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.

- **Stern 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 on 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:


2016–2017 Participating organizations

| AbbVie | Janssen Pharmaceutical | Johns Hopkins University | Karolinska Institute, Department of Medicine | LifeSpan Hospitals | 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) | Pharmocological Evaluation Institute of Japan | Plurionics | Purdue Pharma | Q-State Biosciences |
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| Janssen Pharmaceutical | Johns Hopkins University | Karolinska Institute, Department of Medicine | LifeSpan Hospitals | 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) | Pharmocological Evaluation Institute of Japan | Plurionics | Purdue Pharma | Q-State Biosciences |

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