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CARDIAC NEWS & NOTES

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FDA-NTP-HESI SIGN MOU!

The National Toxicology Program (NTP), FDA Center for Drug Evaluation and Research (CDER) and HESI recently signed a new memorandum of understanding (MOU). This formalizes an existing partnership already in place allowing the three entities to work together to advance novel approaches to predict cardiovascular safety liabilities.

This MOU will help our committee build on the goals of our May 2018 workshop, developing more mechanistic-based assays and improving prediction of human outcomes.

NTP is already committed to a new human cardiovascular health focus and is in the process of hiring two fellows to work on related projects.

Additionally, HESI hopes to leverage this formal collaboration to apply for government funding to further support our objectives.

Overall, this is a new frontier in collaborative science that HESI is very excited to explore!

Check out the full the announcement online and don't miss the shout out to our very own HESI Cardiac Safety Committee! https://factor.niehs.nih.gov/2019/3/science-highlights/cardiovascular/index.htm

FDA CARDIOTOX WORKSHOP—MARCH 29, 2019

FDA will convene a workshop on *Cardiomyocytes for Mechanistic CV Safety Liabilities* March 29th, 2019. The workshop will focus on use of human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs) in non-clinical studies, including strengths and limitations of these approaches. Presentations from experts in the field will cover a wide range including strategies for validation, building confidence in the approach, case studies, applications and more!

This meeting is free to attend but registration is required.

Registration: www.eventbrite.com/e/cardiomyocytes-for-mechanistic-cv-safety-liabilities-tickets-54353537895

Location: FDA White Oak Bldg 31

10903 New Hampshire Avenue

Building 31 Conference Center, the Great Room White Oak, MD 20993

JOIN US TO CELEBRATE HESI'S 30TH ANNIVERSARY!

2019 marks 30 years at HESI and our Annual Meeting will celebrate this milestone! See the agenda and register online: http://hesiglobal.org/hesiannualmeetings/

Don't miss the Anniversary Member highlights in HESI's monthly newsletter *Insights:* http://hesiglobal.org/hesi-insights.

NEW CROSS-COLLABORATION! IMPLANTED TELEMETRY SUBTEAM

A new Subteam on Implanted Telemetry is a cross-collaboration between the Integrative Strategies and ProA Working Groups. This group, led by Simon Authier, CiToxLab, was initiated in early 2019. Implanted telemetry use is on rise but an evaluation of how this may impact endpoints in toxicology studies has been lacking. The Subteam plans to conduct a retrospective analysis using data obtained in repeat dose toxicology studies and compare to jacketed external telemetry (JET) study data. The Subteam will be reaching out to the full Cardiac Safety Committee and asking for data contributions for this important study. Contact Jennifer Pierson or Stan Parish for details or to join the group!

INTEGRATIVE STRATEGIES WORKING GROUP

The Integrative Strategies Working Group is moving towards completing their manuscript on the echo/telemetry analysis based off their contractility study. Furthermore, the 2 completed cell systems manuscripts, that outline criteria for in *vitro* based assessment of contractility and the application of those criteria to the iPSC model systems is completing final reviews before submission to Frontiers *in Pharmacology*.

PROA WORKING GROUP

The ProA Working Group has several Subteams actively wrapping up manuscripts including the Phase 2 Subteam who will submit their final paper in March. This paper is a follow on the Vargas *et al.,* 2015 and Park *et al.,* 2018 papers detailing concordance between nonclinical assays (hERG, APD, in vivo QTc) and clinical TQT studies. A final draft will be shared with the Working Group soon!

Additionally, the High-Throughput Systems (HTS) Subteam is wrapping up their manuscript on the results from the first phase of the HTS study highlighting data for the 4 main ion channels, hERG, peak and late Nav and Cav. They have narrowed down the target journal to *Nature Scientific Reports* and hope to have a final draft to share in the coming weeks.

The J-T Peak Subteam is finalizing their data analysis, which will include a formal statistical evaluation and exploration of the exposure-response relationships. Once the data is compiled, they plan to write up the results for the peer-reviewed literature.

As these groups begin to wrap up their work, the ProA Working Group will start to brainstorm about future projects. Ongoing discussions will be held on their monthly teleconferences.

CARDIAC BIOMARKERS WORKING GROUP

The Cardiac Biomarkers Working Group is in the process of drafting their first manuscript based on the POC2 study. This manuscript will describe the observations associated with high vs. low fat diet on the Zucker Diabetic Fatty Rat model. Subsequent manuscripts will build on those observations and address what was observed when in combination with doxorubicin. Finally, the group has begun to move forward in their discussions for a POC3 study. Currently, the group is discussing which drug class and model they intend to investigate, in addition to incorporating potential *in vitro* methodologies to test side-by-side with the *in vivo* model.

STEM CELL WORKING GROUP/MYOCYTE SUBTEAM

The Myocyte Subteam continues work on a 'best practices' paper, which, will describe advantages and limitations to using iPSC-CM approaches, expectations for assays that are used for screening vs. regulatory purposes, and of course, best practices. The goal is to bring awareness to some of the 'fit-for-purpose' aspects of these assays and how they can best be used for decision making.

The Stem Cell Working Group has their eye to the future and as discussed back in December 2019, a small scoping team was formed to determine next steps for the Working Group. After reviewing a survey of opinions on the topic, the scoping team determined a collaborative study on the maturation of iPS-CMs would be of tremendous value. The scoping team plans to present their ideas on the April Stem Cell Working Group call (planned for Apr 17th at 10:00 am EDT.)

CiPA

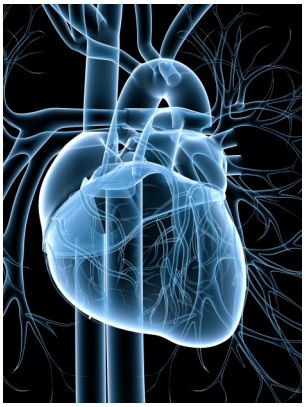
The CiPA Work Streams are all hard at work on several manuscripts including the Myocyte best practices (see above), ion channel definitions around safety margin for hERG block, JT Peak state of the science review, and a response to a letter to the editor in *Clinical Pharmacology and Therapeutics.*

In addition to the manuscripts, FDA continues collaborative partnerships with academic centers to collect additional manual patch clamp data. The ECG clinical trial data is publicly available on the CiPA website, which has spurred further work as well as external collaborations with clinical ECG experts. Lastly, FDA has plans to hire another fellow to continue work on TQT study data.

Progress continues on the ICH front and the Implementation Working Group will begin convening monthly meetings in Q1 2019 to discuss the concept paper and work plan. They will likely form subgroups to address the various aspects of the work plan and bring their discussions to the planned ICH in-person meeting in June. The CiPA Steering Team will continue to monitor this progress and several members are involved and providing input and additional data as requested.

The latest news and publications can always be found on the CiPA website: www.cipaproject.org.

IN THE NEWS



FDA CDER recently entered into a Research Collaborative Agreement with Dana Solutions LLC to explore use of artificial intelligence in advancing drug development. The groups plan to collaborate using deep learning platforms and human cell models, including iPSCs, with the aim to improve predictivity and assay sensitivity.

While not associated with HESI, members may find this news relevant and related to our interest in developing mechanistic-based assays. Read more online: https://www.danasolutionsllc.com/dana-fda-collaboration.html.

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

HESI OPEN FORUM

The HESI Emerging Issues Open Forum is the newest way to submit a new idea to HESI. Find the forum online to learn more or submit an idea: http://hesiglobal.org/propose-a-project/openforum. Note any ideas related to the Cardiac Committee should be brought directly to Jennifer or Stan so they can bring it to the leadership for further discussion and consideration. The Open Forum is meant to share new ideas that our Committee or HESI isn't already tackling.

UPCOMING MEETINGS

Related Meetings: Society of Toxicology—March 10-14, 2019, Baltimore, Maryland ■ HESI Annual Meeting & 30th Anniversary—June 2019, Alexandria, Virginia ■ Safety Pharmacology Society—September 23-26, 2019, Barcelona, Spain ■ American College of Toxicology—November 17-20, 2019, Phoenix, Arizona ■ American Heart—November 16-18, 2019, Philadelphia, PA

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Since 1989, the Health and Environmental Sciences Institute (HESI), a non-profit 501c3 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.