Comprehensive *in vitro* and *in silico* torsadogenic risk assessment using multi ion channel data and multi-scale human heart simulator

Global Cardiovascular Assessment

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Eisai Co., Ltd.

2016.11.9

hhc

human health care

Content

- **Background**
  - **Drug induced QT prolongation/Torsades de points**
  - **CiPA (Comprehensive *in vitro* proarrhythmia assay) activity**

- **Proarrhythmia prediction using *in silico* tool**
  - **Prediction of TdP risk in multi-scale heart simulator (UT-Heart)**
  - **Virtual clinical QT/TdP risk assessment**

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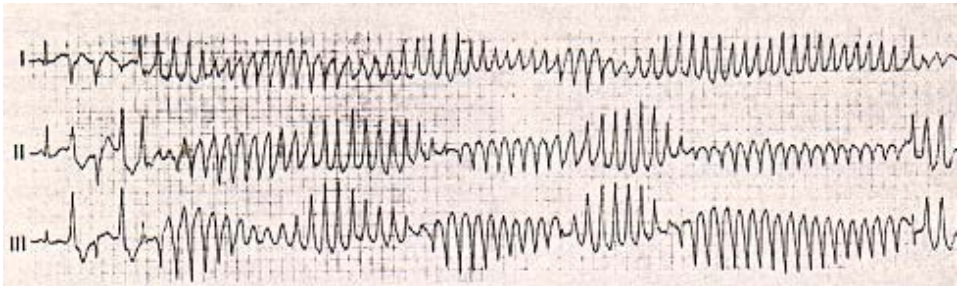
Drug-induced severe arrhythmia (TdP)

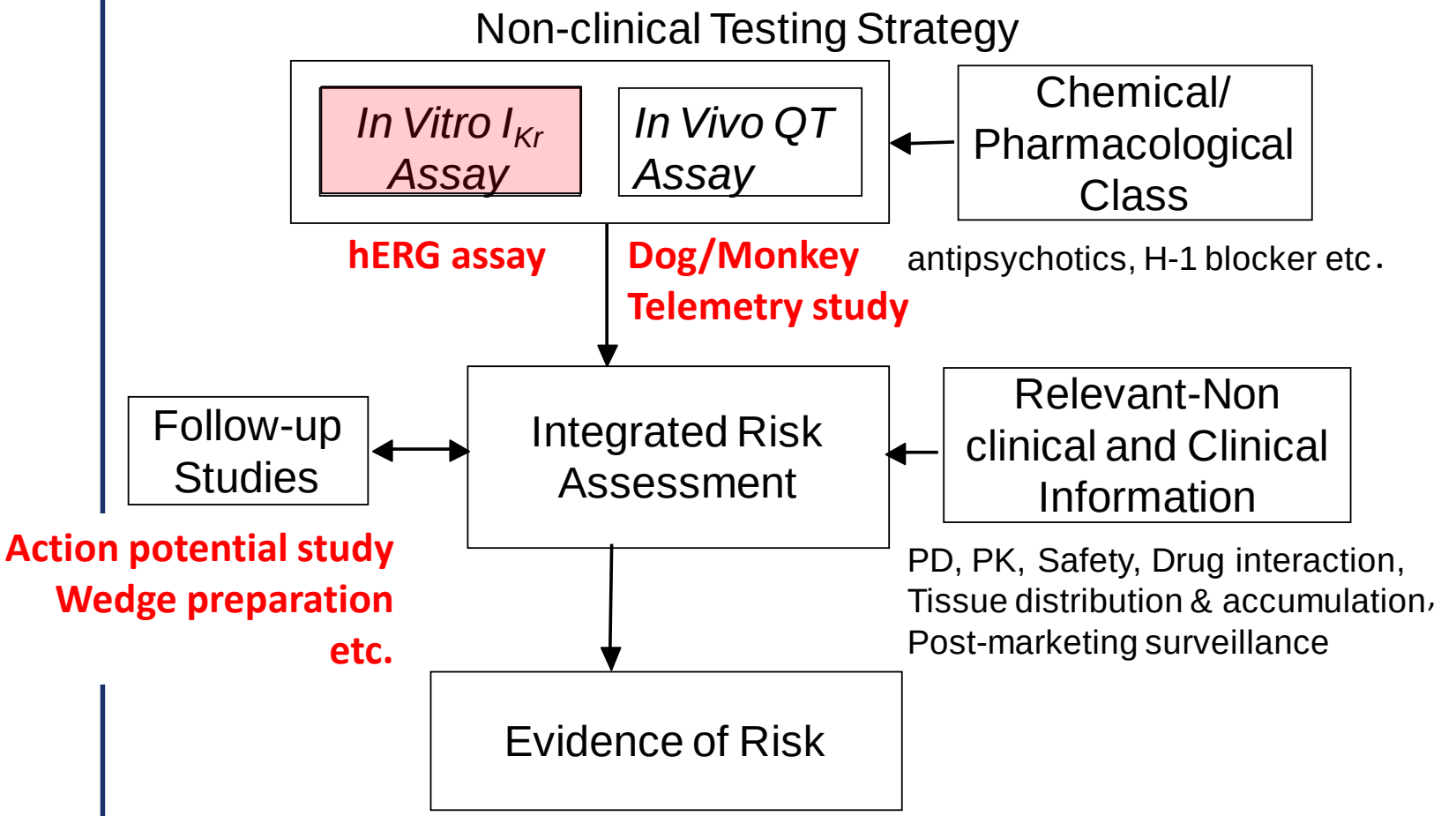


Torsade de pointes (TdP)

Year withdrawn	Drug	Indication	Major Safety Concern
1991	Terolidine	Urinary Incontinence	QTc prolongation, TdP
1996	Sparfloxacin	Antibiotic	QTc prolongation
1998	Terfenadine	Antihistamine	QTc prolongation, TdP
1999	Astemizole	Antihistamine	QTc prolongation, TdP
1999	Grepafloxacin	Antibiotic	QTc prolongation, Arrhythmias
2000	Cisapride	Gastroesophageal reflux	QTc prolongation, Arrhythmias
2001	Droperidol	Schizophrenia	QTc prolongation, TdP

ICH S7B Guideline

The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals



ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Challenge for the proarrhythmia prediction in clinical situation

Workshop on
Rechanneling the Current Cardiac Risk Paradigm

Cardiac Safety Research Consortium

HESI

US FDA White Oak Conference
Center Silver Spring, Maryland, USA

FDA

(July 23, 2013)

Proposal of

- **Abolition of ICH E14 (TQT study)**
- **Revision of ICH S7B**

human health care

Latest report from CiPA

OPINION

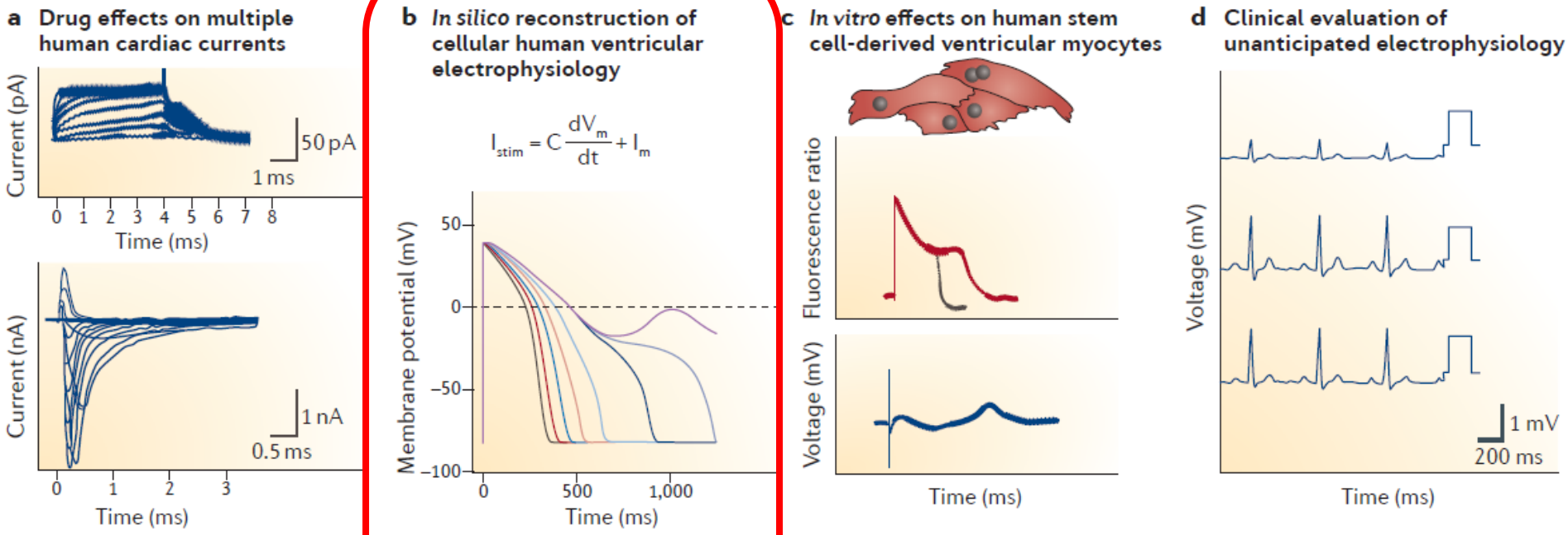
Evolution of strategies to improve preclinical cardiac safety testing

Gary Gintant, Philip T. Sager and Norman Stockbridge

Abstract | The early and efficient assessment of cardiac safety liabilities is essential to confidently advance novel drug candidates. This article discusses evolving mechanistically based preclinical strategies for detecting drug-induced electrophysiological and structural cardiotoxicity using *in vitro* human ion channel assays, human-based *in silico* reconstructions and human stem cell-derived cardiomyocytes. These strategies represent a paradigm shift from current approaches, which rely on simplistic *in vitro* assays that measure blockade of the K_v11.1 current (also known as the hERG current or I_{Kr}) and on the use of non-human cells or tissues. These new strategies have the potential to improve sensitivity and specificity in the early detection of genuine cardiotoxicity risks, thereby reducing the likelihood of mistakenly discarding viable drug candidates and speeding the progression of worthy drugs into clinical trials.

Nature Reviews Drug Discovery (2016)

Elements of the Comprehensive in vitro Proarrhythmia Assay



Ion vitro:
Multi-ion channel assay

In silico:
Single ventricular cell model

Ion vitro:
Human stem cell Cardiomyocyte assay

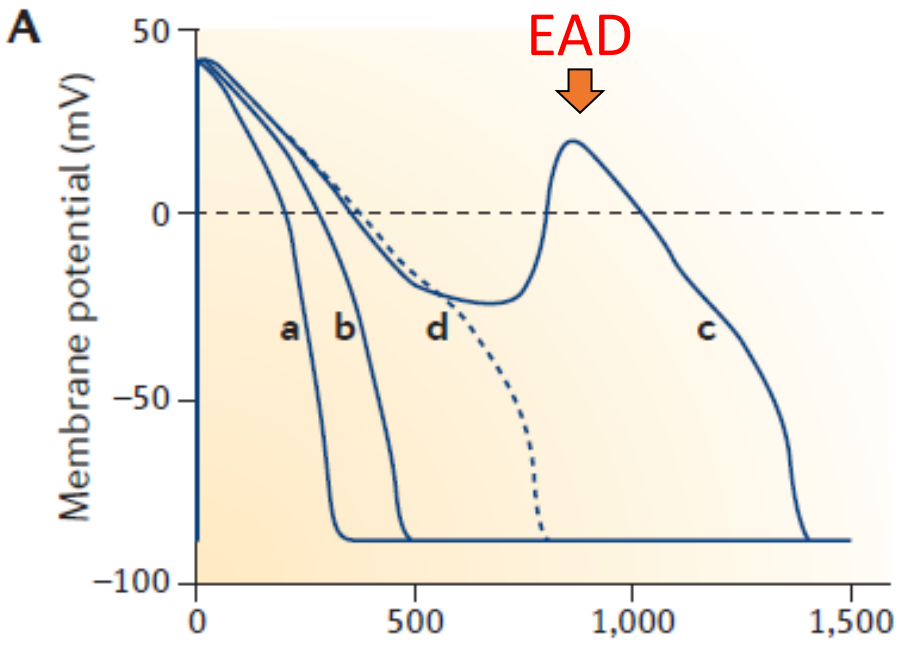
Clinical (in vivo):
ECG

Nature Reviews Drug Discovery (2016)

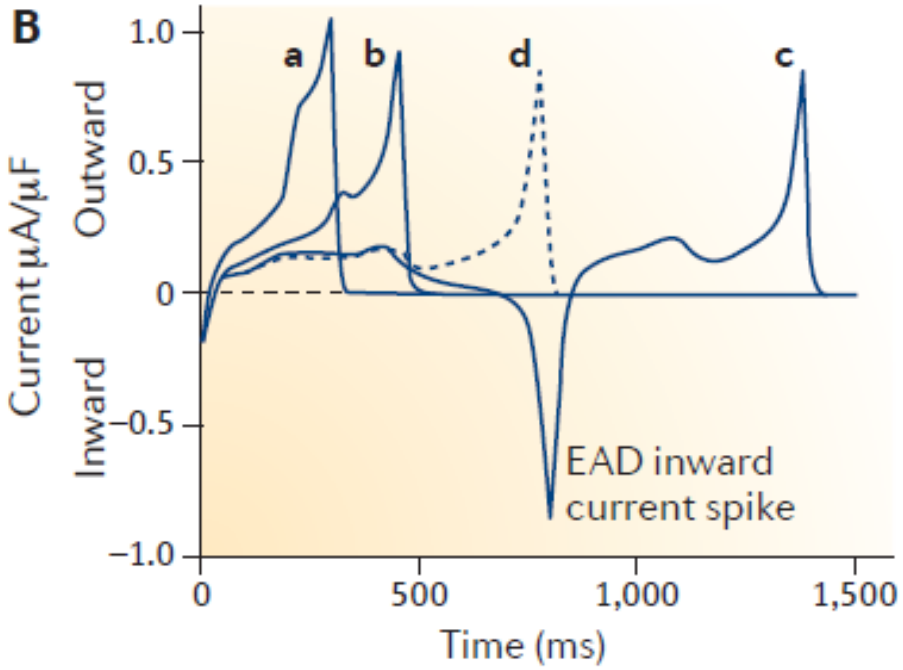
Role of delayed repolarization and multi-channel blockade in defining proarrhythmic risk

Simulation of action potential

Simulation of ion currents



I_{Kr} (% block)	0	50	85	85
I_{CaL} (% block)	0	0	40	0



Nature Reviews Drug Discovery (2016)

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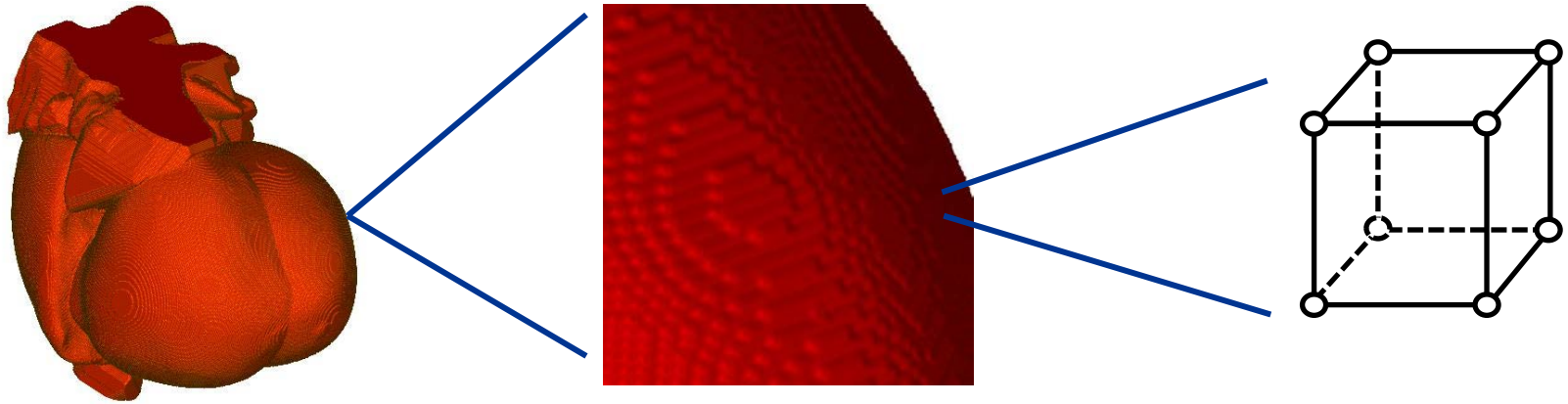
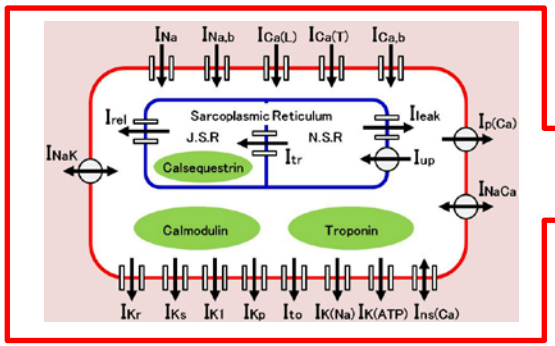
  - **Virtual clinical QT/TdP risk assessment**

Construction of heart; Finite Element Method (FEM)

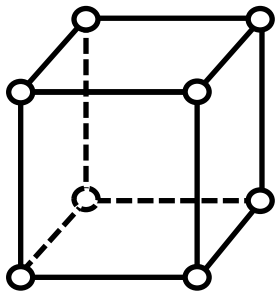
The FEM is numerical technique for finding approximate solutions to partial differential equations



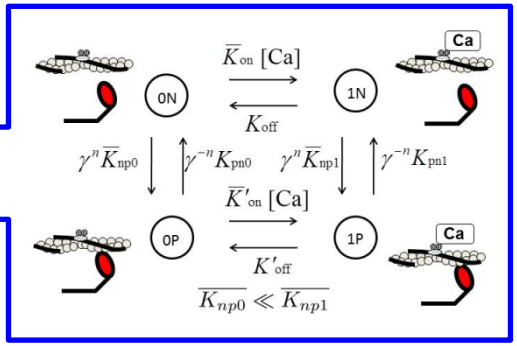
Electrophysiological model



Element



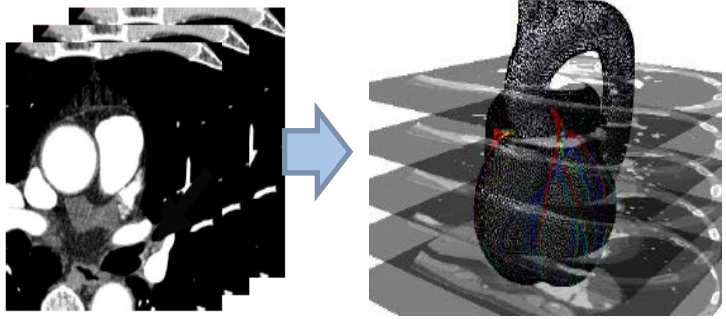
Excitation-contraction coupling model



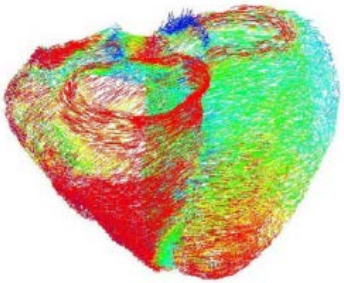
UT-Heart:
Multi-scale multi-physics heart model

CT (MRI) images

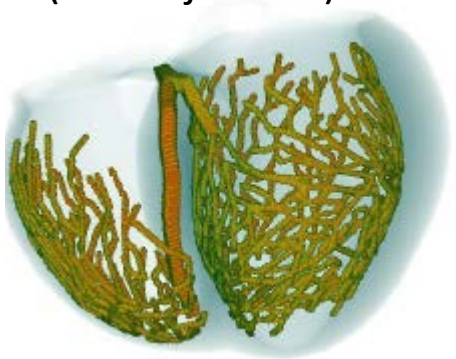
3 D Reconstruction



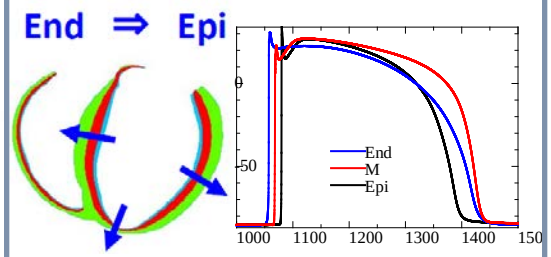
Fiber orientation

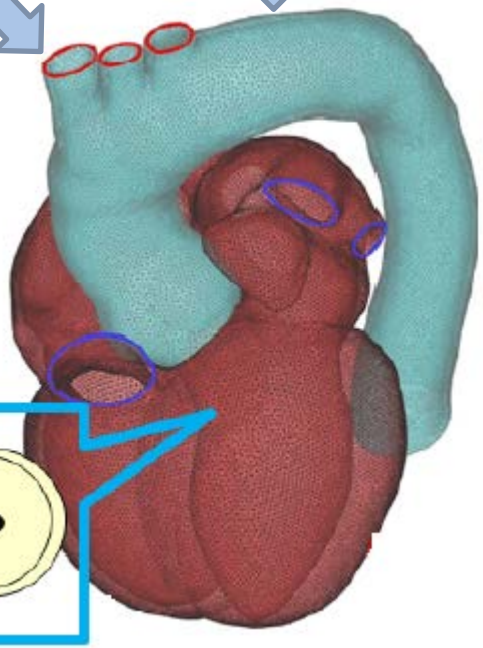


Conduction system
(Purkinje fiber)

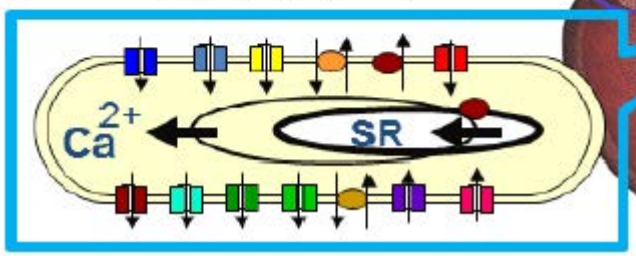


Action potential





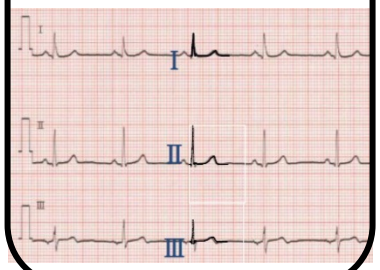
Cell model



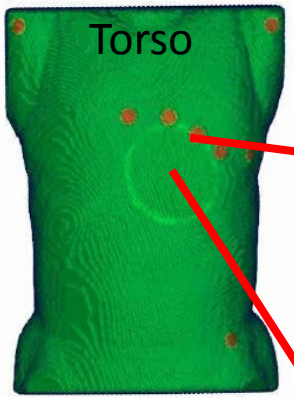
Heart mesh
(0.2[mm])
26,000,000 nodes
(26 million cells)

In silico simulation of 12-lead ECG

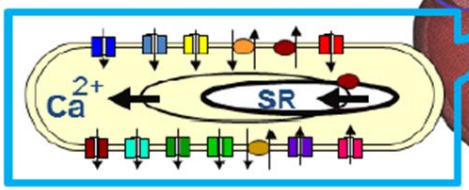
Real ECG data

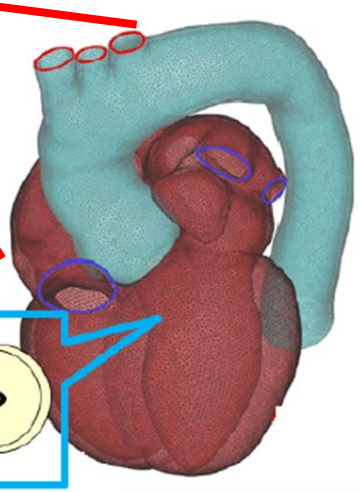


Torso

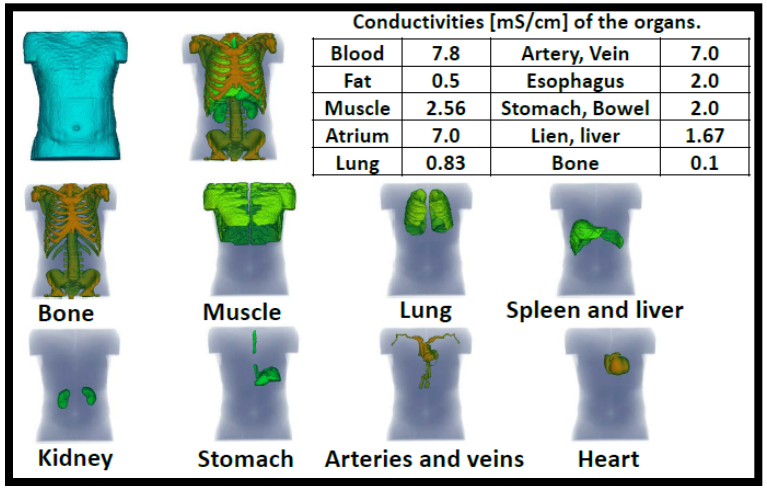


Cell model

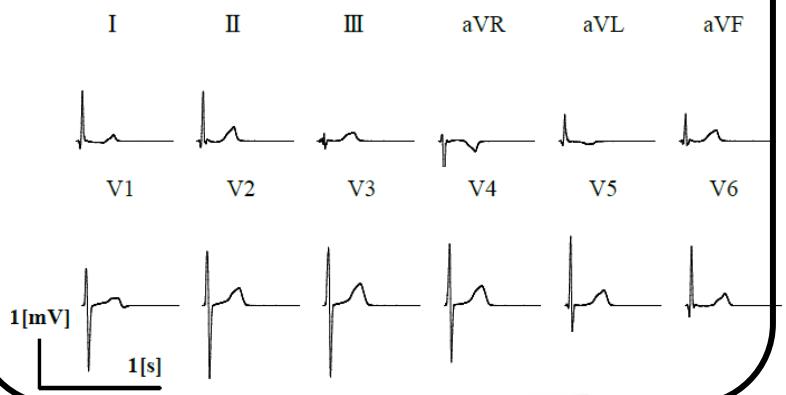




Finite element model of the Torso

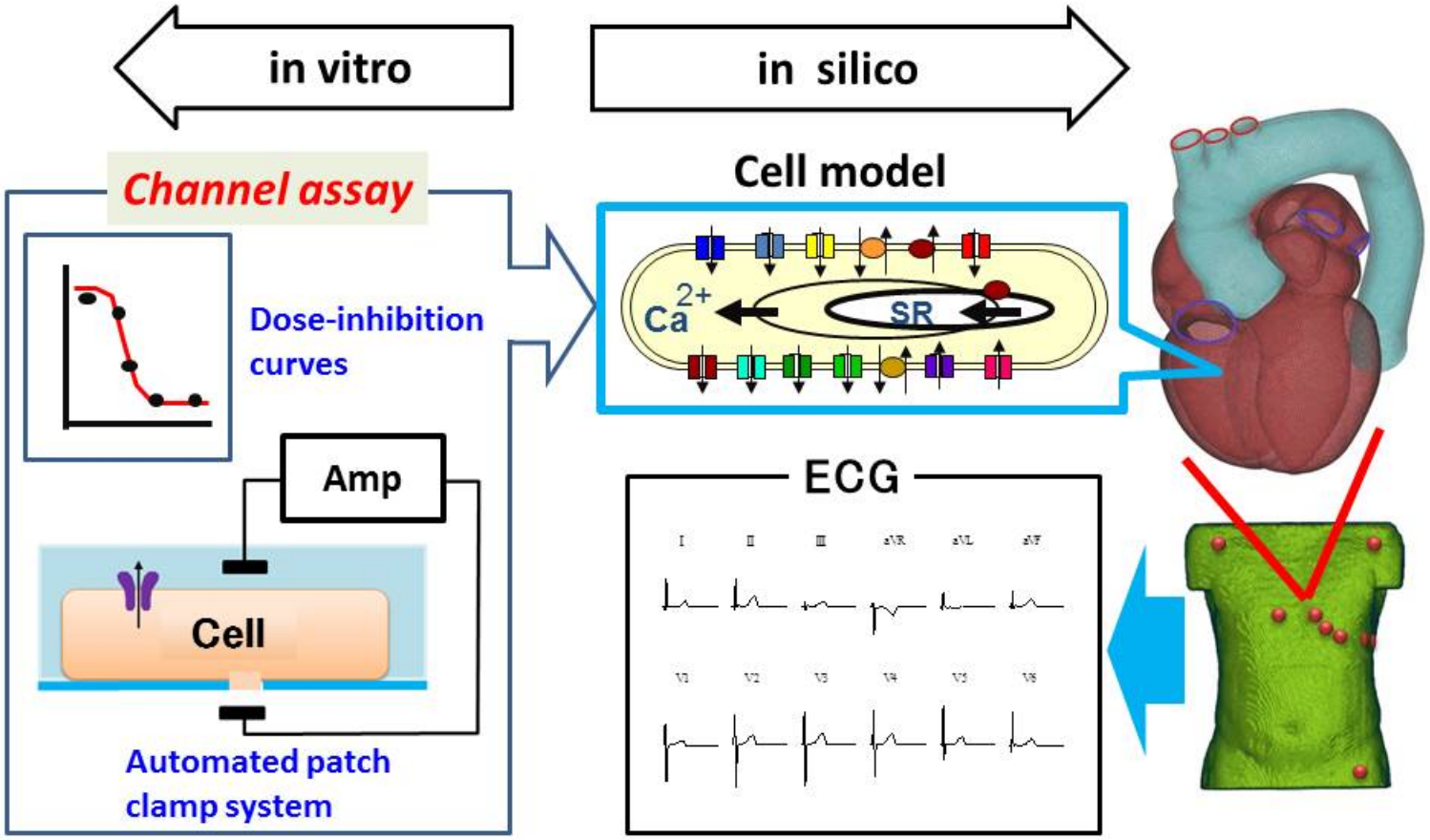


Simulated 12-lead ECG



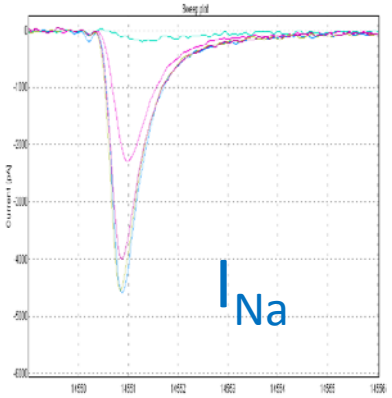
human health care

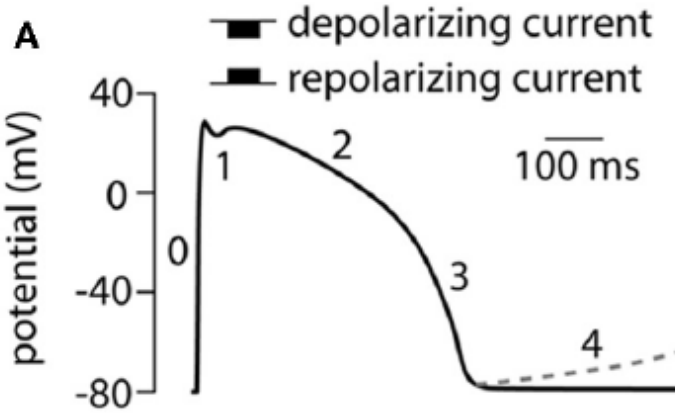
Diagram of the Arrhythmia Prediction system

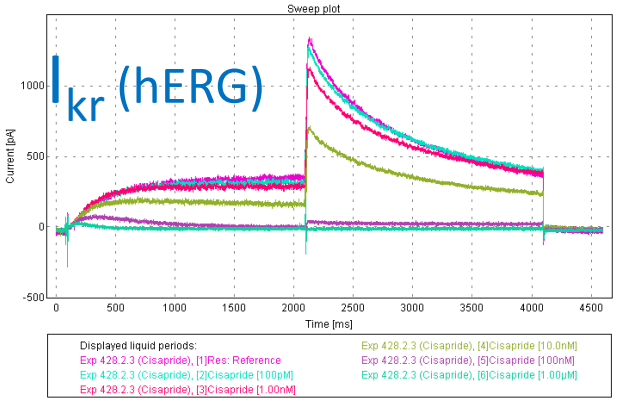


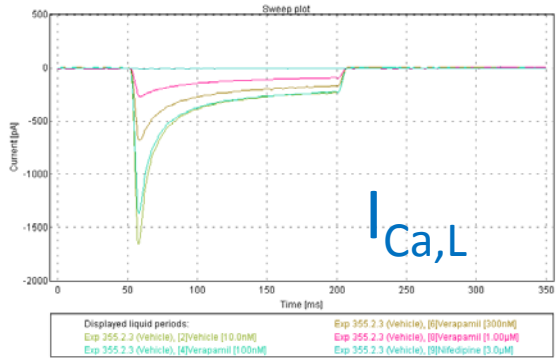
- Concentration-inhibition curves of drugs were obtained using the automated patch clamp system (QPatch-HTX).
- The 12-lead ECG waveform were calculated by high performance computer.
- The effects of drugs on ECG waveforms were simulated based on the ion channel inhibition data.

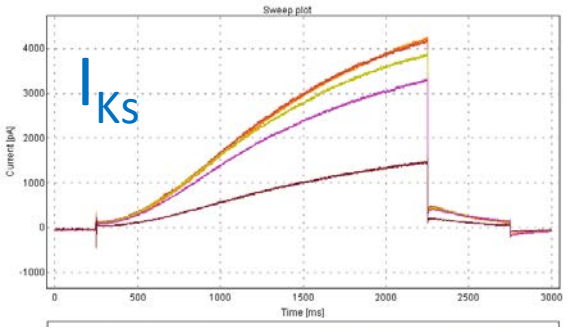
Multi-ion channel data is essential for QT and arrhythmia risk prediction

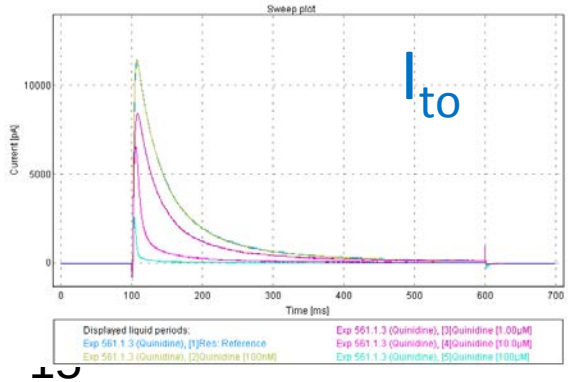


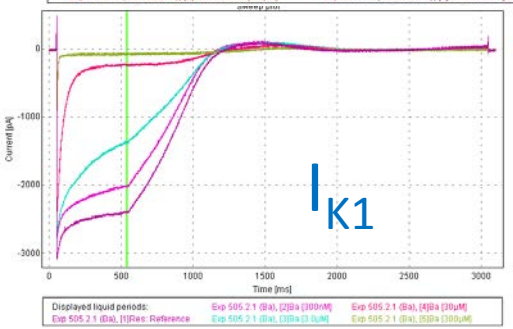




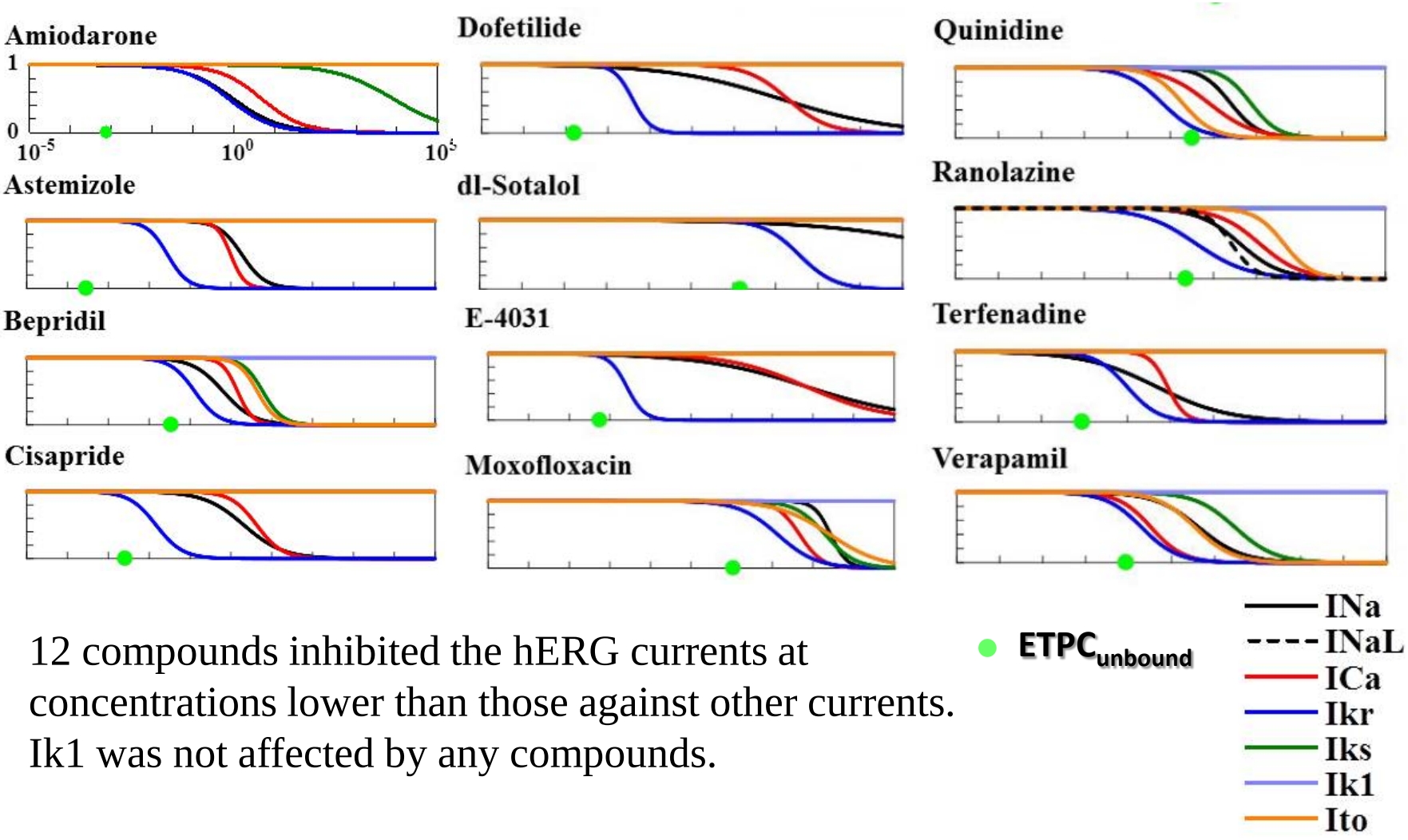








Concentration-inhibition curves for six ion channels



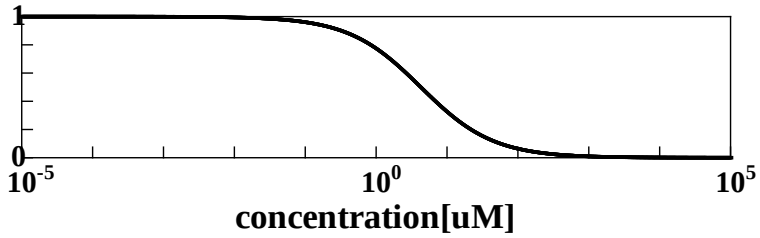
12 compounds inhibited the hERG currents at concentrations lower than those against other currents. Ik1 was not affected by any compounds.

J. Okada *et al.*, *Science Advances Vol.1 no.4 e1400142(2015)*

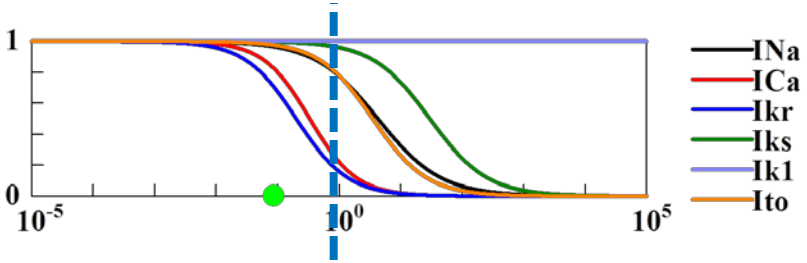
Concentration-inhibition curves for six ion channels

- Ion channels: hERG (I_{Kr}), Nav1.5, (I_{Na}), Cav1.2/β2/α2-δ (I_{Ca}), KCNQ1+KCNE1 (I_{Ks}), Kir2.1 (I_{K1}) or Kv4.3+KChiIP2 (I_{to}) channels
- Methods: automated patch clamp systems(the Sophion QPatch HTX system), general voltage protocols, room temperature
- Calculated parameters, IC_{50}, Hill coefficient, relative current

$$\text{Relative current} = \frac{1}{1 + 10^{(logIC_{50} - logx)\cdot n_H}}$$



- Example of Drug Effect Modeling

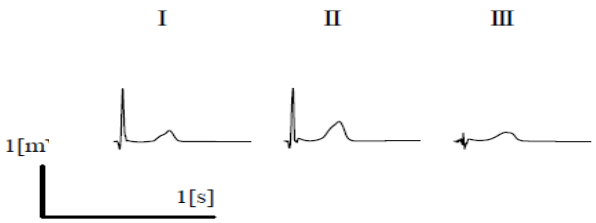


INa* = INa × 0.793039
ICaL* = ICaL × 0.246904
ICaK* = ICaK × 0.246904
ICaNa* = ICaNa × 0.246904
IKr* = IKr × 0.177410
IKs* = IKs × 0.96401
IK1* = IK1 × 1.000000
Ito* = Ito × 0.798373

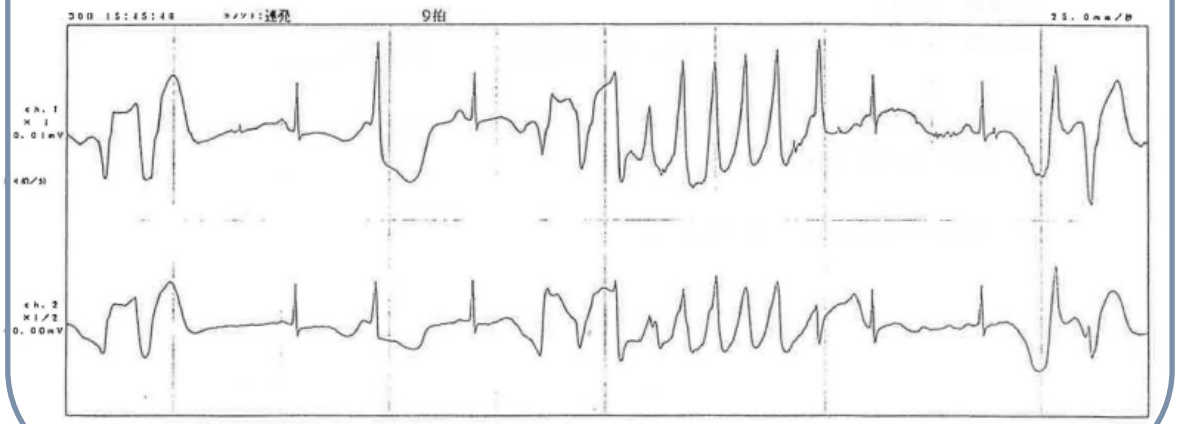
E-4031 induced TdP

Simulated ECG

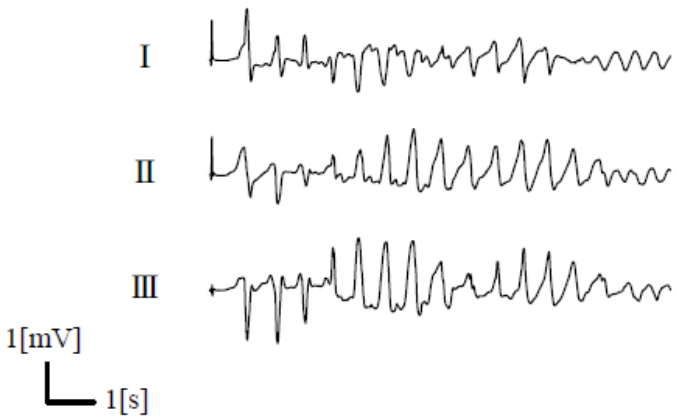
Basal condition



Clinical case of TdP with E4031: 9mg/man, day 6



E-4031: 10 times of $ETPC_{unbound}$



Simulated ECGs for test drugs at HR60: positive and negative for TdP induction

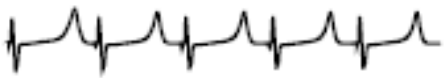
Control

Negative drugs

Amiodarone (x100)

Moxifloxacin (x100)

Verapamil (x50)



Positive drugs

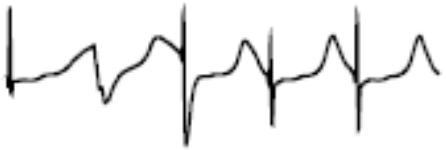
Astemizol (x200)

Bepridil (x10)

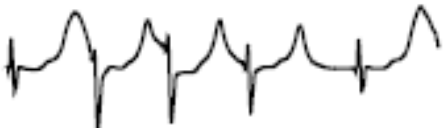
Cisapride (x20)

D,l-Sotalol (x75)

Quinidine (x7.5)



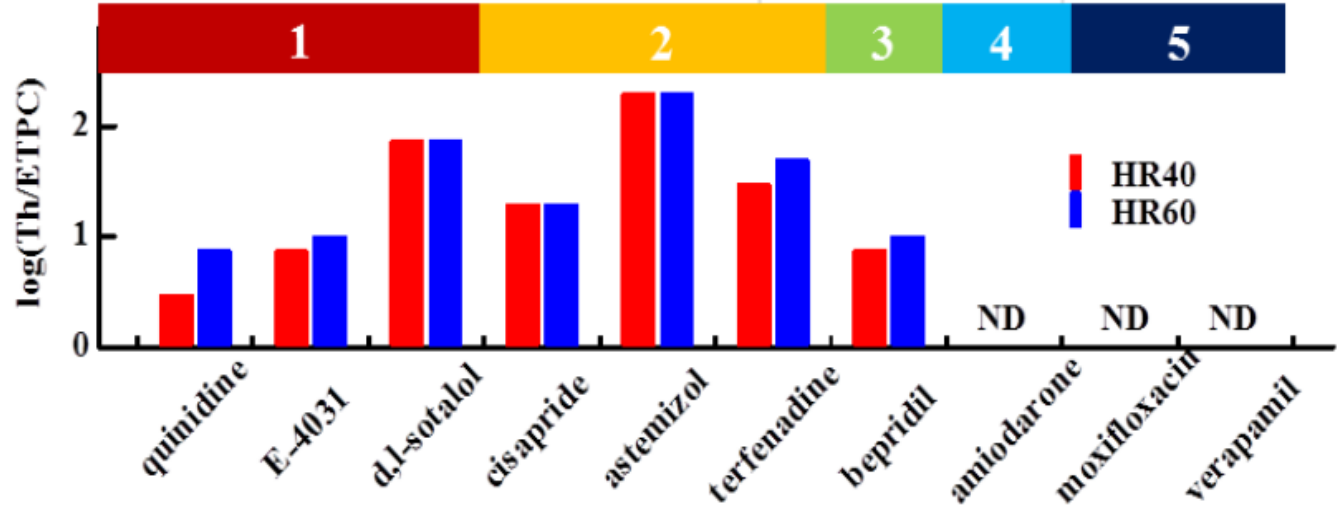
Terfenadine (x100)

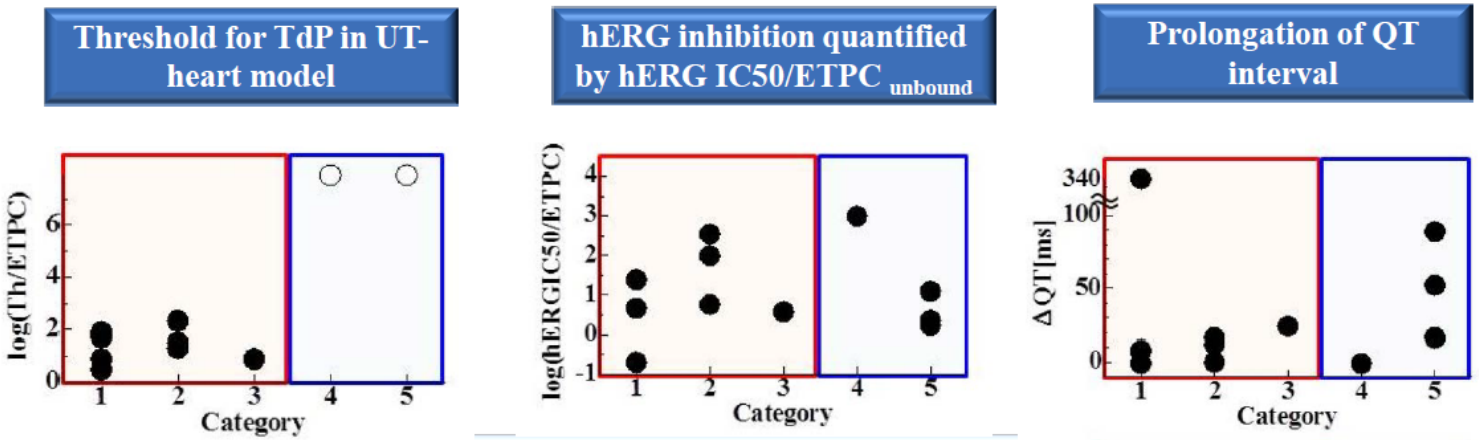


J. Okada *et al.*, *Science Advances Vol.1 no.4 e1400142(2015)*

Correlation of simulated threshold level with TdP risk, QT or hERG

The TdP risk categories by Redfern





Threshold values relative to $ETPC_{unbound}$ are shown for each drug categorized as high risk (1, 2, and 3) or safe (4 and 5). ND: not detected.

J. Okada *et al., Science Advances Vol.1 no.4 e1400142(2015)*

For the virtual QT/TdP risk assessment

	Candidate A	Candidate B	Candidate C
Relative current at;	1x ETPC	10x ETPC	10x ETCP
Ikr	0%	30%	40%
INa	0%	0%	10%
ICa	0%	10%	30%
Iks	0%	20%	0%

No change

?

?

For the virtual QT/TdP risk assessment

Five dimensional electrocardiogram database is developing.

The following inhibition rates were assumed for 5 ion channels.

Ikr(%): 0,10,20,30,40,50,60,70,80,90,100	(11 patterns)
Iks(%): 0,10,20,30,40,50,60,70,80,90,100	(11 patterns)
ICa (%): 0,10,20,30,40	(5 patterns)
INa (%): 0,10,20,30,40	(5 patterns)
INaL (%): 0,25,50	(3 patterns)

Database: 11×11× 5 ×5×3 = 9075 cases

The computational cost: 72,600,000 [core hours]

K computer

Yakushi (Machine in UT laboratory)

Intel Xeon E5–2680 4736 cores

98.5 Tera Flops (0.1Peta Flops)

It takes 15 hours for the calculation of 5 beats

K computer (RIKEN, Kobe)

Fujitsu SPARC64 VIIIfx

705024 cores

10 Peta Flops

The power of "K-computer" extends the limit of our simulator

3D Hazard map for arrhythmia

Unpublished

Summary and Conclusions

The development and improvement of *in silico* simulation for the cardiac electrophysiology such as ventricular action potentials and ECGs are progressed in the safety pharmacology field.

Using *in vitro* (multi-ion channel inhibition) data, UT-heart could predict the drug-induced arrhythmogenic risk potential of TdP-negative or –positive drugs.

Applying this technology, the hazard map for arrhythmia using ECG database based on the various combinations of multi-ion channel inhibition data has been developed.

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Thank you
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