The New Paradigm: Next Steps

Norman Stockbridge, MD, PhD
Director, Division of Cardiovascular and Renal Products
FDA

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Time has come

- Urgency
  - We have probably labeled drugs as risky when there is none
  - Drug developers are probably making suboptimal decisions about which compounds to bring forward in development
- Feasibility
  - Basis of TdP pretty well understood
    - Vulnerable repolarization
    - Asynchronous activity
  - Vulnerability can be assessed now in human ion channels

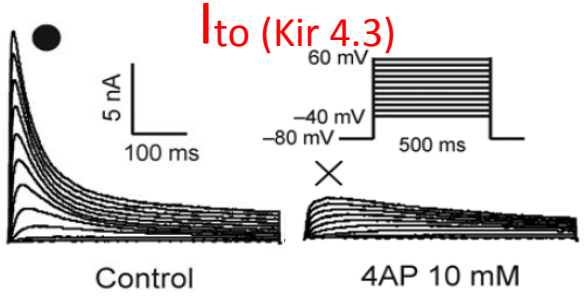
Contributors to assessment of feasibility

- Darell Abernethy/FDA
- Arthur Brown/ChanTest
- Thomas Colatsky/FDA
- Christine Garnett/Pharsight
- Gary Gintant/AbbVie
- Craig January/U Wisconsin
- Lars Johannesen/FDA
- John Koerner/FDA
- James Kramer/ChanTest
- Naomi Kruhlak/FDA
- Derek Leishman/Lilly
- Marek Malek/U London
- Sebastian Polak/Simcyp
- Philip Sager/Stanford Univ
- David Strauss/FDA
- Robert Temple/FDA
- Nick Thomas/GE
- Douglas Throckmorton/FDA
- Jiwen Zhang/GE

Engineering team - 1

- HESI ProArrhythmia Working Group, Safety Pharmacology Society, FDA
  - What channels to study
  - What voltage clamp protocols
  - Other aspects of protocol specification

Pulse sequences: Ito



ID	Channel /Current	Species/cells	CPD	Temp	Vh (mV)	Prepulse (ms, mV)	Activation (ms, mV)	Voltage -Dependence (ms, mV)	Interval/ frequency
47	hKv4.3/hKChIP2.2	CHO	Methadone	RT	-90		300, 40		
49	rKv4.3	Mouse/L cell	Vanoxerine	RT	-80		300, 20		15s
50	hKv4.3	HEK293	Alfuzosin	RT	-80		300, 20		15s
206	Ito	Rat/VM	Zacopride	24	-40		n/a	500, -40 to 80 (Δ10)	
210	Ito	Human/AM	Cyamemazine	32-34	-50		500, 60		
214	Kv4.3	Monkey/COS7	Pentamidine	n/a	-80		n/a	500, -40 to 60	
215	Ito	Canine/VM	Pioglitazone	n/a	-80	5ms, -40	n/a, 50		
220	Ito	Rat/VM	Ajmaline	RT	-75		300, 60		
221	rKv4.2, rKv4.3	HEK293	RSD1235	25	-80	Brief, -50	250, 60		1Hz
222	Ito	Rat/VM	FK-506	22-24	-80		n/a, 50	1000, -50 to 70	0.1Hz
224	hKv4.3	HEK293	Allitridi	22-23	-80		300, 60	300, -80 to 60	
245	Ito	Human/AM	DPO	RT	-80		150, 40		
256	Ito	Rabbit/VM	Carvedilol	34	-60		300, 40	300, -50 to 60	
263	Kv4.3	CHO (transient)	Spironolactone canrenoic acid	RT	-80		250, 50	250, -90 to 50	10s
267	Ito	rat/VM	Ebastine	n/a	-90		n/a, 75	n/a, -30 to 75	
273	Ito	Canine/VM	Thymol	37	-80	5ms,- 40	400, 50	400, -10 to 60	
281	rKv1.4	Xenopus Oocyte	Haloperidol	22	-80		300, 0		
283	Ito	Human/AM	Clotrimaxole	21-22	-50		300, 50	300, -40 to 60	0.2Hz

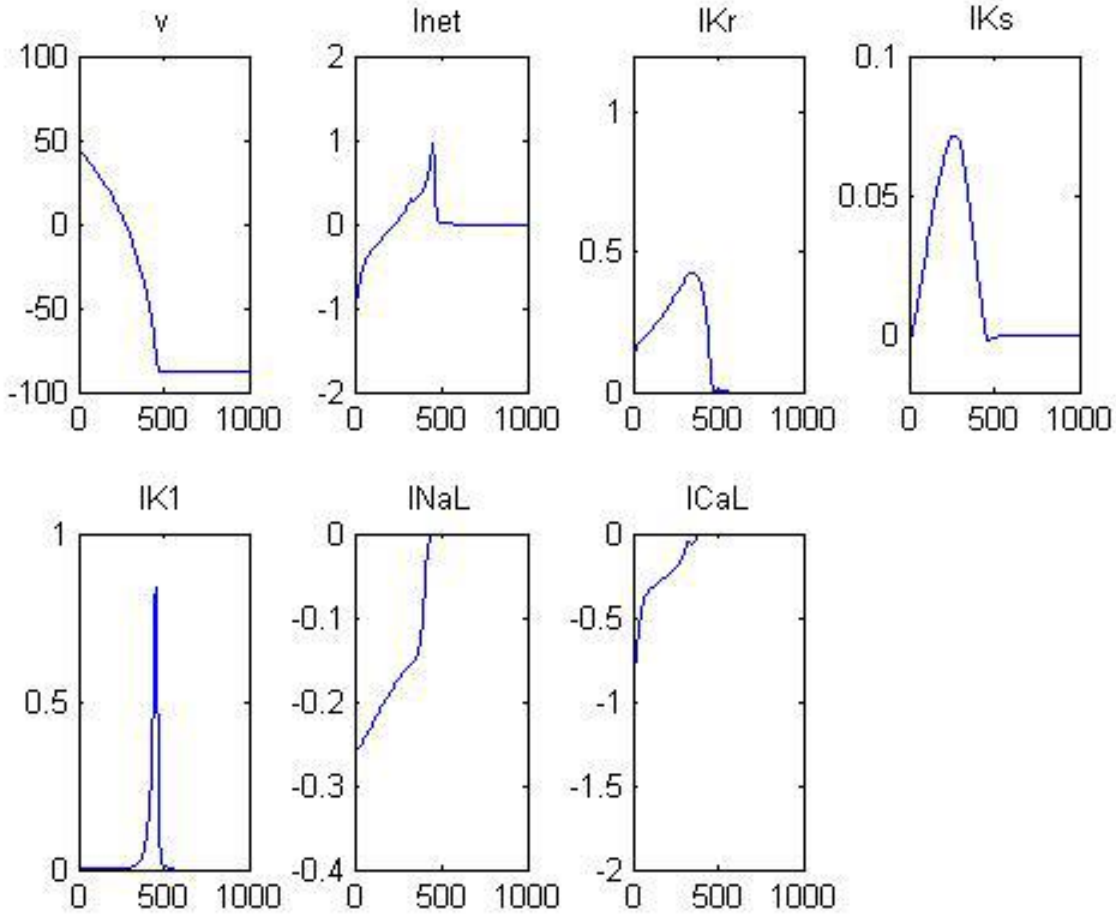
VM= ventricular myocyte. AM= Atrial myocyte

From EJ Park, FDA

Engineering team - 2

- FDA, academia, pharma
  - What channel models to use
  - What proarrhythmia metric
  - How to fit drug effect data

O’Hara-Rudy model of human myocyte



Tom Colatsky, FDA

Engineering team - 3

- HESI Myocyte Working Group?
  - Can you confirm the adequacy of voltage clamp assessment of drug effects?
  - What is the best cell line?
  - What is the best approach to recording?
  - Can these cells be made more like the adult human?

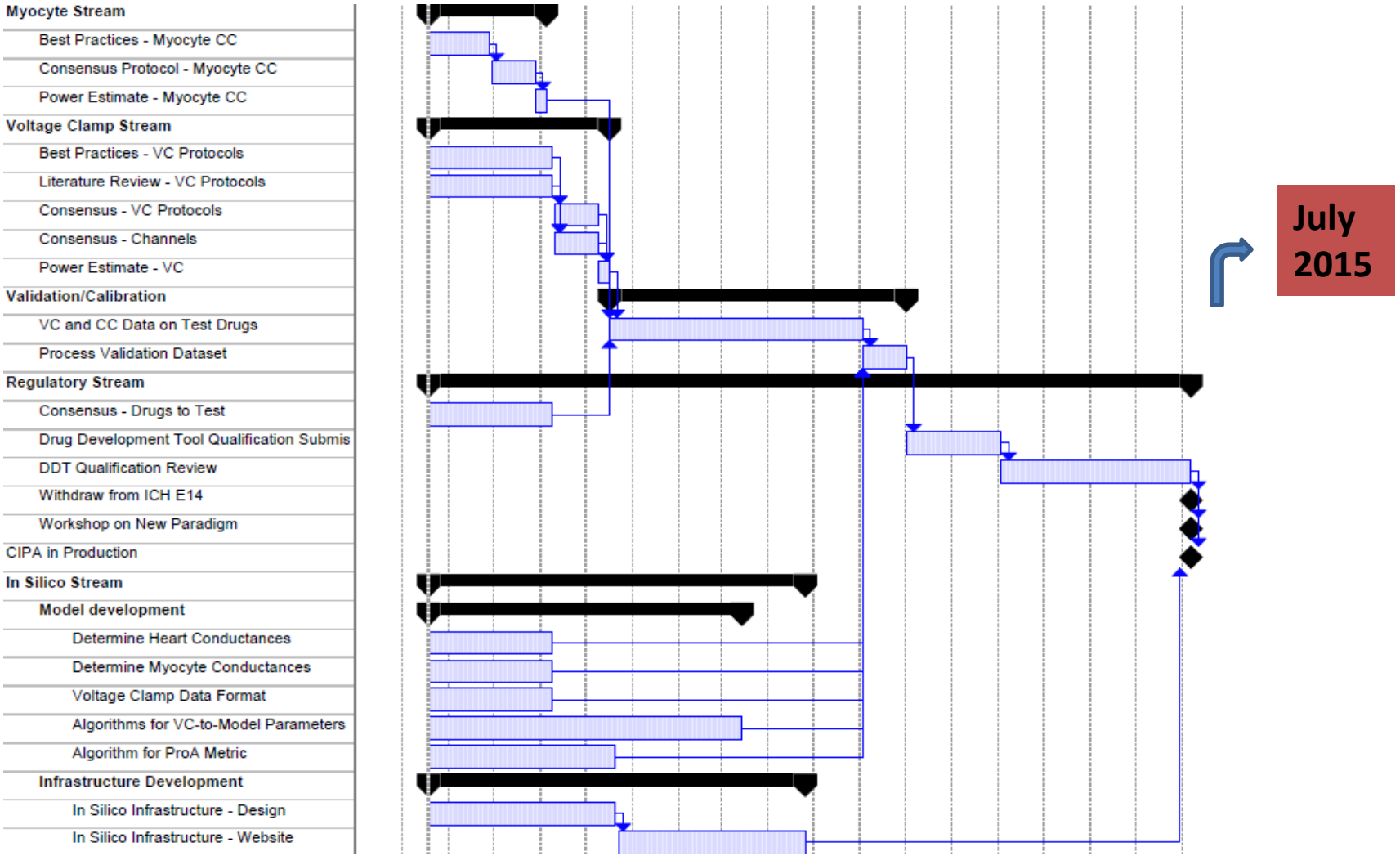
Engineering Team - 4

- Cardiac Safety Research Consortium, ICH E14 Working Group
  - What drugs, performance would allow one to replace the TQT study?
  - What would go into a Drug Development Tool Qualification package?

Future vision

- Relabeling of some existing drugs
- Better labeling for future drugs
- More and better drugs in development
- More efficient drug development
- No TQT studies

Work plan in progress



Call to action

- Whether this happens “on time” – or at all – depends upon the cooperative efforts of many stakeholders. Volunteer.
  - https://www.ilsiextra.org/hesi/science/cardiac/cipa/SitePages/Home.aspx
  - Norman.Stockbridge@fda.hhs.gov
  - Psager@Stanford.edu
  - Gary.Gintant@abbvie.com