

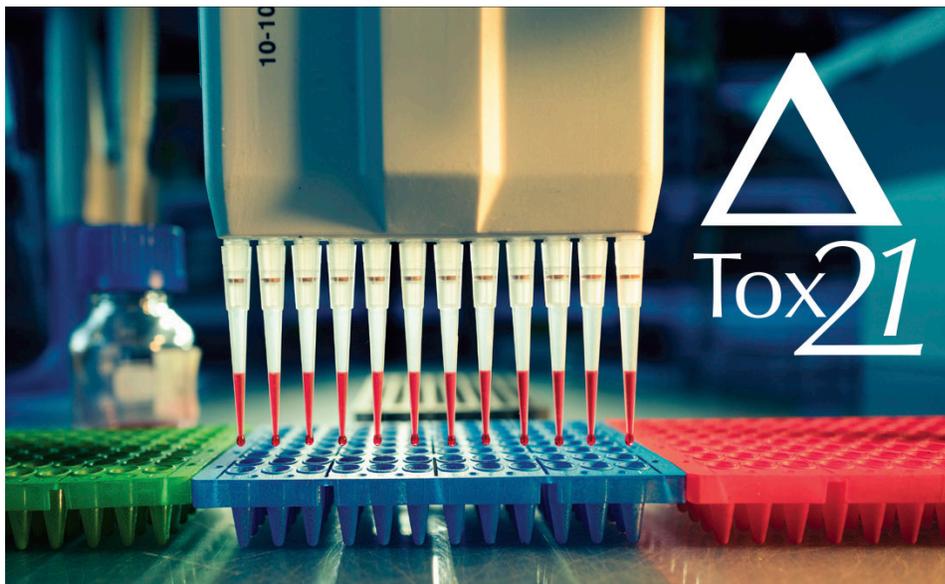
UNITED STATES FEDERAL GOVERNMENT TOX21 COLLABORATION ADVANCING TOXICOLOGY TO IMPROVE ENVIRONMENTAL HEALTH AND PHARMACEUTICAL SAFETY

Overview

Traditional approaches to toxicity testing have posed multiple challenges for evaluating the safety of industrial and environmental chemicals, pesticides, food additives, food contaminants, and medical products. The challenges include the number of chemicals that need testing, time and resources required for traditional testing, and the unexpected adverse effects that can still occur in clinical trials for drugs despite the extensive toxicological testing.

Over a decade ago, the U.S. Environmental Protection Agency (EPA), National Toxicology Program (NTP) headquartered at the National Institute of Environmental Health Sciences, National Center for Advancing Translational Sciences (NCATS), and the Food and Drug Administration (FDA) formed the Tox21 Consortium. Tox21 is a US federal research collaboration focused on driving the evolution of Toxicology in the 21st Century by developing methods to rapidly and efficiently evaluate the safety of commercial chemicals, pesticides, food additives/contaminants, and medical products. The goals of Tox21 are to (1) identify mechanisms of chemically-induced biological activity; (2) prioritize chemicals for more extensive testing; and (3) develop more relevant and predictive models of *in vivo* toxicological responses.

The Tox21 Consortium has achieved numerous successes over the years, but many challenges remain. To chart out a path for addressing these challenges, the Tox21 Consortium recently released a new strategic and operational plan (Thomas et al, 2018) that expands the focus of research



activities to address key challenges in advancing toxicology testing in the 21st century. If successful, it will make substantial progress towards improved evaluation of chemicals for health effects.

Tox21 Consortium Successes

To date, the Tox21 Consortium has been successful generating data on pharmaceuticals and thousands of data poor chemicals, developing a better understanding of the limits and applications of the *in vitro* methods, and enabling the new data generated to be incorporated into regulatory decisions.

Generated data on pharmaceuticals and thousands of data poor chemicals

- Tox21 has screened thousands of chemicals in approximately 70 high-throughput assays covering over 125 important processes in the body and generating more than 120 million data points.

- Tox21 data is publicly available through the National Library of Medicine's PubChem, the EPA's Computational Toxicology Dashboard, and NTP's Chemical Effects in Biological Systems.

- Detailed assay annotations, protocols, and performance statistics are publicly available on the EPA's Computational Toxicology website (www.epa.gov/comptox) and the NIH tripod web site (<https://tripod.nih.gov/tox21>).

Developed a better understanding of new approaches

- Tox21 has published over 200 scientific peer-reviewed articles in approximately 55 journals.
- The top five Tox21 articles have been cited an average of more than 100 times.
- Over 80 Tox21 publications have been cited in U.S. National Academy of Sciences Reports.



Application to regulatory decisions

- US EPA's Endocrine Disruption Screening Program (EDSP) is using Tox21 data to prioritize chemicals for additional testing. Currently, Tox21 data for estrogen receptor activity are used in a computational model to predict potential endocrine activity and have been accepted as alternative tests within the current EDSP Tier 1 testing requirements.
- The World Health Organization's International Agency for Research on Cancer (IARC) has used Tox21 data as supporting mechanistic evidence for chemical carcinogenesis.

Strategic Direction for the Next Five Years

Over the years, the predominant Tox21 research activities focused on developing and applying high-throughput screening to toxicity testing. To more broadly address the challenges in toxicology, Tox21's new strategic and operational plan expands the focus of its research activities. The new focus areas include developing an expanded portfolio of alternative test systems that are predictive of human toxicity, addressing technical limitations in *in vitro* test systems, curating legacy animal (*in vivo*) toxicity testing data, establishing scientific

confidence in the *in vitro* test systems, and refining alternative methods for characterizing pharmacokinetics and disposition in *in vitro* assays. Initial research activities under the new strategic vision and operational plan include the following cross-partner projects. The cross-partner projects may change over time depending on priorities and research outcomes.

1. Development of a High-Throughput Assay to Identify 5- α Reductase Inhibitors for Orthogonal Evaluation in an Androgen-Dependent Human 3D Prostate Microtissue

Goal: Develop additional human-based, cellular test systems to more completely model androgen pathway activity.

2. Cell Line Selection for High Throughput Transcriptomics (HTT)

Goal: Develop a strategy for selecting maximally diverse cell types/lines to maximally cover biological targets and pathways for high-throughput chemical screening using gene expression (i.e., transcriptomics).

3. Profiling Environmental, Drug, and Food-Related Chemicals that Inhibit Acetylcholinesterase Activity

*Goal: Develop a high-throughput *in vitro* test system to identify and characterize new compounds that block the activity of acetylcholinesterase.*

4. *In Vitro* Chemical Disposition

*Goal: Understand the impact of chemical disposition within *in vitro* test systems across a broad range of chemical categories and develop a computational model to predict differences between the "nominal" concentration of a chemical compared with "true" concentration in the media and cells.*

5. High-Throughput Transcriptomic Analysis

Goal: Develop a common chemical reference dataset for interpretation of high-throughput transcriptomic screening data.

6. Predictive Modeling of Developmental Toxicity with Human Pluripotent Stem Cells

Goal: Evaluate a human-based, induced pluripotent stem cell (iPSC) test system to predict developmental toxicity.

7. Toxicodynamic Variability in Developmental Neurotoxicity

Goal: Incorporate genetic variation into cell-based test systems to better understand potential population differences in response to chemicals that may cause toxic neurological effects.

8. Performance Based Validation of Alternative Test Systems and Models

Goal: Develop an evaluation framework for the development of performance standards which can be used to establish confidence in alternative test systems and models.

History

The Tox21 collaboration was formalized in 2008 through a memorandum of understanding (MOU) between the National Institutes of Health, including the National Toxicology Program (NTP) and National Human Genome Research Institute's National Chemical Genomics Center (NCGC, now a part of NCATS), and the EPA's National Center for Computational Toxicology. The Food and Drug Administration (FDA) joined the Tox21 collaboration in 2010. The Tox21 Consortium recommitted to the collaboration in 2015 by signing a new MOU.

More information available – www.tox21.gov

Tox21 Strategic and Operational Plan Citation

Thomas, R.T, Paules, R.S, Simeonov, A, Fitzpatrick, S, Crofton, K, Casey, W and Mendrick, D. The US Federal Tox21 Program: A Strategic and Operational Plan for Continued Leadership. ALTEX. (2018). doi:10.14573/altex.1803011

