEATM has shown that it is now possible to accurately identify many allergy hazards without using animals," explains Stokes. "Any animal testing that is still required can be accomplished using a recently adopted procedure that uses only a small number of mice. Based on recent progress, we expect that most if not all chemical skin allergy hazards will soon be identified without using animals."

The Japan workshop focused on using methods to identify skin allergy hazards based on key events that occur in the adverse outcome pathway (AOP) leading to skin allergy reactions. Stokes spoke about the NICEATM development of an integrated testing and decision strategy. The testing strategy, presented at the 2012 meeting of the Society of Toxicology, can identify most chemical allergens without animals and reduces overall animal use by 72 per cent. Stokes also participated in a meeting of the validation management team of a Japanese-led study of a new AOP-based test method to identify potential skin sensitizers without using animals.

NICEATM workshop reviews new *Leptospira* vaccine testing approaches

Later in September, over 80 scientists from around the world gathered in Ames, Iowa, at the NICEATM-sponsored "International Workshop on Alternative Methods for *Leptospira* Vaccine Potency Testing: State of the Science and the Way Forward." Workshop participants reviewed available improved methods for *Leptospira* vaccine potency testing, which uses many laboratory animals and causes significant pain and distress to the animals used.

Participants in the workshop, including both vaccine manufacturers and regulators, discussed steps that could be taken to achieve wider use of *in vitro* replacement methods for *Leptospira* vaccine potency testing developed by the USDA's Center for Veterinary Biologics. These included exploration of new approaches to validation and sharing of data, reagents, and best practices.

Workshop participants also proposed the development and application of serological methods, which measure the levels of specific antibodies in the blood of immunized test animals. These methods use fewer animals and reduce or eliminate animal pain and distress compared to traditional methods. Participants agreed on specific characteristics that serological methods must have and what regulatory agencies would require of acceptable methods.

In those cases where animal use is still needed for *Leptospira* vaccine potency testing, the workshop participants also identified steps that should be taken to reduce animal use and proposals for avoiding or minimizing animal pain and distress.

"Action on the proposals from this workshop can immediately reduce and eventually replace animal use for *Leptospira* vaccine potency testing, while still protecting human and animal health," comments Stokes.

Slides presented by speakers are available on the NICEATM website[1], and a summary of the workshop will be posted here soon. A workshop report will be published next year as a special issue of *Biologicals*.

[1] http://iccvam.niehs.nih.gov/meetings/LeptoVaccWksp-2012/LeptoVaccWksp.htm

IIVS News & Views

Memorandum of understanding signed with EPAA

During its 8th annual conference in Brussels, the co-chairs of the European Partnership for Alternative Approaches to Animal Testing (EPAA) signed a memorandum of understanding with IIVS President, Rodger Curren. The agreement signifies the establishment of a strategic partnership between the two groups dedicated to combining resources and collaborating to promote international awareness and education in non-animal testing methods.

Held on 16 November, the annual conference was attended by 150 delegates from regulatory agencies, the European Commission, and representatives from the seven industries that EPAA represents. DG Enterprise and Industry's deputy director general, Antti Peltomäki, stressed that while Europe has pioneered efforts in the 3Rs, further progress could only be secured through international cooperation. "Strong international cooperation is the future of alternatives to animal testing" stated Peltomäki during his keynote speech.

To support this effort the EPAA will provide sponsorship of up to € 100,000 over the next two years to support IIVS international training activities in key regions of the world where regulatory agencies still require animal testing.

IIVS wins first annual Training Prize by Lush Cosmetics

IIVS received the first annual Lush Training Prize during an award ceremony in London on 15 November. The prize, a joint project between Lush and Ethical Consumer magazine, recognizes individuals or organizations that have excelled in establishing training programs to make scientists aware of the range of available non-animal testing methods.

"At IIVS we believe the change to non-animal testing methods will be hastened through education and training. Seeing, touching, using these methods firsthand and understanding the results will change perceptions and practices," said Rodger Curren, President of IIVS, during the awards ceremony. This thought was echoed by IIVS's Vice President of Program Development, Erin Hill, who stated: "Our trainings change the fuzzy image of 'alternatives' into the reality of better science and the removal of animal pain and suffering."

The Lush Training Prize is one of 5 categories the cosmetics company recognized. Others include the Science Prize, Young Researcher Prize, the Public Awareness Prize, and the Lobbying Prize. Over 180 nominations were submitted and a panel of 10 independent judges picked the winners from a shortlist compiled by the Lush Prize Team.

IIVS shares the award with InterNICHE, an international network focusing on animal use and alternatives within biological sciences, medical, and veterinary medical education. To learn more about the Lush Prize or view the award ceremony video, please visit: http://www.lushprize.org

IIVS Supports the 1st Latin American Congress on Alternative Methods for Use of Animals in Education, Research, and Industry: COLAMA 2012

Styled after the World Congress on Alternatives and Animal Use in the Life Sciences, COLAMA provided a forum for Latin American countries interested in alternative methods. The host country Brazil recently created the Brazilian Center for the Validation of Alternative Methods (BraCVAM) through cooperation between the Oswaldo Cruz Foundation (FIOCRUZ), the National Health Surveillance Agency (ANVISA) and the National Network of Alternative Methods (RENAMA), an initiative by the Ministry of Science, Technology and Innovation. The conference was organized in Niteroi and attended by almost 200 people including over 40 speakers and 12 supporting organizations. The Congress

spanned 4 days and the program themes included:

I - Ethical considerations, policies and laws regarding the use of animals in science and industry
II - Alternative methods for teaching and training – Humane Education
III - Animal welfare and refinement for high-quality science
IV - Reduction and replacement of animal use in science and industry

Rodger Curren was an invited speaker to COLAMA 2012. His presentation on "The Use of 3-D Models for the Assessment of Genotoxicity" highlighted the utility of using 3-D reconstructed human tissues for a variety of toxicity endpoints. IIVS was proud to be a Bronze Sponsor of the event. Future meetings will be held every 3 years with Cuba as the next anticipated host country.

Recent IIVS publications

Forsby, A., Norman, K., El Andaloussi-Lilja, J., et al. (2012). Using Novel In Vitro NociOcular Assay Based on TRPV1 Channel Activation for Prediction of Eye Sting Potential of Baby Shampoos. *Toxicol Sci 129*, 325-331.

This article on eye sting was selected as the Editor's Choice. Toxicological Sciences Editor Michael L. Cunningham notes, "Replacing animal testing for pain induction by chemicals is a goal of animal welfare research. Forsby et al. make a significant advancement in this field by the development of the NociOccular test for baby bath and shampoo formulations. This assay is a recombinant neuronal *in vitro* model of activation of the Transient Receptor Potential Vanilloid type 1 channel, a well characterized pain-inducing receptor. This research opens the way for the development of future assays to predict pain induction without the use of animals."

Baldea, I., Costin, G.-E., Filip, A., et al. (2012). Biphasic pro-melanogenic and apoptotic effects of all-trans-retinoic acid on human melanocytes – time course study. *Pigment Cell Melanoma Res 25*, 692.