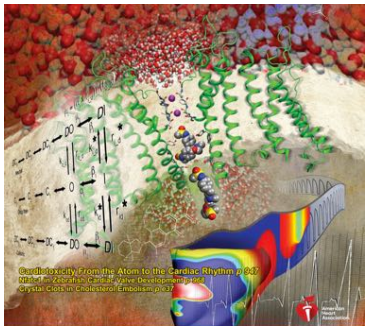
2021 Frontera User meeting

Atomistic simulations on Frontera for a predictive multi-scale safety pharmacology pipeline



Igor Vorobyov

University of California, Davis

Department of Physiology and Membrane Biology

January 29, 2021

Prescription drugs can cause cardiac arrhythmia

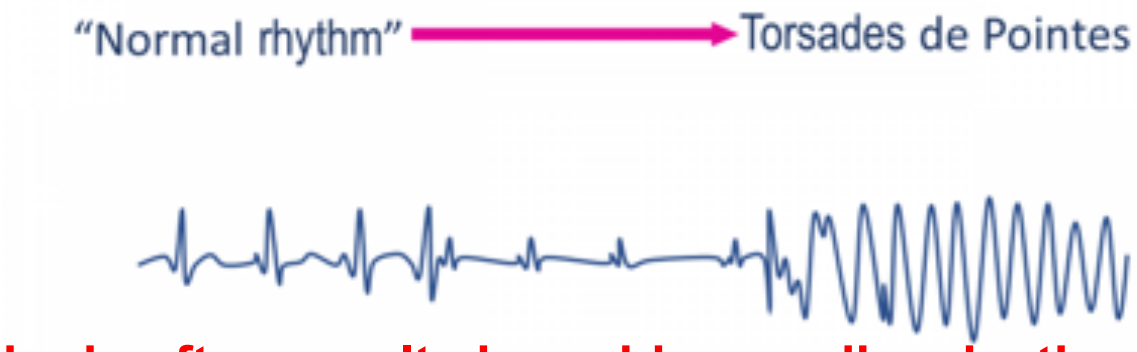
"Poisons and medicine are often the same substance given with different intents"
Peter Mere Latham (1789-1875)

- Up to 3% of prescription drugs carry arrhythmia risks.
- Cardiotoxicity account for 22-28% US post-market drug withdrawals.
- Up to 50-70% of small molecule leads are eliminated early in drug development due to potential for causing arrhythmias.
- This impedes drug development and greatly increases its $$$.
- Multiple drug classes are affected: most anti-arrhythmics, some antibiotics, anti-cancer drugs, allergy medications, GI drugs, COVID-19 medications etc.

Drug induced arrhythmia – a major regulatory problem

- In 1990s-2000s some drugs were withdrawn and some got limited distribution.

- These drugs can cause Torsades de Pointes (TdP) arrhythmias



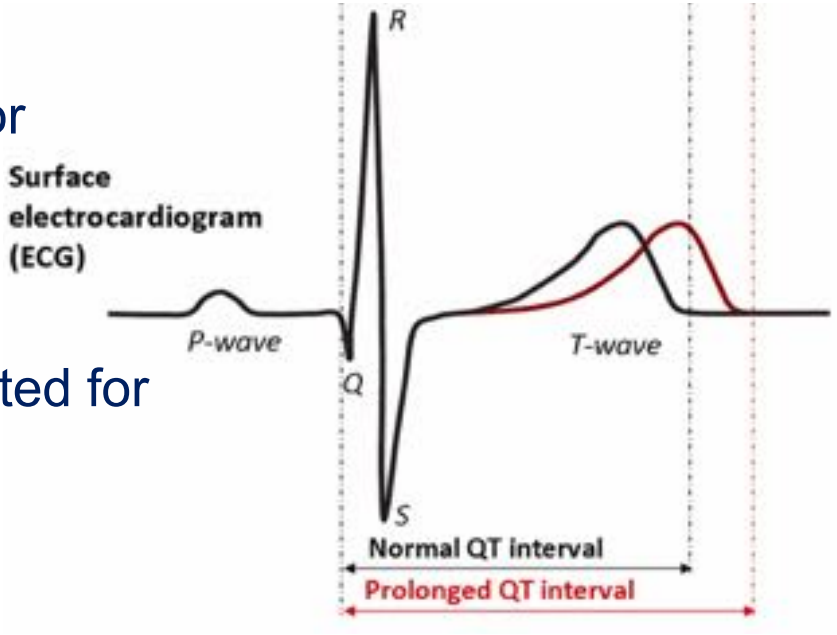
TdP arrhythmia often results in sudden cardiac death.

https://www.fda.gov/drugs/regulatory-science-action/impact-story-improved-assessment-cardiotoxic-risk-drug-candidates-comprehensive-vitro-proarrhythmia

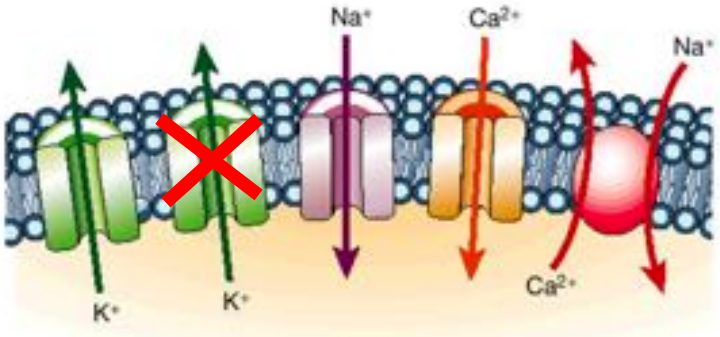
Drug induced arrhythmia – a major regulatory problem

- In 2005 two key international guidelines were developed to solve this problem.

1) During clinical trials drugs are tested for QT interval prolongation on ECG



2) During pre-clinical testing drugs are tested for hERG channel inhibition



hERG channel moves K^+ ions across cardiac cell membranes and drives heart electrical activity to the resting state.

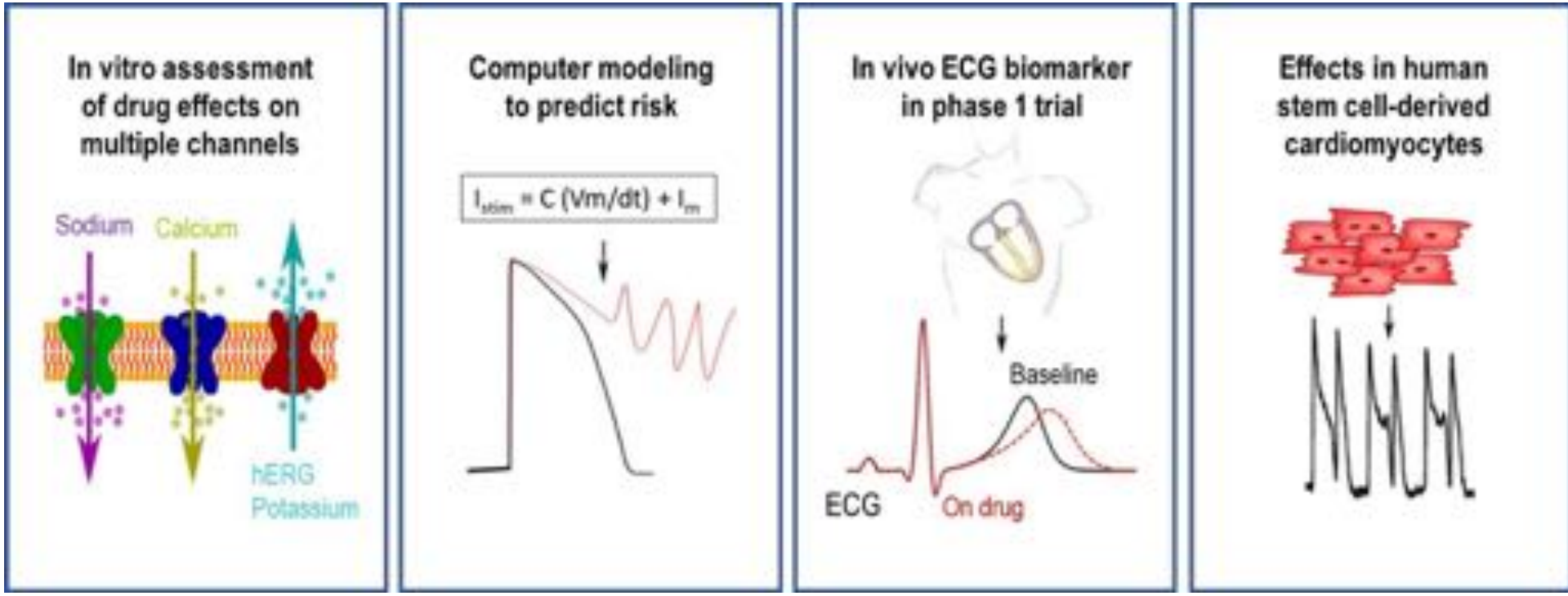
hERG channel is a promiscuous drug anti-target.

- No hERG blocking and QT prolonging drugs can enter the market.

Not all hERG blockers cause arrhythmia

- QT prolongation and hERG block are not selective criteria for drug-induced arrhythmia.
- Many hERG blocking drugs are cardiac safe. Grapefruit juice can cause QT prolongation.
- This can lead to abandonment of safe and effective drug candidates.

Comprehensive in vitro Pro-arrhythmia assay (CiPA) initiative.



It is a combination of experimental and computational techniques developed and used by multiple research groups in US and around the world. http://cipaproject.org/about-cipa/#1

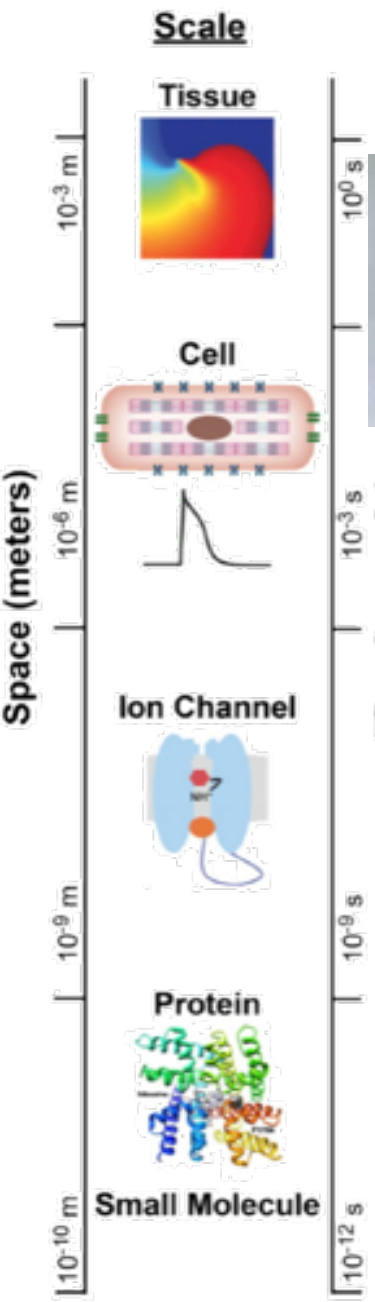
However, CiPA initiative does not provide a ready-to-go recipe on how to predict drug-induced pro-arrhythmia from drug chemical structure.

https://www.fda.gov/drugs/regulatory-science-action/impact-story-improved-assessment-cardiotoxic-risk-drug-candidates-comprehensive-vitro-proarrhythmia

In silico safety pharmacology

UCDAVIS HEALTH

NIH National Heart, Lung, and Blood Institute



UC Davis modeling team leaders

Prof. Colleen Clancy
Physiology

Prof. Vladimir Yarov-Yarovoy
Physiology

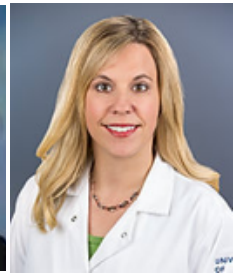
Prof. Tim Lewis
Mathematics

UC Davis experimental team leaders

Prof. Fernando Santana
Physiology

Prof. Jon Sack
Physiology

Prof. Heike Wulff
Pharmacology



Prof. Crystal Ripplinger
Pharmacology

Collaborators

Prof. Sergei Noskov
U. Calgary

Prof. Slava Bekker
ARC

Prof. Kazuharu Furutani
Tokushima Bruni U.

Researchers & trainees

Dr. Pei-Chi Yang
Project scientist

Dr. Kevin DeMarco
Postdoc

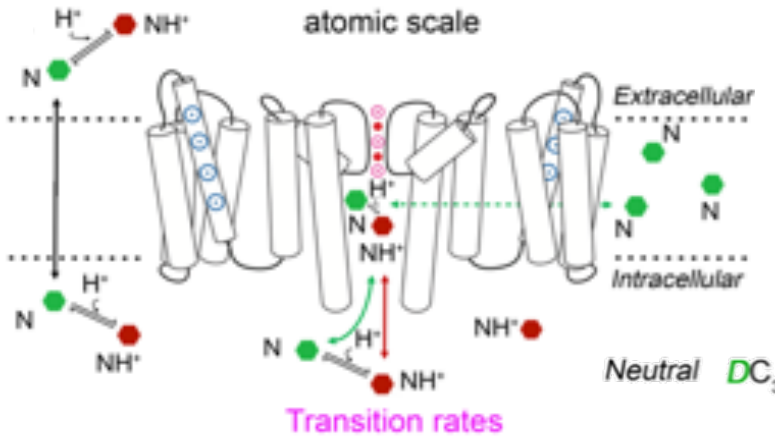
Dr. Parya Aghasafari
Postdoc

Mr. John Dawson
Grad. student

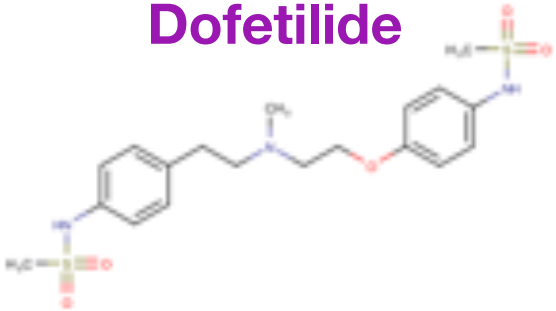
Goal: to predict drug-induced arrhythmogenicity from drug chemical structure using a multi-scale modeling pipeline guided by experiments.

Clancy et al. Ann Biomed Eng. 2016, 44: 2591

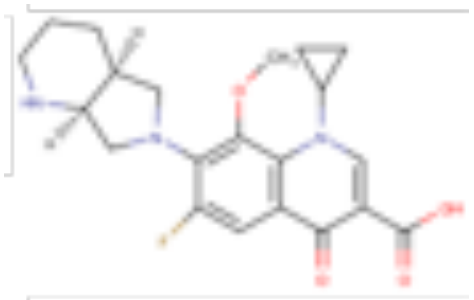
In silico pipeline to predict cardiotoxicity: from atom to rhythm

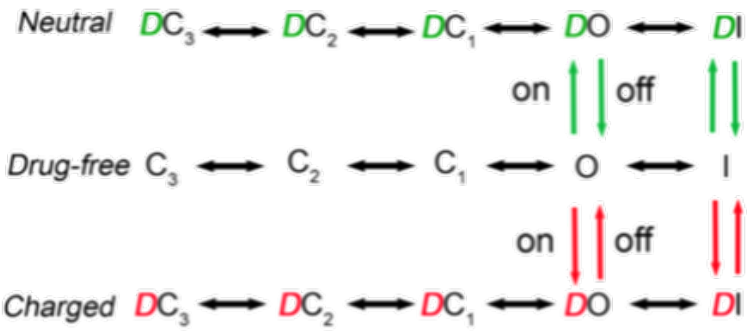


Dofetilide



Moxifloxacin

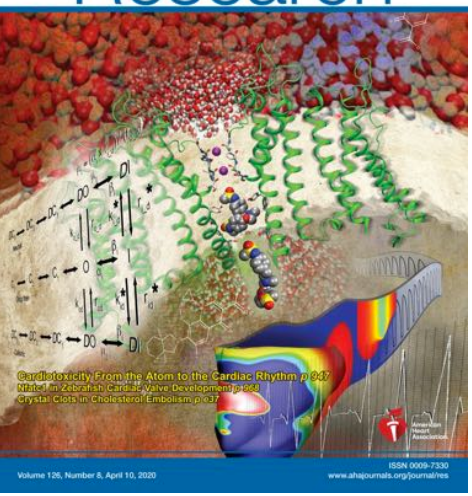




Atom

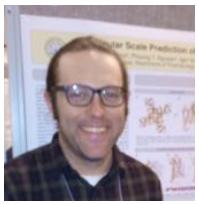
Function

Heart Rhythm

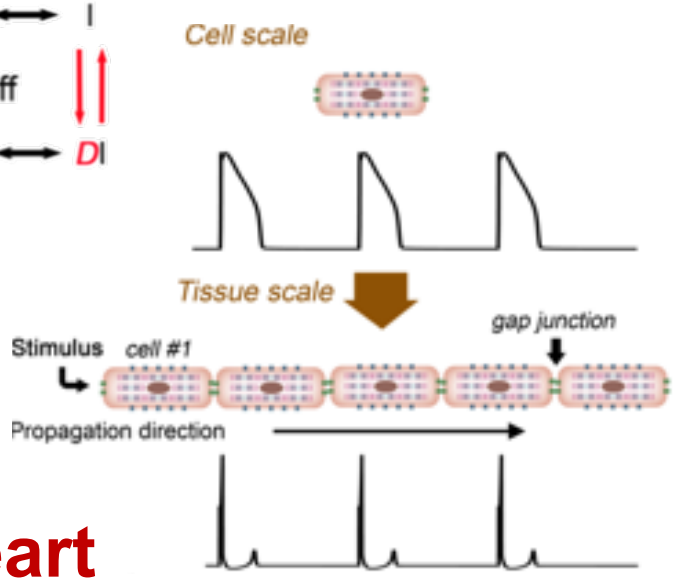


Professor Colleen Clancy

Dr. Pei-Chi Yang



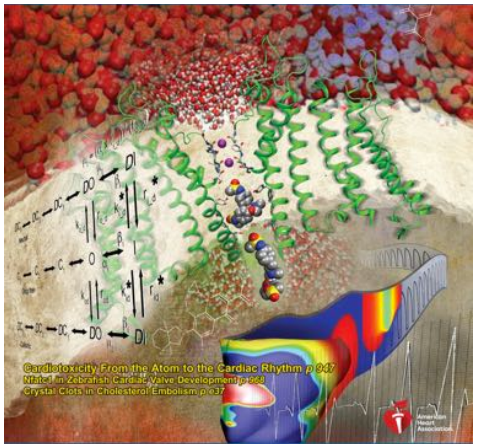
Dr. Kevin DeMarco



Pseudo ECG

Yang et al Circ Res 2020, 126(8): 947

What can our multi-scale safety pharmacology pipeline do?



- Move beyond hERG block and QT prolongation paradigm for cardiac drug safety testing.
- Translate microscopic drug – protein interaction data into their clinical effect on heart rhythm.
- Incorporate sex differences in drug testing.
- Include co-morbidities (e.g., heart failure) in drug testing.
- Account for patient specific genetic variations (mutations, polymorphism) for personalized medicine approach.
- Predict arrhythmia risks for chemically similar drugs.
- Rehabilitate promising drug candidates & repurpose existing medications
- Develop new cardiac-safe and efficient treatments.
- Reduce costs of drug development and save human lives!

High-performance computing (HPC) are crucial for the pipeline

✦ **Atomistic molecular dynamics (MD) simulations are computationally demanding.**
100 ns or 1/10,000,000 second long simulation ~ 50M energy & force computations.
5 days for NAMD 2.14 on Nvidia Tesla P100 GPU for a 130,000 atom system.

✦ **We need to perform ~100 or more simulations in parallel .**
Enhanced sampling MD simulations like Hamiltonian replica exchange umbrella sampling MD (HREUS-MD): 90 "windows" spaced 0.5 Angstrom (5×10^{-11} m) apart to efficiently sample energy barrier crossing and drug tumbling in the channel pore.

✦ **We need to do these simulations for multiple drug and ion channel states.**
Multiple drugs, their stereoisomers, different protonation states, ion channel conformational states (open, closed, inactivated) and mutants as well.

✦ **TACC state-of-the-art peta-scale Frontera CPU and Longhorn GPU architectures using NAMD software are ideally suited for these calculations!**
Longhorn GPU nodes are for long unbiased and/or equilibration/drug pulling runs.
Frontera CPU nodes are ideal for HREUS-MD simulations.

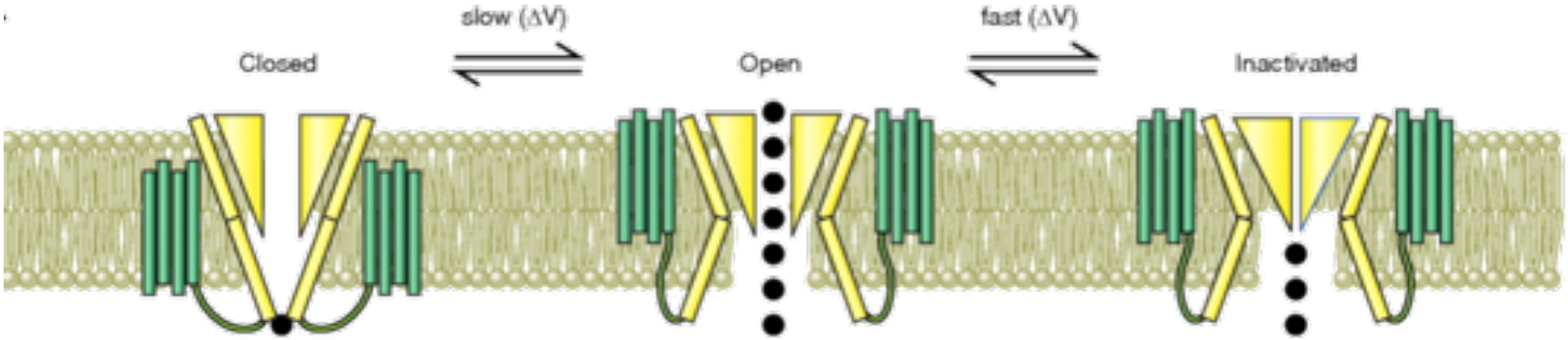
NAMD
Scalable Molecular Dynamics

intel inside Xeon

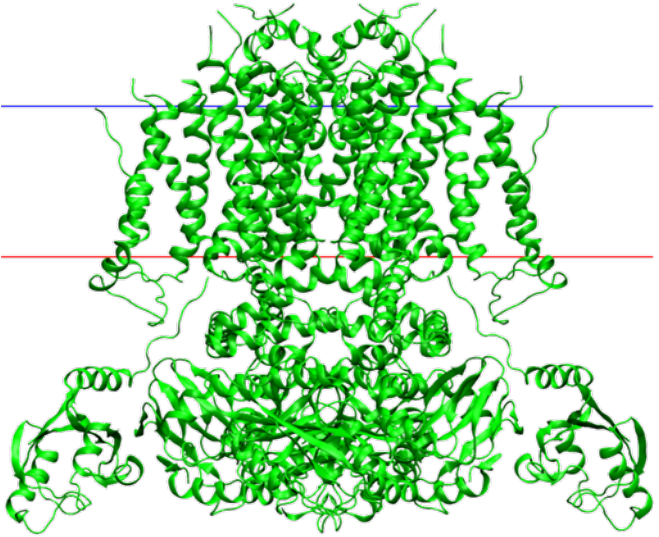
NVIDIA CUDA

hERG channel structural model: state elucidation

hERG channel exists in multiple conformational states. Drug binding is state-dependent.

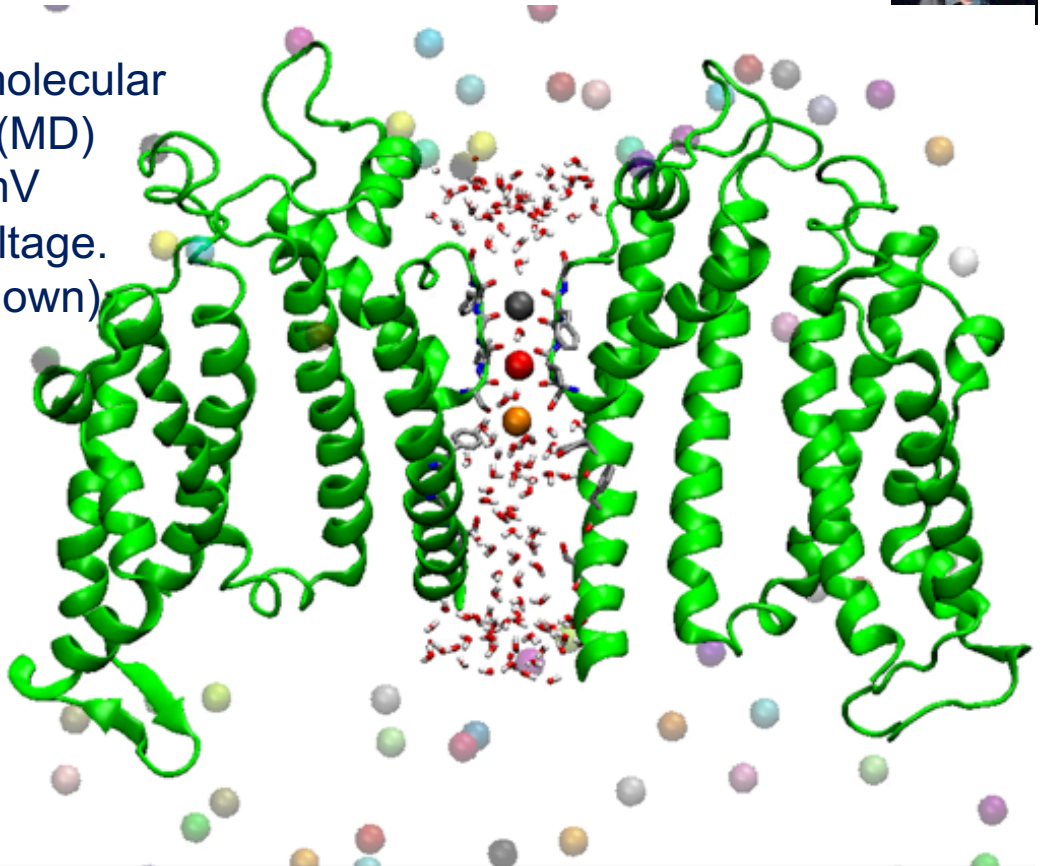


Vandenberg et al Physiol Rev 2012



Cryo-EM structure
PDB ID: 5VA2
(3.7 Å resolution)
Which state is it in?

All-atom molecular dynamics (MD) with 750 mV applied voltage. (300 ns shown)

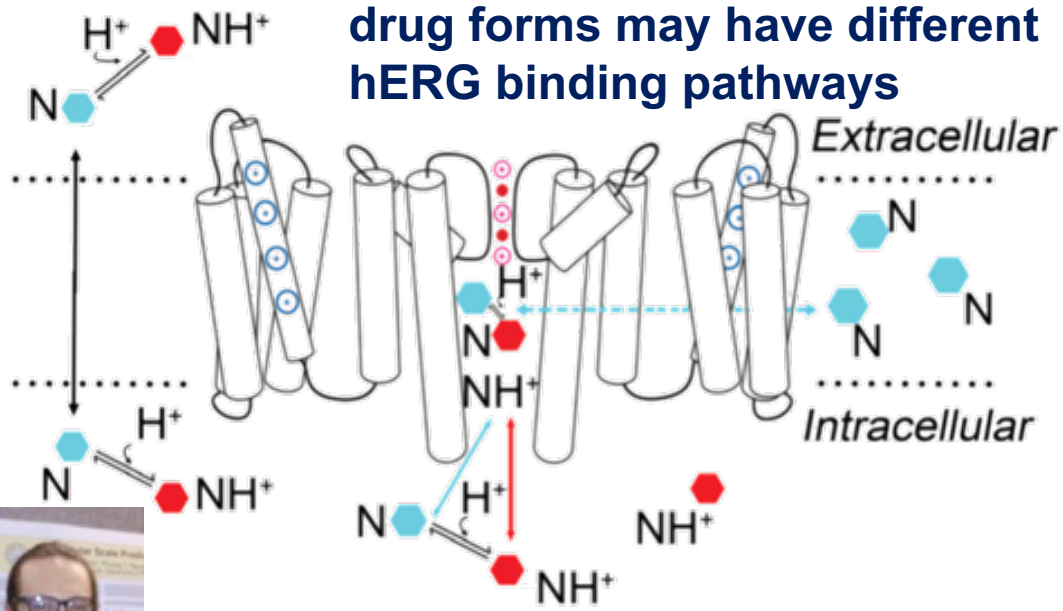


Multiple K^+ conduction events. Open hERG state.

Yang et al Circ Res 2020, 126(8): 947

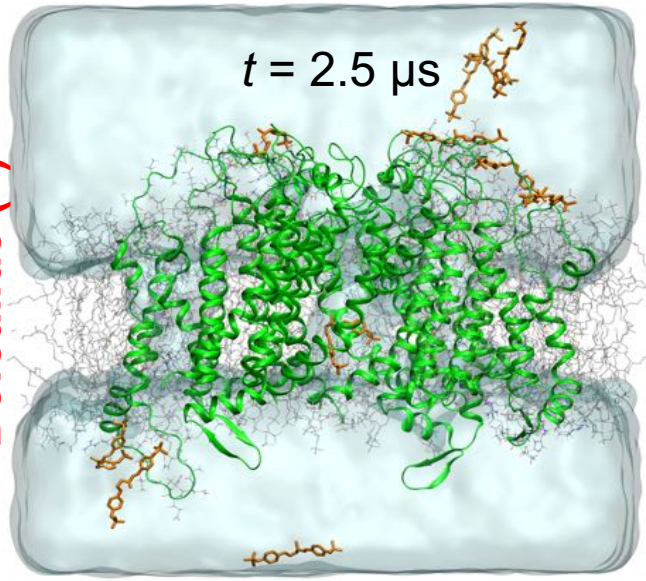
hERG – drug "flooding" MD reveal binding pathways and sites

Charged(+) and neutral(0) drug forms may have different hERG binding pathways

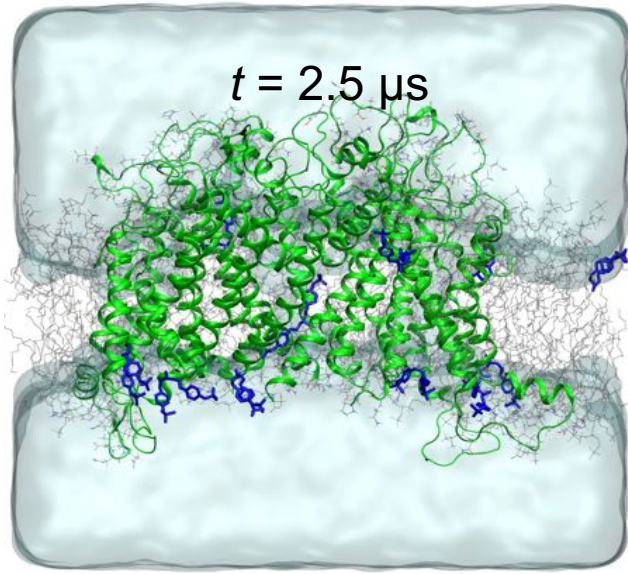


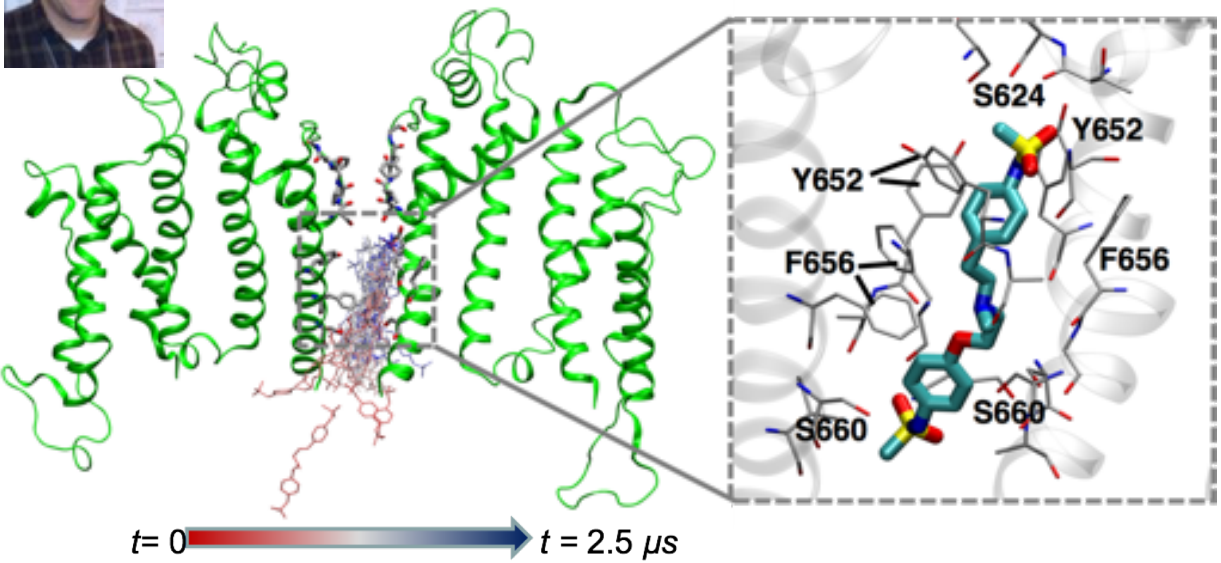
All-atom drug "flooding" unbiased MD runs.

Dofetilide (+)



Dofetilide (0)

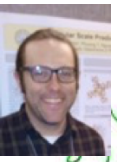




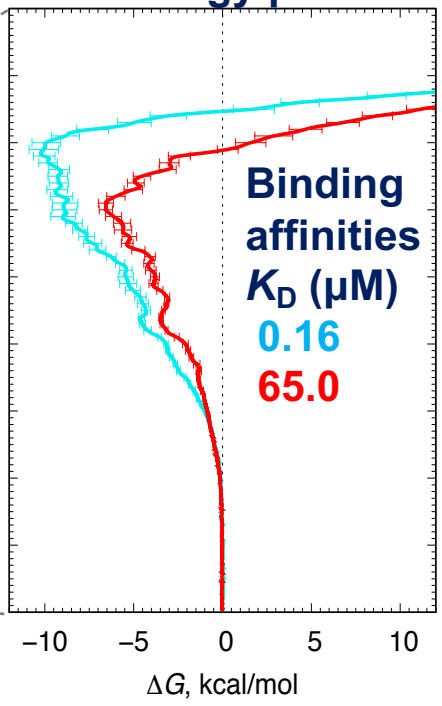
DeMarco et al bioRxiv 2019 https://doi.org/10.1101/635441

Umbrella sampling MD provides hERG – drug affinity &kinetics

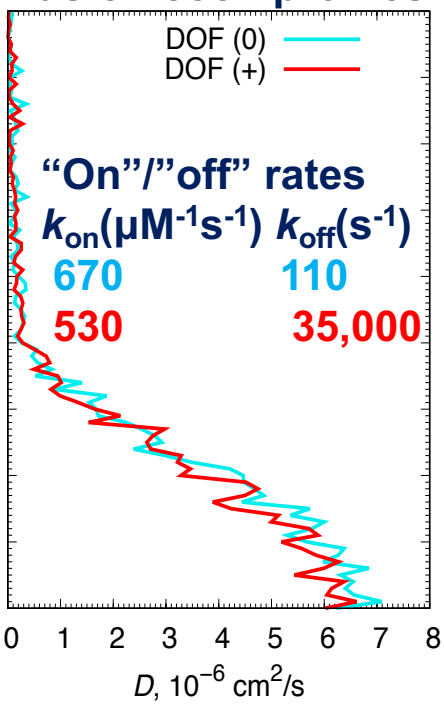
Umbrella sampling MD simulations of hERG – dofetilide (DOF) interactions



Free energy profiles

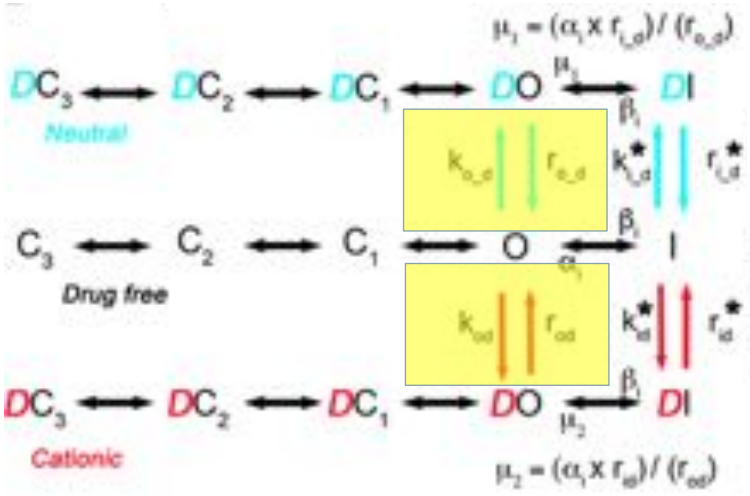


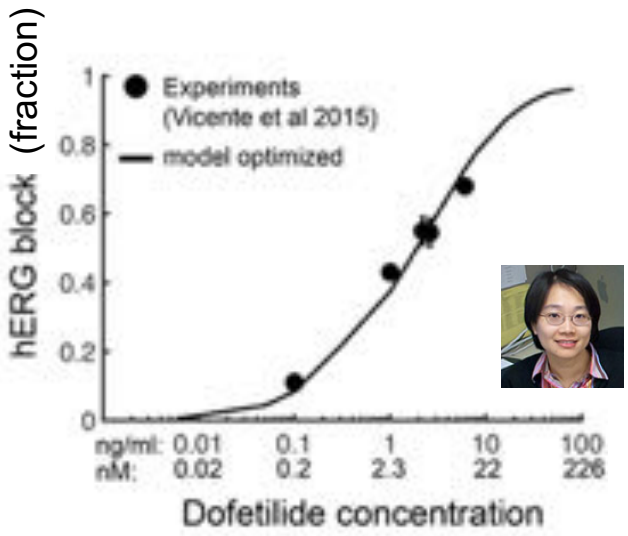
Diffusion coef. profiles



"On"/"off" rates (k_{on}, k_{off}) are functional kinetic hERG-drug model parameters **(yellow)**.

Good agreement with experimental hERG block curve.

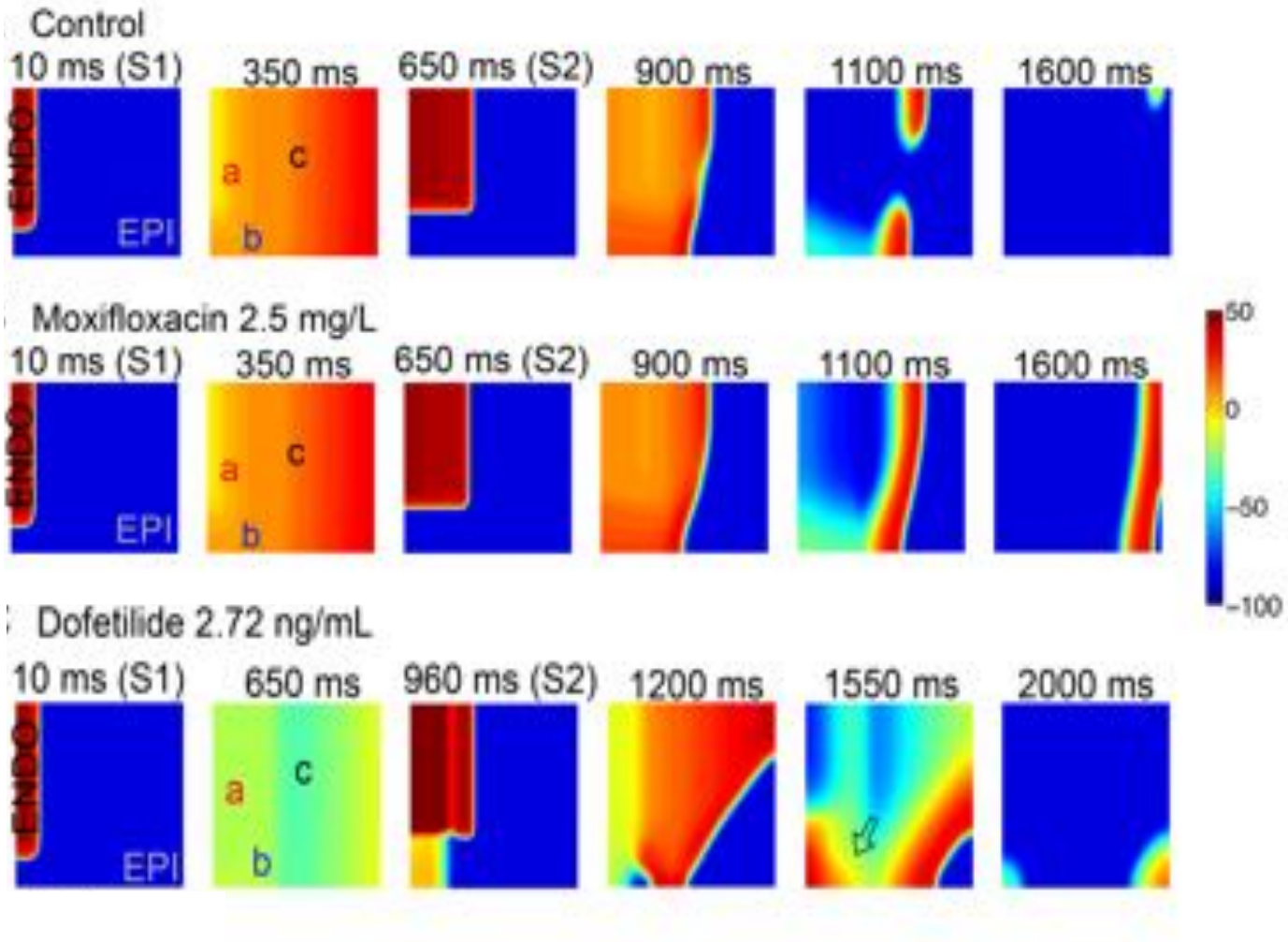


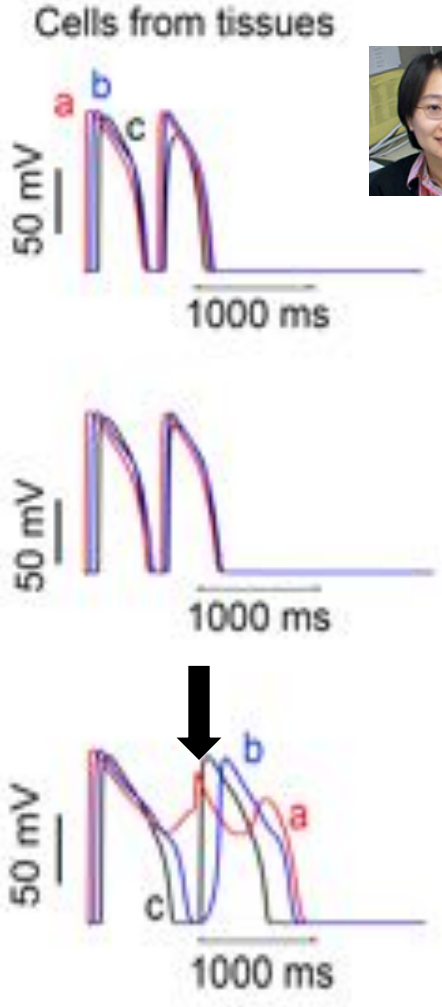


Yang et al Circ Res 2020, 126(8): 947

Drug pro-arrhythmia emergence in 2D tissue simulations

Cardiac action (electric) potential propagation in time and space in 2D ventricular cardiac tissue (5 x 5 cm^2) after application of electrc stimuli (S1 & S2).





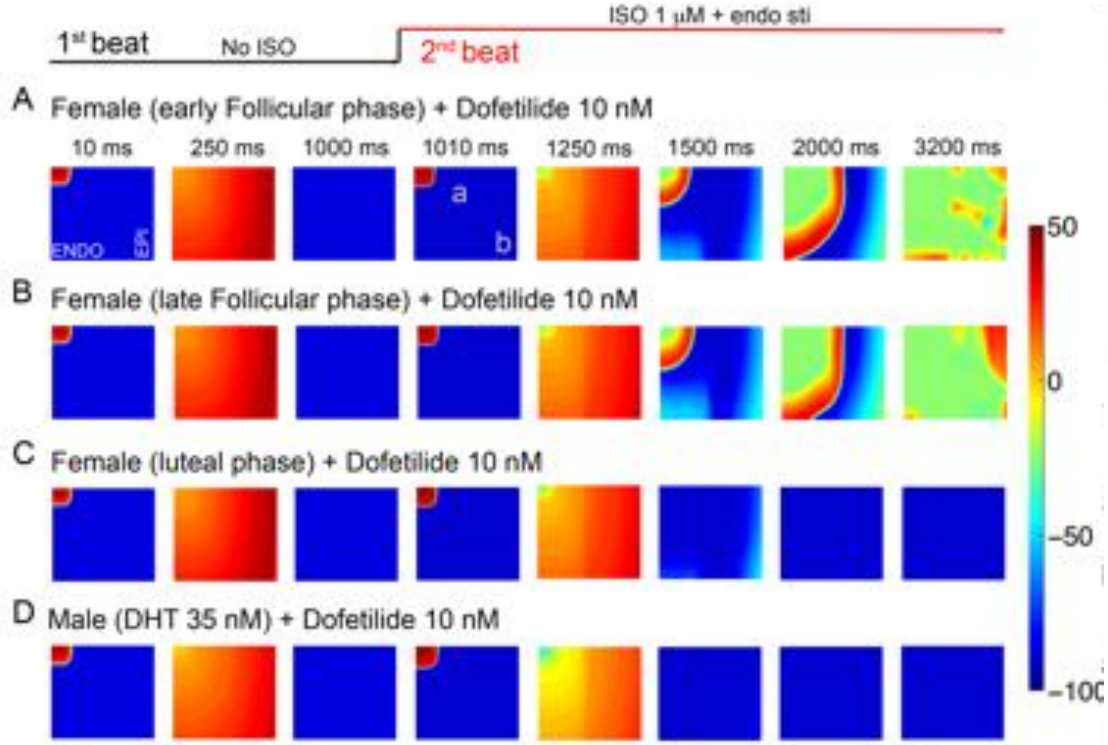
Pro-arrhythmia triggers, spatial repolarization gradients (white arrow) and early afterdepolarization (black arrow), are induced with dofetilide but not moxifloxacin.

Yang et al Circ Res 2020, 126(8): 947

Dofetilide arrhythmia proclivity & sex hormone effects

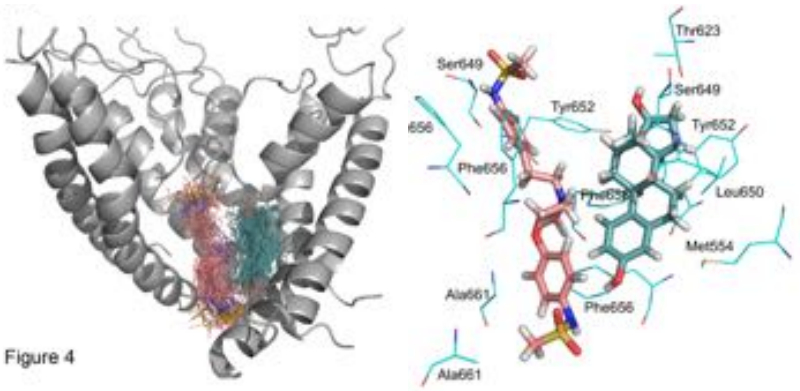
Female sex is an independent risk factor for drug-induced arrhythmia (up to 70%)

Dofetilide + sex hormones: 2D cardiac tissue simulations



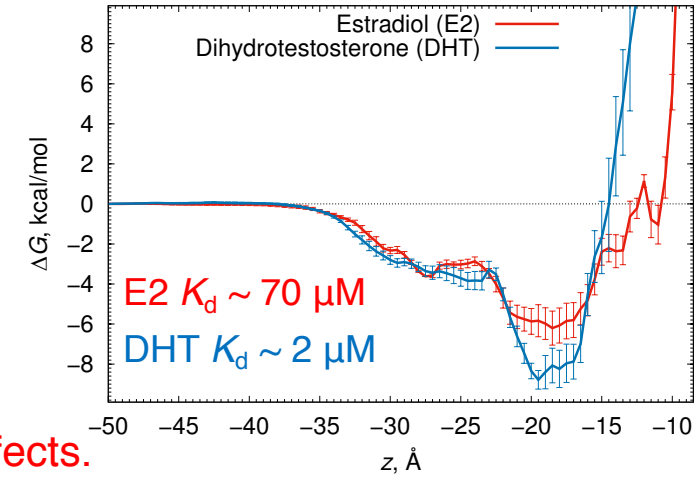
Menstrual cycle	17β-estradiol (E2)	Progesterone (Pg)
Early follicular stage	0.1 nM	2.5 nM
Late follicular stage	1.0 nM	2.5 nM
Luteal stage	0.7 nM	40.6 nM

Atomistic MD simulations



cooperative binding of estradiol & dofetilide in the hERG pore

Atomistic US-MD of hERG+hormone



Estradiol increases proclivity for drug-induced arrhythmias, whereas testosterone and progesterone have protective effects.

AHA career development award (2019-22).

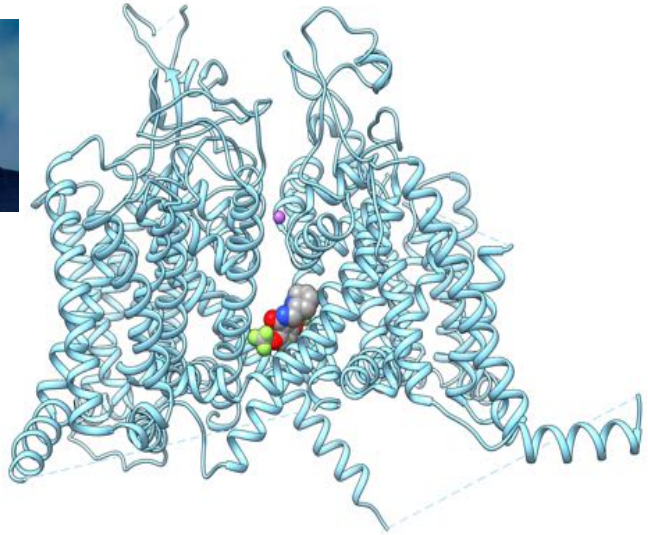
Collaboration with Prof. Junko Kurokawa (U. Shizuoka)

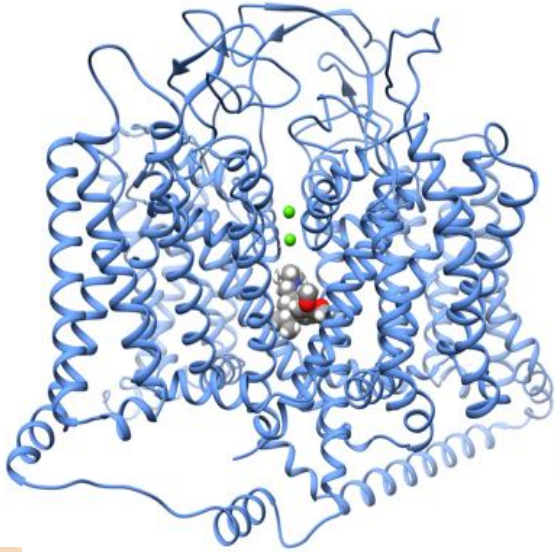
Yang et al J Physiol 2017, 595(14): 4695-4723 https://doi.org/10.1113/JP273142

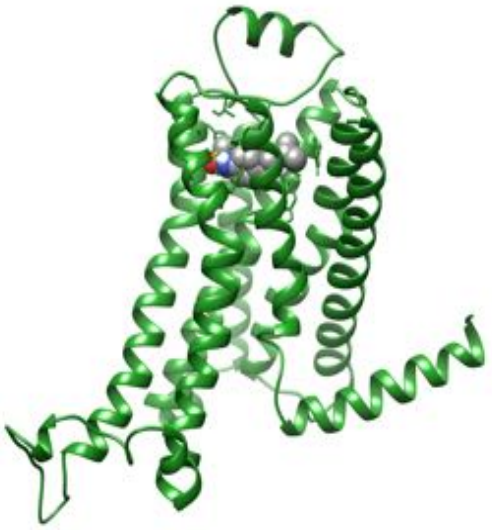
Extension to multi-target block in safety pharmacology pipeline

Many hERG blocking and QT prolonging drugs bing to other cardiac proteins, which may modify their pro-arrhythmia proclivities (also investigated through CiPA initiative)

Drug	Category/Clinical Use	TdP Risk	Y652	F656	Multichannel	State Preference	pKa	% ionized
Bepridil	anti-anginal	high	X	✓	K and Ca	open/inactivated	7.9	75.97
Sotalol	class II/III antiarrhythmic	high	✓	?	K and bAR	open	8.3	88.82
Amiodarone	class III antiarrhythmic	int/low	✓	X	K and Ca	open/inactivated	6.56	12.63
Cisapride	gastroprokinetic	int	✓	✓	K	open/inactivated?	8.2	86.32
Quinidine	class I antiarrhythmic	high	✓	✓	K, Na, aAR	open/inactivated	8.56	93.53
Nifekalant	class III antiarrhythmic	low	✓	✓	K	open	7.9	75.97







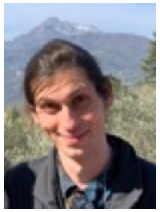
$Na_V1.5$/flecainide

$Ca_V1.2$/verapamil

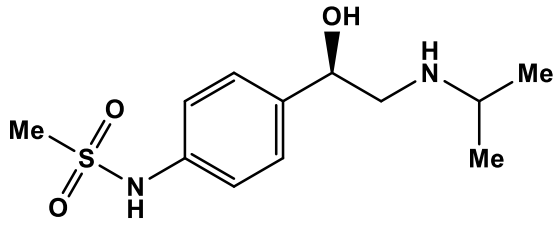
β_4AR/sotalol

Courtesy of Prof. V. Yarov-Yarovoy, Dr. Phuong T. Nguyen, Aiyana Emigh & John R. D. Dawson

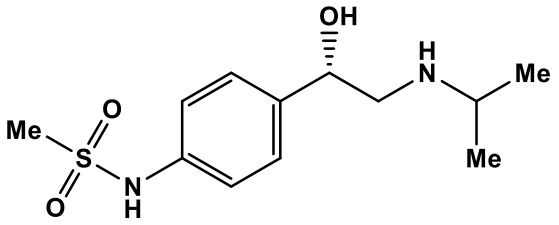
Sotalol: anti-arrhythmic drug with beta-blocking activity



John Dawson

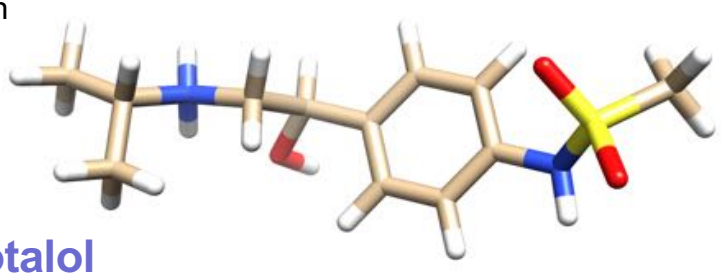


(*R*)-*N*-(4-(1-hydroxy-2-(isopropylamino)ethyl)phenyl)methanesulfonamide



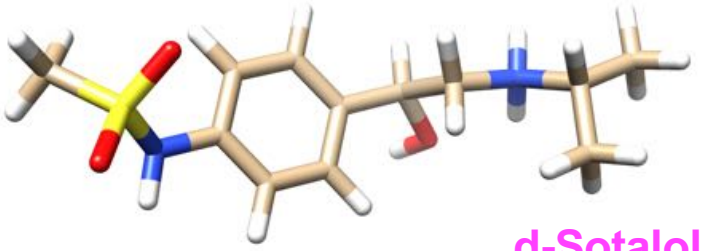
(*S*)-*N*-(4-(1-hydroxy-2-(isopropylamino)ethyl)phenyl)methanesulfonamide

Prof. Heike Wulff



l-Sotalol

l - levorotary or (-), counterclockwise



d-Sotalol

d - dextrorotary or (+), clockwise

Dr. Vikrant Singh

- **Class III & II antiarrhythmic drug:**
  - **Racemic mixture & d isomer block hERG (IC_{50} ~ tens-hundreds μM);**
  - **l isomer is a competitive antagonist of β-adrenergic receptors (IC_{50} ~ 2.4 μM).**
- **Failed SWORD (Survival With ORal D-sotalol) trial: pure d isomer**
  - **Mortality was 2x compared to placebo;**
  - **Trial was terminated prematurely.**
- **dl-Sotalol is prescribed with consideration of dose-dependent pro-arrhythmia risks.**

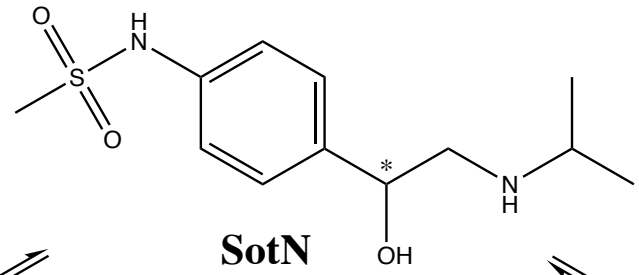
Does beta-block alleviate hERG block or there are stereospecific hERG blocking affinities as well ?

Sotalol: multiple ionization states

pK_{a1} = 8.3; pK_{a2} = 9.8

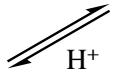
At pH = 7.4

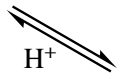
Dominant in membrane interior

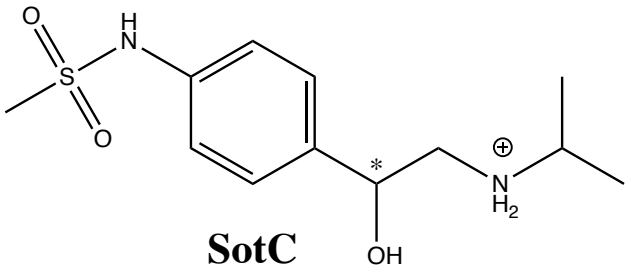


μ = 5.6 D

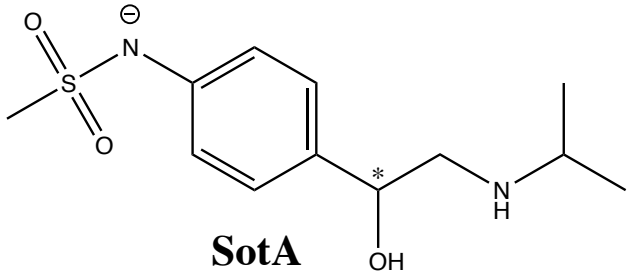
Dominant in water



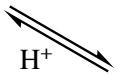




~11%

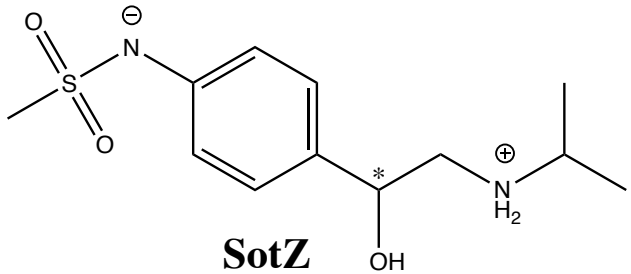


μ = 16.9 D



~89%

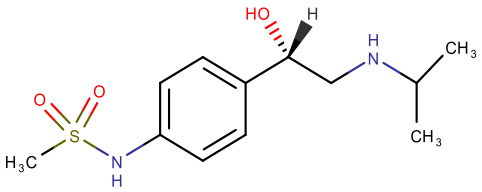
μ = 15.5 D



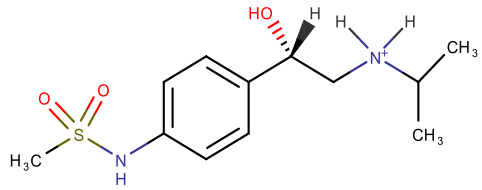
μ = 28.6 D

DeMarco et al Frontiers Pharm 2018 https://doi.org/10.3389/fphar.2018.00026

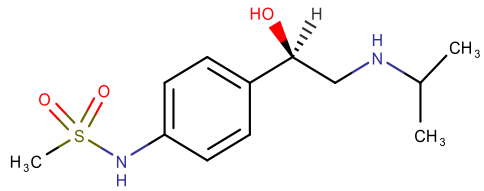
hERG – sotalol all-atom “drug” flooding MD simulations



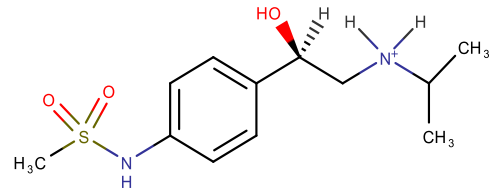
d-sotalol (0)



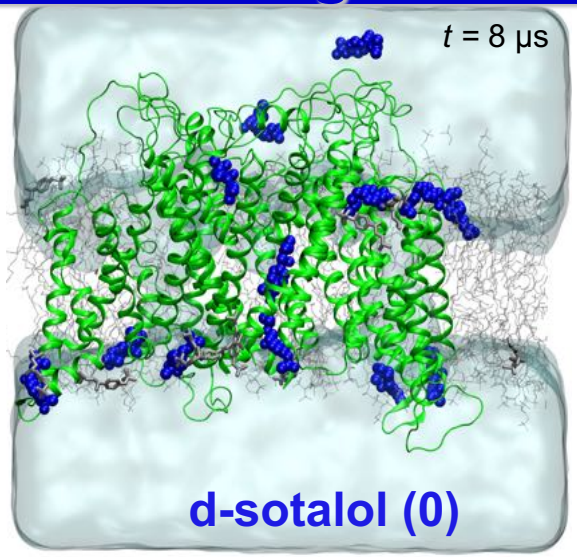
d-sotalol (+)

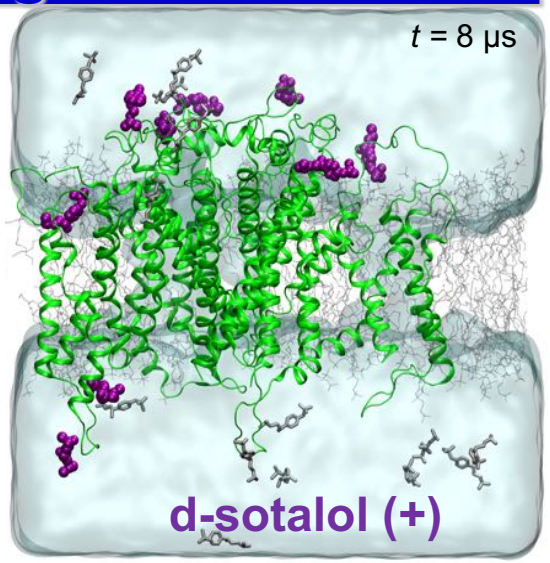


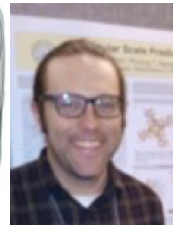
l-sotalol (0)

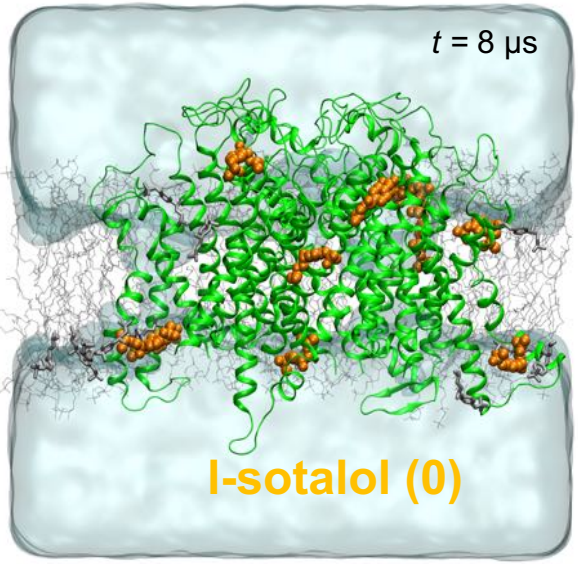


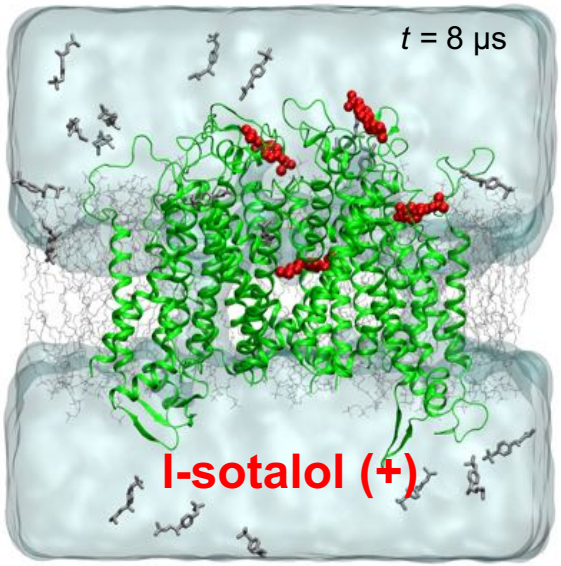
l-sotalol (+)





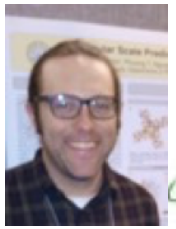


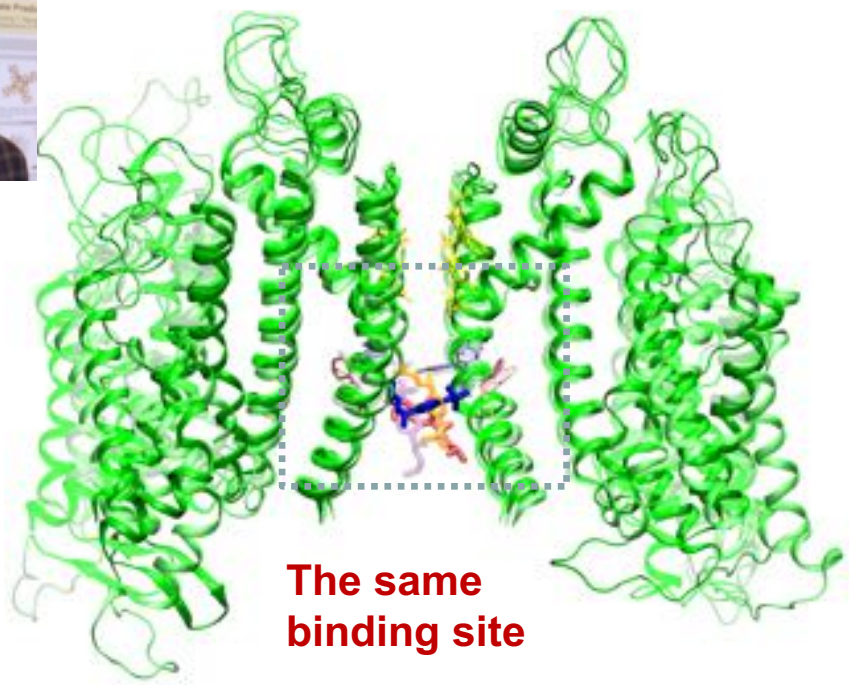




Cationic d- and l-sotalol mostly remains in bulk aqueous solution (gray sticks), whereas neutral d- and l-sotalol largely interacts with hERG channel and lipid membrane as shown by colored space-filled molecules.

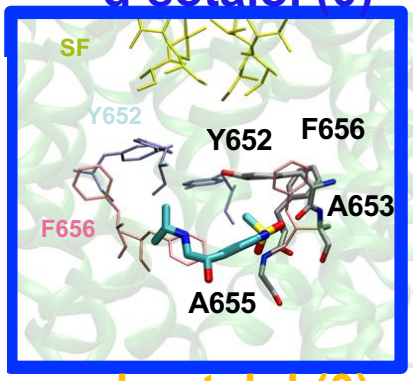
hERG – sotalol all-atom umbrella sampling MD (US-MD) simulations



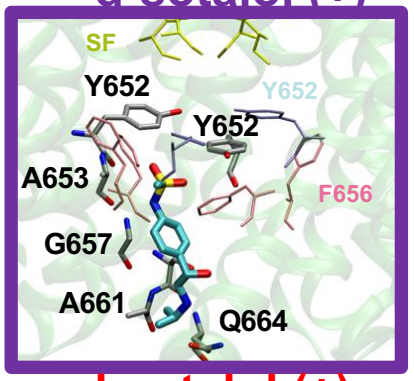


The same binding site

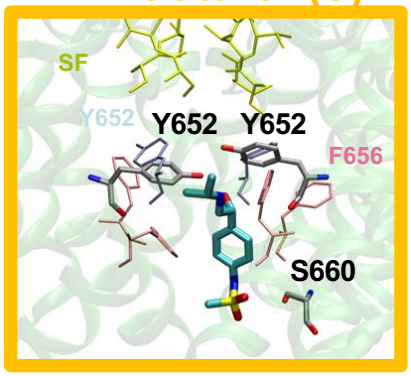
d-sotalol (0)



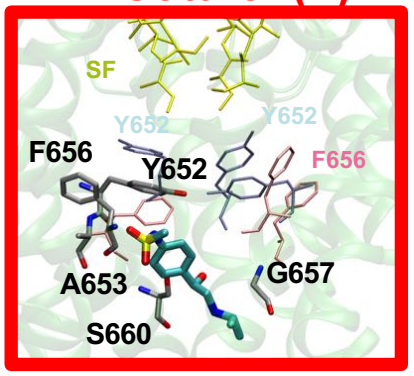
d-sotalol (+)

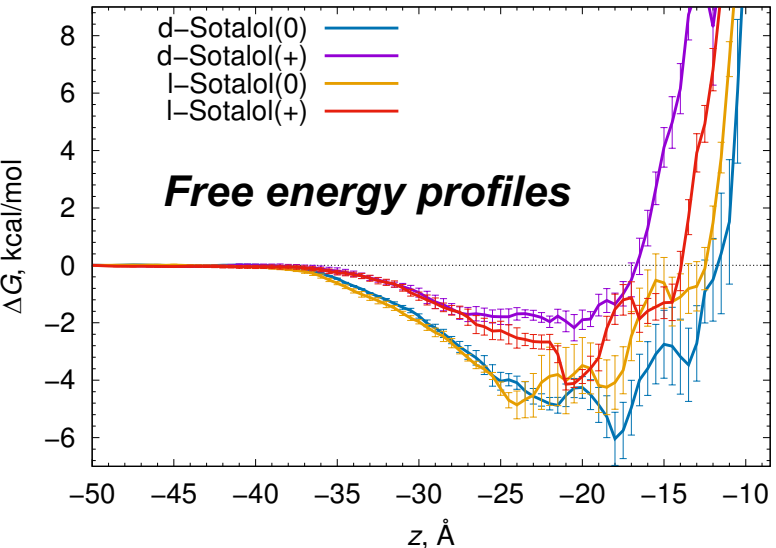


l-sotalol (0)



l-sotalol (+)





K_D (mM)

d-Sot(0): 0.17

d-Sot(+): 23.3

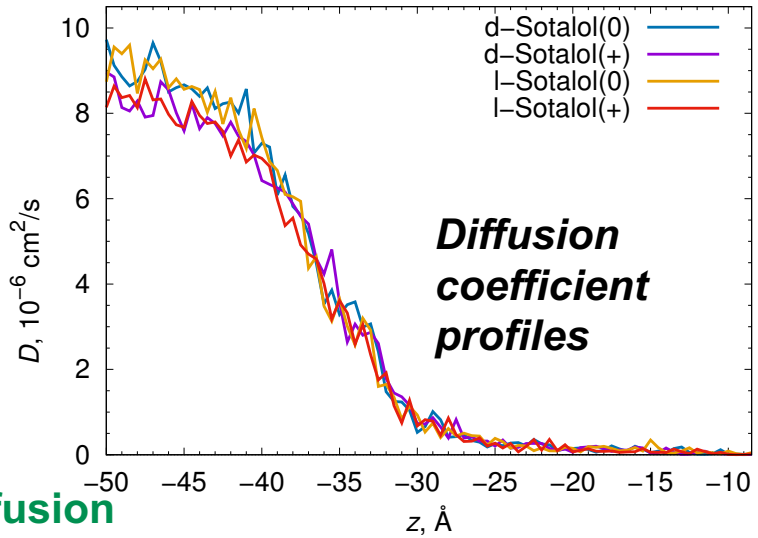
d-Sot(pH=7.4): 2.3

l-Sot(0): 0.60

l-Sot(+): 2.9

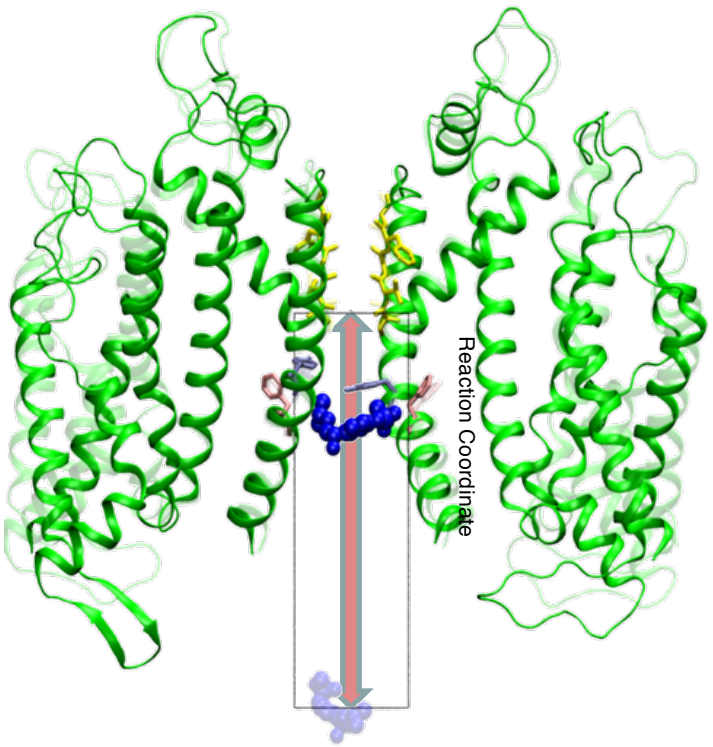
l-Sot(pH=7.4): 2.0

Very similar affinities and diffusion



hERG – sotalol interactions: connecting scales

Atomistic scale



k_{on} ($\mu M^{-1}s^{-1}$)

d-Sot(0): $7.4 \cdot 10^2$

d-Sot(+): $3.6 \cdot 10^2$

l-Sot(0): $7.9 \cdot 10^2$

l-Sot(+): $4.4 \cdot 10^2$

k_{off} (s^{-1})

d-Sot(0): $1.3 \cdot 10^5$

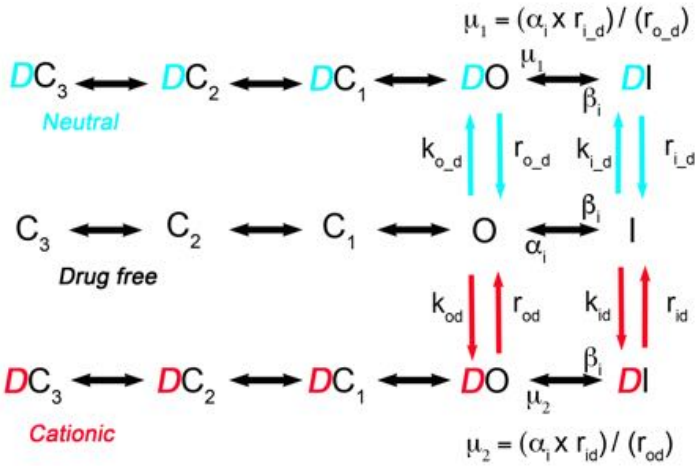
d-Sot(+): $8.3 \cdot 10^6$

l-Sot(0): $4.7 \cdot 10^5$

l-Sot(+): $1.3 \cdot 10^6$

Protein scale

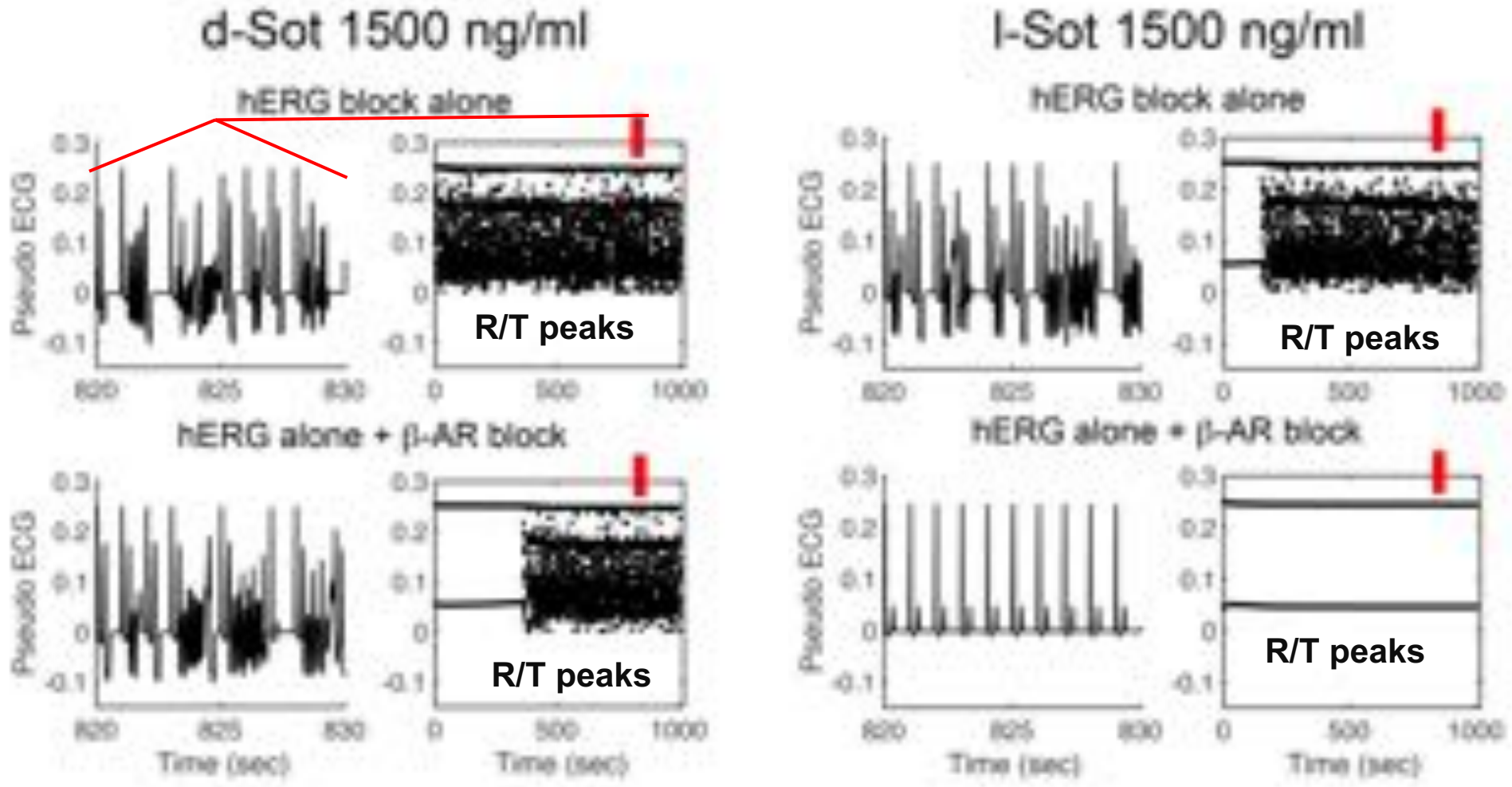
Dr. Pei-Chi Yang



Umbrella sampling MD simulation

Markov kinetic model

hERG – sotalol interactions: concentration dependence of pro-arrhtythmia



Using model 1: Based on ventricular myocyte data from Duff et al 1995

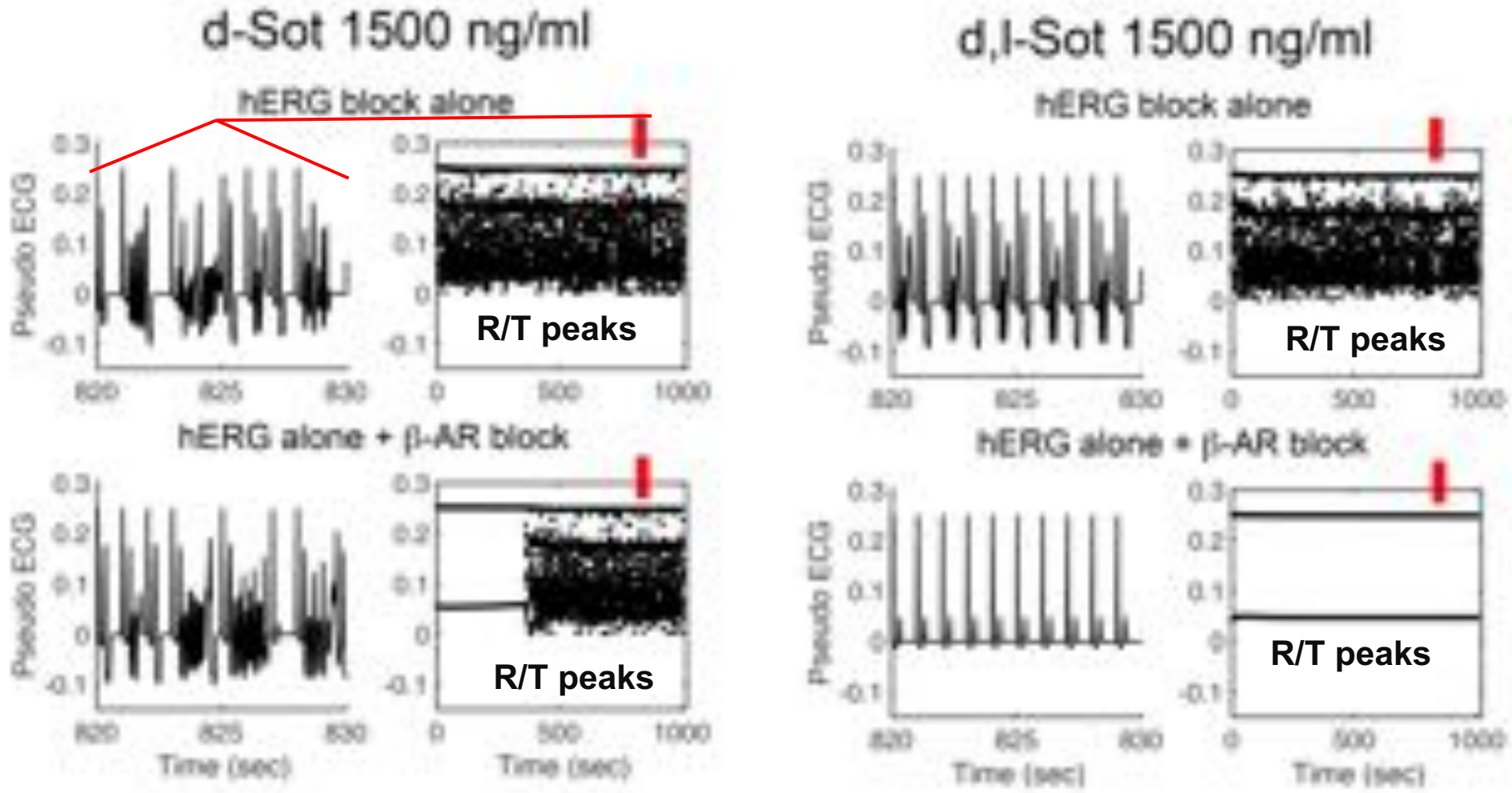
Dr. Pei-Chi Yang

Therapeutic plasma concentrations: 500-4000 ng/ml (1.84-14.7 μM)

Left: For d-sotalol EADs remain even with beta-block (bottom panels).

Right: For l- and dl-sotalol EADs disappear with beta-block (bottom panels).

hERG – sotalol interactions: concentration dependence of pro-arrhtythmia



Using model 1: Based on ventricular myocyte data from Duff et al 1995

Therapeutic plasma concentrations: 500-4000 ng/ml (1.84-14.7 μM)

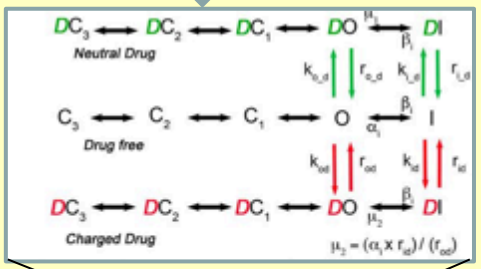
Left: For d-sotalol EADs remain even with beta-block (bottom panels).

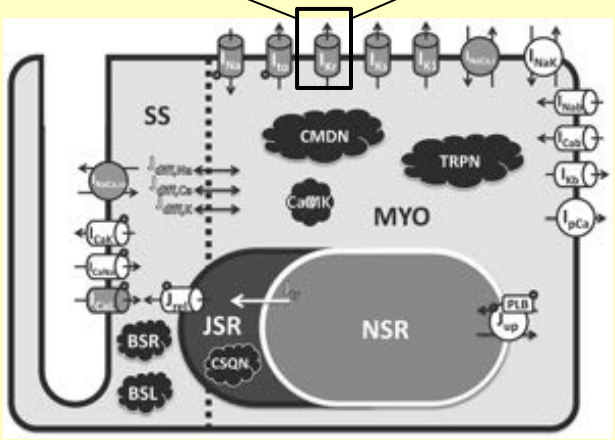
Right: For l- and dl-sotalol EADs disappear with beta-block (bottom panels).

Dr. Pei-Chi Yang

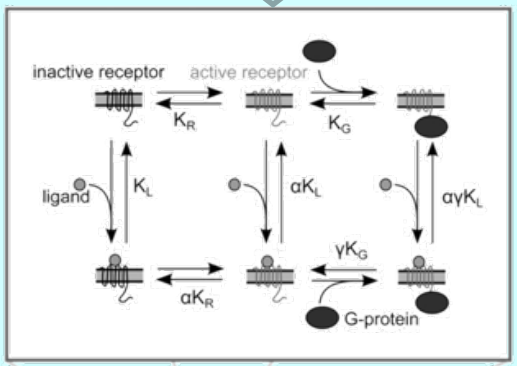
Next: combine with state-specific beta-blockade model

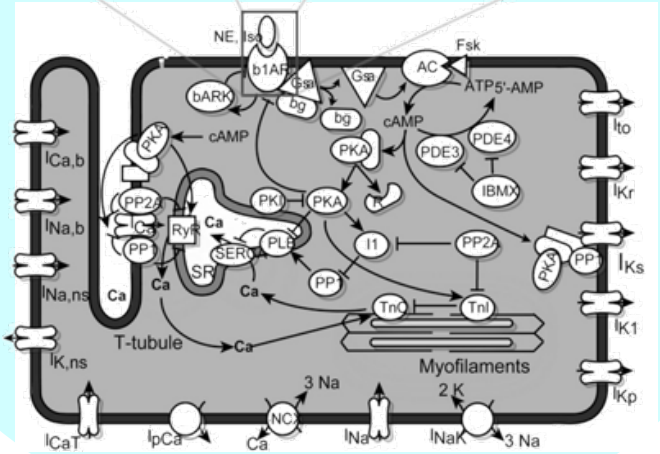
Drug – hERG MD affinity / kinetics data





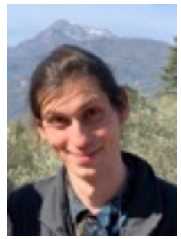
Drug – β_1AR MD affinity / kinetics data





O'Hara, T., Virág, L., Varró, A., & Rudy, Y. (2011). PLoS Comp. Biol., 7(5), e1002061.

Amanfu, R. K., & Saucerman, J. J. (2014). *Mol. Pharm.*, *86*(2), 222-230.



The combined model will consider not only state specific hERG blockade (left) but also state-specific beta-adrenergic receptor block (right).

Conclusions

- Molecular dynamics simulations on TACC Frontera and other HPC resources provided us atomic-detail structural and dynamic information for cardiac ion channel function and drug – channel interactions, crucial to understand molecular mechanisms of their effects on heart rhythm.

- Drug binding affinities and kinetics from atomistic molecular dynamics simulations was used as parameters for drug – channel functional models to predict emergent pro-arrhythmia triggers on cellular and tissue levels.

- Our prototype multi-scale safety pharmacology pipeline was able to correctly predict arrhythmogenic risks of two hERG blocking drugs, dofetilide and moxifloxacin, and stereospecific pro-arrhythmia proclivities of hERG and beta-blocking d/l-sotalol.

- Next: other drugs, sex hormones, consider channel gating modification (e.g., facilitation), multi-target block ($Na_V1.5$, $Ca_V1.2$, βAR etc.), mutagenesis (LQTS/SQTS, polymorphism)

Acknowledgments

University of California, Davis:

Prof. Colleen Clancy, Dr. Pei-Chi Yang, Dr. Kevin DeMarco, John Dawson, Dr. Parya Aghasafari, Mao-Tsuen Jeng, Gonzalo Hernandez, Brightany Li, Dr. Divya Kernik, Dr. Steffen Docken

Prof. Tim Lewis, Emily Meyer, Adam Rose, Dr. Stephanie Dodson

Prof. Vladimir Yarov-Yarovoy, Prof. Jon Sack, Prof. Kazuharu Furutani, Dr. Phuong T. Nguyen, Dr. Jan Mally, Aiyana Emigh & other lab members

Prof. Heike Wulff, Dr. Vikrant Singh, Dr. Brandon Brown & other lab members

Prof. Luis Fernando Santana, Prof. Crystal Ripplinger, Prof. Ele Grandi

American River College: Prof. Slava Bekker

University of Calgary (Canada): **Prof. Sergei Y. Noskov** & his lab members

TACC Frontera team

Computing:, TACC (Frontera & Longhorn), XSEDE, Oracle for research, PSC (Anton 2), NCSA (Blue Waters).

$$$ Funding: UC Davis, NIH NHLBI, NIH Common Fund, American Heart Association.

Thank you!!!