



Corners

CAATfeed

CAAT 2013-14 Research Grant Awardees and Renewals

- Patrick Allard, University of California Los Angeles
Design and validation of reproductive and multi-generational assays in *C. elegans*
- Maria Teresa Cruz, University of Columbia
In chemico, in silico and *in vitro* modeling to predict human respiratory allergens
- Sabra Klein, Johns Hopkins University
Human respiratory epithelial cell cultures as a surrogate system for assessing the effects of estrogenic compounds on pulmonary disease pathogenesis
- Yusuke Marikawa, University of Hawaii
Novel axial elongation morphogenesis systems using embryonic stem cells to investigate teratogenic factors
- Nicole zur Nieden, University of California Riverside
Skeletal teratogenicity of environmental chemicals predicted with human induced pluripotent stem cells *in vitro*

CAAT-Europe News

François Busquet, Policy Coordinator for CAAT-Europe, was a featured speaker at

the following events in December 2013:

- Think Tank “ecolo-ethik,” December 5, on invitation of the French Senate in Paris to discuss “Animals and Economy” (economics and alternatives) steered by French Senator Chantal Jouanno.
- La Cité des sciences, Debate on alternatives to animal testing. A podcast is available: <http://www.cite-sciences.fr/fr/conferences-du-college/programme/c/1248139021895/-/p/1239022827697/>
- Radio show on France Inter; La tête au carré. A podcast is available: <http://www.franceinter.fr/emission-la-tete-au-carre-le-choix-des-auditeurs-les-alternatives-a-lexperimentation-animale>

Metabolomics Information Day

This conference brought together scientists from academia and industry to present the current status of metabolomics technology and its applicability in toxicology on November 13 in Baltimore.

In Vitro Sciences and Green Chemistry Information Day

Green toxicology is the application of the principles of toxicology to chemicals with the specific intent of deriving design pro-

ocols for hazard reduction. The twelve principles of green chemistry outline a strategy to reduce hazard through molecular and process design. Reducing toxicity is at the core of green chemistry and sustainability, therefore the input of toxicologists early in the chemical enterprise is essential to inform the choices of molecular designers in selecting less hazardous design strategies. Information derived from mechanistic and computational toxicology combined forms the nexus between toxicology and green chemistry. This conference, held on November 22 in Baltimore, provided a forum for collaboration among scientists working in complementary fields to discover common ground in the quest for safer chemicals.

In Vitro Medical Devices Testing Symposium

This symposium, hosted by the Johns Hopkins Center for Alternatives to Animal Testing (CAAT) on December 11, examined how the National Academy of Sciences' *Toxicity Testing in the 21st Century* could be applied to Medical Devices. The program examined current requirements and testing approaches, followed by an examination of *in vitro* assays useful in medical device testing. http://altweb.jhsph.edu/news/2012/med_device_symp.html



Upcoming CAAT Events

Fourth International Conference on Alternatives for Developmental Neurotoxicity Testing (DNT)

May 12-14, 2014, The Inn at Penn, Philadelphia, PA

Developmental neurotoxicity from chemical exposures is a growing concern. The developing human nervous system is susceptible to pharmaceuticals and environmental contaminants, and exposure during development is known to cause lasting neurological deficits.

This conference will bring together diverse stakeholders from around the globe, including research scientists, regulators, industry representatives, academics, and pediatricians.

Full details and registration: <http://caat.jhsph.edu/programs/workshops/DNT4/index.html>

Call for Abstracts has been extended until February 10, 2014.

You are invited to submit an abstract on the following DNT topics:

- Development and use of alternative testing methods and strategies
- Automation of test methods
- Models of chemical-induced neurological deficits
- The impact of international legislation on chemical testing and data interpretation
- Toxicity pathways: Linking molecular events to adversity (AOP and PoT)
- Predictive molecular and cellular biomarkers of DNT
- Modeling gene/environment interactions that impact neurodevelopment
- Epigenetic changes and neural development

Recent publications by CAAT/CAAT-Europe faculty

Scholz, S., Sela, E., Blaha, L., et al. (2013). A European perspective on alternatives to animal testing for environmental hazard identification and risk assessment. *Regulat Toxicol Pharmacol* 67, 506-530. doi: 10.1016/j.yrtph.2013.10.003

Thomas, R. S., Philbert, M. A., Auerbach, S. S., et al. (2013). Incorporating new technologies into toxicity testing and risk assessment: moving from 21st century vision to a data-driven framework. *Toxicol Sci* 136, 4-18.

EUSAAT

*European Society for
Alternatives to Animal Testing*

News from EUSAAT

EUSAAT, the European Society for Alternatives to Animal Testing, the European 3Rs Society, welcomes the opportunity to present recent and upcoming activities in the EUSAAT news corner of our official journal ALTEX. In this issue, our commentary announces the establishment of a Task Force to discuss, and possibly align, EUSAAT's objectives and informs you of a number of scientific conferences at which EUSAAT Board members represent our society.

Task Force – EUSAAT's mission revisited

During the EUSAAT Annual General Assembly (AGA) 2012 in Linz, the assembly entrusted the Secretary General with the task to establish a Task Force to discuss the goals of EUSAAT with the aim of updating them, as necessary. Starting at the beginning of 2014, this Task Force will convene and pursue its work via electronic mail correspondence. It shall prepare suggestions for amending the mission and goals of EUSAAT to be submitted to

the next AGA for further discussion, and, hopefully, approval.

Already at the AGA 2012, a number of EUSAAT members signed up for the Task Force. We would like to invite further EUSAAT members and all those dedicated to the 3Rs principle to participate in the Task Force, either as active members or by submitting ideas and suggestions.

The Task Force is scheduled to take up its work by the end of January 2014. Brainstorming will take place until the end of March. The Secretary General will collect all ideas, points of discussion, and



suggestions the Task Force participants put forward and will compile all issues into a single document. April and May will be dedicated to discussion of the ideas within the Task Force. The concrete work plan for that stage will be decided upon based on the outcome of the brainstorming. Upon finalization of these discussions, the Secretary General will draft recommendations concerning the objectives of EUSAAT. This draft will be submitted to the Task Force for a final round of comments to take place in June. The finalized recommendations will be submitted to the EUSAAT board in July in time for the AGA 2014, which will take place during the 9th World Congress on Alternatives and Animal Use in the Life Sciences which will be held on August 24-28, 2014 in Prague, Czech Republic.

Please contact the Secretary General (ursula.sauer@EUSAAT.org) for further information or to submit your contributions, etc.

In preparation of our Task Force we would like to remind you of EUSAAT's current objectives as stated in Article 2 of our bylaws (see <http://www.EUSAAT.org>):

The European Society for Alternatives to Animal Testing (EUSAAT) is an amalgamation of scientists from universities, industry and public authorities, as well as other private and public institutions and organisations, interested in the issue of animal testing and alternatives to animal testing based on scientific animal protection. The Society pursues in particular the following objects:

- a) *To promote the dissemination and validation of alternatives to animal testing according to the principle of the 3 Rs (reduce, refine, replace).*
- b) *To promote research in alternatives to animal testing according to the principle of the 3 Rs.*
- c) *To promote alternative methods to reduce the use of animals in education and further education.*
- d) *To promote endeavours to refine, i.e., to promote and disseminate measures and methods that improve the breeding, keeping, experimental procedure, experimental approach and experimental conditions for experimental animals in order to reduce animal stress and suffering.*
- e) *To perform expert functions and expert counselling of public institutions, au-*

thorities, companies, universities, universities of applied sciences and private institutions.

f) *To inform the general public.*

Recent and upcoming events

On November 28, 2013 in Berlin, Germany, the *German Society for Dermatopharmacy (GD)* held a symposium on *Dermatotoxicological and other safety testing methods without animals* in honor of EUSAAT's President Prof. Dr Horst Spielmann (see <http://www.gd-online.de>). Also having been Board member and President of the GD for 16 years, Horst Spielmann retired from that position in Spring 2013 and was appointed honorary member of the GD. At the symposium in November, Horst Spielmann gave the introductory speech on the *Ban of cosmetics testing in animals and roadmap for toxicity testing in the EU "Horizon 2020" research programme*. Scientific Chair of the symposium was EUSAAT's Vice President Professor Dr Ellen Fritsche, who became GD Board member in March 2013. At the GD symposium, she spoke about *3D in vitro models for developmental neurotoxicity testing*. Further EUSAAT Board members participating at the symposium were Vice President Dr Eleonore Haltner and Secretary General Dr Ursula G. Sauer, who gave a presentation on the results of a BASF study on rat precision-cut lung slices for nanomaterial toxicity testing (performed by the team of Dr Robert Landsiedel, BASF, Ludwigshafen, Germany). In her presentation, Ursula Sauer took the opportunity to underline Horst Spielmann's long lasting and outstanding dedication to promoting the 3Rs principle, especially as president of EUSAAT and organiser of the Linz conferences on alternative methods since their inception in 1991.

The evolvement and activities of EUSAAT were addressed in detail at the 26th annual conference of the *Japanese Society for Alternatives to Animal Experiments* (<http://www.jsaae26.jp/index-e.html>), which took place on December 19-21, 2013 in Kyoto, Japan. Horst Spielmann gave a lecture on EUSAAT's activities and included a chronology of our society beginning with the first Linz conference in 1991. The next milestone was in 1993,

when MEGAT was founded in Linz, Austria. MEGAT stood for the *Middle European Society for Alternatives to Animal Experiments*. From the beginning, MEGAT supported the Linz congresses and the ALTEX journal. Since soon colleagues from neighboring countries joined MEGAT (e.g., Czech Republic, Italy, the Netherlands, Slovakia, Sweden), in 2006 the congress language changed from German to English. In 2009, the name of MEGAT was changed to EUSAAT, European Society for Alternatives to Animal Testing, the European 3Rs society.

While we were writing these EUSAAT news, EUSAAT Vice President Dr Eleonore Haltner was invited to represent our society at the *10th International Conference and Workshop on Biological Barriers*, which will take place on February 16-21, 2014 at the University of Saarland, Saarbrücken, Germany (<http://www.uni-saarland.de/info/wirtschaft/kwt/messe-kongresse/biobarriers-2014.html>).

Additionally, EUSAAT has officially become supporting society of the *9th World Congress on Alternatives and Animal Use in the Life Sciences* (<http://www.wc9prague.org/supporting-societies/>). Since there are no EUSAAT / Linz conferences during years in which the World Congresses take place, we invite our EUSAAT members and all supporters of the EUSAAT / Linz conferences to actively participate at the WC9: Calls for abstracts are already open with the abstract submission deadline being April 1, 2014.

These events underline EUSAAT's close international cooperation with other scientific societies sharing with us the common goal to promote the 3Rs principle in the furtherance of a more humane and improved science. EUSAAT, therefore, in 2012 agreed to cooperate with the *Japanese Society for Alternatives to animal Experiments (JSAAE)* and is currently planning a cooperation with the *American Society for Cellular and Computational Toxicology (ASCCT)*; (<http://www.ascctox.org>).

Ursula G. Sauer
Secretary General of EUSAAT
the European 3Rs Society
on behalf of the Board



NTP
National Toxicology Program
U.S. Department of Health and Human Services



News from NICEATM and ICCVAM

ICCVAM requests information on skin sensitization testing activities

ICCVAM is developing a plan of action to advance alternative test methods and testing strategies for skin sensitization. As part of this process, ICCVAM is interested in receiving information on the state of the science of test methods and testing strategies for skin sensitization and about activities in this area of which ICCVAM may not be aware. ICCVAM requested this information November 13 in the *U.S. Federal Register*.

Activities under consideration by ICCVAM include: organizing workshops; developing guidance documents; collaborating with international organizations that are conducting relevant validation studies or preparing relevant guidance; providing support to NICEATM's efforts in this area; and providing information about funding resources and agency priorities to test method developers. To coordinate these efforts, ICCVAM recently established a skin sensitization working group of scientists from relevant Federal agencies.

ICCVAM invites its stakeholders to consider its proposed activities. Stakeholders may comment on the role ICCVAM should play in the development and evaluation of alternative skin sensitization test methods and testing strategies, as well as the potential contributions that regulated industries or non-government organizations and other interested parties might make toward these efforts.

ICCVAM will also request comment from the OECD and from partners in the International Cooperation on Alternative

Test Methods (ICATM). ICCVAM will then consider all comments as it develops plans to augment and support activities that will advance the state of the science for alternative skin sensitization test methods and testing strategies.

Please submit comments or information in response to this request to iccvam@niehs.nih.gov. Additional information and a link to the Federal Register notice are available at <http://ntp.niehs.nih.gov/go/40498>.

NICEATM launches new website

In an effort to make information on NICEATM and ICCVAM activities more accessible to stakeholders, NICEATM launched a new website in December 2013. The new website condenses summaries of past and current NICEATM and ICCVAM activities into a reduced number of webpages for easier navigation, highlights ongoing NICEATM activities that support new approaches to toxicological testing, and includes a section dedicated to ICCVAM processes and activities.

The new NICEATM website is available at <http://ntp.niehs.nih.gov/go/niceatm>. ICCVAM activities are available at <http://ntp.niehs.nih.gov/go/iccvam>.

International Cooperation on Alternative Test Methods partners meet

A coordination meeting of the International Cooperation on Alternative Test Methods (ICATM) was held on November 26-27 at the European Commission (EC) Joint Re-

search Centre's headquarters in Ispra, Italy. ICATM is an international partnership of government validation organizations that promotes the advancement of replacement, reduction, and refinement alternatives for animal testing. ICATM currently consists of organizations representing the EC, the US, Japan, Canada, and South Korea.

At the November meeting, ICATM partner organizations presented updates on current activities and discussed opportunities for future cooperation. Specific topics of the meeting included coordination of recommendations, strategic selection and prioritization test method, coordination of validation studies to improve efficiency, and conducting peer reviews that meet the needs of all member countries. The attendees also toured the *in vitro* GLP laboratory facilities at the Joint Research Centre. A summary of the meeting will be published in January 2014.

Proceedings available from workshop on alternatives for Leptospira vaccine testing

Proceedings from a September 2012 NICEATM-sponsored workshop on alternative methods for *Leptospira* vaccine potency testing were published in November as a dedicated issue of *Biologicals*. The proceedings are available on the Biologicals website at <http://www.sciencedirect.com/science/journal/10451056/41/5>.

Participants at the workshop reviewed available alternative methods for *Leptospira* vaccine potency testing and defined efforts necessary to achieve their global acceptance and implementation. Specific



actions were identified that should be taken by both regulators and industry to facilitate broader use of USDA-validated ELISA antigen quantification methods, which would replace animal use. Where use of the ELISA methods is not appropriate, approaches to reduce and refine animal use were identified, including serological assays, use of analgesics and humane endpoints, potential elimination of back titrations for calculation of LD₅₀, and harmonization of regulatory requirements for the number of animals used for testing.

A summary of the workshop, workshop presentations, and a link to the proceedings are available on the NTP website at <http://ntp.niehs.nih.gov/go/leptowksp>.

Upcoming workshops on alternatives sponsored by U.S. government agencies

On March 6-7, a workshop titled “Validation and Qualification of New *In Vitro*

Tools and Models for the Pre-clinical Drug Discovery Process” will be held at the National Institutes of Health in Bethesda, MD. This is the fourth in a series of workshops to create validation guidelines for investigators developing new tools for the preclinical drug development process. The upcoming workshop will build upon the results and recommendations of the previous workshops, with emphasis on model systems that may augment or replace animal models in the U.S. drug approval process.

The workshop is being organized by the National Institute for Biomedical Imaging and Bioengineering (NIBIB) and the American Institute for Medical and Biological Engineering. Information and a link to registration are on the NIBIB website at <http://www.nibib.nih.gov/news-events/meetings-events/fourth-aimbenih-workshop-validation-and-qualification-new-vitro-tools>.

On April 14, the U.S. Food and Drug Administration (FDA) will convene a workshop on methods used for thrombogenicity testing of blood-contacting medical devices. The workshop will take place at the FDA White Oak campus in Silver Spring, MD.

Current testing of medical devices for thrombogenicity relies heavily on animal studies. These procedures have been called into question by experts due to inconsistent and unreliable results, as well as the expense to conduct this testing and animal welfare concerns. The April workshop will bring together academics, industry professionals, and FDA regulators to discuss the advantages and limitations of both *in vivo* and *in vitro* thrombogenicity test methods. Ideas generated during this workshop will facilitate development of new guidance and standards for thrombogenicity testing.

For information about the workshop, please contact Dr James Kleinedler at the FDA at James.Kleinedler@fda.hhs.gov.



IIVS News & Views

Integrated Testing Strategies for Skin Sensitization: Focus on Direct Peptide Reactivity Assay (DPRA)

A common characteristic of skin sensitizers is their reactivity with skin proteins. The Direct Peptide Reactivity Assay (DPRA) measures a chemical's ability to react with proteins, which is a key upstream event in the mechanism of skin sensitization. In the DPRA, the test chemical is incubated with two small model peptides which contain nucleophilic residues, cysteine or lysine, for 24 hours.

Following this reaction period, peptide depletion is analyzed by HPLC-UV. Data have demonstrated significant peptide depletion by skin sensitizers.

Developed at the Procter & Gamble Company by Frank Gerberick and colleagues, the DPRA has proven to be an effective tool to screen a chemical's ability to induce skin sensitization. The assay has been evaluated for transferability, reproducibility, and accuracy, and following successful inter-laboratory investigations has reached an advanced stage of pre-validation with ECVAM. EURL ECVAM has endorsed the DPRA as part of an in-

tegrated testing strategy to assess skin sensitization potential, and an OECD test guideline for the assay is being drafted.

IIVS is currently in the process of transferring the DPRA into the laboratory. Given the complex cascade of events leading to skin sensitization, it is generally thought that an integrated testing approach combining multiple assays will be needed to replace the animal based methods. As described during a recent IIVS hosted webinar on “Integrated Strategies for Skin Sensitization,” there is a significant effort underway to ascertain how the non-animal assays may be combined most



effectively to assess skin sensitization potential. IIVS plans to add the DPRA as a complement to the currently offered KeratinoSens skin sensitization assay.

Chinese National Toxicological Congress 2013

IIVS' Hans Raabe and Quanshun Zhang attended the 6th Chinese National Toxicological Congress of the Chinese Society of Toxicology in Guangzhou on November 13-15. This activity was supported by the European Partnership for Alternative Approaches to Animal Testing (EPAA). IIVS presented a poster outlining the structure of the EPAA and introduced the attendees to the mission and activities of the group. In addition to this poster, IIVS presented recent work on the successful validation of the skin sensitization assay, KeratinoSens. This poster announced the successful validation of the assay and outlined the validation approach taken, including some valuable lessons learned. The meeting, with over 2,000 attendees, provided valuable networking with Chinese scientists and regulators.

University of Maryland Bioengineering Society Training

On November 23, IIVS hosted 20 students from the Bioengineering Society of the University of Maryland to participate in an introductory *in vitro* toxicology course. Through a combination of lectures and hands-on laboratory sessions, the students were exposed to how bioengineers could work together with toxicologists to develop *in vitro* testing strategies. This is the second time that IIVS has partnered with the University of Maryland to provide the course and we look forward to continuing this partnership in the future.

Technical Training in Non-Animal Safety Methods Held in China

The Institute for In Vitro Sciences (IIVS), with support from its Industry Council for the Advancement of Regulatory Acceptance of Alternatives (ICARAA), conducted a training course on September 23-27 for *in vitro* safety testing methods for scientists from China's NIFDC (National Institutes for Food and Drug Control), a division of the China Food and Drug Administration.

The training was held at the Institute for Food and Cosmetic Control (IFCC) of the National Institutes for Food and Drug Control (NIFDC) in Beijing. The goal of the training was to familiarize NIFDC scientists with the biological relevance, critical techniques and data interpretation of *in vitro* (non-animal) methods for safety testing. Twenty-eight participants from 18 provincial Institutes for Food and Drug Control, Institutes for Medical Device Control, and Institute for Food and Drug Safety Evaluation of NIFDC attended. Lectures and hands-on laboratory sessions focused on methods for eye irritation, skin irritation, and sensitization.

Wang Youchun, Vice Director-General of NIFDC, spoke at the opening ceremony and emphasized that it is "very necessary to expedite training and research of *in vitro* cosmetic safety evaluation methods and promote *in vitro* safety evaluation technology application and academic exchanges in Food and Drug Control systems in order to adapt to the international cosmetics testing technology development and to meet the requirements for actual inspection work."

The CFDA is currently responsible for the registration and subsequent post market surveillance of cosmetic products. While previous regulations have relied on animal testing, the regulatory and scientific community within China is investigating how existing knowledge of ingredients and *in vitro* testing could be incorporated into their regulatory framework.

"*In vitro* methods can provide significant technical advantages over animal models. Our training courses highlight the key technical steps that are necessary to generate relevant and reliable data," explains Erin Hill, IIVS co-founder and Vice President for Program Development. According to NIFDC participants "the training not only facilitated the application of *in vitro* test methods in the domestic cosmetic industry, but also laid a solid foundation for the further academic exchange, technical cooperation, and personnel training between NIFDC and IIVS."

Congratulations to the 2013 LUSH Prize Recipients

The 2nd Annual Lush Prize was awarded in November in London, UK. Recognizing efforts to reduce the use of animals in experimentation, the prize is given in each of 5 categories including training, lobbying, and research. IIVS was honored to be the recipient of the 1st Annual Lush Training Award in 2012 and was among the groups short-listed for the training prize again this year. Please visit the LUSH prize website at www.lushprize.org for a full list of nominees and recipients of 2012 and 2013 awards.