Cardiovascular Health Effects Innovation Program

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Problem Statement

Chronic progressive cardiovascular (CV) disease is a primary cause of morbidity and mortality in the United States and globally. Current approaches to environmental hazard assessment do not include specific assessments of CV bioactivity and hazards despite growing evidence that environmental exposures contribute to the onset, risk, or progression of chronic CV disease. Additionally, current hazard assessment paradigms are better designed to identify overt injury or dysfunction in normal biology than exacerbation of a comorbidity. There is no defined approach to identify agents that might be contributing to contemporary and common CV diseases.

Objectives

The Cardiovascular Health Effects Innovation (CV HEI) Program is structured around the following three objectives:

1. Leverage existing knowledge to define key CV "failure modes" as a framework for modeling, link those modes to mediators of mechanistic bioactivity and screen existing databases to identify putative CV hazards.

2. Develop a suite of assay/testing/modeling/knowledge management capabilities that aligns to the current Division of the National Toxicology Program (DNTP) Translational Toxicology Pipeline and apply it, in an integrated fashion, to provide an evidence-based approach to assessing CV bioactivity of environmental substances.

3. Develop and implement an innovative capability for identifying potential environmental contributors to specific and contemporary clinical CV diseases.

Rationale

Public Health Context

CV disease in all its clinical manifestations is the most significant cause of morbidity and mortality in many developed countries and, increasingly, in those that are experiencing significant economic growth and prosperity. Lifestyle choices and genetics have clearly been demonstrated to be significant contributors but cannot alone or even in combination account for all the risk of developing CV disease and the individual variability in which people experience that disease. Environmental exposures are presumed to contribute to the risk of developing CV disease and, in some cases like air pollution, there is compelling evidence to support that likelihood. A broader recognition of potential contributors is limited because current approaches to environmental hazard assessment do not specifically interrogate CV

health effects with any reasonable specificity or sensitivity, or because existing testing endpoints (e.g., mitochondrial function, oxidative stress) have not been adequately linked to CV disease phenotypes. An evidence-based capability for identifying CV bioactivity that aligns with the DNTP Translational Toxicology Pipeline will provide better insights into the potential for environmental exposures to contribute to human disease burden. Furthermore, designing an innovative approach to modeling fundamental CV disease biology by connecting key molecular and cellular events with mechanistic failure modes and adverse outcomes will support DNTP's ability to identify environmental contributors to diseases with high prevalence in society today.

Alignment with Mission, Goals, Strategic Pipeline

The CV HEI Program intends to engage the full breadth of the DNTP mission and goals. CV disease is clearly a contemporary public health challenge. The program's path towards capability development will enable evidence-based approaches—beginning with in silico QSAR modeling and medium- to high-throughput bioactivity screening and continuing through complex in vitro confirmatory assays and holistic in vivo assessment in animal models enhanced for assessment of fundamental physiologic measures. Early predictions informed by in silico models and in vitro bioactivity will be qualified in progressively complex assay systems allowing us to build confidence in early pipeline steps, assess model applicability domain, and identify capability development needs. The assay systems used will be aligned to known human CV failure modes and reflect human biology as much as the complexity of the system permits with a goal of optimizing the translational relevance of the outcomes. We will define a novel paradigm for environmental hazard assessment working collaboratively with government, academic, and industry colleagues via the Health and Environmental Safety Institute (HESI) Cardiac Safety Technical Committee. Postdoctoral trainees will contribute to key projects. The CV HEI Program will define and test a full pipeline of capabilities. The outcomes of our efforts will be communicated in the varied channels available to us, including usual scientific communications (abstracts, presentations, peer-reviewed manuscripts), National Institute of Environmental Health Sciences media platforms and, when appropriate, NTP-branded publications.

Stakeholder Interest and Engagement

Steps Taken to Engage Stakeholders

This initiative was developed as an "environmental" complement to an existing HESI Cardiac Safety Technical Committee project with a narrower focus and pharmaceutical perspective. The HESI Committee includes government regulators, nonregulatory government, academic, and industry scientists. Brian Berridge is co-chair of that committee, and DNTP is providing chemistry support for the effort.

We have engaged colleagues at the U.S. Environmental Protection Agency (EPA) to get their perspective and engaged an investigator with a history of work in the area, Kevin Dreher, who has joined as an adjunct member of our team. We have also recently engaged a National Center for Advancing Translational Sciences (NCATS) investigator, David Gerhold, who is studying effects of tobacco ingredients on human endothelial cells. We intend to collaborate with Dr. Gerhold to lead the development of our in vitro vascular endothelial modeling capabilities supported through an existing interagency agreement with the NCATS.

We have hosted several webinars with academic and commercial capability providers and will continue to investigate technical capabilities to support our "pipeline of capabilities."

Ongoing and Continuing Interactions

Stakeholder	Issue	Role of Stakeholder
US FDA	Concern about the human relevance of current preclinical safety assessment approaches	Partner
US EPA	Concern about environmental contributions to CV morbidity, specifically, atrial fibrillation; Experience with using in vitro methods to characterize CV hazards	Partner; potential collaborator; adjunct Program Management Team member
NCATS	Experience using in vitro endothelial cell systems to characterize to effects of tobacco products	Collaborator; adjunct Program Management Team member
HESI (Cardiac Safety Technical Committee)	Concern about the human relevance of current preclinical safety assessment approaches	Collaborator

Input Received

Some individuals at the U.S. Food and Drug Administration (FDA) are concerned that preclinical animal models overpredict human drug-induced CV liabilities and provide very little mechanistic insights into those liabilities when they occur. The consequence of that "false positive" is potentially terminating useful drug therapies. The broader stakeholder population is most concerned about liabilities not identified in preclinical testing. The pharmaceutical industry is plagued by CV safety-related attrition largely occurring late in preclinical or clinical development.

EPA has a relatively small effort in the CV space currently (see engagement with K. Dreher above) but there is interest in Divisional leadership to build on that effort. A short discussion with EPA staff established mutual interest and recognition of the general gap in our CV assessment capabilities.

We know from our internal experiences that CV hazard assessment is a weakness in our current capabilities and paradigm. The epidemiologic and mechanistic literature associating some environmental exposures with CV disease continues to grow, prompting our efforts to fill this gap. Notably, there is skepticism by some that environmental agents are truly CV threats at human-relevant exposures. Although epidemiologic associations suggest otherwise, it is possible that environmental agents are less of an acute overt hazard than a more chronic contributor to pre-existing, heritable, or spontaneous disease. Accordingly, we aim for our approaches to identify bioactivities at clinically relevant exposures in the absence of overt morphological injury.

Our engagement with capability vendors and developers has identified several existing in vitro modeling systems that could support the paradigm represented here. There is no single modeling platform that will encompass the breadth of CV biology we will need to interrogate, but there are relevant capabilities that align to key failure modes that we can access externally or develop internally to provide a foundational starting point.

Likewise, a number of in vivo capabilities are well-established and applied routinely by the pharmaceutical industry; namely, single dose CV function studies in instrumented animals. We will use those resources to build our understanding of the acute functional effects of environmental agents with

putative CV bioactivity. Less well-established are capabilities that can efficiently assess longer-term functional effects and, in particular, investigate more occult bioactivities (e.g., those that involve some impairment in CV reserve capacity that might be inconsequential in a normal animal or human but would be significant in one with existing CV disease).

Milestones and Metrics

The CV HEI Program is fundamentally a capability development effort intending to fill a perceived gap in current DNTP capabilities and the broader field of environmental hazard assessment. Accordingly, the products of this effort will include the evidence that environmental agents do indeed represent human-relevant CV hazards, a strategic approach to identifying those hazards, and the technical capabilities to execute on that strategy.

Key products and temporal milestones will include:

- A testing framework defined by key pathobiological CV failure modes to include a discrete list of testable mechanistic bioactivities that can be used for high or medium-throughput screening (Year 1)

- A discrete list of putative CV hazards and strength of evidence underlying environmental exposure associations generated by leveraging existing data (Year 1: hazard identification, Year 2: evidence map of the literature)

- CV QSAR screening tool (Year 1–2: build, Year 3: test)

- Predictive transcriptomics resource (Weighted Gene Co-Expression Network Analysis-based) (Year 1: build, Year 2: test)

- A suite of external and internal in vitro testing platforms to characterize CV-relevant bioactivities for in vivo relevance (Year 1–2 [including FDA/HESI collaboration])

- In vivo CV assessment capability (Year 1: capability and paradigm definition, Year 1–2: pilot/proof of concept studies, Year 3+: integration into testing paradigm)

- Hypertension in U3 (understudied, underrepresented, under-served) populations gap analysis and assessment strategy (Year 1: gap analysis, Year 1–3: capability build, Year 3+: disease-screening application)

- An implementation strategy and decision framework for characterizing human-relevant environmental CV hazards (Year 3)

Progress to date:

- Developed a testing framework aligned to key CV failure modes and the DNTP Translational Toxicology Pipeline (concept manuscript pending)

- Extraction and integration of existing CV-relevant high-throughput bioactivity screening data; ToxPi analysis conducted to identify putative environmental CV toxicants (manuscript in review)

- Ongoing evaluation of existing CV-relevant in vitro capabilities; initiated development of internal cardiac organoid culture systems (ongoing)

- CV-relevant Drug Matrix data used to develop WGCNA modules (manuscript in preparation)

- Initiated literature-based evidence mapping project to determine associations between environmental exposures and adverse cardiovascular outcomes (ongoing)

- Initiated literature-based scoping reviews to identify biomarkers of hypertensive diseases of pregnancy and nontraditional stresses underpinning minority health disparities (ongoing)

- CV HEI Concept presented at DNTP Staff Engagement (June 2019), NTP BSC Meeting (June 2019), FDA Toxicology Seminar Series (March 2020)

Value Proposition and Summary

The CV HEI Program aims to build a capability that currently does not exist in an area of public health that represents the most significant cause of morbidity and mortality in the world. Accordingly, it fills an important gap in DNTP's portfolio of models, assays, and assessment approaches. It will provide unique insights into environmental contributions to a significant public health burden and broaden DNTP's approach to identifying human-relevant environmental health hazards. Building this pipeline de novo and aligning it to our fundamental understanding of CV pathobiology should strengthen our ability to experientially build confidence in the predictivity of mechanistic bioactivity screens. Building an innovative disease-screening paradigm will substantially enhance our ability to link environmental exposures to important and contemporary diseases.