Mapping the Human Toxome by Systems Toxicology

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Technological advances allow high-resolution biological phenotyping of the responses of cells and organisms for the elucidation of mechanisms of toxicity; these include the various omics, high-throughput and high-content technologies. Some of these information-rich tools have the potential to provide a molecular understanding of toxicological mechanisms and are the focal point of our transformative research project. The NIH Project "Mapping the Human Toxome by Systems Toxicology" (NIEHS grant R01ES020750) is a collaboration of Johns Hopkins Bloomberg School of Public Health, Brown University, The Hamner Institute, Georgetown University, U.S. EPA National Center for Computational Toxicology and Agilent; it aims to establish a workflow for the systematic identification and annotation of pathways of toxicity (PoT). A Human Toxome knowledge database and its governance shall be established. The project uses untargeted mass spectrum-based metabolomics and gene array-based transcriptomics. The pilot model is the estrogenic response of MCF-7 cells, a well-established and pre-validated test for endocrine disruption.

In line with the project work plan, the model was established in two laboratories and standard operation procedures were developed. The feasibility of transcriptomics and metabolomics were demonstrated. Priority was given to a number of quality assurance measures and the seminal dataset defined by the consortium is being generated, which comprises several hundred gene arrays and several thousand metabolomics profiles representing different concentrations and time points of treatment. Tools for combined multi-omics data analysis, data integration and visualization are being developed, since the bioinformatics tools associated with the PoT concept represent a core deliverable. In this ambitious project, a number of challenges arose and were tackled by the Human Toxome consortium. The concept of distinct and conserved PoT valid for different cell systems and hazards is a hypothesis to be verified. A working PoT definition was established and will be further refined. A key question is, how many PoTs there are? Challenges include also the quality and standardization of the toxicological test systems (especially *in vitro* systems) and the omics technologies. The bioinformatics tools for identification, annotation, proof of causality and validation, as well as the link of PoT to adversity are not yet fully available. A number of workshops, organized in the frame of this project, as well as commissioned white papers complement the consortium technical work to answer these questions.