

# Emerging Systems Toxicology for the Assessment of Risk (eSTAR)



## Our Mission

The committee's mission is to develop and deliver innovative systems toxicology approaches for risk assessment. The committee aims to catalyze adoption of new translational and predictive tools that guide decision-making based on mechanistic understanding of toxicological response.

## Chairs

### Public Chair

Dr. Brian Chorley  
(US Environmental Protection Agency)

### Private Chair

Dr. Deidre Dalmas Wilk  
(GSK)

## HESI Staff

Ms. Connie Mitchell  
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## Webpage

<https://hesiglobal.org/emerging-systems-toxicology-for-assessment-of-risk-committee/>

## 2022 Committee Highlights



### Participating Organizations

12 government/regulatory agencies, 19 academic/research institutes, 18 industry, 1 other



### Supplemental Funding

- FDA U01 Drug Development Tools Grant, \$250,000



### Publications

4 publications, 2 in progress



### Web Tools, Assays and Resources

- 1 webtool, 1 assay
- Tgx-DDI DNA damage classification tool (<https://cebs.niehs.nih.gov/tgxddi/>)
- TgX-DDI genomic biomarker approach is under review by as part of the US FDA's Biomarker Qualification program.



### Collaborations

- 1 internal, 2 externals
- HESI GTTC - exploration of a project on error corrected sequencing approaches for evaluating genomic modifications.
- US NIEHS - carcinogenomics working group.
- US EPA and NIH's NIDDK - exosomal miRNA evaluation.



### Scientific Meetings and Trainings

- 1 meeting
- eSTAR Annual Meeting (virtual; +150 attendees)

## 2022 Committee Highlights (continued)



### Outreach

2 posters, 1 oral presentation, 2 webinars

#### 13th International Conference on Environmental Mutagens

- Poster: MicroRNA Biomarkers of Nephrotoxicity Demonstrate Different Variability and Directionality in Exosomal Fraction Compared to Whole (Unfractionated) Urine.
- *TGx-DDI for High-Throughput, High-Content Identification of DNA Damaging Substances*. Dr. Carole Yauk (University of Ottawa).

#### Society of Toxicology Annual Meeting

- Poster: A Collaborative Initiative to Establish Molecular Biomarkers for Assessing Risk of Chemical Carcinogenesis to Reduce Reliance on Conventional Rodent Carcinogenicity Studies.

#### Webinars

- *Phenotypically Anchored mRNA & miRNA Expression Profiling in Zebrafish Reveals Flame Retardant Chemical Toxicity Networks*. Dr. Subham Dasgupta (Oregon State University).
- *Tox-GAN: An AI Approach Alternative to Animal Studies – a Case Study with Toxicogenomics*. Dr. Weida Tong (FDA NCTR).



### Geographic Representation

Canada, France, Germany, Netherlands, Sweden, United Kingdom, United States

## Working Groups

- **Use of a Transcriptomic Point of Departure (POD) for Chemical Risk Assessments.** This working group has compiled a broad membership of experts across sectors and chemical classes to write a recently accepted manuscript on the state of the science on the use and potential applications of transcriptomic PODs. Future work will include discussion of bioinformatic methods to derive transcriptomic PODs.
- **Carcinogenomics.** A manuscript was accepted describing the group's strategy to create transcriptomic biomarkers for particular pathways leading to rat tumors. Current work is to derive and refine the biomarkers. There is also planned experimental work to see gene expression difference in wild type and knock out rats in response to reference compounds.



**miRNA Biomarkers.** Designed and launched a multi-site experimental program on the use of exosomal miRNAs expressed in response to renal toxicants. Initiating a study to interrogate *in vitro* miRNAs to inform translational relevance in safety studies.

- **TgX-DDI.** Significant forward progress to biomarker qualification by FDA – Awarded a U01 grant application to FDA (\$250,000 USD) to facilitate for a final multi-lab validation study as requested by FDA. Secured novel in-kind commitments to supplement the above prospective analytical validation ring trial.
- **FFPE.** A manuscript on DNA de-modification analysis of clinical tumor samples was accepted; the project will sunset after an educational webinar.



**Cell Painting.** This newly formed group is planning a proof-of-concept study to see if Cell Painting data (with or without transcriptomic data) can be predictive of existing rat liver data.



**Error Corrected Sequencing.** This newly formed group is exploring the use of error corrected sequencing to detect clonal expansion of non-genotoxic carcinogens.

## Areas of Focus for 2023

- Carcinogenomics group will focus and refine specific gene signatures based on compounds with existing liver transcriptomic data for MIEs known to lead to rat liver tumors.
- The POD group will explore bioinformatic methods to derive transcriptomic points of departures, including the planning of a workshop to discuss best practices.
- The miRNA group will further define the use of miRNAs for translational safety assessment by completing an *in vitro* study to better understand the mechanistic release of miRNAs in response to nephrotoxicants.
- The TgX-DDI program will continue the analytical validation ring trial required as part of the qualification process. The TgX-DDI biomarker may also be developed as an OECD IATA case study.
- The Cell Painting group will continue to plan and execute a study to evaluate the use of Cell Painting for safety assessment.
- The Error Corrected Sequencing group will continue to explore the use of the technology to detect clonal expansion of non-genotoxic carcinogens, with potential new experimental work to build confidence.

## Strategic Impact Areas

### Enhanced Efficiency and Accuracy in Safety Assessment Practice

The Committee has and is actively developing applied transcriptomic methods (biomarkers, points of departure, etc.) that provide more efficient means for conducting hazard or safety assessments for drugs and/or chemicals.



### Catalysis of New Science

The Committee has developed novel methods for extracting usable DNA sequence information from stored Formalin-Fixed Paraffin Embedded (FFPE) samples and, thus, opened archives of stored information that was previously inaccessible. The miRNA and Carcinogenomics groups continue to develop biomarkers to detect toxicities. New programmatic work on error corrected sequencing and Cell Painting methods will also yield novel scientific insights into emerging methods and their application in safety assessment.



### Enhancement of the Societal Knowledge Base on Human Biological Processes of Relevance for Protecting Human Health

The Committee's Carcinogenomics Project is generating novel insights into pathological and transcriptomic mechanisms associated with rodent liver tumorigenesis and fostering critical discussions around the relevance of these mechanisms to human health protection. The Committee's work on miRNAs is also providing foundational data on the presence and biological significance of miRNAs.



### Increasing the Audiences for Collaborative Safety Science

Launching our new programs (Cell Painting and Error Corrected Sequencing) have brought in additional stakeholders, some to HESI for the first time. We also are working to broaden our audiences at scientific meetings (like SOT and EMGS).



### Development of Scientists Skilled in Translational Science

The Committee funded a summer intern for the Carcinogenomics Group to assist with data compilation related to existing rat cancer data.





## Publications

### Published

Wehmas et al. 2022. Organocatalyst treatment improves variant calling and mutant detection in archival clinical samples. *Nature Scientific Reports*. <https://www.nature.com/articles/s41598-022-10301-0>

Corton et al. 2022. A Collaborative Initiative to Establish Genomic Biomarkers for Assessing Tumorigenic Potential to Reduce Reliance on Conventional Rodent Carcinogenicity Studies. *Toxicological Sciences*. <https://doi.org/10.1093/toxsci/kfac041>

Johnson and Auerbach et al. 2022. A Transformative Vision for an Omics-Based Regulatory Chemical Testing Paradigm. *Toxicological Sciences*. <https://doi.org/10.1093/toxsci/kfac097>

Buick et al. 2022. Integrated Genotoxicity Testing of three anti-infective drugs using the TGx-DDI transcriptomic biomarker and high-throughput CometChip® assay in TK6 cells. *Frontiers in Toxicology*. <https://doi.org/10.3389/ftox.2022.991590>

### In Progress

MicroRNA Biomarkers of Nephrotoxicity Demonstrate Different Variability and Directionality in Exosomal Fraction Compared to Whole (Unfractionated) Urine.

Bioinformatic methods to derive transcriptomic points of departure.



## Participating Organizations

### Government/Regulatory Agencies

BC Cancer Agency (Canada)  
 Dutch Medicines Evaluation Board  
 European Commission, Joint Research Center  
 Environment and Climate Change Canada  
 Federal Institute for Drugs and Medical Devices  
 (BfArM, Germany)  
 Health Canada  
 National Institutes of Health (NIH), National Cancer  
 Institute (NCI)  
 National Institutes of Health (NIH), National Institute  
 of Diabetes and Digestive and Kidney Diseases  
 National Institutes of Health (NIH), National Institute  
 of Environmental Health Sciences (NIEHS)  
 US Army  
 US Environmental Protection Agency (EPA)  
 US Food and Drug Administration (FDA)  
 US Food and Drug Administration (FDA), National  
 Center for Toxicological Research (NCTR)

### Academic/Research Institutes

The Broad Institute of Harvard and MIT  
 Cambridge University  
 Cornell University  
 Georgetown University  
 Indiana University  
 McGill University  
 Michigan State University  
 Massachusetts Institute of Technology  
 North Carolina State University  
 Newcastle University  
 Orebro University  
 Oregon Health & Science University  
 Swansea University Medical School  
 University of Ottawa

University of California, Riverside  
 University of Cambridge  
 University of Michigan  
 University of North Carolina  
 University of Pittsburgh

### Industry

AbbVie  
 Amgen  
 AstraZeneca  
 Bayer  
 Boehringer Ingelheim  
 Corteva Agriscience  
 FMC Corporation  
 GSK  
 Janssen Pharmaceuticals  
 Merck & Co., Inc.  
 Newcells Biotech, Ltd.  
 Novartis Pharmaceuticals  
 Pfizer, Inc.  
 Sanofi  
 Syngenta  
 Taconic Biosciences  
 Takeda Pharmaceutical Company, Ltd.  
 TwinStrand Biosciences

### Other

Lhasa Ltd.  
 PETA International Science Consortium

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Burleson Research Technologies  
 Procter and Gamble