



# HESI Cardiac Safety Committee

Summer 2023 Newsletter

## Celebrating 15 Years!

2023 marks 15 years as the official HESI Cardiac Safety Committee! Our Committee is a pioneering and dedicated group that has served a vital role in ensuring the safety and integrity of cardiovascular safety assessments over the course of our history. Established in 2008, the committee's primary objective has been to assess, research, and develop comprehensive approaches to evaluate drug-induced cardiac risk. Throughout this journey, we have collaborated with hundreds of leading experts, pharmaceutical companies, regulatory bodies, government agencies, healthcare professionals, and more to implement cutting-edge methodologies and strategies for assessing cardiac safety. This Committee milestone stands as a testament to your enduring dedication and profound impact on cardiac safety and ultimately patient well-being.

## Welcome to new HESI Staff, Dr. Claire O'Brien



Dr. Claire O'Brien holds a PhD in Pharmacology and Toxicology from the University of California, Davis, and an MPH in Environmental Health from San Diego State University. She comes to HESI with experience as a Regulatory Specialist at a biotech company where she helped to develop a regulatory strategy for bringing innovative infant nutrition products to market. She also has experience in safety assessment and toxicology of dietary supplements, educational outreach on environmental health topics within a community setting, and as a lead clinical trials coordinator for a major research study. Dr. O'Brien will work on the Cardiac Safety Committee, PBPK Committee, and the PATB Committee.

## Blood Pressure Meeting with FDA

The revised draft FDA guidance on the "Assessment of Pressor Effects of Drugs" released in Feb 2022 recommends a stand-alone thorough assessment of blood pressure in the intended patient population for systemically bioavailable drugs intended for chronic use; irrespective of any other nonclinical and/or clinical data. HESI Cardiac Safety Committee members met with FDA to discuss this guidance to understand perspectives and discuss options for a path forward. Following the meeting, HESI members agreed to form a new Subteam to explore this topic in more detail. Contact Jennifer Pierson ([jpierson@hesiglobal.org](mailto:jpierson@hesiglobal.org)) with questions or if you're interested in joining the Subteam.

# 2023 Early Career Seminar Series Awardees

The HESI Cardiac Safety Committee awarded its second annual Early Career Seminar Series earlier this year. This competitive award is given to postdoctoral or early career scientists who have compelling research related to cardiovascular safety and risk assessment. The Committee will be seeking new applications starting in September. Visit the website to learn more: <https://hesiglobal.org/cardiac-safety/>. The 2023 Awardees were Drs. Loukia Yiangou (Leiden University Medical Center) and Louise Hesketh (King's College London).

Dr. Yiangou presented her work on the optimization and use of genetically encoded voltage and calcium indicators in hiPSC-derived cardiomyocytes and how they can be used to model cardiac arrhythmias such as long QT2 syndrome. Moreover, she presented work on how these reporters can be used for drug toxicity assays by looking at calcium handling as well as how they can be used to study gene function. The second part of the talk focused on the use of hiPSCs-derived cardiovascular cell types to model hypertrophic cardiomyopathy (HCM). Through the use of 2D and multicellular 3D models, Dr. Yiangou demonstrated that HCM disease phenotypes can be modeled faithfully and how these hiPSC-derived physiological models can be studied for further understanding disease mechanisms.

Dr. Hesketh presented on *Utilising the prodrug concept and translational ex vivo animal models to assess and improve the therapeutic index of antiarrhythmic drugs*. Her presentation detailed her research into two hypoxia-activated antiarrhythmic prodrugs, namely diltiazem N-oxide and lidocaine N-oxide, and their potential application to the prevention of sudden cardiac death. Using the ex vivo Langendorff-perfused rat heart model, and an experimental protocol designed specifically to estimate the 'translational' therapeutic index of existing and novel antiarrhythmic drugs, her research demonstrated that both N-oxide prodrugs exhibited antiarrhythmic effectiveness in the absence of adverse effects. In comparison to existing antiarrhythmic drugs, these novel hypoxia-activated antiarrhythmic prodrugs have a favourable 'translational' therapeutic index, and thus represent a promising avenue for future safe antiarrhythmic drug development.

## 2023 -2024 Meetings

The HESI Cardiac Safety Committee will be presenting working at the following meetings:

### *Safety Pharmacology Society Annual Meeting September 2023, Brussels, Belgium*

- An Evaluation of Drug-Induced Blood Pressure Changes in a Standard Canine CV Safety Pharmacology Study: A HESI-sponsored consortium, Koshman et al., P55. Presented by Yevgeniya Koshman, AbbVie
- In Vitro Assessment of Long-Term Cardiotoxicity Using Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes, Kettenhofen et al. Presented by Ralf Kettenhofen, Fraunhofer IBMT
- Development of a Pharmaceutical Database to support the Nonclinical Evaluation of Drug-Induced Cardiac Toxicity, De Alwis et al., P138. Presented by Jennifer Pierson, HESI
- Heart Rate Corrected JTp and TpTe as Proarrhythmia Biomarkers in Safety Pharmacology Non-Human Primate Studies: Outcome from a HESI Consortium Prospective Study, Authier et al., P025. Presented by Todd Wisialowski, Pfizer
- The Impact of Collaborative Science on Cardiovascular Safety Evaluation – A 10-Year Update of the HESI Cardiac Safety Committee, Blinova et al., P140. Presented by Jennifer Pierson & Claire O'Brien, HESI

### *American College of Toxicology Annual Meeting, November 2023, Orlando, Florida, USA*

- Heart Rate Corrected JTp and TpTe as Proarrhythmia Biomarkers in Safety Pharmacology Non-Human Primate Studies: Outcome from a HESI Consortium Prospective Study, presented by Brian Roche, CRL.

### *Society of Toxicology Annual Meeting, March 2024 Salt Lake City, UT, USA*

- Symposium Session: Take Heart: Learning from Our Past to Improve Cardiovascular Safety Assessments of Pharmaceuticals in the Future, co-chaired by Jean-Pierre Valentin, UCB & Jennifer Pierson, HESI.