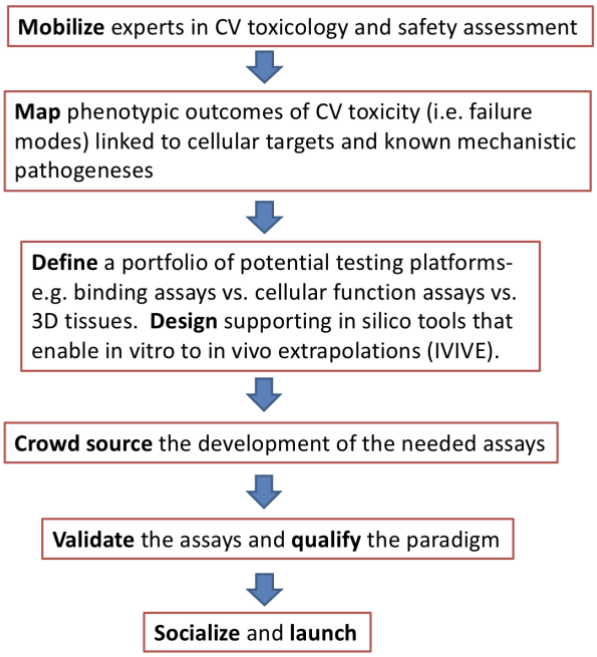
Project Title: Human-relevant and Mechanistic Cardiovascular Drug Safety Screening Initiative

Project Description:

This project is a partnership between the Food and Drug Administration, (Norman Stockbridge, Dir. Division of Cardiovascular and Renal Products, CDER), the National Institute of Environmental Health Sciences National Toxicology Program (Dr. Brian Berridge, Scientific Director) and the Cardiac Safety Technical Committee of the Health and Environmental Sciences Institute (HESI; Syril Pettit, Executive Director).

The overall aim of this initiative is to design, build and test a novel framework for pharmaceutical and environmental chemical cardiovascular hazard assessment. The current paradigm is largely reliant on low-throughput animal studies conducted late in preclinical development. Accordingly, development-limiting liabilities are identified late and are presumed relevant to human patients. The current paradigm would benefit from an approach that is more efficient in cost and time, mechanistically informative and human relevant. An improved screening and testing approach would enable earlier recognition of development-limiting liabilities, fewer false positives leading to premature development termination, more relevant biomarkers, increased mechanistic understanding, and decreased late-stage attrition. The HESI Cardiac Safety Technical Committee will leverage its considerable breadth of expertise and network of technology developers to design this novel approach.

This outline displays the approach of the committee.



Within this outline, a number of projects will be supported by research trainees with discrete work plans. Funding for the fellow's stipend, insurance, operating expenses, and travel will be managed through the ORISE Fellowship Program. The projects are:

Project #1: In Silico Screening for Cardiovascular Safety: Leveraging existing mechanistic in vitro cardiovascular data.

Aims

- Collation and curation of mechanistic in vitro cardiovascular data from public data sources and peer reviewed literature.
- Annotate performance standards (dynamic range, reproducibility, reference chemical predictivity) for the endpoints measured.
- Map the available data and testing platforms to CV failure modes defined by the HESI Cardiac Safety Technical Committee.
- Develop in silico methods to apply cheminformatics (e.g. QSAR analyses) and in vitro to in vivo extrapolation (IVIVE) approaches.
- Propose integrated testing strategies that cover CV failure modes and provide human-relevant mechanistic information coupled with exposure estimates.

Description: Within public data repositories and the peer reviewed literature is a considerable volume of CV-relevant mechanistic data that provides a significant set of information from which to assess currently available assays and endpoints. These data include varying levels of in vivo correlation to either animal or human outcomes (e.g. animal toxicology studies, pre-clinical, and clinical data). This project will identify publicly-accessible databases and published works of in vitro cellular activity data generated in cardiomyocytes or in assays assessing endpoints relevant to the CV system (e.g. EPA's ToxCast, NTP Tox 21). The trainee will identify, extract, and collate relevant CV data into a structured format for efficient integration, evaluation, and analysis. Using the cardiovascular failure mode map developed by the HESI Cardiac Safety Technical Committee, and an associated controlled effects vocabulary, the data will be annotated for linkages to relevant modes of action. The data will be assessed for dynamic range, reproducibility, performance against reference chemicals, and relevance to in vivo outcomes of interest. The data will be the basis for identifying capability gaps (i.e. failure modes that lack alignment to current assays), proposing integrated testing strategies for failure modes with sufficient mechanistic coverage, as well as constructing CV-specific in silico tools for QSAR modeling. In silico capabilities for extrapolating in vitro cellular activity concentrations to predicted in vivo exposures will be further developed and applied to data for CV outcomes. The trainee will integrate principles of PBPK and TKTD with links from mechanistic endpoints to recognized CV failure modes. Human relevant data for known cardioactive therapies will be used to build and test the capability of the developed models and integrated testing strategies.

Trainee requirements: Candidates should have obtained a PhD in a relevant biomedical field, and possess knowledge of and experience with phenotypic and genomic databases. Experience

with literature review, and the ability to extract, synthesize, and collate data in varying formats are necessary. Basic programming skills, ideally in R and/or Python, in silico modeling experience, and the application of computational methods to high-throughput screening data are highly desirable. Excellent verbal and written communications skills, creativity, curiosity, and the ability to work using diverse tools are essential. The trainee will conduct this work at NIEHS under the mentorship of Dr. Nicole Kleinstreuer.

Project #2: In Silico Screening for Cardiovascular Safety: Pathway-based modeling of CV hazards with Whole Genome Co-Expressed Network Analysis (WGCNA)-based approaches

Aims:

- Extract, collate and curate cardiac-relevant transcriptomics data from DrugMatrix, and other sources as available
- Apply approaches defined by Sutherland et al. to construct cardiac-relevant WGCNA modules from both in vivo (rat heart) and in vitro (rat and human cardiomyocyte) models systems.
- Where possible, map associations between WGCNA module perturbations and pathological manifestations observed in the DrugMatrix data
- Identify modules that exhibit conservation across model systems/species with goal of understanding where in vitro systems best model toxicological response

Description: Gene expression provides broad insights into test compound-related effects in biological systems. The complexity and variability of biology over time and among individuals complicates the ability to reproducibly relate individual gene changes to phenotypic outcomes. Further, the high dimensionality of the data creates statistical power challenges that limit the ability to identify associations between gene expression and apical phenotypic outcomes. By using a data-driven reduction process that identifies networks of co-expressed genes it becomes possible to more effectively associate perturbations with curated biological pathways and increase the power to identify associations with phenotypic outcomes. Sutherland et al. used a (WGCNA) approach to construct 'modules' of co-expressed gene networks that could be applied to both in vitro and in vivo experimental systems for forecasting pathological manifestations in liver following toxicological challenge. This project aims to replicate the work of Sutherland et.al. for target tissues important in cardiovascular safety assessment (e.g. myocardium/cardiomyocytes and arterial blood vessels). Application of the modules identified with these efforts will help to determine in which circumstances in vitro systems can effectively recapitulate in vivo patterns of response to toxicological challenge. Such findings will provide guidance on the most effective use of cardiac-related in vitro systems for testing and identify areas for further model development.

Trainee requirements: PhD in a relevant biomedical field (i.e. human genetics, bioinformatics, or computational biology). Applicants will ideally have experience with gene expression data analysis and handling/manipulation of large data sets. In addition, basic programming skills in R

or Python are desired along familiarity with the application of tools contained in Bioconductor or equivalent Python tool set. The trainee will conduct this work at NIEHS under the mentorship of Dr. Scott Auerbach.