Leveraging Human-Relevant Cardiomyocytes in Nonclinical Studies to Provide Mechanistic Insights into Cardiovascular Safety Liabilities: **Overview of Gaps and Challenges.**

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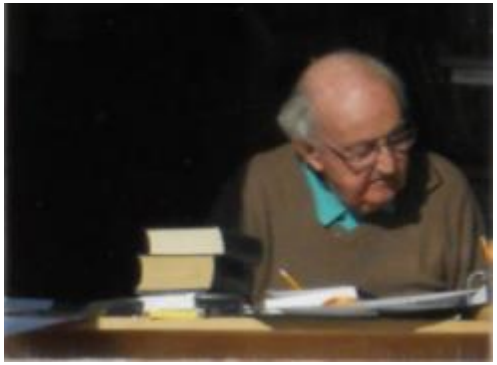
Outline

- Models and Expectations
- General Areas of Interest/Application
- Model = Biology + Experimental Approaches
- Key Concerns and “Fit for Purpose” Applications

Expectations of Models:
George Box – Engineer & statistician. 1919-2013



"Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful."

- *Samuel Langley* believed a full sized airplane could be build and flown largely from **theory alone**… Disasterous flight experiments … almost drowned his pilot.

- The *Wright Brothers* designed, built, and flew the first successful airplane after hundreds of **experiments,** multiple years with **multiple models**.

For this talk: Understanding and defining the limits of biological models as translational tools for cardiac safety evaluations

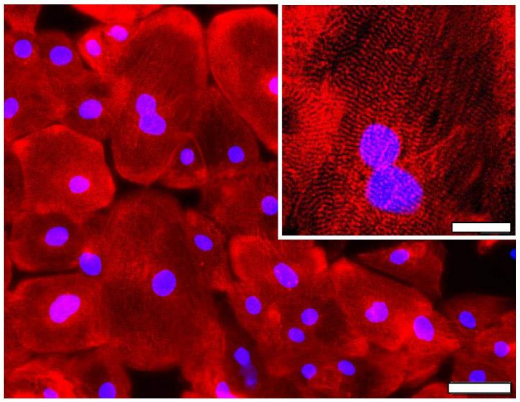
Where we start: Commercially available human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs)

- Dec 2009: First hiPSC-CM commercial product launched
  - More sources now (Commercial, academic, patient-specific)

- Enthusiasm for NEW (improved) human-derived model
  - Unlimited supply, reduce (eliminate) animal-based studies
  - Cardiac markers present, but…
    - Morphology not ventricular-like, cells spontaneously active,
    - Predominant ventricular electrical phenotype demonstrated, focuses attention on proarrhythmia studies
  - New techniques: field potential [MEA], optical (voltage sensing dyes), High Throughput Screening (HTS) approaches

<u>Model(s)</u> & <u>Techniques</u> both "Novel"

Require Evaluation of Strengths, Limitations



Ma et al., Am J Physiol., 2011

hiPSC-CMs: Three General Areas of Interest

Areas of Interest:

- Electrophysiology (Proarrhythmia)
- Contractility (Inotropy)
- Structural Cardiotoxicity (Injury, Damage)

- Each with different approaches/technology platforms
- Opportunity for integration of multiple responses with one preparation (removing the “silos”)

General Utility- Expectations May Differ:

- Safety
  - Early Drug Screening (Internal decision making)
  - Later Candidate Selection (Regulatory evaluations)
  - Drug Combination Studies (?)
  - Qualitative vs. Quantitative Assessments
- Efficacy
  - Drug Discovery Efforts
  - Personalized Medicine: Safety & Efficacy Studies

Overall Considerations/Limitations

Myocytes Often Display "Immature" Phenotype

- Gene expression profile of 2D myocytes resemble fetal/neonatal
- More complex preps (patterning, fibroblasts, smc's endothelial cells) (imitating native environment) affecting more adult phenotype

Acute and Subacute Direct Effects Amenable to Study:

- Indirect effects (cardiovascular signaling) not readily tested
  - Those requiring integrated systems may use "organs on a chip"
- Optimal stable "windows" for studies/screening need to definition
  - Studies of disease alteration/toxicity progression (pts in dish)
  - Multi-parameter studies possible

Model Utility Based on Limitations, Context of Use

hiPSC-CMs: Heterogeneity of Biological Models

Different Starting Biological Preparations: Heterogeneity

- "Generic/Standard myocytes" (assuming uniform conditions)
  - Single-type myocytes vs. population-based studies
  - Tissues with multiple cell types (myocytes 30% of adult heart)

- "Diseased"- or "personalized" myocyte models
  - For efficacy and safety study applications

Assay = Biological Model + Experimental Approach(s)

- Numerous (unique) combinations provide challenges for understanding the assay and its "translation" to the clinic

hiPSC-CMs: Bioengineering Meets Assay Development

Heterogeneity of Biological Models

- More complex models **may better replicate native myocytes**
  - Single cells, 2D monolayers, Organoids, Spheroids, Tissues

- More complex models **may hamper reproducibility, availability**

- **Standardization of Models Remains a Challenge**
  - Ex: 2D constructs – cell sources, plating density, culture time, substrate). Biological engineering.
  - Different from ex vivo preparations (rat papillary muscles)
  - Assay calibration essential for model characterization
  - Early efforts at standardization may be premature,
    - No clear definition of similarity to native preparations (single, or multicellular).

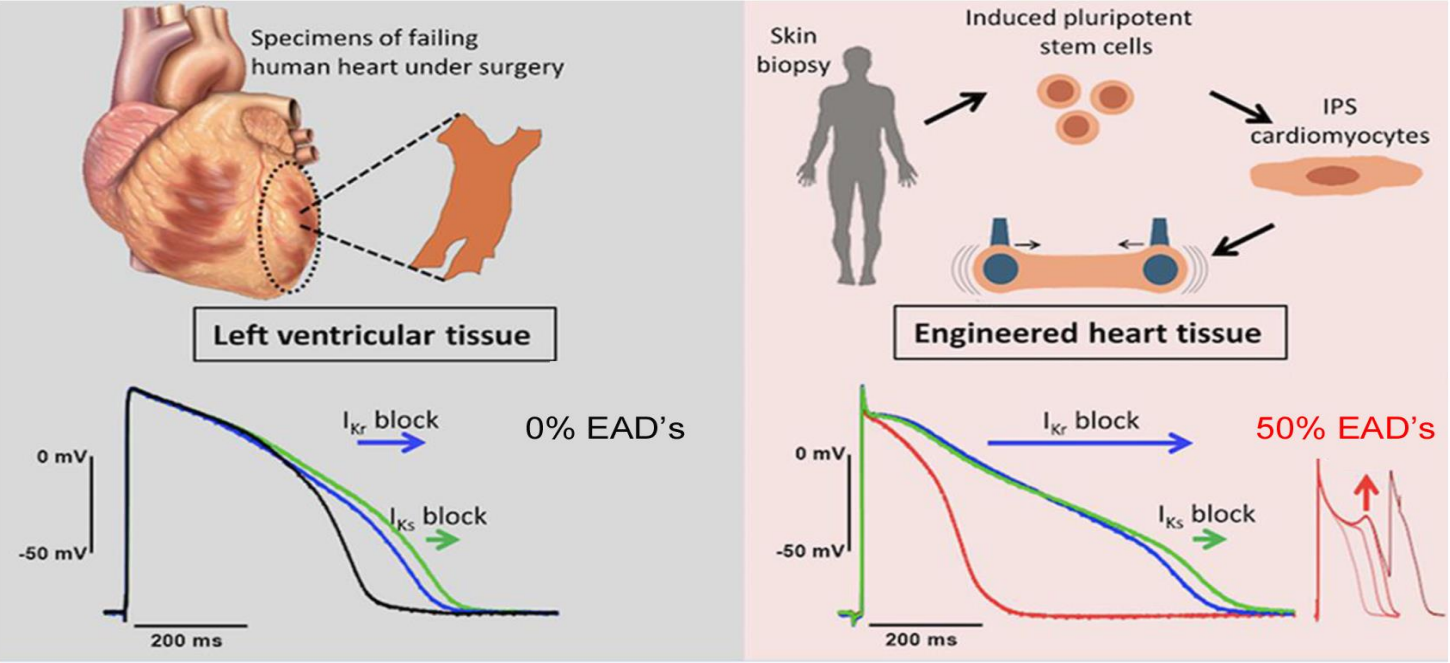
What's a Researcher/Regulator to Do?

Human-derived models

Non-human ex-vivo models

Key Concerns: Translational Fidelity
Reproducibility,
Cost/Availability

hiPSC-Cardiomyocytes as Evolving Test Systems: Sensitivity vs. Adult Human Ventricular Myocytes



Human iPS cardiomyocytes in engineered heart tissue vs. left ventricular tissue

- Upstroke velocity ↔
- Action potential duration ↓
- Ivabradine-sensitive diastolic depolarization
- Reverse use-dependence ↑
- Action potential prolongation to I_{Kr} block ↑
- EAD sensitivity to E-4031 ↑
- No EADs due to moxifloxacin or verapamil ↔
- I_{Ks} contribution ↔

adapted from Lemoine et al., Circ (Arrhythmias/Electrophysiology); 2018

Assay Calibration Essential to Define Experimental Sensitivity, Translational Fidelity

What's a Researcher to Do?

Need to:

- Define "fit for purpose" applications
  - Not all models or approaches may be suitable for questions being addressed. How to define limits?

- "Validate" assay vs. appropriate clinical "gold standards"
  - "Standards" may not be available
  - Surrogate endpoints: limiting, lacking, not well understood

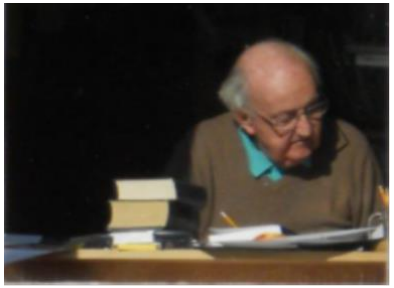
- Be transparent in describing experimental details
  - Aid in establishing reproducibility
  - Promote evolving standards, comparisons to demonstrate advantages/utility of new models

Models from an Artist's Perspective

Picasso, Museum Fine Arts, Boston

How Perfect Must a Model Be to be Useful?

Summary



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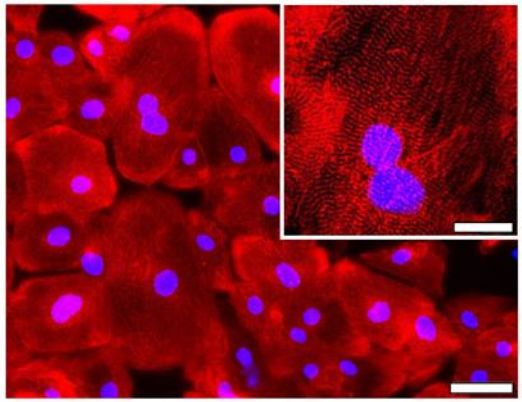

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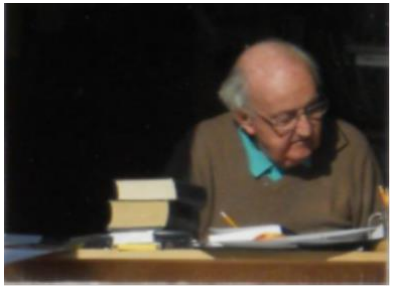
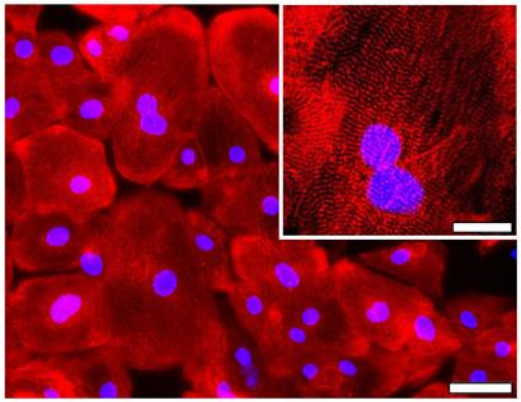
Summary



"Remember that all models are **wrong**; the practical question is how wrong do they have to be to not be useful."

Remember that all models are **right**; the practical question is **how right is the question asked** based on a models' characteristics and limitations.



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Thank you for your attention