Thomas Hartung Interviewed in New Book, Rigor Mortis: How Sloppy Science Creates Worthless Cures, Crushes Hope, and Wastes Billions

Excerpt:

Thomas Hartung has been experimenting for a while with brain cells that proliferate in the lab but also morph into different brain cell types, forming round clumps of cells, called organoids. The cells in his lab come from patients with autism and Down syndrome. The clumps apparently can't think – though they do generate electrical signals, just like brain cells, and organize themselves in a manner reminiscent of how they are juxtaposed in the brain. They also use the chemical signals that underlie brain function. “If we create conditions in cell culture which are mimicking the organism, we are more likely to get relevant results,” he told me. “You can do personalized toxicology with these cells. If I took your cells, I could tell you are more sensitive than another person to certain drugs, for example.” These are early days for this technology, but there’s a rapidly growing industry around cultivating disembodied blobs of cells in the lab. The Defense Advanced Research Projects Agency, which funds far-out ideas, has poured money into this line of research at multiple labs. So has the NIH. And Hartung has private money to work on the problem as well.

Thomas Hartung and David Pamies Featured in Shanghai Project’s Seeds of Time Exhibition

From its initial Chapter in 2016, the Shanghai Project has been an experiment, a laboratory for testing the boundaries of existing assumptions, and for considering how ideas might expand beyond the confines of individual silos of knowledge. *Seeds of Time* engages with the public in Shanghai through an exhibition, a publication and public programs such as screenings, performances, workshops and social interventions. Facing the specter of extinction, the Shanghai Project seeks to inspire discussion and action regarding the sustainability of our futures in the 21st century and the potential for solutions through interdisciplinary collaboration.

Exploring the causes and effects of ecological transformation, Shanghai Project participants address sustainability through the lens of interdisciplinarity. Liu Chuang engages with the research of Thomas Hartung and David Pamies, shedding light on efforts to find scientific solutions to environmental problems.


Big Data, Big Deadlines Spur Change in Toxicity Testing

*Excerpted from* Chemical and Engineering News:

UL’s REACHAcross software has roots in an effort to work with a big, new database – the data trove amassed at the European Chemicals Agency, which administers REACH. The software effort was led by Thomas Hartung, a professor at Johns Hopkins University’s Center for Alternatives to Animal Testing who previously worked for the European Commission and helped develop the REACH legislation and organize test guidance.

According to Hartung, companies associated with the Johns Hopkins center, including Dow, BASF, ExxonMobil, and many drug and cosmetics firms, have been using read-across for years. He estimates that 75% of REACH filings include read-across-generated data derived by expert statisticians.

“The trouble is, there are very few experts who know how to do this,” he says. “And they all work at the big companies.” His group set out to build information technology support for nonexperts.

Hartung credits Thomas Luechtefeld, a Ph.D. student at Johns Hopkins, with spearheading the software development. “We built a web crawler for getting data out of REACH,” Luechtefeld says. “The really interesting thing about REACH is that it’s the largest repository for *in vivo* toxicological data ever.”

For example, he says, REACH has skin sensitization data on 5,000 chemicals. Comparable public data before REACH covered about 250 chemicals.

Luechtefeld and a partner launched a spin-off, ToxTrack, to develop the software, signing a product development contract with UL two years ago. Craig Rowlands, senior toxicologist at UL, says his company saw opportunity in REACH’s looming 2018 deadline for registering toxicity data on 20,000 to 40,000 chemicals. Moreover, UL sees wider application ahead for the software. It is working on a phase two of REACHAcross with broader capabilities.

Full Article: http://cen.acs.org/articles/95/i17/Big-data-big-deadlines-spur.html?h=206916587

The Beauty of Mini Brains (Scientific American)

*Excerpted from* Scientific American:

Lab-grown miniature brains are poised to shake up drug testing for everything from Alzheimer’s disease to Zika. Each bundle of human brain cells is so tiny that it could fit on the head of a pin. Researcher Thomas Hartung and his colleagues at Johns Hopkins University created these mini brains using stem cells that, over the course of two months, morph into supporting cells and various types of neurons, which quickly connect to one another and start communicating.

These three micrographs were taken with lasers to illuminate colorful fluorescent dyes. The cells’ nuclei appear purple or blue. The mini brain on the right features a tangle of axons (pink) – extensions of neurons that send and receive signals. More axons (red) and neurons that produce the neurotransmitter dopamine (green) are highlighted in the middle brain. The left one shows nerve cell bodies and their projecting dendrites (both green), as well as supporting astrocytes (red).

4th Symposium on Social Housing of Laboratoy Animals and 2nd Workshop on Macaque Pair Housing

May 1-5, 2017
Atlanta, GA

On May 1-2, 2017, CAAT held its 4th Symposium on Social Housing of Laboratory Animals at the Centers for Disease Control and Prevention in Atlanta, GA in conjunc-
tion with the NIH Office for Laboratory Animal Welfare, the US Department of Agriculture Animal Welfare Information Center (AWIC), and the Johns Hopkins School of Medicine’s Department of Molecular and Comparative Pathobiology. This symposium was a continuation of successful symposia on this topic held in 2013, 2014 and 2016 that were instituted to address the challenges of fulfilling new US and European guidelines, the implementation of which can be formidable without basic knowledge of the animals’ normal behavioral needs, ability to recognize abnormal behavior, and training to apply behavioral interventions. The first day of the symposium covered social housing of dogs, rabbits, swine, and rodents. The second day was dedicated to nonhuman primates, particularly macaques, in conjunction with the primate behavior group at Emory University, which served as the first day of their separate hands-on 2nd Workshop on Macaque Pair Housing. Selected presentations from the workshop will be posted on the AWIC website (https://www.nal.usda.gov/awic/social-housing).

Think tank on “New test strategies for developmental and reproductive toxicity (DART)”
May 15-17, 2017
Konstanz, Germany

This workshop brought together experts in the field of reproductive and developmental toxicology for extensive exchange of knowledge, definition of the status quo, identification of shortcomings and gaps in this field.

CAAT-ITLF Think Tank
“Optimizing drug discovery by Investigative Toxicology: Current and future trends”
July 10-12, 2017
Ranco, Italy

“Investigative Toxicology” is a relatively young discipline in pharmaceutical safety assessment, which sees itself complementarily to regulatory toxicology. Whereas regulatory toxicology’s boundaries are set by international guidelines and its methods and technologies have matured over the last decade, Investigative Toxicology is more driven by the individual company needs. Investigative Toxicology is seen as a discipline, which moves safety assessment from a descriptive to a mechanistic understanding and an improved human translation. Based on such mechanistic understanding, Investigative Toxicology’s primary task in drug development is the identification of the most promising (safe) drug candidates and to deselect the most toxic drugs from the portfolio as early as possible to reduce clinical attrition.

A group of 14 European-based Investigative Toxicology leaders from the pharmaceutical industry (AstraZeneca, Bayer, Boehringer Ingelheim, GSK, Janssen, Lundbeck, Merck, Novartis, Novo Nordisk, Orion Pharma, Roche, Sanofi, Servier and UCB-Biopharma) have formed the Investigative Toxicology Leader (ITL) Forum. This forum aims for an exchange of pre-competitive knowledge among the companies and an interaction with experts from academia and regulatory bodies in the field of Investigative Toxicology. The objective is to elaborate robust, reliable and accepted Investigative Toxicology concepts for decision making for early safety-related attrition, de-risking, and mechanistic elucidation of effects. Another key aspect is the translation of \textit{in vitro} to \textit{in vivo} mechanistic data. Furthermore, the adoption of new technologies (e.g. micro-physiological systems) and assays into the drug discovery back-bone is targeted by the workshop.

**Upcoming Events**

**CAAT Academy 2017 Hands-on Training Program in Europe**

The 2017 CAAT Academy Hands-on Training sessions, which are all based in Europe, include:

- September: \textit{In vitro} tools for assessing EDC
- September: \textit{In vitro-in vivo} extrapolation (IVIVE) to support accurate prediction of hepatic drug disposition
- October: \textit{In silico} tools in chemical’s hazard assessments
- October: \textit{In vitro} skin & eye models – Part 2
- October: Kidney toxicity testing – Season 2

November: \textit{In vitro} lung models

Website: http://www.caat-academy.org

**Recent Publications**


ecopa Annual General Assembly

The General Assembly of ecopa elected a new board on June 14:

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<th>Member</th>
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<td>Academia</td>
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<td>Tuula Heinonen (FI) (Vice-President)</td>
<td>Philippe Vanparys (BE)</td>
<td>2018-2019</td>
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<td>Industry</td>
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<td>Erwin Roggen (DK)</td>
<td>Costanza Rovida (IT)</td>
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<td>Animal Welfare</td>
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<td>Marianna Norring (FI)</td>
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<td>Government</td>
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<td>Philippe Hubert (FR, President)</td>
<td>Stefano Lorenzi (IT)</td>
<td>2018-2019</td>
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<td>Secretary</td>
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<td>Francois Busquet (FR)</td>
<td>Costanza Rovida (IT)</td>
<td>2018-2019</td>
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<td>Treasurer</td>
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<td>Philippe Vanparys (BE)</td>
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Norecopa
The newsletters from the Norwegian 3R centre, Norecopa, will from now on be issued in English. The first of these is available at https://norecopa.no/news/newsletters/3-2017.

Norecopa publishes approx. 6-8 newsletters a year. They cover international events and advances related to the Three Rs, as well as news from Norway. Norecopa also maintains a comprehensive international Meetings Calendar, which is linked to the newsletters.

The latest newsletter contains the first details of new guidelines and a checklist for planning animal experiments, called PREPARE. These guidelines will be made available on Norecopa’s website at https://norecopa.no/PREPARE.

IPAM
IPAM organized an event on alternative methods to animal models in dermatology in Rome on June 8, 2017.

EUSAAAT
European Society for Alternatives to Animal Testing

Elections in 2017: EUSAAAT Board and Audit Committee

The 2017 elections of the EUSAAAT Board (EB) and of the Audit Committee (AC) will be held electronically this August. Elections are usually held during the Annual General Assembly (AGA) at the EUSAAAT congresses in Linz. However, since there is no EUSAAAT congress this year owing to the 10th World Congress (WC10) in Seattle, it was decided by the AGA 2016 in Linz to hold the 2017 elections electronically. The EUSAAAT Board has asked the Secretary General (SG) to start planning the elections...
and to consult with the AC in order to ensure that the voting procedure is in line with the statutes. It was recommended to use electronic signatures, if possible.

For the elections of the EUSAAT Board, the AC will count the votes, and for the AC, the president and the AC will count the votes.

Since new members are most welcome on the EUSAAT Board and AC, the SG will invite all EUSAAT members to serve on these committees. All candidates should provide a short CV and a photograph, which the SG will circulate with the voting documents.

To meet the legal requirements of the statutes, both EUSAAT Board and AC have decided that members who have not paid their membership fees in full cannot participate in the elections, neither as candidates nor by voting.

**EUSAAT AGA 2017 at EUROTOX 2017 in Bratislava**

The EUSAAT Board has decided to hold the AGA 2017 during the EUROTOX 2017 Congress http://www.eurotox2017.com/ on September 10-13, 2017 in Bratislava, Slovakia. As several members of the EUSAAT Board and AC including the president will not be able to attend EUROTOX 2017, the agenda of the AGA 2017 will be reduced compared to previous years. The planning of the EUSAAT 2018 congress as well as the financial report of the SG will be the major topics of discussion.

The SG will inform the members about the time and venue of the AGA 2017 when circulating the invitation and agenda.

On behalf of the EUSAAT Board
Horst Spielmann, SG

**EUTOXRISK**

Interested audience and stakeholders will find the scientific results of the EU-ToxRisk project frequently published in peer-reviewed journals. As the project has a multidisciplinary approach and as it covers several endpoints and target organs, i.e., repeated dose and developmental toxicity as endpoints for the liver, kidney, lung and the neuronal system, the results of the EU-ToxRisk project will be reported in a variety of different scientific journals. This corner highlights exemplary publications which illustrate the multidisciplinary features of the project and present the strategy and the fitness of the overall concept of the project.

The EU-ToxRisk project started out with a summer school and an internal mandatory project and present the strategy and the fit of the multidisciplinary approach and as it covers several endpoints and target organs, i.e., repeated dose and developmental toxicity as endpoints for the liver, kidney, lung and the neuronal system, the results of the EU-ToxRisk project will be reported in a variety of different scientific journals. This corner highlights exemplary publications which illustrate the multidisciplinary features of the project and present the strategy and the fitness of the overall concept of the project.

The first paper introduced here is a workshop report by Pamies et al. (2017) supported by EU-ToxRisk. David Pamies revises and updates the guidance for Good Cell Culture Practice for modern cell culturing technologies. The authors address the unique procedures of stem-cell driven systems, of organotypic culture methods, the complexity of model systems and long-term cultures. Furthermore, special quality assurance needs of iPSC methodologies are addressed. Moreover, the report describes the establishment of an International GCCP Collaboration, an initiative aiming at the development and implementation of cell culture quality standards in research and development (contact caat@jhsph.edu).

To complete the picture of EU-ToxRisk, two recent workshops shall be presented here is a review article coordinat-
ed here. A workshop on “Data Handling” was held in April 2017. It followed new EU guidance on FAIR data, and intended to implement an understanding of the importance of the FAIR criteria (Findable, Accessible, Interoperable, and Re-usable). In this workshop, common approaches for calculation of summary parameters from experimental data were discussed and agreed. The second workshop was on “New test strategies for developmental and reproductive toxicity (DART)”, which was held in May 2017. DART is a key area of health concern, one of the large systemic toxicity areas not yet covered by accepted animal-free methods. It remains one of the most animal-intensive areas of regulatory toxicology. The development of animal-free approaches is particularly important in this area. This workshop brought together relevant experts in the field of DART, including the Acting Assistant Administrator for US EPAs Office of Research and Development and relevant EU-ToxRisk partners, to discuss functionality and fitness-for-purpose of promising non-animal DART approaches from academic, industrial and regulatory points of view.

At the present time point the project’s progress corresponds to the schedule of the project set by the European Commission. Further progress will be shared in the next issue and on other platforms (at twitter (@EU_ToxRisk) and facebook (public group and page)).

Mardas Daneshian

Roadmap for New Approaches for Evaluating Chemical Safety Discussed at ICCVAM Public Forum

A roadmap for moving closer to the goal of replacing animals in U.S. safety testing, as well as collaborations that made progress to date possible, were highlighted at the May 23 Interagency Coordinating Committee on the Validation of Alternative Methods public forum. Presenters’ slides and the webcast recording of the ICCVAM public forum are available at https://ntp.niehs.nih.gov/go/iccvamforum-2017.

Many of the presentations for this year’s annual forum, held at the National Institutes of Health in Bethesda, Maryland, described collaborations among U.S. federal agencies, between federal agencies and stakeholder groups, and among countries. Some of these efforts have already reduced the need to use animals for chemical safety testing. Other efforts advanced technologies that may improve hazard prediction while further reducing animal testing.

Most public comments at the forum focused on the roadmap, which was presented by NICEATM Director Warren Casey. Representatives from industry, animal welfare organizations, and other commenters welcomed the roadmap effort and discussed topics the roadmap should address.

More information about the roadmap is available at https://ntp.niehs.nih.gov/go/natl-strategy. Comments on the roadmap will be accepted through August 31. A draft document will be discussed at the September 18-19 meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (more information at https://ntp.niehs.nih.gov/go/32822). SACATM advises NICEATM, ICCVAM, and the National Institute of Environmental Health Sciences director on ICCVAM activities. The final roadmap document is anticipated to be published in December.

FDA Partners with Industry to Develop Organs-on-Chips

On April 11, the U.S. Food and Drug Administration announced a multi-year research and development agreement with Emulate, Inc., to evaluate the company’s “Organs-on-Chips” technology in laboratories at the FDA’s Center for Food Safety and Applied Nutrition. The project will focus first on developing a liver chip, but the agreement may expand to kidney, lung, and intestine models in the future. The ultimate goal is to predict how specific organs will respond to potential chemical hazards found in foods, cosmetics, or dietary supplements more precisely than with current methods.

More details about the agreement are available in an FDA blog article by FDA ICCVAM representative Suzanne Fitzpatrick at http://bit.ly/2ovDVNC.

References

Recent NICEATM Publications and Media Coverage

— A paper in *Journal of Chemical Information and Modeling* describes computer models that use molecular structures to estimate the physicochemical features of a wide range of chemicals. The models may be useful for researchers seeking to assess human toxicity of chemicals that have little experimental data available. The paper was recognized in the April issue of the NIEHS Environmental Factor newsletter as an NIEHS Intramural Paper of the Month. Zang et al. (2017). In silico prediction of physicochemical properties of environmental chemicals using molecular fingerprints and machine learning. *J Chem Inf Model* 57, 36-49. doi:10.1021/acs.jcim.6b00625

— NICEATM Deputy Director Nicole Kleinsteuer and a number of NICEATM collaborators in academia, industry, and animal welfare organizations commented on progress toward replacing animals for chemical safety testing in the April 24 issue of *Chemical and Engineering News*. The article “Big Data, Big Deadlines Spur Change in Toxicity Testing” is available at http://bit.ly/2osK26z.

IIVS Opens New Respiratory Toxicology Laboratory

IIVS officially opened its new respiratory toxicity laboratory on June 12, 2017. The new state-of-the-art facility allows the modeling of respiratory exposures of aerosols, smoke, particulates, vapors and gases onto *in vitro* and *ex vivo* tissue models to gain better insights into potential human health risks to inhaled chemicals and particulates.

In addition to aerosol exposure capabilities, IIVS has developed automated methodologies to deliver nanoliter microdroplets topically onto tissue models in a manner not previously achievable using conventional micropipettor dosing techniques. These procedures allow for extremely uniform, volume-controlled deliveries of liquids to precisely model vapor droplet deposition onto a variety of epithelial tissue surfaces.

By working with IIVS, industry will have the ability to rapidly evaluate potential respiratory hazards associated with novel ingredients and chemicals for use in fragrances, personal care products, household, automotive, and institutional cleaning products, and a wide range of traditional and emerging tobacco products.

For more information, visit http://www.iivs.org.

Free Webinar on Skin Tone Modulation

IIVS hosted a free one-hour webinar on June 29 on optimized *in vitro* testing platforms using pigmented tissue models that assess the capacity of ingredients and formulations that impact skin tone. Guest speakers included IIVS study director, Dr Gertrude-Emilia Costin, and Johnson & Johnson principal scientist, Dr. Manpreet Randhawa. A recording of the webinar will be made available on http://www.iivs.org.

IIVS Scientists to Present at the American Chemical Society National Meeting

Several IIVS scientists will be presenting at the 254th American Chemical Society (ACS) meeting, August 20-24, 2017 in Washington, DC. The ACS is the world’s largest scientific society.

— “Advanced *in vitro* test systems provide human-relevant results to support regulatory decision-making”, Holger Behrsing.

— “Changes in TSCA Drive New Strategies for Eye Irritation Hazard Assessments”, Hans Raabe

— “Relevance of the test system: When 21st century tools can’t ensure test method acceptance”, Quanshun Zhang

— “*In Vitro* methods available for chemical risk assessment under Amended TSCA for skin sensitization evaluation”, Tinashe Ruwona

For more information about the ACS meeting, visit https://www.acs.org.

Read the Latest IIVS Publications


For the latest IIVS news, visit http://www.iivs.org.