Welcome to the fall edition of the CNN! This edition will be different from past editions because it highlights new committee proposals, features new contributors in the ‘From the Leadership’ column and includes a bonus page (pg 5) with a recent Science article on CiPA.

2016 Activities Update and 2017 Budget

As usual, fall is the time to finalize the budget for the coming year. Your Program Managers have already provided an updated budget for 2017, and we were happy to announce a reduction in the annual assessment fee thanks in part to our membership growth and efficiencies in our collaborative nature. In 2016, we continued to be an effective and productive committee with over 80 public and private organizations and 2 new grant programs that are not only new to our committee but a first for HESI! There were 2 new published manuscripts, 3 new manuscripts submitted and another 3 in progress. The committee also had a strong presence (via oral and poster presentations) at more than 7 different international conferences this year alone. The committee is also leading the CiPA initiative (http://cipaproject.org/) through several different working groups and has initiated a new partnership with the cardio- oncology community to develop THRIVE (http://hesithrive.org/), which will offer seed funding for translational research. HESI THRIVE was also just named as a partner in the White House Cancer Moonshot initiative.

The full 2016 Update/2017 Budget Request slide set is available on SharePoint here. Don’t have access to SharePoint? Email Melissa Gilden.

Finally, HESI introduced a new communication tool this year that is tailored to individual sponsor companies so they can better see the impact and value of HESI. These have been shared with the organizational representatives and if you’d like to see a copy, contact Jennifer Pierson.

Scientific Foresight

The last scientific mapping exercise was completed in 2009 and resulted in a publication and Combined Challenges Map (available here). This year HESI is again embarking on a mapping exercise, dubbed ‘Scientific Foresight,’ to reflect how this new activity will evolve and help shape the organization moving forward. The Scientific Foresight exercise aims to identify emerging human and environmental health and safety (HEHS) challenges and opportunities, technological trends and societal or regulatory trends that may impact HEHS. The HESI Program Strategy and Stewardship Committee and Board of Trustees are developing a final Scientific Foresight plan, and the current proposal includes ‘mini-mapping’ exercises for each HESI scientific committee. These maps will identify emerging trends that are directly related to the scope of each of the 14 scientific committees, including our Cardiac Safety Committee. The HESI Scientific Foresight exercise will also include existing resources from organizations like the Institute for the Future and the International Council for Science. By building on these existing resources and committee “maps”, HESI will have a broad but relevant tool that committees and the board can use to identify new scientific opportunities and align with emerging trends.

Our committee will embark on a series of webinars featuring novel topics and new speakers through the end of the year. In early 2017, we plan to conduct out mini-mapping exercise in the Washington DC area. More details will be shared soon in the meantime, look forward to a webinar series coming to a computer near you!

Speaking of new ideas…

HESI’s 2017 Call for Proposals is now open. Proposals are due Dec. 9th. Learn more here.
FROM THE CARDIOVASCULAR BIOMARKERS WORKING GROUP—BIOMARKER PROFILING TO DETECT VASCULAR ADVERSE EVENTS

Brought to you by Drs. Eric Schultze and Marjory Brooks of the Cardiovascular Biomarkers Working Group

In the summer issue of Cardiac News and Notes (Vol 2, Issue 2), Drs. Brian Berridge and Norman Stockbridge challenged members of working groups within the Cardiac Safety Technical Committee to make science more relevant and interpretable to the general public. They also highlighted their concerns with the current emphasis on morphologic changes in toxicity testing, the limited ability to perform high throughput drug safety testing, and the scarcity of relevant animal models of human cardiac injury and dysfunction. We in the Cardiovascular Biomarkers Working Group are happy to share our progress in these areas and lay out our vision for future research.

Our working group is focused on discovering new, translatable biomarkers to screen for thrombotic complications early in the drug development pipeline. Off-target activities that induce vascular adverse events (VAE) including arterial, venous, and small vessel thrombosis and thromboembolism are impossible to detect in cytotoxicity assays, yet these drug-induced events are increasingly recognized in patient populations. Our approach to biomarker discovery concentrates on rodents – the animals used for initial screening of new molecules in development, and utilizes serum and plasma – as routinely collected body fluid samples applicable for safety assessment studies in both animals and people (Schultze et al, Toxicologic Pathology, 41: 445-453, 2013). Our studies combine traditional toxicity testing with new global measures of coagulation and fibrinolysis such as thrombin generation assays, overall hemostasis potential, and thromboelastography (TEG), and novel assay platforms including microRNA arrays and high sensitivity vesicle flow cytometry. Our first proof-of-concept study explored the effects of systemic inflammation on coagulation by administering low dose endotoxin to rats. This study revealed circulating biomarker changes consistent with a hypercoagulable state and later return to hemostatic balance. Results of this work were shared in several abstracts and are under review for publication. We are now analyzing data from a second proof-of-concept study, using the Zucker Diabetic Fatty rat strain to model the influence of diet and cardiac compromise in patients with metabolic syndrome. We recognize that no single analyte will capture the complex mechanisms that manifest as VAE in diverse patient populations. Our strategy is to develop a series of conserved biomarker “signatures” that differentiate physiologic versus pathologic hemostatic responses to prothrombotic stimuli. This process is iterative; starting with a specific thrombotic trigger and pathway analyses to define informative downstream regulatory and response biomarkers, then testing these biomarkers against varied stimuli. Ultimately, the refined set of biomarkers that recognizes drug-induced prothrombotic signatures in pre-clinical testing will reduce the risk of VAE in later phase trials.

Disclaimer: The content of this article represents solely the authors’ view and may not reflect the position of their employers.

PROARRHYTHMIA—NEW ECG IN VIVO PROPOSAL

As the existing ProA Working Group projects wrap up (the HESI-FDA Database paper has been provisionally accepted and final edits are in progress and the HTS Subteam has begun their novel data collection efforts), the team begins to think towards future projects. One proposal to the group aims to characterize \( \text{T}_{\text{peak}} \) and \( \text{T}_{\text{peak}}-\text{T}_{\text{end}} \) ECG segments in nonclinical species. This study follows closely to the recent Johannesen et al., (2014, DOI: 10.1002/cpt.205) paper that used vectorcardiograms to perform \( \text{T}_{\text{peak}} \) and \( \text{T}_{\text{peak}}-\text{T}_{\text{end}} \) analyses using human ECG data.

The proposal from Simon Authier (CiToxLab) includes retrospective and prospective data collection and analyses of ECG segments in nonclinical species (e.g. canines or NHPs). This proposal will help bridge gaps in knowledge between humans and animal models and give a complete picture that translates to the clinic. The Working Group will work to ensure adding this type of biomarker will have value and understand what variability exists with these endpoints.

This type of data will be useful as an intermediate to the CiPA ion channel data and coordinate the in vitro and in vivo responses so sponsors and regulators alike can trust the results.

The Working Group will define next steps and develop a more detailed project plan as well as identify willing contributors. For more information or to participate in this project, contact Jennifer Pierson.
SYSTEMS BIOLOGY APPROACH TO EVALUATING CARDIAC CONTRACTILITY

HESI staff have attended several conferences over the past month and heard some pioneering talks about modeling, which highlighted new ways to analyze some of our usual data generated in in vivo and in vitro studies. Through these techniques, we can not only gain a better understanding of the mechanistic changes occurring, but also gain more value out of the same dataset generated in a typical nonclinical study.

When one such idea came to HESI, we were immediately intrigued and sat down to figure out how HESI might get involved.

Darrell Abernethy (FDA) has begun collaborative work to explore a systems pharmacology model to predict drug-induced depression of cardiac contractility. The proposal calls for data from in vitro, in vivo and in silico models to be collected for use in a more meaningful systems model. The aim is to couple animal models with human-pluripotent stem cell cardiomyocytes (hPSC-CM) for data that will provide for a mechanistic mathematical model. Ultimately, this data would translate into humans to predict LV dysfunction cardiotoxicity.

The HESI Cardiac Safety Committee can contribute in several ways including organizing a collaborative group to help standardize methodologies for evaluating animal models and hPSC-CM assays. Another component would be to evaluate 2D and 3D hPSC-C models and determine how all of the in vivo and in vitro models can improve predictivity and translate to the clinic.

CIPA Update Meeting: The next CIPA Update meeting will be held December 6, 2016 in Rockville, MD at the Hilton Washington/Rockville Hotel and Executive Meeting Center. Each of the CiPA work streams will provide an update on progress with most presenting new data/results as well as an opportunity to discuss with experts and provide your input!

Register online and view the agenda. HESI members should register as an ‘Industry Member’ to receive the discounted registration fee.

The CIPA Steering Team recently launched a new website: http://www.cipaproject.org. Check out the FAQs, related meetings and webinars and publications!
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.

Related Cardiac Meetings: ACT, November 6-9, Baltimore, Maryland ▪ AHA, November 12-16, New Orleans, Louisiana ▪ CiPA Update Meeting December 6, 2016, Rockville, Maryland ▪ SOT March 12-15, 2017, Baltimore, Maryland.


A few publications of interest are highlighted here. Have a publication or article you think your colleagues would find interesting? Contact HESI staff to include it in the next issue of CNN!


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