2017–2018 Activities and Accomplishments

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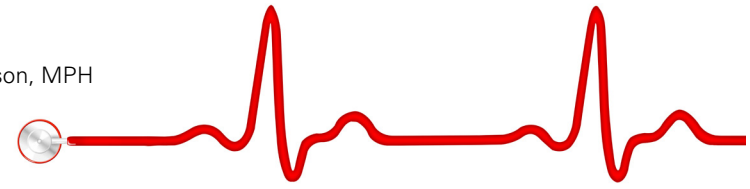

This scientific program is committed to:

- 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.
- Bringing 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.
- Working toward better understanding and characterizing mechanistic assays using human components that may eventually reduce, replace, or refine 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 human cardiac ion channel effects and *in silico* reconstruction of the human ventricular action potential and *in vitro* confirmation of drug effects in human stem cell–derived cardiomyocytes (hSC-CMs).
- Assisting in the discovery of translatable cardiovascular biomarkers in early preclinical studies of blood coagulation and thrombosis in healthy and diseased rats and rodent models of human disease.
- Developing better analytic methods to 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, including functional and structural toxicities.
- Evaluating high-throughput methods for cardiac ion channel screening for early drug discovery processes.
- *New for 2018!* Identifying cardiovascular failure modes that would benefit from a human-relevant, mechanistically informed approach and evaluating assays to assess these.

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 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) was published, and a manuscript for the second phase (understanding of mechanisms of discordance found in the HESI-FDA database) was drafted. The High-Throughput Systems (HTS) Subteam completed the second phase of the automated patch clamp ion study and submitted data to the FDA. Data from the Phase I HTS is being included in a draft manuscript. A new subteam exploring use of the J-Tpeak biomarker to understand proarrhythmic potential was initiated; a retrospective study as proof of concept was completed and a manuscript was submitted for publication.
- *Cardiac Contractility.* Two additional documents highlighting additional endpoints and alternative statistical strategies were published using the data generated from the earlier study assessing contractility in dogs. A poster with results from the combined echocardiography-telemetry study was presented at the 2017 Safety Pharmacology Society Annual Meeting and a manuscript is in progress. A new partnership was launched with the University of Surrey and Imperial College London to explore using mathematical modeling to assess contractility. A manuscript was written outlining a framework of criteria for using non-animal cellular systems to assess contractility.
- *Stem Cell–Derived Cardiomyocytes.* The pilot study text exploring use of human induced pluripotent stem cells (hIPSCs) on the microelectrode array (MEA) platform was accepted for publication. The Myocyte Subteam completed the core validation study with the assistance of funds received through an FDA Broad Agency Announcement (BAA) and submitted a manuscript with the results, which included the development and use of a novel statistical model. They presented the body of work related to the Comprehensive *In Vitro* Proarrhythmia Assay (CiPA) Initiative to the ICH S7B/E14 Working Group in April 2018 in preparation for further discussions around the guidance. A CiPA Update meeting was co-sponsored by HESI in May 2018 and the Myocyte Subteam, along with other groups, presented the latest findings.
- *Biomarkers.* The second proof-of-concept study, modeling prothrombotic states associated with metabolic syndrome in the Zucker diabetic fatty rat fed high-fat diets, was completed and a manuscript with the results is in progress. A poster with preliminary results of the second proof-of-concept study was presented at the 2017 Safety Pharmacology Society Annual Meeting. Approval was received for a third proof-of-concept study and planning began.
- *Mechanism, Human-Based Assay Evaluation.* A workshop was convened in May 2018 to focus the committee's mission on identifying and evaluating human-relevant, mechanism-based testing. At this meeting, cardiovascular failure modes were identified, and possible solutions as well as challenges and opportunities with moving in this direction were discussed.

The Committee's focus for May 2018–May 2019:

- *Proarrhythmia*. The manuscripts in progress for both the Database Phase II and HTS Phase I work will be completed and submitted. The J-Tpeak Subteam will execute a larger prospective study in collaboration with the FDA to ensure that alignment with their clinical study is in place.
- *Cardiac Contractility*. The combined echocardiography-telemetry text will be submitted for publication, as will the cellular systems document. A study to quantify the framework to understand challenges and opportunities when using *in vitro* methods to evaluate contractility methods will also be planned. The partnership with the University of Surrey and Imperial College London will continue with milestone checkpoints on project progress.
- *Stem Cell–Derived Cardiomyocytes*. The validation study results will be published, and results will be shared with the broader scientific community. The group will also facilitate further interactions and discussions with the ICH S7B/E14 Working Group. This team will also have a large role in scoping future projects focused on mechanism-based assays.
- *Biomarkers*. The results from the second proof-of-concept study will be published, which highlight not only the effects of diet on the Zucker diabetic fatty rat model but also the effects of doxorubicin on various biomarkers associated with hypercoagulability and prothrombosis. In addition, the protocol for the third proof-of-concept study will be discussed, finalized, and launched.
- *Mechanism, Human-Based Assay Evaluation*. Discussions within the committee will continue around this topic and projects identified during the May 2018 workshop will be pursued, with cellular systems being one example.

Recent publications:

Boulay E, Pugsley MK, Jacquemet V, Vinet A, Accardi MV, Soloviev M, Troncy E, Doyle JM, Pierson JB, Authier S (2017) Cardiac contractility: correction strategies applied to telemetry data from a HESI-sponsored consortium. *J Pharmacol Toxicol Methods*. 87:38–47.

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

Chiang AY, Guth BD, Pugsley MK, Foley CM, Doyle JM, Engwall MJ, Koerner JE, Parish ST, Dustan Sarazan R (2018) The evaluation of endpoint variability and implications for study statistical power and sample size in conscious instrumented dogs. *J Pharmacol Toxicol Methods*. 92:43–51.

Park EJ, Gintant GA, Bi D, Kozeli D, Pettit SD, Pierson JB, Skinner M, Willard J, Wisialowski T, Koerner J, Valentin JP (2018) Can nonclinical repolarization assays predict the results of clinical thorough QT studies? Results from a research consortium. *Br J Pharmacol*. 175(4):606–617.

Pugsley MK, Guth B, Chiang AY, Doyle JM, Engwall M, Guillon JM, Hoffmann PK, Koerner JE, Mittelstadt SW, Pierson JB, Rossman EI, Sarazan DR, Parish ST (2017) An evaluation of the utility of $LVdP/dt_{40}$, QA interval, $LVdP/dt_{min}$ and Tau as indicators of drug-induced changes in contractility and lusitropy in dogs. *J Pharmacol Toxicol Methods*. 85:1–21.

2017–2018 Participating organizations

AbbVie
ACEA Biosciences, Inc.
Amgen Inc.
Axion Biosystems
Axol Biosciences
Bayer HealthCare Pharmaceuticals
Biogen Idec MA Inc.
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Bristol University
Celgene Corporation
Cellular Dynamics International, A Fuji Film Company
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
George Washington University
GlaxoSmithKline
Harvard University
Health Canada
InvivoSciences, Inc.
Ipsyte
Jagiellonian University Medical College
Janssen Pharmaceuticals
Johns Hopkins University
Karolinska Institute
Lifespan Hospitals
Medicines and Healthcare Products Regulatory Agency (UK)
Merck & Co., Inc.
Miami University
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
National Toxicology Program
Ncardia
Northwestern University
Novartis Pharmaceuticals
Ohio State University
Pfizer Inc.
Pharmaceuticals and Medical Devices Agency (Japan)
Pharmacological Evaluation Institute of Japan
Purdue Pharma
Q-State Biosciences
Quintiles
Roche
Sanofi
Scintillon Institute
Sony
Stanford University
Stony Brook University
SUNY Buffalo
Takara Bio Europe AB
Takeda Pharmaceutical Company Limited
TARA Biosystems
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Tokyo Medical and Dental University
UCB-Biopharma
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University of Oxford
University of Tokyo
University of Tübingen, Natural and Medical Sciences Institute
University of Washington
University of Wisconsin
US Environmental Protection Agency
US Food and Drug Administration
Vala Sciences, Inc.
Vanderbilt University
VistaGen Therapeutics, Inc.

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