Development of a Human Adipose Stem Cell Model for Characterization of Chemical Modulation of Adipogenesis

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The use of in vitro assays for toxicological safety assessments requires models that can accurately predict adverse health outcomes in humans. Fit-for-purpose assay development begins with these endpoints in mind to design models specifically oriented to the key molecular and cellular events contributing to an adverse response. The technologies outlined in this project incorporated minimal engineering with maximum biologically relevant design elements to bridge the current gaps toward more predictive toxicity testing.

Identifying adverse developmental effects related to endocrine disrupting chemical exposure remains a top priority for the U.S. Environmental Protection Agency’s (EPA) Endocrine Disruption Screening Program. Human health outcomes connected to developmental toxicity are heavily focused on areas such as early embryogenesis and neurogenesis; however, emerging areas of interest include development of endocrine organs, such as adipose tissue, to address critical health issues tied to metabolic disease (Heindel et al., 2015). The National Toxicology Program has emphasized the need to develop more physiologically-based in vitro models for predicting chemical effects on adipose tissue development and has noted the utility of using high-throughput screening data for prioritizing chemical bioactivity specific to metabolic endpoints (Thayer et al., 2012). The most recent profiling of chemicals from both Phase I and II of ToxCast™ for endocrine activity has included modes of action geared toward key metabolic toxicity pathways (e.g. PPARs and glucocorticoid receptor) (Filer et al., 2014); however, little data has been generated on the activity of these compounds in human stem cells.

This project used an integrated approach to design and evaluate a system to screen for endocrine disrupting chemical effects on human adipose tissue development. The model aimed to generate human relevant data to test the hypothesis that pre-natal and early-life chemical exposures could contribute to obesity outcomes in childhood and later life (La Merrill and Birnbaum, 2011). In this project, we completed the development of a first-generation human stem cell model for characterization of chemical effects on progenitor cell differentiation. We developed a second-generation model with improved parameters and have used it to screen a subset of 60 chemicals prioritized in Phase I of EPA’s ToxCast™ screening program. A series of five additional orthogonal assays representing eight different molecular endpoints for PPARG-dependent adipogenesis were developed to assess the function of the ToxCast™ prioritized chemical set on developmental modulation of adipogenesis. Assays were designed with a common core concentration-response design to enable seamless inter-assay comparability, as well as efficient integration of data into the most recently developed ToxCast™ analysis pipeline released by the National Center for Computational Toxicology. Collectively, the generated data sets provide more insight into the capacity of prioritized chemicals to function as PPARG ligands in primary human stem cells during development.

Implications: The transition to high-throughput in vitro chemical testing for bioactivity profiling has led to questions regarding the relevance of findings to human safety assessments. Second tier testing paradigms in assays fit for the purpose of evaluating human responses have been proposed as one means of narrowing down specific activity. To reduce uncertainty in data generated from single endpoint in vitro assays, integrated approaches to testing and assessment (IATAs) establish a framework for targeted phenotypic in vitro and in silico assay batteries that can provide greater weight of evidence to high-throughput in vitro findings. The project outlined here used an integrated approach to assess endocrine activity of prioritized chemicals in a second tier screening battery for human stem cell differentiation designed to test the hypothesis that chemical exposures contribute to the developmental origins of obesity and metabolic disease. The project serves as a model for the design and implementation of human-based cellular assays for targeted phenotypic chemical testing of data generated from high volume screening efforts.

This abstract was prepared by the principal investigator for the project. Please see www.americanchemistry.com/lri for more information about the LRI.
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References:


