CAAT*feed*

Call for Expression of Interest: P4M – Public Private Partnership for Performance Standards for Microphysiological Systems

Organo-typic cultures with elements of organ architecture and functionality are flourishing, increasingly moving even to multi-organ systems.They promise to boost the relevance of *in vitro* work, fueled also by the increasing availability of high quality human cells due to stem cell technologies. CAAT has been part of and actively promoted these developments. In various stakeholder discussions, we perceived the need to complement the technical developments with quality assurance aspects. Our ongoing efforts toward Good Cell Culture Practice (GCCP), *in vitro* reporting standards and *in vitro* risk-of-bias assessments already go in this direction.

As a next step, we would like to invite all stakeholders to join us in starting a discussion about performance standards for microphysiological systems (MPS). This will encompass questions like:

What makes a cell culture an MPS?

- What is a good MPS, e.g., fit-for-purpose, reproducibility, relevance, validity?
- How does an MPS need to be documented and reported?
- How can a lab show proficiency in testing with an MPS?
- What quality assurance and management need to be in place?

This call for expression of interest wants to identify possible partners from academia, regulatory agencies, industry (users and technology providers), and others (e.g., NGOs). You are invited to contact us at caat@jhu.edu. Letter of motivation and referrals to relevant activities in this area you are part or aware of are most welcome. We will start organizing the dialogue with the exact form depending on the responses received.

Become part of an exciting process helping to revamp the relevance of *in vitro* work!

Ending *In Vivo*: When Will Better Alternatives to Animal Testing Be the New Standard? Article in *Hopkins Bloomberg Public Health*

View a PDF of the article here: http://caat.jhsph.edu/media/Ending%20In%20Vivo%20HBPH%20Summer%202018.pdf

Upcoming Events

Pan-American Conference for Alternative Methods 2018

August 23-24, 2018
Rio de Janeiro, Brazil

Starting in 2016 in Baltimore, now 2018 in Rio and planned for 2020 in Canada, the series Pan-American Conference for Alternative Methods brings South, Central, and North America together to further alternatives to animal testing and build collaboration for the exchange of scientific ideas.

Details, registration, and agenda may be found here: http://caat.jhsph.edu/programs/workshops/PanAmerican2018/index.html

Workshop on Pyrogen Testing Methods

September 18-19, 2018
Bethesda, Maryland

NICEATM is co-organizing a workshop on September 18-19 with the PETA International Science Consortium to discuss non-animal approaches for pyrogen testing. The workshop will be held at NIH in Bethesda, MD, and will focus on the use of the monocyte activation test (MAT) as a standalone release test for medical devices.

Thomas Hartung will give the keynote lecture.

Registration and materials will be posted at https://ntp.niehs.nih.gov/go/mat-2018 when available.

20th International Congress on In Vitro Toxicology (ESTIV 2018)

Hosted by ESTIV, CAAT, and Gesellschaft für Toxikologie
October 15-18, 2018
Berlin, Germany

Details and Registration: http://www.estiv2018.com/

Recent Events

5th Annual Symposium on Social Housing of Laboratory Animals

June 4-5, 2018
USDA Agricultural Library
Beltsville, MD

This symposium brought together experts in the behavior and science of laboratory animal species to exchange information with scientists, Institutional Animal Care and Use Committee (IACUC) members, veterinarians, and animal care technicians about the welfare needs of social laboratory animal species and the means to achieve optimal social housing conditions in a variety of settings. The format included two days of lectures in the morning followed by interactive breakout sessions in the afternoon.

These lectures gave participants a strong foundation in the relevant research underlying socialization and behavioral management efforts, while the breakout sessions allowed participants to get feedback specific to their own facilities from experts and colleagues.

This year, the keynote highlighted play behavior and positive affective states in several species, followed by talks focused on the specific housing needs of rabbits, swine, and rats. The afternoon commenced with input from the USDA, OLAW, and AAALAC regarding current policies and guidance, followed by a breakout session. The second day began with housing considerations and harm/benefit analysis and then covered the current best practices for the social housing of old world monkeys. In the afternoon, the discussion addressed the psychological well-being of fish before ending with another breakout session.

The event included a pre-symposium visit to the National Zoo in Washington, D.C.

Keynote Talk: Three Road Maps for Alternatives – One Goal

Louis "Gino" Scarano (EPA), Suzy Fitzpatrick (FDA), Warren Casey (NIEHS)
May 30, 2018

FDA, EPA, and NTP have published draft roadmaps over the last six months to further the use of alternative methods. In this talk we examined a unique opportunity to compare and understand the synergies that together can transform safety testing in the US.

This keynote talk kicked off the CAAT spring board meeting in Baltimore on May 30th, 2018. You can watch the full video here: https://www.dropbox.com/s/3nrphg4aqdehf44/2018-05-30_EHE_Becton.mp4?dl=0 (download full video before watching if you have viewing issues)

EUTOXRISK

Key project deliverable on RDT

Repeated-Dose-Toxicity (RDT) is one of the large and complex problems of toxicology, so new approach methods (NAM) that can help to predict RDT are urgently needed. Recent EU projects have started to address this problem. For instance, prediction of RDT was a major objective of the FP7 projects SEURAT-1 (Hengstler et al., 2012) and PREDICT-IV (Wilmes et al., 2013). Several partners from these projects joined EU-ToxRisk with their experience and model systems. Additional systems have been developed for neurons in transnational projects (Smirnova et al., 2016; Cosset et al., 2015) and also for the liver (Messner et al., 2013; Ramaiahgari et al., 2014), to name just some examples.

One of the ultimate goals of EU-ToxRisk is to incorporate such systems into microphysiological systems that allow long-term drug testing (Marx et al., 2016). EU-ToxRisk partners have further exemplified this approach in a transatlantic collaboration (Skardal et al., 2017). The key question to be answered before embarking on an RDT NAM project is, "What is essentially meant by RDT?" or in other words, how are "R", "D", and "T" to be understood in the EU-ToxRisk context. Project partners delivered an extensive document dealing with the definition of RDT and exemplifying differences between short-term dosing and RDT in 10 different experimental test methods.

Project strategy

The Collaboration Agreement (CA) between the EU-ToxRisk project, represented by the coordinator UL, and the JRC is now officially signed. The JRC (EURL-ECVAM) has been an important collaboration partner throughout the project and adds great value. Nevertheless, it is comforting to have now also a formal basis for the collaboration.

The second big strategic step in this period was the "Action-plan Read-Across (RAx)" to accelerate and leverage the running EU-ToxRisk efforts in this area. The package of activities included:

(i) May: 2-day steering team strategy meeting to define evaluation criteria for read-across case studies of the first generation, and to define a selection procedure for second-generation case studies.

(ii) June: 2-day working meeting of all case study teams to prepare case studies for (mock) regulatory submission.

(iii) July: 2-day steering team meeting to evaluate the status of case studies and to prepare for submission. (iv) July: 3-day workshop on internationalization of RAx and on strategies for lowering barriers to its use.

Dissemination events and training

EU-ToxRisk Summer School on Modelling and Extrapolation
March 6-9, 2018 in Konstanz, Germany

The summer school was organized with the aim to increase familiarity with the use of *in vitro* to *in vivo* extrapolation approaches to generate inputs for physiologically based pharmacokinetics (PBPK), to understand

how to quantify AOP coherently with experimental data, and to gain an insight into using machine learning methods. More than 40 participants including PhD students and postdocs were trained by the coordinators Dr Iain Gardner (CERTARA), Dr Frederic Bois (INERIS) and Dr Daniel Mucs (SweTox).

Technical meeting for policy advisers on the methodologies available to assess endocrine disruptor properties
May 6, 2018 in Brussels, Belgium

A technical meeting was co-organized with the European parliament liberals-ALDE group to present the methodologies covering endocrine disrupter assessment included in the ECHA-EFSA draft guidance document.

Joint H2020 workshop "Advancing the Assessment of Chemical Mixtures and their Risks for Human Health and the Environment"
May 29-30, 2018 at the Joint Research Centre in Ispra, Italy

EU-ToxRisk partners presented the current state-of-the-art of the *in silico* and *in vitro* toolbox to assess chemical safety and then actively participated in workshop discussions.

Publications & Outlook

The scientific output of EU-ToxRisk addressed a broad range of topics. The advantage of key project technologies was presented by Wink et al. (2018), concerning high content imaging of cellular stress responses, and by Wolters et al. (2018), concerning the use of multi-omics to predict liver toxicity. The *in silico* side of the project is exemplified by a QSAR publication on blood-brain barrier transport of pesticides (Toporov et al., 2018), and by prediction of LAT-1 transporter substrates, which is also important for drug and toxicant penetration into the brain (Singh and Ecker, 2018). Ramirez et al. (2018) showed how liver toxicity can be predicted from metabolomics data.

Equally important as primary research papers, new concepts and reviews were put forward. The field of Systems Toxicology was extensively covered by Smirnova et al. (2018), while Pamies et al. (2018) produced an important consensus document on Good Cell Culture Practice for stem cells and organoids.

A new aspect of the publication strategy of EU-ToxRisk will be the first wave of case study and RAx papers, to be expected in the second half of 2018.

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Giorgia Pallocca and Marcel Leist