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PROJECT PROPOSAL

Topic: Predictive Cardiovascular Risk Assessment by Genomic Methods

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The drug development community has recently been plagued by a number of high-profile, non-QT cardiovascular safety issues in late-stage or marketed compounds. Though our preclinical safety assessment paradigms provide a fair opportunity to identify acute cardiovascular effects of novel therapeutic compounds, they are not as useful for identifying longterm risk associated with insidiously progressive alterations in cardiac physiology. Nor are they crafted to understand the effects of xenobiotics in the context of pre-existing cardiovascular disease. Paradoxically, this limitation is in the context of target patient populations with a significant background of cardiovascular disease. Predictive cardiac genomics could provide an opportunity to identify risky drug-related changes in cardiac physiology (particularly energy metabolism and myocardial remodeling) long before these changes result in a clinically detectable endpoint.

This effort would fall squarely within the stated mission of the HESI Genomics Committee to "advance the scientific basis for the development and application of genomic methodologies to mechanism-based risk assessment". It would also build on current efforts of this group evaluating a doxorubicin model of cardiac injury in rodents. Additionally, this work could link efforts in and outside HESI focused on various aspects of cardiovascular safety and biomarker development (i.e. ILSI-HESI Cardiac Troponin Working Group, Critical Path Institute's Cardiac Safety Research Consortium). Lastly, this effort could bring together experts in the fields of experimental, clinical, and preclinical cardiac disease to progress the understandings of cardiac physiology, pathophysiology, toxicity, and morpho-functional-genomic correlates.

This effort might begin with a workshop to convene relevant experts in the fields of preclinical and clinical cardiac disease/toxicity to understand the background of cardiovascular disease in target patient populations as well as commonalities in the adverse cardiovascular events that have complicated development and application of these efficacious molecules. A consequent expert working group would convene to identify relevant animal models and test compounds. Transcriptional data would be gathered in these models in the context of more routine endpoints like morphology and cardiac function to provide the appropriate biological context. Those data sets could be interrogated in a discovery paradigm to uncover previously undescribed relationships but could also be evaluated in a supervised way to identify well-recognized pathologic pathways (e.g., perturbations in energetics, myocardial remodeling, etc.).