



Corners

CAATfeed

CAAT turns 30!

For more than 30 years, the Johns Hopkins Center for Alternatives to Animal Testing has worked to promote the development, use, and validation of the 3Rs of alternatives. CAAT celebrated by hosting the opening reception at the 8th World Congress on Alternatives and Animal Use in the Life Sciences, which took place August 21-25 in Montréal, Canada.

CAAT is not only a year older but also busier and more productive than ever. We are proud to announce that CAAT is the recipient of a \$ 6 million grant from the National Institutes of Health (NIH) to pioneer potentially revolutionary new methods for toxicological testing to improve human health and reduce animal testing. CAAT Director Thomas Hartung, MD, PhD, and his team at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, along with partner Agilent Technologies and noted scientists from government and industry, received the funding for a consortium to develop a new technological methodology for mapping the molecular pathways of toxicity within cells. Funding for the project comes from the Common Fund's NIH Director's Transformative Research Projects Program (R01), which is designed to support exceptionally innovative, high risk, original and/or unconventional research that has the potential to create or overturn fundamental scientific paradigms. See: <http://altweb.jhsph.edu/news/current/caatnihgrant.html>

Dr Hartung and Dr Hogberg were also awarded a \$ 1.2 million project "*Identification of pathways of developmen-*

tal neurotoxicity for high throughput testing by metabolomics" by US FDA.

There exists a critical concern that exposures to drugs and chemicals during early life contribute to the increasing incidence of neurodevelopmental disorders in children, such as lowered IQ, learning disabilities, autism and attention deficit and hyperactivity disorder (ADHD). The developing brain is more susceptible to substance-induced injury compared to the adult brain due to the complex developmental processes, the absence of a functional blood/brain-barrier and a diminished ability to detoxify chemicals. Demanding animal tests have been devised, but because of low frequencies of hazardous substances and manifestations, as well as complex underlying mechanisms, limitations of current approaches are enormous. The area is therefore of key interest for new approaches, as outlined in the NRC vision document for a toxicology in the 21st century and the critical path initiative. In a 6-year project including organization of two international conferences, promising models and prototypic test substances have been identified. Extending our recent metabolomics and genomics approaches, a systems toxicology approach now shall be applied, in order to identify and validate critical pathways of toxicity (PoT). PoT-specific reporter gene models shall then be established allowing higher test throughput.

To carry out the extensive array of projects now under way, CAAT has recruited the following new team members:

– Dr Liang Zhao, a Research Analyst, will be largely responsible for the application of different types of mass

spectrometers in proteomics and metabolomics.

- Dr Martin Stephens, Senior Research Associate, will coordinate the activities of the newly developed Evidence-based Toxicology Collaboration (EBTC).
- Dr Mounir Bouhifd, a Research Associate, will work in the area of metabolomics, setting up the workflow of the testing facility activities.
- Dr Andre Kleensang will work as a Research Associate in the Department of Environmental Health Sciences. His main responsibilities will be to combine various data-rich omics approaches to identify pathways of toxicity and develop and implement novel tools for pathway of toxicity identification and validation.

Dr Hartung also has been named Editor-in-Chief of *Frontiers in Predictive Toxicity*. The Frontiers Research Foundation (FRF) is a Swiss-registered not-for-profit organization. The FRF has a social mission to enhance research knowledge societies. A core strategy of the FRF is to support equal opportunity open-access research publishing. See: http://www.frontiersin.org/predictive_toxicity

CAAT recently partnered with ILSI/HE-SI Developmental and Reproductive Toxicology (DART) to sponsor a workshop on Testicular Toxicology In Vitro Models, held in Baltimore, USA in October, 2011. The workshop brought together experts in testis physiology and toxicology with tissue engineers to brainstorm ways of creating environments *in vitro* that might be more conducive to maintaining spermatogenesis, with the goal of finishing with ideas for two to seven models that could feasibly be tried in the near future.



CAAT honors four awardees at World Congress in Montréal

The CAAT Recognition Award, presented at every World Congress, honors an organization or individual that has made an outstanding contribution to the field of the 3Rs, the development of alternative methods, or the field of *in vitro* science. The 2011 recipients of this award are Dr Kevin Crofton and Dr Manfred Liebsch.

Dr Kevin Crofton was chosen from a list of international nominees for an exceptional body of work in the field of neurotoxicology, especially in the area of developmental neurotoxicology (DNT). Dr Crofton is an Acting Assistant Director in the National Health and Environmental Effects Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina. He has worked as a toxicologist at EPA since 1986, receiving Scientific and Technological Achievement Awards and a Gold Medal for Commendable Public Service.

Dr Crofton's interests and expertise include areas such as developmental neurotoxicity, the cumulative risk of thyroid disruptors, and development of alternative testing methods. He served as the Developmental Neurotoxicity Team Lead for many years with the goal of fostering the development of alternative models for screening chemicals for developmental neurotoxicity. His current efforts include development of *in vitro* and alternative methods for detecting thyroid disrupting chemicals.

Dr Manfred Liebsch was selected from a list of international nominees for outstanding expertise in and dedication to the assessment, validation, and promotion of alternative methods. Dr Liebsch is the Scientific Director of Germany's Federal Institute for Risk Assessment (BfR) and Head of the "Centre of Alternative Methods to Animal Experiments" (ZEBET) unit at the BfR. He has served as Main Contractor, Co-coordinator, Participant, or Consultant on a variety of successful validation studies on alternative *in vitro* methods, both at the national and the European level. His work has focused on the fields of topical toxicity (eye- and skin-irritation and corrosion, phototoxicity,

and skin absorption), and ecotoxicology (acute aquatic toxicity). Dr Liebsch also provides Expert Consultancy in the validation of new toxicological methods for hazard identification in National, European, and International Working Groups, including the ECVAM Scientific Advisory Board, the OECD Test Guidelines Program, and ISO 194. He also played a key role in convening the Working Group M12 for Biological Evaluation of Medical Devices. He has published numerous papers and is a frequent invited speaker at conferences.

Alicia Z. Karas, DVM, is the 2011 recipient of the Charles River Laboratories' Excellence in Refinement Award. She is noted for her expertise and dedication in enhancing the well-being of laboratory animals and in alleviating the pain and distress they may experience.

Sponsored by Charles River Laboratories, in cooperation with the Johns Hopkins Center for Alternatives to Animal Testing (CAAT), the award honors an individual who has made an outstanding contribution to the development, promotion, and/or implementation of refinement alternatives. "Refinement," one of the 3Rs of alternatives, refers to methods aimed at minimizing pain and distress for laboratory animals.

Karas, currently Assistant Professor of Clinical Sciences in anesthesia at Tufts School of Veterinary Medicine, has devoted her career to easing the life of laboratory animals. Her primary research interests include the assessment and treatment of pain or distress in laboratory animals, animal well-being, pain management, and pain medicine.

For information on the Charles River Laboratories' "Humane Care Initiative," please see: <http://www.criver.com/en-US/AboutUs/HumaneCareInitiative/Pages/home.aspx>

Emily McIvor, Senior Policy Adviser for Humane Society International/Europe, won the 2011 Henry Spira Award. She has worked on animal welfare issues at European Union level for many years, specializing in the use of animals in research and testing. As one of the lead animal welfare lobbyists in political ne-

gotiations of the EU Cosmetics Directive 7th Amendment, REACH regulation, and most recently, the revision of Europe's legislation for the protection of animals used for scientific purposes, McIvor has extensive experience with regulatory test issues and the development and validation of alternative, non-animal methods.

McIvor represents HSI/Europe on the stakeholder "mirror group" of the European Partnership for Alternative Approaches to Animal Testing, and on the management panel of the European Union-funded AXLR8 (pronounced "accelerate") project. On broader animal welfare issues, McIvor has contributed to discussions relating to the current and future Community Action Plans on the Protection and Welfare of Animals and has addressed the European Parliament's Animal Welfare Intergroup.

McIvor's dedicated efforts to improving animal welfare reflect the criteria presented by Peter Singer in the book *Ethics into Action: Henry Spira and the Animal Rights Movement*. Singer distills the methods Spira used over the years into "Ten Ways to Make a Difference." The selection criteria for this award are based upon these methods: See <http://caat.jhsph.edu/programs/awards/spira/index.html>

For additional information about CAAT's Awards Programs, see: <http://caat.jhsph.edu/programs/awards/index.html>

CAAT-Europe hosts workshop on scientific ways forward for replacement of systemic toxicity testing for cosmetics and chemicals

From 10-12 October, 35 experts from both sides of the Atlantic convened in Konstanz, Germany, to discuss five white papers prepared by David Basketter, Harvey Clewell, Thomas Hartung and Annamaria Rossi for the areas of sensitization, toxicokinetics, carcinogenicity, reproductive and repeated-dose toxicity. Four to five respondents per paper and an extensive discussion with all participants led to agreement on all papers. They are currently being prepared for publication



in ALTEX 1/2012. The papers set priorities for test/model optimization, validation, integrated testing strategies and the link to Toxicology in the 21st Century with its pathway-based approaches. A two-day event to present and discuss these papers will take place in Brussels in March 2012 (contact: Mardas Daneshian, caat-eu@uni-konstanz.de). This will be jointly hosted by a number of stakeholder organizations including ASCCT, CAAT, COACH/SEURAT-1, DZF, ecopa, ESTIV, HSI, IIVS, IVTIP, ToxCast – other organizations are in the process of deciding on co-hosting the event. It is hoped that this priority setting will help define future programs for replacement options for these complex endpoints.

Further CAAT and CAAT-Europe activities

Promotion of the 3Rs involves policy issues as well as scientific concerns. Dr Paul Locke, an environmental health scientist and attorney responsible for CAAT's policy program, and his team regularly visit Capitol Hill to discuss policy issues associated with humane science and alternatives. Much of the discussion about chemical regulation under the Toxic Substances Control Act (TSCA) focuses on the goal of protecting human health, but Locke led a Capitol Hill briefing in October, along with Rep. Jim Moran (D-VA), co-chair of the Congressional Animal Protection Caucus, to draw attention to the need for alternatives to animal testing.

"More must be done to require agencies including US EPA, the National Institutes of Health and the Food and Drug Administration along with the chemical industry to end animal testing," Locke said.

Locke recently gave a presentation at the Animal Law Conference in Portland, Oregon entitled "Humane Science: Is the End of Animal Testing Within Reach?"

See: <http://altweb.jhsph.edu/news/current/animaltoxics.html>

CAAT Europe and the Transatlantic Think Tank for Toxicology (t⁴) hosted a workshop on developmental neuro-

toxicity testing with the goal of defining pathway-based and mechanism-related compounds relevant for developmental neurotoxicity (DNT) on October 4-6, 2011 in Konstanz. The experts from areas of pharmacology, toxicology, biology and alternatives to animal experiments discussed the identification of mechanistically defined compounds to map pathways for DNT and the classification of established DNT compounds according to expected *in vitro* effects and mechanisms. The results of the workshop will be published in the near future.

CAAT Europe hosted its second Information Day, this time on the topic "Status and Future of Systemic Toxicity Testing for Chemicals and Cosmetics" on October 13, 2011 in Konstanz. Speakers from academia, industry and animal welfare organizations focused on the scientific state of the art, challenges and opportunities for testing complex toxicological hazards without animals. This reflects the ongoing development of new strategies for chemicals and cosmetic ingredients safety testing in Europe and the US.

CAAT had a booth at the recent meeting of the American Association of Laboratory Animal Science (AALAS) in San Diego, California. The meeting drew 5,000 participants in the laboratory animal field. We had the opportunity to talk with many people about the 3Rs and to offer them copies of ALTEX and our new CAAT brochure.

Upcoming CAAT events

CAAT-US Information Day
Food Information Day
November 15, 2011
Baltimore MD, USA
<http://caat.jhsph.edu/programs/workshops/foodinformation.html>
For program and registration, contact: Marilyn Principe (mprincipe@jhsph.edu)

Evidence-based Toxicology Workshop
January 24-25, 2012
EPA, Research Triangle Park, USA
For further information contact: mprincipe@jhsph.edu

*Workshop: Stakeholders Meeting
re Cosmetic Review*
March, Brussels, Belgium (TBA)

For up-to-date listings and information about CAAT programs and events: <http://caat.jhsph.edu/programs>

Recent Publications

Christiansen, S. H., Selige, J., Dunkern, T., et al. (2011). Combined anti-inflammatory effects of $\beta(2)$ -adrenergic agonists and PDE4 inhibitors on astrocytes by upregulation of intracellular cAMP. *Neurochem. Int.* 59, 837-846. doi:10.1016/j.neuint.2011.08.012. PubMed PMID: 21871511.

Mattsson, C. L., Csikasz, R. I., Chernogubova, E., et al. (2011). $\beta 1$ -Adrenergic receptors increase UCPI in human MADS brown adipocytes and rescue cold-acclimated $\beta 3$ -adrenergic receptor KO mice via nonshivering thermogenesis. *Am. J. Physiol. Endocrinol. Metab.*, 2011 Aug. 30, Epub ahead of print. doi:10.1152/ajpendo.00085.2011.

Hogberg, H. T. and Bal-Price, A. K. (2011). Domoic acid-induced neurotoxicity is mainly mediated by the AMPA/KA receptor: comparison between immature and mature primary cultures of neurons and glial cells from rat cerebellum. *J. Toxicol.* 32, 158-168.