

The Cardiac MPS: Collaboration with Simula and Future Applications

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Grant/Research Support
- Consulting Fees/Honoraria
- Major Stock Shareholder/Equity
- Royalty Income
- Ownership/Founder
- Intellectual Property Rights
- Other Financial Benefit

Company



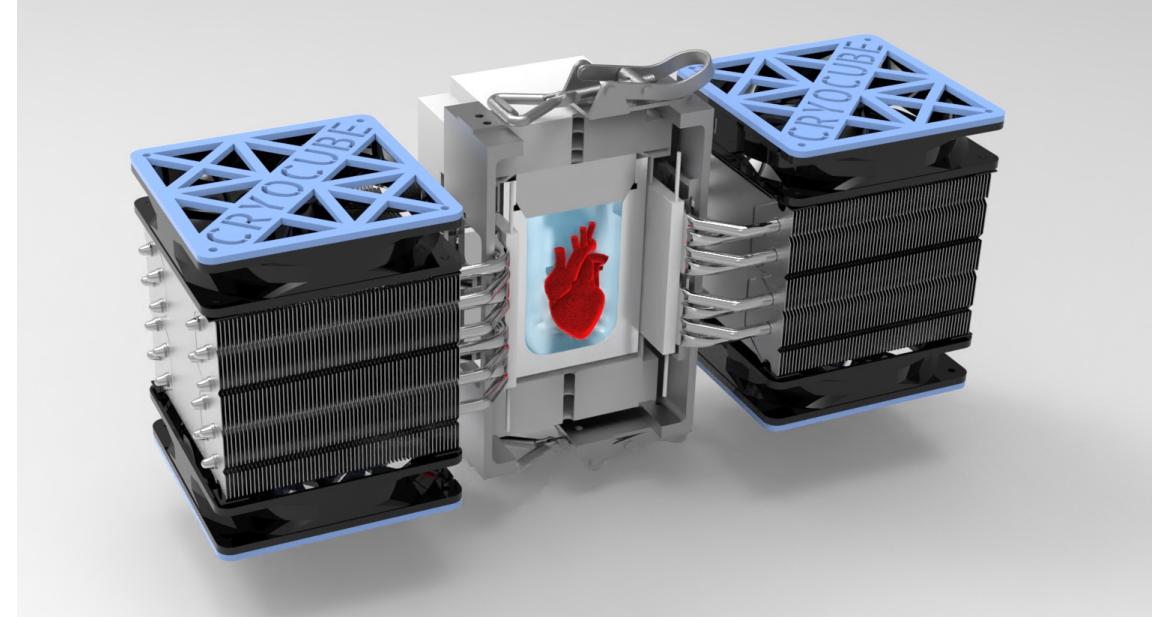
- None - Federal Only
- Abbott Vascular, Valitor
- CaridoRegenX, Valitor, Organos
- UCB
- CaridoRegenX, Valitor, Organos
- CaridoRegenX, Valitor, Organos
- Speaking Honoraria

Microphysiological Systems Applications

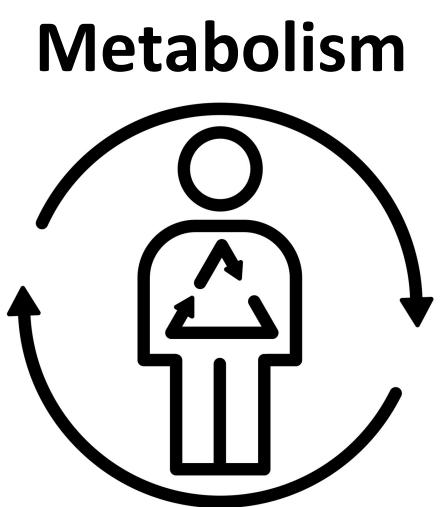
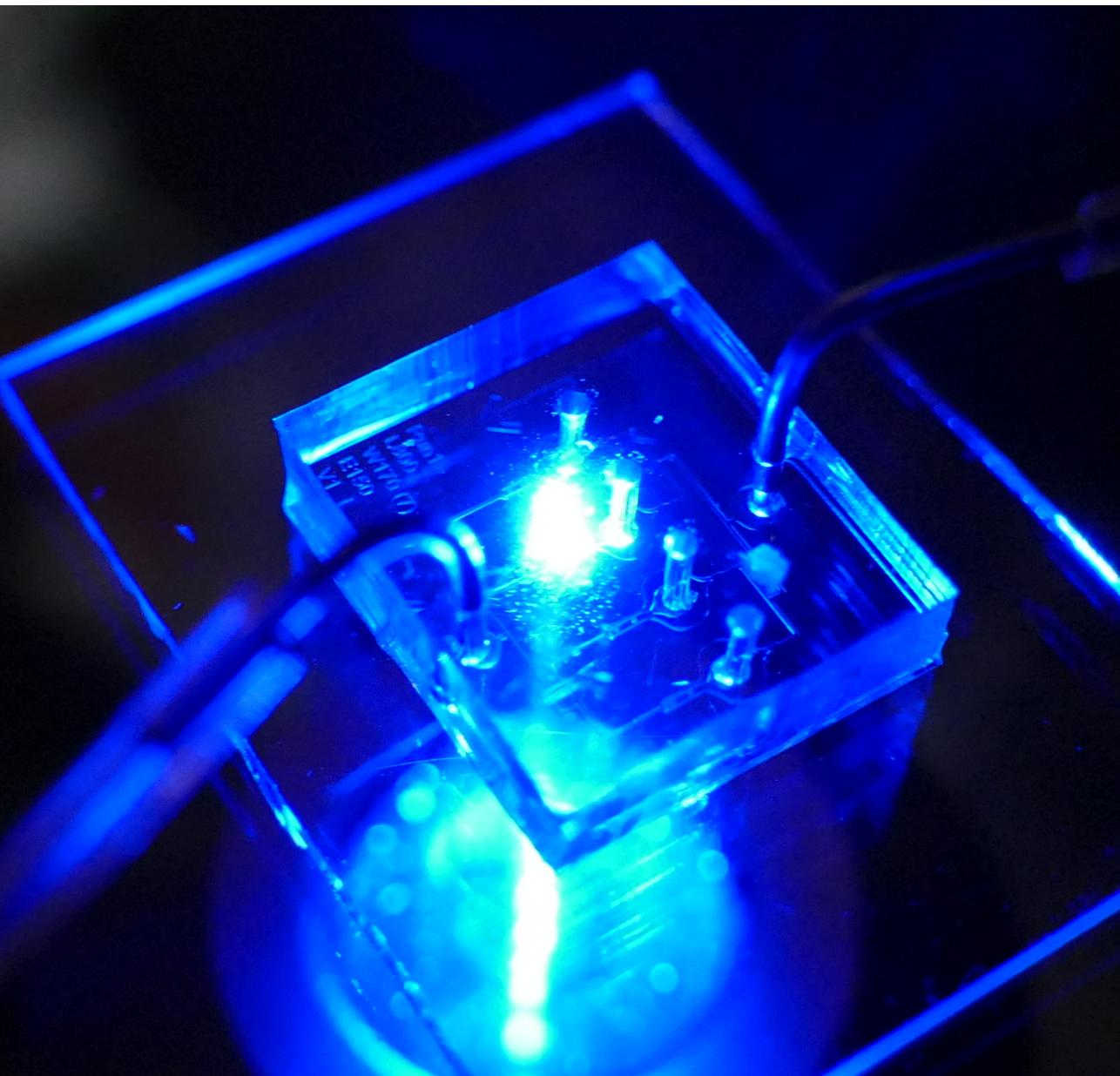
Safety Pharmacology



Organ Storage & Transport



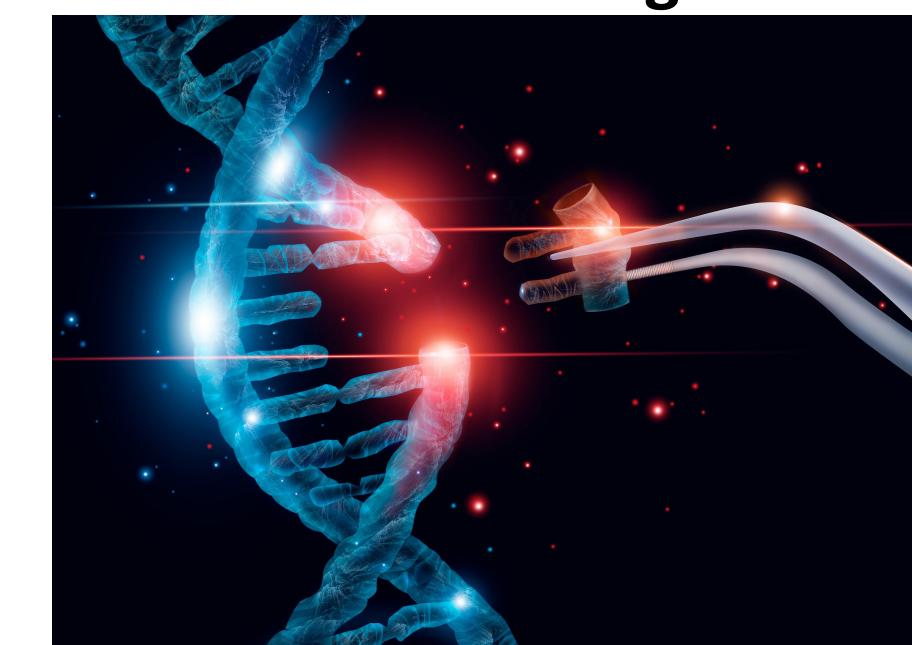
Countermeasures & Threat Detection



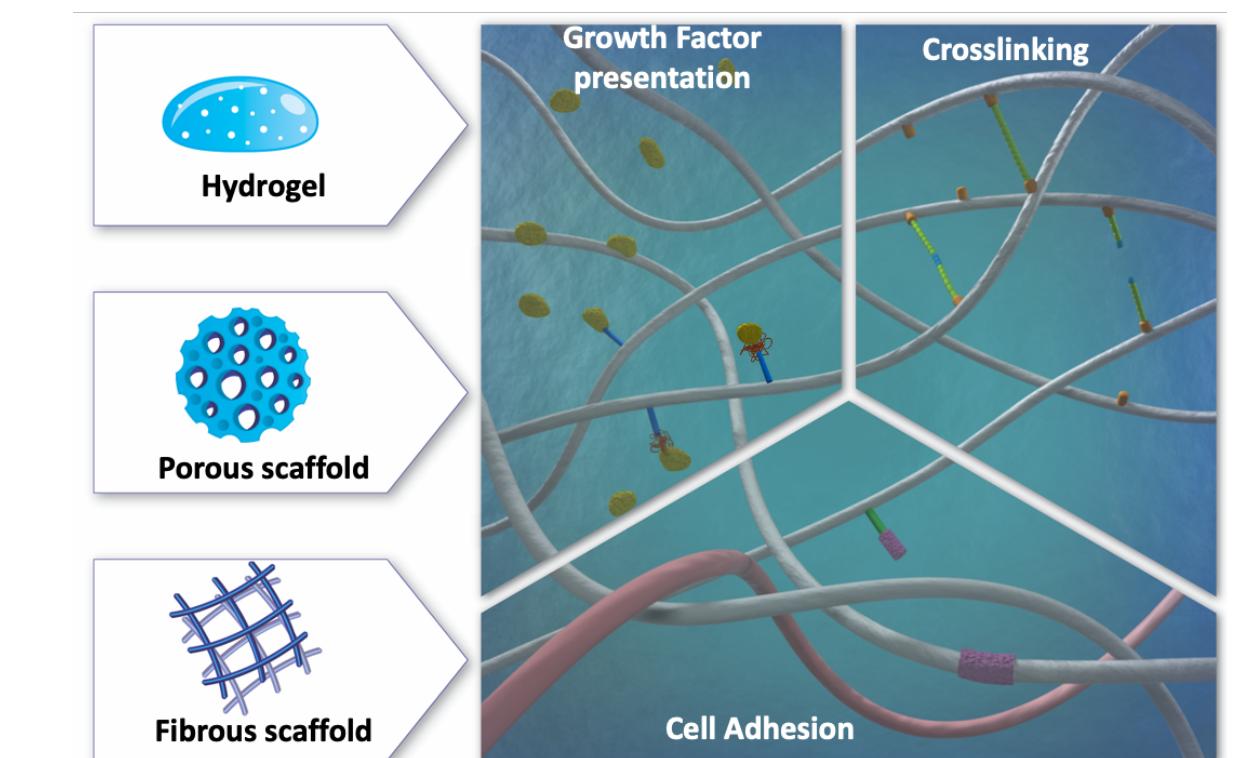
Toxins



Gene Editing



Biomaterials Therapy



Drug-induced Arrhythmias are a Major Safety Concern



All drugs screened for proarrhythmia risk prior to first-in-human trials



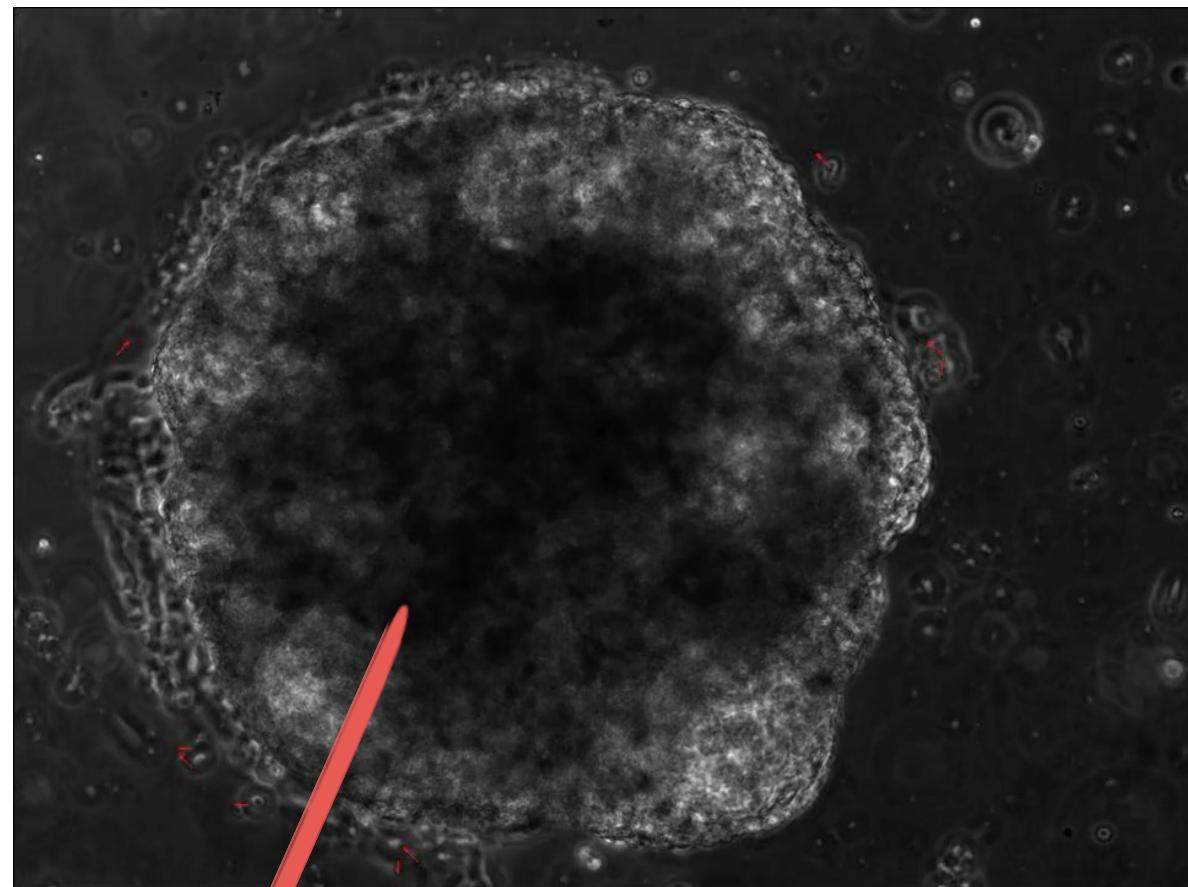
Torsade de Pointes (TdP)

State-of-the-Art Practice Not Predictive of Drug Risk

Heart Disease is a **Tissue** Level Disease

State-of-the-Art Practice (2D plate biology) Not Predictive of Drug Risk

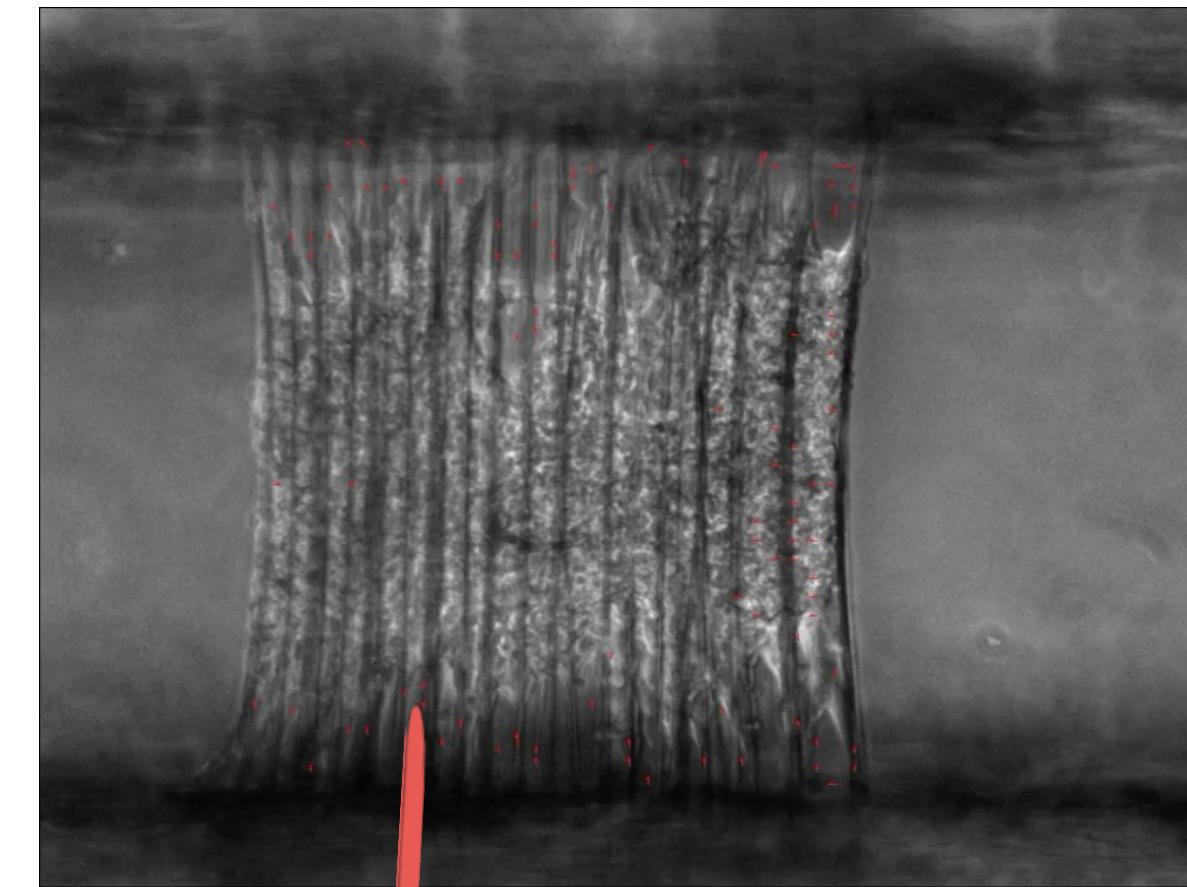
Heart Organoid



Ma, Z., et al., *Nature Comm.*, 14, 6:7413 (2015)

Drug Screening on fetal development

3D Cardiac Tissue

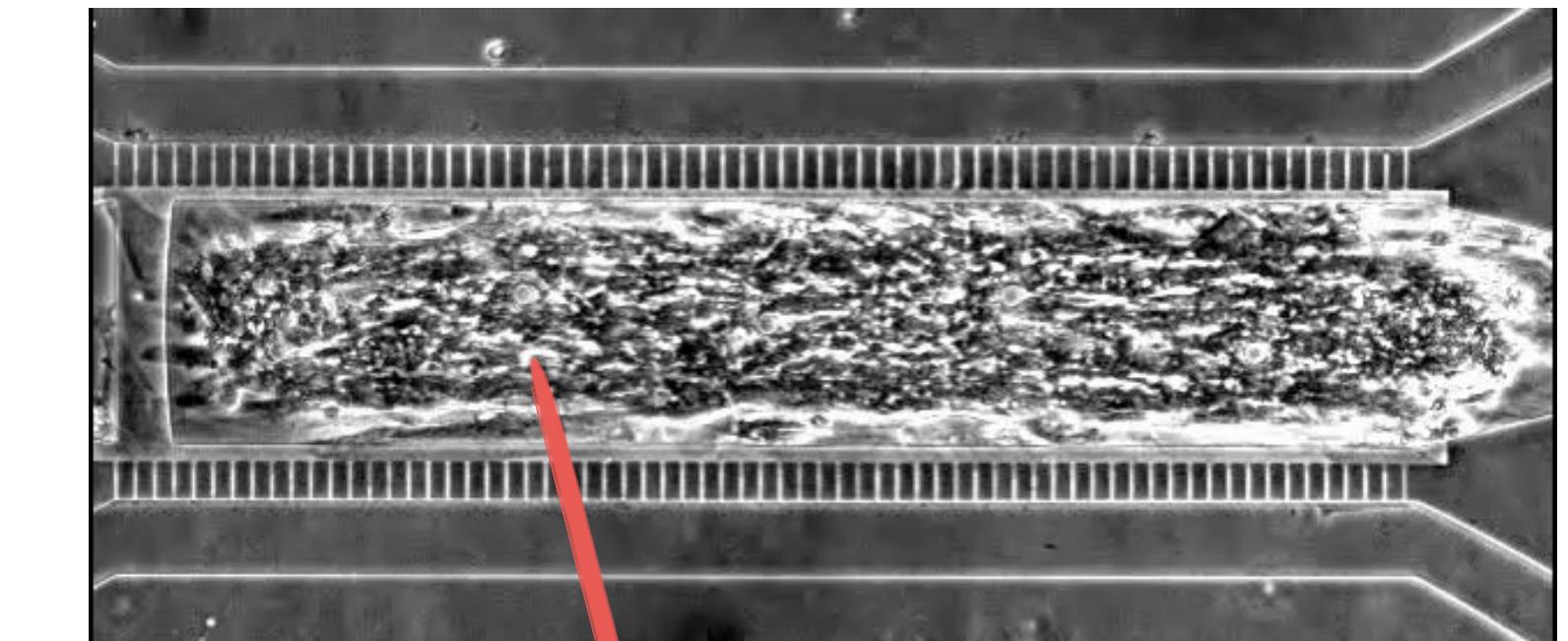


Ma, Z. et al., *Biomaterials* 35(5), 1367 (2014)

Ma, Z., & Huebsch, N., et al.,
Nature Biomedical Engineering, 2, 955-967 (2018)

Genetic Disease Modeling

Cardiac MPS Tissue Chip

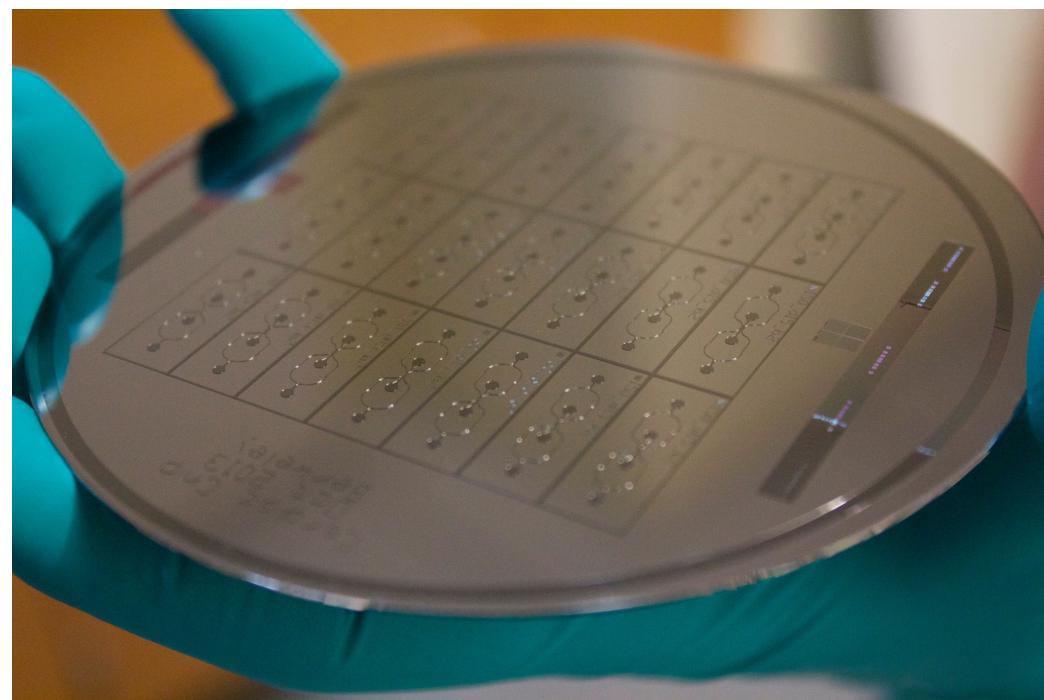


Charrez, B., et al. *Clin. Transl. Sci.* 14, 1155 (2021)

Mathur, A., Loskill, P., et al., *Scientific Reports*, 5:8883 (2015)

Safety pharmacology and 'clinical trials'

Microphysiological Systems

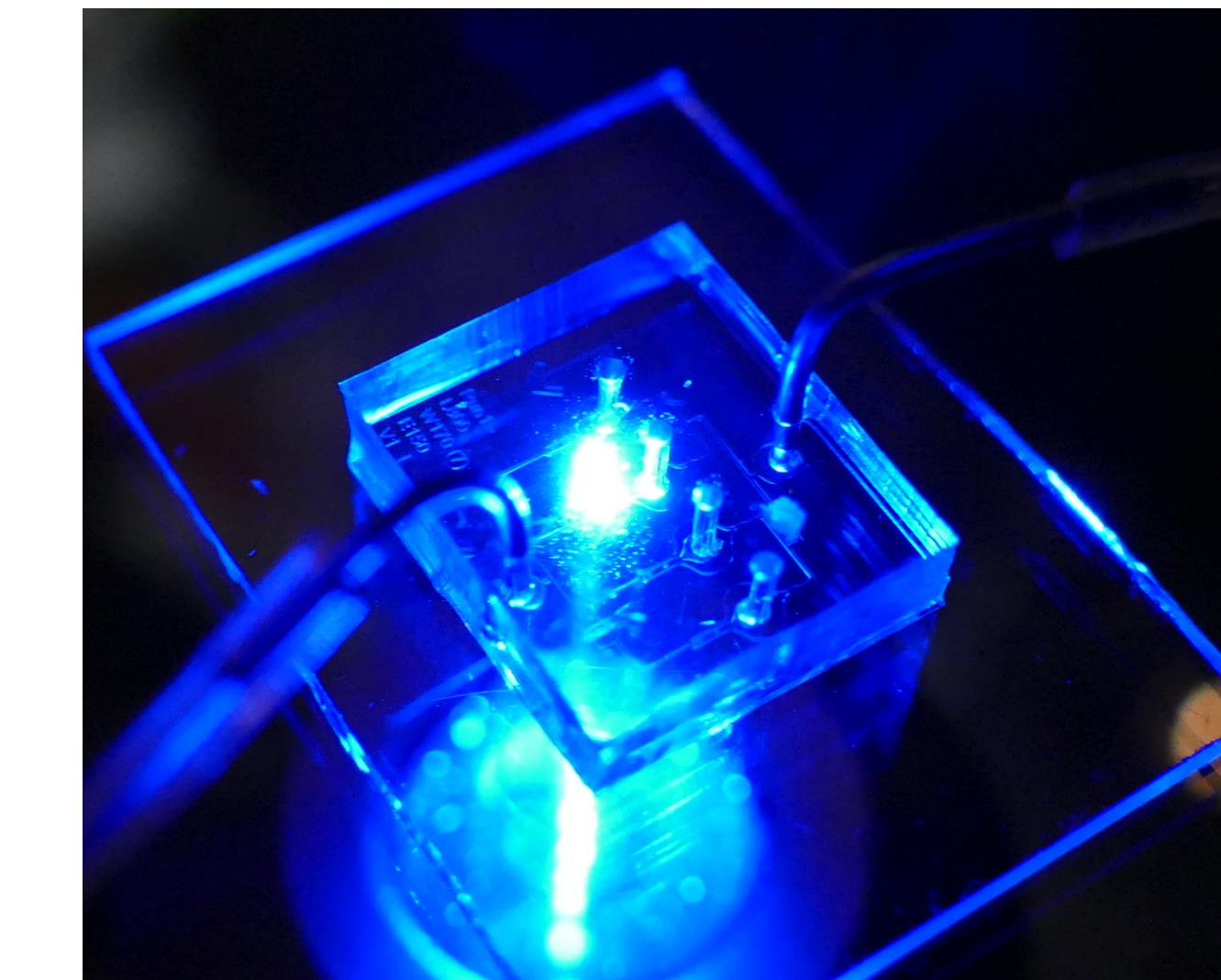


**Microfabrication
Technology**

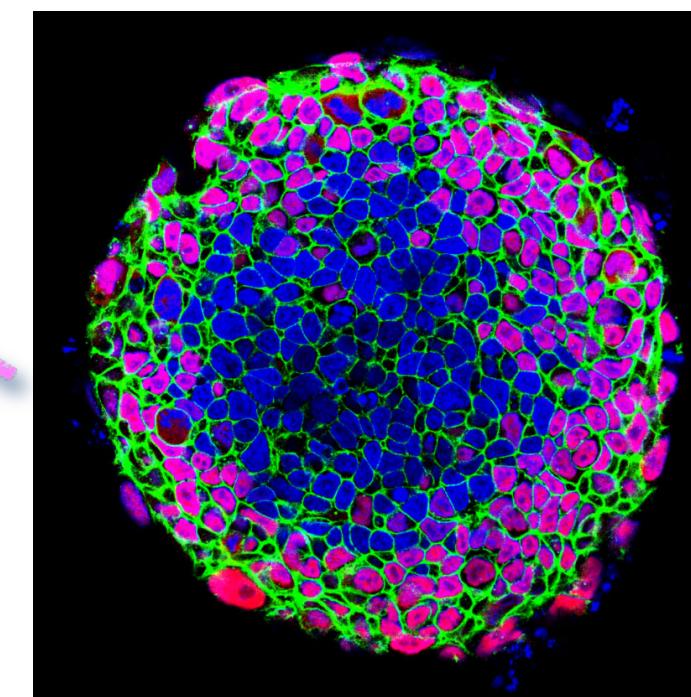
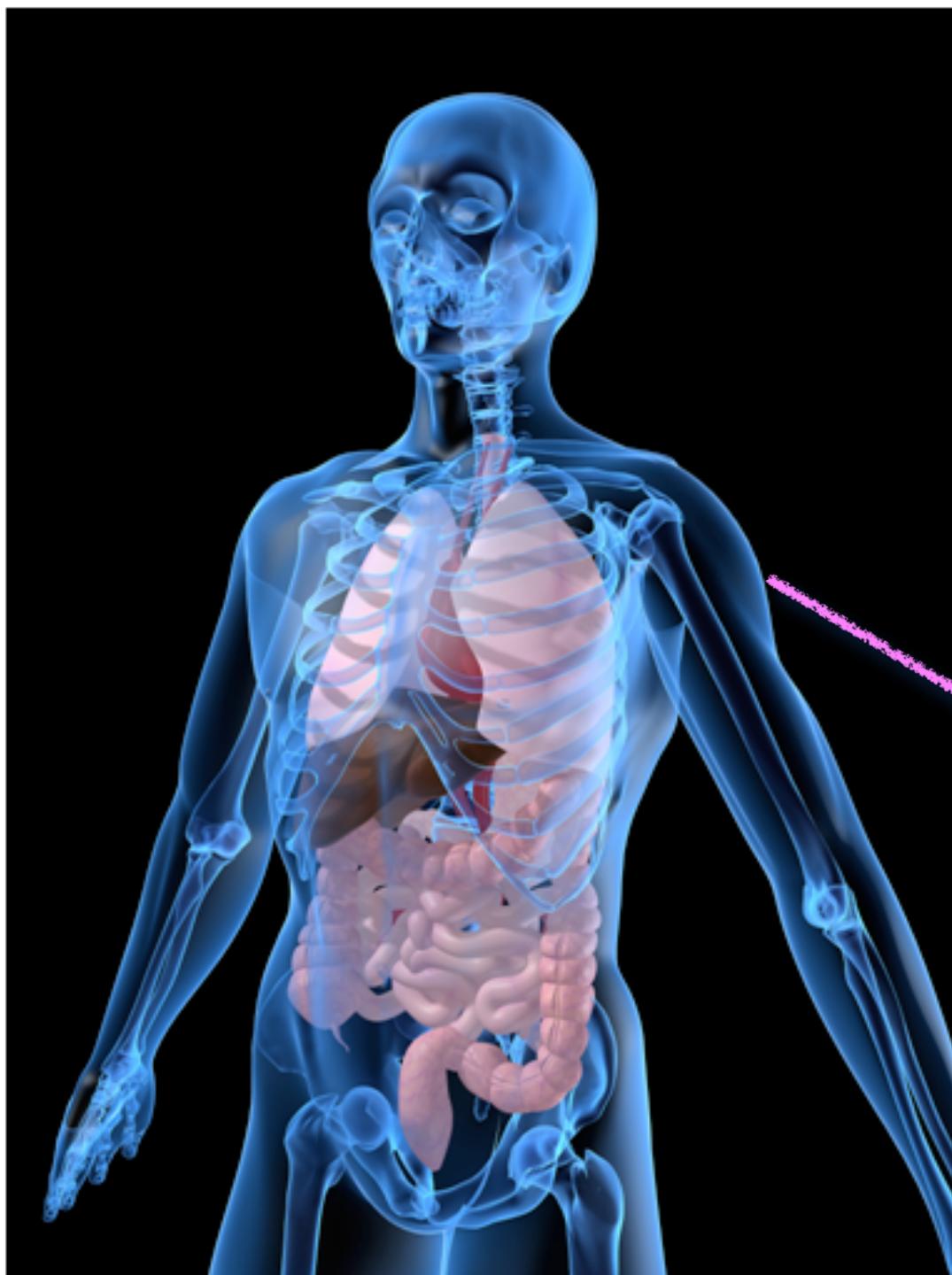
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Microphysiological Systems (MPS)



**Human induced pluripotent
stem cells (hiPSC)**



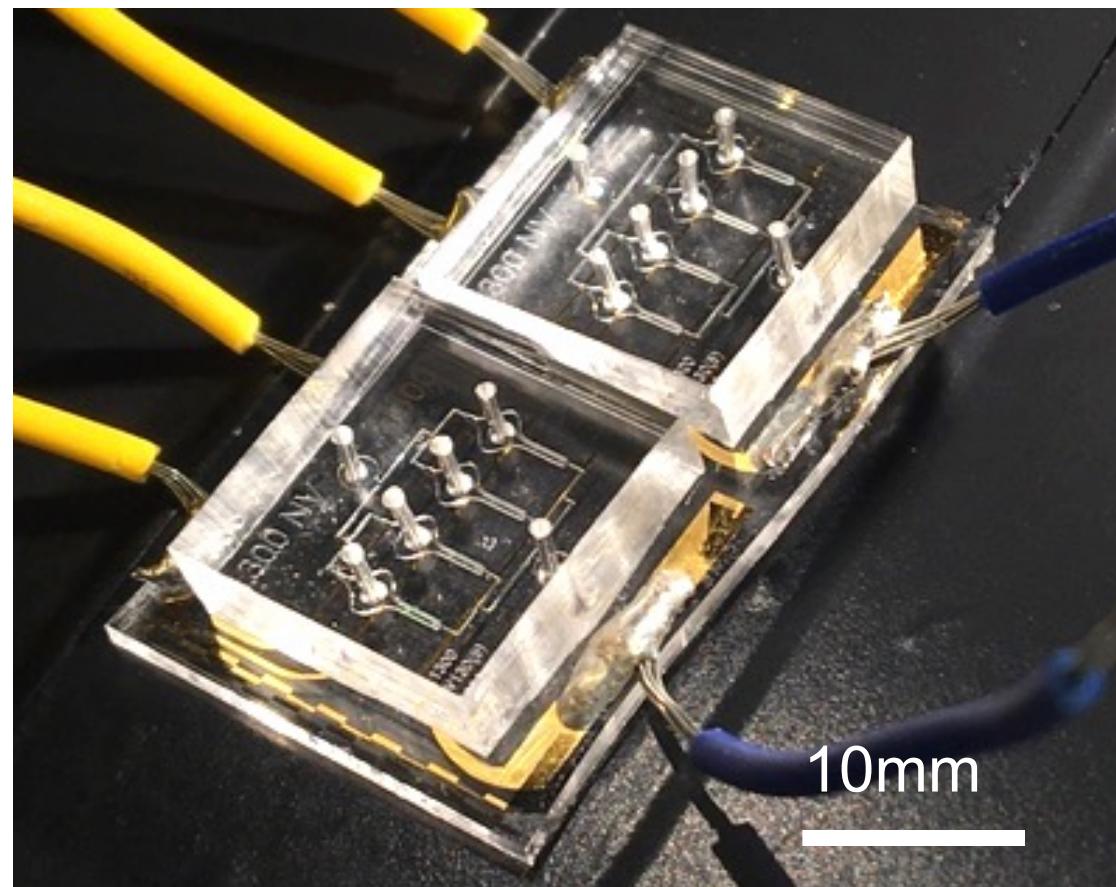
**Carries patient's genetics
healthy or diseased**

- **Biofabricated tissue**
- **Clinically relevant**
- **Phenotypic tissue model**
- **Population-based**

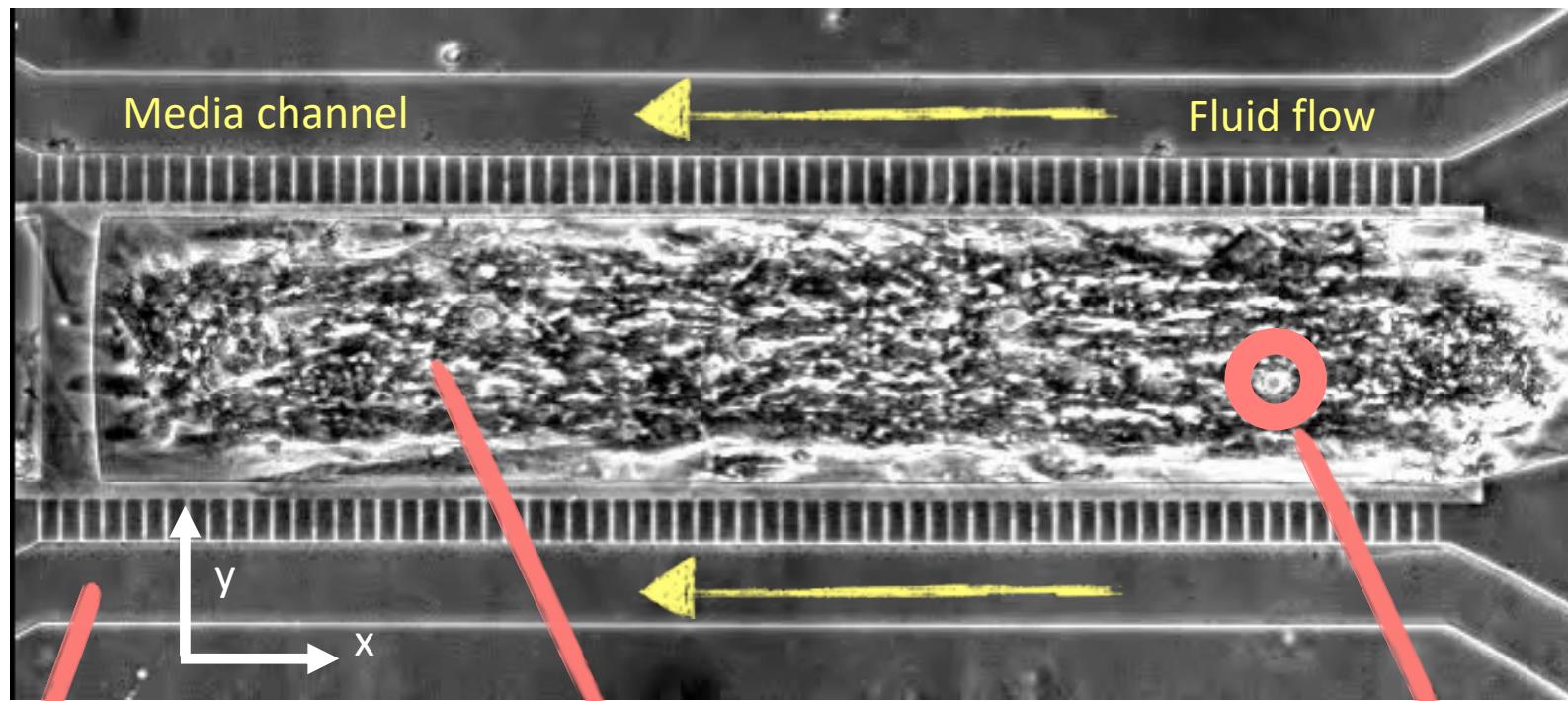
Cardiac Micropysiological System - Heart Micromuscle

Multiplexed cardiac MPS

Multiplexed tissue chambers per device
Integrated pacing electrodes



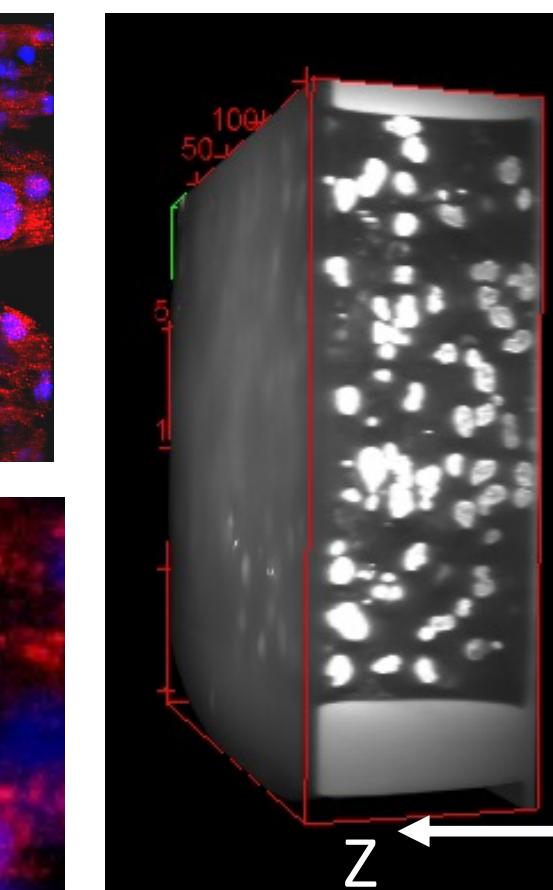
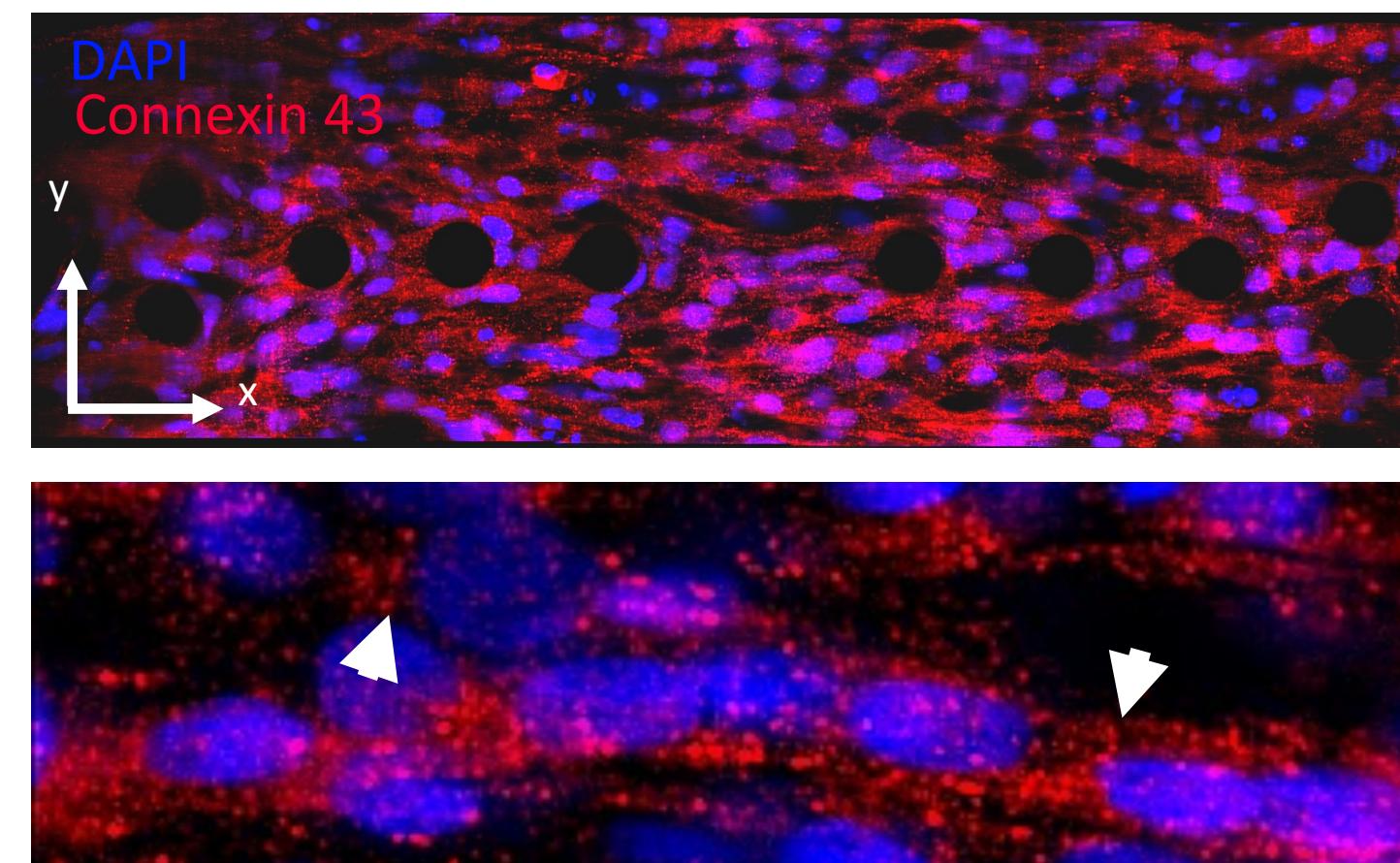
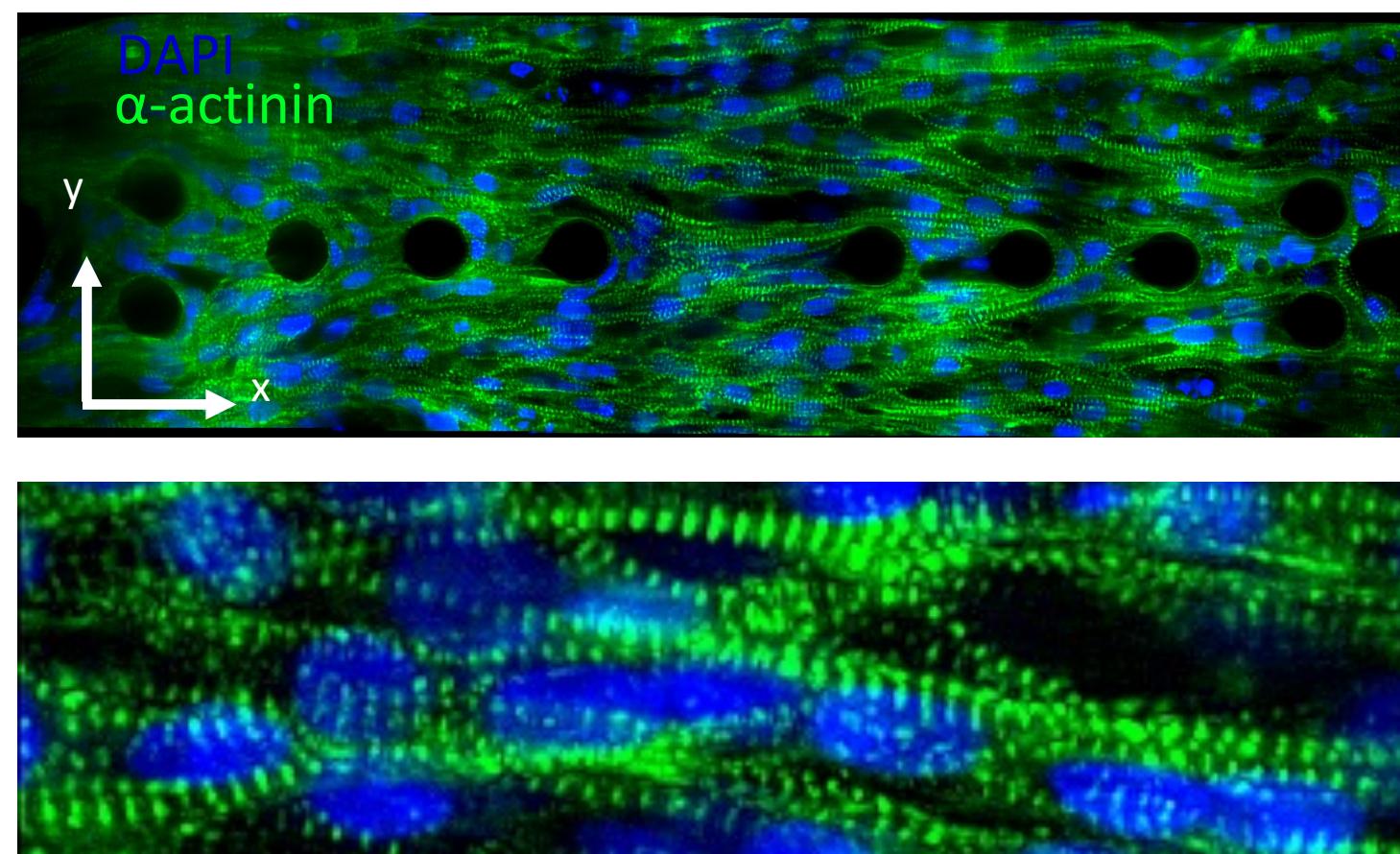
3D cardiac microtissues



Biomarker
Mass spectrometry

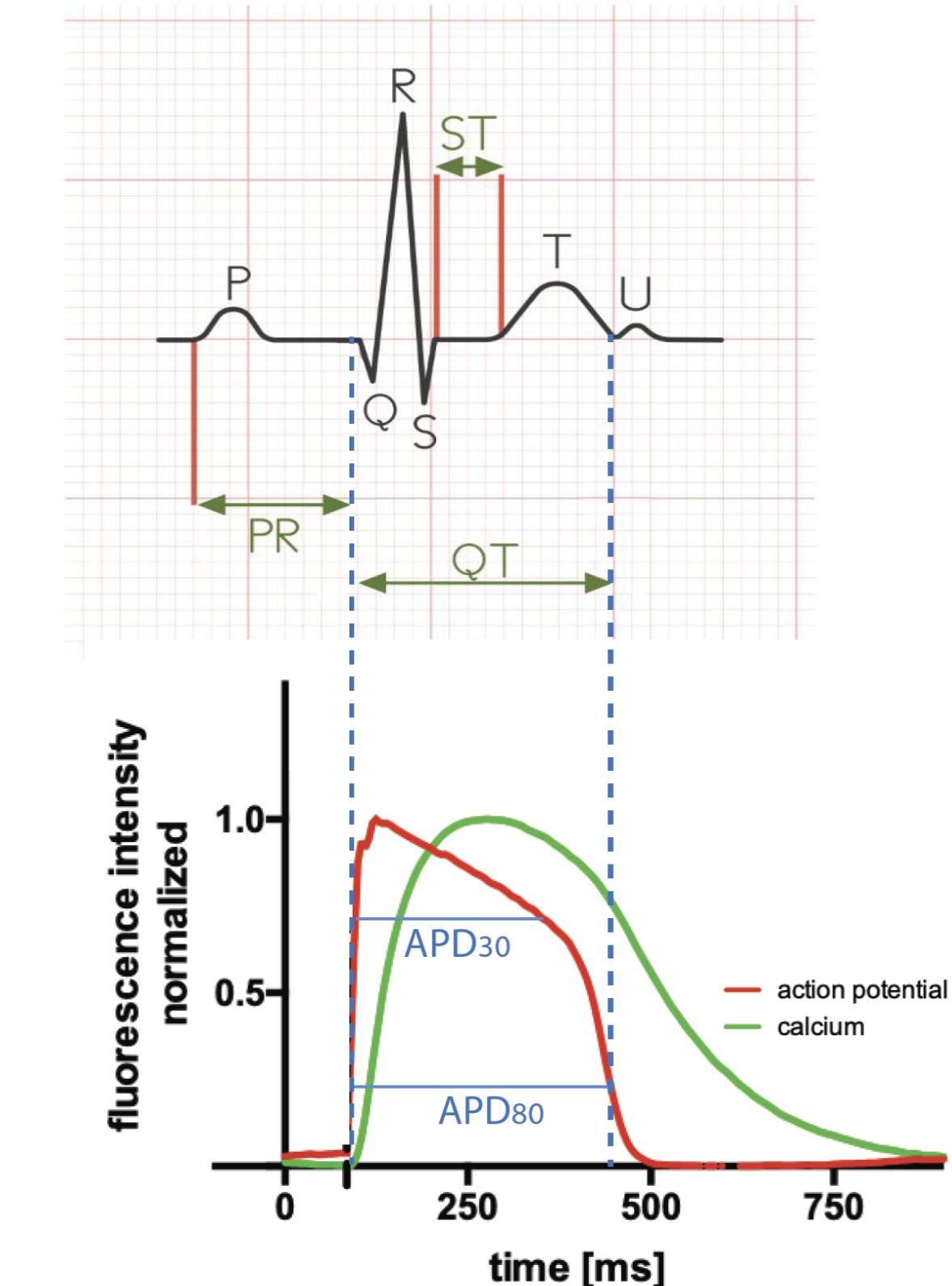
Reporter cell lines for
real-time live cell imaging

Flexible pillars for
force measurement



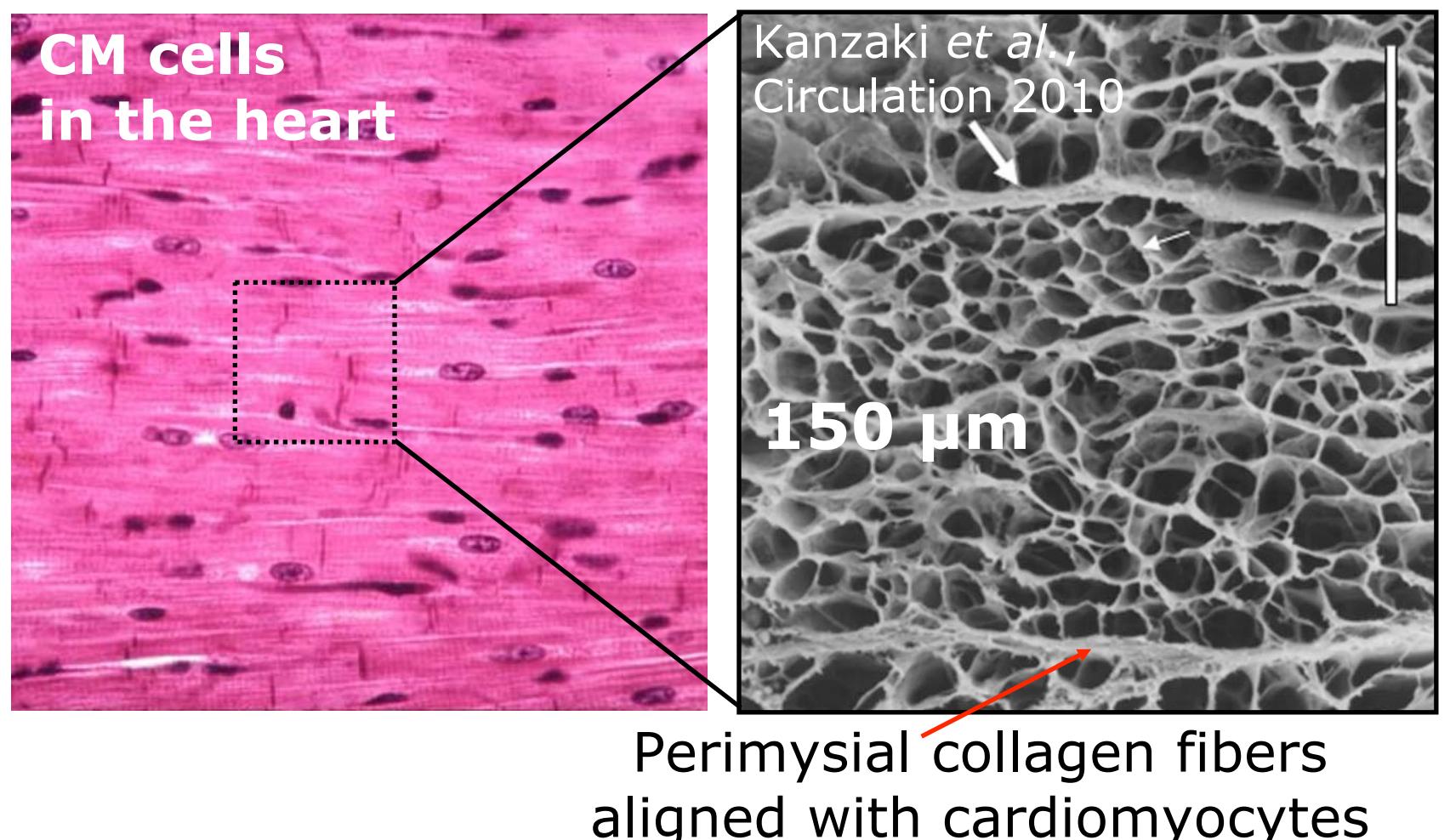
Metrics

- Spontaneous and externally paced beating
- Voltage and calcium transients
- Beat rate, action potential duration (QT proxy), beat shape metrics, arrhythmic events



Cardiac Microphysiological System

What is the minimal tissue or organoid size to assist in drug discovery?



Cell channel mimics perimysial fiber spacing

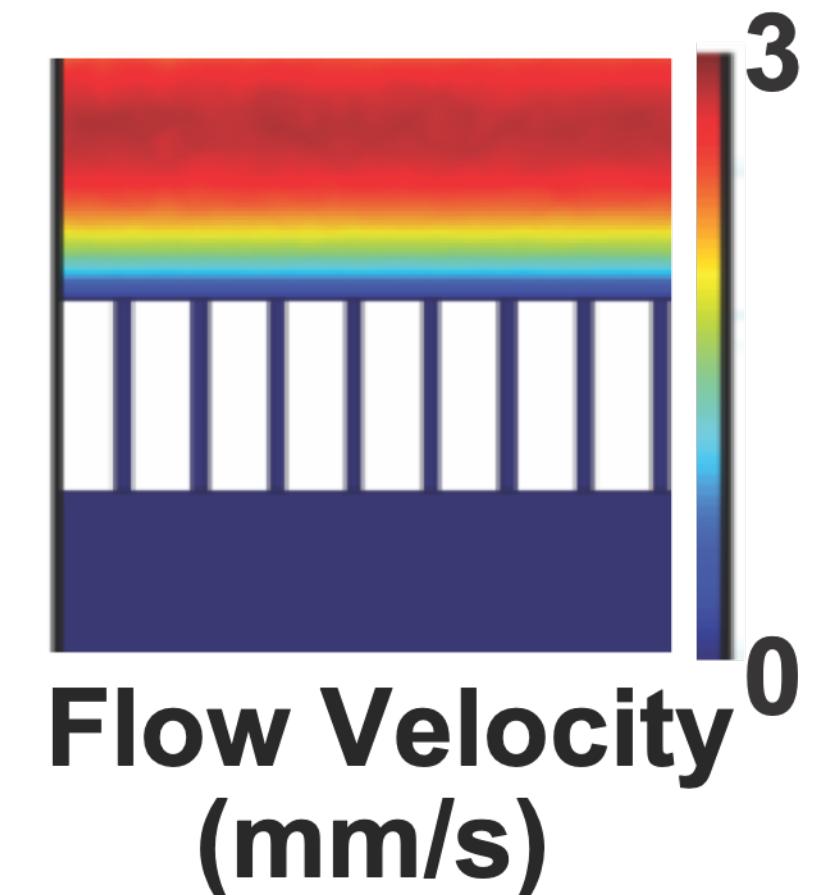
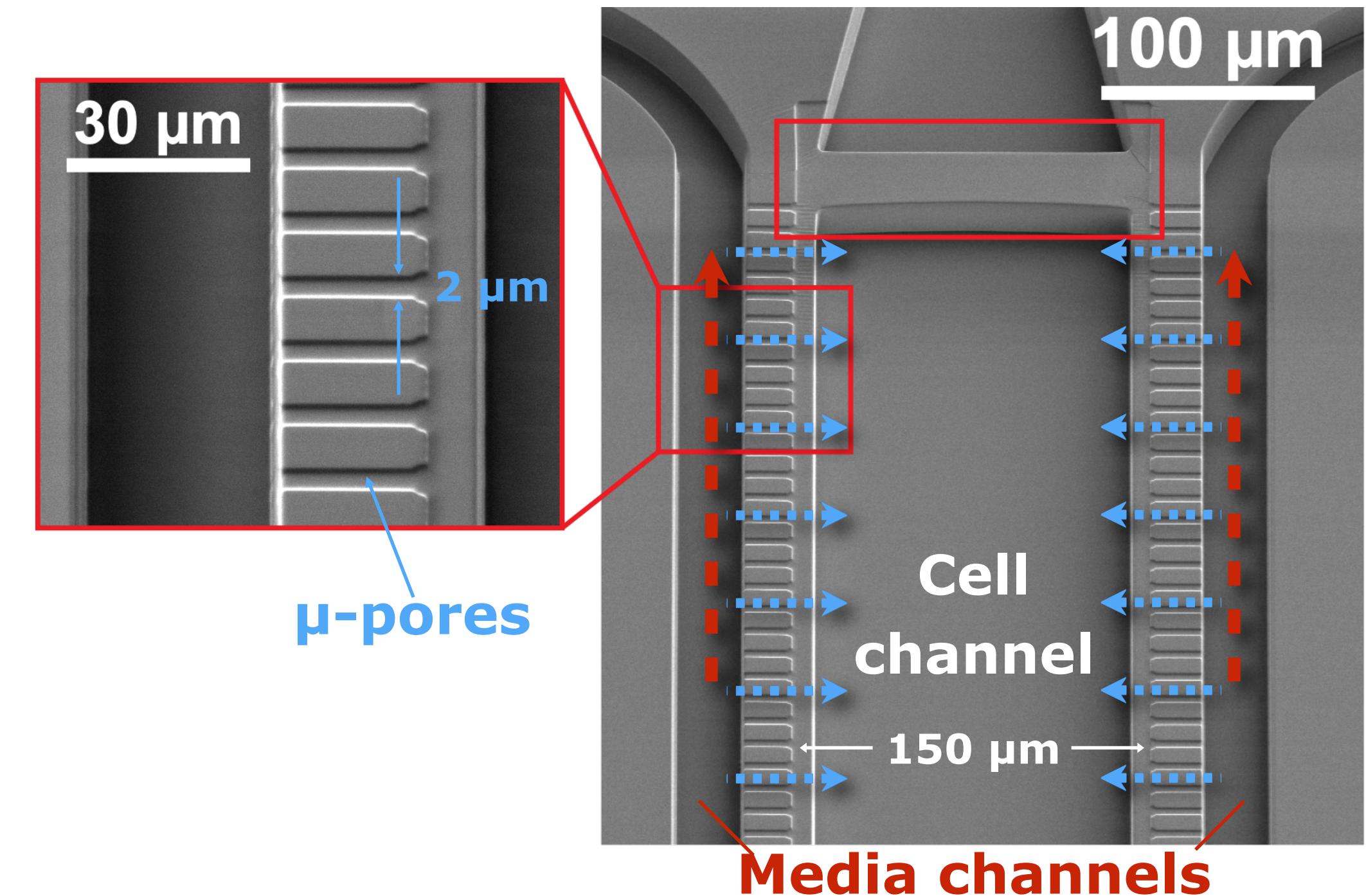
Separate media and cell channels

μ -pores between media and cell channels - “endothelial barrier”

Convective transport in media channels

Diffusive transport to tissue (no shear)

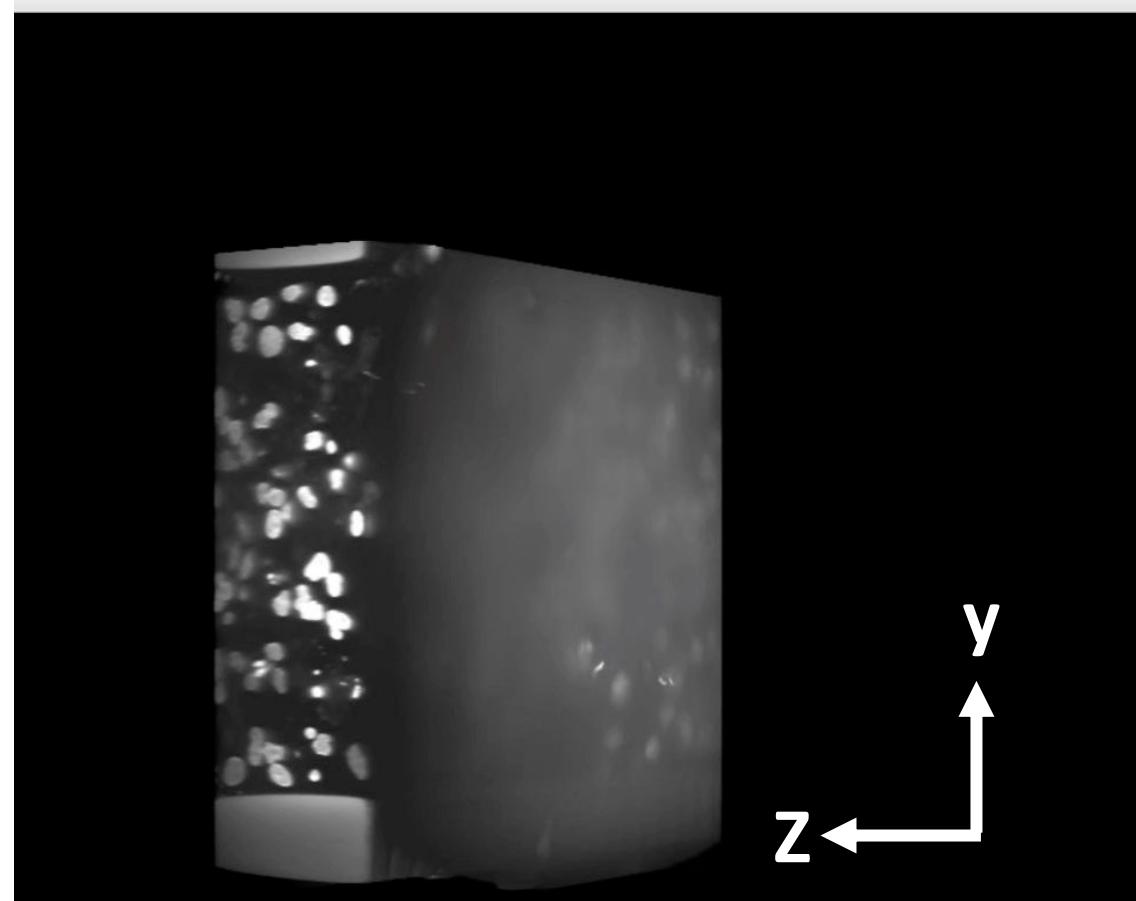
Physiologically relevant tissue to media volumes



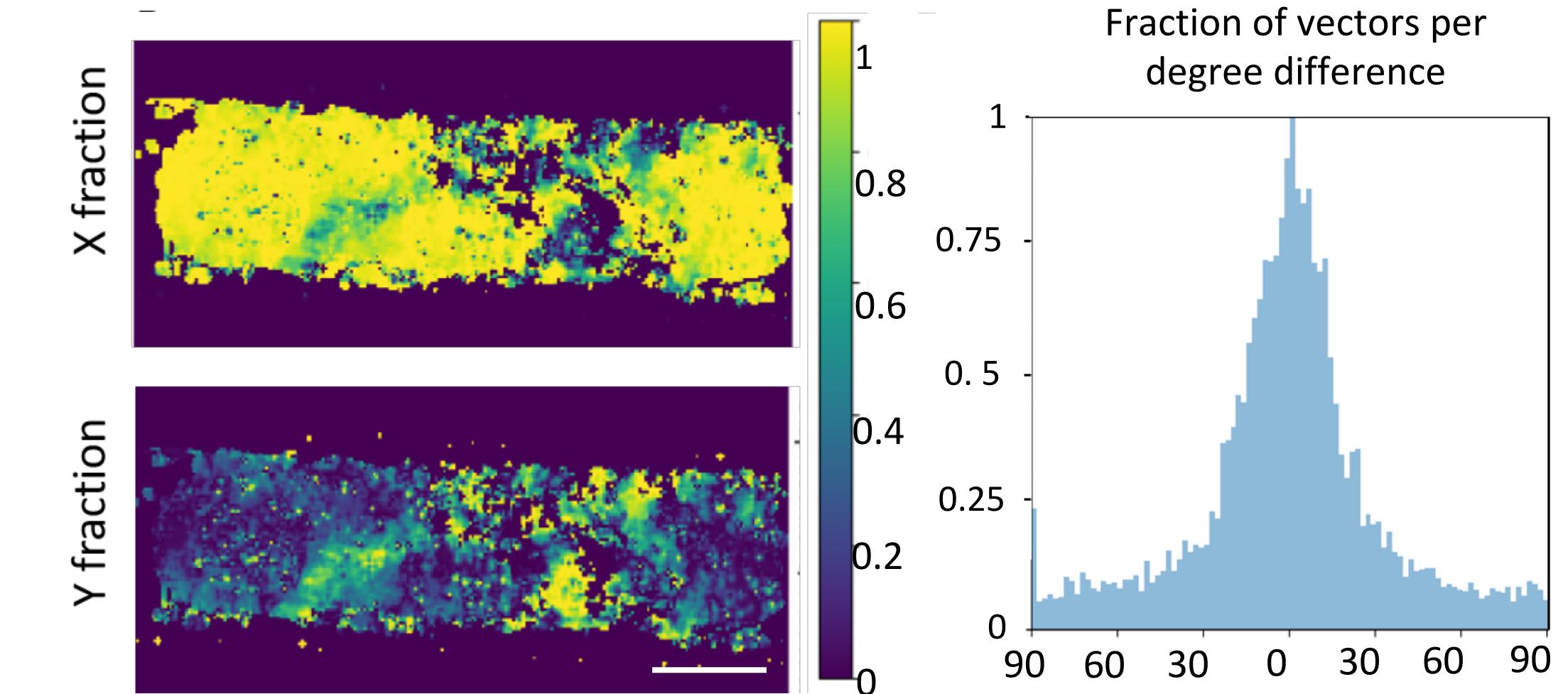
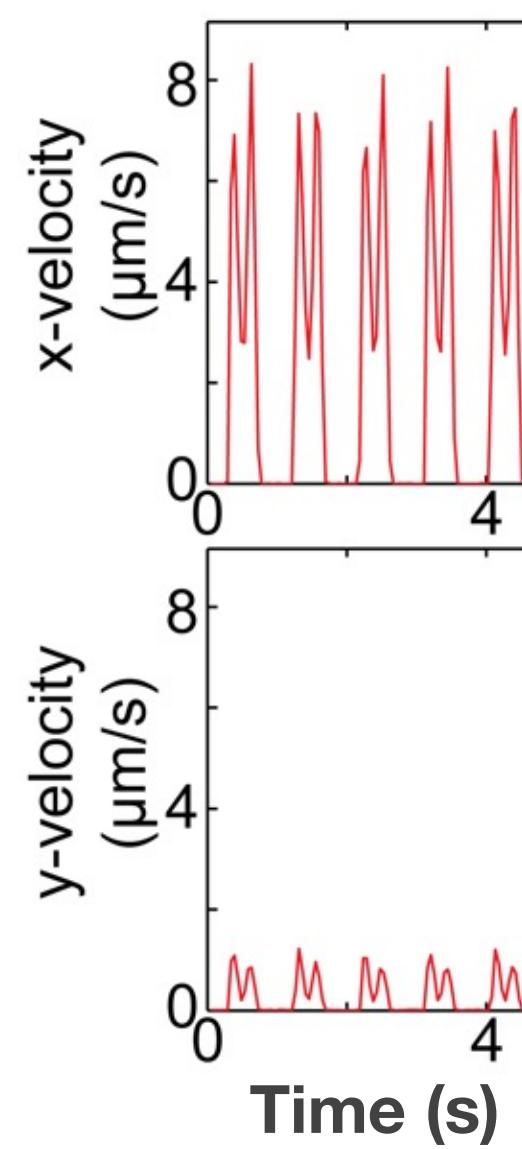
Physiological Platform for Human Myocardium-on-a-Chip



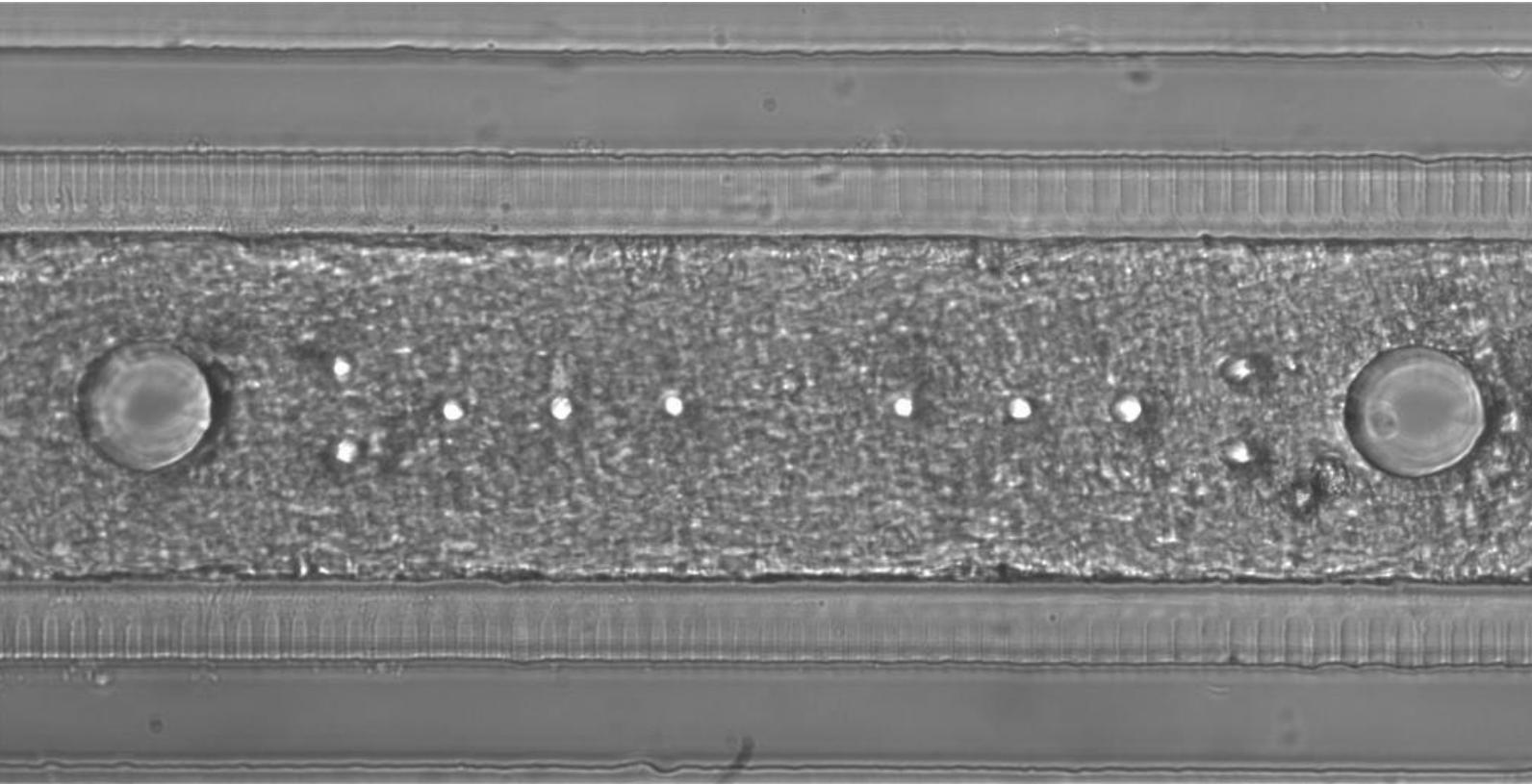
How Important is Structure?



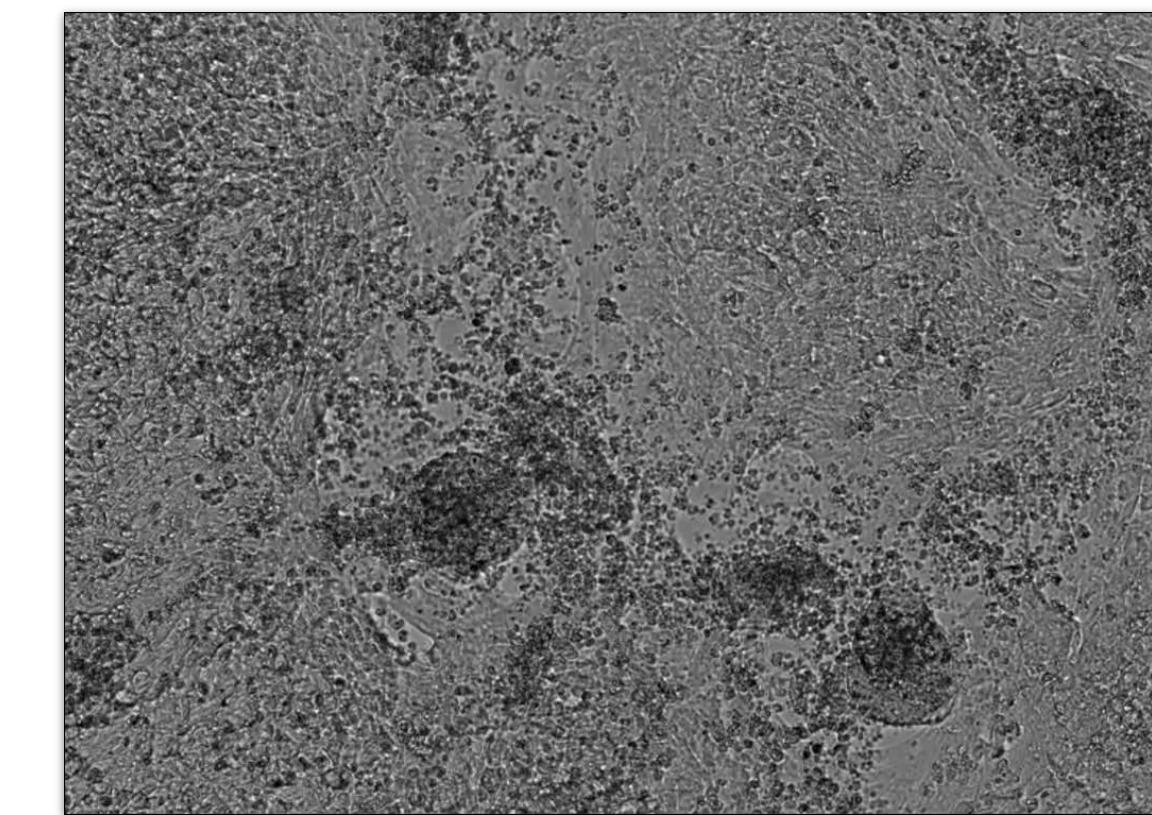
Promotes cell maturity



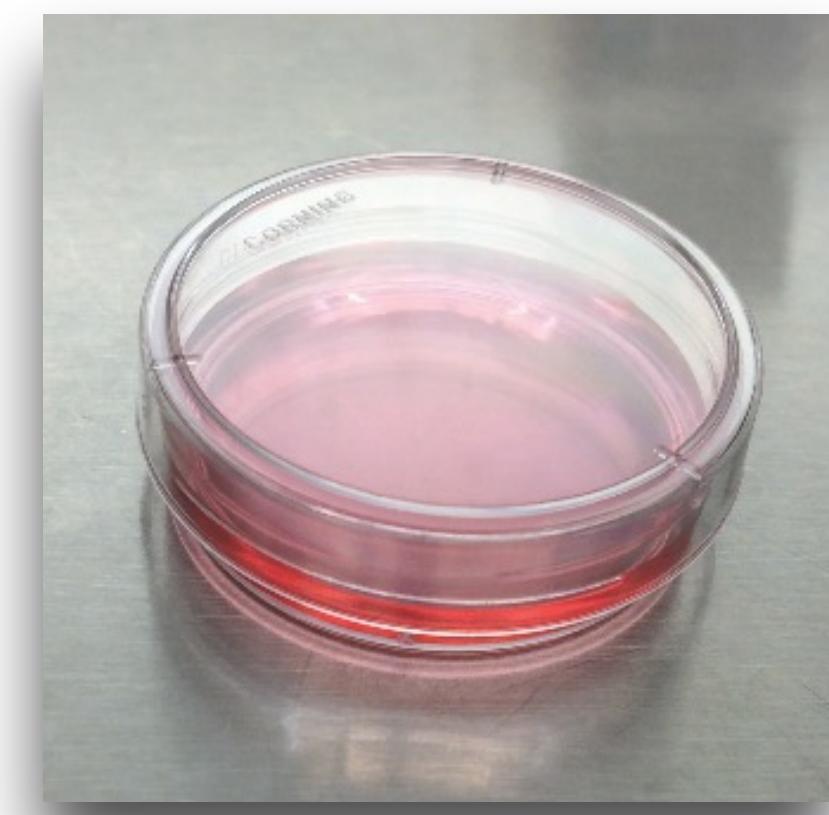
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↑
→ x



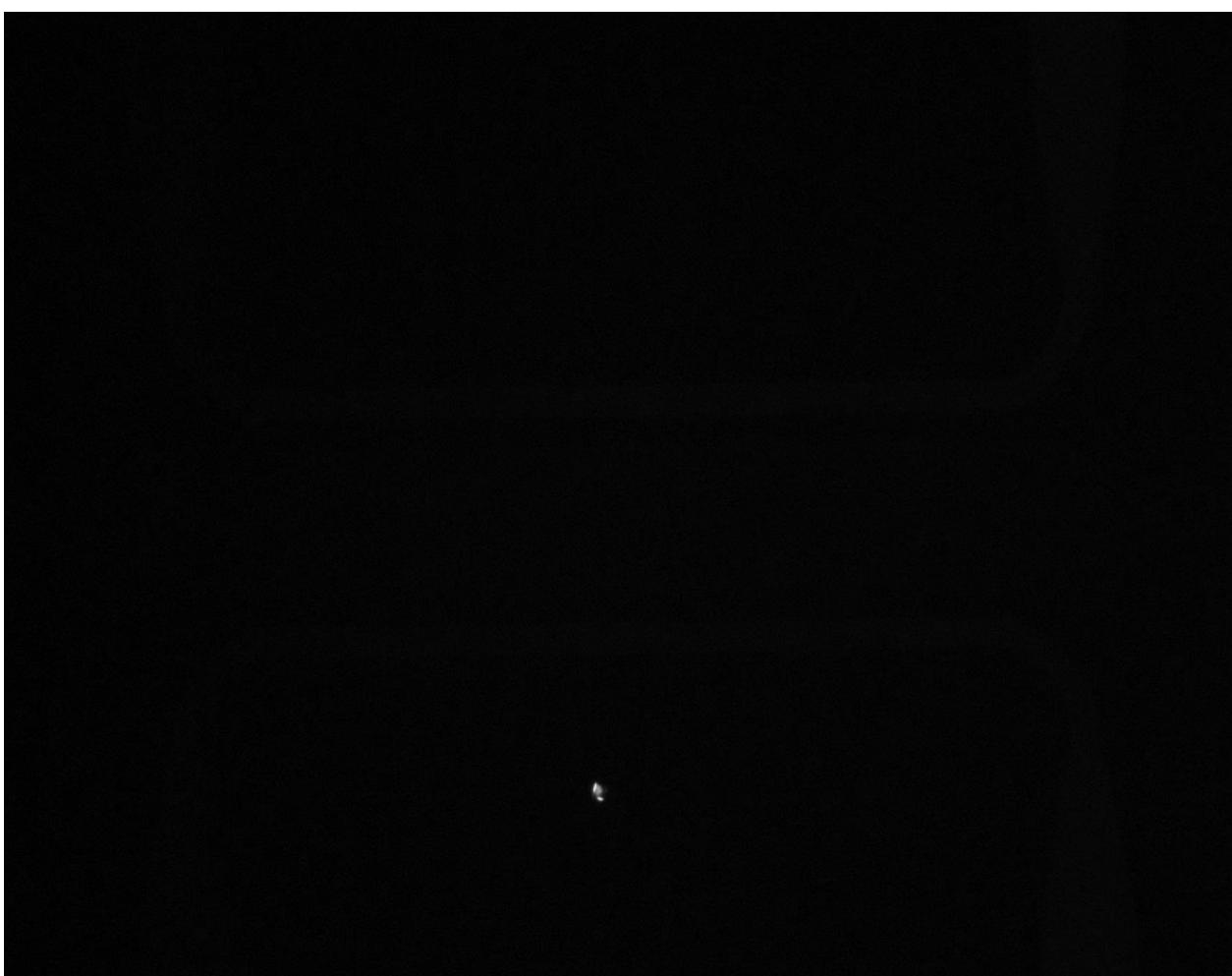
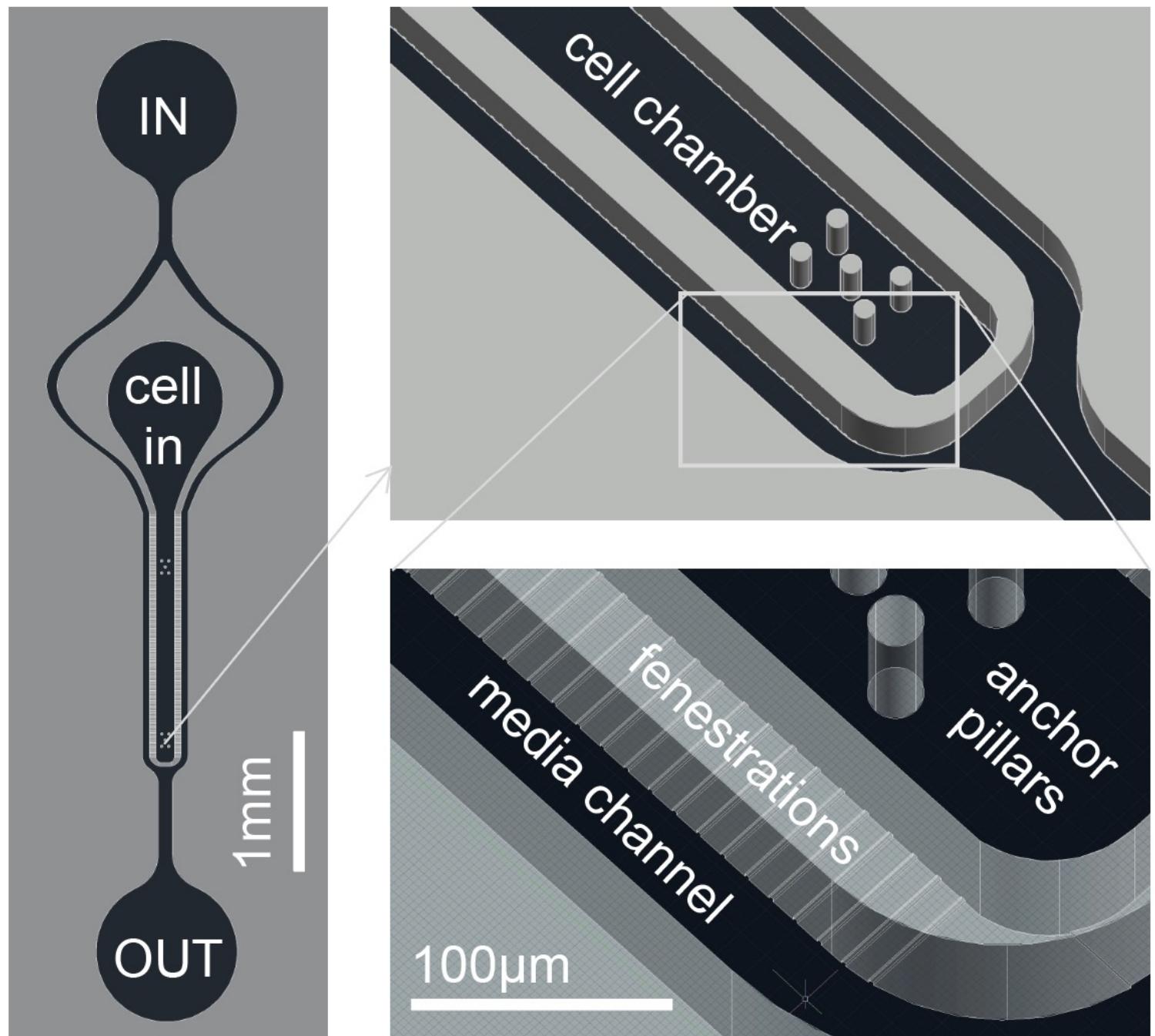
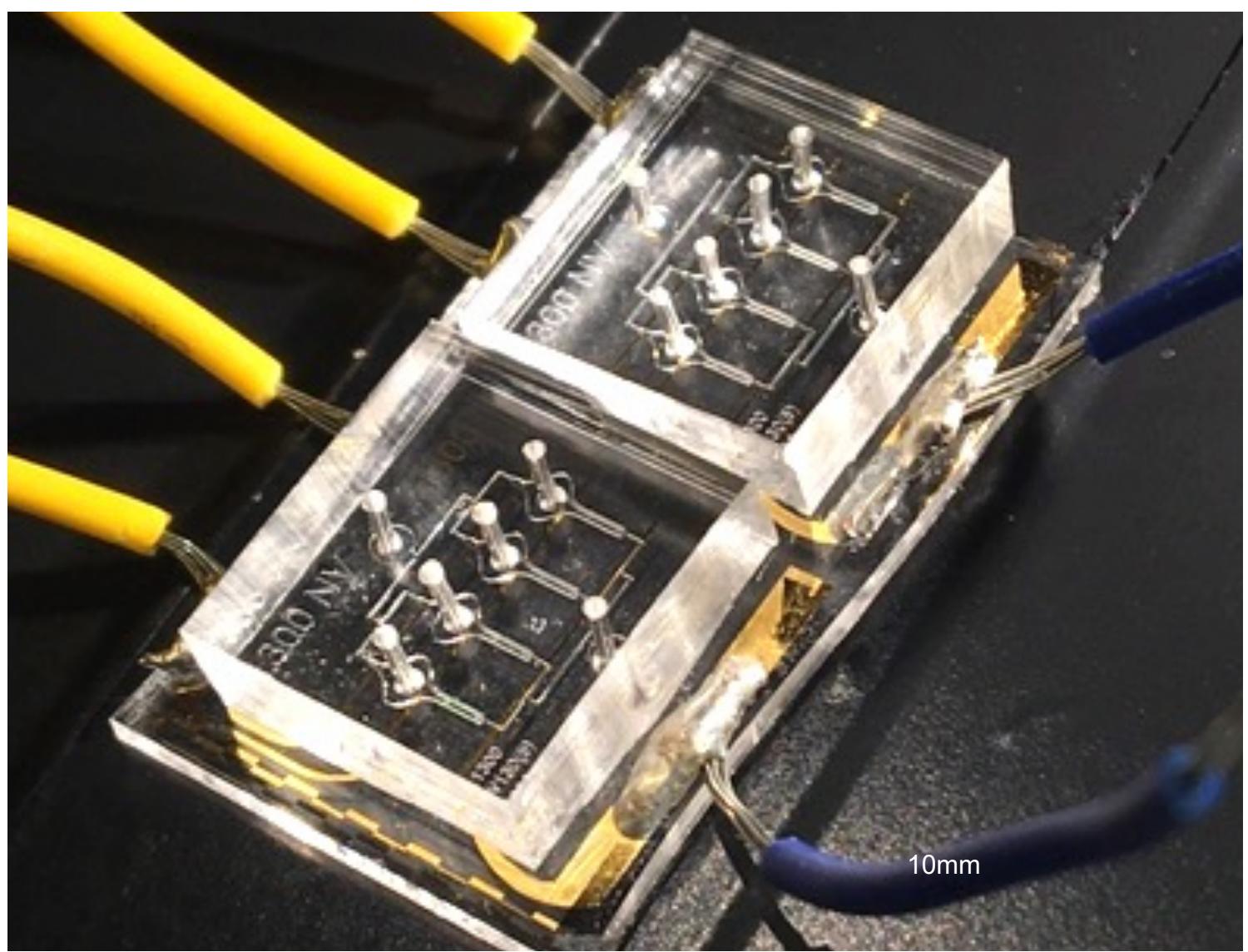
- 3D cardiac micromuscle
- Organized beating
- Coordinated contraction magnitude & direction



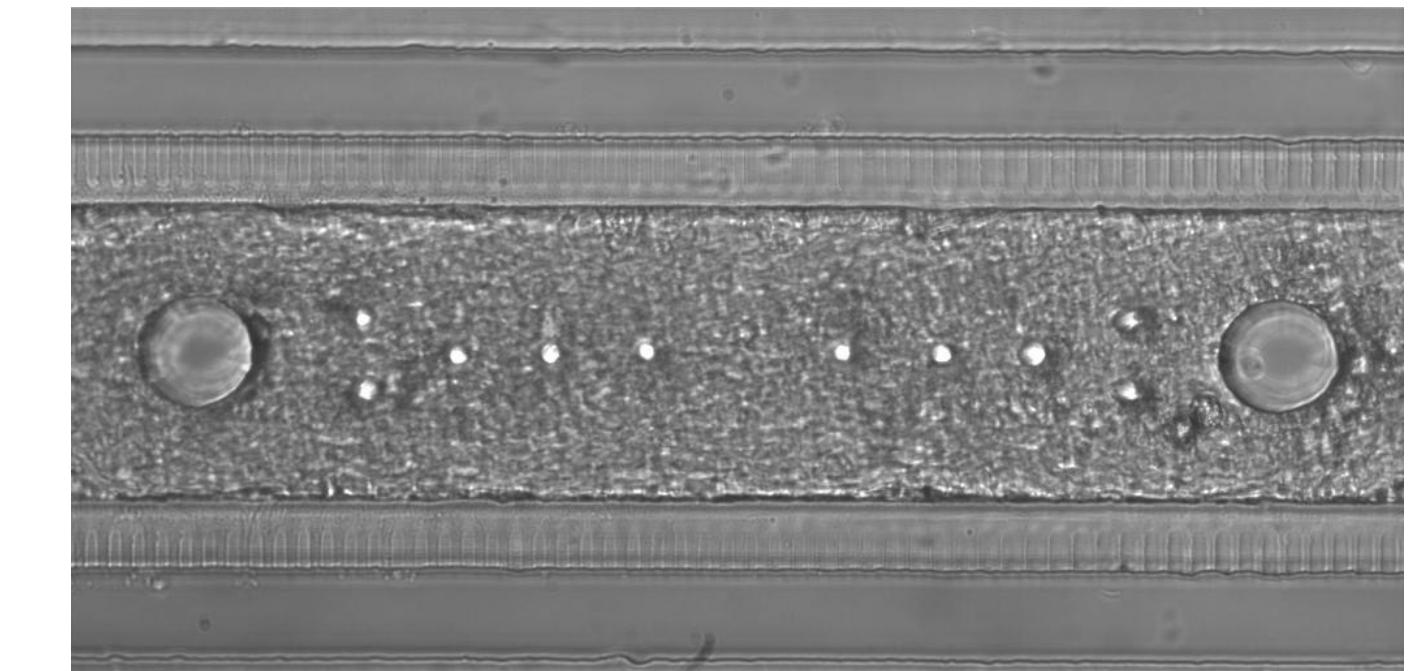
- 2D classic cell culture
- Disorganized beating
- Variable contraction magnitude & direction



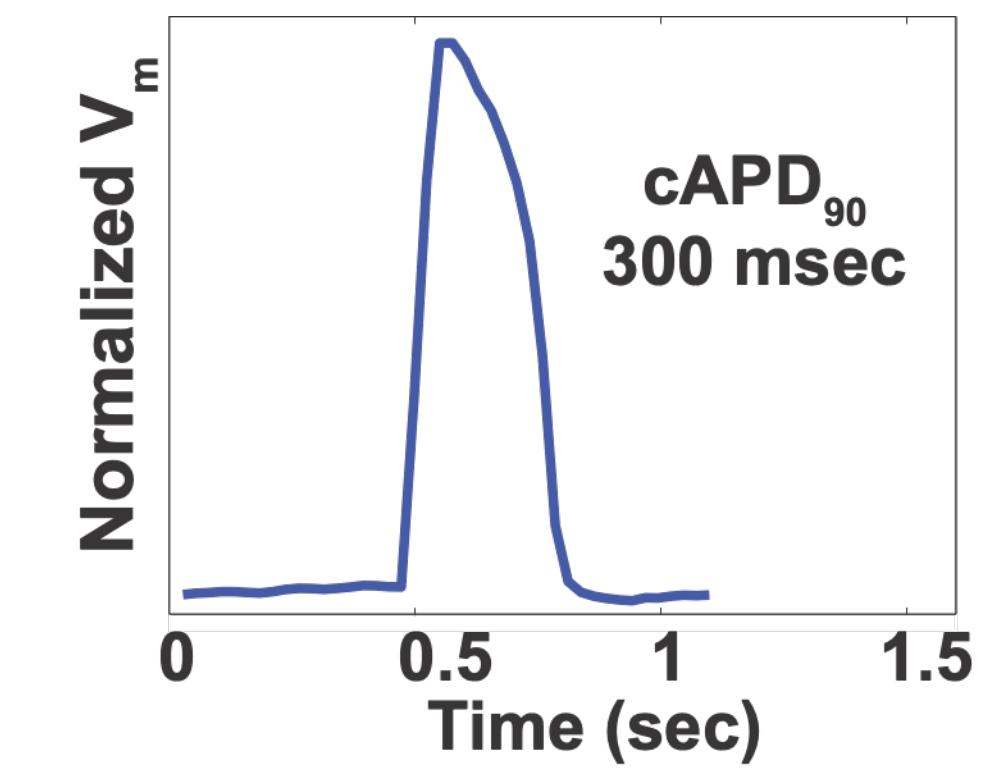
Cardiac Chip - Realtime Clinically Relevant Measurements



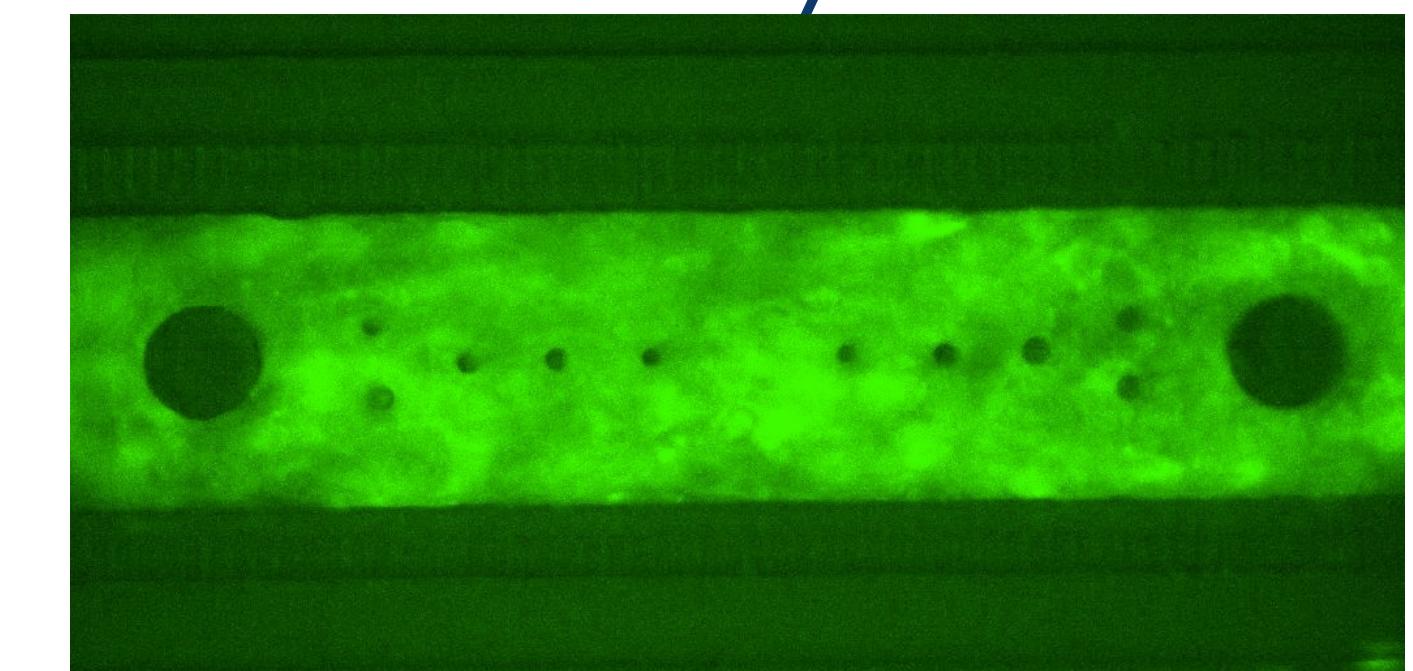
Beat Rate (bpm) & Contraction Force



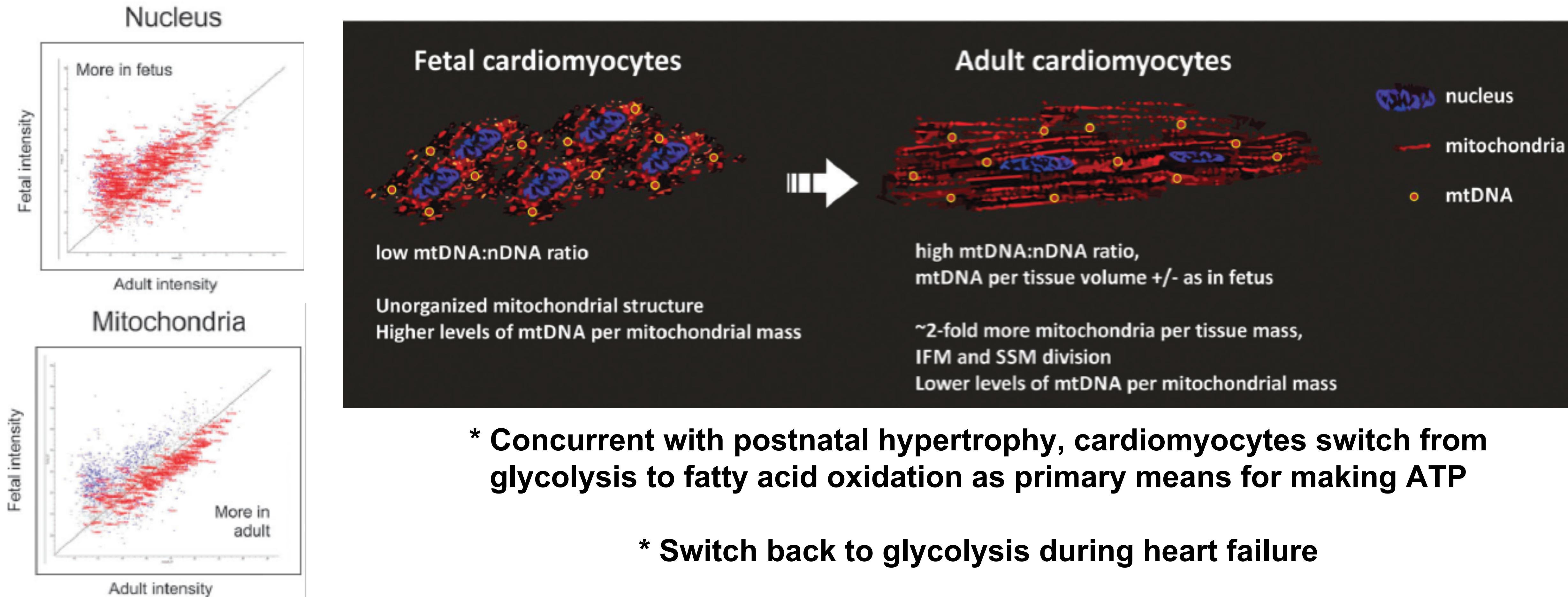
Action Potential Duration ~ QT



Calcium Dynamics

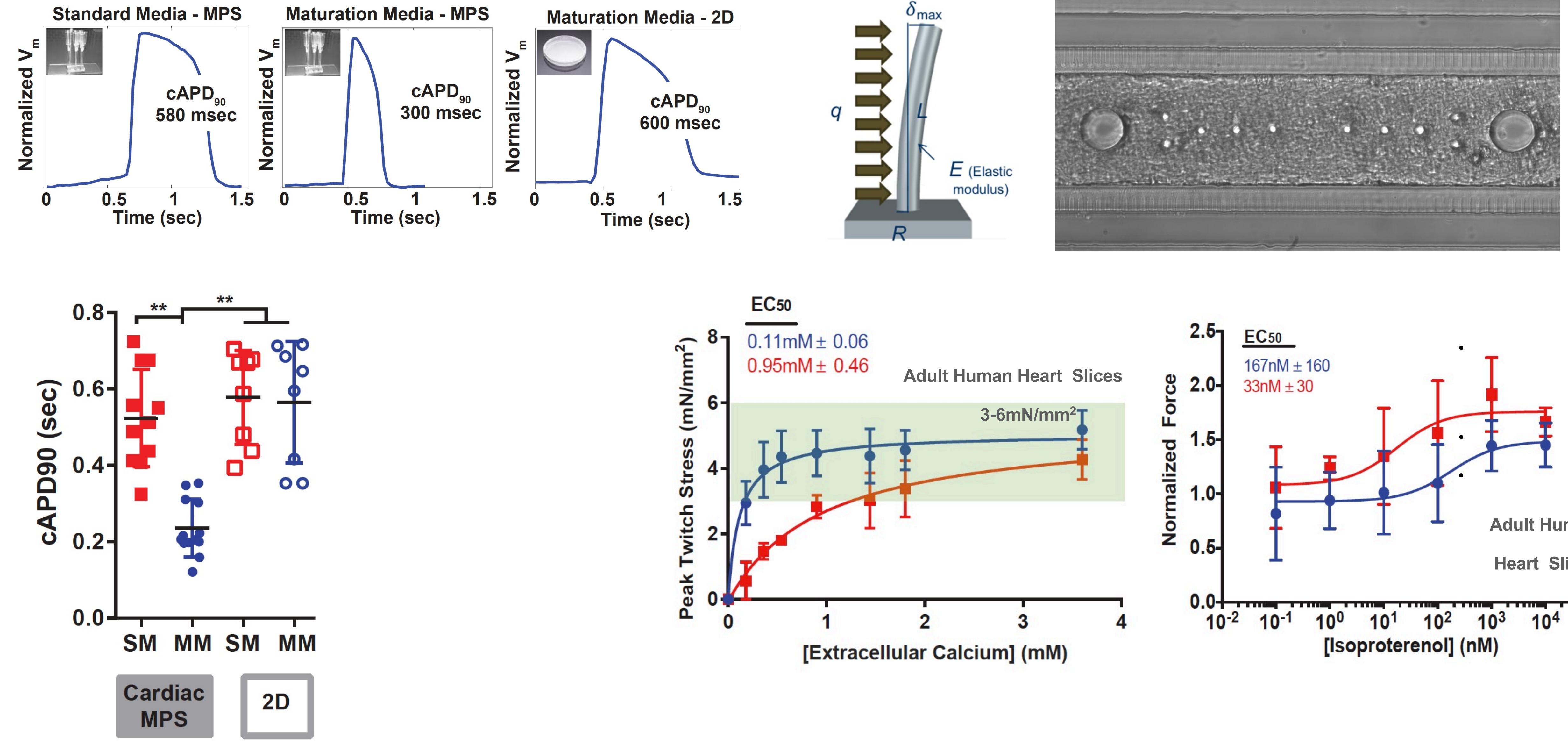


ATP Sourcing Changes and Mitochondrial Development in Postnatal Cardiomyocytes

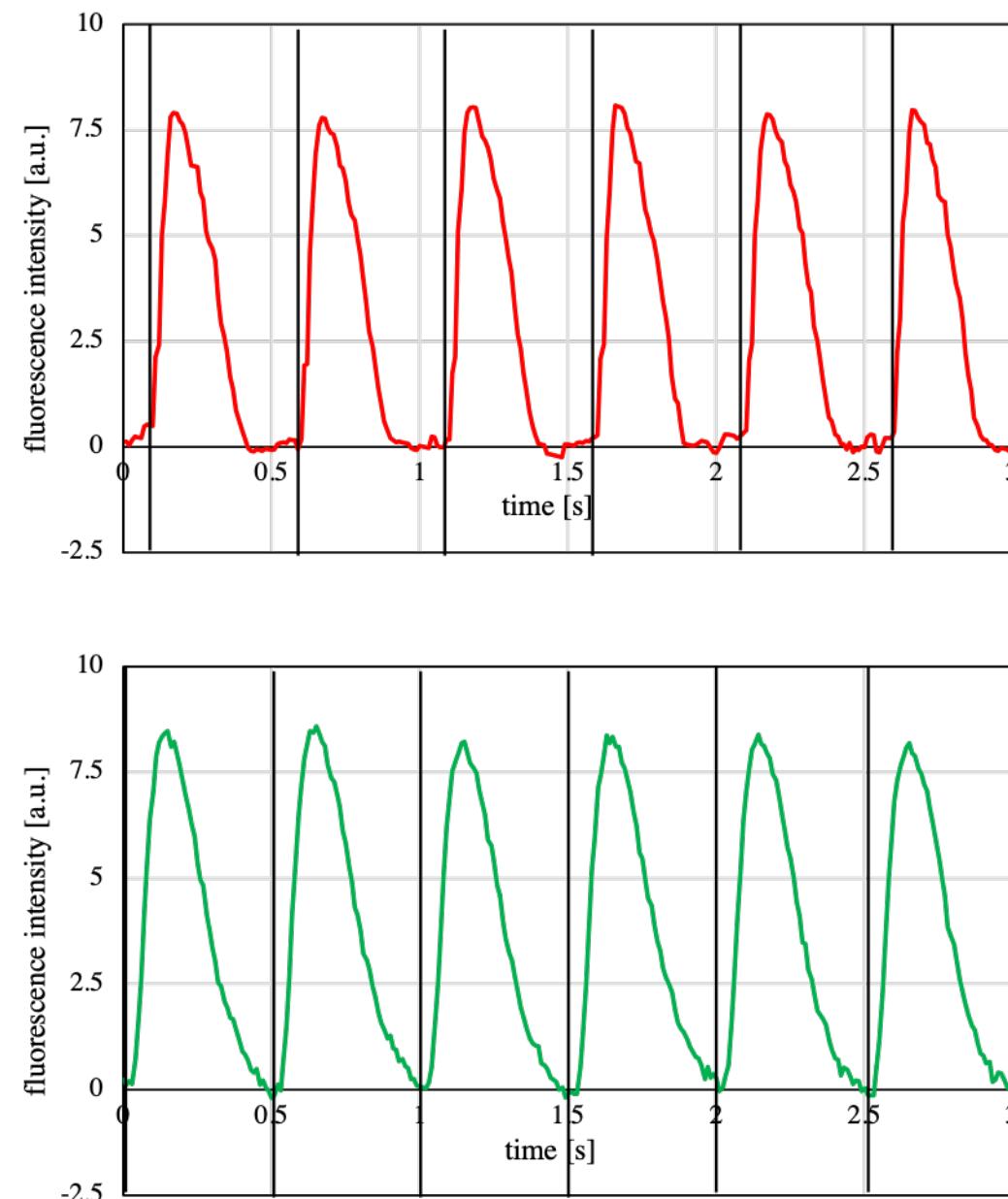


Hypothesis: switching ATP source will enhance maturation of hiPSC-CM in Cardiac MPS

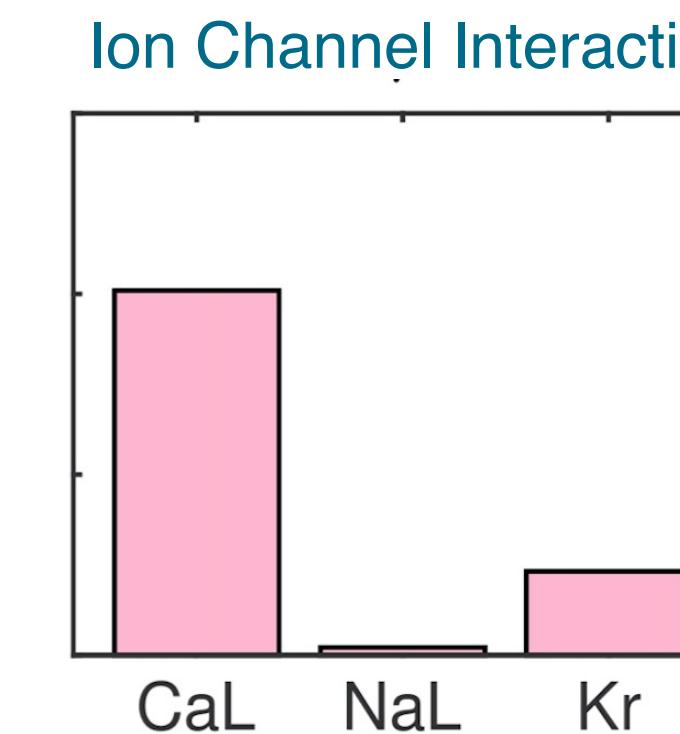
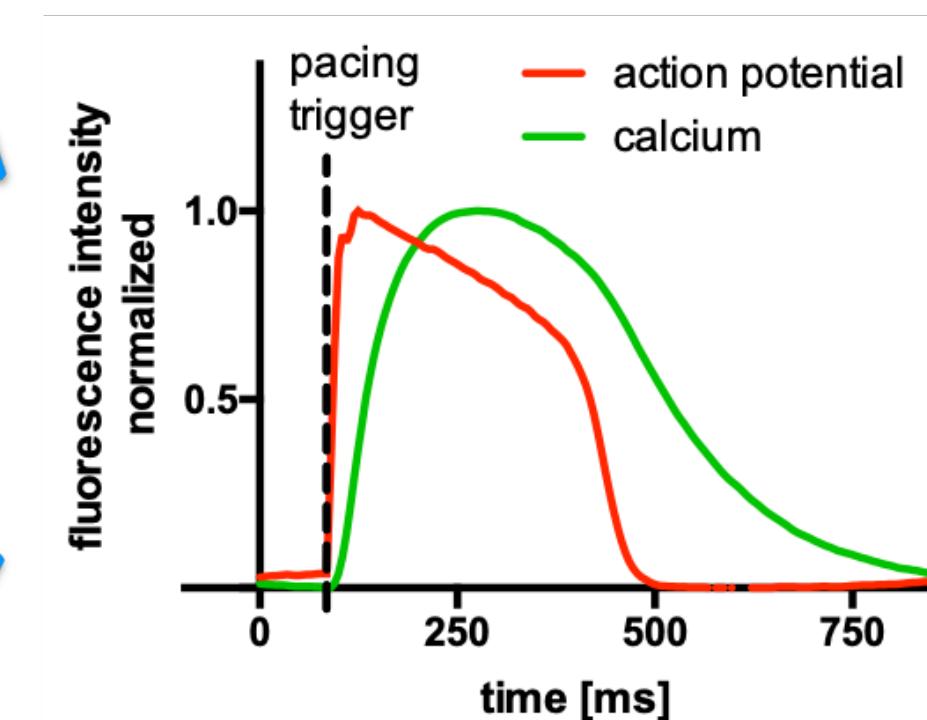
Maturation Media Enhances Cardiac MPS Electrophysiology & Inotropy



In Silico Maturation of Cardiac MPS Data - Prediction of Adult Drug Response



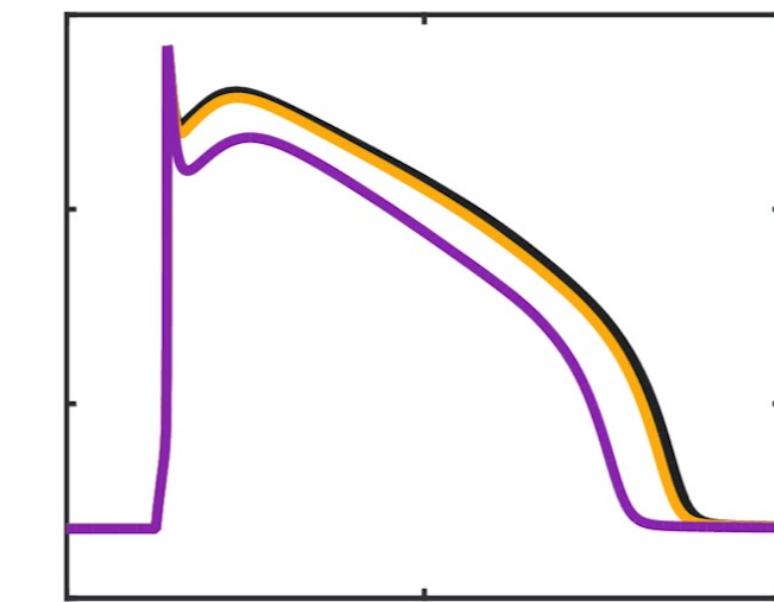
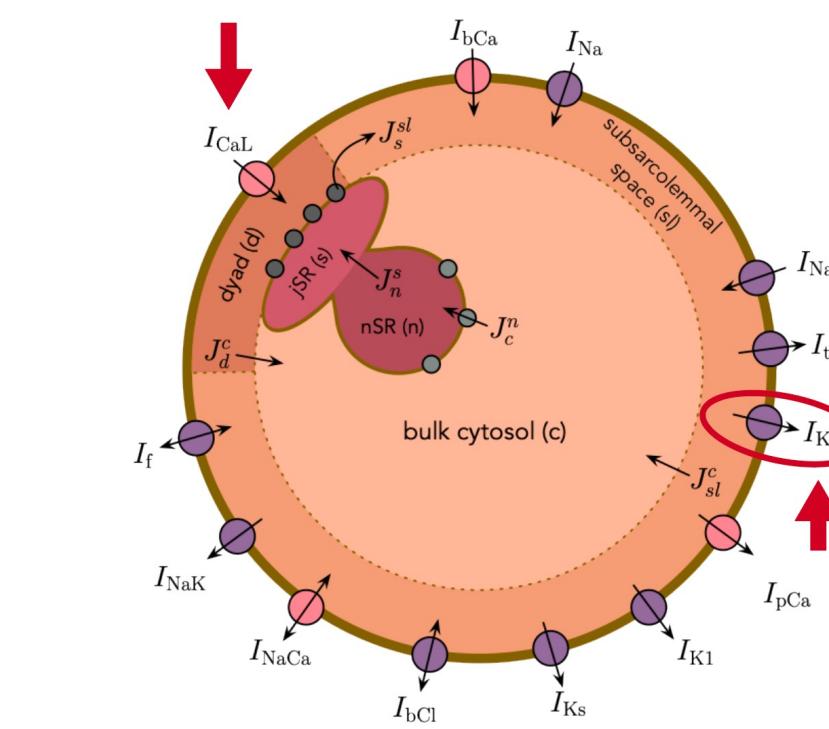
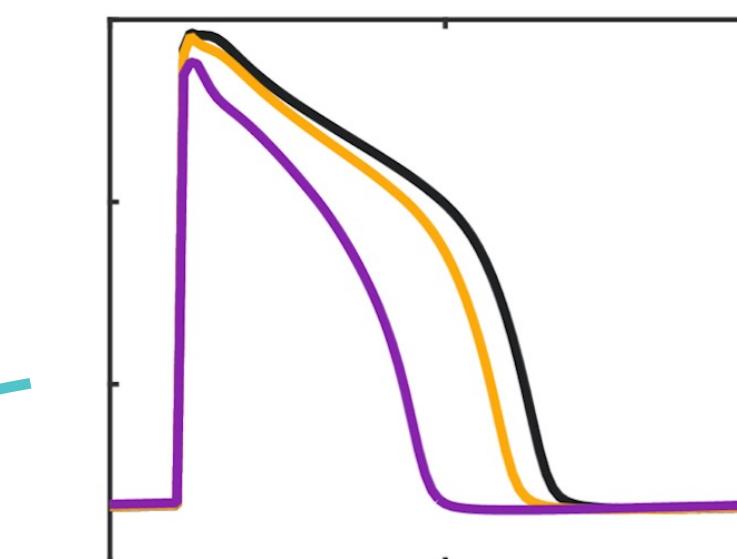
simula



Mechanism of Action

- ◆ *Will* compounds change the behavior of adult cardiac cells?
- ◆ What are the *mechanisms* of change?
- ◆ What is the predicted effect *in vivo*?

Action Potential



Adult Predictions

Tveito, A., Jæger, K.H., Huebsch, N., Charrez, B., Edwards, A.G., Wall, S. & Healy, K.E. Inversion and computational maturation of drug response using human stem cell derived cardiomyocytes in microphysiological systems. *Scientific reports* **8**, 1-14 (2018).

Jæger, K.H., Charwat, V., Charrez, B., Finsberg, H., Maleckar, M.M., Wall, S., Healy, K.E. & Tveito, A. Improved computational identification of drug response using optical measurements of human stem cell derived cardiomyocytes in microphysiological systems. *Frontiers in pharmacology* **10**, 1648 (2020).

Charrez, B., Charwat, V., Siemons, B.A., Goswami, I., Sakolish, C., Luo, Y.S., Finsberg, H., Edwards, A.G., Miller, E.W., Rusyn, I. & Healy, K.E. Heart Muscle Microphysiological System for Cardiac Liability Prediction of Repurposed COVID-19 Therapeutics. *Front Pharmacol* **12**, 684252 (2021).

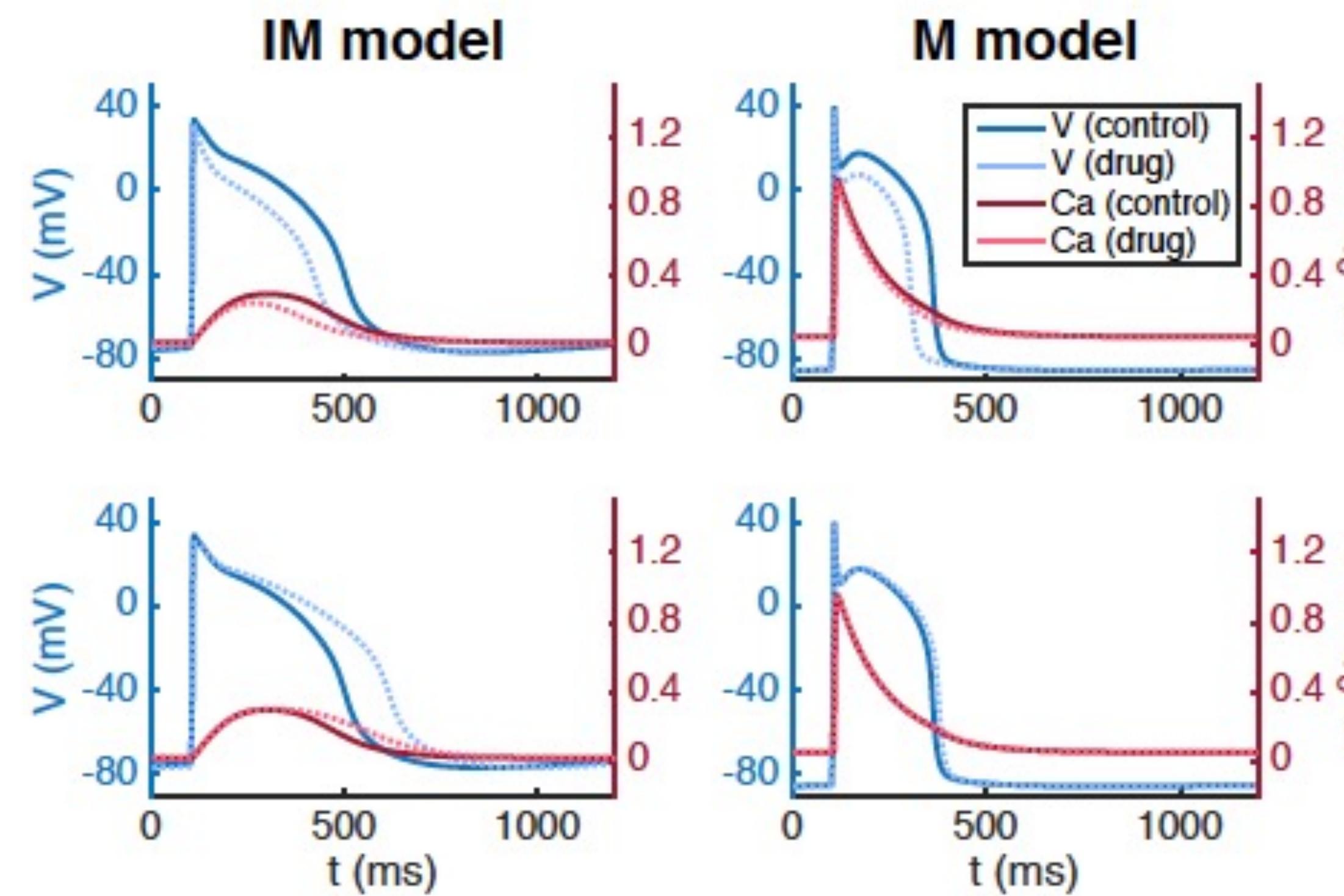
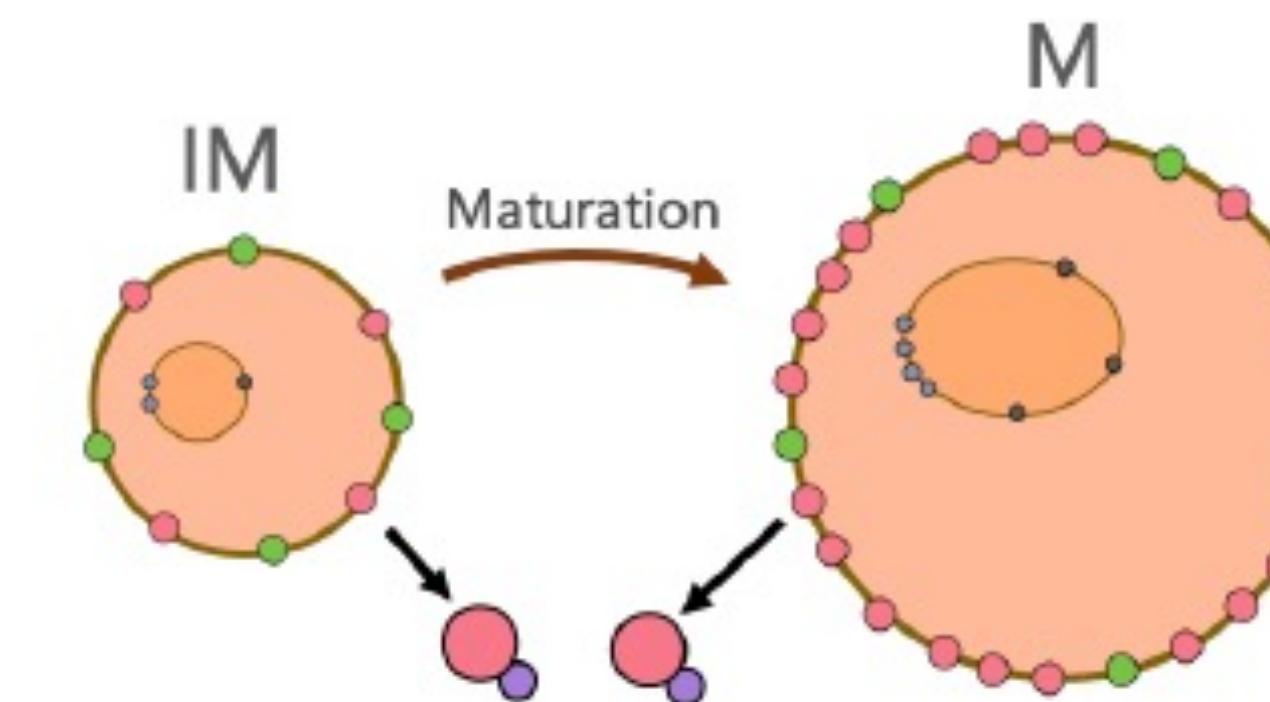
Charrez, B., Charwat, V., Siemons, B., Finsberg, H., Miller, E.W., Edwards, A.G. & Healy, K.E. In vitro safety “clinical trial” of the cardiac liability of drug polytherapy. *Clinical and translational science* **14**, 1155-1165 (2021).

Jæger, K.H., Charwat, V., Wall, S., Healy, K.E. & Tveito, A. Identifying drug response by combining measurements of the membrane potential, the cytosolic calcium concentration, and the extracellular potential in microphysiological systems. *Frontiers in pharmacology* **11**, 569489 (2021).

Huebsch, N., Charrez, B., Neiman, G., Siemons, B., Boggess, S.C., Wall, S., Charwat, V., Jaeger, K.H., Cleres, D., Telle, A., Lee-Montiel, F.T., Jeffreys, N.C., Deveshwar, N., Edwards, A.G., Serrano, J., Snuderl, M., Stahl, A., Tveito, A., Miller, E.W. & Healy, K.E. Metabolically driven maturation of human-induced-pluripotent-stem-cell-derived cardiac microtissues on microfluidic chips. *Nat Biomed Eng* **6**, 372-388 (2022).

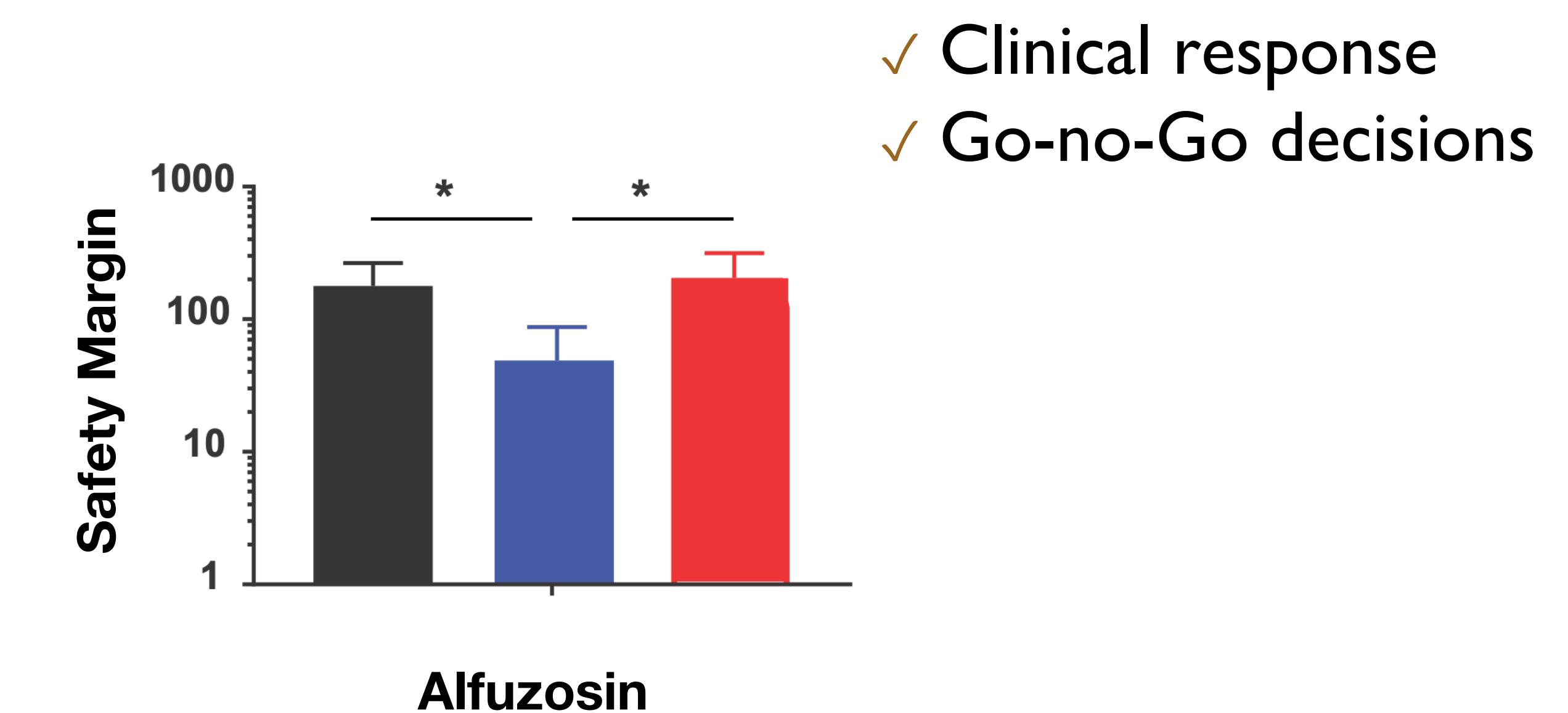
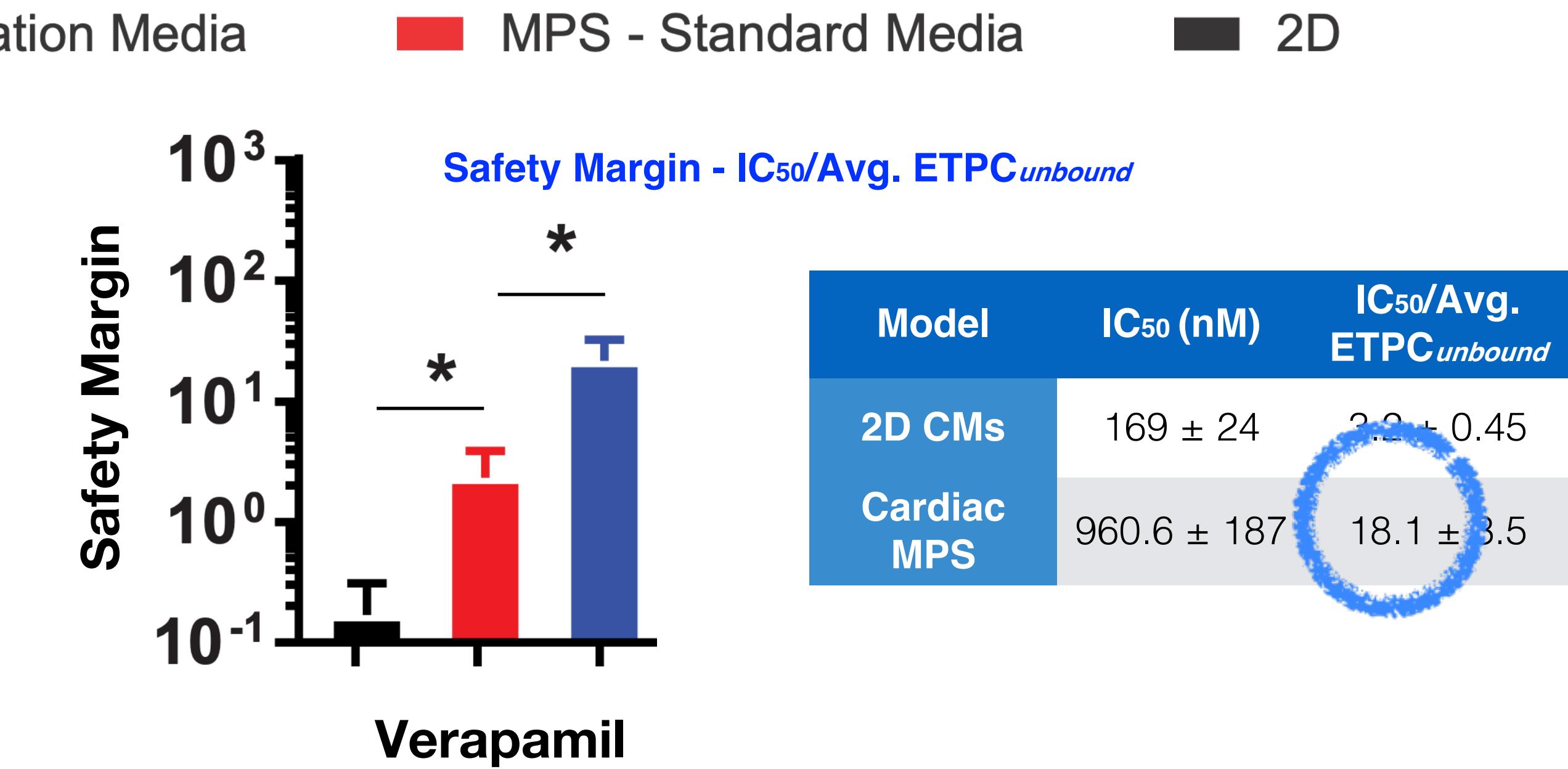
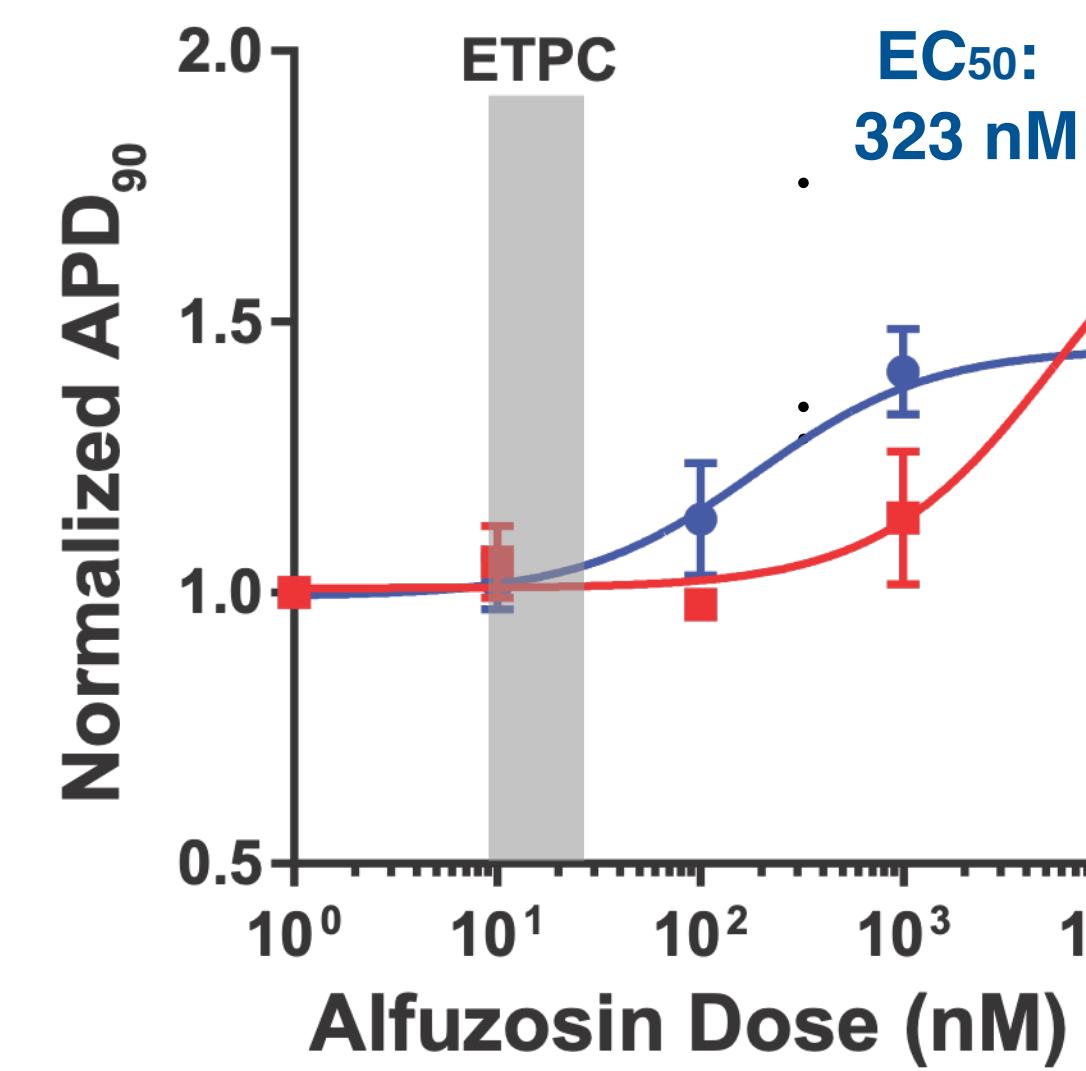
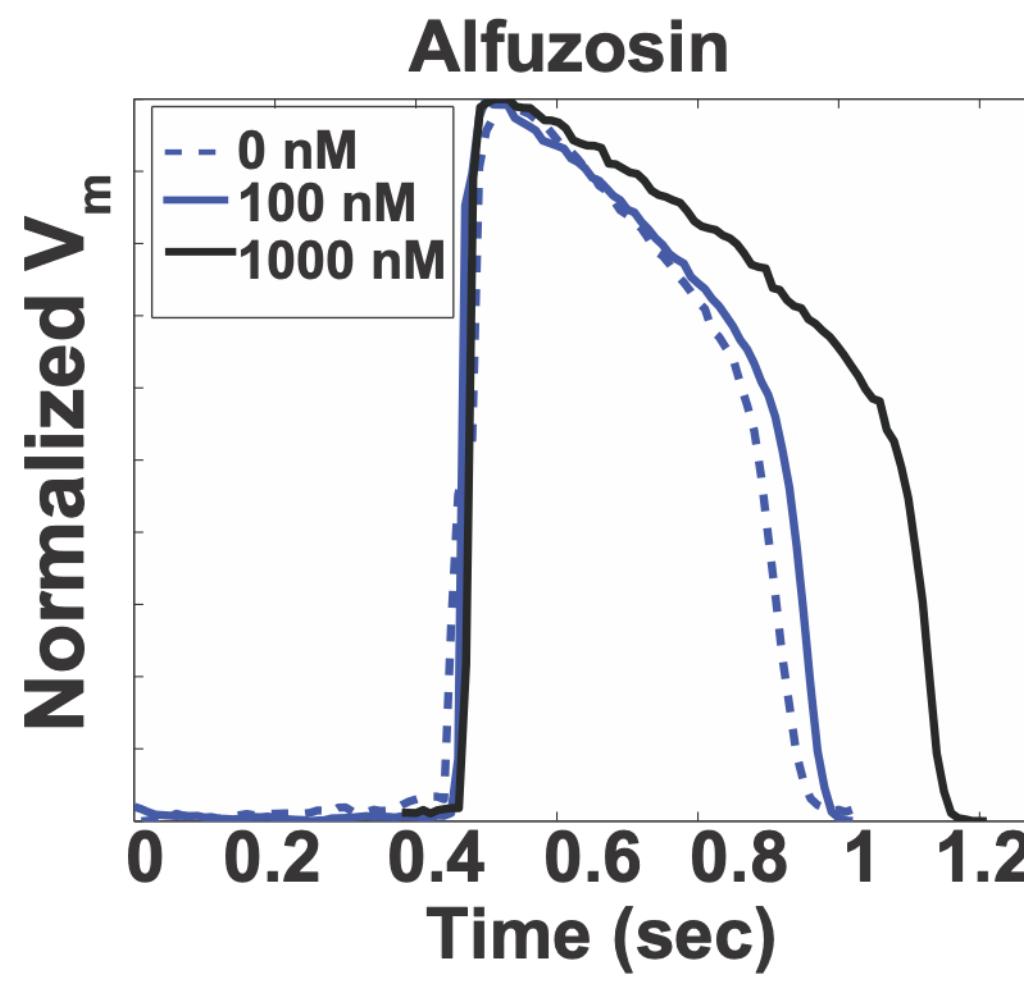
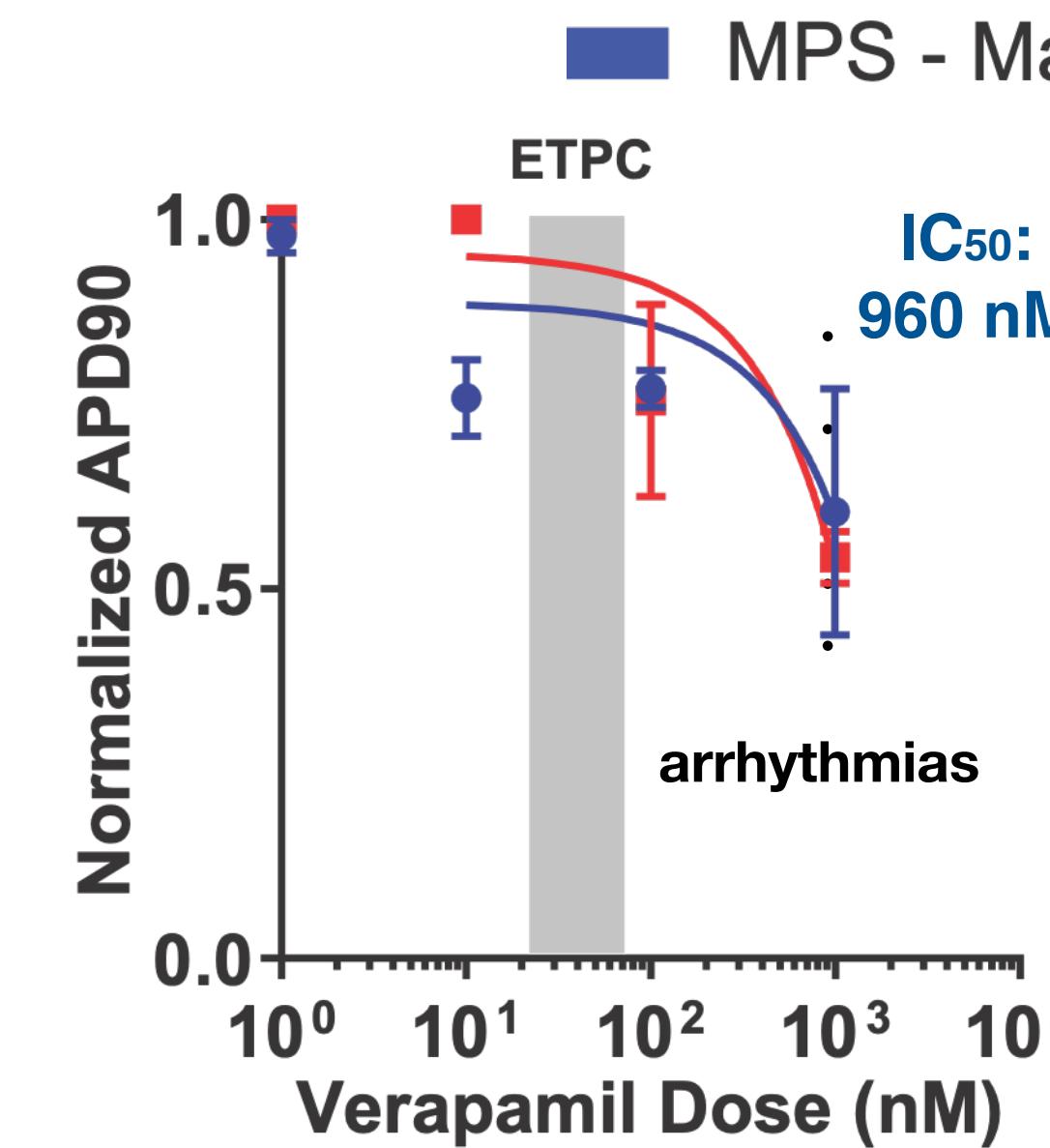
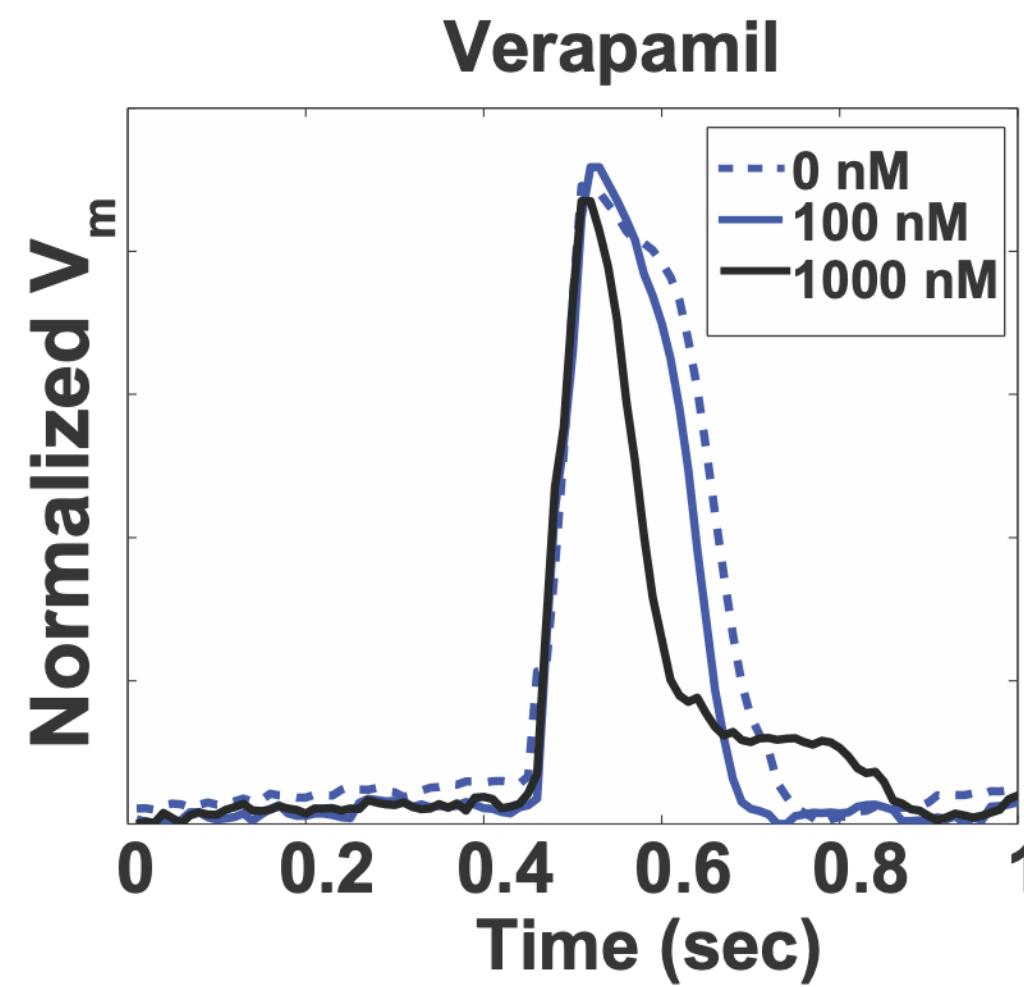
Charwat, V., Charrez, B., Siemons, B.A., Finsberg, H., Jæger, K.H., Edwards, A.G., Huebsch, N., Wall, S., Miller, E., Healy, K.E. & Tveito, A. Validating the Arrhythmogenic Potential of High-, Intermediate-, and Low-Risk Drugs in a Human-Induced Pluripotent Stem Cell-Derived Cardiac Microphysiological System. *ACS Pharmacology & Translational Science* (2022).

In Silico Maturation of Cardiac MPS Data - Prediction of Adult Drug Response



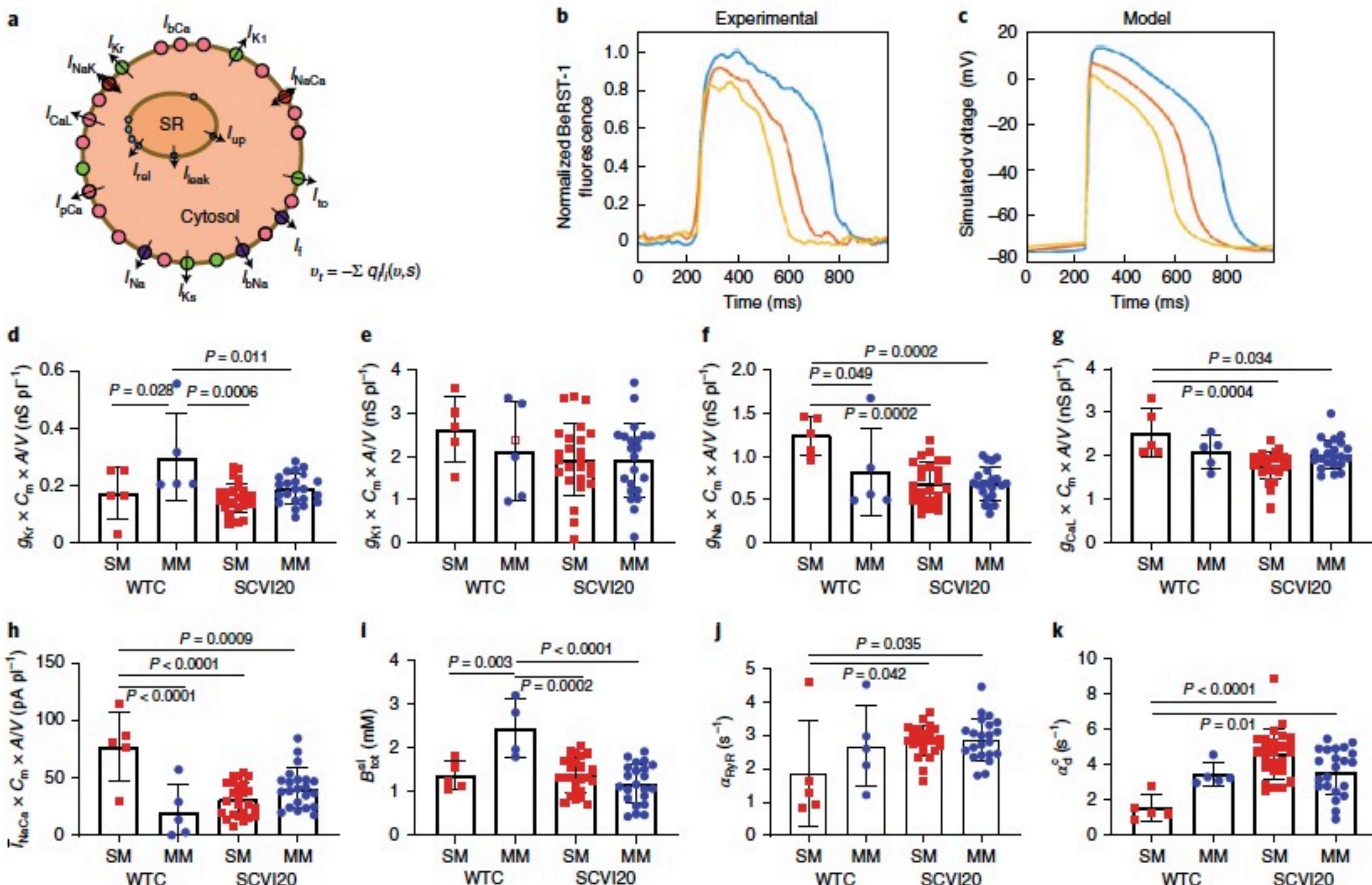
	True drug parameters	Inverted drug parameters
Verapamil	$\lambda_{Na} = 0$ $\lambda_{CaL} = -0.5$ $\lambda_{Kr} = -0.25$ $\lambda_{K1} = 0$	$\lambda_{Na} = -0.00$ $\lambda_{CaL} = -0.50$ $\lambda_{Kr} = -0.25$ $\lambda_{K1} = -0.01$
Cisapride	$\lambda_{Na} = 0$ $\lambda_{CaL} = 0$ $\lambda_{Kr} = -0.5$ $\lambda_{K1} = 0$	$\lambda_{Na} = -0.03$ $\lambda_{CaL} = -0.03$ $\lambda_{Kr} = -0.52$ $\lambda_{K1} = -0.00$

Case Studies - *Eliminating False Positives & Negatives*



✓ Clinical response
✓ Go-no-Go decisions

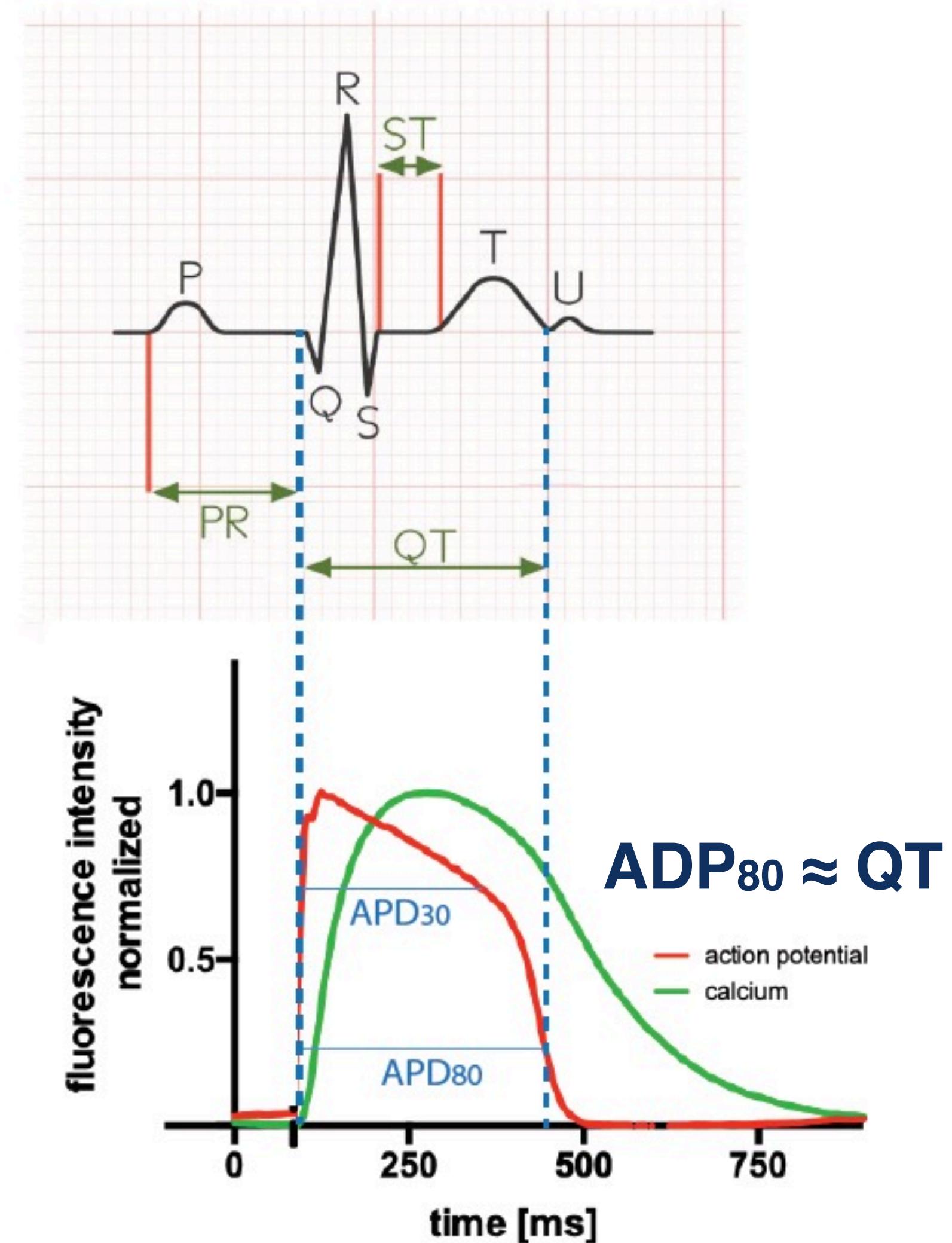
Modeling the Effect of Maturation Media on Ion Currents and Calcium Handling



Case Studies - Arrhythmia Classification

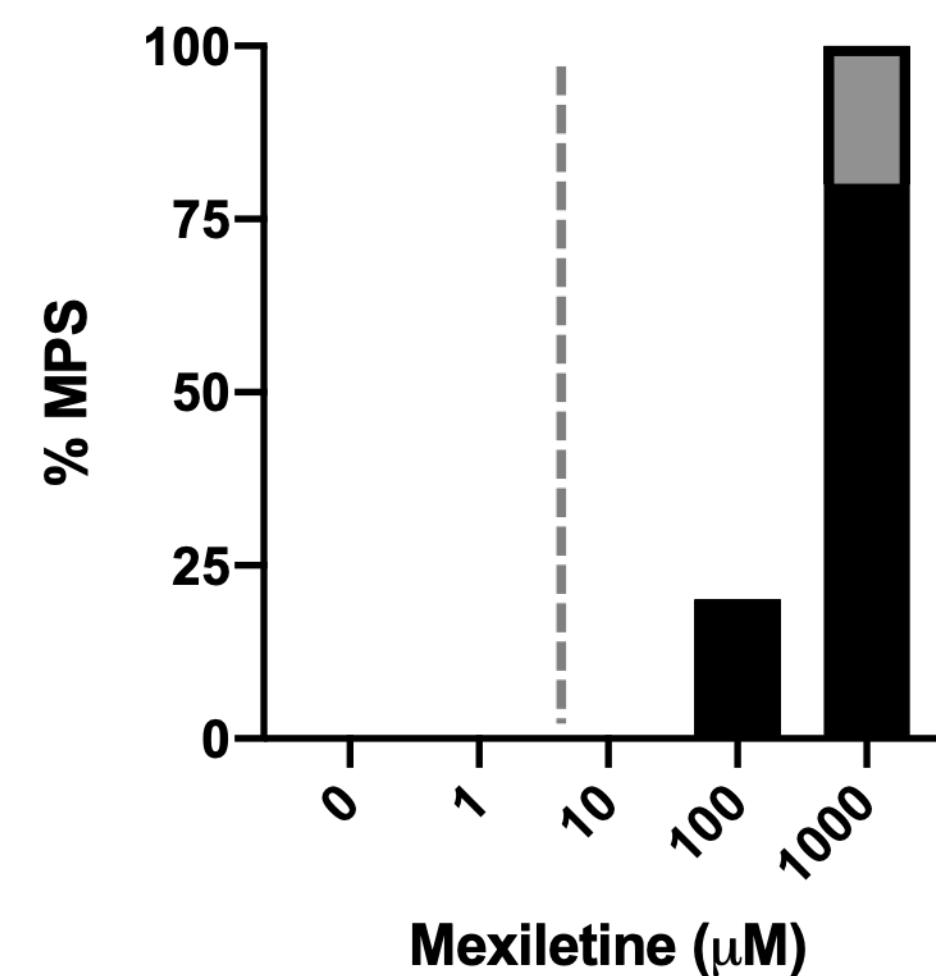
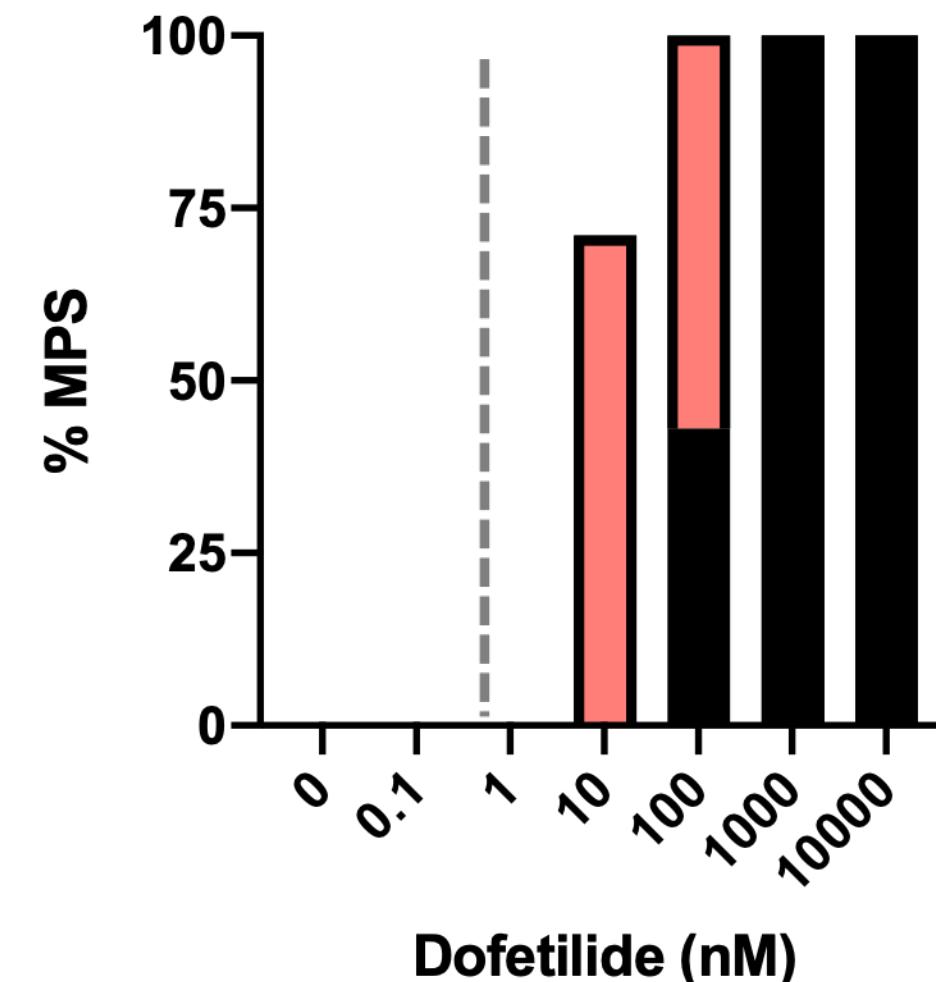
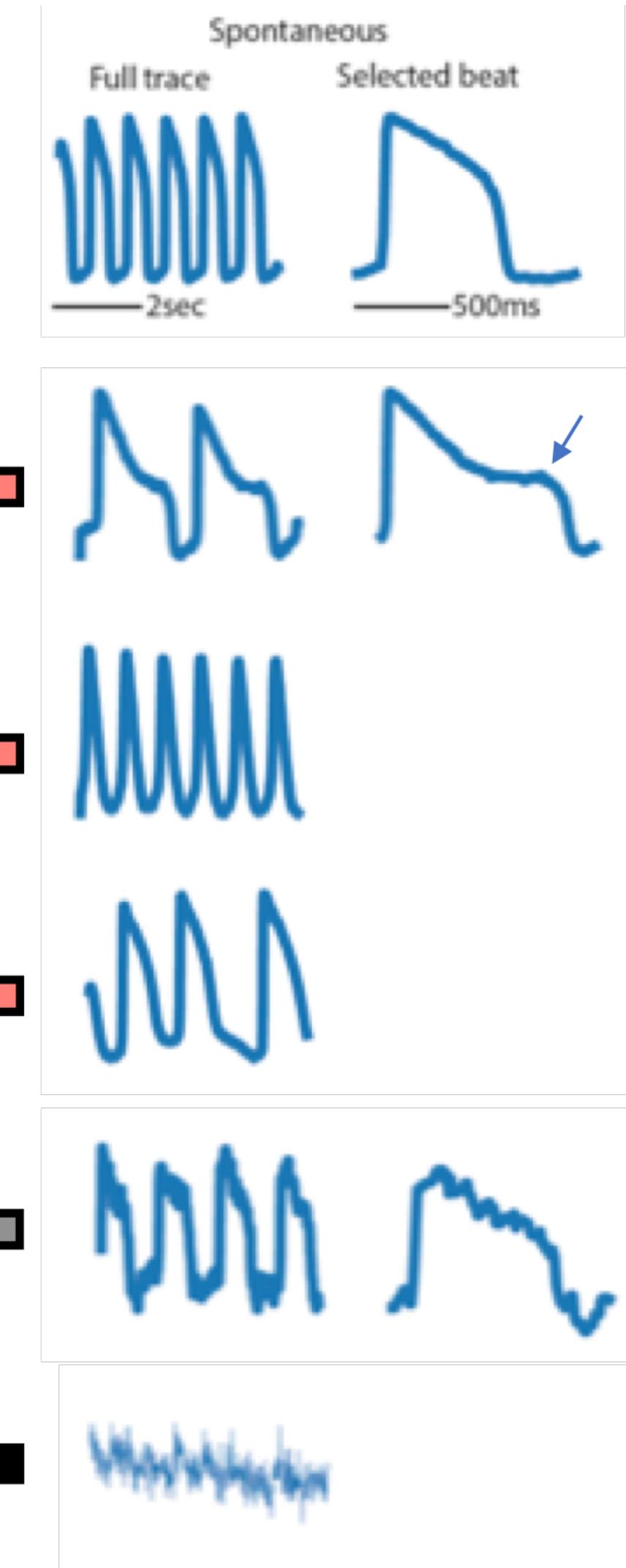
FDA E14 Guidance

Upper 95% confidence bound mean $\Delta\Delta QTc < 10$ ms

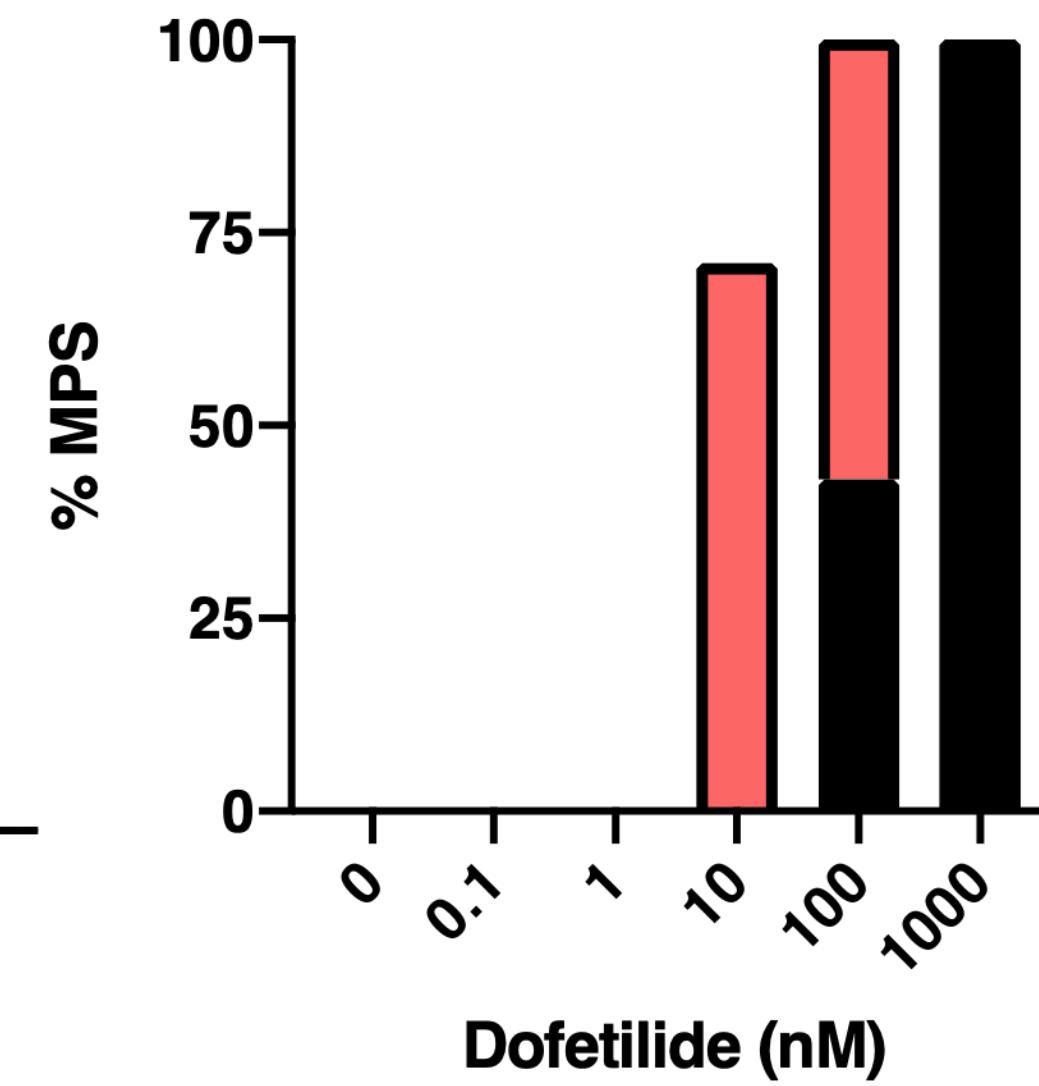
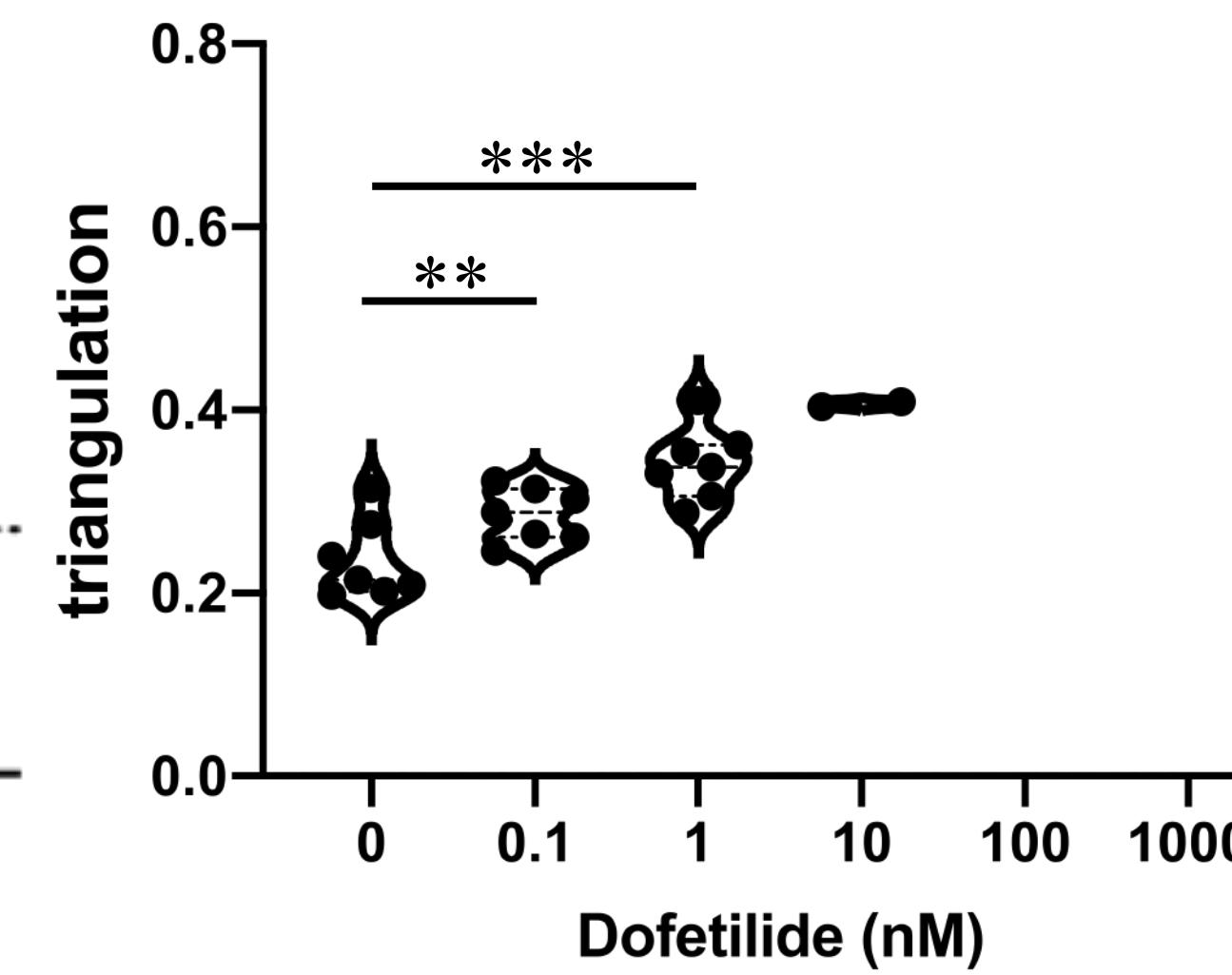
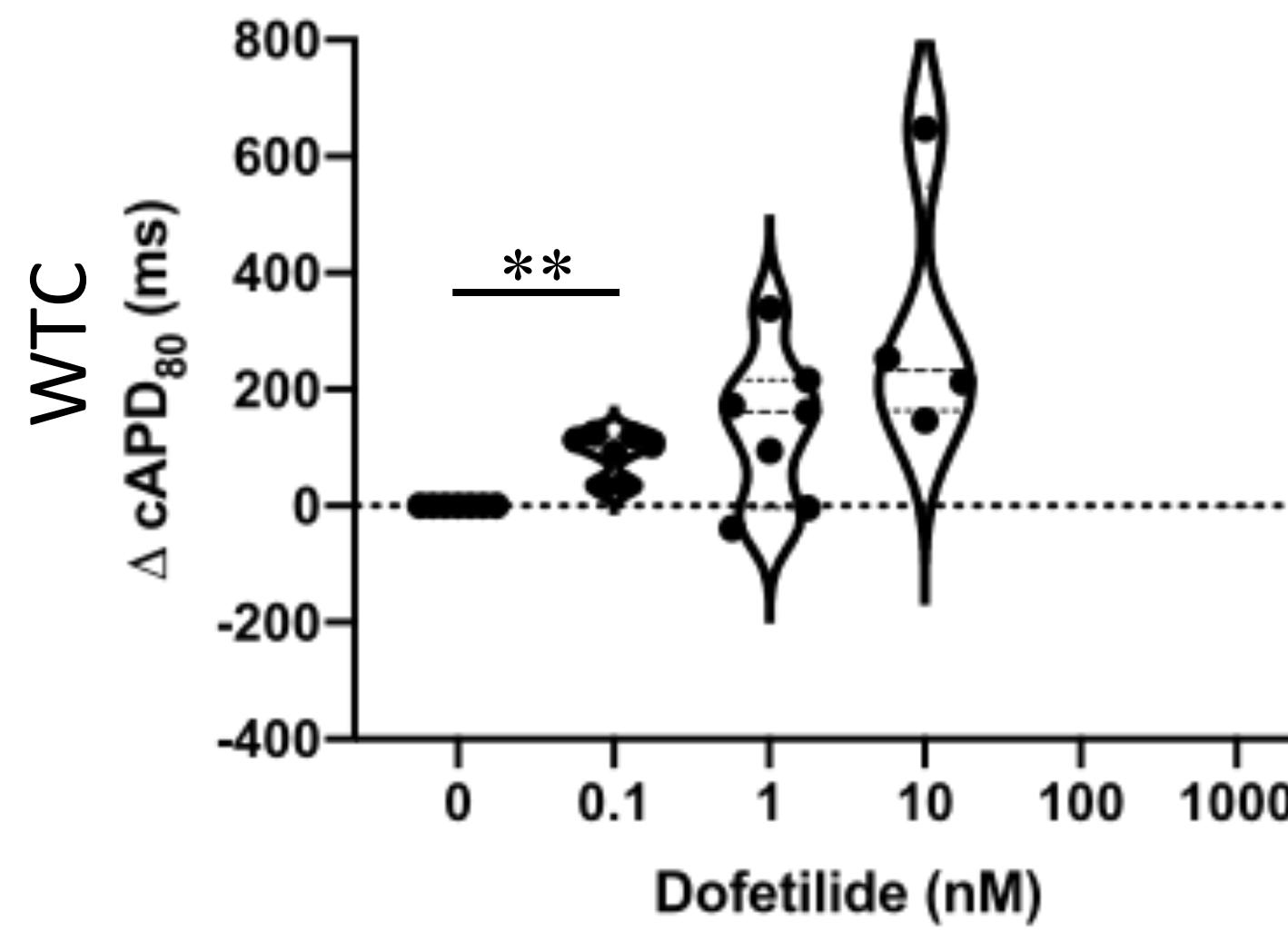


Arrhythmic events

- Regular trace
- Unstable repolarization (EAD)
- Fibrillation (no baseline)
- Irregular beating
- Very weak signal (beat shape cannot be analyzed properly)
- Non beating

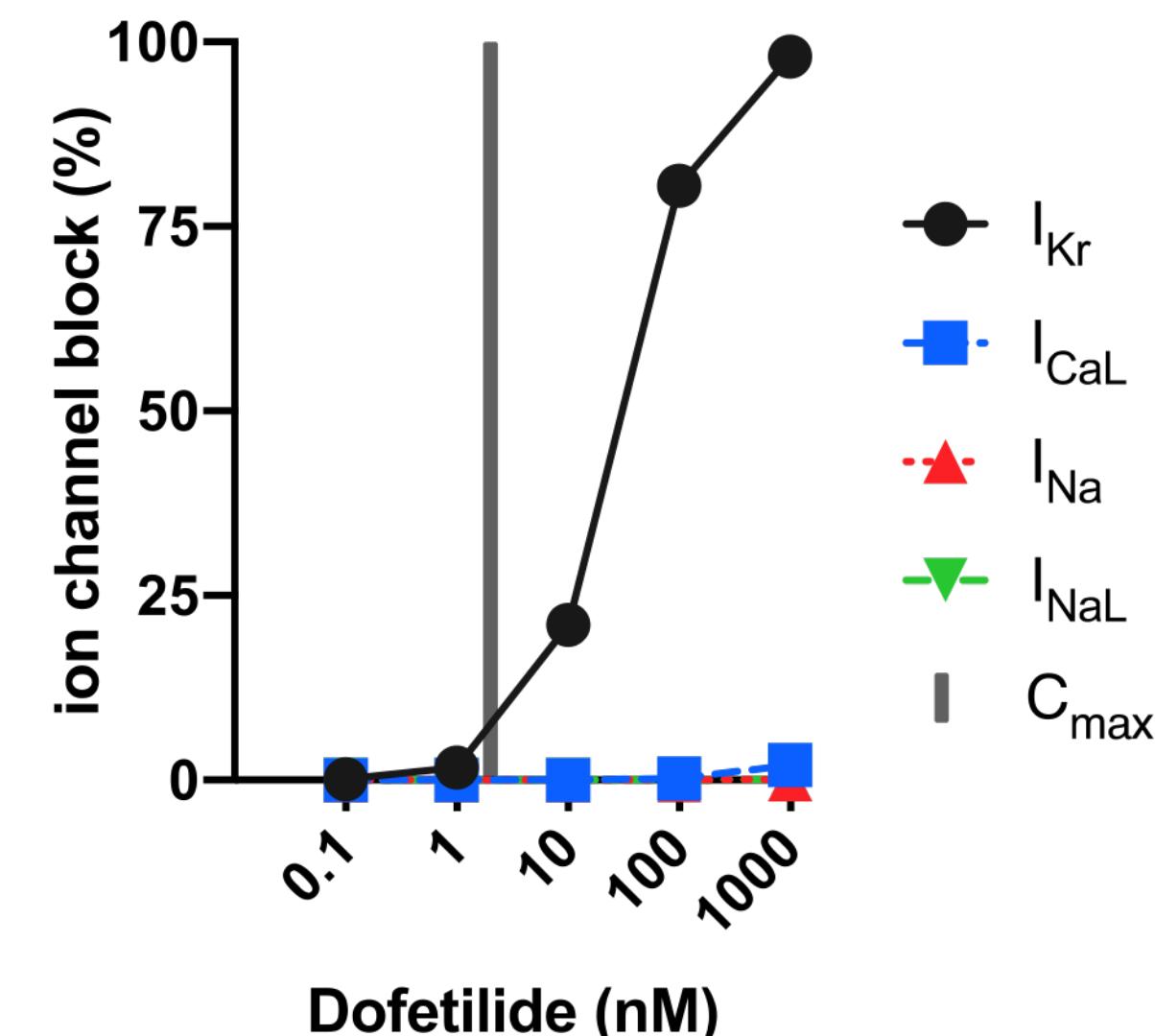
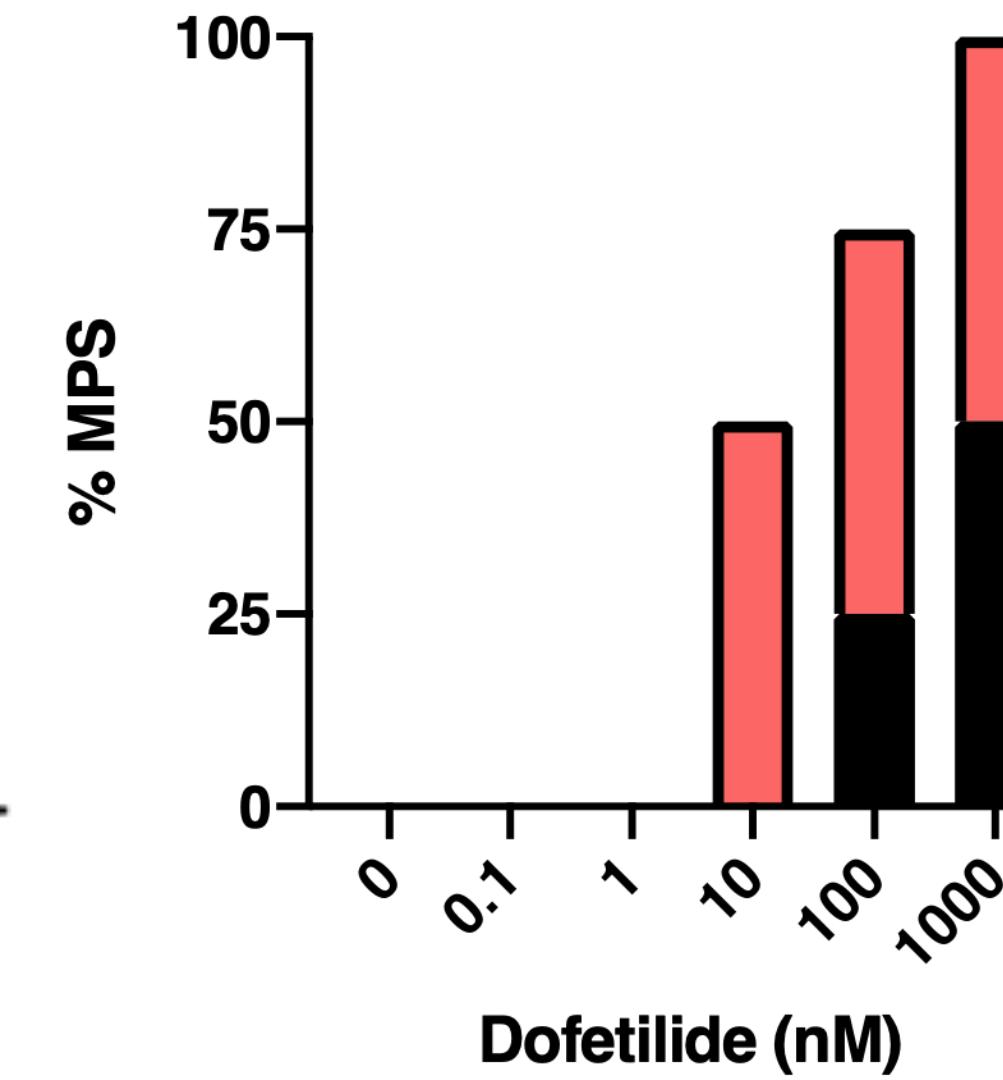
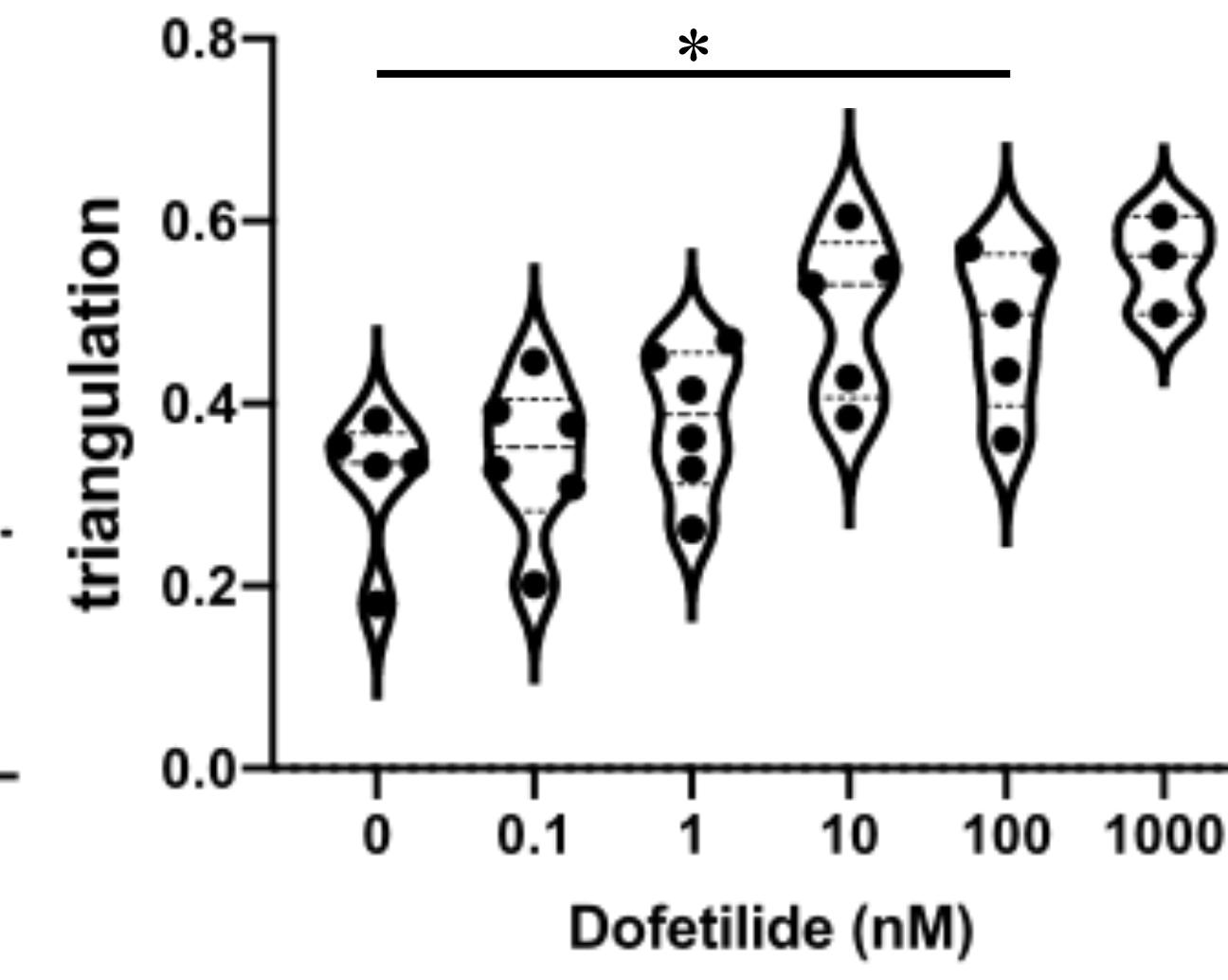
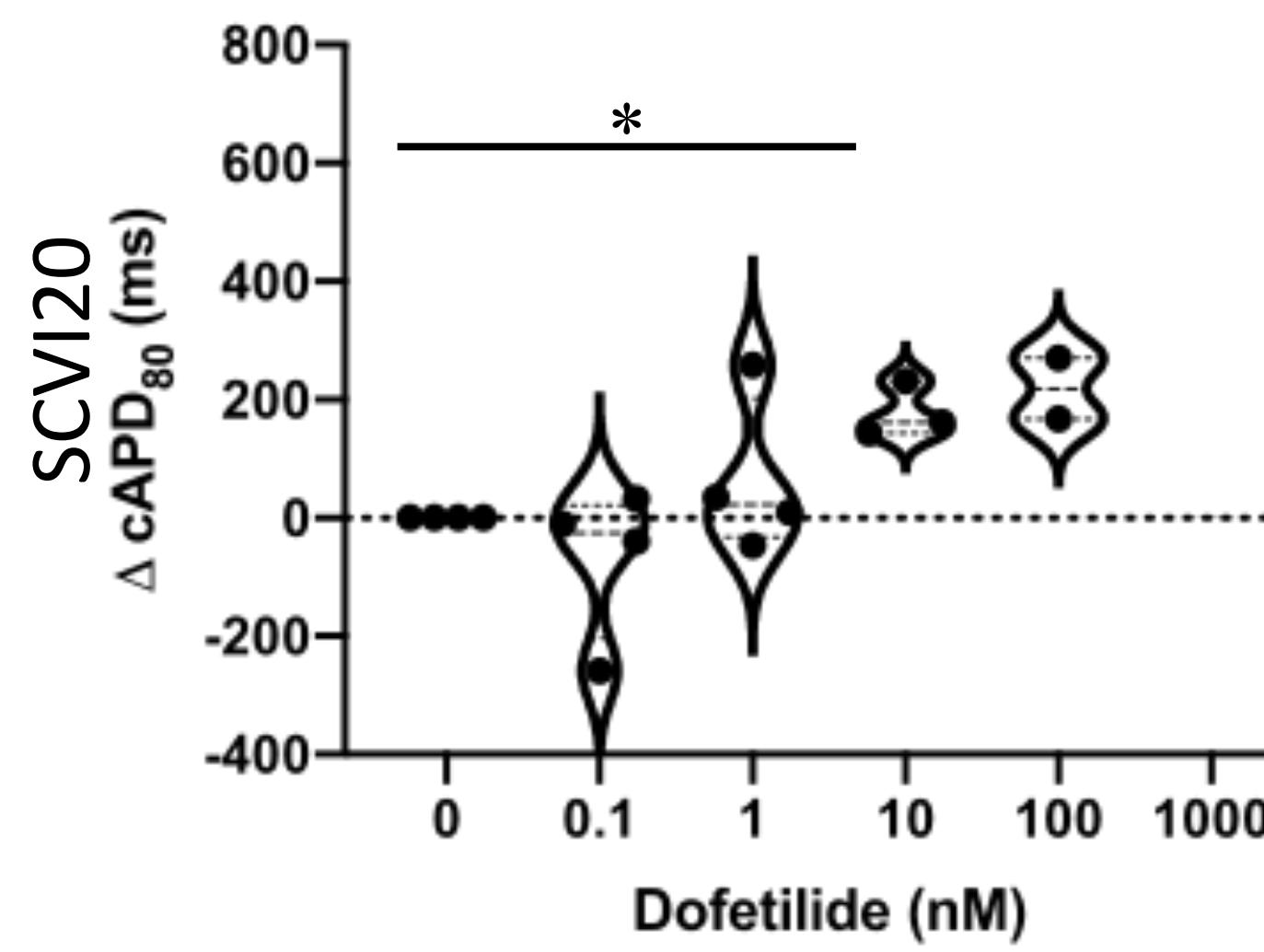


Cardiac MPS Predicts Clinical Arrhythmias & Drug Risk

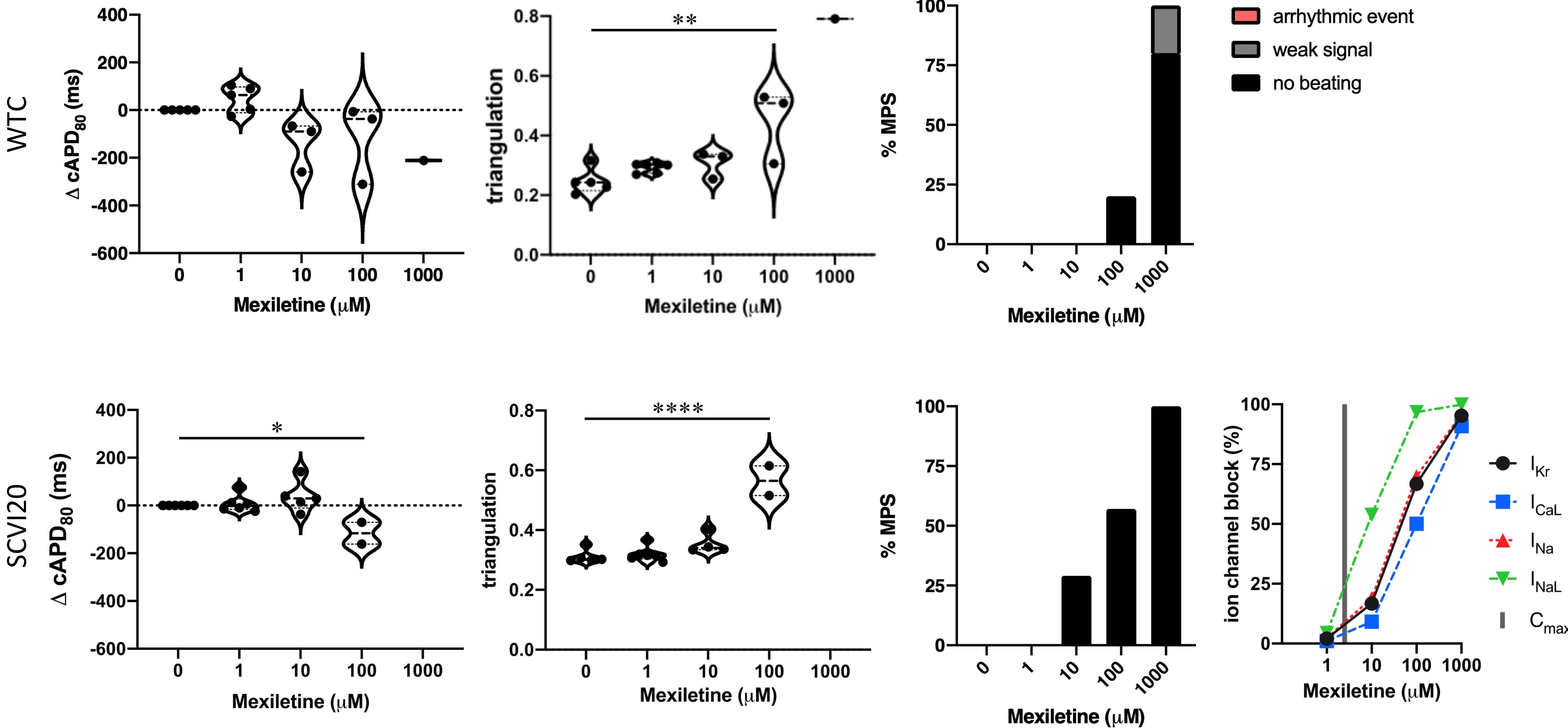


Legend:

- arrhythmic event (red)
- weak signal (grey)
- no beating (black)



Cardiac MPS Predicts Clinical Arrhythmias & Drug Risk

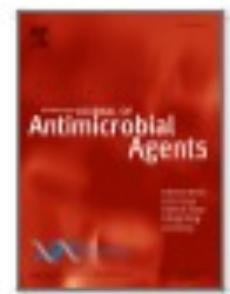


Clinical Trial Case Study - HCQ + AZM to treat COVID-19

Goal: Perform a mock COVID drug QT/QTc screen in the cardiac chip



International Journal of Antimicrobial Agents



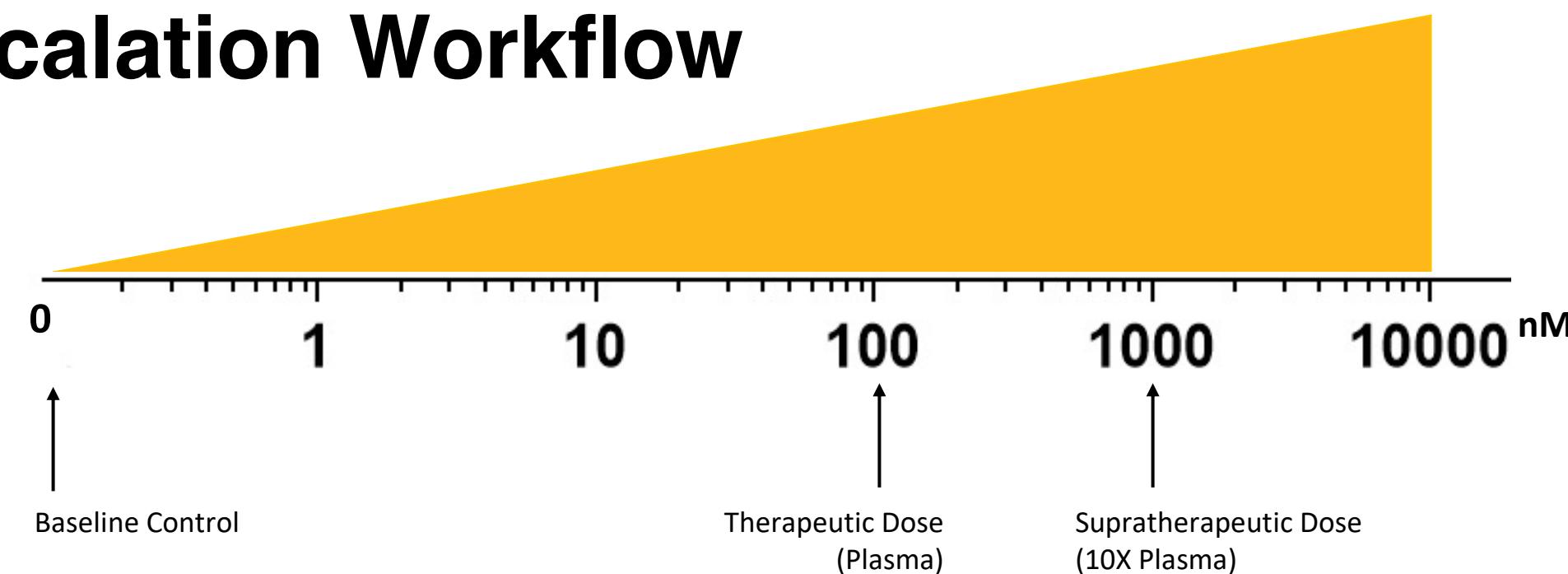
Available online 20 March 2020, 105949

In Press, Journal Pre-proof

Typical QT/QTc Study Costs \$2-4 Million

- Usually 50-60 subjects per treatment arm
- Required to assess a new drug's potential to delay cardiac repolarization

Dose-Escalation Workflow



Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Philippe Gautret ^{a, b, \$}, Jean-Christophe Lagier ^{a, c, \$}, Philippe Parola ^{a, b}, Van Thuan Hoang ^{a, b, d}, Line Meddeb ^a, Morgane Mailhe ^a, Barbara Doudier ^a, Johan Courjon ^{e, f, g}, Valérie Giordanengo ^h, Vera Esteves Vieira ^a, Hervé Tissot Dupont ^{a, c}, Stéphane Honoré ^{i, j}, Philippe Colson ^{a, c}, Eric Chabrière ^{a, c}, Bernard La Scola ^{a, c}, Jean-Marc Rolain ^{a, c}, Philippe Brouqui ^{a, c}, Didier Raoult ^{a, c, k}

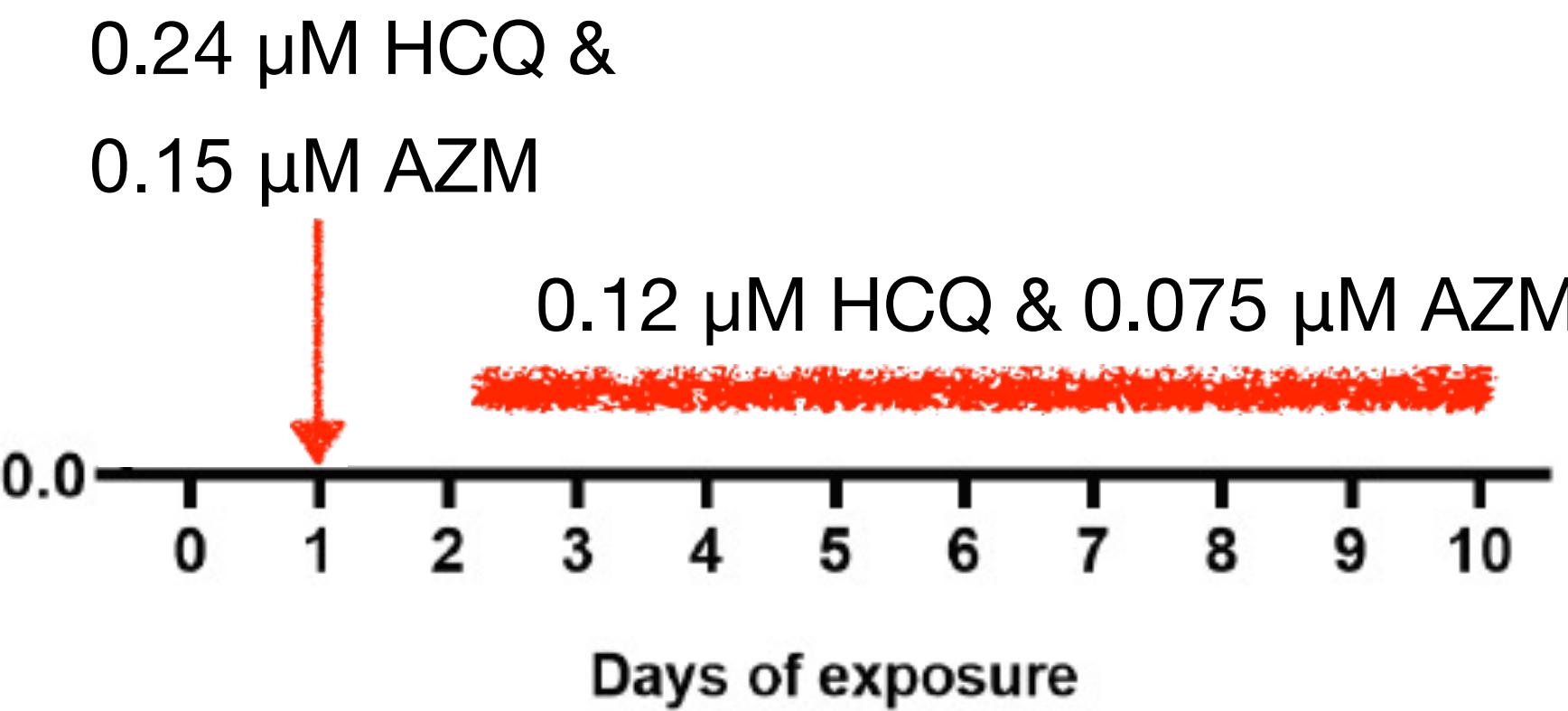
Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

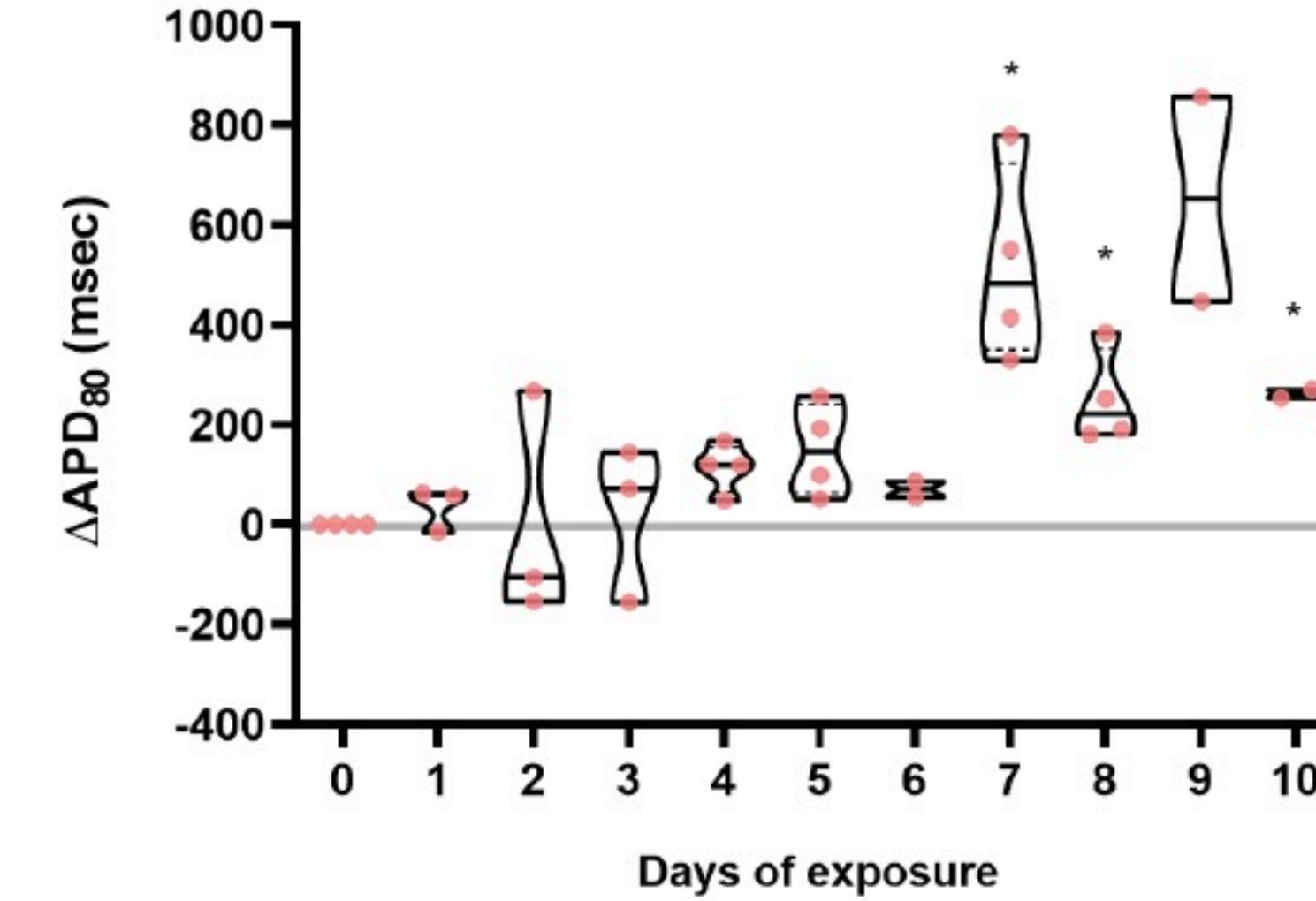
Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Clinical Trials in a Dish for COVID-19 Drug Repurposing

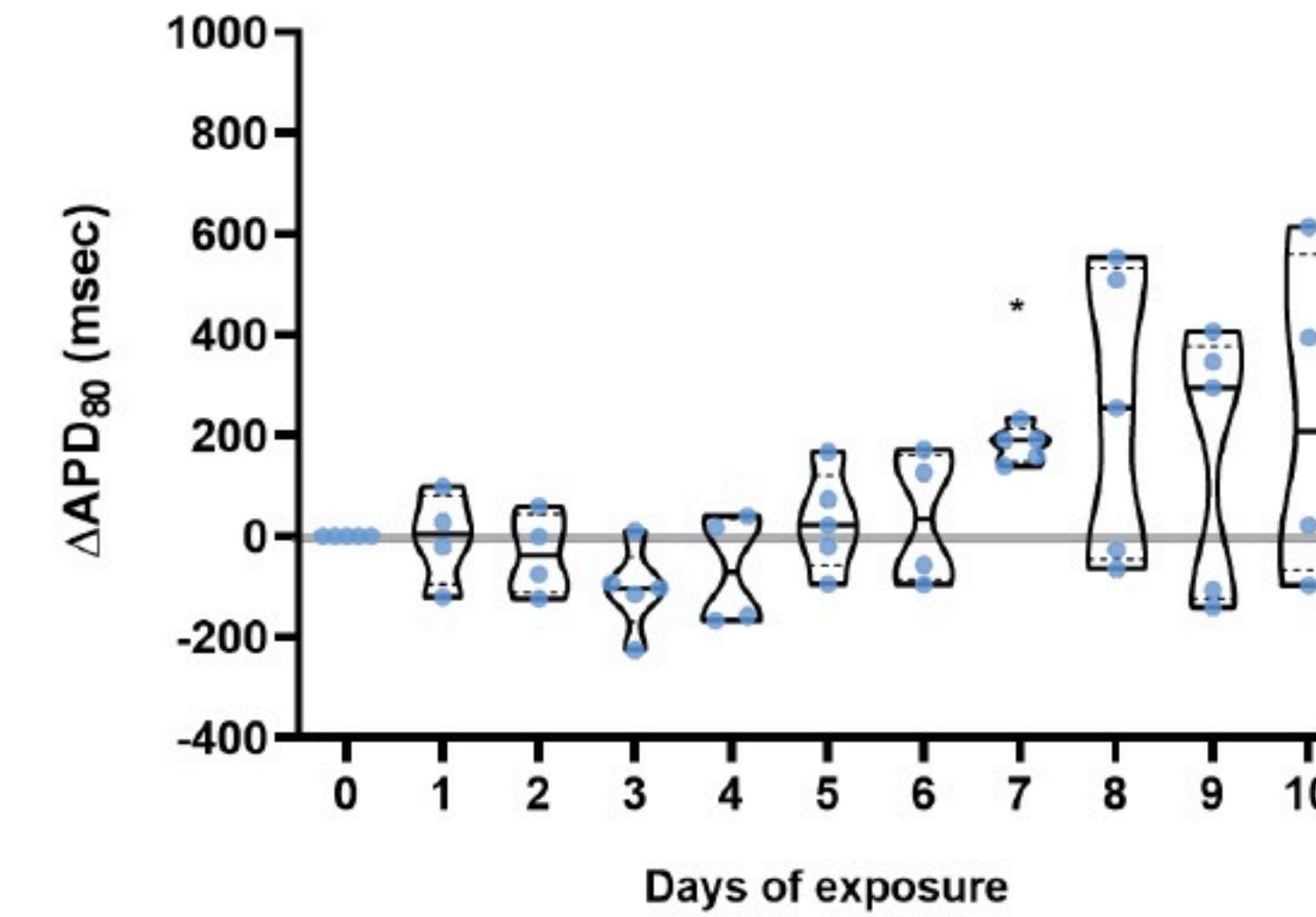
In vitro safety ‘clinical trial’ workflow



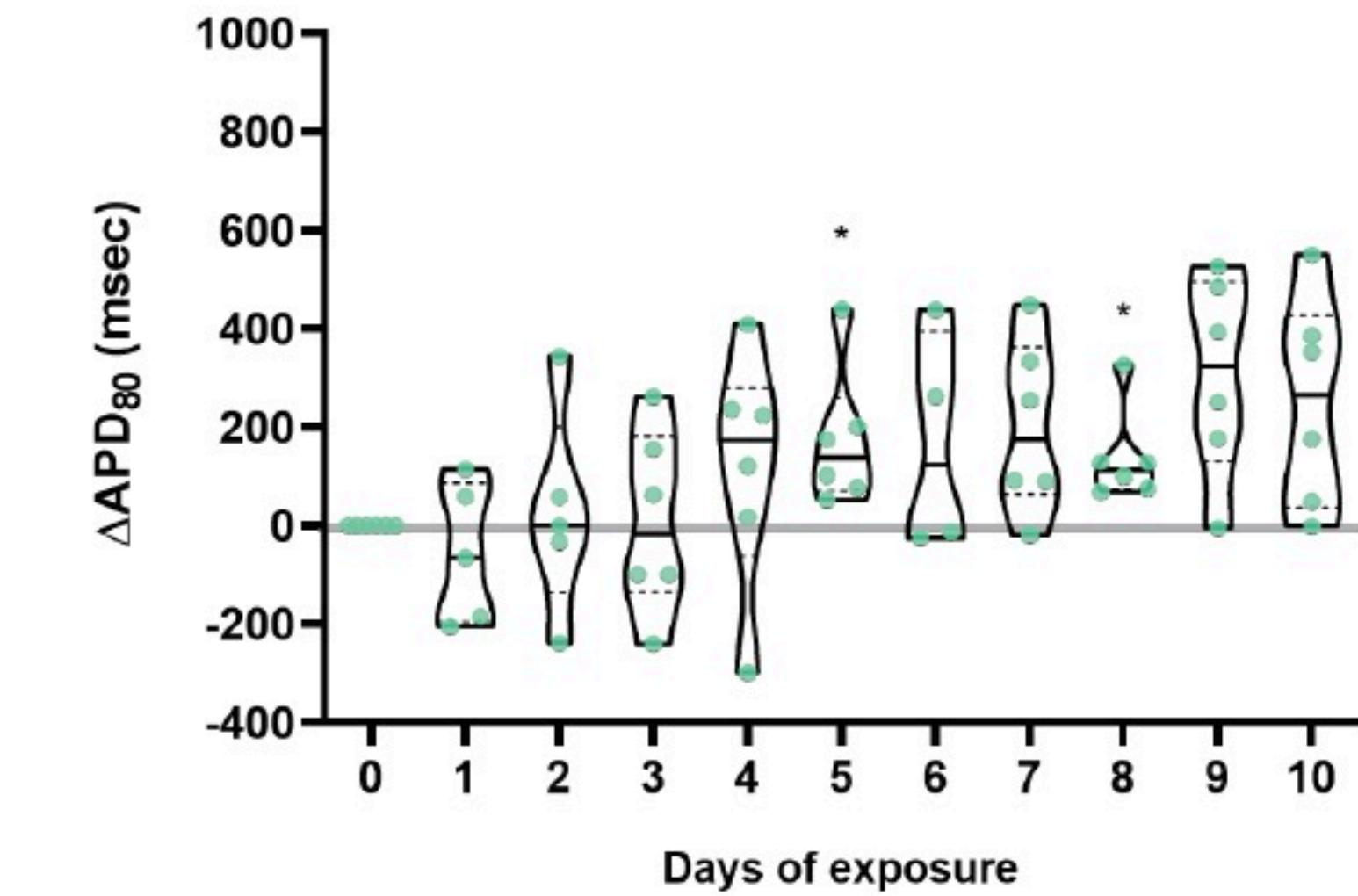
HCQ



AZM

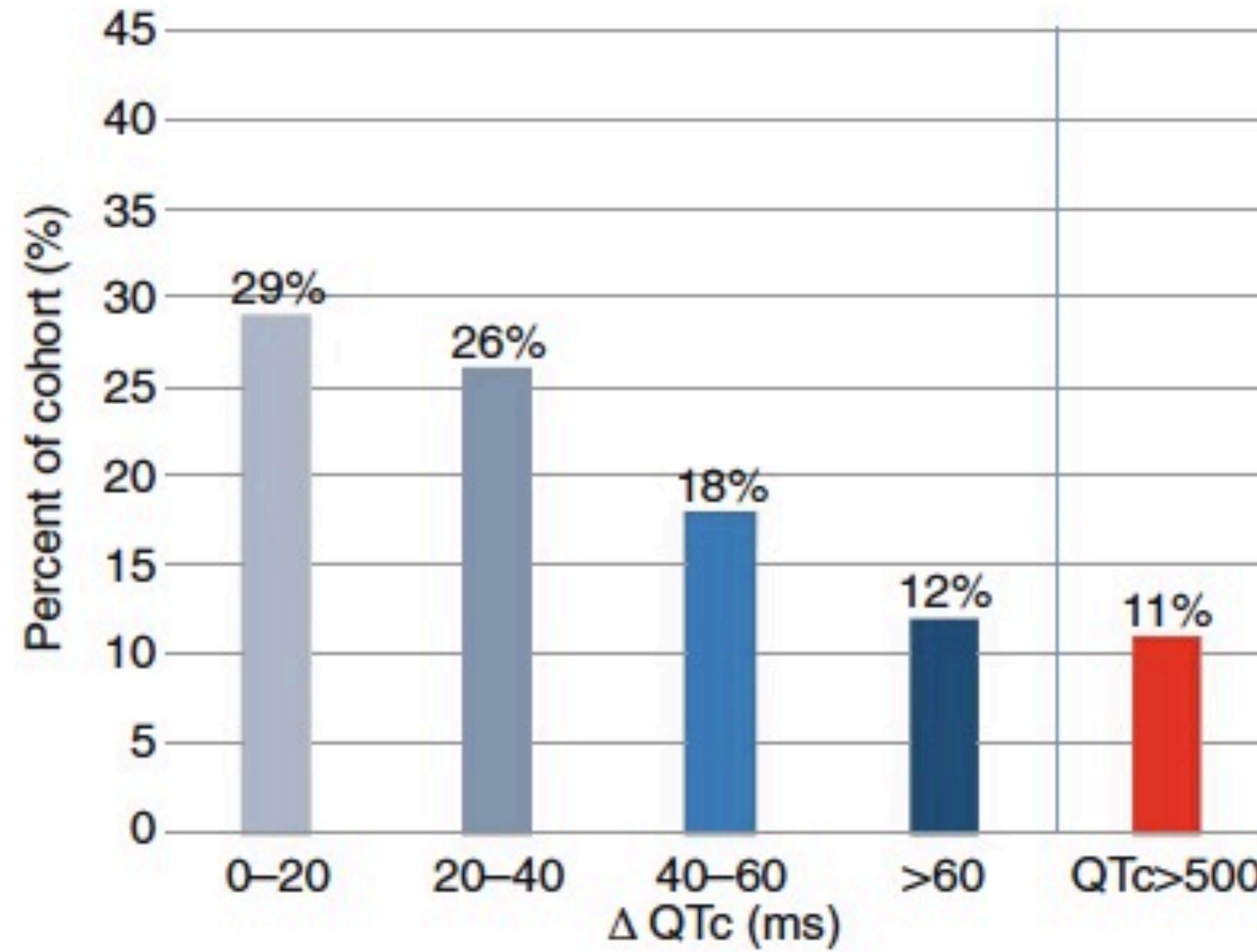


HCQ + AZM

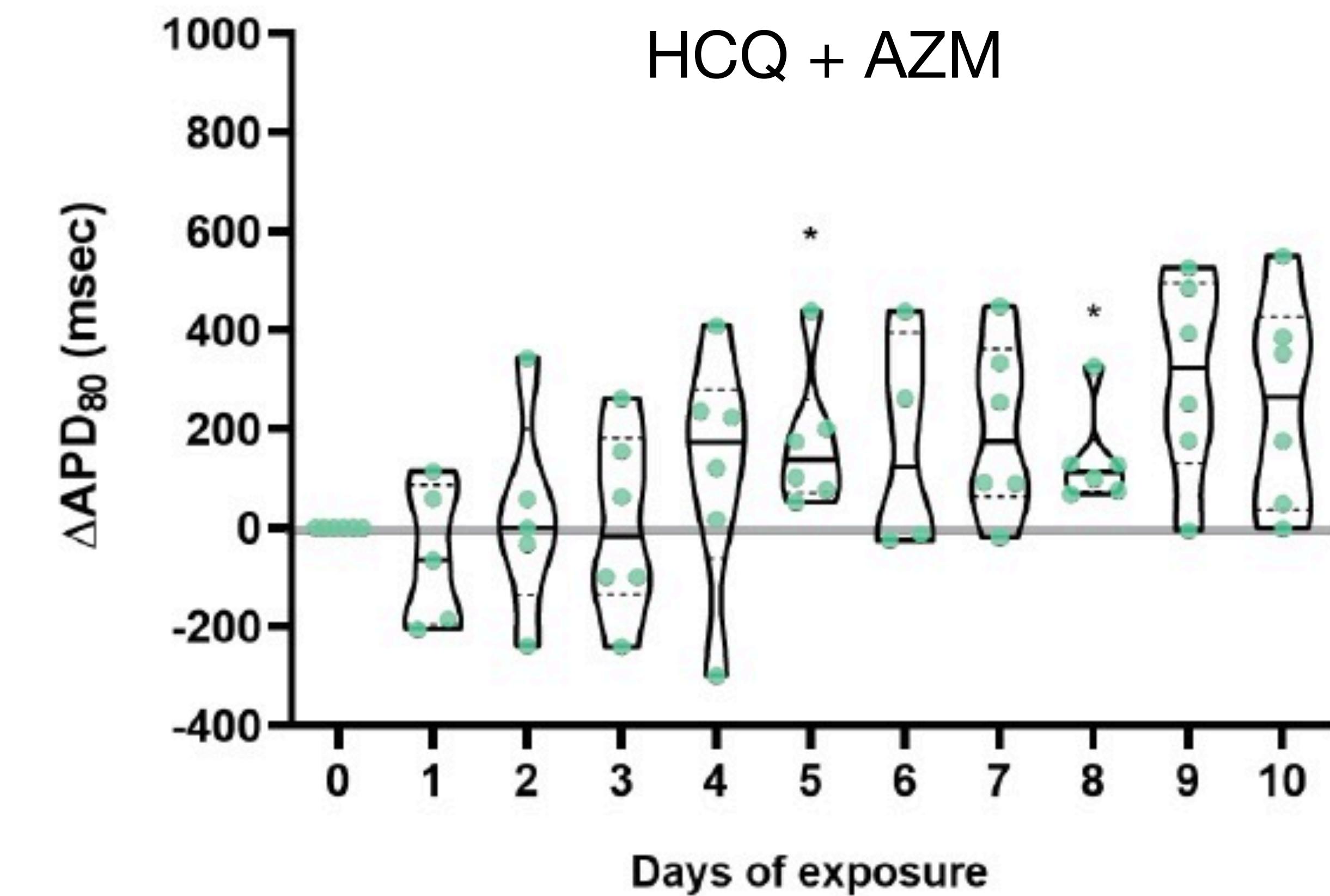


The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin

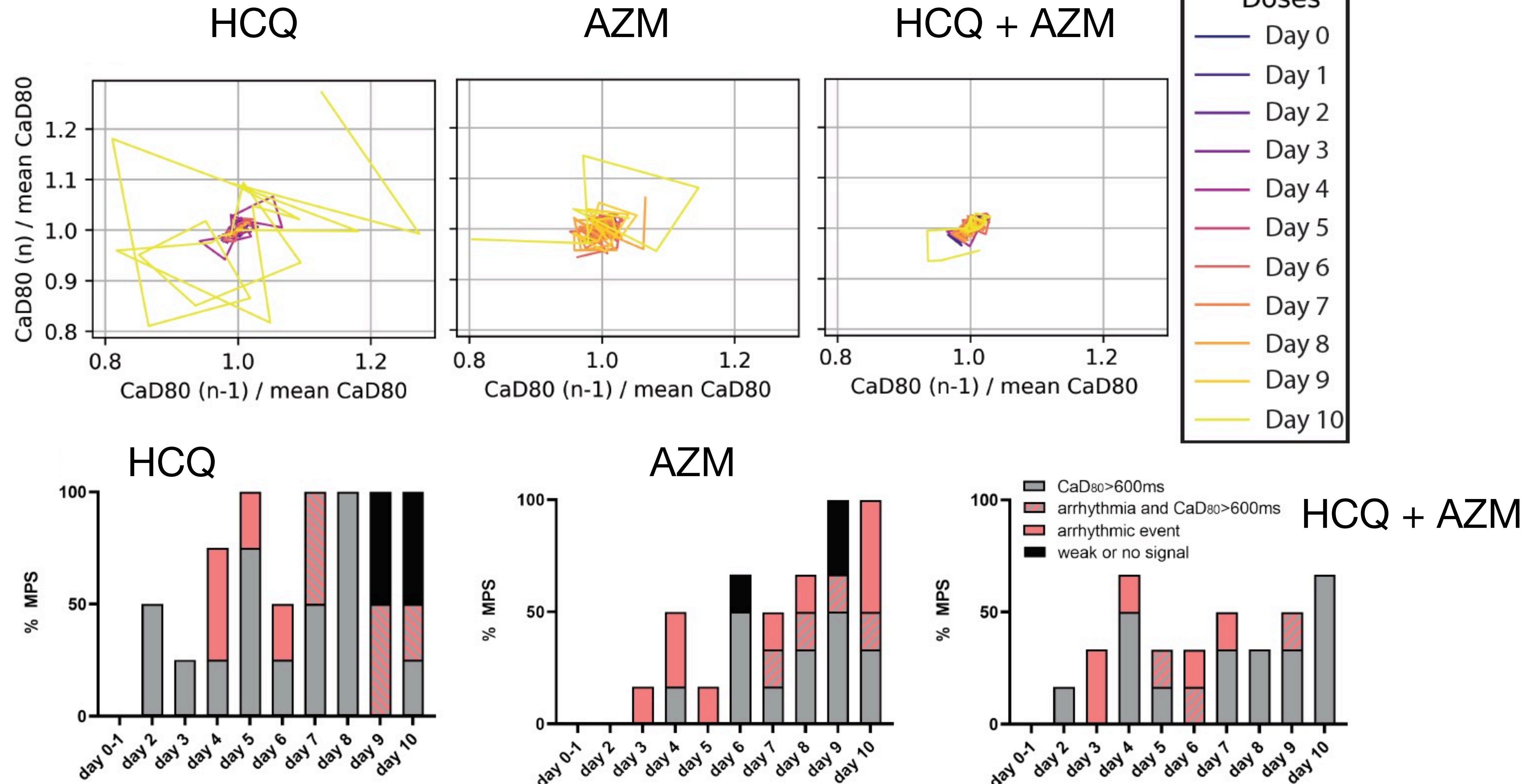
Chorin, E., et al., *The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin*. 2020.



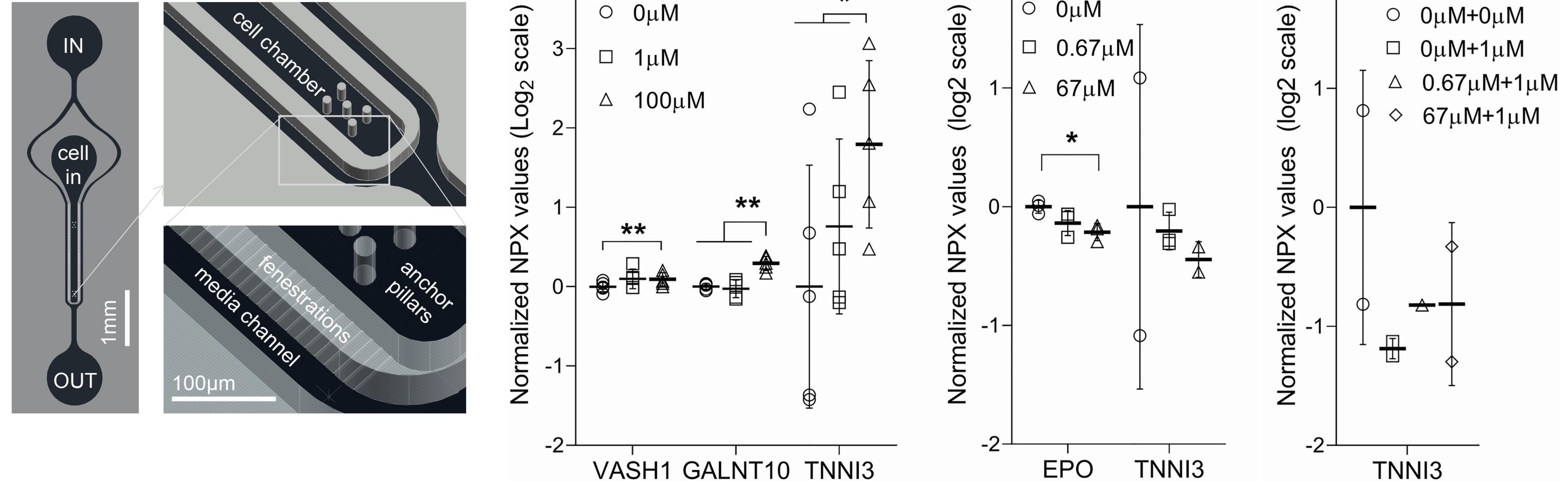
Clinical Trial Protocol on Chip



Clinical Trials in a Dish for COVID-19 Drug Repurposing



Clinical Trials in a Dish for COVID-19 Drug Repurposing



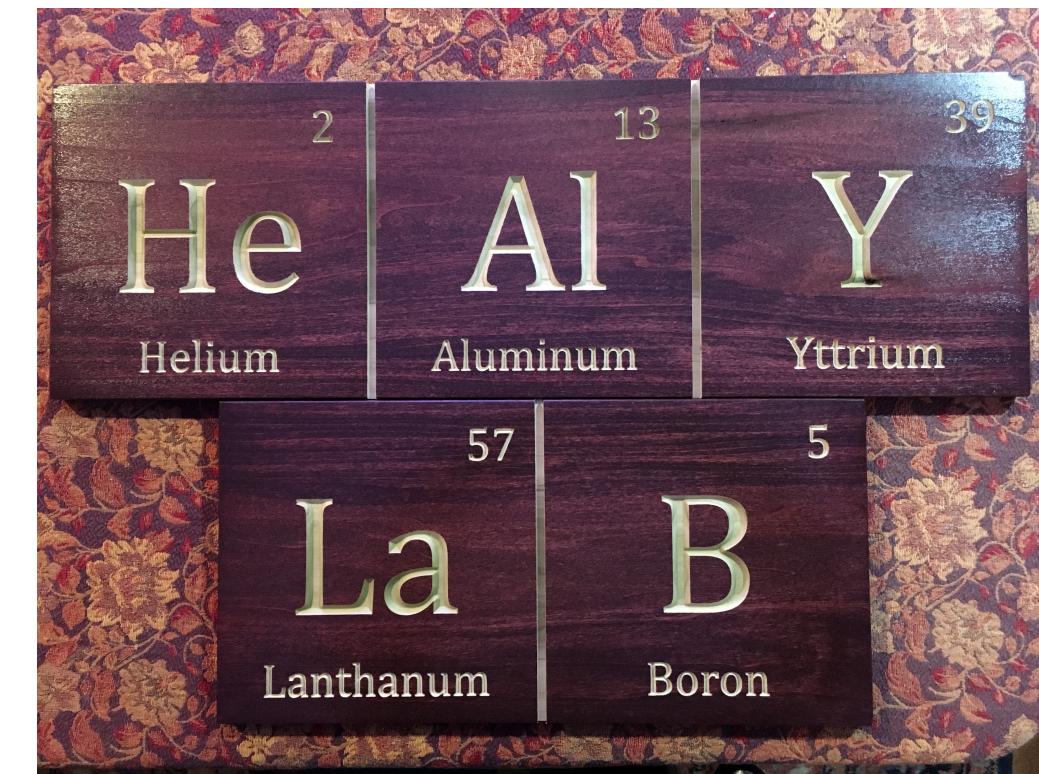
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University of California, Berkeley

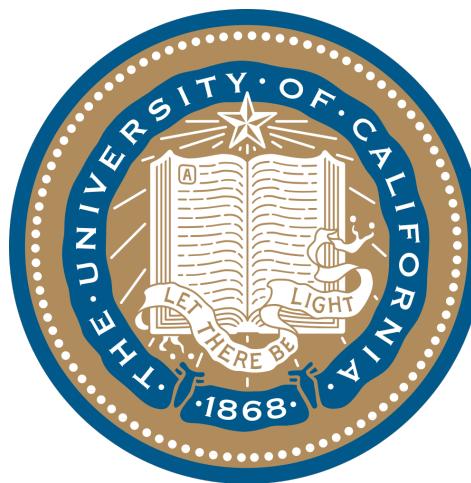
Prof. Evan Miller Prof. B. Rubinsky Prof. C. Dames
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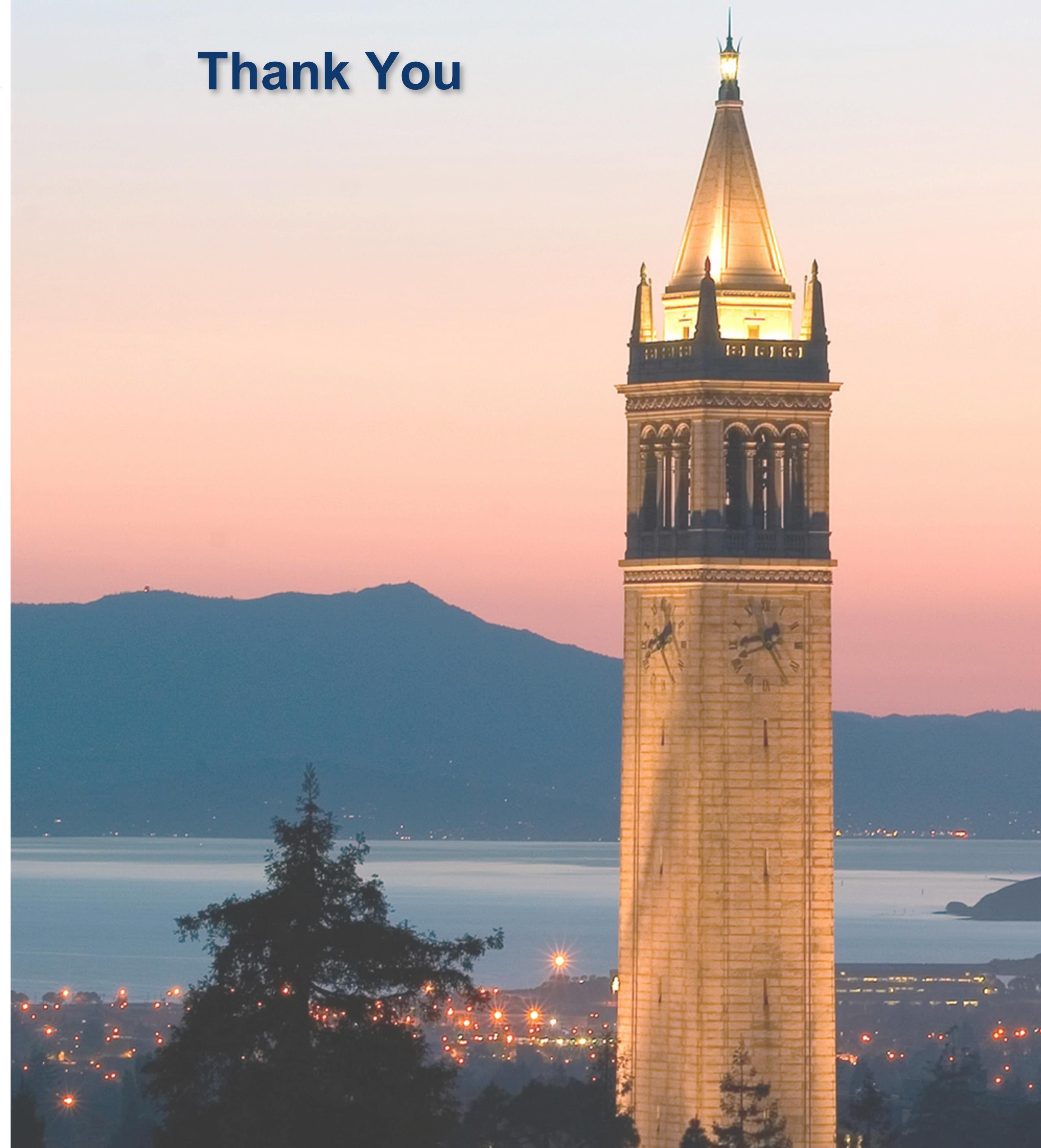
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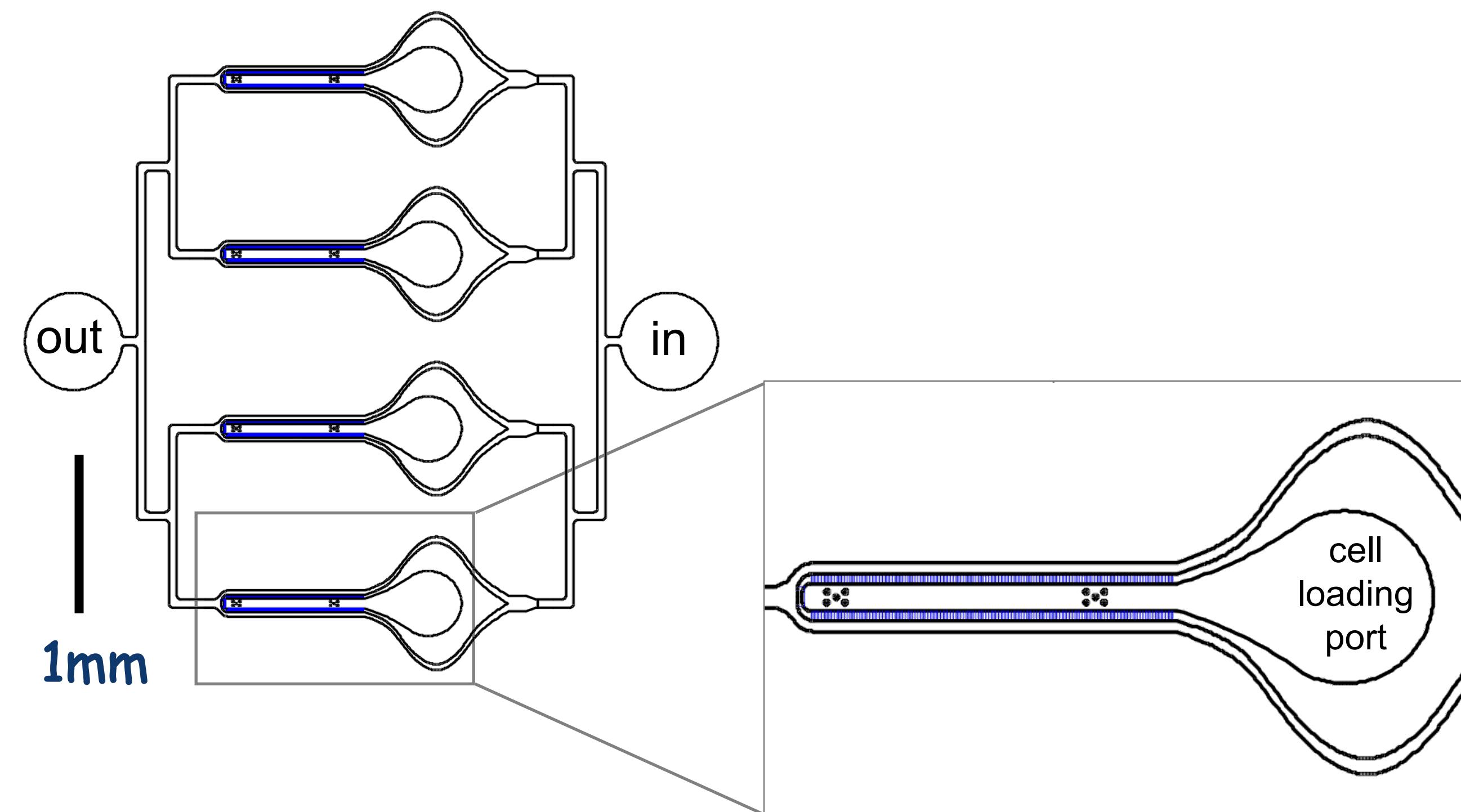
Thank You



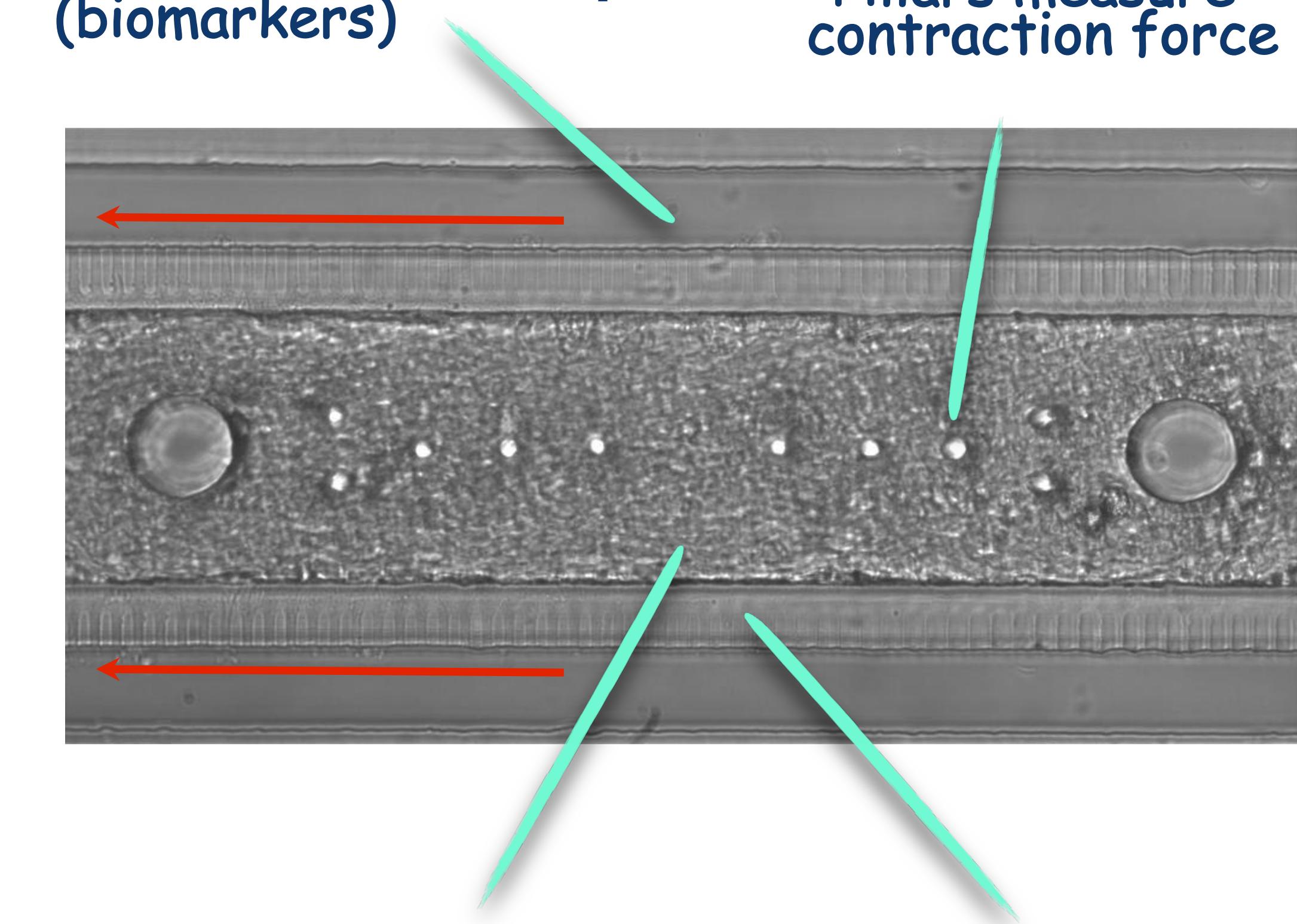
Cardiac Micromuscle - Microphysiological System

A hybrid system with on chip electrical and mechanical measurements

Real Time Sampling



Blood vessel-like channels - $50\mu\text{m}$ (biomarkers)



Pillars measure contraction force