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# PROJECT PROPOSAL

**Topic:** Embryonic Model Systems as a Surrogate Assay for Proliferative Potential of Test Compounds

**Submitted by:** Bristol-Myers Squibb, Drug Safety Evaluation

The ILSI-HESI Toxicogenomics Committee (technical committee for the "application of genomics to mechanistic based risk assessment") has focused its previous efforts largely on in vivo expression profiling associated with target organ toxicity in rat liver, kidney and heart. These efforts have provided relevant fundamental data that has contributed to the growing use of transcriptional profiling data in hazard identification. In many drug safety evaluation groups, transcriptomic profiling in short term repeat-dose toxicology studies has become a routine component of nonclinical safety assessment, and when compared to in-life, hematology, clinical chemistry, and histopathology results, transcriptional profiles show some utility for predicting target organ toxicities. Moreover, transcriptional profiles can also be utilized in short term studies to make decisions on back-up compounds without completion of full toxicologic assessments.

While transcriptional profiling has shown utility in assessing target organ toxicities, there has been less effort directed toward evaluating transcriptomic profiles that may predict chronic toxicity (including carcinogenicity) or efforts to utilize in vitro models to evaluate or predict both acute and chronic toxicity. To that end, there is an opportunity to expand the application of transcriptional profiling data to safety evaluation and risk assessment by determining whether transcriptomic profiles from shorter term repeat dose studies can be correlated with more chronic toxicities. Proactive identification of these liabilities would enable strategic decisions on the timing and design of nonclinical studies to address such safety concerns.

The proposed work will focus on hyperplasia or cell proliferation as a major endpoint, with the overarching objective being to determine whether hyperplastic potential can be predicted by development of in vitro model systems capable of confirming cellular proliferative responses in vivo. Embryonic cell model systems are potentially robust in vitro models for such purposes, given the broad pluripotency of cell populations, their high proliferative capacity, and the expression of pathways associated with the balance between proliferation and differentiation (eg, protooncogenes, growth factors, tyrosine kinases, wnt pathway, Homeoboxes, )[1-8].

Research efforts would be initiated with exploratory work to determine whether in vitro developmental models are suitable for verifying proliferative potential of compounds and to determine whether this liability can be identified from transcriptomic profiles. The test systems would include rat whole embryo culture and/or mouse embryonic stem cells, and the study will

include cell cycle and proliferation measurements (using multiple methods and markers) following treatment with reference compounds known to produce positive or negative proliferative responses. Once methods have been optimized and proof-of-concept achieved, additional studies will be conducted with a small set of tool compounds that have been profiled by transcriptomics and have produced hyperplastic responses in representative target organs including liver or mammary gland (and potentially other tissues) in repeat-dose toxicology studies.

The proposed work is exploratory in nature, but if successful, would add to our scientific understanding of hyperplasia, a common event seen in many toxicology studies. Furthermore, a major benefit derived from the focus on in vitro models is the possible application of these tools for hazard identification and risk assessment relative to current regulatory restrictions on the use of animals in toxicology testing (i.e. REACH legislation in the EU). Finally, although the collaborative work is consistent with the ILSI-HESI efforts in toxicogenomics, it is also applicable to and consistent with efforts to predict long-term outcomes from shorter-term studies, a collaborative effort presently ongoing within the ILSI-HESI Cancer Hazard Identification Committee. As such, a focused, collaborative effort on the application of embryonic model systems to transcriptional profiling and hazard identification relative to hyperplasia and carcinogenic outcome is consistent with broad initiatives within ILSI. A collaborative research effort to assess the feasibility and predictivity of this experimental approach would greatly facilitate the generation of data, and the body of work in its totality would provide important new information on the application of in vitro test systems for transcriptional profiling evaluation along with the prediction of chronic toxicities from short-term and/or in vitro studies.

**References:**


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