

Comprehensive In Vitro Proarrhythmia Assay (CIPA) Update Meeting

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CIPA Steering Committee

Agenda

- Session I: CIPA Overview and Scientific Underpinnings
- Session II: In Silico Modeling and Ion Channel Approaches
- Session III: Myocyte Efforts
- Session IV: Phase 1 ECG assessment Under CiPA
- Session V: CIPA Regulatory Acceptance and Implementation

Meeting Overview

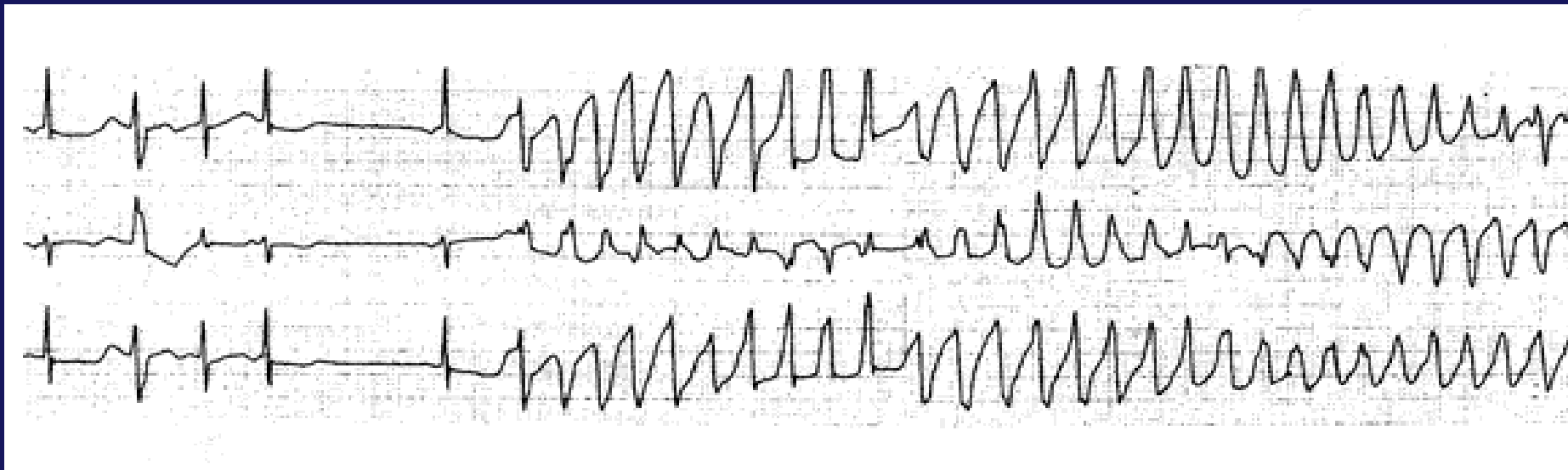
The purpose of the meeting is to provide an update on CiPA and a forum for all stakeholders to provide input

- **Robust discussion time**
 - Discussion is strongly encouraged!

Presenters have promised to stay within their allotted time limit 😊

The Need for a New Approach to Assessing the Proarrhythmic Potential of Drugs and Overview of CiPA

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QT Prolongation/Drug-Induced Torsade

- 2002-2005 ICH Regulatory Discussions
- ICH E14/S7B
- Focus on surrogates- HERG and QTc testing
 - Both are sensitive but not very specific for predicting a drug's proclivity to cause proarrhythmia
- HERG/QT Testing has had major impact on drug development
 - Whether drugs progress into humans
 - Whether their development is continued
 - Delays in approval
 - Labeling implications
 - Costs: > 1 Billion \$

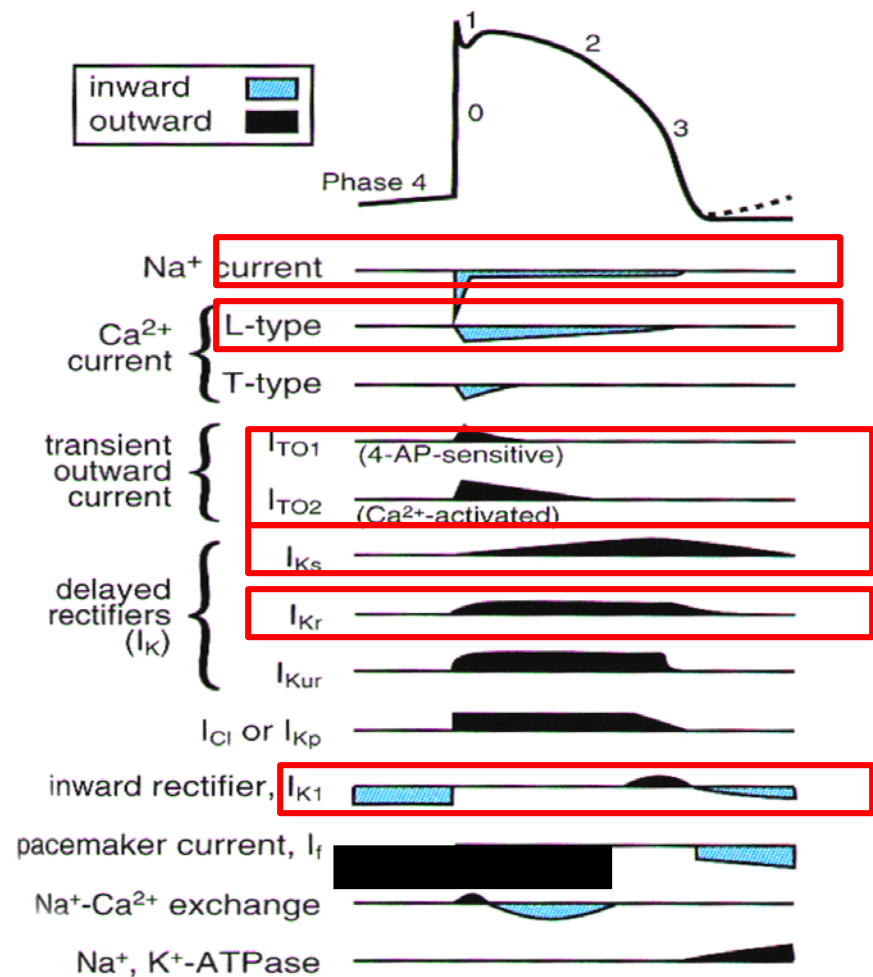
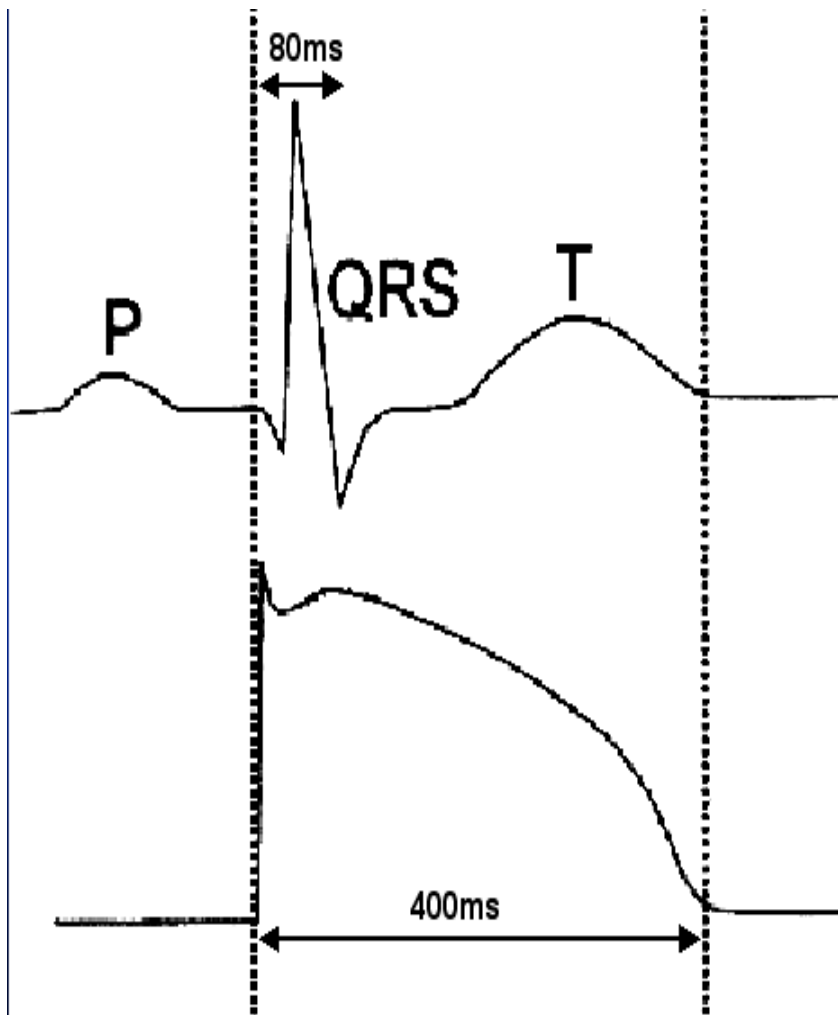
QT Prolongation: Dissociation from TdP

- Sodium Pentobarbital
 - Prolongs QT but no TdP
 - Inhibits I_{kr} , I_{ks} , and late I_{Na}
- Amiodarone
 - TdP very rare
 - Inhibits I_{kr} , I_{ks} , late I_{Na} , and I_{ca}
- Verapamil
 - Inhibits I_{Kr} but also Ca influx
- Ranolazine
 - Prolongs QT but no TdP
 - Inhibits late I_{Na} , I_{kr} , and I_{NaCa}

QT Prolongation: Dissociation from TdP

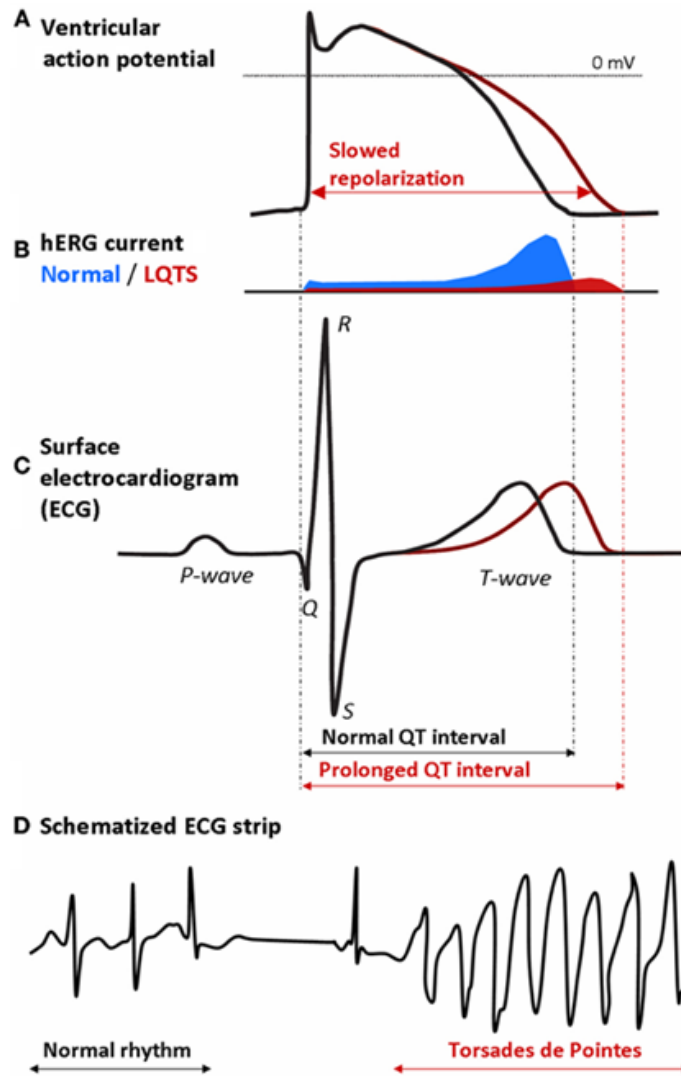
- Sodium Pentobarbital
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 - **No EAD's, reduces dispersion**
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 - **No EAD's, reduces dispersion**
- Verapamil
 - Inhibits I_{Kr} but also Ca influx
 - **No QT prolongation or TdP**
- Ranolazine
 - Prolongs QT but no TdP
 - Inhibits late I_{Na} , I_{kr} , and I_{NaCa}
 - No EAD's, reduces dispersion;
 - **Suppresses E4031 induced TdP**

Prolonged QT need not lead to TdP if there is also block of sodium or calcium currents



Current Proarrhythmia Evaluation

- ICH E14/S7B have resulted in no drugs with unrecognized risk being approved or removed from the market
- Overall agreement- negative impact on drug development
 - Premature discontinuation due to hERG or QT “signal”
 - (Inaccurate) perception of risk leading to drug discontinuation
 - Estimates of up to 60%
 - Concerns regarding development burden, costs, labeling
 - Many potentially good compounds never get evaluated in humans due to a hERG effect
 - Drug development in specific areas- CNS
 - Many drugs with QT labeling are unlikely to be proarrhythmic
 - Engineering-out hERG- applicability/other effects



Goal: Develop a new *in vitro* paradigm for cardiac safety evaluations of new drugs that provides a more accurate and comprehensive **mechanistic-based** assessment of proarrhythmic potential

Focus: On proarrhythmia (not QT prolongation)

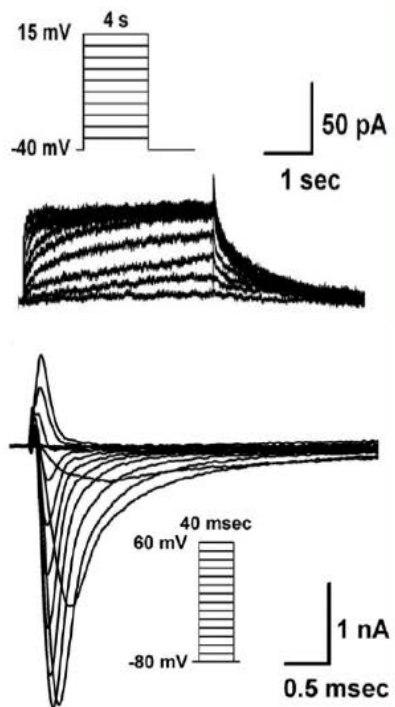
We understand the mechanism of TdP: EADs in the setting of impaired regional coupling

New Paradigm: Focus on Proarrhythmia

- QT prolongation \neq Proarrhythmia
- HERG block \neq Proarrhythmia
- Reduce the premature termination of drugs with favourable benefit:risk profiles
 - Permit straightforward clinical dev. and clean labelling of drugs with a low proarrhythmic risk, despite QT prolongation
 - Support the development of “difficult compounds”
- Make drug development more efficient
 - Move the bulk of proarrhythmic assessment to the discovery phase; simplify clinical development
 - Earlier removal of regulatory uncertainty
 - Use the assays to potentially guide candidate selection
 - Obviate the TQT study
- Enhance the accuracy with which existing and/or new drugs are labelled relative to actual proarrhythmic risks

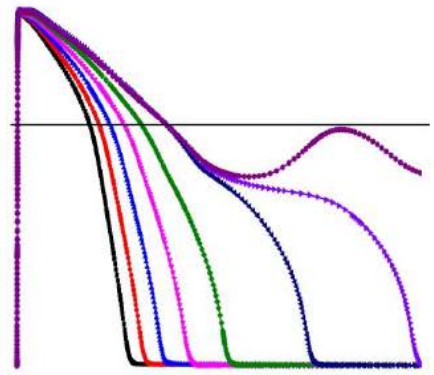
Components of CiPA

Drug Effects on Multiple Human Cardiac Currents

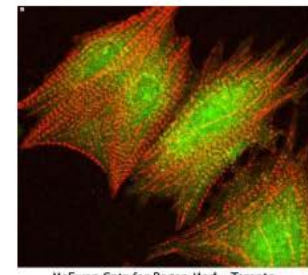


In Silico Reconstruction Cellular Human Ventricular Electrophysiology

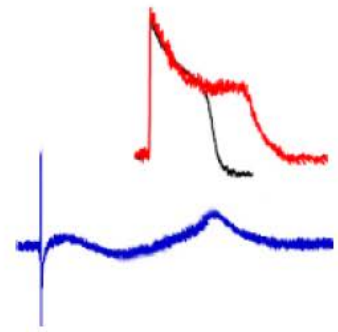
$$I_{stim} = C \frac{dV_m}{dt} + I_m$$



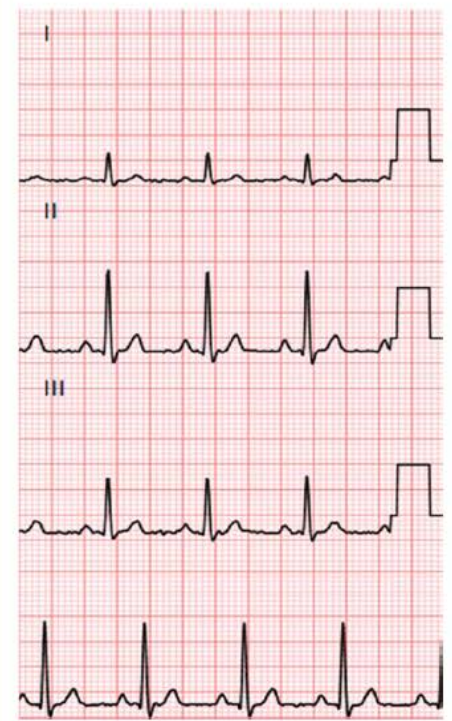
In Vitro Effects Human Stem-Cell Derived Ventricular Myocytes



McEwen Cntr for Regen Med., Toronto



Clinical Evaluation Unanticipated Electrophysiology



Proarrhythmia Risk Score

CiPA is Not a Biomarker Validation Project

History of TQT Study

- In 2001, QTc was chosen as the biomarker to assess drug risk for development of Torsade de pointes (TDP)
- QTc is a known biomarker for TdP but its sensitivity and specificity for central tendency changes with respect to TdP development were not well defined
- The TQT Study metrics were not based on clinical data beyond placebo datasets
 - A confirmation or validation was not performed
- It is appreciated that:
 - TdP risk is somewhat drug-specific, despite similar degrees of QT prolongation

Confirmation of CiPA

CiPA is based on a deep understanding of the mechanism of TdP

- Drugs interfere with processes for restoring the cardiac membrane potential to its “resting” state and preventing re-excitation before the next beat. This is directly amenable to study
- As long as the heart is responding in synchrony, the likelihood of an arrhythmia developing is very low. Heterogeneity in response allows irregular activity in one part of the heart to propagate elsewhere and back, creating a self-perpetuating circuit.
- We now have a deep mechanistic understanding of the ionic factors that result in TdP
 - Such insights permit the evaluation of an individual drug’s proclivity for causing TdP using in silico reconstruction
- Confirmation is primarily based on testing the in silico model’s predictive abilities with respect to a series of reference compounds
 - The same compounds will be evaluated in IPS cardiomyocytes

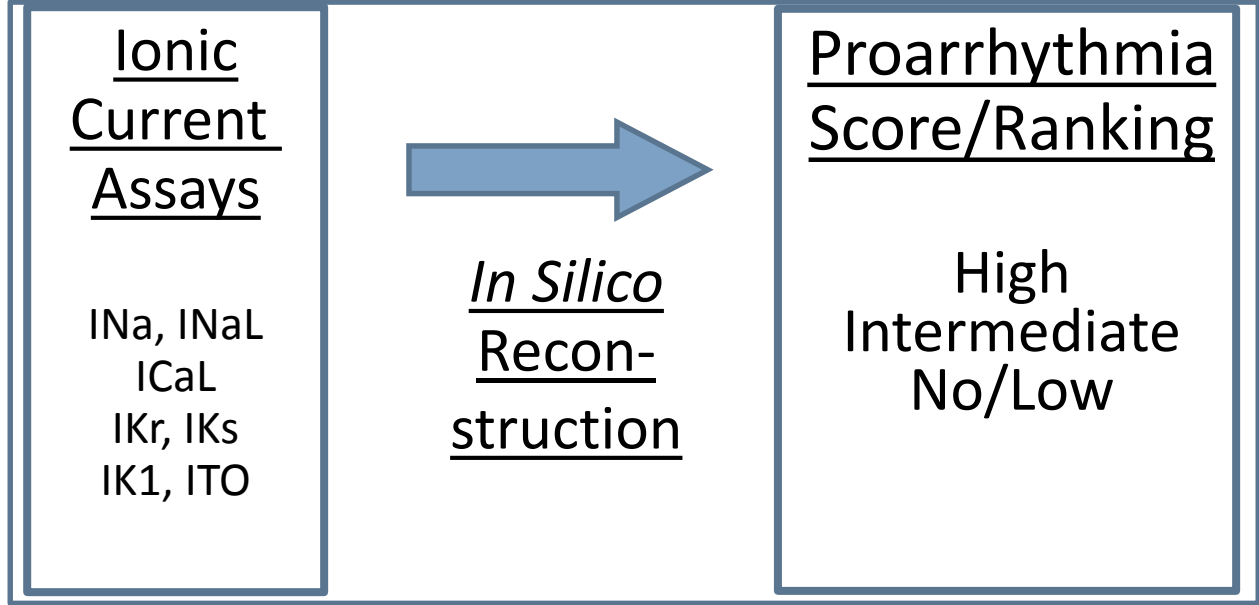
Ion Channel Working Group

- Initial Ion Channel focus
 - High throughput
 - I_{Na} , I_{Kr} , I_{Ks} , I_{CA} , I_{K1} , I_{To}
- Standardized ion channel assay development
 - Physiologic temperature
 - IC_{50} and exposure-response
 - Information on kinetics-, voltage- and use-dependence

In Silico Working Group

- To develop a computer model of the adult human ventricular myocyte that can be used to predict TdP risk
- Being modified from the O'Hara-Rudy model
 - Built using experimental data from human hearts
- Key requirements for model development:
 - Preserve an immediate and direct relationship to experimentally derived and verifiable data sets
 - Make the computer code and supporting data sets available as a community resource

CiPA Non-Clinical Testing Schema



hSC-Myocytes (2015)

- Detect / Confirm Effects on Currents**
Integrated
"Signature" Responses
- Field Potentials (MEA)
 - Action Potentials (VSO)
 - fAPD↑ , Spike amplitude

hSC-Myocytes (Future)

- Confirm Proarrhythmic Score**
- Integrated Responses
 - Field Potentials (MEA)
 - Action Potentials (VSO)
 - fAPD↑ , Spike amplitude
 - EAD incidence, Tachyarrhythmias

Human Phase 1 ECG's Under CIPA

- Human ECG evaluation is necessary for safety determinations independent of effects on cardiac repolarization
 - Sinus node effects, AV block, QRS prolongation
- To confirm that there is no clinically significant discordance between the preclinical data and the human ECG effects
- Identify preclinical false negatives
 - Human-specific metabolites, differences in protein binding
 - Untested ion channels
- Lack of concordance, might indicate a need for additional analysis

Current ECG Measurements

- PR- Fast I_{Na} , I_{Ca} , Autonomic factors, Heart Rate
- QRS- Fast I_{Na}
- QTc- Multiple currents (I_{Na} , I_{kr} , I_{ks} , I_{Ca} , I_{K1} , I_{To})
Not useful for assessing multi-channel block during repolarization

CiPA

- Will involve additional J-Tpeakc measurement to identify I_{Kr} + late I_{Na} or I_{Ca}

Collaborators

- CiPA Steering Comm.
 - Drs. Stockbridge, Gintant, Petit, Colatsky, Strnadova, Garnett, Strauss, Fermini, Leishman, Valentin, Pierson, Zhang, Shinagawa, Kolaja, Prasad, Trayanova, Sekino, Sager
- FDA, EMA, PMDA, JiCSA, Health Canada
- CSRC
- HESI
- SPS
- In Silico Modelers
- Numerous Academic Groups
- Pharmaceutical and Device Companies
- CRO's

Thank you

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