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ToxCast Profiling in a Human Stem Cell Assay For Developmental Toxicity

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Abstract:
We correlated the ToxCast library in a metabolic biomarker-based in vitro assay (Stemina devTOXqP) utilizing human embryonic stem (hES) cells (H9 line). This assay identifies the concentration of a chemical that disrupts cellular metabolism in a manner indicative of teratogenicity [Palmer et al. 2013]. Undifferentiated H9 cells were exposed for 72h and media from the final 24h period was analyzed by LC-MS to determine the ornithine to cystine ratio (ORN/CYSS). ORN is derived from arginine breakdown during the citric acid cycle and CYSS is formed by oxidation of cysteine molecules that covalently link via a disulfide bond, and the corresponding 'teratogen index' based on ORN/CYSS falling below 0.88. To date, the raw and plate-normalized data for 286 samples in concentration series (269 chemicals plus replicates, n=3) and another 812 samples at a single concentration (n=4) have been entered into the ToxCast pipeline for QA, processing, analysis and eventual release to the public. A preliminary analysis revealed the following trends. First, 166 compounds (15.5% of the tested compounds) were 'active' based on the default ORN/CYSS threshold (0.88). These included many known teratogens, such as trans-retinoic acid (LEC = 3 nM), 5-fluorouracil (100 nM), methotrexate (100 nM), thalidomide (300 nM), and carbamazepine (3 uM) among others. Second, for 23 compounds with FDA codes (A,B,C,D,X) or ECVAM classifiers, the default model had a balanced accuracy of 84% (sensitivity 0.80, specificity 0.88). Third, Many chemicals not yet classified were predicted positive, including the angiogenesis inhibitors TNP-470 (10 nM) and 5HPP-33 (10 uM). Fourth, at the concentrations tested specificity was demonstrated for a parent-metabolite pair where only the proximate teratogen was active; for chemical stereoisomer pairs where only one compound was active; and for 3 closely-related structural isomers where only one structure was active. Cross-referencing with ToxCastDB (in vitro) and ToxRefDB (in vivo) is being undertaken to assess the added value of the devTOXqP assay performance in computational models built for predictive teratogenicity in a human cell-based system. (Disclaimer: this abstract does not reflect EPA policy).
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