

Predictive toxicology advances with new paper and data challenge

By Eddy Bal

In July, partners in the Tox21 consortium published a new study on pathway profiling of the Tox21 compound library, and announced a chemical toxicity data model competition.

"We are entering an exciting phase of **Tox21**,"

(<http://www.niehs.nih.gov/news/newsletter/2012/1/spotlight-tox21/file56736.pdf>)

said NIEHS and NTP Director Linda Birnbaum, Ph.D. "According to the latest count from NCATS [National Center for Advancing Translational Sciences], the consortium partners have screened the 10,000 compound library against cell-based assays and produced nearly 50 million data points."

"Now the challenge is to develop advanced predictive models for analyzing and understanding this massive amount of data," she said. "This is an important part of our ongoing mission to improve environmental public health and prevent disease, by addressing the backlog of thousands of untested chemicals."

The new **study**,

(<http://www.ncbi.nlm.nih.gov/pubmed/25012808>)

published July 11 in Nature Publishing Group's Scientific Reports, contains the latest data emerging from screening of the Tox21 library of approximately 10,000 (10K) environmental chemicals and drugs, for agonists and antagonists of the estrogen receptor (ER) alpha signaling pathway. The 22-member team included NTP scientists, led by Biomolecular Screening Branch head Raymond Tice, Ph.D., and scientists from Tox21 consortium partner agencies (see sidebar).

The Tox21 chemical toxicity data model **competition**,

(<http://www.ncats.nih.gov/news-and-events/features/tox21-challenge.html>)

launched by NCATS, is an effort to crowdsource data analysis by independent researchers, to reveal how well they can predict a compound's interference in biochemical pathways, using only chemical structure data. The compound profiling studies and data model competition are key components of the Tox21 initiative to develop next-generation predictive toxicology using quantitative high-throughput screening (qHTS) of chemicals.

Profiling potential endocrine-disrupting compounds

Using two ER reporter gene cell line assay formats, the Tox21 team screened chemicals for their effects on the ER alpha signaling pathway that may disrupt endocrine function in humans through unwanted interactions of chemicals with steroid hormone receptors.

Estrogenic effects occur through the numerous ER target genes that are either upregulated (agonized) or downregulated (antagonized) in response to ligand-induced activation of ERs. Both responses to estrogen produced by the body, or to such compounds as therapeutic agents, industrial chemicals, pesticides, and plasticizers can have potentially adverse effects on development, reproduction, and metabolic homeostasis, or balance.

According to the researchers, the results of their study support the feasibility of qHTS to identify environmental chemicals with the potential to interact with the ER alpha signaling pathway. Additionally, the two different assay formats improve the confidence in correctly identifying these chemicals.

Tox21

Tox21 is a collaborative effort among NIH partners NTP and NCATS, the U.S. Environmental Protection Agency, and the U.S. Food and Drug Administration.

Now in Phase II of the program, the consortium is working to develop a model for anticipating adverse responses to potentially harmful drugs and chemicals, rapidly, through in vitro screening, using multiple assay approaches, and prioritizing chemicals for more comprehensive testing with more resource-intensive test methods.



Tice was part of the five-member team of lead researchers who designed the study, which tested the 10K library in triplicate for each assay and evaluated the performance of the two assays. (Photo courtesy of Steve McCaw)

Helping the data speak a language we can understand

"The Tox21 program is a wonderful example of what can be accomplished when government agencies join forces and pool resources," said NCATS Director Christopher Austin, M.D., in the announcement of the competition.

"Our researchers have generated more data about chemical toxicity than we can realistically analyze and understand without additional collaboration," he explained. "Similar to many other large-scale scientific endeavors that generate public data, we have created the [2014 Tox21 data challenge](#) (<https://tripod.nih.gov/tox21/challenge/>) to crowdsource the best predictive models from researchers across the globe."

The computational model submission deadline is Nov. 14. NCATS will announce the winners in January 2015.

Citation: Huang R, Sakamuru S, Martin MT, Reif DM, Judson RS, Houck KA, Casey W, Hsieh JH, Shockley KR, Ceger P, Fostel J, Witt KL, Tong W, Rotroff DM, Zhao T, Shinn P, Simeonov A, Dix DJ, Austin CP, Kavlock RJ, Tice RR, Xia M. (<http://www.ncbi.nlm.nih.gov/pubmed/25012808>) 2014. Profiling of the Tox21 10K compound library for agonists and antagonists of the estrogen receptor alpha signaling pathway. *Sci Rep* 4:5664.



Austin began his career at NIH in 2002 as the senior advisor to the director for translational research at the National Human Genome Research Institute. In 2012, he was appointed the first permanent director of NCATS. (Photo courtesy of NIH)

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