

## ***The Future of Tox21 – Improving on Biological Coverage and Human Relevance***

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The Toxicology in the 21<sup>st</sup> Century or Tox21 effort is a multiagency collaboration among the US National Institutes of Health's National Institute of Environmental Health Sciences (NIEHS)/National Toxicology Program (NTP) and the National Center for Advancing Translational Sciences (NCATS), the US Environmental Protection Agency (EPA) and the US Food and Drug Administration (FDA). The goal of the Tox21 program is to improve identification and characterization of adverse effects from chemical exposures, to prioritize chemicals for further toxicological evaluation and to improve human risk assessments. This involves a shift from dependency on traditional rodent toxicological studies to an incorporation of target-specific, mechanism-based and systems biology approaches using in vitro systems and simple model organisms. Tox21 Phase I and Phase II involved qHTS profiling of approximately 10,000 chemicals across a set of primarily nuclear receptor and stress response cell-based assays. Recognizing certain limitations in the current approach, Phase III of Tox21 is designed to expand biological coverage exploiting genomic approaches as well as to improve human relevance with more physiologically-relevant cell models and lower organism systems. Cell systems under evaluation for bringing increased human physiological relevance include human cells with metabolic capabilities reflective of the tissue of origin as well as ES- and iPS-derived cell systems that reflect developmental processes as well as tissue specificity in response to chemical exposures. Developmental, reproductive and behavior effects from chemical exposures will also be explored in lower organisms such as embryonic zebrafish. Development of a mid to high throughput transcriptomic approach utilizing a target gene set (S1500+) as well as whole transcriptome approaches are under evaluation for bringing a systems biology evaluation into chemical screening.