Chemical Compound Profiling of Cell-based Toxicity Assays Using Quantitative High-Throughput Screening

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Traditionally, toxicological profiles of drugs or chemicals rely on in vivo studies in laboratory animals. While these profiles provide useful information about the safety of chemical compounds, this approach is expensive, low-throughput, and inconsistently predictive of human biology and pathophysiology. To overcome these limitations, we have begun to develop a battery of cell-based assays to profile the toxicity of chemical compounds in a variety of cell types using quantitative high throughput screening (qHTS). The ultimate goal is to identify in vitro chemical signatures that could act as predictive surrogates for in vivo toxicity. Importantly, and distinct from conventional single concentration HTS screening, qHTS is capable of generating high-confidence positive and negative activity data, making it suitable for the comprehensive profiling of potentially toxic compounds. Thus far, the activity of 1,408 compounds from the National Toxicology Program (NTP) has been determined in assays for cytotoxicity and caspase 3/7 activity. Corresponding human and rodent cell lines derived from 6 tissues that are common targets of xenobiotic toxicity (liver, blood, kidney, brain, lung, and skin) were used in these assays. Data analysis has identified compounds that are toxic to all cell types at similar concentrations, as well as compounds that exhibit selective toxicity to particular cell types. In addition, some compounds appear to utilize the caspase 3/7 pathway as a mechanism for cytotoxicity, while others exhibit cytotoxicity independent of this pathway. These proof-of-principle data are being used to scale-up the profiling effort to incorporate more assay

conditions, assay and cell types, and compounds. The resulting large data sets will provide a rich source of information for the development of in vitro toxicological signatures and the prediction of toxic effects of new chemical entities.