SBS 17th Annual Conference
March 27-31, 2011 Orlando, FL

Session: Prediction & Elucidation of Target Liabilities

Elucidation of Adverse Bioactivity Profiles as Predictors of Toxicity Potential

Keith Houck
National Center for Computational Toxicology, Office of Research and Development, US EPA

Toxicity testing in vitro remains a formidable challenge due to lack of understanding of key molecular targets and pathways underlying many pathological events. The combination of genome sequencing and widespread application of high-throughput screening tools have provided the means to extensively explore the interactions of small molecules with many potential targets of toxicity. Through the ToxCast program, we have evaluated the effects of a diverse set of environmental chemicals with known in vivo toxicities on a diverse array of molecular targets and pathways using biochemical assays focusing on numerous protein super-families as well as with cellular assays looking at effects on a variety of signaling pathways and phenotypic endpoints. Initial results included identification of unique bioactivity profiles that correlated with animal toxicity endpoints including liver cancer, developmental and reproductive toxicity and disruption of vasculogenesis. To increase our coverage of potential toxicity targets we have expanded our assay diversity to include screens focused on critical signaling pathway nodes. In addition, we have broadened the chemical diversity beyond our initial focus on pesticides to encompass many classes of chemicals of environmental significance. Importantly, we also included a collection of human pharmaceuticals and drug candidates that failed during clinical development or post-launch due to toxicity issues. These compounds may serve to bridge species differences between standard laboratory models and human effects. Preliminary results show that differences between environmental chemicals and pharmaceuticals lay primarily in differences in potency with both groups of chemicals showing relatively wide target promiscuity. Collation of the in vivo toxicity information for both environmental chemicals and pharmaceuticals in to a relational database is underway and will serve as an anchor for developing new models correlating in vitro bioactivity profiles with in vivo, adverse endpoints. *This work was reviewed by U.S. EPA and approved for publication but does not necessarily reflect official Agency policy.*