The Impact of Collaborative Science on Cardiovascular Safety Evaluation: A 10-Year Update of the HESI Cardiac Safety Committee

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ABSTRACT

The Health and Environmental Sciences Institute (HESI) is a nonprofit organization focused on resolving global health challenges through collaborative science. HESI achieves this by engaging scientists from around the world in the public, including health regulatory authorities, and private sectors and coalescing around a specific topic. The HESI Cardiac Safety Committee (CSC) officially formed in 2008 to improve public health by reducing unanticipated cardiovascular (CV)-related adverse effects from pharmaceuticals or chemicals. Since the publication by Pierson et al. (2013) outlining achievements, the HESI CSC has continued to champion cardiac safety, having a major impact on the field of CV safety assessments. This has been attained through numerous prospective studies, retrospective analyses, workshops, symposia and publication of 24 peer review manuscripts. The lasting impact of collaborative science on the field of CV safety is best exemplified by the Comprehensive In vitro Proarrhythmia Assay (CiPA) initiative, subsequent updated ICH E14/S7B Q&A guideline as well as the human stem cell validation studies and best practice articles. Challenges and opportunities in earlier detection of potential failure modes using in vivo, in vitro and in silico models are a hallmark of the HESI CSC that facilitates better drug development and study design. HESI teams are investigating promising new biomarkers to detect hemostatic changes earlier in the process of adverse CV toxicity pathways and also focusing on blood pressure measurement in non-clinical safety studies. Answering challenging questions as a collaborative team, sharing data for the benefit of the larger scientific and regulatory communities, and helping young scientists advance their careers are just a few of the outcomes of the last 10 years of the CSC. Future challenges ahead and the direction of the CSC will be offered for input.

CARDIAC BIOMARKERS WORKING GROUP

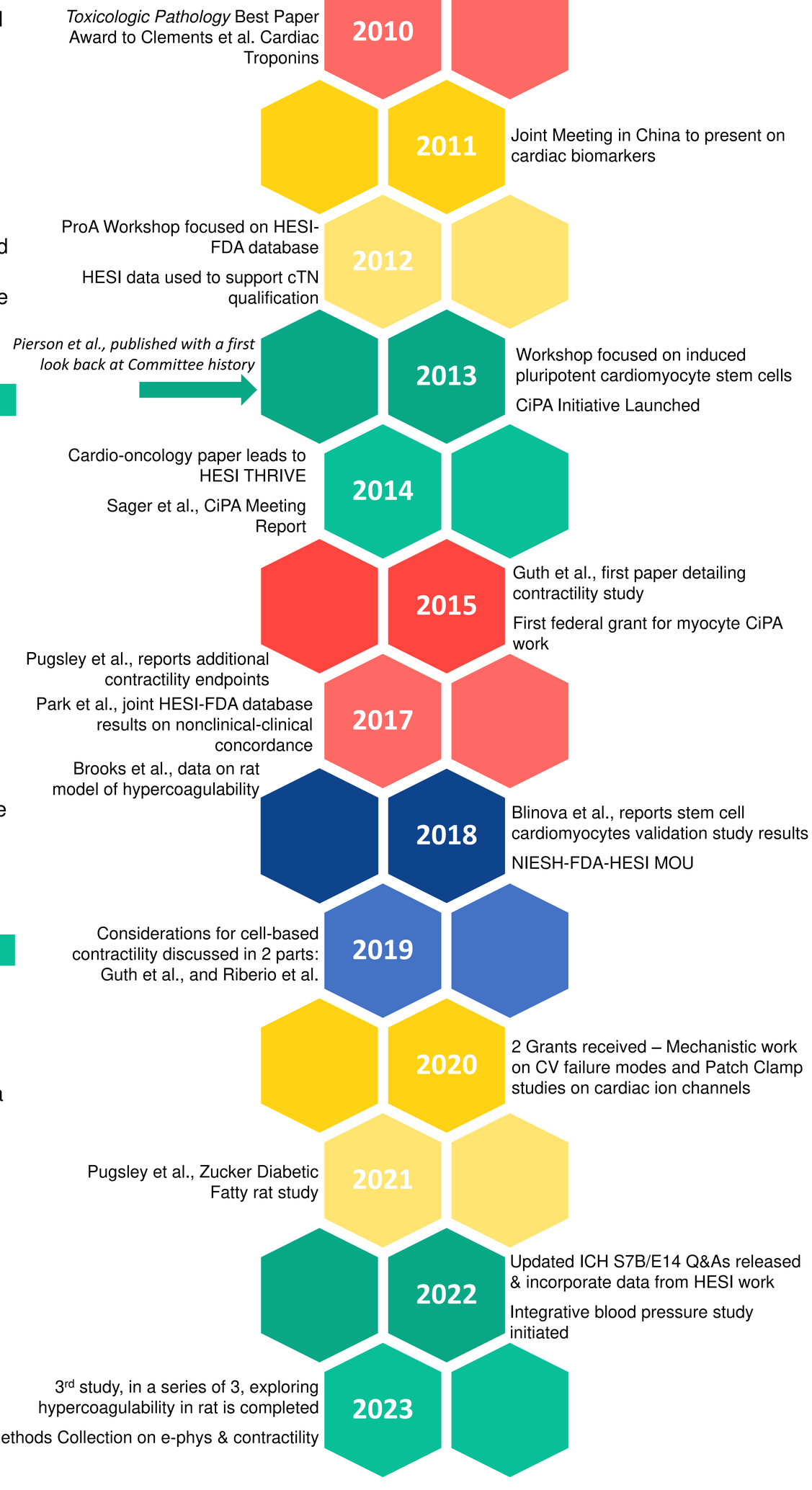
Since 2012, the Cardiac Biomarkers WG has been investigating preclinical cardiac biomarkers of hypercoagulation in both normal and diseased states. Initial studies included the use of a rat endotoxin model to evaluate biomarkers of inflammation-induced hypercoagulability and Zucker diabetic fatty rats to identify biomarkers of hypercoagulability relevant to patient populations with complications of diabetes and obesity. A third rat model study to qualify biomarkers of hypercoagulability and prothrombotic hemostatic imbalance in response to two distinct, well-defined stimuli: a procoagulant agent, thromboplastin (tissue factor), and an antifibrinolytic agent, tranexamic acid is now in progress. Preliminary data indicate that subsets of the biomarkers may be combined into sensitive and specific panels to detect mechanistically distinct conditions of prothrombotic imbalance.

INTEGRATIVE STRATEGIES WORKING GROUP

Following a Think-Tank in 2009, the HESI Integrative Strategies WG formed with the goal to bring structural and functional issues under the same focus. They focused their effort on understanding contractility assays and completed a multisite *in vivo* study that resulted in five publications and a collaboration with Kings College London, who are developing an attractor model to predict correlation between blood pressure and left ventricular pressure. The WG also developed a two-part publication on considerations for an *in vitro*, cell-based assay to detect contractility changes. Most recently, the WG is conducting a study with the objective to assess drug-induced blood pressure changes in a standard *in vivo* CV dog safety pharmacology study.

Scan to learn more about the HESI Cardiac Safety Committee and get a copy of the poster!

HESI CARDIAC SAFETY TIMELINE



IMPACTS & FUTURE CONSIDERATIONS

HESI's Cardiac Safety Committee (CSC) formed with the intent to identify and solve pressing CV safety challenges for drug developers, regulators and researchers. By joining their collective expertise and knowledge, conducting numerous studies and generating novel data and more, the CSC has had a major impact on CV safety and assessments. Future challenges for CV safety assessment remain. ICH E14/S7B Discussion Group will soon consider a second phase for the updated Q&As. HESI CSC aims to help identify and address some of the remaining questions and data gaps.

- *What do you think is needed for this second phase of the ICH S7B/E14 Q&As?*

Additional attention to blood pressure is now a focus and the recent draft guidance from FDA highlights the importance of understanding blood pressure changes.

- *Could an integrated risk assessment using nonclinical data be valuable?*

Identifying new biomarkers for CV endpoints is important. Novel nonclinical work is underway.

- *How can new biomarkers be validated and incorporated into regular assessments?*

Finally, there are many topics, AI/Machine Learning, NAMs, 3Rs principles and more

- *What do you think will have the biggest impact on CV safety assessments next?*

Email us your thoughts! Cardiacsafety@hesiglobal.org

PROA WORKING GROUP

HESI initiated cardiac-related activities in 2001 were based on the need to better understand the scientific basis for drug-induced delayed ventricular repolarization (QTc prolongation) and Torsades de Pointes (TdP.) The ProArrhythmia (ProA) WG later evolved to further investigate mechanisms of proarrhythmia. The WG published 3 papers aiming to assess the concordance between nonclinical assays and clinical results, including a first-of-its-kind database with FDA IND and NDA data. The WG has also lent expertise to the CiPA initiative as well as conducted retrospective studies exploring implanted telemetry outcomes. Currently, they are exploring a new ECG biomarker and drafting a manuscript focused on the sodium channel and conduction issues.

CARDIAC STEM CELL WORKING GROUP

The Stem Cell WG formed in 2013 with the goal of understanding and characterizing the use of stem-cell derived cardiomyocytes in cardiac safety assessments. An initial workshop launched the WG and soon thereafter a project was introduced in support of the CiPA initiative. Studies conducted by this group, including pilot and validation studies, have resulted in the identification of biomarkers to allow reliable assessment of TdP liability. Over the past 2 years, this group has moved onto broader cardio-toxicology studies and the latest collaborative multi-site/multi-platform study is examining chronic cardiotoxic actions in cultured systems for periods of up to 6 days. The practical work was completed by early 2023 and analysis and submission for publication is targeted for the end of 2023.

CONCLUSIONS & ACKNOWLEDGEMENTS

We believe the collaborative efforts of this committee hold the promise of advancing our understanding of drug-induced CV toxicity and pave the way for advances in the science that can result in safer and more effective medicines.

The authors would like to acknowledge all participants, past and present, of the HESI Cardiac Safety Committee. Without their participation, none of this would be possible. We extend gratitude and thanks to each individual, who made this collaborative science effort possible.