The use of cardiomyocytes for the assessment of proarrhythmic risk

SOT | CONTEMPORARY CONCEPTS in TOXICOLOGY

October 25–26, 2016

Arlington, Virginia

PROGRAM
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York Tomita
US Food and Drug Administration, Silver Spring, Maryland, USA
Dear Colleagues,

I am pleased to welcome you to the Use of Cardiomyocytes for the Assessment of Proarrhythmic Risk conference. This international congress will provide a forum to discuss the increasing use of human stem cell-derived cardiomyocytes (hiPSC-CM) in drug discovery, toxicity assessment, and cell-based treatment. Distinguished domestic and international scientists from government agencies, pharmaceutical industry, and academia will discuss the state-of-the-art approaches and path forward.

This meeting is planned to provide ample time for interactions with the plenary speakers and the Networking and Poster Reception will offer the opportunity to discuss emerging science and potential collaborations with scientists from around the globe.

Three key areas will be addressed:

• Understanding the phenotype and limitations of working with hiPSC-CMs;
• Learning how researchers are using stem cells currently and facilitating information sharing among one another; and
• Investigating advanced uses, such as how hiPSC-CMs potentially can be applied in the future.

As with all of the Society of Toxicology Contemporary Concepts in Toxicology (SOT CCT) conferences, this meeting aims to enhance scientific development and to build improved understanding and dialogue around emerging science with the potential to help create a safer and healthier world.

Enjoy the meeting!

Sincerely,

John B. Morris, PhD, ATS
SOT President
Human stem cell-derived cardiomyocytes (hiPSC-CMs) are increasingly used in drug discovery, toxicity assessment, and cell-based disease treatment. In vitro screening assays also are used to make decisions about which drug candidates to progress into development. From the public health perspective, assessing the cardiovascular toxicity potential of any new drug product or environmental toxicant is important. Comprehensive in vitro proarrhythmia (CiPA) assay is a new risk assessment paradigm proposed to replace the current thorough QT study that is currently needed for each new drug application. One of the proposals included in CiPA is to use hiPSC-CM to test drug-induced effects on the myocardial action potential to confirm the outcome of in silico modeling of drug-induced effects. The in silico modeling is based on the blocking activity of a given drug on the most important human myocardial ion channels involved in myocardial depolarization and repolarization. It is therefore important to understand the functional, morphological, and biochemical hallmarks of hiPSC-CMs and how this may relate to factors including the maturity of the hiPSC-CMs used and the specific conditions used to culture the cells. We need to understand how these cells behave in comparison to adult human ventricular or atrial CMs. Only when this is understood can we determine if they will provide a useful model for predicting in vivo activity. In addition, the acceptable translation of effects in stem cell-derived CM tested with environmental chemicals to human environmental exposure levels requires a thorough understanding of these same parameters.

In light of the potential utility of this emergent technology, this workshop will engage experts in presenting and discussing various aspects of the phenotype of these cells (functional, proteins, biochemical) and comparing them to adult ventricular CMs, as a basis for assessing their potential uses in drug and chemical safety testing. Topics covered include description of cell phenotypes from different sources, in vitro culture conditions and quality assessment, assay methods and validation, in vitro/in vivo correlation, current experience and challenges, and outlining and prioritizing the further work needed. This workshop will include domestic and international scientists from government agencies, pharmaceutical industry, and academia to discuss the current state-of-the-art approach and the path forward.
Program

Tuesday, October 25, 2016

7:00 AM–8:00 AM
REGISTRATION AND CONTINENTAL BREAKFAST NETWORKING

8:00 AM–8:15 AM
GREETING AND MEETING OBJECTIVES

Janet Woodcock, MD, Center for Drug Evaluation and Research, US FDA, Silver Spring, Maryland, USA; and Norman Stockbridge, MD, PhD, US FDA, Silver Spring, Maryland USA

8:15 AM–9:30 AM
SESSION 1—Essential Qualities of hiPSC-CM for Use in Assessing Human Arrhythmia Potential

The goal of this session is to assess the current state of our understanding of human stem cell-derived CMs and whether these cells are appropriate for use in high-throughput screening and regulatory assays. Issues to be discussed are as follows:

1. The current state-of-the-art approach in assessing the stem cell-derived cardiomyocytes (SC-CMs) including hiPSC-CMs. The electrophysiologic characterization needed to qualify the fit-for-purpose utility of hiPSC-CMs.
2. In vitro assay methods to standardize the qualification of hiPSC-CM.
3. The minimum set of markers needed for a qualification of hiPSC-CMs.

The meeting participants should finish the session with a clear idea of what the state-of-the-art approach is for hiPSC-CM characterization and what needs to be done in the future to improve the quality of the cells and potential for use in regulatory assays.

Moderators: Jennifer B. Pierson, MPH, HESI; and Ajay Pillai, PhD, NIH

8:15 AM–8:40 AM
Screening Proarrythmia Potential Using SC-Derived Cardiomyocytes

Gary Gintant, PhD, AbbVie, North Chicago, Illinois, USA

8:40 AM–9:05 AM
Assessment of Concentration-Dependent Drug-Induced Repolarization Delay and Arrhythmias in an iPS Cell-Derived Cardiomyocytes Model

Yuko Sekino, PhD, NIH, Tokyo, Japan

9:05 AM–9:30 AM
Cellular Markers for Assessing Maturation of Human iPSC-Derived Ventricular Cardiac Myocytes for Proarrhythmia Assessment

Todd Herron, PhD, University of Michigan, Ann Arbor, Michigan, USA

9:30 AM–9:45 AM
Break
9:45 AM–11:00 AM
SESSION 1—continued

Moderators: York Tomita, PhD, US FDA; and Yvonne Will, PhD, Pfizer

9:45 AM–10:10 AM
Cardiotoxicity Caused by Protein Kinase Inhibitors: Gene Expression Signatures in iPSC-Derived Myocytes
Eric Sobie, PhD, Mount Sinai School of Medicine, New York, New York, USA

10:10 AM–10:35 AM
Rate Correction of Field Potential Duration in hiPSC-Derived Cardiomyocytes: Sense and Nonsense
Georg Rast, PhD, Boehringer-Ingelheim, Biberach, Germany

10:35 AM–11:00 AM
Regulatory Applications of Cardiomyocytes As a Tool to Assess Arrhythmic Risk
David Strauss, MD, PhD, US FDA, Silver Spring, Maryland, USA

11:00 AM–12:00 Noon
SESSION 1—Panel Discussion

Moderators: Todd Herron, PhD, University of Michigan; and Yuko Sekino, PhD, NIH Japan

12:00 Noon–1:00 PM
LUNCH ON OWN (SEE PAGE 8 FOR OPTIONS)
SESSION 2—Best Practices in Use of hiPSC-CM for Proarrhythmia Assessment

This session will build on Session 1 by relating the experience of stem cell-derived CMS users in drug discovery and development projects, as well as applications in environmental science. Practical use of these CMS will be discussed, bringing out the positive aspects as well as the areas where improvement is needed to replicate human in vivo effects. Meeting participants will leave this session with an understanding of the current applications of these CMS, and where improvements need to be made in order to better predict human arrhythmia potential.

Moderators: Ksenia Blinova, PhD, US FDA; and Ling Pang, MD, US FDA

1:00 PM–1:25 PM
Subtype-Specific Promoter-Driven Optical Action Potential Recordings for Precise Disease Modeling and Drug Testing in iPSC-Derived Cardiomyocytes
Daniel Sinnecker, MD, Technical University of Munich, Germany

1:25 PM–1:50 PM
The Role of iPS Cardiomyocytes in Cardiac Safety Assessment of Drugs: A Novartis Perspective
Peter Hoffmann, MD, PhD, Novartis, East Hanover, New Jersey, USA

1:50 PM–2:15 PM
Deconvoluting Kinase Inhibitor-Induced Cardiotoxicity
Matt Peters, PhD, AstraZeneca, Waltham, Massachusetts, USA

2:15 PM–2:40 PM
Predictivity of a hiPSC-CM Model for Preclinical Cardiac Electrophysiological Safety Screening: A GSK Experience
Kate Harris, PhD, GlaxoSmithKline, Ware, United Kingdom

2:40 PM–2:55 PM
Break
2:55 PM–3:45 PM
SESSION 2—continued

Moderators: Frank Weichold, MD, PhD, US FDA; and Douglas Keller, PhD, Sanofi

2:55 PM–3:20 PM
Are hPSC-Cardiomyocytes Functionally Relevant If IKs Is Absent but Beta-Adrenoceptor Signalling Is Present?
Chris Denning, PhD, University of Nottingham, University Park, United Kingdom

3:20 PM–3:45 PM
Human Stem Cell-Derived Cardiomyocytes: An Alternative Model to Evaluate Environmental Chemical Cardiac Toxicity and Development of Predictive Adverse Outcome Pathways
Kevin Dreher, PhD, US EPA, Research Triangle Park, North Carolina, USA

3:45 PM–4:45 PM
SESSION 2—Panel Discussion

Moderators: Peter Hoffmann, MD, PhD, Novartis; and Lucie Low, MSc, PhD, NIH

4:45 PM–6:45 PM
NETWORKING AND POSTER SESSION

Wednesday, October 26, 2016

7:00 AM–8:00 AM
CONTINENTAL BREAKFAST AND NETWORKING

8:00 AM–9:30 AM
SESSION 3—Advanced Uses of Stem Cell-Derived Cardiomyocytes

This session will highlight new models being developed for more integrative assessment of arrhythmic potential for in vitro-in vivo correlations. 2D and 3D constructs from stem cells as well as dosimetry will be covered. Future developments and applications of these models will be discussed by leaders in this field.

Moderators: Todd Herron, PhD, University of Michigan; and Peter Clements, BVM&S, PhD, GlaxoSmithKline

8:00 AM–8:30 AM
Organs on Chips: New Tools for Tox
Francesco S. Pasqualini, PhD, University of Zurich, Zurich, Switzerland

8:30 AM–9:00 AM
Human Cardiac Biowires As a New Platform for Cell Maturation, Drug Discovery, and Safety Testing
Milica Radisic, PhD, University of Toronto, Toronto, Ontario, Canada
9:00 AM–9:30 AM
Microphysiological Systems for High-Content Drug Screening
Kevin E. Healy, PhD, University of California, Berkeley, Berkeley, California, USA

9:30 AM–9:50 AM
Break

9:50 AM–10:50 AM
SESSION 3—continued
9:50 AM–10:20 AM
Engineered Heart Tissues As a Drug Screening Platform
Arne Hansen, MD, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
10:20 AM–10:50 AM
PSCs for Accelerating Drug Discovery
Joseph Wu, MD, PhD, Stanford University, Palo Alto, California, USA

10:50 AM–11:50 AM
SESSION 3—Panel Discussion
Moderators: Brian Guth, PhD, Boehringer-Ingelheim; and Francesco S. Pasqualini, PhD, University of Zurich

11:50 AM–12:20 PM
PANEL DISCUSSION—Select Speakers and Moderators to Review Key Messages from the Meeting
Moderators: Gary Gintant, PhD, AbbVie; and Jane Bai, PhD, US FDA

12:20 PM–12:30 PM
CONCLUDING REMARKS
Joseph Wu, MD, PhD, Stanford University

12:30 PM
MEETING ADJOURNS

1:00 PM–3:00 PM
POST-MEETING ACTION DISCUSSION (INVITATION ONLY)
**Poster Information**

**Poster Presentation Instruction/Times**

Posters are available for viewing on both days of the meeting. Poster presentations will occur during the Networking and Poster Reception on Tuesday, October 25 from 4:45 pm to 6:45 pm.

**Poster Set-Up and Removal Dates and Times**

Posters can be mounted on Tuesday, October 25 at 9:30 am. Posters must be taken down by 12:45 pm on Wednesday, October 26.

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**Online Material**

**Access Materials Online**

[www.toxicology.org/hipc](http://www.toxicology.org/hipc)

Invited Speaker and Poster Presentation Abstracts • Program • Attendee List

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**Food and Beverage Breaks**

A continental breakfast and light snacks will be served both days. Lunch options at hotel include grab and go at the Marketplace and a $15 buffet at Relish.
Baltimore, Maryland
March 12–16, 2017
Baltimore Convention Center

Mark Your Calendar—Key Deadlines

Early-Bird Registration
January 13, 2017

Housing Reservation
February 8, 2017

Standard Registration
February 10, 2017
The Society of Toxicology appreciates the generous contributions of these meeting Supporters: