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Implementation and Implications of Non-Clinical Proarrhythmia Assessment

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How CiPA is like Manhattan Project

- Both are substantial engineering efforts
- Both large-scale, international social enterprises
- Both operated with sense of urgency
- Both involve very bright people



Manhattan Project Luminaries



Bohr, Oppenheimer,
Feynman, Fermi

Einstein, Szilard



CiPA Luminaries



...and many others too modest to allow their pictures to appear on the internet



How CiPA is NOT like Manhattan Project

Manhattan Project	CiPA
Secret	https://www.ilsixtra.org/hesi/science/cardiac/cipa/SitePages/home.aspx
Massive budget	No budget
Dedicated staff	Dedicated; just not compensated
Command structure	Self-organized



Colonel
Leslie
Groves



CiPA goal: ↓ ICH E-14 by 31 July 2015

- Loose structure has probably slowed our progress
- Some remaining issues
 - Compound selection
 - Voltage clamp protocols
 - Data analysis
 - Proarrhythmia metric
 - Verification



Issue: Compound selection

- For validation, need compounds that have various types of channel activity—which we do—and whose proarrhythmic potential is fairly well understood—which we don't.
 - Fairly easy to identify quite safe and quite risky compounds; not so easy to agree on ordering of ones with intermediate risk
 - Risk is dependent on
 - Intrinsic factors—drug itself
 - Extrinsic factors
 - Underlying proarrhythmic substrate
 - Concomitant drugs
- Probably going to have to settle for H/M/L classification for “knowns”



Issue: Voltage clamp protocols

- Simplest forms of block, perhaps most common, are relatively straightforward—block solely dependent on drug concentration, but some compounds only evidence their block under certain stressed conditions (“use dependence”)
- Voltage clamp protocols are being cataloged
- Corresponding ionic current models will need to be developed and incorporated into the in silico myocyte model



Issue: Data analysis

- Data from 4-7 ion channel types, across range of drug concentrations, replicated to bound model rate constants
- In silico reconstruction is also computationally intensive, and the reference model is going to evolve as gaps are identified and addressed.
- These problems are best addressed using a central data analysis and modeling facility
 - Level playing field
 - All data in one place



Issue: Proarrhythmia metric

- What is it that drugs do to the cardiac action potential than makes TdP possible or likely? EADs are dramatic indicators of failure of repolarization, but lesser degrees of risk—including antiarrhythmic activity—ought to be recognizable, too.
- Several candidate metrics are being evaluated, the most straightforward of which is current injection during repolarization to assess how far the myocyte is from having regenerative activity
- May need to model some kinds of vulnerable substrates



Issue: Verification

- The voltage clamp assessment will always have certain issues
 - Not all channel types are being assessed
 - Might miss use-dependence
- ...so need some independent verification that you didn't miss something important
- This could be stem-cell-derived myocytes, so work is ongoing to select protocols and measurement technology.
- This could also be done from human ECG, with less than “thorough QT” data, so work is ongoing to correlate specific channel activity with ECG morphology changes.



Unfulfilled promise

- Better regulatory decisions
 - Avert false positives in future labeling
 - Revise false positives in existing labeling
- Better decisions about compound selection
 - Based on integrated understanding of the implications of a constellation of ion channel effects
 - Much bigger financial and clinical impact than the savings on QT studies.

