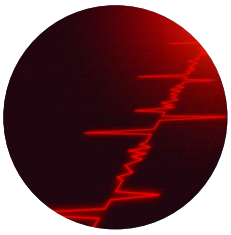
# Cardiac Safety



## OUR MISSION

*The committee's mission is to improve public health by reducing unanticipated cardiovascular-related adverse effects from drugs or chemicals and develop innovative approaches to support early detection and prediction as well as improved understanding of cardiovascular toxicology and pathobiology.*

## CHAIRS

### Public Chairs

Dr. Norman Stockbridge
(US Food and Drug Administration)
Dr. Brian Berridge
(National Toxicology Program)

### Steering Team Members

Dr. Norman Stockbridge (US Food and Drug Administration)
Dr. Eugene Herman (National Institutes of Health)
Dr. Gary Gintant (AbbVie)
Dr. Eric Schultze (Eli Lilly and Company)
Dr. Jean-Pierre Valentin (UCB)
Dr. Michael Pugsley (Cytokinetics)
Dr. John Koerner (US Food and Drug Administration)
Dr. Marjory Brooks (Cornell University)
Dr. Frank Sellke (Lifespan Heart Center)
Dr. Brian Berridge (National Toxicology Program)

## HESI STAFF

Ms. Jennifer B. Pierson, MPH
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Dr. Stan Parish
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## 2019 COMMITTEE HIGHLIGHTS

### Participating Organizations

**11** government/regulatory agencies, **31** academic/research institutes, **2** other, **40** industry

### Publications

**2** accepted/published, **1** submitted, **4** in progress

### Scientific Meetings and Trainings

**2** advisory/other meetings: Cardiac Failure Modes Advisory Group (Washington, DC) and Workshop on Cardiomyocytes for Mechanistic CV Safety Liabilities (March 2019 in Silver Spring, Maryland)

### Outreach

**2** posters, **2** presentations

- Cardiac Failure Modes Advisory Group (Washington, DC)
- Workshop on Cardiomyocytes for Mechanistic CV Safety Liabilities (March 2019 in Silver Spring, Maryland)

### Collaborations

**3** external

- University of Surrey and Imperial College London, European Bioinformatics Institute
- Safety Pharmacology Society
- CiPA Steering Team

### Geographic Representation

Australia, Belgium, Canada, China, Denmark, France, Germany, Japan, Netherlands, Poland, Singapore, Sweden, Switzerland, United Kingdom, United States

## WORKING GROUPS

- **ProArrhythmia Working Group.** This working group is dedicated to investigating mechanisms of proarrhythmic risk. The most recent projects have focused on concordance/discordance between nonclinical assays (hERG, APD, QTc *in vivo*) and clinical TQT studies. Additional work focused around CiPA has also been initiated, including two subteams: high-throughput systems (HTS) ion channel work and JT peak ECG work in nonclinical species. This group is engaged in cross-collaborations with the Stem Cell Working Group and Myocyte Subteam and Integrative Strategies with the Implanted Telemetry Subteam.
- **Stem Cell Working Group.** This group is working to understand and characterize use of stem cell–derived cardiomyocytes in cardiac safety assessments. The Myocyte Subteam is working to support data collection for CiPA.
- **Cardiac Biomarkers.** This working group is dedicated to investigating preclinical cardiac biomarkers of hypercoagulability induced under a thrombotic state, in both normal and diseased states.
- **Integrative Strategies.** This working group has examined the sensitivity within a preclinical species to assess the function of contractility. Additionally, it has provided guidance on what parameters need to be met within an *in vitro* system to have confidence in that assay to assess contractility.

## AREAS OF FOCUS FOR 2020

- Alignment to mechanistic, human relevant approaches
- Working toward implementation of the 3Rs and human relevant work
- Supporting the goals of the CiPA program through publication and data development

## STRATEGIC IMPACT AREAS

**Enhanced Efficiency and Accuracy in Safety Assessment Practice**

The committee works to increase efficiency and accuracy of the current paradigm as well as impacting 3Rs. Working to implement *in vitro* technologies, such as stem cells, in cardiac safety assessment will allow for improved decision-making at earlier phases in drug development. Within both the biomarkers and integrative working groups, having a better understanding of *in vivo* pathways and useful application of preclinical species increases efficiencies and accuracy in results derived through *in vivo* studies.

**Catalysis of New Science**

Stem cells and related assay platforms are still new technology in drug safety and development. HESI is working to test and validate these technologies.

**Increasing the Audiences for Collaborative Safety Science**

HESI was asked to manage several projects under CiPA and continues to see additional projects come to this group. The Blinova paper was made possible through an FDA Broad Agency Announcement that was awarded to HESI based partly on our reputation for rigorous science.

## 2019 AWARDS AND GRANTS

The HESI Cardiac Safety Committee was awarded two publicly funded grants in 2019. The first is a multi-year U01 grant from the US Food and Drug Administration (FDA_ on the Evaluation of Integrated Human-Relevant Approaches to Identify Drug Induced Cardiovascular Liabilities. This grant will support HESI in procuring and managing novel, *in vitro* experimental studies to develop targeted mechanistic data to inform drug safety assessment for key cardiac 'failure modes'. This program of work is expected to provide a robust complement to the committee's existing efforts in this space. The second award is an 18-month Broad Agency Announcement grant from the US FDA on assessing variability and reproducibility of manual and automated patch clamp platforms. HESI will organize and manage a multi-site study with manual and automated patch clamp platforms and the 28 CiPA compounds to help set expectations, limitations, and confidence in the ion channel platforms. Results will provide objective data and confidence in the risk assessment approach proposed as part of CiPA, including further testing and validation of the in silico model.

In 2019, HESI partnered with the FDA Center for Drug Evaluation and Research and the National Toxicology Program (NTP) in a new Memorandum of Understanding (MOU) to support improved cardiovascular safety and reduce the use of animals for testing. This first of its kind MOU across the three organizations will allow HESI to work with experts in the cardiotoxicology space to identify and evaluate innovative efforts focused on human-relevant assays, and will expand existing work by the Cardiac Safety Committee and formalize the partnership between HESI, NTP, and FDA.

## PUBLICATIONS

Guth BD, Engwall M, Eldridge S, Foley CM, Guo L, Gintant G, Koerner J, Parish ST, Pierson JB, Ribeiro A, Zabka T (2019) Considerations for an *in vitro*, cell-based testing platform for detection of drug-induced inotropic effects in early drug development. Part 1: general considerations for development of novel testing platforms. *Frontiers in Pharmacology*. 10:884. doi: 10.3389/fphar.2019.00884.

Ribeiro A, Guth B, Engwall M, Eldridge S, Foley CM, Guo L, Gintant G, Koerner J, Parish ST, Pierson J, Brock M (2019) Considerations for an *in vitro*, cell-based testing platform for detection of drug-induced inotropic effects in early drug development. Part 2: designing and fabricating microsystems for assaying cardiac contractility with physiological relevance using human iPSC-cardiomyocytes. *Frontiers in Pharmacology*. 12019;10:934. doi: 10.3389/fphar.2019.00934.

Valentin et al. Why is it so difficult to predict drug effects on repolarization in humans? *Submitted.*

Gintant et al. Using human induced pluripotent stem-cell derived cardiomyocytes for *in vitro* repolarization studies: examples and best practices. *Final draft in progress*.

Kramer et al. Evaluation of high throughput automated platforms for assessing drug effects on cardiac currents in recombinant cells: the high throughput screening CiPA pilot study. *Final draft in progress*.

Pugsley et al. A high fat diet induces hypercoagulability and dyslipidemia and exacerbates renal insufficiency progressing to mortality in male ZDF rats. *Final draft in progress*.

Rossman et al. Evaluation of drug-induced changes in cardiac inotropic in dogs: echocardiogram results. *Final draft in progress.*

# PARTICIPATING ORGANIZATIONS

## Government/ Regulatory Agencies

European Medicines Agency
Health Canada
Medicines and Healthcare Products Regulatory Agency (UK)
National Institute of Health Sciences (Japan)
National Institutes of Health
National Toxicology Program
Pharmaceuticals and Medical Devices Agency (Japan)
Pharmacological Evaluation Institute of Japan
UK National Institute for Biological Standards and Control
US Environmental Protection Agency
US Food and Drug Administration

## Academic/ Research Institutes

Boston University
Bristol University
Columbia University
Cornell University
George Washington University
Hamburg University
Harvard University
Jagiellonian University Medical College
Johns Hopkins University
Michigan State University
Natural and Medicines Institute, University of Tubingen
National Shanghai Center for New Drug Safety Evaluation and Research
Northwestern University
Ohio State University
Scintillon Institute
Stanford University
SUNY Buffalo
Toho University Medical School
University of Alberta
University at Buffalo
University of Calgary
University of California, Davis
University of Glasgow
University of Hamburg
University of Miami
University of Michigan
University of Nottingham
University of Tokyo
University of Washington
University of Wisconsin
Victor Chang Institute

## Other

Lifespan Hospitals
Marshview Life Science Advisors

## Industry

AbbVie
ACEA Biosciences, Inc.
Amgen Inc.
Axion Biosystems
Bayer
Biogen Idec MA Inc.
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Celgene Corporation
Cellular Dynamics International, A Fujifilm Company
ChanTest, A Charles River Company
Charles River Laboratories
CiToxLAB
Covance
Cyprotex
Dana Solutions
Data Sciences International
Eli Lilly and Company
Genentech
GlaxoSmithKline
InvivoSciences, Inc.
IPSyte
Janssen Pharmaceuticals
LSI Medience
Merck & Co., Inc.
Metrion Biosciences Ltd.
MyoKardia
Nanion Technologies
Nanosurface
Ncardia
Novoheart
Pfizer Inc.
Roche
Sanofi
Sony
Stemonix
Takeda Pharmaceutical Company Limited
TARA Biosystems
UCB-Biopharma
Vistagen