# 2023 Genetic Toxicology Association Annual Meeting

Genetic Toxicology Association

Translating Genetox

**John M. Clayton Hall Conference Center**
**University of Delaware**
**Newark, Delaware**
**May 3-5, 2023**

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The Genetic Toxicology Association (GTA) is a tax-exempt 501c3 educational and scientific organization that was founded in 1975 and incorporated in 1981 under the laws of the state of Delaware. Its primary purpose is to promote the development of the science of genetic toxicology and to foster the exchange and dissemination of information concerning the field.

Find up-to-date information on the GTA at https://gta-us.org/

# *2023 Annual Meeting of the GTA*

## May 3-5, 2023
## John M. Clayton Hall Conference Center
## University of Delaware,
## Newark, DE

## 2023 GTA Meeting
https://gta-us.org/annualmeeting/

## 2023 GTA Meeting Online Portal
https://virtual.oxfordabstracts.com/#/event/4242/information

## Keynote Address

**Prof. Carole Yauk, PhD**
***University of Ottawa, Ottawa, Canada***

## Scientific Program

**Workshop 1**
*Navigating the Genetic Toxicology Testing Battery – Strategies & Case Studies*

**Workshop 2**
*Genetic Toxicology & Carcinogenicity Testing – Regulatory Updates*

**Symposium I**
*New Technologies for Genetic Toxicology Testing*

**Symposium II**
*Artificial Intelligence, Machine Learning and Modeling Advances in Genetic Toxicology Testing*

**Symposium III**
*Genetic Mechanisms in Metals Carcinogenesis*

**Symposium IV**
*Titanium Dioxide Risk Assessment and Updates*

**Symposium V**
*Nitrosamine Risk Assessment, Part 1 – In silico and In vitro Approaches*

**Symposium VI**
*Nitrosamine Risk Assessment Part 2 – In vivo Approaches*

# *2023 Annual Meeting of the GTA*

## May 3-5, 2023
## John M. Clayton Hall Conference Center
## University of Delaware,
## Newark, DE

Dear Colleagues,

The 2023 GTA meeting takes place once again at the Universtiy of Delaware in Newark, DE and marks our return to an in-person meeting of the GTA following the successful completion of 2 virtual meetings during the COVID-19 pandemic.

This years Scientific Program Committee and Session co-chairs have put together an exciting program that includes 2 workshops, a Keynote Address by Prof. Carole Yauk PhD (University of Ottawa, Canada) and 6 Symposia, including 25 invited speakers. Additionally, our Poster Presentation session will include 2 minute speed talks from each of our student and early investigator poster presenters.

We are pleased to note that the majority of speakers at this years meeting will be attending in person, which will once again foster in-person discussions, networking and meetings. Meals and refreshments will be served as indicated in the program. As always speaker presentations will be made available in the Scientific Meeting Presentations section of the Members portal on GTA website.

Following the successful completion of 2 virtual meetings, we are excited to be returning to an in-person meeting in 2023. We hope that you can join us in Newark, DE for our 2023 Annual Meeting of the Genetic Toxicology Association.

Sincerely,

**Sheroy Minocherhomji PhD; MSc; DIC**
2022-2023 GTA Chair

**Penny Leavitt MS, DABT**
2022-2023 GTA Chair Elect

Genetic Toxicology Association
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# GTA Corporate Sustaining Members

*We thank the following companies for their support in 2023. If you would like to renew your sponsorship or are interested in information on how your company can support the GTA as a corporate sustaining member and/or a meeting sponsor please click here.*

(alphabetical order)

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# 2023 GTA Meeting Sponsors

(alphabetical order)













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# 2023 GTA Meeting Exhibitors

(alphabetical order)







*2023 Annual Meeting of the GTA*

**May 3-5, 2023**
**John M. Clayton Hall Conference Center**
**University of Delaware, Newark, DE**

# 2023 Annual GTA Meeting: Wednesday, May 3rd

***Lobby A / Registration Desk***

**12:45 – 5:00 PM** ***Conference Registration***

**1:00 – 3:00 PM** **Auditorium 125**

***Workshop 1***
**Navigating the Genetic Toxicology Battery – Strategies and Case Studies**

Co-chairs*:* Yi Yang PhD, DABT, AbbVie Inc. & Dan Levy PhD, US FDA (retired)
Panelists*:* Dan Roberts MS, Toxys, John Nicolette MS, J&J, Tim McGovern PhD, US FDA, Maria Donner PhD, Consultant

Speakers: Ronee Baracani, Eli Lilly; Stephanie Kellum, Corteva Agriscience.; John Nicolette, J&J; Marie Vasquez, Helix3, Inc; and more!

In this workshop, speakers will bring their tough and intriguing cases to a group of panelists for assessment and recommendations. A variety of topics will be discussed, including:

- Genetic toxicology data interpretations
- Design of a repeat genetic toxicology test
- Follow up characterization within genetic toxicology batteries
- Follow up characterization outside genetic toxicology batteries

*Bring your questions, take the challenges, and be ready for an interactive discussion in a fun and entertaining format!*

**3:00 – 3:15 PM** **Lobby A**

***Coffee Break***

**3:15 – 4:15 PM** **Auditorium 125**

***Workshop 2 – Part 1***
**Genetic Toxicology & Carcinogenicity Testing – Regulatory Updates**

Co-chairs: Maria Engel MS, Pfizer & Rosie Elespuru PhD, Discovery Life Sciences

| | |
|---|---|
| 3:15 – 3:20 PM | **Pig-a Assay Introduction: Welcome and Overview of Workshop Part 1**<br>Maria Engel MS, Pfizer |
| 3:20 – 3:40 PM | Sources of variability in the Pig-a assay and how to control them<br>*Vasily Dobrovolsky PhD, FDA* |
| 3:40 – 4:00 PM | Approaches for evaluating the quality of historical negative control data: *Pig-a* examples<br>*Stephen D. Dertinger PhD, Litron Laboratories* |
| 4:00 – 4:15 PM | Pig-a Assay Discussion / Q+A Period |

| 4:15 – 5:30 PM | Auditorium 125 |
|---|---|
| ***Workshop 2 – Part 2***<br>**Genetic Toxicology & Carcinogenicity Testing – Regulatory Updates** | |
| | Co-chairs: Maria Engel MS, Pfizer & Rosie Elespuru PhD, Discovery Life Sciences |
| 4:15 – 4:20 PM | **ICH S1B updates: Welcome and Overview of Workshop Part 2**<br>Rosie Elespuru PhD, Discovery Life Sciences |
| 4:20 – 4:40 PM | ICH S1B(R1): US regulatory perspectives on the new Weight of Evidence approach<br>*Timothy McGovern PhD, US FDA, USA* |
| 4:40 – 5:00 PM | Developing a Pragmatic Consensus Procedure Supporting the ICH S1B WoE Carcinogenicity Assessment<br>*Arianna Bassan PhD, Innovatune, Italy* |
| 5:00 – 5:20 PM | Using Adverse Outcome Pathways as a Framework for Carcinogenicity Assessment in ICH S1B(R1)<br>*Susanne Stalford PhD, Lhasa Limited UK* |
| 5:20 – 5:30 PM | ICH S1B update Discussion / Q+A Period |

# 2023 Annual GTA Meeting: Thursday, May 4th

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|---|---|---|
| **7:30 – 8:30 AM** | ***Conference Registration*** | ***Lobby A / Registration Desk*** |

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| | | **Room 101 A** |
| **7:30 – 8:30 AM** | ***Breakfast*** | |

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| | | **Auditorium 128** |
| **8:30 – 8:40 AM** | **Welcome and Introduction**<br>*Sheroy Minocherhomji PhD, Eli Lilly and Company*<br>*2022-2023 GTA Chair* | |

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|---|---|---|
| **8:40 – 9:45 AM** | | **Auditorium 128** |
| ***KEYNOTE ADDRESS*** | | Pfizer |
| 8:40 – 8:45 AM | **Introduction**<br>*Co-chairs: Sheroy Minocherhomji PhD, Eli Lilly & Penny Leavitt MS, DABT, Bristol Myers Squibb* | |
| 8:45 – 9:45 AM | I didn't catch your NAM: Advancing genotoxicity testing strategies through multi-sector collaborations.<br>*Prof. Carole Yauk PhD, University of Ottawa, Canada* | |

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| **9:45 – 10:00 AM** | | **Lobby A** |
| ***Coffee Break*** | | Environmental Mutagenesis and Genomics Society |

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|---|---|---|
| **10:00 – 11:30 AM** | | **Auditorium 128** |
| ***Symposium I***<br>**New Technologies for Genetic Toxicology Testing** | | CORTEVA agriscience |
| 10:00 – 10:10 AM | **Introduction**<br>*Co-chairs: Dan Roberts MS, Toxys & Wen Sun PhD, Pfizer* | |
| 10:10 – 10:30 AM | Duplex Sequencing studies to characterize chemical mutagenic mechanisms in mouse somatic tissues and germ cells<br>*Francesco Marchetti PhD, Health Canada, Canada* | |
| 10:30 – 10:50 AM | The reconstructed skin MN (RSMN) assay – next steps to improve use and aid implementation<br>*Ashley Allemang MS, Procter & Gamble, USA* | |
| 10:50 – 11:10 AM | DNA Repair-Profiler, a new in vitro assay for DNA repair and genotoxic mode of action assessment<br>*Giel Hendriks PhD, Toxys Inc., Netherlands* | |
| 11:10 – 11:30 AM | Use of Chicken egg assay as an animal alternative testing model to evaluate the genotoxic potential of Drugs and chemicals.<br>*Yax Thakkar MS, New York Medical College, USA* | |

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| **11:30 – 12:00 PM** | | **Auditorium 128** |
| ***Awards Ceremony and Presentation – Part I*** | | |
| 11:30 – 11:40 PM | **ESA Introduction**<br>*Chair: Dan Roberts MS, Toxys* | |
| 11:40 – 12:00 PM | **Excellence in Service Award Presentation** | |

**12:00 – 1:00 PM** — **Room 101 A**

***Networking Lunch***

**1:00 – 2:30 PM** — **Auditorium 128**

***Symposium II***
**Artificial Intelligence, Machine Learning and Modeling Advances in Genetic Toxicology Testing**

Bristol Myers Squibb™

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|---|---|
| 1:00 – 1:05 PM | **Introduction**<br>*Co-chairs: Wen Sun PhD, Pfizer & Penny Leavitt MS, DABT, Bristol Myers Squibb* |
| 1:05 – 1:30 PM | Role of DNA Repair in Modulating Susceptibility to Mutations and Cancer induced by N-Nitrosodimethylamine (NDMA)<br>*Prof. Bevin P. Engelward, ScD. Massachusetts Institute of Technology, USA* |
| 1:30 – 1:55 PM | Tox-GAN: An Artificial Intelligence Approach Alternative to Animal Studies-A Case Study with Toxicogenomics<br>*Xi Chen, Ph.D. National Center for Toxicological Research US FDA, USA* |
| 1:55 – 2:20 PM | Genotoxicity Predictions for Rapid Compound Screening: A Case Study for Accurate Classification using Machine Learning<br>*Seda Arat, Ph.D , Pfizer, USA* |
| 2:20 – 2:30 PM | Panel Discussion Q&A |

**2:30 – 2:50 PM** — **Lobby A**

***Coffee Break***

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**2:50 – 4:30 PM** — **Auditorium 128**

***Symposium III***
**Genetic Mechanisms in Metals Carcinogenesis**

CORTEVA™ agriscience

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|---|---|
| 2:50 – 2:55 PM | **Introduction**<br>*Co-chairs: Laura Markley PhD, US FDA & Jamie Young PhD, University of Louisville* |
| 2:55 – 3:15 PM | Mechanisms of Genomic Rearrangements: How Hexavalent Chromium, a Major Environmental Concern, Induces Chromosome Instability<br>*Prof. John P. Wise, Department of Pharmacology and Toxicology, University of Louisville, USA* |
| 3:15 – 3:35 PM | Arsenic is a potent co-mutagen of ultraviolet light<br>*Prof. Ke Jian "Jim" Liu, Stony Brook Cancer Center, Stony Brook University, USA* |
| 3:35 – 3:55 PM | Potential mechanisms of tungsten-induced carcinogenesis<br>*Prof. Koren Mann, Lady Davis Institute for Medical Research, McGill University, Canada* |
| 3:55 – 4:15 PM | Utilizing a stem cell based GFP reporter assay to demonstrate the mechanism of transition metal induced genotoxicity.<br>*Dan Roberts, MS, Toxys Inc, USA.* |
| 4:15 – 4:30 PM | Panel Discussion Q&A |

**4:30 – 5:00 PM** — **Auditorium 128**

***Poster Presentation (Speed Talks, ~2 mins each) Student and Early Investigator***

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|---|---|
| 4:30 – 4:35 PM | **Introduction**<br>*Co-chairs: Ashley Allemang MS, Procter & Gamble & Yi Yang PhD, DABT, AbbVie Inc.* |
| 4:35 – 5:00 PM | 2-minute Speed Talks (chronological order) |

| 5:00 – 7:00 PM | Lobby A |
|---|---|
| ***Poster Session & Cocktails*** | |
| 5:00 – 6:00 PM | **Odd numbered posters**<br>*Presenters available at their posters* |
| 6:00 – 7:00 PM | **Even numbered posters**<br>*Presenters available at their posters* |

| 7:00 – 8:30 PM | Room 101 A |
|---|---|
| ***Dinner (included in the 2-day registration)*** | |

# 2023 Annual GTA Meeting: Friday, May 5th

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| **7:00 – 8:15 AM** | ***Conference Registration*** | ***Lobby A / Registration Desk*** |

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| | | **Room 101 A** |
| **7:15 – 8:15 AM** | **Breakfast** | |

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| | | **Auditorium 128** |
| **8:15 – 8:30 AM** | **Welcome to Day 3**<br>*Penny Leavitt MS, DABT, Bristol Myers Squibb*<br>*2022-2023 GTA Chair-Elect* | |

| **8:30 – 10:00 AM** | **Auditorium 128** |
|---|---|
| ***Symposium IV***<br>**Titanium Dioxide Risk Assessment and Updates** | charles river |
| | *Co-chairs: David Kirkland PhD, Kirkland Consulting & Leon Stankowski PhD, CRL* |
| 8:30 – 8:45 AM | Introduction and Updates on the genotoxicity of $TiO_2$: Part 1, data gaps and new data<br>*David Kirkland PhD, Kirkland Consulting, Tadcaster, UK* |
| 8:45 – 9:15 AM | Investigating the in vivo genotoxicity of titanium dioxide: a testing strategy for new data generation<br>*Carol Beevers, PhD, Corteva Agriscience, Abingdon, UK* |
| 9:15 – 9:45 AM | Selectivity And Specificity of Food-Additive Titanium Dioxide for Lysomac Immune Cells of the Small Intestine<br>*John W Wills, PhD, Department of Veterinary Medicine, University of Cambridge UK* |
| 9:45 – 10:00 AM | Updates on the genotoxicity of $TiO_2$: Part 2, Regulatory opinions, industrial approaches to alternatives to $TiO_2$, and new initiatives<br>*David Kirkland PhD, Kirkland Consulting, Tadcaster, UK* |

| **10:00 – 10:15 AM** | **Lobby A** |
|---|---|
| ***Coffee Break*** | MERCK |

| **10:15 – 11:30 AM** | **Auditorium 128** |
|---|---|
| ***Symposium V***<br>**Nitrosamine Risk Assessment, Part 1 – *In silico* and *In vitro* Approaches** | gentronix |
| 10:15 – 10:20 AM | **Introduction**<br>*Co-chairs: Melisa Masuda-Herrera MS, DABT, Gilead & Kevin Cross PhD, Instem* |
| 10:20 – 10:40 AM | Framework for Establishing Acceptable Intakes for Drug Substance Related Nitrosamines<br>*Krista Dobo PhD, Pfizer* |
| 10:40 – 11:00 AM | From Theory to Practice: Use of Computational Methods for Nitrosamine Assessments<br>*Suman Chakravarti PhD, MultiCASE, USA* |
| 11:00 – 11:20 AM | Extension of the CADRE Platform: A Quantum-Mechanical Tool for Predicting the Carcinogenic Potency of N Nitroso Impurities in Pharmaceuticals<br>*Jakub Kostal, PhD, ToxFix USA* |
| 11:20 – 11:30 AM | Panel Discussion Q&A |

**11:30 – 12:30 PM** — **Room 101 A**

***Networking Lunch***

**Auditorium 128**

**12:30 – 1:00 PM** — **GTA 2023 Business Meeting**

**1:00 – 1:45 PM** — **Auditorium 128**

***Awards Ceremony and Presentation – Part II***

1:00 – 1:15 PM — **Student and Early- Stage Investigator Awards**
*Co-chairs: Sheroy Minocherhomji PhD, Eli Lilly & Penny Leavitt MS,DABT, Bristol Myers Squibb*

1:15 – 1:25 PM — **ESA Introduction**
*Chair: Dan Roberts MS, Toxys. Introduction by Krista Dobo PhD, Pfizer*

1:25 – 1:45 PM — **Excellence in Science Award Presentation**

**1:45 – 2:00 PM** — **Lobby A**

***Coffee Break***

charles river

**2:00 – 3:15 PM** — **Auditorium 128**

***Symposium VI***
**Nitrosamine Risk Assessment Part 2 – *In vivo* Approaches**

HESI Genetic Toxicology Technical Committee

2:00 – 2:05 PM — **Introduction**
*Co-chairs: Joel Bercu PhD, DABT, Gilead Sciences & Jennifer Cheung BS, Pfizer*

2:05 – 2:25 PM — EMA-Mutamind Analysis of Drug Substance Related Nitrosamines
*Kevin Cross PhD, Instem, USA*

2:25 – 2:45 PM — Mutation induction in Muta™Mouse following exposure to N-Nitrosodimethylamine (NDMA) with evidence for sub-linear mutation accumulation following repeat dosing
*Anthony Lynch PhD, GSK Plc, UK*

2:45 – 3:05 PM — *In vivo* genotoxicity assessment of N-nitrosodiethylamine with Error-Corrected Next-Generation Sequencing
*Shaofei Zhang PhD, Pfizer, USA*

3:05 – 3:15 PM — Panel Discussion Q&A

**Auditorium 128**

**3:15 – 3:30 PM** — **Concluding Remarks**
*Penny Leavitt MS, DABT, Bristol Myers Squibb*
2022-2023 GTA Chair-Elect

# Invited Speaker Biographies

## Keynote Address

Carole Yauk PhD

### About/Bio

Carole Yauk was the lead scientist of the Genomics Laboratory in the Environmental Health Science and Research Bureau at Health Canada for 18 years. She joined the University of Ottawa's Department of Biology as a full professor in September 2020, where she holds the Canada Research Chair in Genomics and the Environment. Her research broadly focuses on the development and implementation of genomic tools for human health risk assessment of environmental chemicals. She is involved in various international committees to advance this area, including within the Health and Environmental Sciences Institute (HESI) Emerging Systems Toxicology in the Assessment of Risk (eSTAR) and Genetic Toxicology Technical (GTTC) Committees. She currently serves as vice-chair of the Board of Trustees for HESI. She is also involved in the Organisation for Economic Co-operation and Development (OECD), where she is currently co-leading the development of the OECD's Omics Reporting Framework. She is Past-President of the Environmental Mutagenesis and Genomics Society and an editorial board member of several journals focused on mutagenesis and genetic toxicology. In her spare time, she's an avid snowboarder, climber, hiker, and runner, who's always up for a challenge. Any takers?

Anthony Lynch PhD

## About/Bio

Anthony is the senior director of Genetic Toxicology and Photosafety at GSK and holds an academic appointment at Swansea University Medical School. He is a former President of the UKEMS and has worked in Genetic Toxicology for over 3 decades.

Arianna Bassan PhD

## About/Bio

Arianna Bassan is a chemist with long-term expertise in toxicology. She graduated at the University of Padova (Italy), and she earned her PhD in Chemical Physics at the Department of Physics of Stockholm University (Sweden). She had worked several years in international environments including Stockholm University, MSD/Merck&Co. and the European Commission. Her main interest lies in the use of computational toxicology for human health hazard assessment. She also led a number of different scientific projects with focus on data management (e.g., development of the EFSA's Hazard database known now as OpenFoodTox, and management of pre-clinical data for pharma) and data curation. She is currently principal consultant in Innovatune, where she is also partner in the firm. Arianna partners with Instem on a variety of scientific activities, including coordination of a working group to support ICH S1B.

Ashley Allemang MS

## About/Bio

Ashley Allemang has over 10 years of industry experience in applied genetic toxicology in the context of in vitro-based safety support. Her research has primarily focused on mode of action determination and distinguishing direct and indirect genotoxicity through various in vitro methods such as the micronucleus assay, the ToxTracker assay and other genomics-based methods such as the TGx-DDI biomarker. More recently her research has employed the HepaRG micronucleus assay to develop in vitro-based genotoxicity potency rankings of pyrrolizidine alkaloids, as well as genotoxicity evaluation of mixtures. In addition to her research activities, her expertise has also expanded to include SAR based risk assessment. Ashley has been actively involved in the HESI GTTC committee since 2017 and has participated in the development of genetox-related AOPs and is currently co-leading the Indirect Genotoxicity subgroup of the In Vitro Work Group evaluating NAMs for genetic toxicity testing.

Bevin P. Engelward ScD

## About/Bio

Dr. Bevin P. Engelward received her doctoral degree from the Harvard School of Public Health in 1996. She joined the MIT faculty in 1997, where she is a leader in the creation and application of mouse models that can be used to study endogenous and exogenous factors that modulate susceptibility to carcinogenic mutations. Specifically, most tumors, if not all, harbor large scale sequence rearrangements as a consequence of homologous recombination events (e.g., large scale sequence rearrangements and loss of heterozygosity). With a passion for environmental health, her laboratory created novel mice wherein mutant cells can be detected within intact tissue via fluorescence. The resultant FYDR and RaDR mice have been used for many basic research studies, including work that has revealed that large scale sequence rearrangements accumulate with age, are driven by cell proliferation, and rise synergistically as a result of co-exposure to inflammation and a DNA damaging agent. Her laboratory has also collaborated with leaders in opto-mechanical engineering to demonstrate that clonal expansion is a major driver of mutant load during aging in the pancreas. By crossing repair deficient mice (that she helped to create) with the RaDR mice, her team demonstrated the importance of specific DNA repair genes as a genetic susceptibility factor for mutations caused by N-nitrosodimethylamine (NDMA), a potent carcinogen in animal models that contaminates Superfund sites and nearby aquifers. In addition to studies in animals, Dr. Engelward has also developed in vitro cell-microarray platforms with applications in environmental health. Specifically, the CometChip, NanoCometChip, HepaCometChip, EpiCometChip, MicroColonyChip, and SpheroidChip contribute in various ways to our ability to quantify the genotoxic, epigenetic, and cytotoxic effects of hazardous chemicals. Dr. Engelward has long been leading research projects and, more recently, research programs involving teams of PIs, making her highly qualified to carry out the proposed research.

Carol Beevers PhD

## About/Bio

Carol Beevers is a Regulatory Toxicologist, specialising in genetic toxicology. After gaining a degree in Microbiology and a PhD in Bacterial Genetics, Carol joined the Genetic Toxicology department at Covance Laboratories (now Labcorp) as an in vitro and in vivo Study Director. After almost 20 years in contract research, she moved to consultancy, first in the Human Health Toxicology group at Exponent International and then the Toxicology Group at Broughton Life Sciences. More recently, Carol joined the toxicology team at Corteva Agriscience. Carol has worked across a variety of industry areas including pharmaceuticals, agrochemicals, food and food contact materials, and industrial chemicals, where she specialised in genetic toxicology risk and mechanism of action assessments. Since 2015 she has been a member of the UK Committee on Mutagenicity of Chemicals in Food, Consumer Products, and the Environment. She is also a member of the OECD Expert Groups for the guidelines on the transgenic rodent gene mutation assay and the comet assay, the Health and Environmental Sciences Institute Genetic Toxicology Testing Committee and the International Workshops on Genotoxicity Testing.

Dan Roberts MS

## About/Bio

Mr. Roberts has a MS from Johns Hopkins University and has spent 19 years in the applied genetic toxicology field with experience in pharma, biotech, and CRO industries. Dan is presently a volunteer to the GTA (ESA Chair / Account Administrator) and is former Chair of the board (2016). He also co-chairs the in vivo follow up working group within HESI's Genetic Toxicology Technical Committee (GTTC) and is the program liaison for the Applied Genotoxicity (AGT) Special Interest Group of the Environmental Mutagen and Genomics Society (EMGS). Mr. Roberts recently joined Toxys, Inc, which specializes in novel in vitro tests serving genetic, developmental, and mechanistic toxicity testing needs. If chemical mode of action is what you seek, he is worth striking up a conversation with.

David Kirkland PhD

## About/Bio

Professor Kirkland has a BSc (microbiology) from the University of London and a PhD (cellular cancer studies) from Brunel University. Following 2 post-doctoral fellowships he became Research Director at Toxicol Laboratories before joining Microtest Research Limited in 1984. As part Covance, over 25 years, he was Head of Genetic Toxicology, Vice-President of Toxicology and of Scientific and Regulatory Consulting. In 2009 he became an independent consultant. He has extensive experience with regulatory issues relating to genotoxicity data, has published >150 peer-reviewed papers and is a regular podium speaker/chairperson.

He was awarded Fellowship of the UKEMS in 2002, and made Honorary Professor of the University of Wales, Swansea in 2006. In 2010 he received the first Industrial Genotoxicity Group (UKEMS) Distinguished Toxicologist Award, and also the US Environmental Mutagen Society Alexander Hollaender Award for global leadership in the regulation of genetic toxicology testing. In 2014 he was awarded The Kitashi Mochizuki Award by the Japanese Environmental Mutagen Society for promotion of international harmonization of genotoxicity tests through the International Workshops on Genotoxicity Testing (IWGT) of which he was chair of the steering committee for 20 years, and in 2015 he received the Jim Parry Award from UKEMS. For many years he was Special Issues Editor for Mutation Research and editorial board member of the Journal of Applied Toxicology. He was a member of the UK Government Advisory Committee on Mutagenicity for 10 years, was UK expert to OECD for genotoxicity guidelines, and Past President of the European EMGS.

Francesco Marchetti PhD

## About/Bio

Dr. Francesco Marchetti is a Senior Research Scientist at Health Canada and Adjunct Research Professor at Carleton University. He chairs the Germ Cell workgroup of the Health and Environmental Science Institute's Genetic Toxicology Technical Committee and is a member of the Organisation for the Economic Co-Operation and Development Expert Group on Genotoxicity Testing. Dr. Marchetti has authored over 125 peer-reviewed publications. He was Editor-In-Chief of Environmental and Molecular Mutagenesis (EMM) during 2012-2016 and serves on the editorial boards of EMM and Mutagenesis. Dr. Marchetti is the current President of the Environmental Mutagenesis and Genomic Society.

Giel Hendriks PhD

## About/Bio

Giel Hendriks has a PhD in molecular cell biology from Utrecht University and worked for four years as a post-doctoral fellow in at Leiden University, studying the relationship between DNA damage and gene mutations. After this he moved to the Leiden University Medical Center to develop in vitro reporter systems to understand the mechanisms of genotoxicity. In 2014, he obtained financing to start Toxys. In 2016, he attracted various investors that allowed Toxys to setup their own laboratory at the Leiden Bio Science Park. As CEO of Toxys, he worked to develop the company into an internationally recognised contract research organisation (CRO) in chemical safety testing for industry. During the past years, Toxys has developed various in vitro assays to ensure the safety of novel medicines, chemicals and consumer products without the use of animals.

Jakub Kostal PhD

## About/Bio

Jakub Kostal is an Assistant Professor of Chemistry at the George Washington University, where his group develops computational methods for the design of safer and efficacious chemicals. At GWU, Dr. Kostal directs the MS Program in Environmental and Green Chemistry, which trains chemists in predictive toxicology, safer chemical and process design. Dr. Kostal is also co-founder and principal at ToxFix (www.toxfix.com), which has served the pharmaceutical and personal care industries for 10 years in reducing animal testing using the CADRE suite of predictive tools. He holds PhD from Yale University (PhD '12) in Theoretical and Biophysical Chemistry and a BA in Chemistry from Middlebury College (BA '06).

John Pierce Wise, Sr. PhD

## About/Bio

John Pierce Wise, Sr. is a Professor and a Distinguished University Scholar in the Department of Pharmacology and Toxicology at the University of Louisville School of Medicine. He earned the prestigious Revolutionizing Innovative, Visionary Environmental Health Research (RIVER) R35 grant from the National Institute of Environmental Health Sciences (NIEHS). He is the recipient of three Society of Toxicology's (SOT) awards for Mentoring, Education, and Career Achievement in Metals. He is also the recipient of the Environmental Mutagenesis and Genomics Society's (EMGS) Education award. Dr. Wise's research focuses on understanding how environmental toxicants affect health and cause cancer from a One Environmental Health perspective considering cellular and molecular mechanisms in both humans and wildlife, with a particular emphasis on lung cancer and chromosome instability. He holds a B.S. with distinction and with recognition in biology from George Mason University, and a Ph.D. in pharmacology from George Washington University. His postdoctoral training focused on molecular epidemiology under Drs. Curtis Harris and Peter Shields at the National Cancer Institute (NCI), followed by training in occupational health and risk assessment as a senior toxicologist at Jonathan Borak and Company. He has served on the faculty of Yale University's School of Medicine and School of Public Health, the University of Southern Maine, prior to joining the faculty at the University of Louisville, School of Medicine. He is the currently President of the International Society for Trace Element Research in Humans (ISTERH) and Vice-President elect for the Carcinogenesis Specialty Section of SOT.

John Wills PhD

## About/Bio

John completed his Ph.D. in 2015 at Swansea University College of Medicine before moving to Ottawa, Canada to pursue post-doctoral studies at Health Canada and the University of Ottawa. During this time, John developed a strong interest in chemical and particle dosimetry using high-content imaging. In the spring of 2017, John was awarded a University of Cambridge Herchel-Smith Fellowship to develop a microscopy, image analysis and machine learning-based technology that permits 'flow-cytometry type' analyses of intact tissue sections. John is currently focussed on demonstrating the capabilities of this approach including investigations to determine the fate and cellular interactions of food-additive titanium dioxide nanoparticles. In 2022, John joined GSK as an Associate Director and currently holds this position jointly with Visiting Fellow positions at Cambridge.

Ke Jian Liu PhD

## About/Bio

Dr. Ke Jian "Jim" Liu is currently a Professor in the Department of Pathology and the Associate Director for Basic Research at the Stony Brook Cancer Center, Stony Brook University, NY. Dr. Liu's research is broadly interested in the molecular mechanisms of toxic metals (such as arsenic and chromium) in disrupting normal physiological processes, leading to the development of various diseases (e.g., cancer, anemia, and brain injury), and in developing interventional strategies to reduce the health effects of environmental exposure to the toxic metals. Research in Liu lab utilizes the multidisciplinary approaches, using techniques ranging from chemical and biochemical to biophysical, at the levels of molecule, cell, animal and human patients, to answer the specific biological questions. He has authored more than 250 peer-reviewed scientific papers and his research program has been continuously supported by numerous NIH grants over 25 years. He has been frequently invited to present at national and international conferences, and gives seminars at academic institutions around the world.

Kevin Cross PhD

## About/Bio

Dr. Kevin P. Cross is a vice-president at Instem, where he is Principal Investigator of U.S. FDA/Leadscope collaborations. His current responsibilities include the collaborative research and development of QSAR models and databases with U.S. FDA Center for Drug Evaluation and Research for prediction of toxicity in support of drug safety, the U.S. FDA Center for Food Safety and Applied Nutrition in support of the Office of Food Safety and supporting the U.S.FDA Center for Devices and Radiological Health, the U.S.FDA Center for Veterinary Medicine and the Office of Women's Health. He is also responsible for the development of the Leadscope Enterprise product. He received his Ph.D. in chemistry from Michigan State University and has been developing chemoinformatics tools and products for over 35 years. He is involved in several collaborative efforts to create protocols and procedures for performing in silico assessments for regulatory purposes as well as to assess their performance. Recently he is: 1) co-leading a project on N-Nitrosamine Structure-Activity Relationships (SARs) involving over 23 companies and institutions, 2) is part of an EMA contract investigating nitrosamine SARs and 3) part of a HESI GTTC sub-team studying nitrosamine testing and SARs. He participated in the 2017 International Workshop on Genetic Toxicity where he helped determine Ames tester strain equivalency and identified in silico toxicity prediction issues related to genetic toxicity testing. In 2023 he will be participating in a IARC workshop discussing the use of the Key Characteristics of Cancer. He has authored over 45 papers.

Koren Mann PhD

## About/Bio

Dr. Mann is a Professor and Chair of the Department of Pharmacology and Therapeutics at McGill University in Montreal, Quebec. She is also a Senior Investigator at the Lady Davis Institute for Medical Research at the Jewish General Hospital. She received her PhD from Boston University studying the immunotoxicity of polycyclic aromatic hydrocarbons on developing B cells, and subsequently, performed a postdoctoral fellowship at McGill University investigating arsenic trioxide as a chemotherapeutic. Her research focuses on the immunotoxic effects of metals, including arsenic and tungsten. She has made significant contributions to our understanding of arsenic-enhanced atherosclerosis via effects on macrophages and the toxicities associated with tungsten exposure. As a Principal Investigator, her current and past research funding includes grants from the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, the Leukemia and Lymphoma Society of Canada, the Cancer Research Society, the Heart and Stroke Foundation of Canada and the US National Institutes of Health. Dr. Mann has published extensively over the past two decades, including >75 peer-reviewed articles and several book chapters. She currently serves as an Associate Editor of Environmental Health Perspectives.

Krista Dobo PhD

## About/Bio

Krista holds a B.S. in Biology from Indiana University of Pennsylvania, and received her Ph. D. in Environmental Toxicology from the University of California, Riverside. Krista joined Pfizer in the Genetic Toxicology department, where she contributed to the team as a study director, subject matter expert, supervisor and department head. During her time at Pfizer Krista has also developed expertise related to impurity qualification and risk assessments. She represents Drug Safety on a multidisciplinary council that provides advice to teams regarding impurity qualification matters. She currently leads Drug Safety's Global Risk Assessment Services Team (GRAS). GRAS collaborates with Pfizer Global Supply manufacturing sites and contributes to the development of risk assessments to address potential safety issues that arise across Pfizer's global marketed product supplies Krista has served two terms as a member of the Genetic Toxicology Association (GTA) Board of Directors and also acted as GTA Chair. She is also a former Councilor of the Environmental Mutagenesis and Genomics Society (EMGS), and served as Co-Chair of the EMGS Applied Genetic Toxicology special interest group. She has been an active participant in PhRMA LDKIT efforts to revise the ICH Genetic Toxicology Testing Guidance (ICHS2R) and develop the ICH M7 Guideline and Addendum. Krista is currently PhRMA topic lead for ICH M7 Expert Working Group, and member of a collaborative team working towards understanding the structure activity relationships of nitrosamines. She also serves on the Board of Trustees for Lhasa Limited and Editorial Board of Environmental and Molecular Mutagenesis.

Seda Arat PhD

## About/Bio

I am a Computational Toxicologist within Pfizer's Drug Safety Research & Development organization focusing on safety applications of Next Generation Sequencing data analysis, bioinformatics, and predictive modeling. Prior to joining Pfizer, I was a postdoctoral associate at The Jackson Laboratory in the field of Computational Genomics and Machine Learning. During my PhD studies, I have involved every aspect of Systems Biology: (1) data generation and experimental validation as I was an intern at the University of Connecticut Health Center; (2) data analysis as I was an intern at GlaxoSmithKline; and (3) mathematical modeling as I was a graduate student at Virginia Tech. I have published several software applications, predictive models and papers in diverse fields such as cancer biology, infectious disease, microbiome, mouse genetics, toxicology and biomarkers. In addition, I have been involved in numerous volunteer activities for the Society of Industrial and Applied Mathematics (SIAM), Association for Women in Mathematics (AWM), Society for Advancement of Chicanos and Native Americans in Science (SACNAS), International Society for Computational Biology (ISCB), National Postdoc Association (NPA), Pfizer Groton Women Resource Group and Latino Community.

Shaofei Zhang PhD

## About/Bio

Dr. Zhang holds a PhD in biochemistry, cellular and molecular biology from University of Tennessee. He is a senior principal scientist at Pfizer's Drug Safety R&D group, where he works on safety assessment of different compounds in pharmaceuticals with traditional and emerging scientific tools, such as Big Blue and Duplex Sequencing.

Dr. Zhang is a co-chair of EMGS In Vivo Mutagenesis (IVM) Special Interest Group (SIG), he also serves as a co-chair of HESI GTTC ecNGS workgroup, where he is attempting to promote the application of ecNGS in the safety assessment and acceptance of this new technology by regulatory agencies.

Xi Chen PhD

## About/Bio

Dr. Xi Chen is a staff fellow of Division of Bioinformatics and Biostatistics at FDA's National Center for Toxicological Research (NCTR/FDA). She is a skilled researcher with extensive research experience in bioinformatics, molecular biology, and developmental biology. With over a decade of experience, Dr. Chen's expertise lies in developing statistical and computational methods to integrate multi-omics data, identify functional variants, and discover biomarkers, with the aim of interpreting medical big data and obtaining a novel and insightful understanding of their biological and clinical significance at the molecular level. She is also interested in using data mining methods and systems biology strategies for both basic biological research and translational medicine investigations. Recently, Dr. Chen has been exploring the use of artificial intelligence (AI) as an alternative method to animal studies. She is developing generative AI frameworks to advance safety assessment in the field of pharmacovigilance and toxicology without using animal testing. With over 20 peer-reviewed publications and a patent, Dr. Chen has received numerous awards for her research. Her ultimate goal is to improve human health by advancing the use of big data and artificial intelligence in biomedical research.

Stephen Dertinger PhD

## About/Bio

Director of Research, Litron Laboratories

Stephen Dertinger, Ph.D. received his post-graduate training from the University of Rochester, Department of Environmental Medicine. At the University of Rochester, he worked with Dr. Thomas Gasiewicz studying the role of AhR signaling on the toxicity of cigarette smoke. Since completing his Ph.D., Dr. Dertinger has served as Director of Research of Litron Laboratories. During this time, he has overseen the development of high throughput in vitro and in vivo cytogenetic damage assays, most notably automated procedures for scoring micronuclei in mammalian cell culture and also blood reticulocytes. These methods have been developed into simple to use kits that are commercially available under the trade name MicroFlow®, and they are used throughout the world by industry and government laboratories to assess chemicals for genotoxic potential. More recently, Stephen's research team developed in vitro and in vivo mutation assays based on the Pig-a gene (MutaFlow®), and a multiplexed high information content in vitro assay that distinguishes between clastogenic and aneugenic modes of action (MultiFlow®). Dr. Dertinger has served on IWGT, ECVAM, and OECD expert working groups. Through these committees, he has helped shape the regulatory requirements for genotoxicity assays in the U.S. and abroad. Honors include: Tibbett's Award recipient, an honor given to NIH grant awardees whose work has had tremendous societal and/or economic impact; Rochester Intellectual Property Law Association Distinguished Inventor of the Year; and EMGS Alexander Hollaender Award, conferred in recognition of outstanding contributions in the application of the principles and techniques of environmental mutagenesis and genomics to the protection of human health.

Suman Chakravarti PhD

**About/Bio**

Chief Scientific Officer and Vice President, MultiCASE Inc

Suman conducts research, develop, and implement computational approaches to assess the toxic properties of drugs and chemicals. Collaborate with external partners from regulatory agencies, industry, and academia to create and implement new computational solutions. Conduct research to innovate and improve cheminformatics and QSAR techniques. Design specialized algorithms and software to support the regulatory aspects of in silico approaches. Develop deep learning and artificial intelligence-based applications and tools for QSAR and computational toxicology. Assist the customer support team in training customers on computational toxicology tasks.

Susanne Stalford PhD

## About/Bio

Susanne Stalford gained a PhD in Biological Chemistry from the University of Leeds in the UK, then went to work for Lhasa Limited and has been there for 15 years. Susanne has significant experience in the development of SAR models for multiple endpoints and now focusses on the development and application of AOPs for carcinogenicity. She currently leads the application of AOPs for ICH S1B(R1) within Lhasa Limited.

Timothy McGovern PhD

## About/Bio

Dr. Timothy McGovern is an Associate Director for Pharmacology and Toxicology in the Office of New Drugs (OND) at the Center for Drug Evaluation and Research, US Food and Drug and serves as a member of the Pharmacology/Toxicology Senior Leadership Team within OND. In this role, he interacts with nonclinical review teams in OND review divisions regarding the review of IND, NDA, and BLA submissions. He participates in the development of policy and guidance related to nonclinical and regulatory issues including FDA and International Council for Harmonization (ICH) initiatives. He is a standing member of CDER's Executive Carcinogenicity Assessment Committee and a member of the Genetic Toxicology Subcommittee. Dr. McGovern is the current Rapporteur for the ICH S1B Expert Working Group. His formal training is in the area of inhalation toxicology.

Vasily N. Dobrovolsky, PhD

**About/Bio**

Dr. Dobrovolsky joined the U.S. FDA's National Center for Toxicological Research in 1998 as a staff fellow, and then as Research Microbiologist. His research interests are focused on design and implementation of innovative in vitro and in vivo models in mutation research. In recent years, Dr. Dobrovolsky contributed to the development and validation of the *Pig-a* assay confirming DNA mutations in mutant phenotype cells measured by flow cytometry and extending the methodology for detecting and analysis of *Pig-a* mutant cells in various mammalian species and in cultures of eukaryotic cell. His research interests include engineering transgenic animals and cell lines via traditional or targeted insertion technologies and their subsequent use for studying mutagenesis. Recently his efforts are concentrated on characterizing chemical-induced mutations in various biological models by whole-genome next generation sequencing and embracing such information for safety assessment of FDA-regulated products.

Vasily received a M.Sc. degree in Biotechnology from the Moscow Institute of Physics and Technology, Moscow Russia, in 1988; a Ph.D. degree in Molecular Biology from Shemyakin Institute of Bioorganic Chemistry, Russian Academy of Sciences, in 1994. His postdoctoral training was with Bob Heflich at NCTR from 1994-1998.

Dr. Dobrovolsky is a member of the Environmental Mutagenesis and Genomics Society since 1995. He participates in the work of several FDA and international committees, including OECD Expert Groups on developing an OECD Test Guideline for the in vivo *Pig-a* gene mutation assay. He has co-authored 90 papers in peer reviewed journals and book chapters.

Yax Thakkar MS

## About/Bio

Yax Thakkar is currently a Senior Scientist and leads the Genetic Toxicology Program at Research Institute for fragrance Materials (RIFM) Inc., in Woodcliff Lake, NJ. His current research includes the evaluation, development and validation of animal alternative models to assess genotoxic potential for Fragrance materials. Prior to joining RIFM, he has worked as a Scientist with various consumer product industries like L'OREAL and COTY INC.

Mr. Thakkar received his B.S in Pharmacy (India), and MS from Long Island University, Brooklyn, NY (2013), working in the evaluation of anti-carcinogenic effect of carvacrol, a phytochemical which is a key component of Oregano. Currently he is also a Doctoral candidate at New York Medical College in the department of Pathology, working to evaluate Chicken egg model as an animal alternative model to assess genotoxic potential for Chemicals.

Mr. Thakkar has co-authored over 500 peer-reviewed Safety assessments for fragrance materials. And has also authored three peer reviewed publications related to various models assessing genotoxic potential for fragrance materials and Chemicals. Mr. Thakkar is also an Associate editor for Medicine. He is also active in GTA HESI-GTTC, EMGS and SOT.

# Poster Presenter Biographies

## P01

Giel Hendriks PhD

### About/Bio

Giel Hendriks has a PhD in molecular cell biology from Utrecht University and worked for four years as a post-doctoral fellow in at Leiden University, studying the relationship between DNA damage and gene mutations. After this he moved to the Leiden University Medical Center to develop in vitro reporter systems to understand the mechanisms of genotoxicity. In 2014, he obtained financing to start Toxys. In 2016, he attracted various investors that allowed Toxys to setup their own laboratory at the Leiden Bio Science Park. As CEO of Toxys, he worked to develop the company into an internationally recognised contract research organisation (CRO) in chemical safety testing for industry. During the past years, Toxys has developed various in vitro assays to ensure the safety of novel medicines, chemicals and consumer products without the use of animals.

## P02

Robert Foster PhD

### About/Bio

Rob completed his masters in Chemistry in 2009 at the University of Sheffield before staying on to complete a PhD in organic chemistry, investigating novel synthetic routes towards pyrazoles using sydnones in cycloaddition reactions, under the supervision of Professor Joseph Harrity.

Having completed his PhD in 2012, Rob spent the next 4 years working for a contract research organisation undertaking various custom and contract synthesis projects for the pharmaceutical and agrochemical sectors. A move away from the laboratory in 2016 brought Rob to Lhasa where he has been involved in the scientific research and development of various Lhasa products.

Initially Rob deciphered metabolism data for predictions of metabolic fate in Meteor and forced degradation pathways for Zeneth, before moving onto developing alerts for multiple toxicity endpoints in Derek and writing AOPs for carcinogenicity in Kaptis. Since 2020, Rob has predominantly focused on the development of genotoxicity solutions at Lhasa in his current role as lead scientist for Sarah (Lhasa's statistical-based tool for mutagenicity predictions) and Lhasa's ICH M7 solution.

## P03

Laura C. Markley PhD

### About/Bio

A toxicologist for 15+ years, Dr. Markley specializes in human health risk assessment, food safety, genotoxicity, metals toxicology, nanotoxicology and carcinogenesis. She graduated from Texas A&M University – Corpus Christi with a Bachelor of Science in Biology, received a Ph.D. from the University of Maine in Molecular Biology and Biochemistry, and held an FDA ORISE postdoctoral fellowship. She has worked in non-profit and consulting before her role as a Toxicology Reviewer at FDA. She began at the Office of Food Additive Safety in 2018 and her current duties include reviewing pre-market notifications of food contact substances and supporting several complex post-market issues related to regulatory science, safety review and policy.

## P04

Susanne Stalford PhD

### About/Bio

Susanne Stalford gained a PhD in Biological Chemistry from the University of Leeds in the UK, then went to work for Lhasa Limited and has been there for 15 years. Susanne has significant experience in the development of SAR models for multiple endpoints and now focusses on the development and application of AOPs for carcinogenicity. She currently leads the application of AOPs for ICH S1B(R1) within Lhasa Limited.

## P05

Glenn J Myatt PhD

### About/Bio

Glenn J. Myatt is the co-founder of Leadscope and currently Senior Vice President, In Silico & Translational Science Solutions at Instem with over 25 years' experience in computational chemistry/toxicology. He holds a Bachelor of Science degree in Computing, a Master of Science degree in Artificial Intelligence and a Ph.D. in Chemoinformatics. He has published 34 papers, 10 book chapters and three books.

## P06

Tomas Lagunas Jr.PhD

### About/Bio

I recently completed my PhD in Molecular Genetics and Genomics with Dr. Joseph Dougherty at Washington University in St. Louis School of Medicine. I am part of a drug development training fellowship at Genentech where they give recent doctoral graduates the chance to gain hands-on training and mentoring in multiple areas of clinical and preclinical drug development. I am currently part of the Safety Assessment team and completing my training in the Investigative Toxicology group.

## P07

Kevin P. Cross PhD

### About/Bio

Dr. Kevin P. Cross is a vice-president at Instem, where he is Principal Investigator of U.S. FDA/Leadscope collaborations. His current responsibilities include the collaborative research and development of QSAR models and databases with U.S. FDA Center for Drug Evaluation and Research for prediction of toxicity in support of drug safety, the U.S. FDA Center for Food Safety and Applied Nutrition in support of the Office of Food Safety and supporting the U.S.FDA Center for Devices and Radiological Health, the U.S.FDA Center for Veterinary Medicine and the Office of Women's Health. He is also responsible for the development of the Leadscope Enterprise product. He received his Ph.D. in chemistry from Michigan State University and has been developing chemoinformatics tools and products for over 35 years. He is involved in several collaborative efforts to create protocols and procedures for performing in silico assessments for regulatory purposes as well as to assess their performance. Recently he is: 1) co-leading a project on N-Nitrosamine Structure-Activity Relationships (SARs) involving over 23 companies and institutions, 2) is part of an EMA contract investigating nitrosamine SARs and 3) part of a HESI GTTC sub-team studying nitrosamine testing and SARs. He participated in the 2017 International Workshop on Genetic Toxicity where he helped determine Ames tester strain equivalency and identified in silico toxicity prediction issues related to genetic toxicity testing. In 2023 he will be participating in a IARC workshop discussing the use of the Key Characteristics of Cancer. He has authored over 45 papers.

## P08

Arianna Bassan PhD

### About/Bio

Arianna Bassan is a chemist with long-term expertise in toxicology. She graduated at the University of Padova (Italy), and she earned her PhD in Chemical Physics at the Department of Physics of Stockholm University (Sweden). She had worked several years in international environments including Stockholm University, MSD/Merck&Co. and the European Commission. Her main interest lies in the use of computational toxicology for human health hazard assessment. She also led a number of different scientific projects with focus on data management (e.g., development of the EFSA's Hazard database known now as OpenFoodTox, and management of pre-clinical data for pharma) and data curation. She is currently principal consultant in Innovatune, where she is also partner in the firm. Arianna partners with Instem on a variety of scientific activities, including coordination of a working group to support ICH S1B.

## P09

Elizabeth Irvin

### About/Bio

I am a second year toxicology PhD student studying DNA damage response and chromatin remodeling using single molecule imaging (SMI) techniques, namely atomic force microscopy imaging as well as a fluorescence-based DNA tightrope assay. I have served on the Graduate Student Association for my graduate program and was recently elected as a Councilor for the Genetics and Environmental Mutagenesis Society for 2023-2026. Additionally, I was awarded one of NCSU's inaugural Goodnight Fellowships for academic merit. I am interested in careers in genetic toxicology and would like to attend this meeting to explore what opportunities exist in the field.

## P10

Roustem D Saiakhov PhD

### About/Bio

Dr. Roustem Saiakhov has been the president of MultiCASE Inc since the year of 2012. His involvement with MultiCASE started in the year 2000 when he joined the company as a computational scientist. In a few years, he was appointed as a Vice President of Research and Development and soon after that as a Chief Operating Officer. Native of Russia, in 1991, Roustem was awarded a Ph.D. through the Kazan State University, the third oldest university of the Russian Federation, where he studied the quantitative structure-activity relationship of complex element organic compounds with advisors Professor Vladimir Galkin and Professor Rafael Cherkasov. Roustem also did his undergraduate work at Kazan University, graduating in 1987 summa cum laude and a degree in chemistry. Dr. Saiakhov joined Professor Michalski's group at the Polish Academy of Science as a postdoctoral chemist in 1995. He relocated to the United States in 1997, where he joined Dr. Gilles Klopman's group at Case Western Reserve University as a postdoctoral scientist. He has over 20 years of experience in teaching and research. His area of expertise includes cheminformatics, molecular modeling, QSAR, organic and computational chemistry, and computational toxicology. In the past several years, Dr Saiakhov was also involved in the risk assessment and safety consulting services provided by MultiCASE. Dr. Saiakhov has been the principal investigator on a number of grant projects and has over 100 scientific publications and presentations. He speaks 3 languages: Russian, Polish, and English.

## P11

Vivian Tang

### About/Bio

Senior Associate Scientist at Pfizer

## P12

Haiyan Lu PhD

### About/Bio

My name is Haiyan Lu. I received a doctorate in Pharmacology & Toxicology from the University of Louisville in 2022. I am a postdoctoral associate in Wise's lab now. My research is focusing on the molecular mechanisms of hexavalent chromium-induced carcinogenesis. Cell culture, in vivo rodent, human tissue, and wildlife studies provide a One Environmental Health perspective of the mechanisms of hexavalent chromium-induced DNA repair inhibition and chromosome instability. I am authored or co-authored 6 peer-reviewed papers, and 50 abstracts.

## P13

Marise Roy MS

### About/Bio

Since 2007, Marise works for Charles River Laboratories where she sits as a Principal Scientist. With a long experience in screening and regulatory assays for genotoxicity assessment, Marise has served as Study Director on more than 370 genetic toxicology projects developed for pharmaceuticals, chemicals and medical devices. She is also responsible for the implementation and validation of new assays focused on identification of mechanism of genotoxicity. She is an active member of the international validation for the ToxTracker assay. She is a co-author of the chapter 'The Bacterial Reverse Mutation Test' in a book 'Genetic Toxicology Testing, A Laboratory Manual' edited by Raymond Proudlock in 2016.

## P14

Cheryl Hobbs PhD

### About/Bio

Dr. Hobbs has >40 years of diverse experience with in vivo and in vitro models of disease and genetic damage incurred by chemical exposure. She has expertise and publications in the fields of genetic and general toxicology, gene regulation, and epigenetic mechanisms of disease and toxicity. Currently, Dr. Hobbs serves as the Director of Genetic Toxicology at Inotiv, overseeing the conduct of genetic toxicity testing for both government agencies and commercial clients, with primary focus on *in vivo* studies conducted at the company's Research Triangle Park site. She was formerly the Director of Toxicology at one of Inotiv's legacy companies, Integrated Laboratory Systems, Inc. Prior to joining ILS, Dr. Hobbs held concurrent appointments at Lankenau Hospital in suburban Philadelphia, and the affiliated Lankenau Institute for Medical Research, where she previously did her postdoctoral training. Before obtaining her doctorate, she worked as a molecular biologist in support of drug discovery programs at Sterling Winthrop, Inc. and cancer research at the Fox Chase Cancer Center. Dr. Hobbs attained her M.S. and Ph.D. degrees in Bioscience and Biotechnology from Drexel University and her B.A. in Biological Sciences and Computer Science from the University of Delaware. She has been a member of several professional societies, expert working groups, validation teams, and journal editorial boards.

## P15

Stephanie Smith-Roe PhD

### About/Bio

Dr. Stephanie Smith-Roe is a genetic toxicologist in the Division of Translational Toxicology (DTT) at the NIEHS. She designs a wide range of genetic toxicity testing strategies for the DTT and serves as the Contracting Officer's Representative (COR) for the DTT's Genetic Toxicity Testing Contract. At the DTT, Dr. Smith-Roe has investigated the genotoxic potential of glyphosate (the active herbicide in Roundup products) and several other high-profile substances such as cell phone radiofrequency radiation and botanical dietary supplements. She has collaborated with scientists across academia, industry, and government to assess new approaches for rapid identification of genotoxicants. Altogether, Dr. Smith-Roe has published in the areas of genetic toxicology, mutagenesis, carcinogenesis, DNA replication and repair, DNA damage signaling, and chromatin remodeling. Dr. Smith-Roe is an enthusiastic contributor to scientific societies and organizations that focus on research related to genetic toxicology, genomic stability, and carcinogenesis, and that are also committed to supporting early career scientists. She is the Vice President of the Environmental Mutagenesis and Genomics Society and will transition to President for 2023 – 2024, and is a Past President of the Genetics and Environmental Mutagenesis Society. Through participation in working groups for the Health and Environmental Sciences Genetic Toxicology Technical Committee, the International Agency for Research on Cancer, and the Organisation for Economic Co-operation and Development, Dr. Smith-Roe has contributed to international efforts to continually improve approaches for genetic toxicity testing and to protect the public from exposures that potentially could cause cancer, birth defects, and genetic disease.

## P16

Zhenning Yang MBBS

### About/Bio

Zhenning Yang is a 4th year Ph.D. student in the Joint Graduate Program in Toxicology at Rutgers University. Her research focuses on studying the genotoxicity and mutagenicity of micro- and nano-plastics (MNPs) in an *in vitro* tri-culture small intestinal epithelium model and a microfluidic human organoid intestine-on-a-chip model. Zhenning's research involves conducting the genetic toxicity testing of MNPs by assessing DNA damage with the CometChip assay and mutagenesis through Duplex Sequencing. Zhenning received her bachelor's degree in clinical medicine from Jilin University in China in 2018. Additionally, She has been serving as a volunteer in the Sino-American Pharmaceutical Professionals Association. Zhenning Yang would like to apply for the abstract award for the 2023 GTA annual meeting, as it will provide valuable support and inspiration for her research on MNP genotoxicity.

## P17

Carol D. Swartz PhD

### About/Bio

Director, In Vitro Toxicology

Integrated Laboratory Systems, LLC, an Inotiv Company, Research Triangle Park, NC, USA.

## P18

Jeffrey C. Bemis PhD

### About/Bio

Dr. Jeffrey Bemis received his PhD in Environmental Health and Toxicology from the University at Albany School of Public Health in Albany, NY. His thesis focused on the effects of combined exposure to the environmental contaminants polychlorinated biphenyls (PCBs) and methyl mercury on central neurotransmitter systems. Jeff then spent three years as a Postdoctoral Fellow in the Department of Environmental Medicine at the University of Rochester School of Medicine and Dentistry in Rochester, NY. Here he investigated molecular and developmental aspects of exposure to PCBs and dioxin using a transgenic reporter mouse model.

Jeff began his work in genetic toxicology when he joined Litron Laboratories in 2006 as a research scientist and is now Director of Clinical Studies. In his current position Jeff serves as a principal investigator for internal research efforts, in-house service work and also manages human studies for clients. Jeff regularly presents at national and international meetings and is an author on over fifty peer-reviewed journal articles and book chapters. Jeff has been a member of the Society of Toxicology for over eighteen years. He served as Program Chair, Council Member and Co-Chair for the Education, Student and New Investigator Affairs committee of the Environmental Mutagenesis and Genomics Society. Jeff also served on the Board of Directors for the Genetic Toxicology Association. Here he spent three years on the program committee for the annual meeting and chaired the committee for two years.

## P19

Lee Pribyl PhD

### About/Bio

I'm a third-year postdoc working in Dr. Bevin Engelward's lab at MIT in Cambridge, Massachusetts. I received my PhD in cancer and developmental biology from the University of Tennessee Health Science Center. My main research focus is on defining the mechanisms of liver carcinogenesis in DNA repair deficient mouse models treated with a particular chemical contaminant, NDMA. However, I am also interested in expanding my research into testing drug therapies in preclinical animal model studies.

## P20

Leslie Recio PhD

### About/Bio

Dr. Leslie Recio is the Chief Scientific Officer of ScitoVation, a contract research and consulting firm located in Research Triangle Park, NC. Dr. Recio received an M.S. and PhD in Toxicology from the University of Kentucky. Dr. Recio became a Diplomate of the American Board of Toxicology in 1997. In 2014 he was appointed as a United States representative to the Organisation for Economic Co-operation and Development (OECD) Genetic Toxicology Expert Group charged with updating the Genetic Toxicology Test Guidelines. Dr Recio served on the Editorial Board and Associate Editor of Toxicological Sciences and on the Editorial Board of Mutation Research – Reviews in Mutation Research. Dr. Recio has authored/co-authored 124 publications in the peer review literature. Dr. Recio's research has focused on molecular biology/toxicogenomics, genetic toxicology, and carcinogenesis using a number of in vitro cell culture methods, in vivo studies using wild-type and transgenic mouse strains, integrated with genomic approaches to understand mode-of-action and genetic susceptibility. In collaboration with the Engelward lab (MIT) and Yauk laboratory (Health Canada/U of Ottwa) Dr Recio laboratory has been centered on New Alternative Methodologies using human-relevant metabolically competent hepatocyte models integrated with traditional and toxicogenomic approaches aimed mode-of-action and risk assessments. Dr. Recio's has experience working across sectors in contemporary toxicology including a nonprofit research organization, pharmaceutical industry at and managing an in vitro and in vivo GLP compliant regulatory testing facility. His current position is aimed at developing and validating New Approach Methodologies for use in risk assessment.

## P21

Daniel Roberts MS

### About/Bio

Mr. Roberts has a MS from Johns Hopkins University and has spent 19 years in the applied genetic toxicology field with experience in pharma, biotech, and CRO industries. Dan is presently a volunteer to the GTA (ESA Chair / Account Administrator) and is former Chair of the BOD (2016). He also co-chairs the in vivo follow up working group within HESI's Genetic Toxicology Technical Committee (GTTC) and the Applied Genotoxicity (AGT) Special Interest Group of the Environmental Mutagen and Genomics Society (EMGS). Mr. Roberts recently joined Toxys, Inc, which specializes in novel in vitro tests to serve genetic, developmental, and mechanistic toxicity testing needs.

## P22

Chibuisi Gideon Alimba PhD

### About/Bio

Dr Alimba C.G. is a genetic and molecular toxicologist. He completed his doctorate in 2013 at the Cell Biology and Genetics unit, Department of Zoology, University of Ibadan, Nigeria. He is a recipient of The World Academy Science fellowship for Research and Advance training at India between 2014 - 2015. He is an Alexandra Von Humboldt Stiftung postdoctoral fellow, Germany between 2017 - 2021. He has attended numerous conference and workshops. He is widely published in peer review journals with high impact factor.

# Invited Speaker Abstracts

## Keynote Address

# I didn't catch your NAM: advancing genotoxicity testing strategies through multi-sector collaborations

Carole Yauk
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### Abstract

Over fifteen years ago, the National Research Council published a vision and strategy to revolutionize toxicological testing. "*Toxicity Testing in the 21st Century*" (2007) called for the development and validation of new approach methodologies (NAMs) to increase the efficiency of toxicity testing, while reducing animal use and providing mechanistic data to better inform human-relevance. The motivation to adopt this strategy is growing, with legislation around the world increasingly requiring consideration of NAMs in decision-making. Significant progress has been made; the extent of tools and mechanistic data available today is staggering and increasingly influencing toxicological practices. As pioneers in NAMs, the genetic toxicology community has the know-how to lead the global community through the last mile to realize regulatory acceptance. Collaborative research to develop and validate NAMS, and multi-sector partnerships to build the frameworks for adoption and demonstrate context of use, have produced powerful genetic toxicology approaches that are effective in decision-making. Modernized strategies include data from high-dimensional test systems (e.g., transcriptomics, cell painting), higher-throughput mechanism-based assays (e.g., MultiFlow, ToxTracker), and novel genomic technologies (e.g., error-corrected sequencing) applied in increasingly sophisticated cell culture models. Frameworks, such as the Clean Sheet and Adverse Outcome Pathways, facilitate data integration across assays and weight of evidence analysis. Quantitative analyses are increasingly applied, supporting a transition from hazard- to risk-based analysis. This presentation will serve as a call-to-action, reviewing and emphasizing foundational strengths, partnerships and examples within the genetic toxicology community that position us to navigate the last mile to transform our testing paradigms.

# Mutation induction in Muta™Mouse following exposure to N-Nitrosodimethylamine (NDMA) with evidence for sub-linear mutation accumulation following repeat dosing

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## Abstract

The N-nitrosamine, NDMA, is an environmental mutagen identified as a contamination impurity in some commonly used drugs, resulting in several product recalls. NDMA was evaluated in an OECD-TG-488 compliant Muta™Mouse assay (28-day oral-dosing) across 7 doses (0.02-4 mg/kg/day) using an integrated study design that assessed mutation at the transgenic lacZ-locus in various tissues and the endogenous Pig-a gene, along with micronucleus frequencies in peripheral blood. Liver pathology was determined together with NDMA disposition. Acute treatments were included to investigate the accumulation and/or additivity of individual dose effects on mutation induction in liver (the most sensitive tissue for rodent mutagenicity and carcinogenicity). NDMA was negative for mutation induction in bone marrow (lacZ) and peripheral blood (Pig-a mutation or micronucleus induction) when tested up to 4 mg/kg/day. There were dose-dependent increases in lacZ mean mutation frequency in liver, lung and kidney following 28-day repeat dosing or in liver after a single dose (10 mg/kg). The No Observed Genotoxic Effect Level (NOGEL) was determined for these tissues. LacZ mutagenicity in liver was not stochastic in terms of mutation additivity with evidence of an overall reduction in mutation frequency following NDMA repeat dosing compared with acute dosing for the same total dose. Liver toxicity was observed (≥1.1mg/kg/day) and these data will be discussed in terms of NDMA exposure, hepatic toxicity, and mutagenicity, including bench-mark dose modelling. The results will be integrated using a putative adverse outcome pathway for nitrosamines and the implications for human risk assessment presented.

# Developing a pragmatic consensus procedure supporting the ICH S1B weight of evidence carcinogenicity assessment

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## Abstract

The ICH S1B carcinogenicity global testing guideline has been recently updated to provide an integrated approach for assessing the human carcinogenic risk of pharmaceuticals (small molecules), based on the use of different weight-of-evidence (WoE) criteria. The WoE factors are evaluated on a case-by-case basis to determine the value and need for conducting a 2-year rat carcinogenicity study.

More than 40 experts from different organizations have joined in an effort to establish a pragmatic consensus procedure supporting the novel integrated assessment described in the ICH S1B guideline. This poster summarizes the status of this standardization activity that aims at ensuring, as much as possible, that this assessment is performed in a transparent, consistent, documented, repeatable, and defendable manner, and thus facilitating the creation and successful submission of the Carcinogenicity Assessment Document. The following elements that are part of the consensus procedure development, will be discussed:

- The relationship among the ICH S1B weight of evidence (WoE) factors is discussed with the goal of highlighting the organization of available evidence that the ICH S1B strategy leverages.

- The WoE factors are analyzed in terms of relevant evidence that supports the decision as to whether the 2-year rat study would add value to the human carcinogenicity assessment. In the case of the target biology WoE factor, a standardized organization of relevant evidence is proposed. In the case of secondary pharmacology, associations of molecular targets with cancer have been explored, i.e., associations between cancer-relevant molecular initiating events/key events and targets included in secondary pharmacology batteries.

- The perspective and the challenges in developing this consensus procedure for the ICH S1B WoE integrated assessment are identified including the need of a pragmatic strategy that incorporates additional investigative approaches and a procedure that is adaptable as science progresses.

# The reconstructed skin MN (RSMN) assay – next steps to improve use and aid implementation

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## Abstract

In vitro genotoxicity assays have been used for decades in regulatory settings as hazard identification tools. When performed as a test battery these assays are highly sensitive, but the specificity is low leading to irrelevant positives when compared to in vivo outcomes. Positive results from the in vitro battery often trigger in vivo follow-up testing, however some industries such as cosmetics are unable to perform such testing due to regulatory constraints. 3D human tissue models have been demonstrated to have the potential to serve as direct replacement of in vivo tests. One such assay is the reconstructed skin MN (RSMN) assay, which has been recommended as an alternative to in vivo follow-up testing of skin relevant compounds. This assay has undergone extensive development and validation and has been accepted into the OECD guideline development program. In our recent work, we have investigated methodological advances to support the use of the assay including incorporation of rat liver S9 and automated analysis. Human skin-specific metabolism is reflected in reconstructed skin models, however there may be scenarios where liver metabolism is expected to be important even for dermally exposed substances. In this context, we evaluated two methods to incorporate rat liver S9 and results will be shown demonstrating that 4-hour S9 exposure is a promising approach. Work will be also shown on the use of imaging flow cytometry to automate the time-consuming analysis portion of the RSMN assay. Automated analysis is expected to increase the speed with which samples can be analyzed, as well as the number of cells scored and thus the statistical power of the assay. Automation would also standardize analysis across different labs further, thereby improving the reproducibility of the method. Both advances presented are expected to increase the utility and support implementation of the RSMN assay into regulatory schemes.

# Key DNA Repair Proteins, Aag and Mgmt, Suppress NDMA-Induced Mutations and Cancer

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## Abstract

*N*-nitrosodimethylamine (NDMA) is a Class 2A carcinogen that has been identified as a contaminant in and near Superfund sites. Additionally, over a dozen drugs have been recalled due to NDMA. When NDMA is metabolized to form a methyldiazonium ion, it reacts with DNA to create 3-methyladenine (3MeA), *O*$^6$-methylguanine (*O*$^6$MeG) and other lesions. While 3MeA is repaired by the Alkyladenine DNA Glycosylase (AAG; a.k.a., MPG), *O*$^6$MeG is repaired by the methylguanine methyltransferase (Mgmt). We have crossed *Aag*-/- mice with mice that harbor transgenes that enable detection of point mutations (gptD) and large-scale sequence rearrangements driven by homologous recombination (using the ROSA26-Direct Repeat [RaDR] transgene). Results show for the first time that unrepaired 3MeA is a strong driver of both point mutations and sequence rearrangements in the liver, and furthermore, that conditions that induce mutations are associated with an increased frequency of tumors. In addition, we have created *Mgmt*-/-;gptD$^{D/D}$;RaDR$^{R/R}$ mice and we have found that *O*6MeG has an even greater impact on susceptibility to NDMA-induced mutations, sequence rearrangements, and tumor incidence. Since the RaDR mice allow for fluorescence detection of recombinant cells, it is possible to do lineage tracing using imaging technologies. Interestingly, in the course of our studies, we discovered that Mgmt also plays a critical role in suppressing NDMA-induced clonal expansion, one of the very earliest steps in cancer development. Results from these studies exhibit innovative mutational burden tracking technology that reveals a stepwise progression by which NDMA ultimately contributes to carcinogenesis. Furthermore, results point to Aag and Mgmt as potential modulators of susceptibility to NDMA-induced cancer.

# Investigating the in vivo genotoxicity of titanium dioxide: a testing strategy for new data generation

Carol Beevers
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## Abstract

The genotoxicity of Titanium dioxide (TiO2) has been the subject of extensive regulatory review within the European Union. Under the REACH legislation for registration of chemicals within Europe, the European Chemicals Agency (ECHA) has identified a concern regarding the safety of TiO2 following exposure via inhalation. In particular, ECHA have focused on the potential for nanoparticles of TiO2 to induce oxidative stress and genotoxicity in the lung. In 2021, the European Food Safety Authority (EFSA) published their opinion on the safety profile of TiO2 with respect to its uses in food (specifically E171). EFSA considered that a genotoxic concern could not be ruled out for TiO2. This prevented EFSA from defining an acceptable daily intake and consequently the use of E171 was no longer considered safe as a food additive. To address the concerns raised by ECHA and EFSA, and to meet the data request of ECHA, the TiO2 industry associations are conducting a program of work designed to generate robust and reliable genotoxicity data to inform these regulatory positions. The studies being conducted will include a series of comet assays with various grades of TiO2 administered via lung instillation and a transgenic rodent gene mutation assay via the oral route with the E-171 grade of TiO2. The considerations regarding the study designs will be discussed and an outline of the proposed plans of work will be presented.

# Utilizing ToxTracker to investigate the toxicological mode-of-action of metals

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## Abstract

The standard *in vitro* genetic toxicity assays evaluate cytogenetic and mutagenic endpoints, but by design they do not inform on biological interactions occurring upstream of the measured adverse event. Understanding these key upstream cellular pathways builds weight of evidence that a material or chemical is (or is not) DNA reactive when faced with a positive genetox test result. Over the last few decades, novel approaches have been engineered to provide mechanistic insight into chemical mode of action. One of these assays, ToxTracker, is a stem cell based GFP reporter system that detects activation of specific cellular signaling pathways to identify direct (i.e., DNA damage) and indirect (i.e., oxidative damage and UPR) genotoxicity. Herein, we present data from ToxTracker on a variety of antimony and cobalt salts, that often have positive *in vitro* and occasional *in vivo* genetox findings, as well as positive rodent carcinogenicity test results. When solubility was not limiting, for nearly all metal compounds tested, significant activation of oxidative damage was observed with no activation of the DNA damage reporters, suggesting a lack of direct DNA reactivity. These data highlight the value of knowing mode of action information when faced with positive genetox test results.

# Updates on the genotoxicity of TiO2

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## Abstract

A brief summary of the conclusions of the Expert Panel review of the genotoxicity of TiO2 (Kirkland et al., 2022) will be presented. This review identified some opportunities for improving the number of highly weighted studies, particularly for endpoints such as gene mutations. Proposals for new studies, including some mandated by the European Chemicals Agency for REACH Substance Evaluation, will be presented by Carol Beevers and John Wills. Some new in vitro gene mutation and micronucleus studies have been performed on grades of (inorganic and organic) coated TiO2 used in cosmetics, and results will be summarised.

In addition, a brief summary of the latest regulatory opinions and current thinking of the pharmaceutical industry on possible replacements for TiO2 will be presented, along with some new initiatives, such as those at GTTC.

# Duplex Sequencing studies to characterize chemical mutagenic mechanisms in mouse somatic tissues and germ cells

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## Abstract

Duplex Sequencing (DS) is rapidly gaining acceptance as a powerful tool for in vivo mutagenesis studies and as a valid alternative to transgenic rodent models such as the MutaMouse. Initial studies conducted in our laboratory have shown the utility of DS for characterizing mutation frequencies and spectra in somatic tissues, such as bone marrow. These studies utilized the Twinstrand's mouse mutagenesis panel of 20 targets spread across autosomal chromosomes totally ~48 kb of genomic DNA. Dose-response studies with benzo(a)pyrene (BaP) and procarbazine (PRC) showed that DS produced results that are qualitatively and quantitatively comparable to those obtained with the Organization for the Economic Co-operation and Development-endorsed lacZ assay. DS generated distinct mutation spectra for BaP and PRC consistent with the known mutagenic mechanism of action of each compound. Moreover, DS highlighted a protective role for transcription-coupled repair that resulted in lower mutation frequencies in genic versus intergenic targets. We have now evaluated the ability of DS to detect chemically induced mutations in germ cells. Studies with N-ethyl-N-nitrosourea and PRC showed significant dose-related increases in germ cell mutations for both chemicals. Interestingly, it appears that animal-to-animal variability in mutation frequencies is higher in germ cells than in bone marrow and that there are slight differences in the PRC mutation spectrum between germ cells and bone marrow. These results suggest that DS is a promising approach for characterizing chemical mutagenesis in both somatic tissues and germ cells and that mutagenic mechanisms operating in germ cells may differ from those in somatic tissues.

# DNA Repair-Profiler, a new in vitro assay for DNA repair and genotoxic mode of action assessment

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## Abstract

Genotoxicity testing is an important part of risk assessment and involves the induction of gene mutations, chromosomal aberrations, and numerical chromosomal changes. Understanding the mode of action (MOA) of genotoxic substances can provide insight into the type of DNA damage that is induced by the compound and is relevant for adverse outcome pathways and weight of evidence approaches. Understanding the MOA can be important for the characterization of novel drugs, for example in oncology.

Identification of the specific DNA repair pathways that are relevant for protection against the detrimental effects of genotoxic substances can provide insight into the type of DNA damage that is induced by a compound. The DNA Repair-Profiler assay can be applied to study the impact of DNA repair on cell viability, genome stability and gene mutation induction following exposure to genotoxic compounds. DNA Repair-Profiler consist of a unique collection of mammalian cell lines, each with a deficiency in one of the major DNA repair pathways.

Here, we showed how DNA Repair-Profiler can be used to build evidence for adverse outcome pathways by determining which DNA repair pathways are involved in repairing oxidative damage induced by methyl methane sulfonate (MMS) and potassium bromate (KBrO3).

# Extension of the CADRE Platform: A Quantum-Mechanical Tool for Predicting the Carcinogenic Potency of N-Nitroso Impurities in Pharmaceuticals

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## Abstract

N-nitroso contaminants (NOCs) in medicinal products are of concern due to their high carcinogenic potency; however, not all of these compounds are created equal, and some are relatively benign chemicals. Here, we report on the utility of the CADRE (Computer-Aided Discovery and REdesign) *in silico* platform, used broadly by the pharmaceutical and personal care industries, and highlight its recent extension to predict carcinogenic potency of NOCs. The present model distinguishes NOCs in three potency categories (potent COC, i.e. cohort-of-concern, compounds, $TD_{50} \leq 0.15$ mg/kg; COC compounds, $0.15 < TD_{50} \leq 1.5$ mg/kg; and low-potency compounds, $TD_{50} > 1.5$ mg/kg) with 77% accuracy in external testing, which surpasses reproducibility of rodent cancer bioassays. Our categorial LDA (linear discriminant analysis) models are further supported by MLRs (multivariate linear regressions) that predict TD50 values for COC NOCs. Robustness of predictions for more complex pharmaceuticals is maximized by capturing key SARs using quantum mechanics (QM), i.e., by hinging the model on the underlying chemistry (vs. chemicals in the training set) via computation of both global and atom-based electronic properties related to kinetic and thermodynamic stability of NOCs. We show that the rate of model mis-predictions does not increase when exceeding applicability domain limits and that the robustness of predictions spans all classes and mechanisms of NOCs. To further boost confidence in applying this model, CADRE computes confidence scores, indicating relative reliability of predictions given the landscape of well-studied N-nitrosamines. Considering its mechanistic transparency, the use of QM to capture NOC metabolism, and the continued robust performance of CADRE for other endpoints in external testing by the pharmaceutical industry, the present approach can be confidently leveraged in quantitative hazard assessments of NOC carcinogenicity to either flag potent carcinogens or to de-risk relatively benign analogs.

# Mechanisms of Genomic Rearrangements: How Hexavalent Chromium, a Major Environmental Concern, Induces Chromosome Instability

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## Abstract

Chromosome instability (CIN) is a driving mechanism in lung cancer, with lung tumors characterized by altered chromosome numbers and rearranged chromosome structures. Homologous recombination repair (HR) is a key pathway that protects cells against CIN as it repairs DNA double strand breaks with high fidelity. Cr(VI) causes human lung cancer; however, its carcinogenic mechanisms are poorly understood. Cr(VI) induces DNA double strand breaks and CIN indicating Cr(VI) may inhibit HR repair. We found Cr(VI) targets RAD51, the protein at the center of the signature step in HR, the formation of the RAD51 nucleoprotein filament, which facilitates the search for a homologous sequence and invasion of the template DNA strand. We found acute Cr(VI) exposure induced the canonical HR repair response, while prolonged Cr(VI) exposure inhibited HR repair and disrupted RAD51 nucleofilament formation. In fact, prolonged Cr(VI) exposure had a profound effect on RAD51: a) inhibiting its function, b) reducing the amount and quality of filament formed, c) altering its subcellular localization and d) reducing its protein and mRNA levels. Moreover, we found the loss of repair and the loss of RAD51 response was a permanent phenotypic change. These outcomes support our hypothesis that the mechanism of particulate Cr(VI)-induced lung cancer involves loss of DNA repair resulting in increased chromosome instability, which has important implications for Cr(VI)-induced cancer and lung cancer in general. This work was supported by the National Institute of Environmental Health Sciences [grants R01ES016893 & R35ES032876 to JPWSr.].

# Selectivity And Specificity Of Food-Additive Titanium Dioxide For Lysomac Immune Cells Of The Small Intestine

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## Abstract

Peyer's patch lymphoid follicles of the small intestine coordinate mucosal and systemic immune responses to the microbiome, food and oral vaccines. In humans, these follicles are also known to accumulate persistent environmental particulates, including titanium dioxide which is taken up largely from ingestion of processed foods and pharmaceuticals. These particles have been shown to accumulate in metabolically and immunologically dormant 'pigment cells' located at the base of the follicle. Here we show that another site of $TiO_2$ accumulation exists – specifically, the immunologically active subepithelial dome region of the Peyer's patch with the 'lysomac' macrophage subset bearing the entire load. We could recapitulate this human scenario in a mouse model using a diet supplemented with food-grade titanium dioxide. Correlative mouse-human dosimetry was achieved via quantitative image analysis of cell and vesicle loading using light and electron microscopy with single-particle detection. Microfold cells in the follicle-associated epithelium were the gateway between the intestinal lumen and the lysomac immune cells with uptake in this specific tissue region being at least three orders of magnitude greater than the regular villous mucosa.

Intestinal Peyer's patches are integral to the gut-associated lymphoid system and have evolved to sample gut-luminal antigen to orientate mucosal and systemic antibody responses. These findings demonstrate that, in humans, this is now happening in the presence of manmade and persistent fine-particle adjuvants of dietary and pharmaceutical excipient origin. We demonstrate how real-world human exposures to $TiO_2$ can be recapitulated in a mouse model offering improved potential for robust safety assessments.

# Arsenic is a potent co-mutagen of ultraviolet light

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## Abstract

Environmental co-exposures are widespread and are major contributors to carcinogenic mechanisms. Two well-established environmental agents causing skin cancer are ultraviolet radiation (UVR) and arsenic. Arsenic is a known co-carcinogen that enhances UVR's carcinogenicity, but the mechanisms are unclear. We utilized primary human keratinocytes and a hairless mouse model to investigate the carcinogenic and mutagenic properties of co-exposure. On its own, arsenic is neither mutagenic nor carcinogenic. However, in combination with UVR, arsenic exposure has a synergistic effect leading to an accelerated mouse skin carcinogenesis as well as to more than 2-fold enrichment of UVR mutational burden. Notably, mutational signature ID13, previously found only in UVR-associated human skin cancers, was observed exclusively in mouse skin tumors and cell lines jointly exposed to arsenic and UVR. This signature was not observed in any model system exposed purely to arsenic or purely to UVR, making ID13 the first co-exposure signature to be reported using controlled experimental conditions. Analysis of existing genomics data from basal cell carcinomas and melanomas revealed that only a subset of human skin cancers harbor ID13 and these cancers exhibited an elevated UVR mutagenesis. Our results provide the first report of a unique mutational signature caused by a co-exposure to two environmental carcinogens and the first comprehensive evidence that arsenic is a potent co-mutagen of UVR. Importantly, our findings suggest that a large proportion of human skin cancers are not formed purely by UVR exposure but rather due to a co-exposure of UVR and other co-mutagens such as arsenic.

# EMA-Mutamind Analysis of Drug Substance Related Nitrosamines

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## Abstract

N-nitrosamines (NAs) are generally considered to be potentially mutagenic and have been classified as a "cohort of concern" in the ICH M7 guideline. Their metabolic activation may lead to the formation of DNA adducts, which in turn may result in mutations, DNA strand breaks and eventually cancer. While many N-nitrosamines are carcinogenic, their potency varies significantly, and some are neither carcinogenic nor mutagenic. In 2022, the European Medicines Agency (EMA) funded three “Mutamind” projects to investigate N-nitrosamine activity and potency with a special focus on Nitrosamine Drug Related Substance Impurities (NDSRIs). These included the: nitrosamine QSAR project, in vitro testing project, and endogenous nitrosation project. The aim of the QSAR project is to investigate metabolic activation, DNA adduct formation and DNA repair mechanisms to distinguish NA classes with distinct mutagenic potency and support NA potency prediction. The aim of the in vitro testing project is to optimize Ames test conditions for mutagenicity testing of NAs and to evaluate the in vitro alkaline Comet assay with liver cell models (HepG2 cells, primary rat and human hepatocytes) for detection of carcinogenic NAs. The aim of the endogenous nitrosation project is to investigate the impact of physiological conditions on the emergence of nitrosamines from APIs, in particular direct introduction of the nitroso group into the API molecule. A summary of the projects will be presented with a focus on a recent data gap analysis, and recent experimental testing results.

# Potential mechanisms of tungsten-induced carcinogenesis

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## Abstract

Tungsten is increasingly used in manufacturing items including construction equipment, ammunitions, jewelry, and medical devices. Due to increased usage, there is also increased exposure occupationally and to end-users. Tungsten exposure has also been linked with a pediatric leukemia cluster, primarily consisting of acute preB lymphocytic leukemia cases. Despite this, there is very little known regarding the toxicities associated with tungsten exposure. We have been investigating the effects of tungsten on developing B cells. We have shown that tungsten accumulates in the bone, likely as phospho-tungstate, and exposure alters B lymphocyte signaling and development within the bone marrow. In vitro and in vivo, tungsten exposure results in increased gH2AX expression. Our current data indicate that tungsten does not induce DNA damage alone, but enhances DNA damage induced by other agents, suggesting an effect on DNA damage repair. Indeed, we find that tungsten inhibits both homologous repair and non-homologous end joining in reporter assays. Thus, tungsten may enhance DNA damage, both via endogenous and exogenous inducers, by inhibition of the DNA damage response.

# Framework for Establishing Acceptable Intakes for Drug Substance Related N-Nitrosamines

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## Abstract

There is an urgent need to establish an agreed framework to support the rapid derivation of acceptable intakes (AIs) for drug substance related N-Nitrosamines. The urgency relates to the complex challenge that has emerged in the process of evaluating commercial pharmaceutical products for the presence or formation of N-nitrosamines. There are several factors that contribute to the current state of this challenge including the prevalence of drug products that require a formal N-nitrosamine risk assessment, lack of agreement on a framework for establishing acceptable intakes, lack of agreement on an Ames protocol to characterize the mutagenic/carcinogenic potential of N-nitrosamines, limited global availability and extended timelines to conduct in vivo transgenic mutation assays. Altogether, this translates to a high degree of uncertainty that an AI will be agreed with regulatory authorities on a timescale that assures continued supply of medicines to patients. Given the current challenges the European Federation of Pharmaceutical Industries and Associations (EFPIA) has developed a decision tree to support rapid assignment of conservative AIs to drug substance related N-nitrosamines. The "branches" of the decision tree, which support AI assignment are based on the outcome of the Ames assay (if data is available), as well as current knowledge of SAR. This decision tree approach and the scientific basis for each of the proposed AIs will be presented.

# Genotoxicity Predictions for Rapid Compound Screening: A Case Study for Accurate Classification using Machine Learning

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## Abstract

One of Genetic Toxicology's function is to identify compounds that have the potential to cause chromosomal damage. The standard regulatory method is the manual microscopic micronucleus assay. Micronucleus can manifest itself via various mechanisms such as non-genotoxic and genotoxic, and genotoxicity can be further classified as clastogen (chromosome fragments-containing micronuclei) or aneugen (full chromosome-containing micronuclei). Aneugens can be further subclassified as tubulin binders and aurora inhibitors. Follow-up assays are routinely needed to differentiate various mode of actions (MoAs) in regulatory settings. Mechanistic information is extremely important as it dictates the compound progression through development. Clastogens cannot progress unless indication justify versus aneugen effects are thresholded, with large enough safety margins, aneugens are considered non-genotoxic at therapeutic concentration and is safe to progress. In this study, we used 101 well-characterized compounds with their full dose response in all 10 endpoints to generate a tiered-random forest modeling approach guided by the established adverse outcome pathways. The predictive power of our model is the highest to distinguish aurora inhibitors from tubulin binders (98% accuracy), followed by non-genotoxicants from genotoxicants (90% accuracy). Our model can differentiate clastogens from aneugens with 75% accuracy. We prospectively monitored our model predictions for several months and we have similar accuracy for all models. The presentation will describe how this prediction tool is being used by genetic toxicologist at Pfizer to screen and classify compounds with a lower genotoxicity risk faster.

# In vivo genotoxicity assessment of N-nitrosodiethylamine with Error-Corrected Next-Generation Sequencing

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## Abstract

The unrepaired DNA damage caused by some substances can be fixed into genome in the form of mutations and result in a variety of diseases including cancer in animals. N-nitrosamines are categorized as a "cohort of concern" in ICH M7 based on the carcinogenicity of some compounds within this class. The development of Duplex Sequencing (DS) technology allows direct measurement of mutations in any genomic region with high accuracy. Here we assessed the mutations caused in the low dose region of N-nitrosodiethylamine (NDEA) in 20 arbitrarily selected regions in rodent genome with DS. The Big Blue® rats were administered at doses of 0.001, 0.01, 0.1, 1 and 3 mg/kg/day NDEA by oral gavage for 28 days followed by 3 days of fixation. No increases in the mutation frequencies (MF) were detected in the liver of rodents exposed to NDEA equal to or lower than 0.01 mg/kg/day. Treatment of rodents with 0.1, 1 and 3 mg/kg/day NDEA included 1.8-fold, 7.6-fold and 15-fold increases in the MF over the vehicle control, respectively. The benchmark dose (BMD) analysis of the DS data shows a BMDL50 of 0.04 mg/kg/day, slightly higher than the BMDL10 of 0.022 mg/kg/day calculated by increased incidence of liver tumors in Colworth-Wistar rats. NDEA treatment also induced a dose related change in the mutational spectra with A:T>G:C found to be the predominant mutation. The trinucleotide spectra caused by NDEA exposure match a mutational signature frequently found in rodent liver tumors. Very similar results were also observed in Big Blue® mice under the same NDEA treatment conditions. This work shows that DS can provide useful mechanistic information in the genotoxicity assessment of nitrosamines for the prediction of potential carcinogenic outcome.

# In vivo genotoxicity assessment of N-nitrosodiethylamine with Error-Corrected Next-Generation Sequencing

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## Abstract

Animal studies are a critical component in biomedical research, pharmaceutical product development, and regulatory submissions. There is a worldwide effort in toxicology toward "reducing, refining, and replacing" animal use. Here, we proposed a deep generative adversarial network (GAN)-based framework capable of deriving new animal results from existing animal studies without additional experiments. To prove the concept, we employed this Tox-GAN framework to generate both gene activities and expression profiles for multiple doses and treatment durations in toxicogenomics (TGx). Using the pre-existing rat liver TGx data from the Open Toxicogenomics Project-Genomics-Assisted Toxicity Evaluation System (Open TG-GATES), we generated Tox-GAN transcriptomic profiles with high similarity (0.997 ± 0.002 in intensity and 0.740 ± 0.082 in fold change) to the corresponding real gene expression profiles. Consequently, Tox-GAN showed an outstanding performance in 2 critical TGx applications, gaining a molecular understanding of underlying toxicological mechanisms and gene expression-based biomarker development. For the former, over 87% agreement in Gene Ontology was found between Tox-GAN results and real gene expression data. For the latter, the concordance of biomarkers between real and generated data was high in both predictive performance and biomarker genes. We also demonstrated that the Tox-GAN models constructed with the Open TG-GATES data were capable of generating transcriptomic profiles reported in DrugMatrix. Finally, we demonstrated potential utility for Tox-GAN in aiding chemical-based read-across. To the best of our knowledge, the proposed Tox-GAN model is novel in its ability to generate in vivo transcriptomic profiles at different treatment conditions from chemical structures. Overall, Tox-GAN holds great promise for generating high-quality toxicogenomic profiles without animal experimentation.

# Approaches for evaluating the quality of historical negative control data: *Pig-a* examples

Stephen Dertinger
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## Abstract

Historical negative control data (HCD) have played an increasingly important role in interpreting the results of genotoxicity tests. A workgroup of the International Workshops for Genotoxicity Testing (IWGT) was convened in 2022 to provide recommendations on this crucial topic. Among the workgroup's conclusions is that HCD can provide useful context for interpreting study results, but this requires supporting evidence that i) HCD were generated appropriately, and ii) their quality has been assessed and deemed sufficiently high for this purpose. This workshop will focus on several techniques for evaluating the quality of HCD. While other approaches may be useful, we will focus on Control Charts, Stability Index, and Variance Components Analysis. These demonstrations will be based on *Pig-a* HCD. The exercises will culminate with the calculation of an interval that describes the historical control distribution of mutant phenotype reticulocytes, and the interval will be used to contextualize results from hydroxyurea and aristolochic acids rat studies.

# From Theory to Practice: Use of Computational Methods for Nitrosamine Assessments

Suman Chakravarti
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## Abstract

The lack of carcinogenicity data greatly hinders the evaluation of NDSRI like complex nitrosamines. Although small nitrosamines with animal carcinogenicity data are currently being used in surrogate-based SARs, limited range of their structural features make them a poor representative of the NDSRIs. This raises the question of whether these small nitrosamines alone can provide a reliable basis for assessing the carcinogenic potency of numerous NDSRIs. In this presentation, we will explore various facets of state-of-the-art surrogate search and evaluation methods. We will also introduce a novel method for predicting the α-carbon hydroxylation potential of N-nitrosamines, which takes advantage of much larger experimental non-nitrosamine xenobiotic metabolism datasets, identifies and quantifies the impact of numerous key structural features, and alleviates the critical issue of data scarcity. This approach may ultimately complement existing methods and help improve nitrosamine risk assessment.

# Using Adverse Outcome Pathways as a Framework for Carcinogenicity Assessment in ICH S1B(R1)

Susanne Stalford
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## Abstract

The relevance, cost, and ethical implications of using rodent studies in the prediction of human carcinogenicity has been questioned, prompting moves to investigate alternative methods of testing in many domains. According to the ICH S1B(R1) addendum, evidence gathered throughout the pharmaceutical development process can be organised into a weight of evidence relating to six factors and conclusions drawn to reduce the animals required. Large amounts of complex evidence may need to be resolved using this approach and knowledge of modes-of-action and data gaps are important to determine human relevance and certainty. Hence a framework to support this assessment will be useful. Adverse outcome pathways (AOPs) provide the perfect means of addressing those needs. Using the structure the AOP concept provides, an approach to assess the evidence for ICH S1B(R1) to aid decision-making has been developed, using multiple in vitro and in vivo assays and in silico predictions organised around 34 AOPs relating to cancer. This system has the advantage of being able to give consistent results as knowledge and data are logically organised, decreasing uncertainty in outcomes. This framework is also naturally adaptable, as inclusion of new approach methodologies and additional data can be achieved without a change to the framework protocol. Finally, transparency of the system allows for the probing of evidence in expert review, thus ensuring outcomes are scientifically robust. An overview of this approach along with an example of how it may be used to fulfil the new ICH S1B R1) addendum will be presented.

# ICH S1B(R1): US regulatory perspectives on the new Weight of Evidence approach

Timothy McGovern
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## Abstract

The ICH S1B(R1) Addendum was formally implemented by FDA in November 2022. This Addendum introduces an additional approach for assessing the human carcinogenic risk of pharmaceuticals that evaluates specific weight of evidence (WoE) criteria to inform whether a 2-year rat study is a likely to add value to a human carcinogenicity risk assessment. The key WoE criteria include data that inform the carcinogenic potential based on drug target biology and the primary pharmacologic mechanism; results from secondary pharmacology screens that inform selectivity and off-target potential; histopathology data from repeated-dose toxicology studies with an emphasis on the 6-month rat study; evidence for hormonal perturbation and immune modulation; and genetic toxicology study data. This presentation will provide a high level overview of the recommendations included in the addendum and the limited FDA experience to date in evaluating WoE assessments.

# Sources of variability in the *Pig-a* assay and how to control them

Vasily Dobrovolsky
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## Abstract

Rodent RBC *Pig-a* assay has been firmly established as a tool for nonclinical safety evaluations of novel pharmaceuticals intended for use in humans. OECD Test Guideline (TG) No. 470 for performing mammalian erythrocyte *Pig-a* gene mutation assay and interpreting its results was published in June 2022. While the TG itself and the references therein contain exhausting information on the inner workings of the *Pig-a* assay, still there might be a need for a simple and straightforward visual explanation how the assay is performed, what exactly it detects, and what steps should be paid attention to in order to generate high-quality results. The workshop presentation will be covering some of these basics with examples from personal experience. Also, specific situations when the use of the *Pig-a* assay might be the most suitable will be briefly discussed.

# Use of Chicken egg assay as an animal alternative testing model to evaluate the genotoxic potential of Drugs and chemicals.

Yax Thakkar
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## Abstract

The genotoxic potentials of four α,ß-unsaturated aldehyde fragrance materials, 2-phenyl-2-butenal, nona-2-trans-6-cis-dienal, 2-methyl-2-pentenal and p-methoxy cinnamaldehyde, were assessed in avian fetal livers using the Chicken Egg Genotoxicity Assay (CEGA). CEGA utilizes the comet assay to detect DNA strand breaks in combination with 32P-nucleotide post labeling (NPL) assay which detects DNA adducts. Quinoline was used as a positive control. The clastogenic/aneugeneic potential of the aforementioned materials was evaluated in the Hen's egg micronucleus (HET-MN) assay. Materials were selected for testing based on their chemical structures together with the results in regulatory approved in vitro and/or in vivo genotoxicity studies conducted according to OECD guidelines. Three out of four tested fragrance materials were negative in CEGA COMET/NPL assay as evident from negative comet, NPL results, and all the materials were negative in HET-MN assay. The findings in the egg models were also congruent with the results of regulatory in vivo genotoxicity assays. In contrast, p-methoxy cinnamaldehyde in both avian models produced DNA damage, including DNA strand breaks, adducts, while it was negative in the in vivo COMET assay. The difference in results between in ovo and in vivo assays can be related to differences in bioactivation of p-methoxy cinnamaldehyde by avian and rodent livers. For example, rapid glutathione depletion could be an important factor. Further experiments conducted by pre-treatment with N-acetyl cysteine reversed the positive outcome in COMET assay suggesting glutathione depletion was the factor generating misleading positive outcome. Overall, our findings support the conclusion that CEGA and/or HET-MN can be considered as a potential alternative to animal testing strategies for assessment of genotoxic potential of fragrance materials, as a follow-up for materials that produce positive outcomes in vitro .

# Poster Abstracts

## P01

# An interlaboratory validation trial of the ToxTracker Assay for Genotoxic Mode of Action Assessment according to OECD guidelines.

Giel Hendriks[1], Els Adriaens[2], Ashley Allemang[3], Jan van Benthem[4], Julie Clements[5], Gabrielle Cole[6], Maria Engel[7], Annie Hamel[8], Darren Kidd[5], Stephanie Kellum[9], David Kirkland[10], Tomomi Kiyota[6], Abby Myhre[9], Valerie Naessens[11], Stefan Pfuhler[3], Marise Roy[8], Raja Settivari[9], Maik Schuler[7], Philippe Vanparys[12], Andreas Zeller[11]
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## Abstract

ToxTracker is a mammalian stem cell-based reporter assay that detects activation of specific cellular signaling pathways upon chemical exposure. ToxTracker contains six different GFP-tagged reporter cell lines that together allow the accurate identification of genotoxic substances and discrimination between induction of DNA damage, oxidative stress and/or protein damage in a single test. More recently, the assay was extended to allow the discrimination between clastogenic and aneugenic compounds.

The ToxTracker assay is currently being evaluated in a large international inter-laboratory validation study, approved by the OECD. The goal of this prospective validation study is to explore the applicability of ToxTracker for regulatory applications, establish the transferability and reproducibility of the assay and to explore how it can be applied to improve the in vitro genotoxicity testing strategies. The validation has been conducted strictly following OECD guidance document 34.

ToxTracker was transferred to seven laboratories. The validation labs were trained to perform the assay and tested a training set of compounds to show their proficiency to run ToxTracker. Next, the labs evaluated a selection of 64 coded, well-established genotoxic and non-genotoxic chemicals with each compound being tested in three labs independently. All the experimental work has been completed and data have been analyzed. The accuracy to predict genotoxicity, as well as the intra- and inter-laboratory reproducibility were determined. In this poster, we will give an overview how the ToxTracker validation was performed and the most important results from this interlaboratory validation.

## P02

# Defining boundaries: which *N*-nitroso compounds might not belong in the cohort of concern?

Robert Foster, David Ponting
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### Abstract

Originally coined by Kroes et al, the term 'cohort of concern' is typically used to refer to chemical classes considered to be high-potency carcinogens. ICH M7 dictates that genotoxic impurities belonging to the cohort of concern (aflatoxin-like, alkyl azoxy and *N*-nitroso) require a compound-specific assessment, as there is appreciable carcinogenic risk below the general 1.5 ug/day TTC limit. The structural definitions of these classes remain vaguely defined by name only; *N*-nitroso compounds are broadly represented by N-N=O. This seems appropriate considering recent pharmaceutical recalls due to dialkyl *N*-nitrosamine impurities, some of which are at least two orders of magnitude more potent than the TTC. However, around half the *N*-nitroso compounds analysed have lower carcinogenic potency than the TTC. High potency is attributed to those *N*-nitroso compounds mechanistically capable of undergoing facile alpha-hydroxylation to form a diazonium ion in close proximity to DNA. Through industry-wide collaborations, an understanding of structural features which mitigate activity has been curated and used to suggest subclasses of *N*-nitroso compounds which are not predicted to exhibit high carcinogenic potential. Refinement of the structural definition of the cohort should allow *N*-nitroso compounds with low carcinogenic risk to reside outside the cohort of concern and be assessed in the same manner as other chemical impurities under ICH M7 without increasing the risk to human health.

## P03

# Developing a pragmatic consensus procedure supporting the ICH S1B weight of evidence carcinogenicity assessment

Arianna Bassan[1], Paul Bradley[2], Jon Chambers[2], Kevin P. Cross[3], Brenda Finney[2], Frances Hall[2], Candice Johnson[3], Douglas A. Keller[4], Raymond R. Tice[5], Glenn J. Myatt[6]
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### Abstract

The ICH S1B carcinogenicity global testing guideline has been recently updated to provide an integrated approach for assessing the human carcinogenic risk of pharmaceuticals (small molecules), based on the use of different weight-of-evidence (WoE) criteria. The WoE factors are evaluated on a case-by-case basis to determine the value and need for conducting a 2-year rat carcinogenicity study.

More than 40 experts from different organizations have joined in an effort to establish a pragmatic consensus procedure supporting the novel integrated assessment described in the ICH S1B guideline. This poster summarizes the status of this standardization activity that aims at ensuring, as much as possible, that this assessment is performed in a transparent, consistent, documented, repeatable, and defendable manner, and thus facilitating the creation and successful submission of the Carcinogenicity Assessment Document. The following elements that are part of the consensus procedure development, will be discussed:

- The relationship among the ICH S1B weight of evidence (WoE) factors is discussed with the goal of highlighting the organization of available evidence that the ICH S1B strategy leverages.

- The WoE factors are analyzed in terms of relevant evidence that supports the decision as to whether the 2-year rat study would add value to the human carcinogenicity assessment. In the case of the target biology WoE factor, a standardized organization of relevant evidence is proposed. In the case of secondary pharmacology, associations of molecular targets with cancer have been explored, i.e., associations between cancer-relevant molecular initiating events/key events and targets included in secondary pharmacology batteries.

- The perspective and the challenges in developing this consensus procedure for the ICH S1B WoE integrated assessment are identified including the need of a pragmatic strategy that incorporates additional investigative approaches and a procedure that is adaptable as science progresses.

## P04

# Using Adverse Outcome Pathways as a Framework for Carcinogenicity Assessment in ICH S1B(R1)

Susanne Stalford
Lhasa Limited, Leeds, United Kingdom

### Abstract

The relevance, cost, and ethical implications of using rodent studies in the prediction of human carcinogenicity has been questioned, prompting moves to investigate alternative methods of testing in many domains. According to the ICH S1B(R1) addendum, evidence gathered throughout the pharmaceutical development process can be organised into a weight of evidence relating to six factors and conclusions drawn to reduce the animals required. Large amounts of complex evidence may need to be resolved using this approach and knowledge of modes-of-action and data gaps are important to determine human relevance and certainty. Hence a framework to support this assessment will be useful. Adverse outcome pathways (AOPs) provide the perfect means of addressing those needs. Using the structure the AOP concept provides, an approach to assess the evidence for ICH S1B(R1) to aid decision-making has been developed, using multiple in vitro and in vivo assays and in silico predictions organised around 34 AOPs relating to cancer. This system has the advantage of being able to give consistent results as knowledge and data are logically organised, decreasing uncertainty in outcomes. This framework is also naturally adaptable, as inclusion of new approach methodologies and additional data can be achieved without a change to the framework protocol. Finally, transparency of the system allows for the probing of evidence in expert review, thus ensuring outcomes are scientifically robust. An overview of this approach along with an example of how it may be used to fulfil the new ICH S1B R1) addendum will be presented.

## P05

# Target Carcinogenicity Assessment

Glenn Myatt[1], Arianna Bassan[2], Paul Bradley[3], Jon Chambers[3], Kevin Cross[1], Brenda Finney[3], Frances Hall[3], Candice Johnson[1]
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### Abstract

The recently introduced ICH S1B addendum (integrated with the original S1B guideline on 4th August 2022) includes a new weight of evidence (WoE) assessment to determine whether performing the rat study would add value to the assessment of human carcinogenic risk. The guideline describes six WoE factors ((1) target biology, (2) secondary pharmacology, (3) histopathology chronic studies, (4) hormonal effects, (5) genotoxicity, (6) immune modulation). This poster will outline how the first WoE factor discussing target carcinogenicity assessment (TCA) could be implemented in a consistent, transparent, and dependable manner. The poster will focus on: a) how to assemble empirical carcinogenicity data on chemicals within the same primary pharmacological class; b) how to assess that the primary pharmacological pathways are well-characterized and there is no potential involvement in cancer development; c) how to evaluate whether there are any relevant carcinogenicity risks related to the pharmacology of any major human metabolites. Notably, this analysis underlying TCA is based on a well-defined workflow (discussed in the poster) to collate relevant evidence from literature and database searches.

## P06

# Integrating a Multiplexed Flow Cytometric Assay and Toxicogenomic Signature for Predictions of Genotoxic Potential

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## Abstract

Genotoxicity assessment is a critical component of nonclinical safety assessment as it helps to predict the mutagenic/carcinogenic potential of compounds of interest. Standard genetic toxicology battery assays are used to fulfill these regulatory requirements and the results are used as part of a risk:benefit analysis. However, these results are usually binary with limited information on the mechanisms underlying the genetic damage. Therefore, we sought to develop an in vitro genotoxicity assay with novel biomarker analysis. Our newly developed genotoxic testing battery consists of the in vitro Litron MultiFlow DNA Damage Assay which multiplexes γH2AX, p53, phospho-histone H3, cleaved PARP, and polyploidization biomarkers into a single flow cytometric analysis. This is coupled with the Toxicogenomic DNA Damage Inducing (TGx-DDI) transcriptomic biomarker for a more comprehensive genotoxicity assessment. We optimized our assay in human TK6 cells and utilized a set of chemicals with previously described aneugenic, clastogenic, or non-genotoxic modes of action (MoA). Data from early and late drug exposures, 4 hrs and 24 hrs respectively, were used to uncover key biomarkers and the time points that are most critical for classifying their MoA. Integrating these biomarker response data was found to group certain chemicals based on their reported MoA and machine learning approaches were found to predict genotoxic MoA with a higher sensitivity and specificity than previously described in the field.

## P07

# Data Gap Analysis of N-Nitrosamines Supporting Structure-Activity Relationships

Kevin Cross[1], Anke Londenberg[2], Sylvia Escher[2], Christina Ziemann[2], Michelle Djuari[2], Markus Christmann[3], Jörg Fahrer[4], Roland Frötschl[5], Bodo Haas[5], Matthias Vogel[5]
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## Abstract

N-nitrosamines (NAs) are generally considered to be mutagenic and have been classified as a "cohort of concern" in the ICH M7 guideline. Their metabolic activation may lead to the formation of DNA adducts, which in turn may result in mutations, DNA strand breaks and cancer. While many NAs are carcinogenic, their potency varies significantly, and some are neither carcinogenic nor mutagenic. In 2022, the European Medicines Agency (EMA) funded three “Mutamind” projects to investigate N-nitrosamine activity and potency with a special focus on characterizing N-Nitrosamine Drug Related Substance Impurities (NDSRIs). The “QSAR for Nitrosamines“ Mutamind project aims to better understand the relevant NA biological processes including the identification of enzymes involved in metabolic activation, DNA adduct formation, kinetics and repair processes. This analysis, including additional in vitro experimental testing, will support development of a structure-activity relationship (SAR) model for prediction of NAs carcinogenicity potency of NDSRIs. Currently, the project has identified existing knowledge and data gaps. A systematic literature search has revealed over 300 publications on NAs on DNA repair and adduct formation, metabolic activation and mutagenic activity in Ames, Comet and rodent carcinogenicity assays. Data models were developed for each endpoint specifying the tested NA, the study design, and the study outcomes. Mechanistically diverse NAs for testing were characterized using a local similarity fingerprint. Comprehensive data were available for only a few, structurally diverse and NDSRIs. The project will test 19 NDSRIs to help fill in the gaps to better support SAR models for NA potency prediction.

## P08

# In Silico Genotoxicity Predictions for the Hazard Assessment of Photoinitiators Used in Food Packaging

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## Abstract

New data indicates that, for some intended uses, photoinitiators applied to the exterior of food packaging may migrate to food. Photoinitiators are molecules that create reactive species when exposed to radiation and are widely used in UV-cured printing inks applied to the exterior of food contact materials (e.g., coatings and varnishes). The purpose of this project is to perform the hazard identification step of the safety assessment paradigm for ~100 photoinitiators potentially used in printing ink substances for food packaging. A new approach methodology (NAM) was utilized using the ChemTunes-ToxGPS database and in silico workflows to determine the Cramer classification and genotoxicity predictions for each of the identified photoinitiators. The Cramer Decision Tree uses chemical structure and predicted chemical reactivity of a substance to categorize substances into three classifications with Class III substances representing the highest predicted toxicological hazard. Based on the Cramer classifications and predicted genotoxicity, the photoinitiators were prioritized to determine those photoinitiators that need further investigation for available toxicity data, intended use, potential migration into food, and possible consideration for further regulation. This qualitative hazard identification approach supports the Agency's mission of incorporating the 3 R's into safety assessments (i.e., Replacement, Reduction, and Refinement) for promoting ethical research, testing, and education using animals. Future work will be to use this NAM approach to characterize and prioritize an estimated >5,000 ink substances and ink components potentially used in printing inks applied on the exterior of food packaging in U.S. markets.

## P09

# R-loop-mediated recruitment of cohesin and CTCF as a potential regulator of 3-D genome structure and DNA repair

Elizabeth Irvin[1,2], Parminder Kaur[1,3], Lai Yee Phoon[4,5], Boya Gao[4,5], Zhubing Shi[6], Anders Hansen[7], Hongtao Yu[6], Li Lan[4,5], Hong Wang[1,2,3]
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## Abstract

3-D genome structure during interphase plays important roles in regulating transcription and DNA repair, and its maintenance is pivotal for promoting genomic stability. Emerging evidence supports a model in which the cohesin complex, assisted by NIPBL, mediates topologically associating domains (TADs) and DNA loops through progressive DNA loop extrusion. CCCTC-binding factor (CTCF) is proposed to stall cohesin-NIPBL mediated DNA loop extrusion and stabilize the loop at CTCF binding sites converging at the loop base. Our lab previously found that cohesin's mutually exclusive SA1 and SA2 subunits bind RNA and R-loops in vitro, plus CTCF is known to bind RNA. We hypothesize that R-loop binding by cohesin-NIPBL and CTCF stalls cohesin's DNA loop extrusion activity and stabilizes DNA loops. Given previous research showing that DNA double-strand breaks (DSBs) induce R-loop formation, we also predict that R-loops serve to recruit cohesin to DNA damage sites in cells. Using atomic force microscopy (AFM) imaging and electrophoretic mobility shift assay (EMSA), we discovered that cohesin-NIPBL specifically binds to R-loops on dsDNA, and CTCF binds R-loops with greater affinity than for its consensus DNA binding sequence. Furthermore, cohesin SA1 and SA2 are recruited to DNA damage sites in an R-loop-dependent manner in cells. These results and our continued work could further our understanding of the role R-loops play in recruiting cohesin-NIPBL and CTCF to DNA damage sites and how these proteins may modulate DNA structure at the damage sites to promote DNA repair and thus genome stability.

## P10

# Exploring Local Structural Environments of Nitrosamine Analogs to Improve Carcinogenicity Read-Across Assessments

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## Abstract

Assessing the carcinogenic potency of N-nitrosamines, especially nitrosamine drug substance-related impurities (NDSRIs), is crucial as these compounds have been identified as potent carcinogens in animals and are suspected to be carcinogenic in humans.

One way to assess N-nitrosamine's carcinogenic potency is to use structural analogs with known carcinogenic data. However, the current database of N-nitrosamines with known carcinogenic data is limited, hindering the ability to assess their carcinogenic potency accurately. Enhancing the chemical space of the N-nitrosamine database by including more structurally diverse compounds will improve the assessment of their carcinogenic potency.

In this study, we evaluated the effect of adding additional N-nitrosamines to the existing QSAR Flex N-nitrosamine potency database of 135 compounds. We identified 59 additional N-nitrosamines with reported experimental data in the public literature. In addition, we explored the structural environment of the newly added compounds compared to the previously compiled dataset and the effect of the expansion of the chemical space on our ability to predict the carcinogenic potency of NDSRIs more efficiently.

Our results showed that the expanded chemical space of the QSAR Flex N-nitrosamine carcinogenic potency database coupled with enhanced algorithms for calculating similarity and with the improved workflow of selecting the proper structural analogs improves the quality of the carcinogenic potency assessments. These findings, as well as the workflow, are illustrated in several case studies.

Our study highlights the importance of expanding the chemical space of the database for a more accurate assessment of carcinogenicity and improving our ability to protect human health.

## P11

# Comparative Analysis of Automated and Manual Micronucleus Scoring in A375 Cells

Vivian Tang[1], Michael Homiski[1], Javier Santiago[2], Shambhu Roy[2], Wen Sun[1], Maik Schuler[1]
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## Abstract

The high-content screening platform (iScreen) utilizes a customized automated image analysis algorithm to identify interphase population, micronuclei, centromere region, and DNA damage response biomarkers. The standard in vitro micronucleus assay involves labor intensive manual slide scoring, which limits the dose that can be analyzed. To understand the concordance between automated and manual micronucleus scoring in A375 cells, we performed a cross-site validation with Inotiv to evaluate the sensitivity and specificity of the two scoring methods.

The validation consists of 14 blind-coded compounds from various classes. For the automated iScreen, A375 cells were seeded into 96 well plates, treated for 30 hours continuously, or pulse treated for 3 hours—with or without S9 metabolic activation—followed by a 27-hour recovery. Each compound was tested at 22 concentrations and over 10000 cells were analyzed at each dose. Image analysis was done using our customized algorithm on Harmony® software. Inotiv used a flask-based, slide scoring A375 protocol previously developed and validated by Pfizer and tested the most relevant condition of each compound pre-identified by Pfizer. Five concentrations from each compound were examined for MN induction and at least 2000 cells were analyzed per concentration.

Overall, there was 93% concordance between automated and manual MN scoring, with image analysis having a higher sensitivity. In addition, automated image analysis has a higher throughput enabling full dose response analysis, and the high content biomarkers provide mechanistic information on genotoxicants. Our data support high-content image analysis as an accurate and viable alternative to traditional micronucleus slide scoring.

## P12

# Translating Particulate Hexavalent Chromium-Induced Genetic Impacts from Human Lung Cells to Lung Tissue

Haiyan Lu
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### Abstract

Particulate hexavalent chromium [Cr(VI)] is a well-established human lung carcinogen, but how Cr(VI) induces lung cancer is unclear. Chromosome instability (CIN), a hallmark of lung cancer, is considered a major driving factor in Cr(VI)-induced lung cancer. Studies in cultured human lung cells show particulate Cr(VI) induces DNA double-strand breaks (DSBs) in the late S and G2 phases of the cell cycle when homologous recombination (HR) repair is the main repair pathway for fixing the breaks. Simultaneously, Cr(VI) suppresses HR repair by targeting RAD51, a key recombinase in HR repair pathway. The combination of breaks with failed repair results in chromosome instability. We translated these outcomes to rats, as this species develops Cr(VI)-induced lung tumors. 12-week-old male and female Wistar rats were exposed to either zinc chromate particles in a saline solution or saline alone by oropharyngeal aspiration. There were two timepoints: 24 hours and 90 days. Cr was found in every rat lung lobe with more Cr in the right lung. We found both DNA double strand breaks and HR repair increased in rat lungs after 24-hour Cr(VI) exposure. However, after 90-day exposure, we found DNA double strand breaks increased, but HR repair decreased. Notably, these effects were distinct in bronchioles and more muted in alveoli. We also considered these outcomes in Cr(VI)-associated human lung tumors and found DNA double strand breaks increased and RAD51 levels decreased in lung tumor tissue compared to adjacent normal lung tissue. Thus, Cr(VI)-induced DNA double strand breaks and HR repair inhibition translates from cells to rat lung tissue and Cr(VI)-associated human lung tumors. This work was supported by the National Institute of Environmental Health Sciences [R35ES032876 and ES016893 to JPW].

## P13

# A Novel Microfluid Liver-on-Chip Model: Application in Regulated Genetic Toxicology Testing

Benjamin Kopp, Ammer Khawam, Karen Di Perna, Marise Roy, Annie Hamel
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## Abstract

Compounds genotoxicity assessment is based on a combination of tests to assess different endpoints associated with human diseases: mutagenicity, clastogenicity and aneuploidy. To this day, there is no single genotoxicity test capable of detecting all mechanisms, and all assays involve rodent metabolic activation system or living rodents, which could lead discrepancy from human accuracy predictivity response.

The objective is to develop an assay to address the different in vitro and in vivo genotoxicity endpoints using a human cells metabolically competent in vitro system to increase human-relevant predictivity outcome and replace animal testing. The model consists of a fluidic flow microphysiological liver-on-chip system using the PhysioMimix™ barrier plate (CN-Bio) co-cultured with human lymphoblastoid TK6 cells in Transwell® insert.

Results obtained with genotoxicants, methanesulfonate, ethyl methanesulfonate, benzo[a]pyrene and cyclophosphamide, were in line with expected in vivo responses for end points evaluated: the comet assay and the micronucleus test. Measured levels of urea, albumin and CYP enzymes activity, also demonstrated appropriate liver properties with metabolic competency.

In conclusion, the human cells model showed appropriate metabolic properties competency without requiring additional rodent metabolic activator and the capability to address genotoxic adverse outcomes within a single system, i.e. induction of damages to the chromosomes or the mitotic apparatus (micronucleus test) and DNA strand breakage (comet assay). The next steps in the development of the model will be to integrate the evaluation of mutagenicity by duplex sequencing analysis and to increase the number of compounds evaluated for a better overview of its accuracy.

## P14

# Quality of Slide and Tissue Samples Prepared for the Comet Assay Assessed Over One Year

Cheryl Hobbs[1], Lincoln Martin[1], Alex Diesing[1], Kelley Hayes[1], Michael Streicker[1], Leslie Recio[2], Stephanie Smith-Roe[3]
[1]Inotiv, Research Triangle Park, NC, USA. [2]Scitovation, Research Triangle Park, NC, USA. [3]Division of Translational Toxicology, NIEHS, Research Triangle Park, NC, USA

## Abstract

The comet assay is routinely used to test chemicals for DNA damaging potential. Sometimes circumstances dictate that analysis of slides or tissue samples prepared for the comet assay be delayed, or result in decisions to re-score a slide to confirm a result, score additional cells, or examine backup slides or frozen tissue samples. However, neither stability during prolonged storage nor the effect of repeated staining on slide quality and data integrity have been determined. We assessed the quality of comet slides prepared from freshly harvested and frozen liver from male Sprague Dawley rats administered vehicle or ethyl methanesulfonate (EMS) after 1 week and at 1-6, 9 and 12 months thereafter. Re-stained and native sets of slides were evaluated by two scorers, assigned either the fresh or frozen tissue slides to minimize potential scorer-related variability. High-throughput CometChips were also prepared and scored to determine effects of re-staining and storage over 3 months on data quality. In addition, the stability of flash frozen cubes of liver, brain, and heart tissue stored for ≥1 year is being assessed in the comet assay. Results thus far demonstrated that comet slides were stable for at least 1 year; overall, re-staining did not significantly impact measured induction of DNA damage in EMS-treated animals. The EMS response in liver was considerably lower as measured by CometChip, but was generally stable out to 3 months. These results confirm that comet slides can be re-stained without compromising data integrity and can be utilized many months following preparation.

## P15

# Adopting Duplex Sequencing™ Technology for Genetic Toxicity Testing: A Proof-of-Concept Mutagenesis Experiment with N-Ethyl-N-Nitrosourea (ENU)-Exposed Rats

Stephanie Smith-Roe[1], Cheryl Hobbs[2], Victoria Hull[2], J. Todd Auman[2], Leslie Recio[2,3], Michael Streicker[2], Miram Rivas[2], Gabriel Pratt[4,5], Fang Yin Lo[4,6], Jacob Higgins[4], Elizabeth Schmidt[4], Lindsey Williams[4,7], Clint Valentine III[8], Jesse Salk[4], Kristine Witt[9]

[1]Division of Translational Toxicology/NIEHS, Research Triangle Park, NC, USA. [2]Integrated Laboratory Systems, LLC, an Inotiv Company, Research Triangle Park, NC, USA. [3]ScitoVation, LLC, Durham, NC, USA. [4]TwinStrand Biosciences, Inc., Seattle, WA, USA. [5]Amazon.com, Inc., Seattle, WA, USA. [6]Generate Biomedicines, Inc., Somerville, MA, USA. [7]Apton Biosystems, Inc., Pleasanton, CA, USA. [8]TwinStrand Biosciences, Inc., Research Triangle Park, WA, USA. [9]Division of Translational Toxicology/NIEHS (Retired), Research Triangle Park, NC, USA

## Abstract

Duplex sequencing (DuplexSeq) is an error-corrected next-generation sequencing (ecNGS) method in which molecular barcodes informatically link PCR-copies back to their source DNA strands, enabling computational removal of errors by comparing grouped strand sequencing reads. The resulting background of less than one artifactual mutation per $10^7$ nucleotides allows for direct detection of somatic mutations. TwinStrand Biosciences, Inc. has developed a DuplexSeq-based mutagenesis assay to sample the rat genome, which can be applied to genetic toxicity testing. To evaluate this assay for early detection of mutagenesis, a time-course study was conducted using male Hsd:Sprague Dawley SD rats (3 per group) administered a single dose of 40 mg/kg N-ethyl-N-nitrosourea (ENU) via gavage, with mutation frequency (MF) and spectrum analyzed in stomach, bone marrow, blood, and liver tissues at 3 h, 24 h, 7 d, and 28 d post-exposure. Significant increases in MF were observed in ENU-exposed rats as early as 24 h for stomach (site of contact) and bone marrow (a highly proliferative tissue) and at 7 d for liver and blood. The canonical, mutational signature of ENU was established by 7 d post-exposure in all four tissues. Interlaboratory analysis of a subset of samples from different tissues and time points demonstrated remarkable reproducibility for both MF and spectrum. These results demonstrate that MF and spectrum can be evaluated successfully by directly sequencing targeted regions of DNA obtained from various tissues, a considerable advancement compared to currently used in vivo gene mutation assays.

## P16

# Genotoxicity of Ingested Polystyrene Micro- and Nano-plastics in an *In Vitro* Small Intestinal Epithelium Model

Zhenning Yang[1], Glen DeLoid[2], Joshua Baw[3], Philip Demokritou[2], Helmut Zarbl[2]
[1]The Joint Graduate Program in Toxicology, Rutgers University, Piscataway, NJ, USA. [2]Environmental and Occupational Health Sciences Institute, Rutgers University, Piscataway, NJ, USA. [3]Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA

## Abstract

Micro- and nano-plastics (MNPs) produced by degradation and fragmentation of plastic waste have become emerging environmental and food chain contaminants with uncertain consequences for human health. Ingestion is considered the most common MNP exposure route in humans. The genotoxicity of ingested MNPs, while gaining increasing attention, remains unclear. This study aimed to investigate the potential genotoxic effects of MNPs using small intestinal epithelium models. Primary carboxylated polystyrene MNP spheres with sizes of 25 and 1000 nm (PS25C and PS1KC) were dispersed in water at concentrations of 0.05, 0.25 and 1.0 mg/mL. MNP suspensions were then subjected to an *in vitro* 3-phase (oral, gastric and small intestinal phases) simulated gastrointestinal tract digestion to prepare physiologically relevant exposures. The final MNP-containing small intestinal digestas were applied to an *in vitro* tri-culture small intestinal epithelium model for up to 48 h. DNA damage was assessed by the CometChip assay, which is a high-throughput method for genotoxicity testing. Our studies identified that exposure to digestas of carboxylated PS-MNPs induced DNA damage in a time- and concentration-dependent manner. Specifically, DNA damage was significantly increased after 48h exposures to digestas of 0.25 and 1.0 mg/mL PS25C and of 1.0 mg/mL PS1KC compared to controls and 24 h exposure groups. To our knowledge, this is the first study to assess the genotoxicity of MNPs in an integrated *in vitro* ingestion platform. These findings suggest that ingestion exposures to high concentrations of MNPs could have serious genotoxic consequences in the small intestinal epithelium.

## P17

# Adopting Duplex Sequencing Technology for Genetic Toxicity Testing: Proof-of-Concept Mutagenesis Experiments with N-Ethyl-Nitrosourea (ENU) and Ethyl Methanesulfonate (EMS) in Human Lymphoblastoid TK6 cells

Carol Swartz[1], Todd Auman[1], Kristine Witt[2], Victoria Hull[1], Miriam Rivas[1], Jasmine Fowler[1], Leslie Recio[3], Jacob Higgins[4], Lindsey Williams[4], Elizabeth Schmidt[4], Fang Yin Lo[4], Clint Valentine[4], Jessie Salk[4], Stephanie Smith-Roe[2]

[1]Integrated Laboratory Systems, LLC, an Inotiv Company, Research Triangle Park, NC, USA. [2]Division of Translational Toxicology, NIEHS, Research TRiangle Park, NC, USA. [3]Scitovation, LLC, Durham, NC, USA. [4]TwinStrand Biosciences, Inc., Seattle, WA, USA

## Abstract

Guideline in vitro genetic toxicity tests for gene mutations rely on phenotypic selection to detect mutagenesis within a limited DNA region (e.g., a single locus), and obtaining mutation spectra using these assays is challenging. Duplex sequencing (DuplexSeq) has an ultra-low error rate, allowing for direct detection of rare mutations. TwinStrand Biosciences, Inc., has created a DuplexSeq Human-50 Mutagenesis Assay, which uses a bait-and-capture approach to sample 20 genic and intergenic target sites throughout the genome (covering approximately 50 kb), that can potentially overcome certain guideline assay limitations. To evaluate the use of DuplexSeq for detection of mutagenesis, TK6 cells were exposed to 0, 25, 50, or 100 mM N-ethyl-N-nitrosourea (ENU) or 0, 0.0125, 0.025, 0.1, 0.3, or 0.6 mM ethyl methanesulfonate (EMS) for 24 h, and cultures were sampled at 24, 48, 72, and 96 h for mutation frequency (MF) and spectra analysis. At the 48-h time point, the overall MF at the top concentrations of ENU or EMS were 2.3-fold or 4.1-fold over the vehicle control, respectively. For both chemicals, the proportion of C:G>T:A mutations was expanded. The non-canonical mutational spectrum of these alkylating agents in TK6 cells was likely due to deficiency for O6-alkylguanine-DNA-alkyltransferase necessary for repair of O6-alkylated guanine residues. The responsiveness of each target region to ENU or EMS was largely similar, thus opening a larger part of the genome for assessment of mutation induction. Our results demonstrate the utility of strategic sampling across the genome via the DuplexSeq method for evaluation of mutagenesis in vitro.

## P18

# Adaptation of the MultiFlow genotoxicity mode of action assay to address high throughput screening of large chemical libraries

Jeffrey Bemis, Steven Bryce, Svetlana Avlasevich, Erica Briggs, Stephen Dertinger
Litron Laboratories, Rochester, NY, USA

## Abstract

The development of new approach methodologies designed for genotoxicity assessment has significantly broadened the application of these methods across product development pipelines. However, in the case of screening very large libraries of compounds such as those found in pharmaceutical or environmental chemical safety testing, options are limited due to practical limitations in sample processing and throughput. To address this we adapted the MultiFlow DNA Damage assay to a 384 well plate format that examines one time point and one concentration per test compound. An initial training phase examined 71 established clastogens, aneugens and nongenotoxicants at 100 µM in triplicate with and without S9 exogenous metabolism. The biomarkers examined were γH2AX, p53, p-H3, and polyploidy and an 80% cytotoxicity limit was chosen. The data were used to generate an optimal Random Forest-based model for predicting genotoxic Mode of Action (MoA) with sensitivity and specificity of greater than 90% each. Analysis of an 80 compound external test set confirmed excellent performance of the machine learning model. We then began an exploration of commercially-available chemical libraries that represented chemical spaces like “DNA Damage” or “FDA Approved”. To date this High Throughput Screening (HTS) method has investigated 2242 FDA approved chemicals. The results show that 73% of these chemicals were below the 80% cytotoxicity limit and of those there were 15.3% clastogen hits and 2.5% aneugen hits. In addition, case examples of carbadox and R788 will provide further insight into the specific calls made by the HTS assay. The HTS screening assay built on the MultiFlow platform appears to provide exceptionally rapid MoA assessment while still maintaining excellent predictive performance. This new approach will help guide more focused and resource-efficient follow up processes that employ lower throughput but higher information content methodologies.

## P19

# Impact of MGMT-Mediated DNA Repair on NDMA-Induced Mutation Susceptibility and Cancer in Mice

Lee Pribyl[1], Joshua Corrigan[1], Jennifer Kay[2], Norah Owiti[1], Amanda Armijo[1], Sebastian Carrasco[3], Robert Croy[1], Stephen Dertinger[4], Dushan Wadduwage[5], John Essigmann[1], Bevin Engelward[1]
[1]Massachusetts Institute of Technology, Cambridge, MA, USA. [2]Silent Spring Institute, Newton, MA, USA. [3]Cornell University, New York City, NY, USA. [4]Litron Laboratories, Rochester, NY, USA. [5]Harvard University, Cambridge, MA, USA

## Abstract

N-nitrosodimethylamine (NDMA) is a Class 2A carcinogen that has been identified as a contaminant in well water supplies near a Superfund site and in a dozen commonly used medications, including valsartan, metformin, and ranitidine (Zantac). When NDMA is metabolized to form a methyldiazonium ion, it reacts with DNA to create methyl lesions, including $O^6$-methylguanine ($O^6$MeG) lesions which are mutagenic and toxic. A major focus of this project is to reveal the role methylguanine methyltransferase (Mgmt) has in modulating the risk of NDMA-induced cancer. $O^6$MeG is repaired by Mgmt, however repair is not perfect and unrepaired $O^6$MeG mispairs with thymine during replication. These mispairs are acted upon by mismatch repair (MMR), which removes the newly synthesized strand, leaving in place the original lesion. Repeated MMR ultimately leads to double strand breaks that can be acted upon by homologous recombination (HR). To learn about the potential for NDMA to cause HR, we used genetically engineered ROSA26-Direct Repeat (RaDR) mice that allow for detection of mutations created by HR. Incorporation of the gpt delta transgene into the genome of RaDR mice, enabled detection of point mutations, which permitted us to examine NDMA-induced mutations at an unprecedented depth over a time course of 1 to 70 days after exposure. Mgmt deficient mice treated with NDMA, displayed a significant increase in point mutations, large scale mutations, tumor burden and overall cancer incidence. Results from this study exhibit an innovative mutational burden tracking technology that presents a stepwise progression by which NDMA ultimately contributes to carcinogenesis.

## P20

# Human Cell Based Genetic Toxicology New Approach Methodologies to Assess Risk to Humans and Reduce Reliance on Animals

Leslie Recio[1], Bevin Engelward[2], Carole Yauk[3]
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## Abstract

The regulatory genetic toxicology test battery used for hazard identification includes bacterial and rodent-based mammalian cell bioassays and rodents to assess genotoxicity and mutagenicity. The rodent cell lines used in the test battery are p53 deficient and are devoid of xenobiotic metabolizing Phase I and Phase II enzymes: key determinants of cytotoxicity and genotoxicity. Highly induced S9 incorporated into the regulatory genetic toxicology test battery is supplemented with CYP450 cofactors and is not a valid model for human biotransformation of xenobiotics, and can produce false positives due bioactivation without Phase II detoxication. We have qualified human-relevant non-animal genetic toxicology testing battery using human TK6 cells can be combined with the CometChip® assay to assess DNA damage, MN assay and expression profiling-based TgX DDI biomarker, to predict genotoxicity. Metabolically competent HepaRG™ cells are a human-relevant genetic toxicology New Approach Methodology testing platform to replace/reduce in vivo genetic toxicology testing. HepaRG™ have been validated as an alternative to primary human hepatocytes for enzyme induction studies required by FDA. We have qualified the MN, CometChip® assays combined with the TgX DDI biomarker to determine genotoxicity outcomes in HepaRG cells. HepaRG™ cell can measure the same genetic toxicology endpoints that are measured in vivo (MN and Comet assay) as required by regulatory agencies. The approach of overlapping genetic toxicology endpoints in human TK6 cells and in HepaRG™ cells is a modern 21st century human-relevant nonanimal genotoxicity testing paradigm aimed at reducing false positives and replace/reduce reliance on animal testing.

## P21

# Elucidating the mode of action of genotoxic substances using a combination of GFP reporter genes and duplex sequencing

Marit E. Hoogenboom-Geijer[1], Jake Castle[2], Georg Papoutsoglou[2], Aaron Boswell[2], Daniel J. Roberts[3]
[1]Toxys, BV, De Limes, Oegstgeest, Netherlands. [2]TwinStrand Biosciences, Seattle, WA, USA. [3]Toxys, Inc, New York, NY, USA

## Abstract

The standard genotoxicity testing strategy typically investigates induction of gene mutations, chromosomal aberrations, and numerical chromosome changes. ToxTracker is an in vitro mammalian stem cell-based reporter assay that detects activation of specific cellular signalling pathways to identify direct DNA damage induction as well as indirect genotoxicity caused by oxidative stress and protein damage. The assay provides insight into the genotoxic mode of action (MOA) and can discriminate between clastogenic and aneugenic compounds. ToxTracker was shown to predict in vivo genotoxicity of compounds with >90% sensitivity and specificity.

The TwinStrand Duplex Sequencing mutagenesis assay uses a highly accurate sequencing technique that tracks both strands of the sequenced DNA molecules to limit sequencing errors. The mutagenesis assay can detect and characterize mutations induced upon chemical exposure and is supported with an easy-to-use bioinformatics pipeline.

To combine the MoA information and accurate detection of gene mutations, we applied the TwinStrand Duplex Sequencing mutagenesis assay in the ToxTracker reporter cells to further unravel the MOA of genotoxic substances and determine their mutagenic potential. Providing a mutational fingerprint of compounds helps to further explore the MoA of genotoxic substances, thereby improving the in vitro genotoxicity prediction. In a pilot study, we have tested the genotoxic substances N-ethyl-N-nitrosourea, benzo[a]pyrene, and potassium bromate in ToxTracker and determined their mutational fingerprint using duplex sequencing.

## P22

# Genotoxicity assessment of micro(nano)-plastics: insight into the induction of genome instability and genotoxic disease syndrome in organisms

Chibuisi Gideon Alimba
University of Ibadan, Ibadan, Oyo State, Nigeria

### Abstract

Micro(nano)-plastic (MPs/NPs) are ubiquitous in the ecosystem. Studies have increasingly reported MPs/NPs in consumer products; sea food, drinks, water, tea, coffee, honey, etc. They have been detected human stool, placenta, breastmilk, testes and semen, liver and blood stream. Therefore, understanding possible deleterious effects of MPs/NPs in human and animal health is necessary. MPs/NPs rarely biodegrade and transports harmful chemicals into the body. The small sizes, positive charge, and high dose of MPs/NPs, make them dangerous to the cells. The ability of MPs/NPs to induce DNA damage / genotoxicity may increase genome instability, the hallmark of genetic disease syndromes including cancer. This presentation examined MPs/NPs ability to induce DNA damage / genotoxicity by altering various biomarkers of genotoxicity in different model organisms, and the mechanisms of MPs/NPs induced genotoxicity were reviewed. The types and sizes of MPs/NPs, concentration and duration of exposure are determining factors considered in their genotoxicity assessment. Furthermore, somatic and germ-line cells are susceptible to DNA damaging effects of MPs/NPs. Comet assay is the most utilized biomarker, while chromosome aberration, the least. Others biomarkers of genotoxicity applied were abnormal sperm morphology, micronucleus assay and toxicogenomic signatures. The mechanisms of DNA damage include generation of free radical and oxidative stress, induction of dangerous inflammatory cells, down-regulation of transcriptional genes related to apoptotic expressions, and increased DNA fragmentation in cells and tissue. MPs/NPs ability to induce DNA damage suggests they are capable of eliciting genotoxic disease syndromes. It is importantly to unequivocally confirm MPs/NPs as genotoxin, mutagen and or carcinogen.

# 2023 GTA Student and Early-Stage Investigator Poster Abstract Award Recipients

## *2023 Poster abstract award – Students*

Genetic Toxicology Association
Translating Genetox

### 2023 GTA Travel Awards
### Students

**Elizabeth M. Irvin**
Toxicology Program
Laboratory of Dr. Hong Wang
North Carolina State University
Raleigh, NC USA

**R-loop-mediated recruitment of cohesin and CTCF as a potential regulator of 3-D genome structure and DNA repair**

**Zhenning Yang, MBBS**
Joint Graduate Program in Toxicology
Laboratory of Dr. Helmut Zarbl
Rutgers, The State University of New Jersey
Piscataway, NJ USA

**Genotoxicity of ingested polystyrene micro- and nano-plastics in an in vitro small intestinal epithelium model**

Genetic Toxicology Association Annual Meeting
May 3-5, 2023

## *2023 Poster abstract award – Early Stage Investigators*

Genetic Toxicology Association
Translating Genetox

### 2023 GTA Travel Awards
### Early-Stage Investigators

**Haiyan Lu, PhD**
Department of Pharmacology & Toxicology
Laboratory of Dr. John Wise
University of Louisville
Louisville, KY USA

**Translating Particulate Hexavalent Chromium-Induced Genetic Impacts from Human Lung Cells to Lung Tissue**

**Vivian Tang**
Genetic Toxicology
Pfizer
Groton, CT USA

**Comparative Analysis of Automated and Manual Micronucleus Scoring in A375 Cells**

Genetic Toxicology Association Annual Meeting
May 3-5, 2023

# 2022 GTA Excellence in Science Award Recipient

## The GTA Congratulates: Stephen Dertinger, PhD.
## The GTA 2022 "Excellence in Science" Recipient

Excerpts from **Stephen Dertinger's** GTA ESA Acceptance Speech
It's an honor receiving the GTA's 2022 Excellence in Science Award. Past awardees have been a great source of inspiration, so it's incredibly flattering to count myself among that group of individuals. Clearly no one that receives this award does so without a lot of help. So, I'd like to take this opportunity to shine a light on some of the individuals that have been especially instrumental to my scientific career.

In my early years working at Litron Laboratories, Andrew and Carol Tometsko, Dorothea Torous, and Nikki Hall helped me understand what good experiments look like, and how to go about executing them. Some of Dr. T's sayings from this period continue to guide me to this day: "if it's real it's reproducible," and "one experiment is worth a thousand opinions."
After several years at Litron I enrolled in the University of Rochester's Toxicology Program. At the U of R I had the great fortune of working under Tom Gasiewicz. It was Tom that taught me the importance of orthogonal evidence.

It's hard to adequately express the amount of help Jim MacGregor has provided over the years. Early on, Jim encouraged me to think of micronuclei as a translational biomarker that should be utilized across species of toxicological interest. He also taught me to stop thinking of genetic toxicology as separate and distinct from toxicology. The same principles apply, and it behooves us to stop trying to excuse ourselves from that paradigm.

I've benefitted from fantastic collaborators at several government agencies. I'd like to thank Bob Heflich and colleagues at NCTR for all the incredible work they put into validating the Pig-a assay, and for spearheading the OECD Test Guideline. Paul White and several Health Canada scientists have greatly inspired our work through the years, most recently with their point-of-departure analyses. Our colleagues at NIH, especially Kristine Witt, Stephanie Smith-Roe, and Dan Shaughnessy, were early supporters of our human blood-based analysis efforts, and NIEHS supported several rounds of grant funding that helped us reduce the methods to practice.

I've been super fortunate to have collaborated with many of the top industry and academic scientists in the field of genetic toxicology. This is not an exhaustive list, but I'd like to highlight some colleagues that Litron has done our most important work with: Leon Stankowski & Dan Roberts; Maik Schuler, Krista Dobo, Ron Fiedler, Michelle Kenyon, Randy Spellman, Maria Engel & Stephanie Coffing; Les Recio, Cheryl Hobbs & Carol Swartz; Andreas Zeller; Azeddine Elhajouji; Anthony Lynch & Julia Kenny; Elisabeth Lorge; Veronique Thybaud; Matt Tate; Laura Custer; Rob Smith; Bas-jan Van Der Leede, Freddy Van Goethem & Sandy Weiner; Sheila Galloway, Patricia Escobar & Zhanna Sobol; Stefan Pfuhler & Ashley Allemang; John Nicolette; George Johnson, Bevin Engelward & Jenny Kay. Thank you all!

One last thought about inter-lab work before I leave this subject. Our best outcomes seem to occur when colleagues feel comfortable telling us difficult truths.

“Honesty is more than not lying. It is truth telling.” J.E. Faust. I have many anecdotes I could share, but the first that came to mind has to do with our Pig-a ring trial. Work was well underway when Anthony Lynch stopped me at a meeting to say not nearly enough reticulocytes were being evaluated. That was a difficult thing to hear, but it made all the difference. We paused the trial and puzzled out an immunomagnetic separation technique that provided an order of magnitude more reticulocytes for analysis. Thank you, Anthony, and all our past and current collaborators for helping ensure we’re doing the best possible work we can.

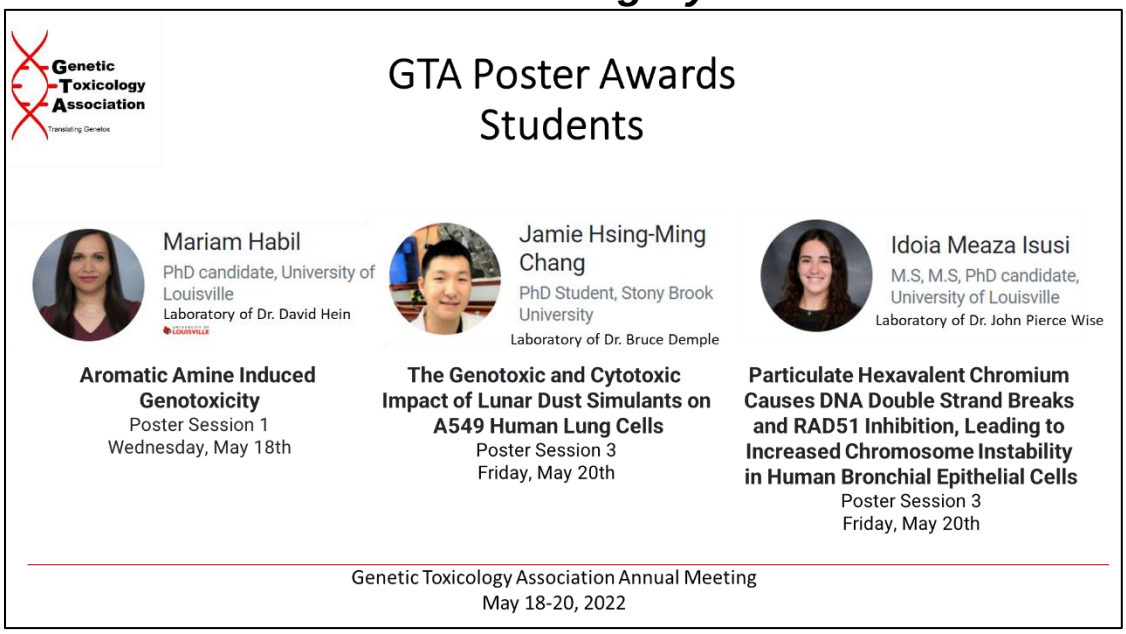
I touched on the early years at Litron, and now want to acknowledge several contemporary co-workers. Jeff Bemis wears many hats at our small company. In doing so, Jeff has a way of making everything we do better. Steve Bryce has advanced every aspect of our research in profound ways, and I really don’t know what we’d do without him. MultiFlow kits and services is just one recent example. We give Svetlana Avlasevich our most difficult benchtop problems. It should no longer surprise me, but I’m always amazed to see how efficiently she cuts through all the issues, one after another. Thank you, Jeff, Steve and Svetlana!

Moving on to my personal life, I need to thank my wife and kids for all their support through the years. Science is decidedly not a 9 to 5 job, and their understanding and support has made all the difference. Thank you, Molly, Samantha, Ben, Trevor, and Claire!

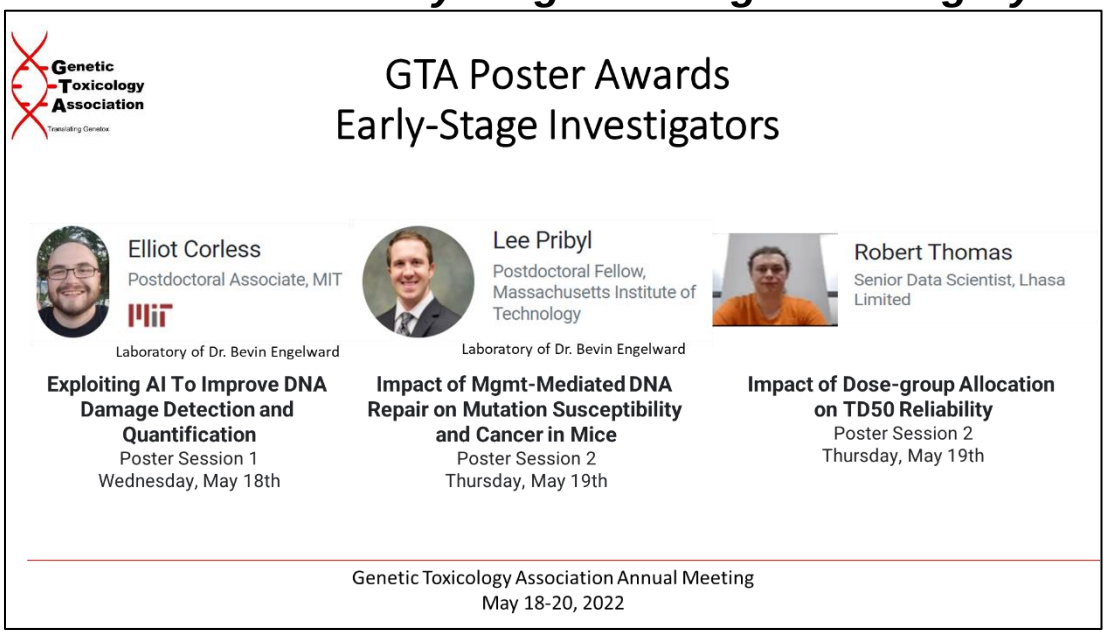
Thank you very much for selecting me for the 2022 ESA. It provided me with a nice opportunity to shine a light on many of the people that shaped my scientific career, and that have contributed to the successes we’ve had a Litron. I hope to see you all, in person, at the 2023 GTA meeting!

# 2022 GTA Student and Early-Stage Investigator Poster Award Recipients

## *2022 Poster award – Student category*

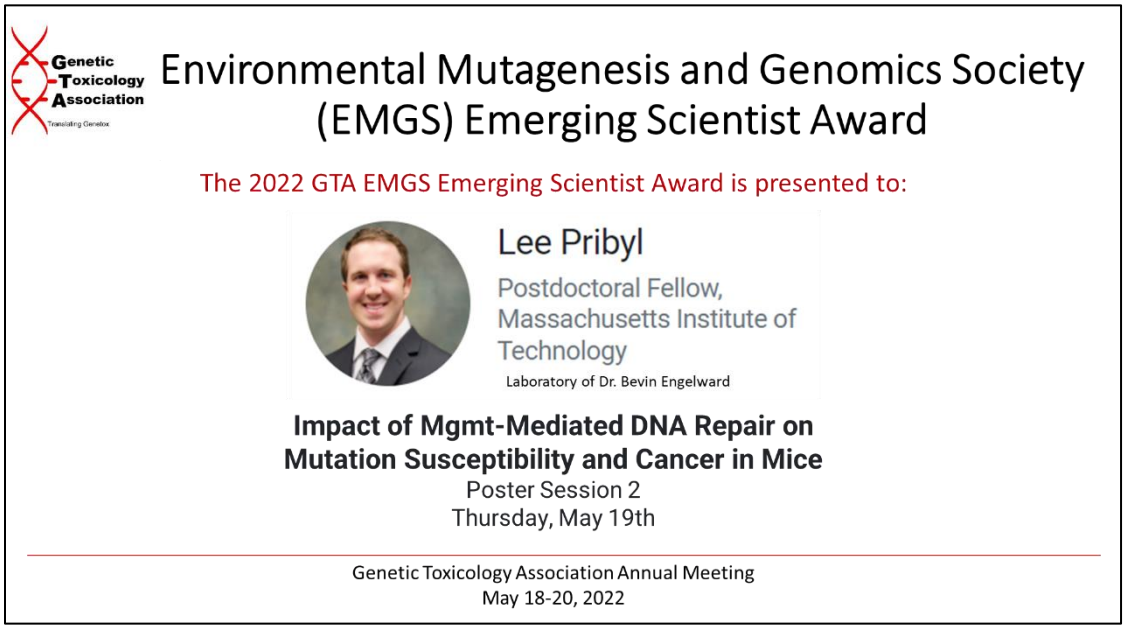



## *2022 Poster award – Early Stage Investigator Category*



# 2022 EMGS Emerging Scientist Award Recipient

## *2022 Environmental Mutagenesis and Genomics Society (EMGS) Emerging Scientist Award*



# GTA Membership Application

www.gta-us.org

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The Genetic Toxicology Association is organized exclusively to meet educational and scientific goals. The primary purpose is to foster the exchange and dissemination of information regarding genetic toxicology and to promote the development of the science of genetic toxicology. Membership is open to anyone interested in the field of genetic toxicology and the annual dues are currently $50. Student memberships are $25 per year. Dues are for the calendar year.

## Renew and pay your membership on-line at www.gta-us.org.

Or send this completed application and appropriate funds (checks made payable to the Genetic Toxicology Association) by regular postal mail to:

Leon Stankowski, Treasurer
Genetic Toxicology Association
c/o 1712 DaVinci Lane
Clarks Summit, PA 18411

# 2024 GTA Excellence in Science & Service Awards
## Call for Nominations!

This award recognizes the contributions of a member who has made particularly notable contributions to the field of genetic toxicology. **All GTA members are invited to submit a nomination.** One awardee each is selected for the Science and Service awards by a committee of past GTA Board Members, specifically former Chairs.

The nomination package consists of a short (up to 1 page) description of the nominee's contributions to GTA and the field of Genetic Toxicology. The nominee must be a current member of GTA, and nominators are encouraged to discuss potential nominations with the nominee to make sure (s)he is aware of the nomination and will be able to attend the GTA meeting in 2024. Nominations should be sent to Dan Roberts, Chair of the ESA selection committee.

**Nominations for the 2024 GTA Excellence in Science & Service Awards are due by December 1, 2023.**

**Please email your nominations to: d.roberts@toxys.com.**

# Announcements

**INVITATION TO EXHIBITORS**

Exhibition space will be available at the in-person 2024 meeting to allow interested vendors the opportunity to showcase their products or services to the conference attendees. Exhibitor spaces are limited, so please inquire as soon as possible.

**GTA CORPORATE SPONSORSHIP**

The Board of Directors and members of the Genetic Toxicology Association (GTA) are inviting organizations to support the GTA's efforts to foster sustained excellence in genetic toxicology. The GTA is a tax-exempt educational and scientific organization, and any contributions will be used to help the GTA continue to support its activities to promote scientific excellence in this field. Several contribution mechanisms are available: **Sustaining Membership** (Gold: $500 or Silver: $250) for general, non-designated use by the GTA; *additional* **Targeted Contribution** towards a specific event or function (e.g., meeting breaks or lunch, offsetting general meeting expenses, student travel award, etc.); and/or *additional* **Session Sponsorship** ($1000), on a first come first serve basis.

**Advertising Space**

We are offering an opportunity for companies to purchase advertising space on our home page and meeting program website.

If interested or for additional information please email the GTA Treasurer, **Leon Stankowski**, at leon.stankowski@crl.com for information and prices.

# Acknowledgements

***For their contributions to the GTA:***
We would like to thank the board members and volunteers. Their dedication and contributions are invaluable to our organization, and we thank you!

***Meeting Exhibitors and Sponsors:***
The Genetic Toxicology Association would like to thank the following Exhibitors and Sponsors for generously supporting our 2023 Meeting.

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# GTA Board of Directors 2022-2023

## Chair (2023): Sheroy Minocherhomji

**Dr. Sheroy Minocherhomji** is currently Senior Director within the Toxicology and Pathology department at Eli Lilly and Company. He has >10 years of industry and academic experience in regulatory and discovery toxicology, impurity qualification of drugs, genomics, precision oncology, DNA repair, and safety assessment of multi-modality therapeutics, from discovery through to marketing and in oncology, cardiometabolic disorders and neuroscience therapeutic areas. He was previously a Principal Scientist/Toxicologist and Head of the Genetic Toxicology Unit within the Translational Safety department at Amgen and an Assistant Professor at the University of Copenhagen, Denmark. He received his MSc. and DIC degrees in Human Molecular Genetics from Imperial College London, UK and his PhD as a Marie Curie Fellow from the University of Copenhagen, Denmark in Health & Medical Sciences. He has been invited to speak at numerous global conferences and has authored more than 20 peer-reviewed publications including 10 as first/co-first and 4 as senior last author in high-impact journals including *Nature*, *Nature Cell Biology*, *PNAS, Molecular Cell* and *Regulatory Toxicology & Pharmacology*. He has been the recipient of numerous awards and grants and most recently the Early-Stage Investigator and Emerging Scientist Awards by the Genetic Toxicology Association (GTA) and the Environmental Mutagenesis & Genomics Society (EMGS). He is also a steering committee member of HESI's Genetic Toxicology Technical Committee (HESI-GTTC) and a past co-chair of the HESI-GTTC ecNGS working group.

## Chair-Elect (2023): Penny Leavitt

**Penny Leavitt** has been dedicated to Genetic Toxicology efforts since joining Bristol Myers Squibb (BMS) in 2011. Current responsibilities are heavily weighted in mutagenic impurities risk assessment with a cross-functional role in Chemical Process Development and CMC Regulatory. Efforts support IND and NDA dossier submissions as well as responding to Health Authority requests as they arise. External efforts include data sharing projects with commercial in silico providers for genotoxic endpoints and contributing expert knowledge in external working groups. In addition, Penny is responsible for ensuring effective external partnerships with CROs and monitoring of Genetox studies. Prior to tenure at

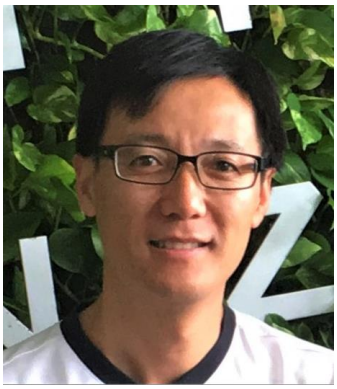
BMS, Penny's career experience spanned multiple areas of drug discovery utilizing a breadth of techniques in both industry and academia, with a particular aptitude for microbiology, biochemistry, and chemistry SAR. Most recently, Penny has expanded horizons in general and regulatory Toxicology, with culmination of earning status as a Diplomate of American Board of Toxicology, achieving position of Nonclinical Safety Project Representative, and responsibilities in review/authoring internal exposure monographs deriving chemical exposure limits to support chemical development and related quality events. Penny has been a member of GTA since 2011. For the past few years she has volunteered to support efforts for the GTA annual meeting, in particular co-chairing the GTA student outreach, aligning with her demonstrated advocacy for mentoring young scientists throughout her 20+ career.

**Maria Engel** is a Principal Scientist in the Global Portfolio Regulatory & Strategy group at Pfizer and is currently responsible for providing nonclinical toxicology support for submissions to regulatory agencies worldwide. She previously worked in genetic toxicology gaining over 20 years of practical experience in the application of genetic toxicology testing in support of pharmaceutical development. Maria contributes to genetic toxicology mutagenicity assessments for marketed products. She is a long time member and volunteer of the Genetic Toxicology Association and served as the Newsletter Editor (2008-2010), Secretary (2011-2015), Student Outreach Chair (2010-2019), previous member of the Board of Directors (2012-2014) and currently serving a second term on the Board as Chair Elect. Maria holds a BS in Diagnostic Genetic Sciences (cytogenetics) from the University of Connecticut and a MS in Pharmaceutical Regulatory Affairs from Temple University.

**Ashley Allemang** is a Senior Scientist in Global Product Stewardship at Procter & Gamble. Ashley has over 10 years of industry experience in applied genetic toxicology in the context of in vitro-based safety support. Her research has primarily focused on mode of action determination and distinguishing direct and indirect genotoxicity through various in vitro methods such as the micronucleus assay, the ToxTracker assay and other genomics-based methods such as the TGx-DDI biomarker. More recently her research has employed the HepaRG micronucleus assay to develop in vitro-based genotoxicity potency rankings of pyrrolizidine alkaloids, as well as genotoxicity evaluation of mixtures. In addition to her research activities, her expertise has also expanded to include SAR based risk assessment. Ashley has been actively involved in the HESI GTTC committee since 2017 and has participated in the development of genetox-related AOPs

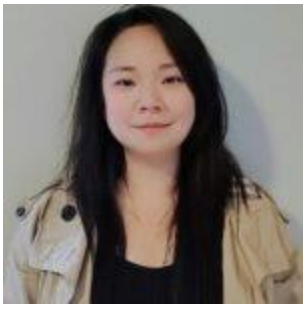
and is currently co-leading the Indirect Genotoxicity subgroup of the In Vitro Work Group evaluating NAMs for genetic toxicity testing. Ashley is also serving as the GTA Secretary.

**Melisa Masuda-Herrera** is a Senior Associate Scientist in the Environmental and Occupational Toxicology group within Nonclinical Safety & Pathobiology at Gilead. Her responsibilities include authoring health-based risk assessments to support product quality and occupational toxicology programs, monitoring and reviewing worker safety studies and environmental risk assessments and providing toxicology support to the Environmental Health and Safety group for global hazard communication programs. Before joining Gilead, Melisa worked as a Scientific Researcher at Genentech in the Product Quality and Occupational Toxicology group. While at Genentech, her primary focus was on authoring and reviewing documents to support Genentech product quality and occupational toxicology programs and conducting and interpreting *in silico* assessments of impurities for potential genotoxic activity using quantitative structure–activity relationship programs. Prior to graduate school, she worked as a Laboratory Assistant/Field Technician at the California Department of Public Health where she assumed the lead role in validating new methods, and assisting in standard methods, of chemical analysis of marine toxins for biotoxin monitoring. Melisa received her Bachelor of Science degree at UC Berkeley in Molecular Toxicology and her Master of Science degree at UC Santa Cruz in Environmental toxicology. She is currently a member of the Society of Toxicology, American College of Toxicology, ELSIE Consortium, and Occupational Toxicology Roundtable.



**Dr. Zhiying (Zane) Ji** is currently a toxicologist at Incyte Corporation in Wilmington, DE. He manages toxicology programs in accordance with global regulatory requirements to support drug discovery and development. Prior to joining Incyte, Dr. Ji worked for Bristol Myers Squibb Company (BMS) in New Brunswick, NJ from 2017 to 2022. He provided scientific leadership in developing genotoxicity testing strategies; conducted mutagenicity hazard assessment for intermediates/impurities in accordance with ICH M7 guideline; and leaded genetic toxicology innovation activities. He also served as Project Toxicologist for multiple programs to support drug discovery and development. Dr. Ji was a Lead Scientist – Genetic Toxicology at Dow Chemical Company from 2012 to 2017. He provided science leadership in genetic toxicology studies to support product development and global registration; acted as Study Director for in-house GLP and non-GLP genetic toxicology studies; acted as Study monitor for GLP and non-GLP genetic toxicology studies conducted at CROs; leaded capability development of innovative genotoxicity techniques. Dr. Ji received his

Ph.D. degree in Toxicology from Chinese Center for Disease Control and Prevention in 2004 and his post-doctoral training under the supervision of Prof. Martyn Smith at University of California, Berkeley. He applied fluorescence in situ hybridization (FISH) in the development of early effect biomarkers for benzene and formaldehyde exposure and investigated the genetic and epigenetic mechanisms of chemical mutagenesis and carcinogenesis. Dr. Ji has authored over 20 peer-reviewed publications. He is an active member of GTA, EMGS and SOT.



**Dr. Wen Sun** is a Senior Principal Scientist in the Genetic Toxicology Department at Pfizer. She received her PhD in Molecular and Cellular Biology (molecular medicine) from the University of Iowa and worked as a post-doctoral researcher at Yale University Pharmacology department prior to joining Pfizer three and half years ago. Since joining Pfizer, Wen lead the development, validation, and implementation of the multiplexed imaging screening platform, which enabled the delivery of regulatory endpoint and mode of action information to project teams in a single assay. The platform also incorporated computational predictive modeling and quantitative dose-response assessment to support pharmaceutical development. Currently, Wen oversees the screening laboratory, provides subject matter expertise guiding teams and chemists away from genotoxicity liabilities. In addition, she serves as the drug safety team lead on projects and participates in genetic toxicology impurity assessment. Wen is an active member of the Genetic Toxicology Association, the Environmental Mutagenesis and Genomics Society, and Health and Environmental Sciences Institute. She has presented her work at numerous conferences and currently contributing to manuscript and AOP preparation. Wen has a particular passion in in vitro assays, adverse outcome pathways, innovative technologies, and alternative testing methods.

# GTA Volunteers 2021-2023

The following individuals are not board-elected but volunteer their time and talents to both enrich our organization and keep it running smoothly.

***Treasurer: Leon Stankowski***

***Assistant Treasurer: Sara Hurtado***

***Secretary, Web Liaison: Ashley Allemang***

***Account Administrator, Communications Co-chair, ESA Chair: Dan Roberts***

***Communications co-chair: Teresa Wegesser***

***Student Outreach: Zhiying Ji***

***Student Outreach: Penny Leavitt***

***Financial Auditor: Chris Farabaugh***

***Account Administrator: Robert Foster***

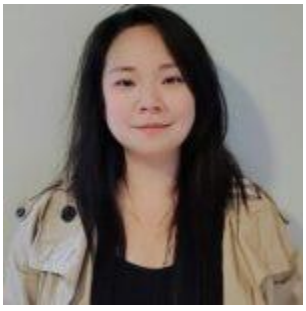
***GTA Photographer: Robert Preston***

***GTA Newsletter: Paula van Rossum and Jennifer Sasaki***

***GTA Historian: Volunteer needed!***

# 2023 GTA Scientific Program Committee

**Dr. Yi Yang** is currently Director of Genetic, Environmental, and Occupational Toxicology at AbbVie. She is also a Therapeutic Area Leader overseeing preclinical safety portfolios in Specialty area. Dr. Yang has 20 years of experience in preclinical safety assessment for a variety of therapeutic modalities, including small molecules, monoclonal antibodies, degradomers, cell and gene therapy. Her areas of expertise include regulatory toxicology, predictive and mechanistic toxicology, genetic toxicology, toxicogenomics, toxicity biomarkers, and biostatistics. Dr. Yang received her MD from Sun Yet-Sen University of Medical Sciences, her Ph.D. in Toxicology and M.S. in Biostatistics from University of Cincinnati. She is also certified as a Diplomat of the American Board of Toxicology. She authored 25 peer-reviewed publications and over 20 regulatory submissions supporting Phase 1 and Phase 2 clinical trials. She is actively involved in several industry-wide collaborations, including the Predictive Safety Testing Consortium and the ILSI-HESI consortium. She also served as Secretary to the American Association of Chinese in Toxicology (2010-2012), Chair to the Applied Pharmaceutical Toxicology (2015-2016), and President to the Midwest Regional Chapter of SOT (2017-2019). Dr. Yang joined GTA in 2022 and is co-chair of the Scientific Program Committee for the 2023 annual meeting.



**Dr. Wen Sun** is a Senior Principal Scientist in the Genetic Toxicology Department at Pfizer. She received her PhD in Molecular and Cellular Biology (molecular medicine) from the University of Iowa and worked as a post-doctoral researcher at Yale University Pharmacology department prior to joining Pfizer three and half years ago. Since joining Pfizer, Wen lead the development, validation, and implementation of the multiplexed imaging screening platform, which enabled the delivery of regulatory endpoint and mode of action information to project teams in a single assay. The platform also incorporated computational predictive modeling and quantitative dose-response assessment to support pharmaceutical development. Currently, Wen oversees the screening laboratory, provides subject matter expertise guiding teams and chemists away from genotoxicity liabilities. In addition, she serves as the drug safety team lead on projects and participates in genetic toxicology impurity assessment. Wen is an active member of the Genetic Toxicology Association, the Environmental Mutagenesis and Genomics Society, and Health and Environmental Sciences Institute. She has presented her work at numerous conferences and currently contributing to manuscript and AOP preparation. Wen has a particular passion in in vitro assays, adverse outcome pathways, innovative technologies, and alternative testing methods.

A toxicologist for 15+ years, **Dr. Markley** specializes in human health risk assessment, food safety, genotoxicity, metals toxicology, nanotoxicology and carcinogenesis. She graduated from Texas A&M University – Corpus Christi with a Bachelor of Science in Biology, received a Ph.D. from the University of Maine in Molecular Biology and Biochemistry, and held an FDA ORISE postdoctoral fellowship. She has worked in non-profit and consulting before her role as a Toxicology Reviewer at FDA. She began at the Office of Food Additive Safety in 2018 and her current duties include reviewing pre-market notifications of food contact substances and supporting several complex post-market issues related to regulatory science, safety review and policy.

# 2022 GTA Annual Meeting Attendees

| Attendee | Affiliation |
|---|---|
| Abby Myhre | Corteva |
| Adam Faranda | FMC |
| Adele Miller | PTC Therapeutics |
| anne chappelle | SafeBridge Consulting |
| Anthony Lynch | GSK |
| Arianna Bassan | Innovatune |
| Arne Burzlaff | EBRC Consulting |
| Ashley Allemang | Procter & Gamble |
| Atish Patel | Cerevel Therapeutics |
| Azeddine Elhajouji | Novartis Pharma AG |
| Bevin Engelward | Massachusetts Institute of Technology |
| Carol Beevers | Corteva Agriscience |
| Carol Swartz | Integrated Laboratory Systems, LLC, an Inotiv Company |
| Carole Yauk | University of Ottawa |
| Channah Pool | EMGS |
| Cheryl Hobbs | Inotiv |
| Chingchai Wanidworanun | New York University |
| Christopher Bradley | Mutagentech |
| Dan Levy | US FDA (Retired) |
| Dan Roberts | Toxys, Inc. |
| David Jacobson-Kram | ToxRox Consulting, LLC |
| David Kirkland | Kirkland Consulting |
| Derek McFerran | Gentronix Limited |
| Elizabeth Irvin | North Carolina State University |
| Emily Dakoulas | Inotiv |
| Erica Briggs | Litron Laboratories |
| Erica Dahl | SafeBridge Regulatory and Life Sciences Group |
| Francesco Marchetti | Health Canada |
| Giel Hendriks | Toxys |
| Grace Kocks | Lhasa Limited |
| Haiyan Lu | University of Louisville |
| Hank Arrington | Charles River Labs |
| Jahan Cooper | FDA |
| Jakub Kostal | ToxFix |
| Jamie Scaglione | ScitoVation |
| Jamie Sly | Inotiv / RTP |

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|---|---|
| Jamie Sly | Inotiv |
| Jamie Young | University of Louisville |
| Jeffrey Bemis | Litron Laboratories |
| Jeffrey Weinberg | Charles River Laboratories |
| Jennifer Cheung | Pfizer |
| Jill Fogleman | Mylan Inc. a Viatris Company |
| Joel Bercu | Gilead Sciences |
| Joel Murray | AbbVie |
| John Nicolette | Janssen |
| John Wills | Cambridge University |
| John Wise | University of Louisville |
| June Hope | TwinStrand Biosciences |
| Ke Jian Liu | Stony Brook University |
| Kevin Cross | GTA |
| Koren Mann | McGill University |
| Krista Dobo | Pfizer |
| Laura Custer | Bristol-Myers Squibb |
| Laura Markley | US FDA |
| Lee Pribyl | Massachusetts Institute of Technology |
| Leon Stankowski | Charles River Laboratories |
| Leslie Recio | ScitoVation |
| Lincoln Martin | Inotiv |
| Liz Rubitski | Pfizer |
| Mac Taylor | SafeBridge Regulatory & Life Sciences Group |
| Maik Schuler | Pfizer |
| Maria Donner | Consultant |
| Maria Engel | Pfizer |
| Marise Roy | Charles River |
| Mary Vagula | Gannon University |
| Matt Tate | Gentronix Ltd |
| Melisa Masuda-Herrera | Gilead Sciences |
| Michelle Grundahl | Inotiv |
| Michelle Schaefer | Boehringer Ingelheim Pharmaceuticals, Inc. |
| Murali Yanda | Inotiv |
| Naomi Kruhlak | US FDA/CDER |
| Nisha Rajamohan | Pfizer |
| Ofelia Olivero | NIH |
| Ofelia Olivero | NIH |
| Patricia Escobar | Merck & Co. Inc. |
| Paul Rawlinson | Gentronix Limited |
| Pavan Gollapudi | Inotiv |
| Penny Leavitt-Misura | Bristol Myers Squibb |

| | |
|---|---|
| Rajib Ghosh | Bristol Myers Squibb |
| Rambabu naravaneni | ITR Laboratories Canada Inc. |
| Robert Cerchio | Bristol Myers Squibb |
| Robert Foster | Lhasa Limited |
| Robert Preston | Janssen Research & Development |
| Ronee Baracani | Loxo at Lilly |
| Rosalie Elespuru | Discovery Life Sciences |
| Roustem Saiakhov | MultiCASE Inc |
| Sanket Gadhia | SafeBridge Consultants |
| Seda Arat | Pfizer |
| Shambhu Roy | Inotiv |
| Shannon Bruce | Inotiv |
| Shaofei Zhang | Pfizer |
| Sheroy Minocherhomji | Eli Lilly & Company |
| Stephanie Kellum | Corteva |
| Stephanie Smith-Roe | Division of Translational Toxicology/NIEHS |
| Stephen Dertinger | Litron Laboratories |
| Suman Chakravarti | MultiCASE Inc. |
| Susanne Stalford | Lhasa Limited |
| Tania Cecilia Cavaliero | Swiss Agency for Therapeutic Products (Swissmedic) |
| Timothy McGovern | US Food and Drug Administration |
| Tomas Lagunas | Genentech, Inc. |
| Troy Griffin | Teva Pharmaceuticals |
| Vivian Tang | Pfizer |
| Vladimir Torres | FMC |
| Wannie Madraymootoo | Inotiv |
| Wen Sun | Pfizer |
| Xi Chen | National Center for Toxicological Research, U.S. Food and Drug Administration |
| Yax Thakkar | RIFM INC. |
| Yi Yang | AbbVie Inc. |
| Zhenning Yang | Toxicology, Rutgers University |
| Zhiying Ji | Incyte Corporation |
| Zuzana Lee | Charles River Laboratories |

**John M. Clayton Hall Conference Center – Map**
**University of Delaware, Newark, DE**