Corners

The American Society for Cellular and Computational Toxicology encourages you to save the date for its 5th Annual Meeting, which will be held September 29-30, 2016, again in Research Triangle Park, North Carolina. This time, it will be held in conjunction with the ICCVAM SACATM meeting September 27-28. Each day of the meeting will have a different topic focus. The first day will feature a plenary by Dr Thomas Hartung of Johns Hopkins University Center for Alternatives to Animal Testing on read-across, and the second day will focus on pluripotent stem cells for toxicology applications, with a plenary speaker to be confirmed as well as a panel discussion featuring regulatory representation. Both days will also include presentations selected from submitted abstracts relevant to the day's main topics as well as free communications.

A main focus of the ASCCT has always been to provide opportunities for interaction among its members and other scientists. This year's meeting will be no different. A long lunch and poster session, an evening reception and awards ceremony, a mentoring activity, and a business meeting will be a part of the meeting agenda. Stay tuned to the ASCCT website, or join the ASCCT, to learn about registration and abstract submission details as they become available.

The most recent ASCCT webinar was held in February. Integrating *In Silico* Predictions with Physiologically Based Pharmacokinetic (PBPK) Modeling was presented by Michael Lawless and John DiBella of SimulationsPlus, Inc. All ASCCT webinars are free for the general public, but members have priority registration and can view recordings of all past webinars via a password-protected portal.

Join now at http://www.ascctox.org to stay on top of news, events, and opportunities in *in vitro* and *in silico* toxicology.

CAATfeed

CAAT Researchers Create "Mini-Brains" in Lab to Study Neurological Diseases

Researchers at CAAT have developed tiny "mini-brains" made up of many of the neurons and cells of the human brain – and even some of its functionality – which can be replicated on a large scale.

The researchers say that these "mini-brains," which were discussed at the American Association for the Advancement of Science conference in Washington, DC on February 12 at a press briefing and in a session on February 13, could dramatically change how new drugs are tested for effectiveness and safety, taking the place of hundreds of thousands of animals used for neurological scientific research in the United States. Performing research using these three-dimensional "mini-brains" – balls of brain cells that grow and form brain-like structures on their own over the course of eight weeks – should be superior to studying mice and rats because they are derived from human instead of rodent cells.

"Ninety-five percent of drugs that look promising when tested in animal models fail once they are tested in humans at great expense of time and money," says Thomas Hartung, MD, PhD, the Doerenkamp-Zbinden Professor and Chair for Evidence-based Toxicology at the Bloomberg School of Public Health. "While rodent models have been useful, we are not 150-pound rats. And even though we are not balls of cells either, you can often get much better information from these balls of cells than from rodents. We believe that the future of brain research will include less reliance on animals, more reliance on human, cell-based models."

Hartung and his colleagues, led by David Pamies and Helena Hogberg, created the brains using induced pluripotent stem cells (iPSCs). These are adult cells that have been genetically reprogrammed to an embryonic stem cell-like state and then are stimulated to grow into brain cells. Cells from the skin of several healthy adults were used to create the mini-brains, but Hartung says that also cells from people with certain genetic traits or certain diseases can be used to create brains to study various types of pharmaceuticals. He says the brains can be used to study Alzheimer's disease, Parkinson's disease, multiple sclerosis and even autism. Projects to study viral infections, trauma, and stroke have been started.

CAAT's mini-brains are very small – at 350 μm in diameter, or about the size of the eye of a housefly, they are just visible to the human eye – and hundreds to thousands of exact copies can be produced in each batch. One hundred of them can grow easily in the same petri dish in the lab. After cultivating the mini-brains for about two months, the brains have developed four types of neurons and two types of support cells: astrocytes and oligodendrocytes, the latter of which go on to create myelin, which insulates the neuron's axons and allows them to communicate faster.

The researchers could watch the myelin developing and could see it begin to sheath the axons. The brains even showed spontaneous electrophysiological activity, which could be recorded with electrodes, similar to an electroencephalogram, also known as EEG. To test them, the researchers placed a mini-brain on an array of electrodes and listened to the spontaneous electrical communication of the neurons as test drugs were added.

"We don't have the first brain model nor are we claiming to have the best one," says Hartung, who also directs the School's Center for Alternatives to Animal Testing. "But this is the most standardized one. And when testing drugs, it is imperative that the cells being studied are as similar as possible to ensure the most comparable and accurate results."

CAAT is applying for a patent for the mini-brains and is developing a commercial entity called ORGANOME to produce them. He hopes production can begin in 2016. He says they are easily reproducible and hopes to see them used by scientists in as many labs as possible. "Only when we can have brain models like this in any lab at any time will we be able to replace animal testing on a large scale," he says.

The work was supported by the National Institutes of Health's National Center for Advancing Translational Sciences (U18TR000547), the Alternatives Research & Development Foundation and the Bart McLean Fund for Neuroimmunology Research/Project Restore.

Other researchers involved in the project include David Pamies, Paula Barreras, Katharina Block, Georgia Makri, Anupama Kumar, Daphne Wiersma, Lena Smirnova, Che Zang, Joseph Bressler, Kimberly M. Christian, Georgina Harris, Guo-li Ming, Cindy J. Berlincke, Kelly Kyro, Hongjun Song, Carlos Pardo, Thomas Hartung, and Helena T. Hogberg.

International Coverage of CAAT's Pioneering "Mini-Brain" Research

Thomas Hartung's discussion of the development of "mini-brains" at the American Association for the Advancement of Science conference in Washington, DC on Feb. 12 has generated an enormous amount of press coverage. Here are some of the highlights:

– WBAL-TV Report (video): "Mini-brains" Could Reduce Need to Use

Animals in Medical Testing; http://bit.ly/1Mh0L2N
- Financial Times: Human Mini-brains Set to Transform Drug Testing; http://on.ft.com/1RaigyP
- The Guardian: "Mini-brains" could revolutionise drug research and reduce animal use; http://bit.ly/241kYj3
- Popular Science: Mini-brains Could Help Scientists Understand How Chemicals Affect the Brain; http://bit.ly/1Raiiqm
- The research was also covered in The Baltimore Sun, Motherboard, Tech Times, The Daily Mail, Medical News Today, Ars Technica, Endgaget, and many more publications.

The research was supported by the National Institutes of Health's National Center for Advancing Translational Sciences (U18TR000547), the Alternatives Research & Development Foundation, and the Bart McLean Fund for Neuroimmunology Research/Project Restore.

CAAT Team's Read-Across Database Featured in *Science* and *Nature*

"A crystal ball for chemical safety" is the title of the article by T. Rabesandratana in *Science* (http://dx.doi.org/10.1126/science.351.6274.651).

"Legal tussle delays launch of huge toxicity database" is the title of the article by N. Gilbert in *Nature* (http://dx.doi.org/10.1038/nature.2016.19365)

Full articles by Luechtefeld et al. in this issue of ALTEX.

Thomas Hartung Cited in *The Scientist* on Animal-Free Toxicity Testing

Thomas Hartung weighed in on an *in vitro* robotic screening tool developed by researchers at the National Institutes of Health National Center for Advancing Translational Sciences (NCATS) and their colleagues. The new tool is able to screen thousands of chemicals in human cell lines systematically.

Hartung is quoted as saying: "I think this is one of the best examples of big data entering (the field of) toxicology. Because of the high quality of the data set and its transparency and data-sharing, this is really an enabling step toward *in vitro* toxicology testing."

Read the full article at http://bit.ly/1PB4aEW

In Memoriam: Prof. Frauke Ohl

We at CAAT are grieving the loss of our European board member, Frauke Ohl. As we learned from the University of Utrecht, Prof. Ohl, Chair of the Department of Animals in Science and Society, has recently passed away. Frauke had just turned 50, and had so many ideals that she wanted to achieve. But she was overwhelmed by her struggle against cancer.

International Press Coverage of CAAT

Recent international press coverage of CAAT and its research included:
- *Esperimenti sugli animali se la questione è morale* (La Republica, Italian, bit.ly/1nWUWMD)
- *Ersatz gesucht* (Zeit Online, German, bit.ly/1JB4g2O)

Recent Events

EU-ToxRisk Kickoff Meeting Held in The Netherlands

EU-ToxRisk, the integrated European "flagship" program driving mechanism-based toxicity testing and risk assessment for the 21st century, was officially launched in January 2016 with a kickoff meeting in Egmond aan Zee, The Netherlands. Over 100 scientists representing academic and industrial institutions as well as regulatory authorities attended the inaugural meeting.

As part of the Horizon 2020 project, endowed with €30 million and including 38 European partners and one from the US (the Center for Alternatives to Animal Testing at Johns Hopkins), EU-ToxRisk was created to drive the required paradigm shift in toxicology towards animal-free, mechanism-based integrated approaches for chemical safety assessment. Stakeholders from relevant disciplines will establish pragmatic read-across procedures incorporating mechanistic and toxicokinetic knowledge as well as hazard and risk assessment strategies for chemicals with minimal background information. The focus of EU-ToxRisk is repeated-dose systemic toxicity (liver, kidney, lung, and nervous system), as well as developmental/reproduction toxicity. The EU-ToxRisk mission is to evolve an adverse outcome pathway (AOP) integrating relevant *in vitro* and *in silico* technologies required for the assessment of chemical safety in humans.

Thomas Hartung presented a talk on "Challenges in Computational Toxicology" and Marcel Leist discussed a realistic roadmap for reaching the goals of the project and explored the impact of the outcome on the future of consumer protection as well as for human-relevant approaches.

SOT Satellite Meeting on 21st Century Toxicology and Related Efforts

March 17, 2016
New Orleans, LA

CAAT and the Human Toxicology Project Consortium (HTPC) held their annual satellite meeting on 21st Century Toxicology Activities and Related Efforts.

The satellite meeting provided an informal setting in which interested stakeholders updated each other on important topics related to Tox21c. The meeting featured a number of invited presentations but also left time for an "open microphone" segment in which participants gave brief presentations. The invited speakers, their affiliations, and their topics included Russell Thomas (US Environmental Protection Agency) – ToxCast, Richard Paules (US National Toxicology Program) – Tox21, David Dix (US Environmental Protection Agency) – EDSP21, Warren Casey (National Toxicology Program Interagency

Center for the Evaluation of Alternative Toxicological Methods) – NICEATM, Rebecca Clewell (ScitoVation) – ScitoVation/Hamner, Michael Schwarz (University of Tuebingen) – SEURAT, Robert van de Water (Leiden University) – EU-ToxRisk, Thomas Hartung (Johns Hopkins) – CAAT, Catherine Willett (Human Toxicology Project Consortium) – HTPC, and Martin Stephens (Johns Hopkins) – Evidence-based Toxicology.

Other CAAT Activities at the Society of Toxicology (SOT) Annual Meeting

Thomas Hartung presented a session on "CAAT and the Work of the Read-Across Steering Group" on Tuesday, March 15 as part of the workshop, "Read-Across: Building Scientific Confidence in the Development and Evaluation of Read-Across for Regulatory Purposes Using Tox21 Approaches."

The EBTC's Martin Stephens gave a presentation on "Evidence-based Approaches for Enhancing the Reproducibility of Toxicological Studies" in an SOT session on Scientific Reproducibility: Does this Pose a Problem for 21st Century Toxicology? The session addressed recent concerns that much of what is published in the biomedical literature cannot be reproduced. This is particularly concerning for those using legacy data to develop the predictive *in vitro* assays and *in silico*-based computational models at the heart of 21st century toxicology.

Stephens argued that the reproducibility of toxicological studies is largely a function of their methodological quality and reporting completeness. Studies with poor methodological quality (e.g., non-random allocation of animals to experimental and control groups) are subject to high and spurious variability in outcomes. Such studies are hard to reproduce, as are studies with limited reporting completeness (e.g., no mention of housing and husbandry conditions). Evidence-based approaches provide tools and concepts that can be used to enhance methodological quality and reporting completeness – and thus the reproducibility – of toxicological studies. Systematic reviews, for example, include an assessment of the methodological quality of the reviewed studies, primarily as a function of risk of bias. Such approaches also can be used prospectively as guidance for minimizing risk of bias in new studies. Guidance on reporting completeness of pre-clinical studies on animals is applicable to animal-based toxicological studies. From the perspective of 21st century toxicology, evidence-based approaches provide guidance on the design and reporting of studies using the new methods. Such approaches also provide a robust means of assessing the quality of the legacy data used to inform and evaluate 21st century methods; such quality assessments can be used as a marker of the legacy data's potential reproducibility.

Posters and presentations from the CAAT team included:

CAAT's Rita Cassia presented a poster on "Developmental neurotoxicity of flame retardants using a rat primary three-dimensional organotypic *in vitro* model."

Georgina Harris presented a poster on "*In vitro* toxicity and resilience of a 3D human dopaminergic model to Rotenone." Georgina was also a graduate student representative, helping with an expert program that arranges meetings between small groups of students and postdoctoral scholars (no more than four people per group) and associate or full SOT members for informal discussions at the Annual Meeting and ToxExpo. She also served as an IVAM Specialty Section Student Representative taking part at the IVAM luncheon.

Katya Tsaioun presented a poster on "A Systematic Review of the Zebrafish Embryological Test as an Alternative to the Mammalian Developmental Test (OECD 414): a Pilot for Evidence Based Toxicology Approach." She also presented a workshop: "Paradigm Change in Toxicology: What Will It Take to Bring Advances in the Science of Toxicology into Regulatory Use?"

Lena Smirnova presented a poster entitled, "Contemporary Concepts in Toxicology (CCT) Meetings."

Helena Hogberg delivered a platform presentation on flame retardants, entitled "Omics Approaches to Evaluate Developmental Neurotoxicity of Organophosphorus Flame-Retardants."

CAAT's Georgina Harris Appointed Graduate Student Representative to *In Vitro* and Alternative Methods Specialty Section

Please join us in congratulating CAAT's Georgina Harris, who is now an incoming officer of the *In Vitro* and Alternative Methods Specialty Section (IVAM). IVAM is a specialty group within the Society of Toxicology whose members have expertise in the application of *in vitro* techniques to problems of cellular toxicity, with a special emphasis on product safety evaluation.

Symposium on Social Housing of Laboratory Animals

March 17-18, 2016
UC Davis School of Veterinary Medicine, Davis, CA

This CAAT symposium was co-hosted by USDA, OLAW, UC Davis School of Veterinarian Medicine, Division of Veterinary Resources NIH, and the Johns Hopkins School of Medicine Department of Molecular and Comparative Pathobiology. The event included a tour of the California National Primate Research Center.

Good Read-Across Practices: Making it Work for You

February 26, 2016
Brussels, Crowne Plaza Hotel

CAAT-Europe, CEFIC-LRI, and EU-ToxRisk hosted a multi-stakeholder forum on Good Read-Across Practices with more than 100 participants representing industry, academia, and regulatory bodies. The REACH regulation has been in force for almost ten years now and more than 10,000 substances have been successfully registered. According to ECHA, about 75% of the dossiers contain a read-across approach for toxicological or environmen-

tal assessment. Even though in many cases the approach was not fully justified by the submitters, it is now clear that read-across may help in defining the toxicological profile of a substance while saving many *in vivo* tests.

At the meeting, this new direction was demonstrated by the participation of many consultants and companies that are strongly interested in the REACH registration process but are rarely present in similar discussions about alternative methods. Read-across itself is not enough if not supported by proper scientific validation, and this necessity was the driving force behind ECHA's decision to publish the RAAF (Read Across Assessment Framework) document to guide REACH submitters on the preparation of proper justification reports.

CAAT is studying the possibility of exploiting the largest dataset of chemicals ever published, i.e., the public ECHA database of registered dossiers. Preliminary results are encouraging, but further work to generate a user-friendly interface is underway. This will be developed only after receiving from ECHA the green light for permission to use the public data for this purpose.

A similar read-across meeting was held in the U.S.; see below for details.

Good Read-Across Practice (GRAP) Guidance Workshop

March 1, 2016
US Food and Drug Administration (FDA)
College Park, MD

This event was co-hosted by the US Food and Drug Administration Center for Food Safety and Advanced Nutrition (FDA-CFSAN) and the Center for Alternatives to Animal Testing (CAAT) at Johns Hopkins and the University of Konstanz. It was co-organized by American Chemistry Council, ASCCT, Cefic LRI, EU-Tox Risk, HTPC, Humane Society International, NIH, UL, and Johns Hopkins University.

Speakers included Mark Cronin (Liverpool John Moores University), Hao Zhu (Rutgers University), Grace Patlewicz (EPA), Nicole Kleinstreuer (NIEHS), and Thomas Hartung (CAAT).

The EBTC's Katherine Tsaioun at ToxForum

Katherine Tsaioun, Director of the Evidence-based Toxicology Collaboration (EBTC), presented a talk on "Translation of Diagnostic Test Accuracy Guidelines to Toxicology Test Method Performance: Zebrafish Embryo Test as a Predictor of Developmental Toxicity" at the 40th Annual Winter Meeting of the Toxicology Forum on Wednesday, February 10 in Washington, D.C.

CAAT Grantee Publishes Study Suggesting Estrogen Protects Women Against the Flu

The female sex hormone estrogen has antiviral effects against the influenza A virus, commonly known as the flu, a new study by a CAAT grantee in *American Journal of Physiology – Lung Cellular and Molecular Physiology* reports.

A virus infects and causes sickness by entering a cell and replicating – make copies of itself – inside the host cell. When released from infected cells, the virus can spread through the body and between persons. How much a virus has replicated determines its severity. Less replication of the virus means the infected person may experience less disease or is less likely to spread the disease to someone else, says Sabra Klein, PhD, of the Johns Hopkins University and lead investigator of the study. Klein is a former CAAT grantee.

Upcoming Events

Pan-American Conference on Alternative Methods

April 12-14, 2016
Johns Hopkins University

This conference brings together experts and stakeholders from across the Americas, with a focus on the Six Rs: *Replacement, Reduction, Refinement, Read-across, Relevance*, and *Roadmaps*. The Organizing committee includes Agilent, ASCCT, Brazilian Society of Alternative Methods, Canadian Council on Animal Care in Science, DOW, Humane Society International, IIVS, INCQS-FIOCRUZ, Inmetro, Johns Hopkins University, MB Research Labs, National Institutes of Health, PCRM, PETA International Science Consortium Ltd., Science to Inform, Shell, Universidade Federal de Goiás, and the University of Sao Paulo.

Save the Date: 10th World Congress on Alternatives and Animal Use in the Life Sciences

August 20-24, 2017
Seattle, Washington

Recent Publications

Blaauboer, B. J., Boobis, A. R., Bradford, B. et al. (2016). Considering new methodologies in strategies for safety assessment of foods and food ingredients. *Food Chem Toxicol 91*, 19-35. http://dx.doi.org/10.1016/j.fct.2016.02.019

Ferrario, D., Gribaldo, L. and Hartung, T. (2016). Arsenic exposure and immunotoxicity: A review including the possible influence of age and sex. *Curr Environ Health Rep*, 1-12. http://dx.doi.org/10.1007/s40572-016-0082-3

da Silva, C. C., Presgrave, O. A. F., Hartung, T. et al. (2016). Applicability of the Monocyte Activation Test (MAT) for hyperimmune sera in the routine of the quality control laboratory: Comparison with the Rabbit Pyrogen Test (RPT). *Toxicol In Vitro 32*, 70-75. http://dx.doi.org/10.1016/j.tiv.2015.12.004

Fasani, R. A., Livi, C. B., Choudhury, D. R. et al. (2016). The Human Toxome Collaboratorium: A shared environment for multi-omic computational collaboration within a consortium. *Front Pharmacol 6*, 322. http://dx.doi.org/10.3389/fphar.2015.00322

Kaesler, S., Skabytska, Y., Chen, K.-M. et al. (2016). Staphylococcus aureus-derived lipoteichoic acid induces temporary T-cell paralysis independent of Toll-like receptor 2. *J Allergy Clin Immunol*, Epub ahead of print. http://doi.org/10.1016/j.jaci.2015.11.043.

EUSAAT

European Society for Alternatives to Animal Testing

EUSAAT 2015 congress report on ARTE TV

To cover recent progress in replacing testing in animals by non-animal alternative methods, a team of eight journalists from the joint French-German cultural TV channel ARTE TV attended the EUSAAT 2015 congress and covered, e.g., the YSTA (Young Scientists Travel Award) session and the "*Practical training course on alternative methods for the assessment of in vitro eye irritation potential for regulatory purposes*." A 30 min report was shown in the XENIUS Science Magazine on February 8, 2016 under the title "*Animal experiments – we cannot yet replace all of them*." This report is available in German and French on the website of the XENIUS Science Magazine at http://www.arte.tv/guide/de/056817-032-A/xenius.

The EUSAAT Board is happy that our annual EUSAAT conferences are finally reaching a wide audience and is proud to show that our mission to promote the use of the 3Rs concept to refine, reduce and replace animal experiments as the most appropriate scientific approach to end animal experiments has proven to be successful.

Moreover, the ARTE TV report was an excellent advertisement for the EUSAAT 2016 congress later this year.

EUSAAT 2016 3Rs congress and 25th Anniversary Congress on Alternatives in Linz, Austria

August 24-27, 2016
http://eusaat-congress.eu/

We cordially invite you to participate in the "*EUSAAT 2016 3Rs Congress Linz*", which is the "20th European Congress on Alternatives to Animal Testing" and the "17th Annual EUSAAT 3Rs Congress." EUSAAT 2016 will be held in Linz, Austria on August 24-27, 2016.

Since the first 3Rs congress was held in Linz in 1991, we will in 2016 celebrate the *25th Anniversary Congress on Alternatives to Animal Experiments in Linz*. Ministries of the Federal Austrian government in Vienna and of the State of Upper Austria and its capital Linz will support the 25th Anniversary Congress in 2016.

As the leading international 3Rs congress in the year 2016, the "*EUSAAT 2016 3Rs Congress Linz*" will provide you with an excellent stage to present and discuss your ideas with colleagues from academia, animal welfare, industry and government institutions around the world. During the past 25 years the Johannes Kepler University Linz has hosted the EUSAAT congresses and contributed to a stimulating and unique atmosphere that participants have always enjoyed.

We are particularly happy that the "Young Scientists Travel Award" (YSTA) program, which we launched for the first time last year at the EUSAAT 2015 congress, was a great success and attracted many active young scientists. We will, therefore, of course continue the YSTA program in order to enable young scientists to share their ideas on how to reduce the suffering as well as the numbers of animals in research, product development and regulation with international colleagues.

EUSAAT has again signed an organization contract with Helmut Appl from "appl communications & consulting" (ACC). Since Helmut has during the past 25 years successfully managed all of the ZET/MEGAT/EUSAAT congresses in Linz, we are confident that the EUSAAT 2016 congress will be another memorable event.

We are indebted to an extremely supportive international group of experts, who are serving on the Scientific Committee (SC) and who have drafted an attractive program. The highlights of the EUSAAT 2016 congress are shown in the DRAFT program below.

We are looking forward to welcoming you to Linz in August at EUSAAT 2016!

EUSAAT 2016

17th Annual Congress of EUSAAT

DRAFT Program EUSAAT 2016 – Topics
http://eusaat-congress.eu/index.php/congress/2016/topics

► 25th Anniversary of 3Rs Congresses on Alternatives in Linz: MEGAT & EUSAAT
coordinators: Helmut Appl, Horst Spielmann

► Global Cooperation on Implementing the 3Rs
coordinators: Rodger Curren, Jarlath Hynes, Hajime Kojima, Mardash Daneshian

► Ethical and Legal Issues
coordinators: Roman Kolar, Katy Taylor

► EU Directive 63/2010
coordinators: Susanna Louhimies, Gilbert Schönfelder

► New Technologies: 3D Models & Multi-Organ-Chips
coordinators: Samuel Constant, Ellen Fritsche, Jems Kelm, Mark Rosowski

► Stem Cells & Reproductive Toxicology (mEST & hEST)
coordinators Jürgen Hescheler, Horst Spielmann

► Refinement & Welfare: Culture of Care, Best Practice Approaches, Avoidance of Severe Suffering
coordinators: Robert Landsiedel, Susanna Louhimies, Katy Taylor, Christa Thöne-Reineke

► Replacement: New Approaches
coordinators: Mardas Daneshian, Candida Nastrucci, Stefanie Schindler

► Predictive Toxicology: QSAR & Read Across
coordinators: Yeyejide Adeleye, Stephanie Bopp, Eric Stilgenbauer, Tzutzuy Ramirez

► Specific Endpoints of Toxicity I: Oral & Repeated-dose Toxicity, Inhalation Toxicity
coordinators: Stephanie Bopp, Rodger Curren, Julia Hoeng, Erwin L Roggen

► Specific Endpoints of Toxicity II: Sensitization, Nano-toxicology & Bio-barriers
coordinators: Claus-Michael Lehr, Helena Kandarova, Klausrudolf Schroeder

► Efficacy and Safety Testing of Drugs, Biologicals and Vaccines
coordinators: Tuula Heinonen, Conraad Hendricksen, Marcel Leist

► Disease Models *in vitro* and *in vivo*
coordinators: Claus-Michael Lehr, Marcel Leist, Horst Spielmann

► CRISPR/cas – Advanced GMO models *in vivo* and *in vitro*
coordinator: Malte Spielmann

► 3Rs in Education and Academia
coordinators: Christa Thöne-Reineke, Monika Schaefer-Korting, Candida Nastrucci

► Free communications
coordinators: Ellen Fritsche, Erwin Roggen Horst Spielmann, Manfred Liebsch

► "Young Scientists" session
coordinators: Lucia Li, Manfred Liebsch, Joachim Wiest

Abstracts & Deadlines for Submissions
Oral presentations and posters may be submitted for all topics/tentative sessions To submit your abstract please use the online submission form.

Deadline for submission of oral presentations & posters: 31st May 2015
https://eusaat2016.online-registry.net/

The European Environmental Mutagenesis & Genomic Society (EEMGS) Annual Meeting will take place in Copenhagen on August 14-18, 2016. This year the topic is "Bridging genomics, human environmental health risk assessment and the 3Rs in animal science." Registration and Abstract submission is now open.

More information can be found on the EEMGS website: http://www.eemsmeeting2016.eu/

ecopa is co-sponsoring the event and co-organizing a session titled "3Rs in genotoxicology" on August 18. It will be followed by ecopa symposia on "Cellular methods come in practice". Last but not least, the ecopa general assembly will also take place on the same day and all *ecopa* members are welcome to participate.

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

UNITED STATES ICCVAM Advancing Alternatives to Animal Testing

NICEATM Scientists Receive NIEHS Merit Award

NICEATM Director Warren Casey, Ph.D., and nine current and former members of the ILS NICEATM contract support team received a Merit Award from the National Institute of Environmental Health Sciences (NIEHS) in a January 27 ceremony. The Merit Award is the highest level honor award given by the NIEHS director and recognizes achievements that support and advance the NIEHS mission. The NICEATM awardees were recognized for validating the use of computational tools to replace a regulatory requirement for animal-based testing, thereby demonstrating the utility of Tox21 efforts.

NICEATM Deputy Director Kleinstreuer to Receive Teratology Society Award

The Teratology Society named NICEATM Deputy Director Nicole Kleinstreuer, Ph.D., to receive the 2016 F. Clarke Fraser New Investigator Award. This award recognizes an active Teratology Society member that has, within 10 years of completion of training, established a successful, independent research career in a field relevant to developmental biology.

The Society will present Kleinstreuer with her award during its annual meeting in June in San Antonio. Kleinstreuer will give a plenary presentation about her research, which focuses on mathematical and computational modeling of biological systems and those systems' susceptibility to perturbations that result in adverse health outcomes. At the annual meeting, Kleinstreuer will also co-chair and speak at a workshop on identifying reference developmental toxicants to validate alternative assays.

NICEATM Director Elected to Lead SOT IVAM Specialty Section

NICEATM Director Casey has been named Vice President-elect of the *In Vitro* and Alternative Methods (IVAM) Specialty Section of the Society of Toxicology (SOT). Casey will serve as Vice President-elect for

2016-2017 and will then serve subsequent one-year terms as Vice President, President, and Past President of the specialty section.

The SOT IVAM Specialty Section members have expertise or special interest in the application of *in vitro* techniques to address problems of cellular toxicity, with a special emphasis on product safety evaluation. IVAM interests include the study of cellular processes involved in adverse outcomes of specific organs as well as whole animals, and the development of systems to predict *in vivo* toxicity for risk assessment purposes. Other topics of interest include *in vitro* test validation and all aspects of test development and acceptance for individual or regulatory purposes.

NICEATM Workshop Addresses Needs for *In Vivo* to *In Vitro* Extrapolation

NICEATM and EPA hosted a February 17-18 workshop on *In Vitro* to *In Vivo* Extrapolation for High Throughput Prioritization and Decision Making. Nearly 100 attendees identified steps needed to better relate results of high throughput tests to chemical effects observed in living systems, allowing the results of high throughput tests to be applied to real-world chemical testing needs.

The goal of *in vitro* to *in vivo* extrapolation (IVIVE) is to use *in vitro* data from exposed cultured cells or biological molecules to predict illness or injury in animals or people exposed to the same chemicals. At the end of two days of presentations and discussions, the participants at the workshop identified specific actions that would allow for more effective expansion and application of IVIVE and enable high throughput test data to begin to address existing testing needs.

A key recommendation was the creation of a central database for IVIVE prediction models and the data used to populate it. Such a database would allow for sharing and testing of the IVIVE prediction models and could help standardize data formatting, model development methods, and terminology. Workshop participants also stressed the need to better understand the differences between environmental and industrial chemicals and pharmaceuticals, and suggested that IVIVE could be used in the near term to help select doses for tests that still need to be done using animals.

Presentation slides and other materials from the workshop are available at http://ntp.niehs.nih.gov/go/ivive-wksp-2016. The workshop conclusions will be summarized in a paper to be submitted this year to a peer-reviewed journal.

NICEATM and ICCVAM Activities at SOT

The SOT Annual Meeting took place March 13-17 at the Ernest N. Morial Convention Center in New Orleans.

NICEATM Director Warren Casey and ICCVAM Co-chair Anna Lowit (U.S. Environmental Protection Agency [EPA]) led a discussion forum on NICEATM and ICCVAM activities. The meeting was intended to be an open discussion of the challenges and opportunities to replace current regulatory requirements using animals, and participants were encouraged to bring forward specific examples of challenges to the implementation of alternatives within their organizations.

Other NICEATM and ICCVAM activities at SOT included:

- *A March 17 satellite meeting:* titled "Updates on Activities Related to 21st Century Toxicology and Related Efforts," featured Casey's update on NICEATM activities and ICCVAM member Richard Paules' (NIEHS) update on Tox21.
- *Workshop sessions co-chaired by ICCVAM members:* Moiz Mumtaz (Agency for Toxic Substances and Disease Registry) co-chaired "Quantitative Cumulative Risk Assessment: Is It Feasible Today?" and Nigel Walker (NIEHS) co-chaired and presented at "Bioactivity-Based Margin of Exposure Safety Assessment: The Next Stop Along the Road to 21st Century Safety Assessments."
- *Platform presentations given by ICCVAM members:* Patience Browne (EPA) on "Screening Chemicals for Estrogen Bioactivity Using Computational Approaches" and ICCVAM Co-chair Abby Jacobs (U.S. Food and Drug Administration) on "CDER Acceptance of Alternative Assays."
- *Platform presentations by NICEATM staff:* Deputy Director Nicole Kleinstreuer on "Skin Sensitization Testing Strategy Evaluation" and David Allen, Ph.D., ILS, on "Integrating Alternative Methods within a Regulatory Framework and the Impact of AOPs in Designing an Integrated Testing Strategy to Replace Repeat Exposure Inhalation Toxicity"

NICEATM staff were co-authors on five posters presented at the meeting, and ICCVAM members were co-authors on 14 posters describing alternative testing methods and strategies.

A complete list of NICEATM and ICCVAM activities at SOT 2016 is available at http://ntp.niehs.nih.gov/go/niceatm-sot16.

EPA and NIH Centers Launch Transform Tox Testing Challenge

U.S. government agencies are offering awards totaling $1 million to improve the relevance and predictivity of data generated from automated technology used for toxicity testing.

EPA is partnering with the National Center for Advancing Translational Sciences and the National Toxicology Program to sponsor the Transform Tox Testing Challenge: Innovating for Metabolism. The challenge calls on innovative thinkers to find new ways to incorporate physiological levels of chemical metabolism into high throughput screening assays. This will help researchers to more accurately assess effects of chemicals and better protect human health.

Participating teams will compete in three stages for a total award of $1 million. The first stage, which closes April 8, seeks practical designs that may be fully implemented. Up to ten entries may receive a prize of $10,000 each and an invitation to continue to the second stage, prototype development.

The final stage will involve testing by the sponsoring agencies of commercially viable methods or technologies.

The challenge is closed to U.S. federal employees acting within the scope of their employment but is open to all other segments of government, industry, academia, or non-governmental organizations.

The challenge was announced in a January 8 EPA press release, available at http://go.usa.gov/cnthF. Details about the challenge and an entry form are available at http://transformtoxtesting.com/.

Recent NICEATM Publications

NICEATM Deputy Director Kleinstreuer is a coauthor of two papers in this issue of ALTEX that were products of an October 2015 workshop on read-across practices:

Ball et al. (2016). Toward good read-across practice (GRAP) guidance. *ALTEX*, Epub ahead of print 11 Feb 2016. http://dx.doi.org/10.14573/altex.1601251

Zhu et al. (2016). Supporting read-across using biological data. *ALTEX*, Epub ahead of print 11 Feb 2016. http://dx.doi.org/10.14573/altex.1601252

A recent publication describes ICCVAM-developed integrated decision strategies for non-animal identification of skin sensitization hazards:

Strickland et al. (2016). Integrated decision strategies for skin sensitization hazard. *J Appl Toxicol*, Epub ahead of print. http://dx.doi.org/10.1002/jat.3281

Two recent publications describe NICEATM-organized workshops on adverse outcome pathways and alternatives to the murine histamine sensitization test:

Arciniega et al. (2016). Alternatives to HIST for acellular pertussis vaccines: Progress and challenges in replacement. Report on an international workshop. *Pharmeuropa Bio and Scientific Notes*, in press. More information about the workshop is available at http://ntp.niehs.nih.gov/go/41498

Kleinstreuer et al. (2016). Adverse outcome pathways: From research to regulation. Scientific workshop report. *Regul Toxicol Pharmacol 76*, 39-50. http://dx.doi.org/10.1016/j.yrtph.2016.01.007. More information about the workshop is available at http://ntp.niehs.nih.gov/go/41375

Shannon Bell, Ph.D., an ILS scientist on the NICEATM support contract, coauthored a recent paper on computationally predicted adverse outcome pathways:

Oki et al. (2016). Accelerating adverse outcome pathway development using publicly available data sources. http://www.ncbi.nlm.nih.gov/pubmed/26809562

Upcoming ICCVAM Meetings

ICCVAM will hold two meetings later in 2016 to provide updates and opportunities for discussion of topics relevant to the development and validation of alternative test methods and approaches. Both meetings are open to the public free of charge and will also be webcast.

- The ICCVAM Public Forum will be held on May 25 at the National Institutes of Health in Bethesda, Maryland. Information about the meeting and links to registration are available at http://ntp.niehs.nih.gov/go/iccvamforum-2016.
- ICCVAM's advisory committee, the Scientific Advisory Committee on Alternative Toxicological Methods, will meet Sept. 26 and 27 at NIEHS in Research Triangle Park, North Carolina. Materials for the meeting will be posted at http://ntp.niehs.nih.gov/go/32822 when available.

IIVS
Institute for In Vitro Sciences
Advancing Science & Animal Welfare Together

IIVS Awarded Grant to Develop Non-Animal Testing Strategy for Respiratory Sensitization

IIVS has received a grant from the Research Institute for Fragrance Materials (RIFM) to develop non-animal test methods for the evaluation of fragrance materials for potential respiratory irritation and sensitization.

The grant was secured in collaboration with Liverpool John Moores University and the Physicians Committee for Responsible Medicine. The proposal, "The use of a novel non-animal platform to characterize respiratory effects of fragrance materials" combines computational approaches as well as *in chemico* techniques, and includes a testing plan in harmony with concepts for the OECD Adverse Outcome Pathway program.

IIVS Presents Posters at SOT 2016

IIVS presented the following posters at SOT 2016, March 13-17 in New Orleans:

- Effect of Acclimation Conditions on 3D Human *In Vitro* ALI Airway Models: Exposure-Induced Inflammatory Response and Sampling Location – Specific Results
- Combining *In Silico* and *In Vitro* Methods to Improve the Accuracy of Skin Sensitization Predictions for Chemicals
- Correlation of Two *In Vitro* EpiOcular Test Methods and Consumer Eye Irritation Data for Cleaning Products
- Evaluation of New Solvents for the Use in the Multi-Dose Reconstructed Human Epidermis (RhE) Phototoxicity Assay

View these posters on the IIVS website at http://www.iivs.org.

IIVS to Host April 2016 Workshop – *In Vitro* Exposure Systems and Dosimetry Assessment Tools for Inhaled Tobacco Products

In support of its Respiratory Toxicology Program, IIVS will host a three-day workshop April 4-6 that promotes the use of *in vitro* models in testing and assessing the potential toxicity of pulmonary toxicants. Presenters from industry, government, academia, and non-profits will explore topics such as:

- Tobacco smoke and e-cigarette aerosols.
- Air-liquid interface – *in vitro* exposure systems
- Dosimetry approaches for particles and vapors
- *In vitro* dosimetry determinations
- Exposure microenvironment/physiology of cells

This workshop is the third workshop of its kind with the first held in December 2014 followed by a second in June 2015. For registration information, a preliminary agenda and information about submitting a poster, visit http://www.iivs.org.

Funding Opportunity: ARDF Soliciting Research Proposals

The Alternatives Research & Development Foundation (ARDF), which funds and promotes alternatives to the use of laboratory animals in research testing and education, is currently soliciting research proposals. The deadline to submit a proposal is May 2, 2016.

IIVS coordinates the review process for grant proposals, working with its wide network of scientists and ARDF to create opportunities for scientists who have compelling research initiatives in the area of non-animal research.

For more information about submitting a proposal, visit http://www.ardf-online.org.

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