2016–2017 Activities and Accomplishments

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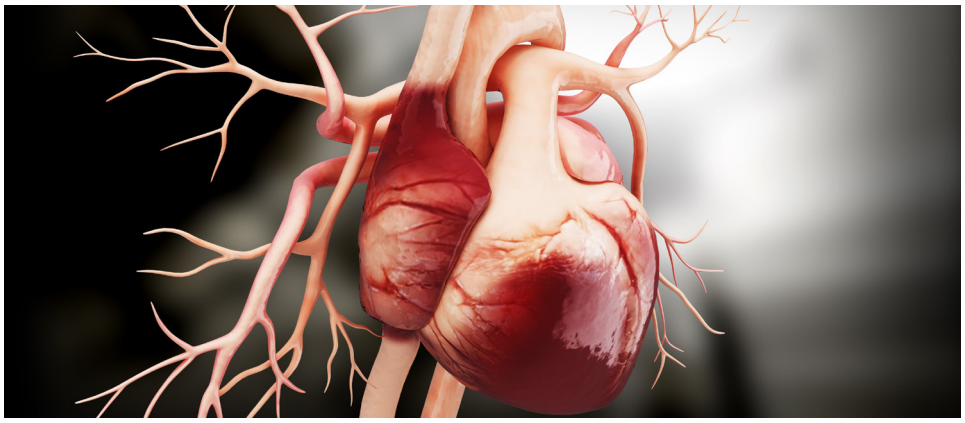

This scientific program is committed to:

- Improving public health by reducing unanticipated cardiovascular-related adverse effects from drugs or chemicals and developing innovative approaches to support early detection, prediction, and elimination of cardiac risk as well as improved understanding of cardiovascular toxicology and pathobiology. The committee brings together experts across a broad range of cardiovascular technical disciplines within the international community of public, private, and government sectors to develop best practices for translation of *in vitro* and nonclinical cardiovascular data. This cross-sector committee is working toward better understanding and characterizing mechanistic assays using human components that will eventually replace some of the animal models used for cardiovascular risk assessment in drug development.

Areas of scientific focus:

- Facilitating the development, refinement, and adoption of a more comprehensive and efficient nonclinical paradigm for assessment of proarrhythmic risk of evolving drug candidates, including a mechanism-based paradigm utilizing assessment of ion channel effects and *in silico* reconstruction of the action potential and *in vitro* confirmation of drug effects in human stem cell–derived cardiomyocytes (hSC-CMs).
- Discovery of translatable cardiovascular biomarkers in early preclinical studies of blood coagulation and thrombosis in healthy and diseased animal models.
- Using statistics and novel mathematical approaches to further explore an existing *in vivo* dataset developed to assess sensitivity and reproducibility of inotropic effects.
- Assessing hSC-CM preparations and applications for cardiovascular risk assessment.
- Evaluating high-throughput methods for cardiac ion channel screening for early drug discovery processes.

Why get involved?

The HESI Cardiac Safety Committee is the leader in the field, with multi-disciplinary scientific experts positively impacting future drug development and regulatory perspectives. No other group is currently working internationally to bridge structural, functional, nonclinical, and clinical approaches to cardiovascular safety.

Key accomplishments:

- *Proarrhythmia.* The first phase of the HESI-FDA database assessing concordance between nonclinical repolarization assays and clinical measures of cardiac repolarization (QT, proarrhythmia) concluded and the manuscript was submitted to a peer-reviewed journal. The second phase is focused on better understanding of mechanisms of discordance found in the HESI-FDA database. A publication is in development and will include discordant compound examples, additional data, and pharmacokinetics/pharmacodynamics. The new High-Throughput Systems (HTS) subteam completed phase 1 of the planned Comprehensive *In Vitro* Proarrhythmia Assay (CiPA) study to assess high-throughput automated patch clamp systems.
- *Contractility.* The second paper detailing additional endpoints from the contractility study in conscious dogs was published. Additional manuscripts are underway, describing results from the contractility canine electrocardiography (ECG) study and detailed statistical analyses. A new symposium titled "Drug-Induced Changes in Vascular Hemodynamics: Clinical and Drug Development Implications" was presented at the 2016 American College of Toxicology Annual Meeting. From this, a new proposal exploring novel mathematical modeling to understand and predict contractile changes was introduced to the committee.
- *Stem Cell–Derived Cardiomyocytes.* The Myocyte subteam completed the core validation study with the assistance of funds received through an FDA Broad Agency Announcement (BAA). Additional sites participated in a noncore study and shared data that will be included in a database aimed at making data more accessible for future analyses and comparisons. A CiPA Update meeting was held in December 2016 and co-sponsored by HESI. The team also contributed to discussions for the Contractility Cellular Systems effort.
- *Biomarkers.* The first proof-of-concept study was published in the open-access journal *PLoS One* and data generated in the study were made available via the open-source Center for Open Science Open Science Framework, a first for HESI. Results from the first study have been presented at several international scientific conferences. The second proof-of-concept study, which modeled prothrombotic states associated with metabolic syndrome in the obese Zucker diabetic fatty rat, has just been completed, and data analyses are in progress.

The Committee's focus for May 2017–May 2018:

- *Proarrhythmia.* Members will continue to actively participate in the CiPA work streams. The HTS subteam will finalize the second phase of their HTS study and provide data to the CiPA initiative. They will also initiate a new subteam focused on characterizing nonclinical ECG biomarkers, specifically JT-Peak. The subteam will conduct a literature search and retrospective data analysis and develop a manuscript detailing the results.
- *Biomarkers.* A manuscript will be submitted to report the findings of the second proof-of-concept study that compares markers of hemostasis in the obese Zucker diabetic fatty rodent model under conditions of varying dietary fat and in response to the cardiotoxic drug, doxorubicin. In addition, a third proof-of-concept study will be initiated to synthesize results from inflammatory, dietary, and drug-induced hemostatic stressors into biomarker profiles of cardiovascular response.
- *Contractility.* The two remaining manuscripts based on the data generated during the contractility study will be completed and submitted for publication. A new subteam, Cellular Systems, will develop a framework to understand challenges and opportunities when using *in vitro* methods to evaluate contractility. A study to quantify these methods will also be planned. Members will also partner with an academic institution to apply new mathematical models to the contractility study data to determine whether the new model can improve prediction and detection of inotropic effects.
- *Stem Cell–Derived Cardiomyocytes.* The phase 2 ongoing multi-site validation study will be published and the data will be used to help complete a draft CiPA package to be presented to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E14 Working Group. Collaboration and coordination with the Japan iPS Cardiac Safety Assessment group will continue to quantitate and standardize results seen in the hSC-CMs for CiPA purposes. With the CiPA study completed, the working group will turn their focus to contractility and 3D cell/tissue constructs. Members will contribute data to the Cellular Systems subteam planned study.

Recent publications:

Brooks MB, Turk JR, Guerrero A, Narayanan PK, Nolan JP, Besteman EG, Wilson DW, Thomas RA, Fishman CE, Thompson KL, Ellinger-Ziegelbauer H (2017) Non-lethal endotoxin injection: a rat model of hypercoagulability. *PLoS One*. 12(1):e0169976.

Colatsky T, Fermini B, Gintant G, Pierson JB, Sager P, Sekino Y, Strauss DG, Stockbridge N (2016) The Comprehensive *In Vitro* Proarrhythmia Assay (CiPA) initiative — update on progress. *J Pharmacol Toxicol Methods*. 81:15–20.

Pettit SD, Lipshultz SE, Cleeland CS, Roberts S, Davis M, Berridge BR, Kirch RA (2016) Enhancing quality of life as a goal for anticancer therapeutics. *Sci Transl Med*. 8(34):344ed9.

Pugsley MK, Guth B, Chiang AY, Doyle JM, Engwall M, Guillon JM, Hoffmann PK, Koerner JE, Mittelstadt SW, Pierson JB, Rossman EI (2017) An evaluation of the utility of LVdP/dt40, QA interval, LVdP/dtmin and Tau as indicators of drug-induced changes in contractility and lusitropy in dogs. *J Pharmacol Toxicol Methods*. 85:1–21.

2016–2017 Participating organizations

AbbVie
ACEA Biosciences, Inc.
Amgen Inc.
AstraZeneca AB
Axiogenesis
Axion Biosystems
Axol Biosciences
Bayer HealthCare Pharmaceuticals
Biogen Inc.
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Bristol University
Celgene Corporation
Cellular Dynamics International, Inc.
ChanTest, A Charles River Company
CiToxLAB
Columbia University
Cornell University
Covance
Coyne Scientific
Cyprotex
Data Sciences International
Eli Lilly and Company
European Medicines Agency
Genentech/Roche
George Washington University
GlaxoSmithKline
Harvard University
Health Canada
IBM T.J. Watson Research Center
InvivoSciences, Inc.
Jagiellonian University Medical College
Janssen Pharmaceuticals
Johns Hopkins University
Karolinska Institute, Department of Medicine
Lifespan Hospitals
Medicines and Healthcare Products Regulatory Agency (UK)
Merck & Co., Inc.
Metrion Biosciences Ltd.
Michigan State University
MultiChannel Systems
Nanion Technologies
National Center for Safety Evaluation of Drugs (China)
National Institute of Environmental Health Sciences
National Institute of Health Sciences (Japan)
National Institutes of Health
New York Stem Cell Foundation
Northwestern University
Novartis Pharmaceuticals
Ohio State University
Pfizer Inc.
Pharmaceuticals and Medical Devices Agency (Japan)
Pharmacological Evaluation Institute of Japan
Pluriomics
Purdue Pharma
Q-State Biosciences
Quintiles
Sanofi
Scintillon Institute
Sony
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Stony Brook University
Takara Bio Europe AB
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University of Wisconsin
US Environmental Protection Agency
US Food and Drug Administration
Vala Sciences, Inc.
Vanderbilt University
Vertex Pharmaceuticals
VistaGen Therapeutics, Inc.
WIL Research

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