



# CARDIAC NEWS & NOTES

## 2018 BUDGET

### INSIDE THIS ISSUE:

SAVE THE DATE! 2

INTEGRATIVE STRATEGIES 2

PROARRHYTHMIA 3

CARDIAC BIOMARKERS 3

STEM CELL/MYOCYTE 3

CIPA 3

PUBLICATIONS & UPCOMING MEETINGS 4

Each Fall, in order to prepare for the budget request, HESI staff share a slideset of activities, accomplishments and the budget for the following year. This presentation was shared via email last month, and is also available on [SharePoint](#).

With 2 manuscripts published, another 8 in development and participation in over 8 scientific conferences, suffice to say 2017 was another busy and productive year!

The 2018 proposed budget reflects our continued, strong membership base and allows unallocated funds to be used for 'research support.' These funds are available as projects develop or new projects emerge.

Based upon input from the HESI membership, the HESI Board is implementing a shift in revenue collection strategy to reduce the

amount of general HESI sponsorship/membership fees. The goal of this strategy is to ensure that supporters are able to invest more of their funds directly in HESI research programs of

interest to them, to reflect new efficiencies that have reduced HESI's general operating budget expenses in recent years, and to maintain high quality staff support for our programs. Most participating sponsors saw a net decrease in their total invoice for HESI in 2017 and these decreases will be maintained for 2018. In June 2017, the Board also approved a



slight increase the support fees for management and coordination directly linked to the scientific programs for the first time in more than six years. The 2018 budget already reflects this increase and will not impact assessment fees in 2018. Thanks for your continued support for HESI! We look forward to another great year!

### SPECIAL POINTS OF INTEREST:

Save the date for the next HESI Cardiac Safety Committee meeting! (page 2)

## Have you seen the latest updates on CiPA?

Visit us online to learn more about the latest publications, project progress and data resources! [www.cipaproject.org](http://www.cipaproject.org)



The CiPA Steering Team is committed to making data available to the scientific community. Data from the two FDA ECG studies are now available as well as the most recent in silico model paper and the open source model code. Additional data will be made available as projects are completed.

<http://cipaproject.org/data-resources/>



## SAVE THE DATE!



We will hold our next Committee face-to-face meeting in Boston, Massachusetts, USA. The meeting will be held at the Langham Boston Hotel on May 15-16, 2018. More details coming soon!!

## INTEGRATIVE STRATEGIES WORKING GROUP

The Integrative Strategies Working Group has been working on a few projects in various phases of work. The Contractility Subgroup has nearly completed two additional manuscripts, in addition to their two previously published manuscripts. One manuscript took a statistics-based approach, while the other detailed the correlation of endpoints collected by either echocardiograph or telemetry. In addition to wrapping up the planned contractility manuscripts, HESI has harvested the data

for a second time for use in other publications and data driven solutions by outside organizations. Currently, there are ongoing discussions that would bring in the expertise of the working group with outside collaborators, including in the area of mathematics.

Finally, a new work stream has recently launched in the area of cellular systems, with the objective of constructing and ultimately testing a framework on the use of non-animal methods to assess contractility. While these discussions

are still in early stages, the group is working towards the goal of setting a series of criteria across various contexts to ultimately use in a position paper. This could possibly be followed by a series of proof of concept studies to “stress test” the criteria outlined.

## PROA WORKING GROUP

The ProA Working Group's Phase 1 manuscript detailing the results of the HESI-FDA database to understand predictivity of nonclinical to clinical proarrhythmic models was accepted at *British Journal of Pharmacology*! (See page 4 for full citation.) They now turn their focus to the Phase 2 manuscript, which will provide possible mechanisms for discordance in the database including example The two newest ProA Subteams, High-Throughput Systems (HTS) and J-T Peak

have made significant progress over the summer months. The HTS Subteam completed the first phase of their study to provide data for CiPA on the 7 ion channels. They began the second phase of the study, which will complete the 28-CiPA compound set and anticipate delivering all data by mid-November. FDA will use this phase 2 data to finalize validation of the in silico model.

The J-T Peak Subteam completed a retrospective, exploratory

study to understand whether or not the J-T Peak biomarker would add value in a preclinical study. They are closely mirroring the ongoing FDA clinical work on J-Tpeak. After an in-person meeting in September and a webinar in October, the team reviewed the available data and are making plans for future work.

This Subteam was also the first group to propose and successfully hire a student intern. Approved by the ProA Working

Group members in February 2017, Committee funds were used for the intern, who was hired and managed by Dr. Simon Authier (CiToxLab and J-T Peak Subteam leader.) This allowed the Subteam to complete a large data analysis in only a few weeks time. It will surely be a model we look to use again in the future, and in fact, was replicated by the Myocyte Subteam over the summer as well!



## CARDIAC BIOMARKERS WORKING GROUP

The Cardiac Biomarkers Working Group has been making progress on their Proof of Concept #2 (POC2) study. With the completion of the in-life portion of the study last year, the group has been analyzing and presenting on selected biomarkers as outlined in their study design. Those potential biomarkers look across various technologies that include microRNA, microparticles and extracellular vesicles, flow cytometry, histology,

and more. The goal is to complete this analysis within the next few months and to begin drafting up a manuscript. This has not only provided a rich dataset on the selected biomarkers tested, but also on the ability to further characterize the model (Zucker Diabetic Fatty Rat) beyond what was previously described in the literature. A series of abstracts are also being drafted with the goal of presenting some of these initial findings

before a more comprehensive manuscript is published.

Finally, the working group has begun discussions surrounding a 3<sup>rd</sup> POC. While no final decisions have been made, the goal over the next few months is to determine if there is a specific model and class of compounds that would be of interest to test.

## STEM CELL WORKING GROUP/MYOCYTE SUBTEAM

The Myocyte Subteam completed the second phase of the CiPA study and both Core and Non-core sites submitted data.

A total of 10 sites submitted data on 2 cell types and 6 platforms. The Core Team worked in concert with scientists at the FDA to develop an analysis plan including a statistical model.

These efforts have been submitted for consideration in a peer-reviewed journal. Once published, the Myocyte Subteam will work to make the data available to the general scientific community, an important goal for all CiPA work streams. The exact details of how this data will be released are still under discussion.

A total of 11 Non-core sites submitted data on 9 platforms and 5 different cell types. In order to process all of the Non-core data submitted, HESI recruited and hired a summer intern to assist with data processing. The results of this effort were presented to the Stem Cell Working Group on their August 2017 teleconference.

As the team completes the second phase CiPA work, they will next turn their focus to contractility. A joint effort with the HESI Integrative Strategies Working Group is planned for 2018. Stay tuned for more details soon.



Don't miss the latest presentations and webinars from 2017!

- SPS Webinar presented by Dr. Zhihua Li (available [here](#))
- FDA Grand Rounds presented by Dr. David Strauss (available [here](#))
- CiPA at SPS—In Silico presentation and CiPA

Challenges and Opportunities Session (more [here](#))

- CiPA In Silico Modeling Workshop at the Cardiac Physiome Conference (more [here](#))

In addition to these communication efforts, the Work Streams have been hard at work generating final data needed to complete the first draft of an inte-

grated CiPA paradigm. The CiPA Steering Team met in early December 2017 to review the final data. The resulting integrated plan will be shared with the ICH E14 Working Group and a public meeting will be planned in 2018 (TBD) for the larger scientific community.

Looking for more specifics on the Work Stream timelines, data resources, or latest up-

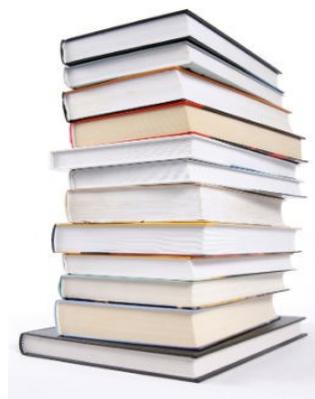
dates? Check out the newly updated CiPA website: [www.cipaproject.org](http://www.cipaproject.org).

## PUBLICATIONS OF NOTE

Can Nonclinical Repolarization Assays Predict the Results of Clinical Thorough QT Studies? Results from a Research Consortium. Park EJ, Gintant GA, Bi D, Kozeli D, Pettit SD, Pierson JB, Skinner M, Willard J, Wisialowski T, Koerner J, Valentin JP. (2017) *British Journal of Pharmacology*. Online ahead of print. DOI: 10.1111/bph.14101. <http://onlinelibrary.wiley.com/doi/10.1111/bph.14101/abstract>

E. Boulay, M.K. Pugsley, V. Jacquemet, A. Vinet, M.V. Accardi, M. Soloviev, E. Troncy, J.M. Doyle, J.B. Pierson, S. Authier (2017) Cardiac contractility: Correction strategies applied to telemetry data from a HESI-sponsored consortium. *JPTM*. 87: 38-47. <https://doi.org/10.1016/j.vascn.2017.04.009>.

M.B. Brooks, J.R. Turk, A. Guerrero, P.K. Narayanan, J.P. Nolan, E.G. Besteman, D.W. Wilson, R.A. Thomas, C.E. Fishman, K.L. Thompson, H. Ellinger-Ziegelbauer, J.B. Pierson, A. Paulman, A.Y. Chiang, A.E. Schultze (2017) Non-Lethal Endotoxin Injection: A Rat Model of Hypercoagulability. *PLOS One*. 12(1). <http://dx.doi.org/10.1371/journal.pone.0169976>.



Have a publication or article you think your colleagues would find interesting?  
Contact HESI staff to include it in the next issue of CNN!

## UPCOMING MEETINGS

**Related Meetings:** Society of Toxicology Annual Meeting—March 11-15, 2018, San Antonio, Texas

- EUROTOX 2018— September 2-5, Brussels, Belgium
- American College of Toxicology—November 4-7, 2018 , Palm Beach, Florida
- American Heart Annual Meeting—November 10-14, 2018, Chicago, Illinois
- Safety Pharmacology Society—September 29—October 3, 2018, Washington, DC



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Since 1989, the ILSI Health and Environmental Sciences Institute (HESI), a non-profit 501c charitable organization, has provided the framework for scientists from the public and private sectors to meaningfully collaborate in developing science for a safer, more sustainable world.

The Cardiac Safety Committee is committed to improving public health through modeling and early detection of adverse cardiovascular risks. The committee brings together scientists and technical disciplines within the international community of public, private and government sectors to develop best practices for translation of *in vitro* and non-clinical cardiovascular data.

