Predicting Toxic and Therapeutic Mechanisms of the ToxCast Chemical Library by Phenotypic Screening

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Addressing safety aspects of drugs and environmental chemicals relies extensively on animal testing. However the quantity of chemicals needing assessment and challenges of species extrapolation require development of alternative approaches. Using 8 primary human cell systems (BioMAP), we screened in concentration-response format 776 chemicals from the ToxCast Phase II library (http://epa.gov/ncct/toxcast/chemicals.html) for perturbation of physiologically important pathways. Cell systems consisted of combinations of endothelial, peripheral blood mononuclear, bronchial epithelial and coronary artery smooth muscle cells; fibroblasts and keratinocytes. Chemical-response signatures from 87 endpoints covering molecular functions relevant to toxic and therapeutic pathways were generated. Assessment of profiling data by unsupervised clustering using Self Organizing Maps and supervised analysis using Support Vector Machine algorithms grouped chemical/concentration by potential mechanism class providing insight into polypharmacology and potential off-target effects of drugs. Clusters contained diverse mechanistic activity including kinase, TNFα, phosphodiesterase and Hsp90 inhibitors; Ah, estrogen and glucocorticoid receptor modulators; disruptors of mitochondrial and tubulin function; histamine antagonists; and statins. Novel associations identified included induction of tissue factor in endothelial cells by ER antagonists, AhR agonists and mTOR inhibitors, all chemical classes with susceptibility to venous thrombosis. Further, structure-based analysis demonstrated associations between chemical categories and mechanism class predictions. Our results yielded an extensive list of potential toxicological targets and biological pathways that we are incorporating into a chemical prioritization strategy for chemicals of concern to the Agency. *This work does not necessarily reflect official Agency policy.*