Towards causal modelling of drug-induced toxicity for preclinical to clinical translation

Computational Toxicology and Safety Guild
Predictive Modelling and Data Analytics (PMDA) Chapter
Pharmaceutical Sciences
Pharma Research and Early Development (pRED)
Roche Innovation Center Basel
F. Hoffmann-La Roche Ltd

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Computational Toxicology and Safety Guild: Andrea Morger, Alberto Valdeolivas Urbelz, Jitao David Zhang, Julia Pletz, Nicolò Milani, Tatyana Doktorova, Zhiwen Jiang

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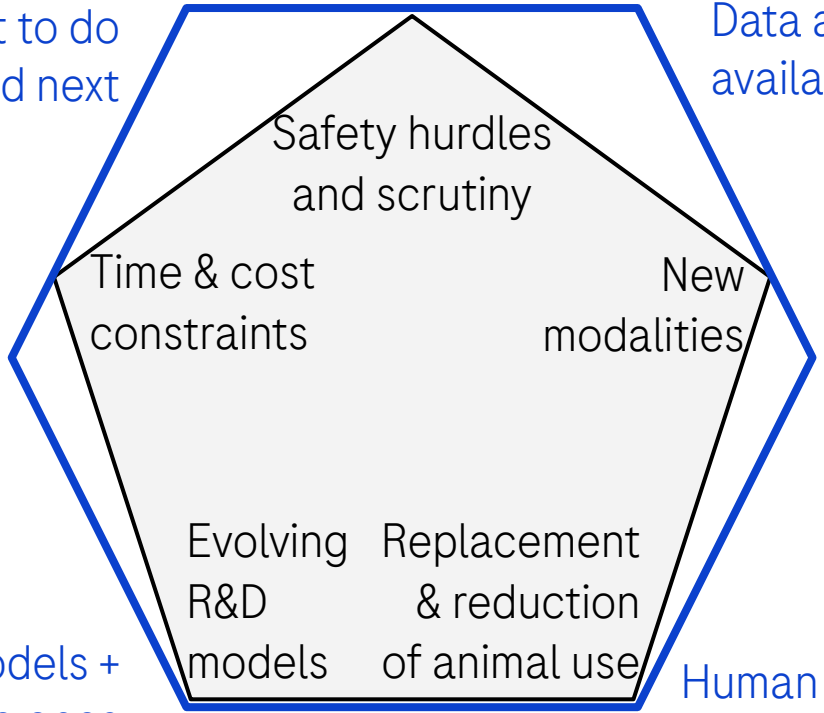
Preclinical safety assessment and risk mitigation face unprecedented challenges and opportunities

Roche's commitment to do now what patients need next

Data awareness, availability, and FAIRness



Diverse minds working on translational safety

High-throughput platforms with high-dimensional data

Off-the-shelf *in silico* models + tools to create bespoke ones

Human model systems

The *Computational Toxicology and Safety* Guild

PMDA Chapter, Pharmaceutical Sciences, Roche Pharma Research and Early Development

We are a new team focusing on computational toxicology in preclinical to clinical translation. We query which issues in drug benefit/risk assessment and risk mitigation can be solved by data and computational methods, and address them as a team in collaboration with other experts.

1. We discover new data sources for toxicity assessment and prediction, *e.g.* human model systems, clinical data, and real-world data.
2. We identify relevant feature types, *e.g.* single-cell and spatial omics, PK/PD data, and molecular modelling and simulation.
3. We develop bespoke models fitting the question, *e.g.* generative models, interpretable machine-learning models, and causal inference.

Our vision: causal modelling of drug-induced toxicity for preclinical to clinical translation

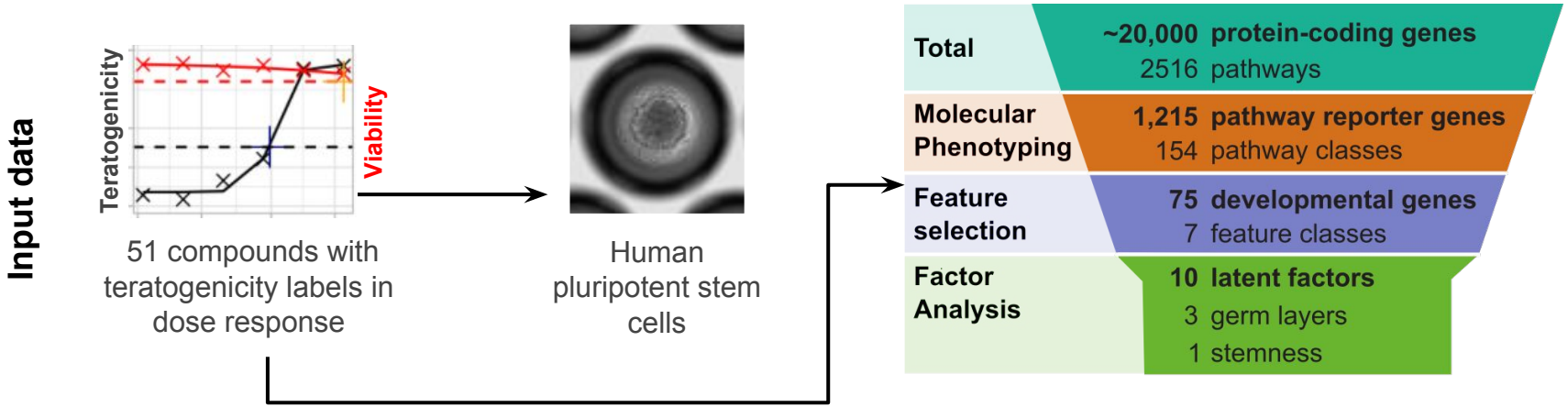
Three main focus areas of our team

- Building computational models and co-developing new *in vitro* assays to screen and profile preclinical drug candidates for safety liability.
- Improving our understanding of molecular and cellular mechanisms causing toxicity and suggest possible mitigations.
- Establishing the causal chain between molecular mechanisms, exposure, patient characteristics, and real-world observations of efficacy and safety.

Optimization of the *TeraTox* Assay for Preclinical Teratogenicity Assessment

Overview of the *TeraTox* assay

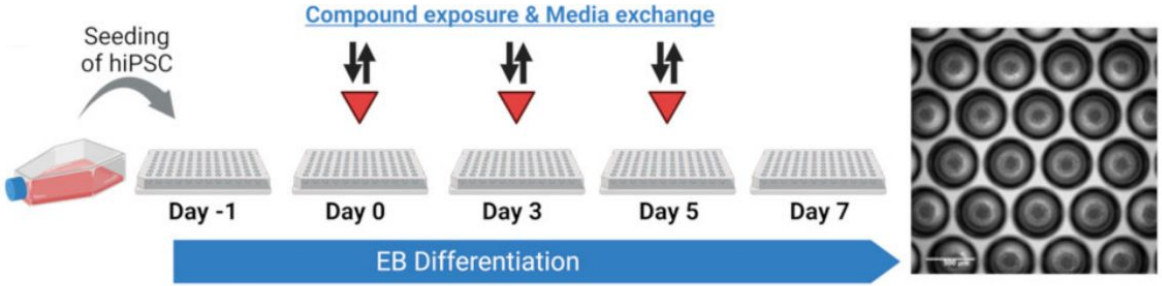
Problem: Current standard for preclinical teratogenicity assessment uses mouse cells and animal studies, which do not work well for human prediction.

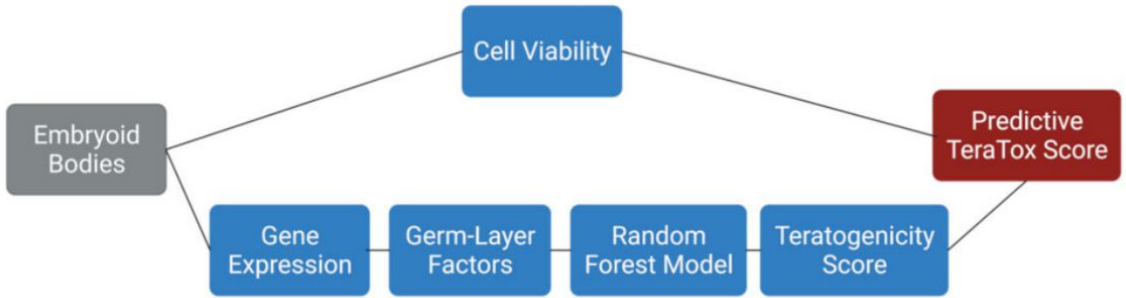


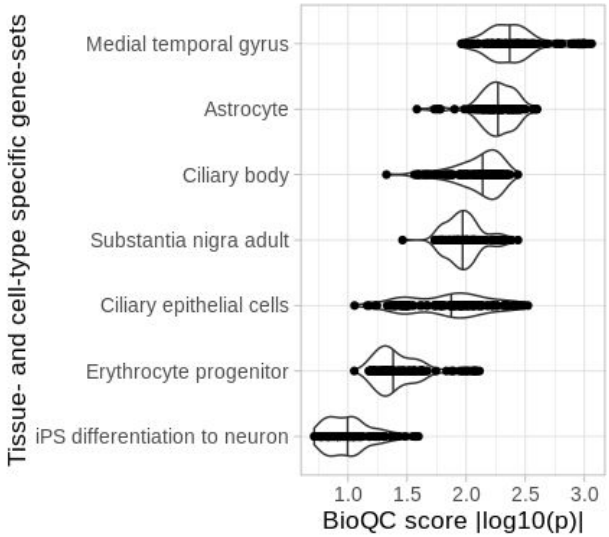
Output: A new assay, *TeraTox*, with a new readout, *Molecular Phenotyping*, empowering predictive modelling and mechanistic understanding.

Methods: factor analysis, random forest, elastic net, Bayesian network.

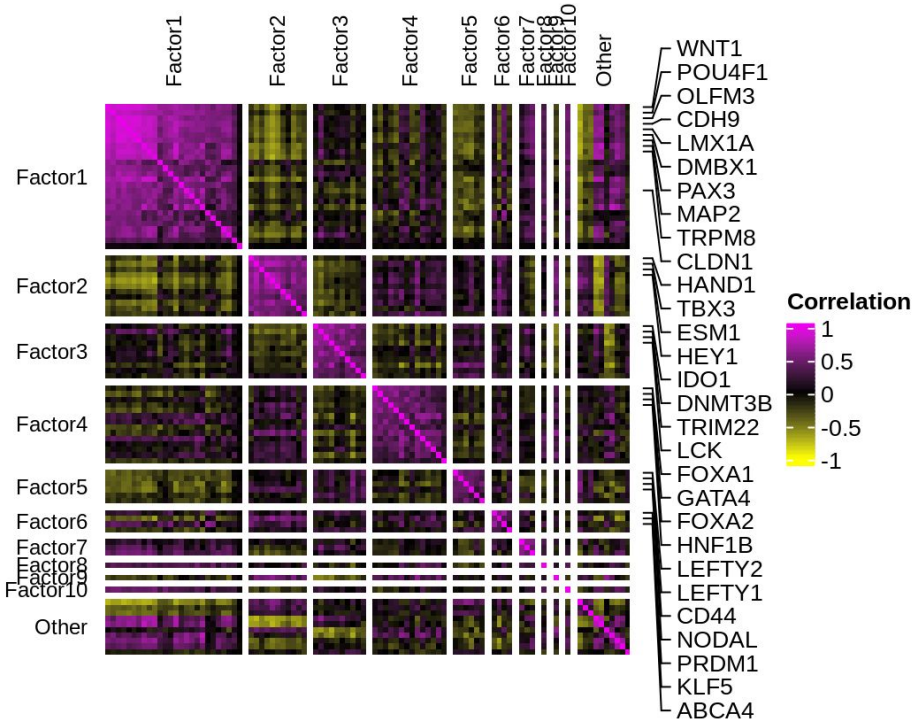
TeraTox predicts compound's teratogenicity with differential gene expression and cytotoxicity induced in embryoid bodies

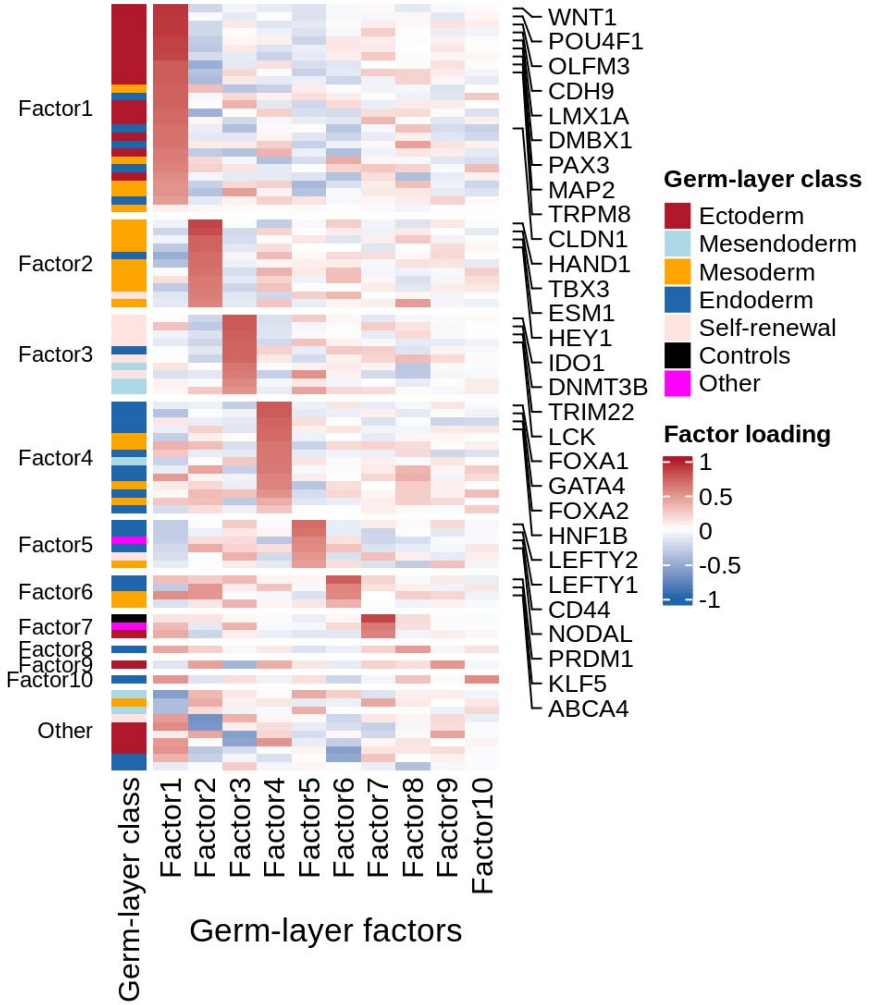




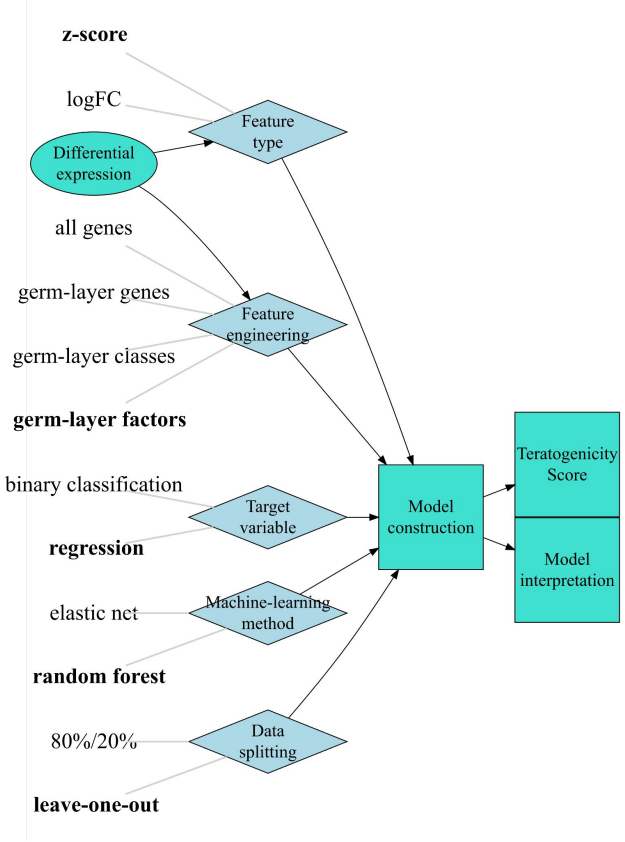


Factor analysis identified unexpected co-regulation of germ-layer markers



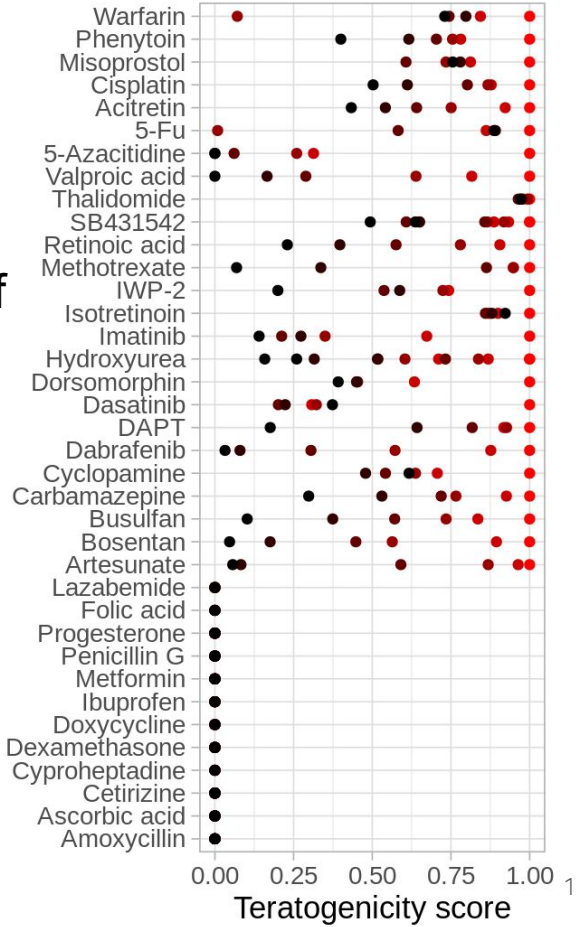


Best model was constructed with germ factors, random forest, and the teratogenicity scores

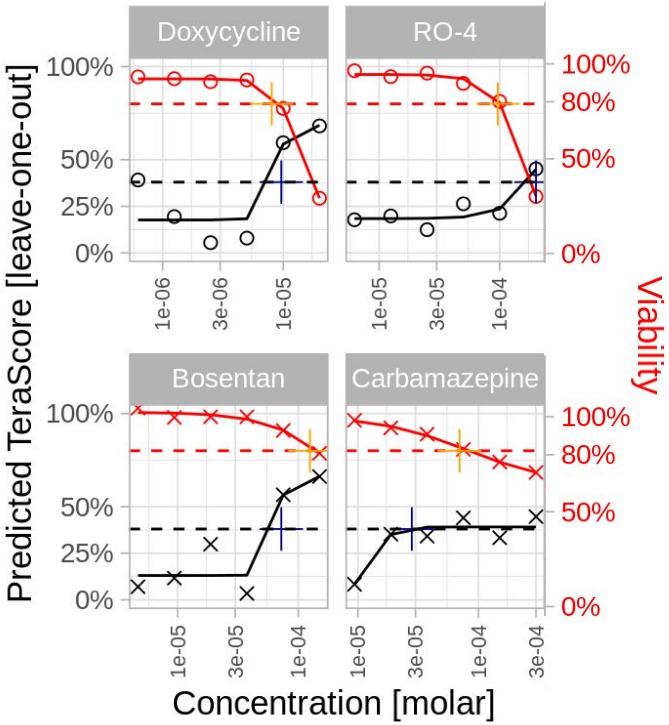


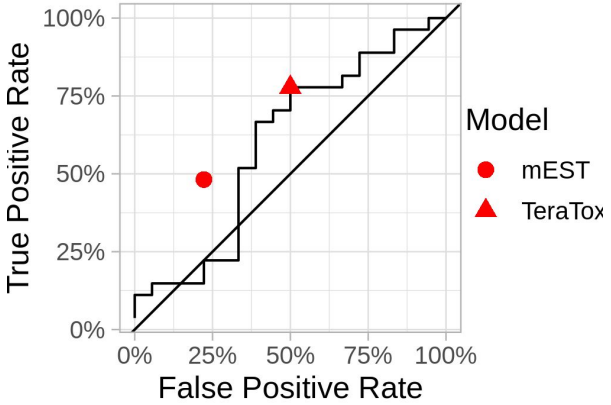
Teratogenicity scores allow dose-dependent, continuous prediction of compound's teratogenicity potential.

Technically, it is defined as the *cosine similarity* of differential gene expression profile with regard to the highest non-cytotoxic dose.



Combining *TeraTox* with mEST delivered optimal results

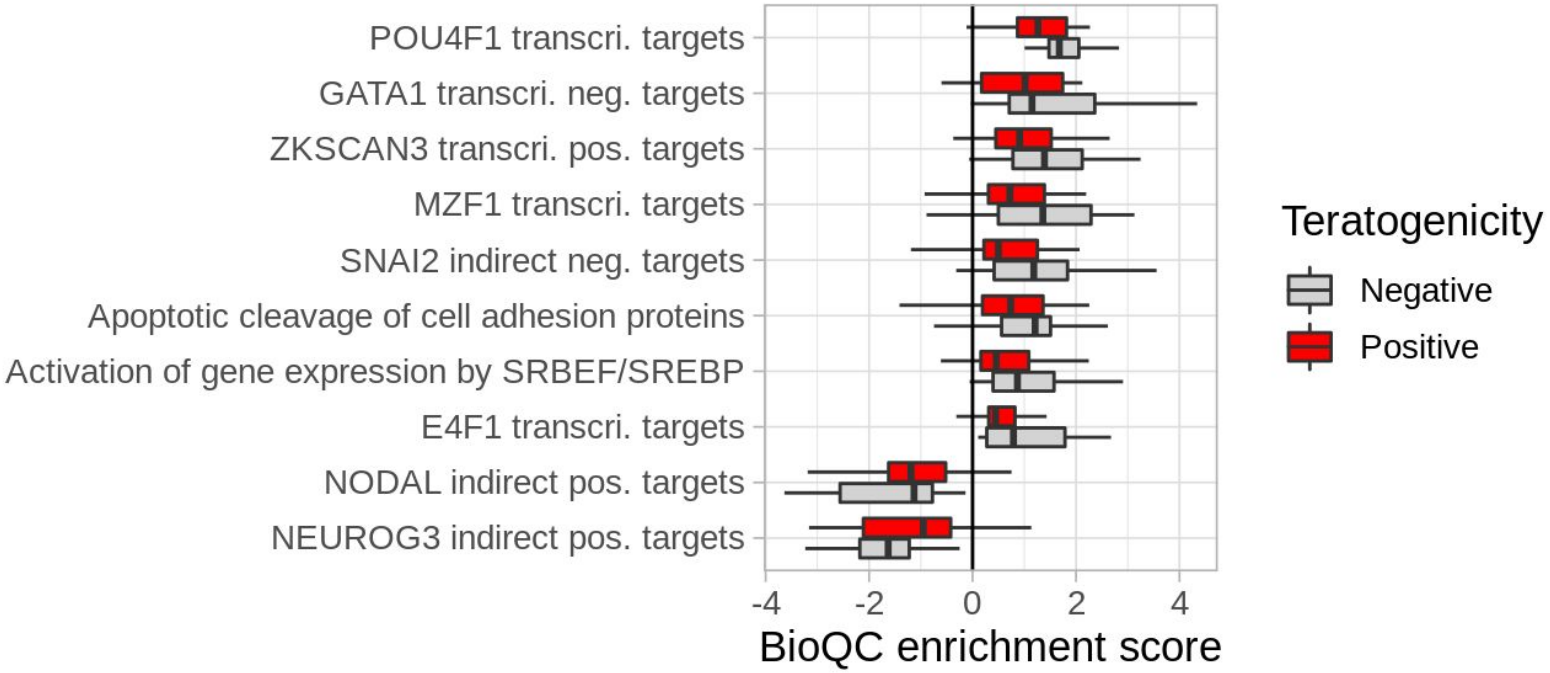




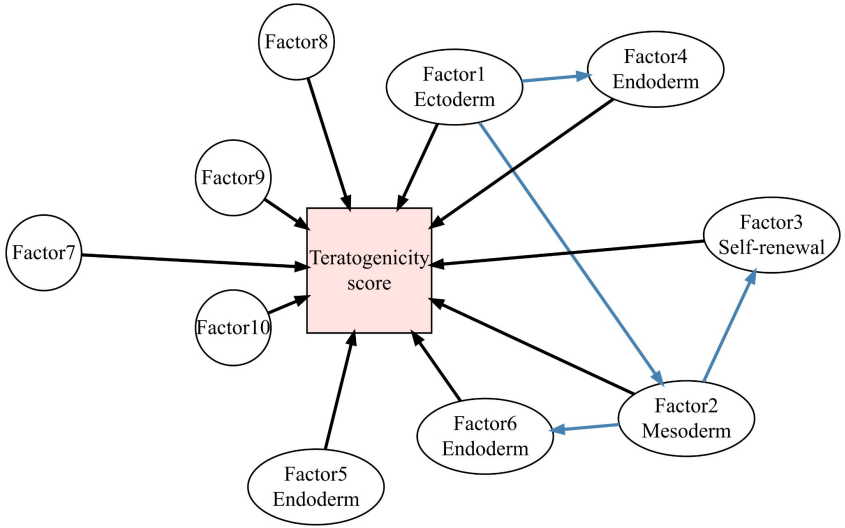
Results are Based on 45 reference compounds in 6 concentrations.

Model	Accuracy	Precision	Recall	Specificity	F_1
TeraTox	69%	73%	**79%**	53%	76%
mEST	58%	76%	46%	**76%**	57%
mEST + TeraTox	**78%**	**85%**	**79%**	**76%**	**82%**

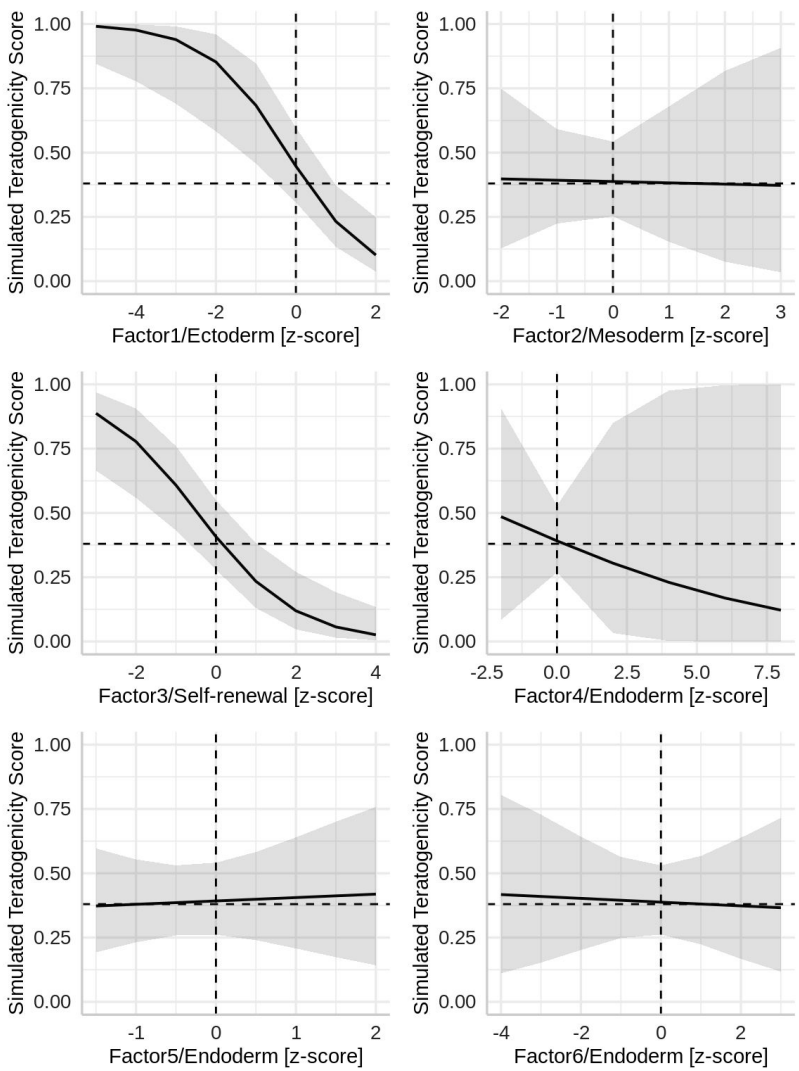
We identified biological processes potentially causing or caused by teratogenicity



Bayesian network and sensitivity analysis reveal biological insights and future directions of development



Left: A directed acyclic graph (DAG) model integrating biological knowledge and learnings from the data. Right: sensitivity analysis based on a beta-regression random forest model implementing the DAG structure.



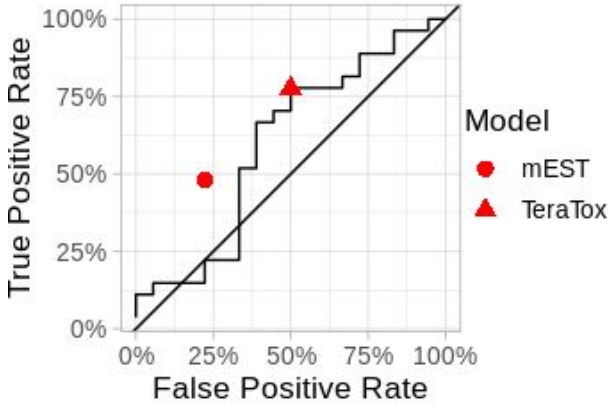
Insights gained from building *TeraTox*

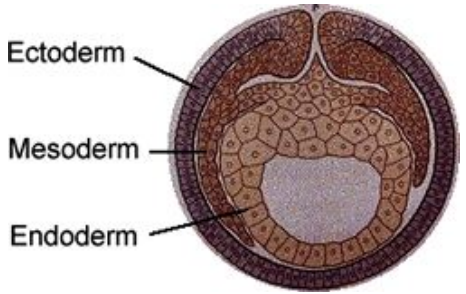
Results: *TeraTox* features higher sensitivity and better performance than the current standard mouse cell assay, potentially refining, replacing, and reducing animal research.

Successes: *TeraTox* predicts teratogenicity and distinguishes it from cytotoxicity.

Challenges: While *TeraTox* is sensitive for teratogens affecting ectoderm, future work to better model mesoderm/endoderm is warranted.

Long term goal: Replace animal studies required by regulatory approval





Manuela Jaklin, Jitao David Zhang, et al. "Focus on Germ-Layer Markers: A Human Stem Cell-Based Model for in Vitro Teratogenicity Testing." Reproductive Toxicology (2020)

Manuela Jalink, Jitao David Zhang, et al. "Optimization of the TeraTox Assay for Preclinical Teratogenicity Assessment." Toxicological Sciences (2022)

Selected ongoing projects of the team

- Developing and optimizing ML models for toxicity endpoints or assay outcome;
- Federated learning for chemoinformatics machine-learning models;
- Toxicogenomics analysis
- Quantitative DMPK prediction using mono and multi-organ-on-a-chip systems
- Expanding the teratogenicity assessment toolbox
- Spatial transcriptomics and machine learning models towards next generation toxicology workflows
- Causal inference of experimental and observational data
- Computational models of safety profiles of nucleotide acid therapeutics

Summary

- We are a young team working on computational toxicology and safety assessment for preclinical to clinical transition.
- We perform interdisciplinary research to discovery new data types, identify relevant features, and develop tailored models. We collaborate with both wet-lab experts and Data Analytics groups to develop new assays and methods for drug safety.
- We work towards the goal of causal modeling of drug-induced toxicity for preclinical to clinical translation.

Doing now what patients need next

Teratogenicity prediction relies on a different set of features from cytotoxicity prediction