# 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 to 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 Institute of Environmental Health Sciences, National Toxicology Program)

### Steering Team Members

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

## HESI Staff

Jennifer B. Pierson, MPH (jpierson@hesiglobal.org)
Dr. Stan Parish (to August 2020)
Dr. E'Lissa Flores (eflores@hesiglobal.org)

## 2020 Committee Highlights

### Participating Organizations

**12** government/regulatory agencies, **31** academic/research institutes, **34** industry, **1** clinical, and **1** other

### Publications

**5** published and **3** in progress

### Outreach

**3** oral presentations

- American College of Toxicology: presentation on "Implanted Telemetry in Toxicology Studies: A Retrospective Analysis by the HESI Consortium" (Dr. Simon Authier, Charles River Laboratories)
- FDA Virtual Seminar: presentations on "Predictability of Cardiac Liabilities: Collaborations Among FDA, NTP, and HESI: HESI's Innovative Approaches to Better Understand Cardiac Safety" (Jennifer Pierson, HESI) and "Cardiovascular Health Effects Innovation at the National Toxicology Program: Re-Defining the Paradigm" (Dr. Brian R. Berridge, NIEHS, National Toxicology Program)

### Collaborations

**3** external

- University of Surrey and Imperial College London
- Safety Pharmacology Society
- CiPA Steering Team

### Geographic Representation

Australia, Belgium, Canada, China, France, Germany, Japan, Netherlands, Poland, South Korea, Sweden, Switzerland, United Kingdom, and United States

## Working Groups

- **Stem Cell Working Group.** This group is working to understand and characterize use of stem cell–derived cardiomyocytes in cardiac safety assessments. An article that included best practices for use of stem cell cardiomyocytes in cardiac safety assessments was published in *Regulatory Toxicology and Pharmacology*. A new group is planning a study to explore *in vitro* assay ability to detect cardiotoxicity.
- **Pro-Arrhythmia Working Group.** This working group is dedicated to investigating mechanisms of proarrhythmic risk. They continue to collaborate with the CiPA Initiative and ICH, and recently published its anticipated high-throughput systems (HTS) ion channel work. A new subteam is scoping a conduction/sodium channel paper to discuss the history and challenges surrounding this topic.
- **Integrative Strategies Working Group.** This working group has examined the sensitivity within a preclinical species to assess the function of contractility. They continue their partnership with University of Surrey and Imperial College London on a mathematical model to predict blood pressure changes. The Implanted Telemetry Subteam explored the impact of telemetry lead placement in toxicology studies (a collaboration with the Pro-Arrhythmia Working Group).
- **Cardiac Biomarkers Working Group.** This working group is dedicated to investigating preclinical cardiac biomarkers of hypercoagulability induced under a thrombotic state, in both normal and diseased states. A

manuscript was submitted detailing a study investigating the effects of doxorubicin in Zucker diabetic fatty rats. A new study is in the planning stages using xenobiotics to induce the procoagulant state and confirm measurements of biomarkers of interest.

**Cardiac Compound Tool (CCT) Database Subteam.** The Cardiac Safety Steering Team established this new subteam in early 2020 to develop and provide a structured resource for use when identifying compounds appropriate in a planned committee study. Delivery of this publicly accessible database is anticipated by the end of 2020.

**COVID-19 Subteam.** This subteam was organized in May 2020 in response to the ongoing pandemic. Subteam members identified that emerging treatments for the novel coronavirus may have cardiotoxicities. The group is exploring how to gather cardiac safety data on five emerging therapies, whether prospective or retrospective, and develop a publication.

## Areas of Focus for 2021

- Alignment to mechanistic, human-relevant approaches.
- Generate de novo data through several of the working groups' planned studies.
- Commence the second phase of the CCT Database to include *in vitro* data.
- Convene a virtual committee meeting to review the portfolio.

## Strategic Impact Areas

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

The HESI Cardiac Safety Committee works to increase efficiency and accuracy of the current drug testing paradigm as well as its impact on the 3Rs. They do this through collaborative work to test and validate new technologies that could allow for improved decision-making at earlier phases in drug development.

**Catalysis of New Science**

The committee is working to test and validate several new assay systems through the Stem Cell Working Group and FDA grants.

**Enhancement of the Societal Knowledge Base on Human Biological Processes of Relevance for Protecting Human Health**

The committee continues to share data through manuscripts, data repositories, and databases for the greater scientific community to benefit from the body of knowledge generated through the studies.

## 2020 Awards, Grants, and Recognition

The HESI Cardiac Safety Committee was awarded two publicly funded grants in 2019, which were both renewed in 2020. HESI completed the first year of the *U01: Consortium-Led Evaluation of Integrated Human-Relevant Approaches to Identify Drug-Induced Cardiovascular Liabilities.* This is a multi-year grant that 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." In the first year, an advisory team was convened, five subaward projects scoped, a compound tool set identified, and three additional subawards selected through a request-for-proposals process.

The second grant, a Broad Agency Announcement grant from the US FDA, focuses on assessing variability and reproducibility of manual and automated patch clamp platforms. HESI established subcontracts with seven laboratories who are working to complete three manual and four automated patch clamp studies. 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.

## Publications

### Published

Gintant G, Kaushik EP, Feaster T, Stoelzle-Feix S, Kanda Y, Osada T, Smith G, Czysz K, Kettenhofen R, Lu HR, Cai B, Shi H, Herron TJ, Dang Q, Burton F, Pang L, Traebert M, Abassi Y, Pierson JB, Blinova K (2020) Using human induced pluripotent stem-cell derived cardiomyocytes for *in vitro* repolarization studies: examples and best practices. *Regulatory Toxicology and Pharmacology*. 117:104756. doi: 10.1016/j.yrtph.2020.104756.

Kramer J, Himmel HM, Lindqvist A, Stoelzle-Feix S, Chaudhary KW, Li D, Bohme GA, Bridgland-Taylor M, Hebeisen S, Fan J, Renganathan M, Imredy J, Humphries ESA, Brinkwirth N, Strassmaier T, Ohtsuki A, Danker T, Vanoye C, Polonchuk L, Fermini B, Pierson JB, Gintant G (2020) Cross-site and cross-platform variability of automated patch clamp assessments of drug effects on human cardiac currents in recombinant cells. *Scientific Reports*. 10:5627. doi: 10.1038/s41598-020-62344-w.

Pfeiffer-Kaushik ER, Smith GL, Cai B, Dempsey GT, Hortigon-Vinagre MP, Zamora V, Feng S, Ingermanson R, Zhu R, Hariharan V, Nguyen C, Pierson J, Gintant GA, Tung L (2019) Electrophysiological characterization of drug response in hSC-derived cardiomyocytes using voltage-sensitive optical platforms. *Journal of Pharmacological and Toxicological Methods.* 99:106612. doi: 10.1016/j.vascn.2019.106612.

Pugsley MK, Brooks MB, Fishman CE, Katavolos P, Chiang AY, Parish ST, Schultze AE, Pierson JB (2020) Use of the ZDF rat to model dietary fat induced hypercoagulability is limited by progressive and fatal nephropathy. *Journal of Pharmacological and Toxicological Methods.* doi: 10.1016/j.vascn.2020.106933

Rossman EI, Cools F, Cordes J, Dhuyvetter D, Doyle JM, Friedrichs GS, Guth B, Neradilek MB, Parish ST, Pierson JB, Polissar N, Tang HM (2020) Echocardiographic and hemodynamic indices of myocardial contractility simultaneously evaluated in telemetered beagle dogs: a HESI-sponsored cross-company evaluation. *Journal of Pharmacological and Toxicological Methods.* doi: 10.1016/j.vascn.2020.106897.

### In Progress

Chaudhary et al. (2021) Understanding conduction issues in context of drug development.

Miraucourt et al. (2021) Incidence of spontaneous arrhythmias in telemetered beagle dogs, Gottingen minipigs and cynomolgus monkeys: a HESI consortium retrospective analysis.

Valentin et al. (2021) Why is it so difficult to predict drug effects on repolarization in humans?

## Participating Organizations

### Government/Regulatory Agencies

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

### Academic/Research Institutes

Boston University
Bristol University
Columbia University
Cornell University
Fraunhofer Institute
George Washington University
Harvard University
Jagiellonian University Medical College
Johns Hopkins University
Karolinska Institute
Michigan State University
Natural and Medical Sciences Institute, University of Tubingen
Northwestern University
Ohio State University
Stanford University
SUNY Buffalo
Toho University Medical School
University at Buffalo
University of Alberta
University of California, Davis
University California, Irvine, School of Medicine
University of Glasgow
University of Hamburg
University of Louisville
University of Michigan
University of Minnesota
University of Nottingham
University of Tokyo
University of Washington
University of Wisconsin
Victor Chang Cardiac Research Institute

### Industry

AbbVie
ACEA Biosciences, Inc.
Amgen, Inc.
AstraZeneca
Boehringer Ingelheim
Bristol-Myers Squibb Company
B'SYS GmbH
Charles River Laboratories
Covance
Curi Bio
Cytokinetics
Eli Lilly and Company
ERT
Fujifilm Cellular Dynamics, Inc.
Genentech
GlaxoSmithKline
innoVitro GmbH
Inocardia
IPSyte
Janssen Pharmaceuticals
Merck & Co.
MyoKardia
Nanion Technologies
NEXEL, Co.
Novoheart
Pfizer, Inc.
Roche
Sanofi
Sony Biotechnology
StemBioSys
Stemina Biomarker Discovery
Takeda Pharmaceutical Company, Ltd.
TARA Biosystems
UCB-Biopharma

### Clinical

Lifespan Heart Center

### Other

European Bioinformatics Institute (EBI/EMBL)