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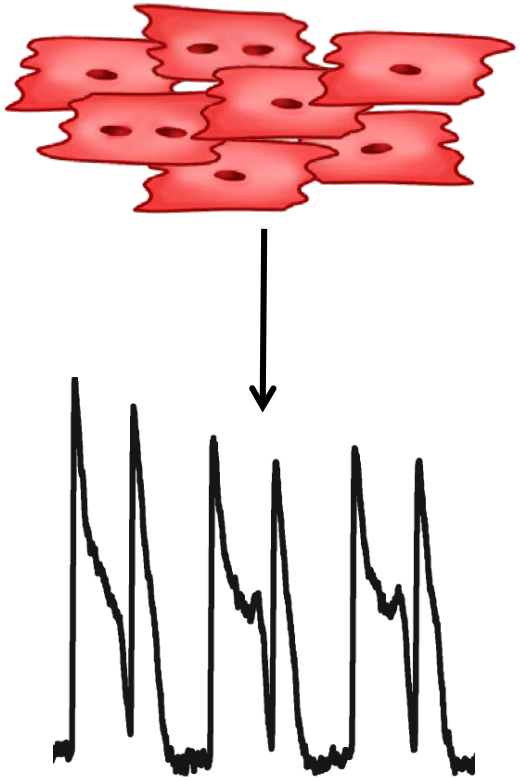

hiPSC Cardiomyocytes: Validation Study Results

Ksenia Blinova, PhD
US Food and Drug Administration

HESI-CSRC CiPA meeting May 21-22, 2018

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Human induced pluripotent stem cell-derived cardiomyocyte (hiPSC-CMs) study at FDA

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TOXICOLOGICAL SCIENCES, 155(1), 2017, 234–247

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Advance Access Publication Date: October 3, 2016
Research article

Comprehensive Translational Assessment of Human-Induced Pluripotent Stem Cell Derived Cardiomyocytes for Evaluating Drug-Induced Arrhythmias

Ksenia Blinova,[*,1] Jayna Stohlman,[*] Jose Vicente,[*,†,‡] Dulciana Chan,[*] Lars Johannesen,[*] Maria P. Hortigon-Vinagre,[§,¶] Victor Zamora,[§,¶] Godfrey Smith,[§,¶] William J. Crumb,[‖] Li Pang,[‖] Beverly Lyn-Cook,[‖] James Ross,[‖] Mathew Brock,[‖] Stacie Chvatal,[‖] Daniel Millard,[‖] Loriano Galeotti,[*] Norman Stockbridge,[†] and David G. Strauss[*,#]

26 drugs+3 drug combinations, 2 hiPSC-CMs lines, voltage sensitive dyes (VSD) and microelectrode array (MEA)

JiCSA hiPSC-CMs study

Journal of Pharmacological and Toxicological Methods 84 (2017) 111–127

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Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Research article

A new paradigm for drug-induced torsadogenic risk assessment using human iPS cell-derived cardiomyocytes

Hiroyuki Ando [a,b,c,*,1], Takashi Yoshinaga [a,b,d,**,1], Wataru Yamamoto [a,e], Keiichi Asakura [a,b,f], Takaaki Uda [a,c], Tomohiko Taniguchi [a,d], Atsuko Ojima [a,d], Raku Shinkyo [d], Kiyomi Kikuchi [d], Tomoharu Osada [a,b,g], Seiji Hayashi [a,b,f], Chieko Kasai [a,b,h], Norimasa Miyamoto [a,d], Hiroyuki Tashibu [a,b,i], Daiju Yamazaki [a,j], Atsushi Sugiyama [a,b,k], Yasunari Kanda [a,j], Kohei Sawada [a,b,d], Yuko Sekino [a,b,j]

Assessment of 60 drugs with microelectrode arrays

CiPA pilot hiPSC-CMs study

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TOXICOLOGICAL SCIENCES
doi: 10.1093/toxsci/kfy110
Advance Access Publication Date: April 27, 2018
Research article

Cross-Site Reliability of Human Induced Pluripotent Stem-Cell Derived Cardiomyocyte Based Safety Assays using Microelectrode Arrays: Results from a Blinded CiPA Pilot Study.

Daniel Millard, Qianyu Dang, Hong Shi, Xiaou Zhang, Chris Strock, Udo Kraushaar, Haoyu Zeng, Paul Levesque, Hua-Rong Lu, Jean-Michel Guillon, Joseph C Wu, Yingxin Li, Greg Luerman, Blake Anson, Liang Guo, Mike Clements, Yama A Abassi, James Ross, Jennifer Pierson, Gary Gintant

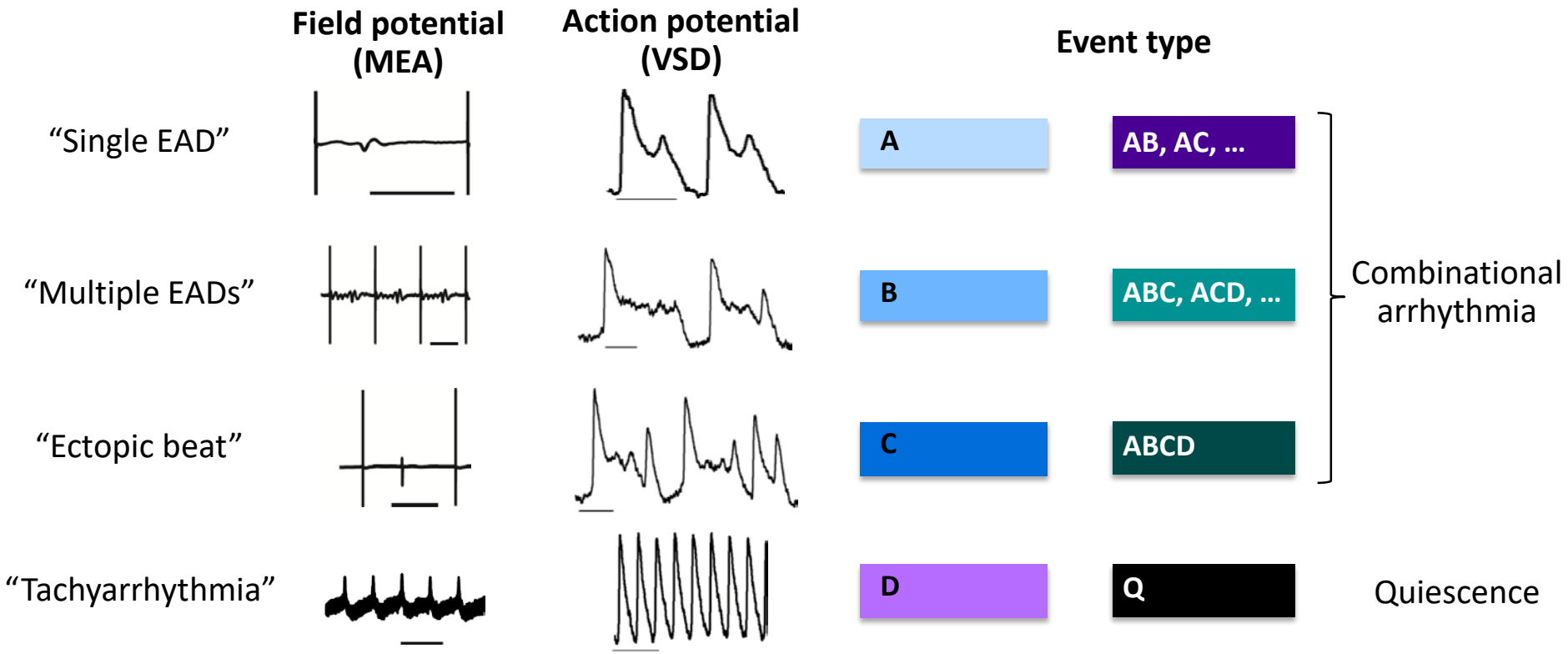
- 8 drugs, 4 hiPSC-CMs lines, 3 MEA platforms
- Generally consistent trends across sites
- Platform significant for 4 out of 8 drugs
- Protocol established as basis for Validation Study

FDA-HESI Myocyte Validation Study

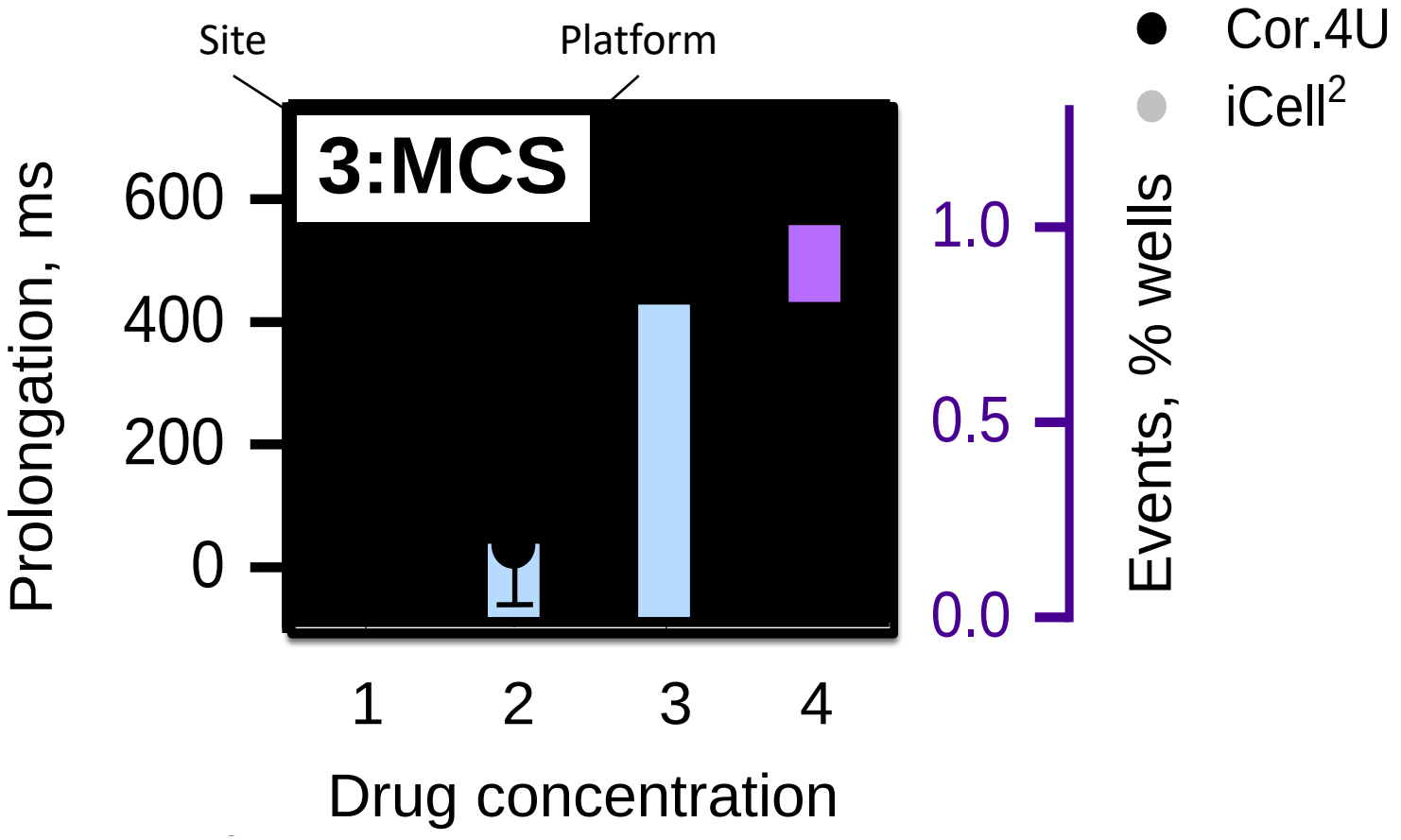
- **Study Design:**
- 10 sites
- 5 electrophysiological devices:
    - 4 microelectrode array (MEA): **AXN** (Axion Biosystems), **MCS** (Multichannel systems), **ECR** (ACEA Biosciences), **AMD** (Alpha MED) and 1 voltage-sensitive dye (VSD): **CLY** (Clyde Biosciences)
- 2 hiPSC-CM lines:
    - **iCell²** (10 datasets), **Cor.4U** (5 datasets)
- 28 blinded drugs, 4 concentrations, 5-6 replicate wells at each concentration
    - Standard proprietary media throughout: serum containing (MEA sites), serum-free (VSD site)
- Acute effects (30 min drug exposure)

Data Analysis

- Data exclusion criteria applied to baseline recordings only (beating rate 20 – 90 bpm; beat period coefficient of variation <5% and within 6 SD of the plate; depolarization amplitude > 300 µV)
- Baseline- and vehicle-controlled, *Fridericia* rate-corrected drug induced changes in repolarization duration calculated: ΔΔAPD90c, ΔΔFPDc
- Drug-induced arrhythmias were classified:

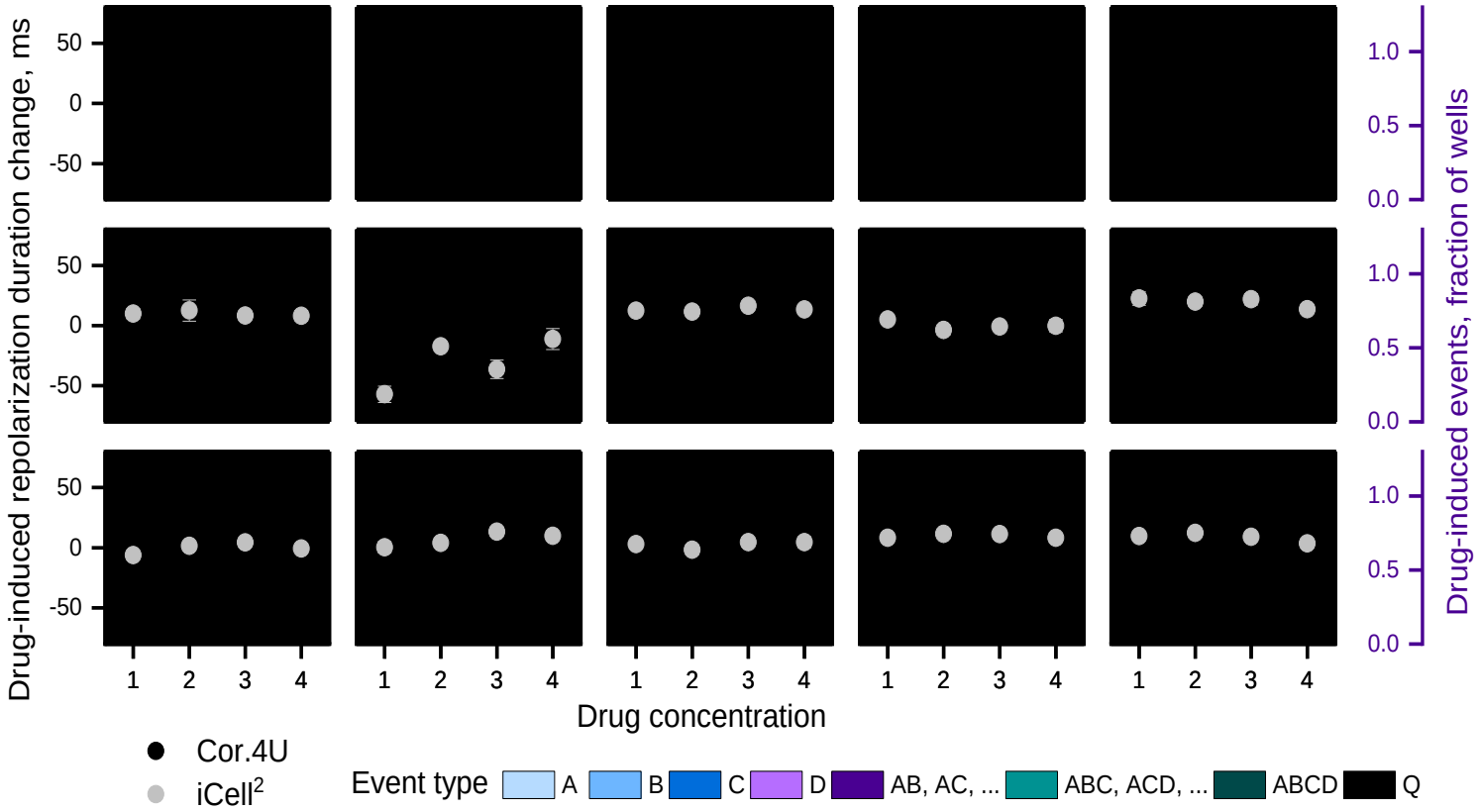


Data format



Event type A B C D AB, AC, ... ABC, ACD, ... ABCD Q

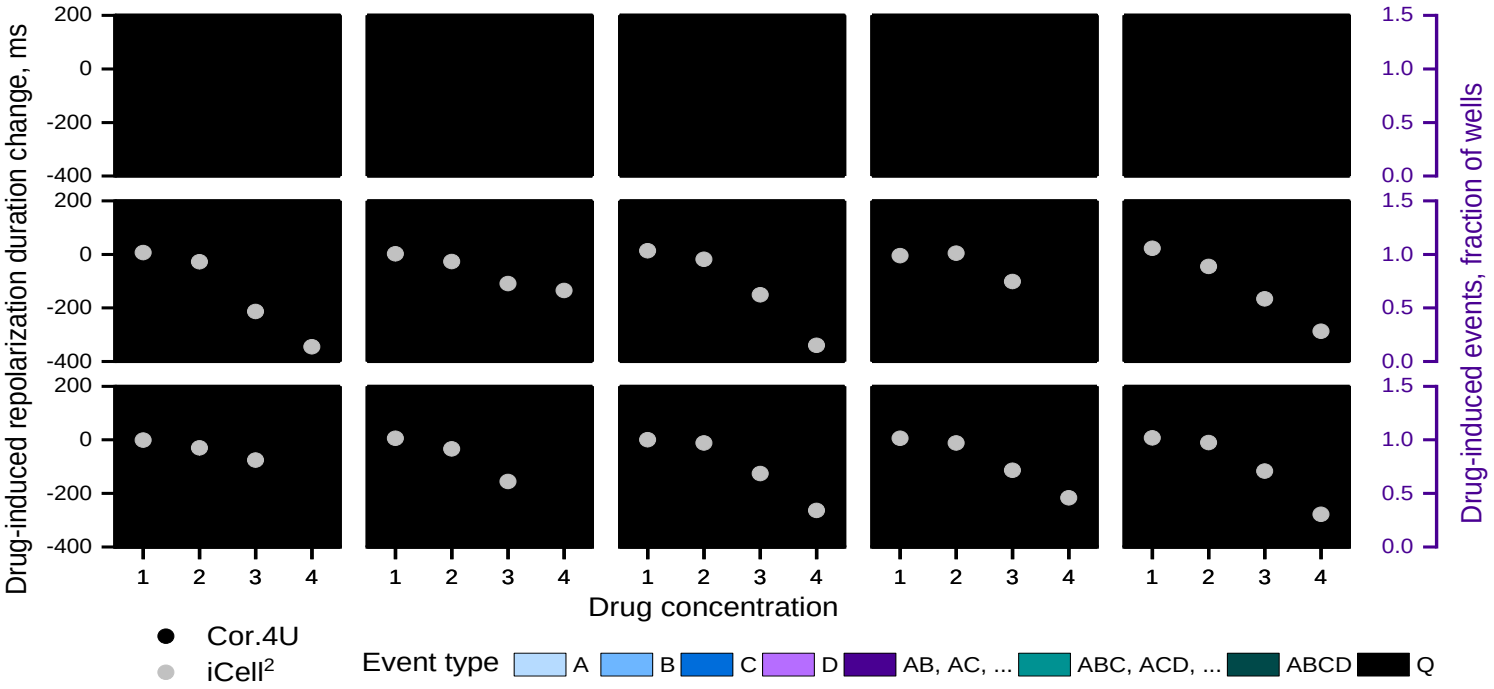
Low risk drug example: loratadine



Cmax, µM	Concentration	1	2	3	4	Interval
0.00045	µM	0.001	0.003	0.009	0.03	1/2 log
	folds Cmax	2.1	6.7	21.1	66.7	

Loratadine had no repolarization effect on myocytes up to 67x clinical Cmax across sites.

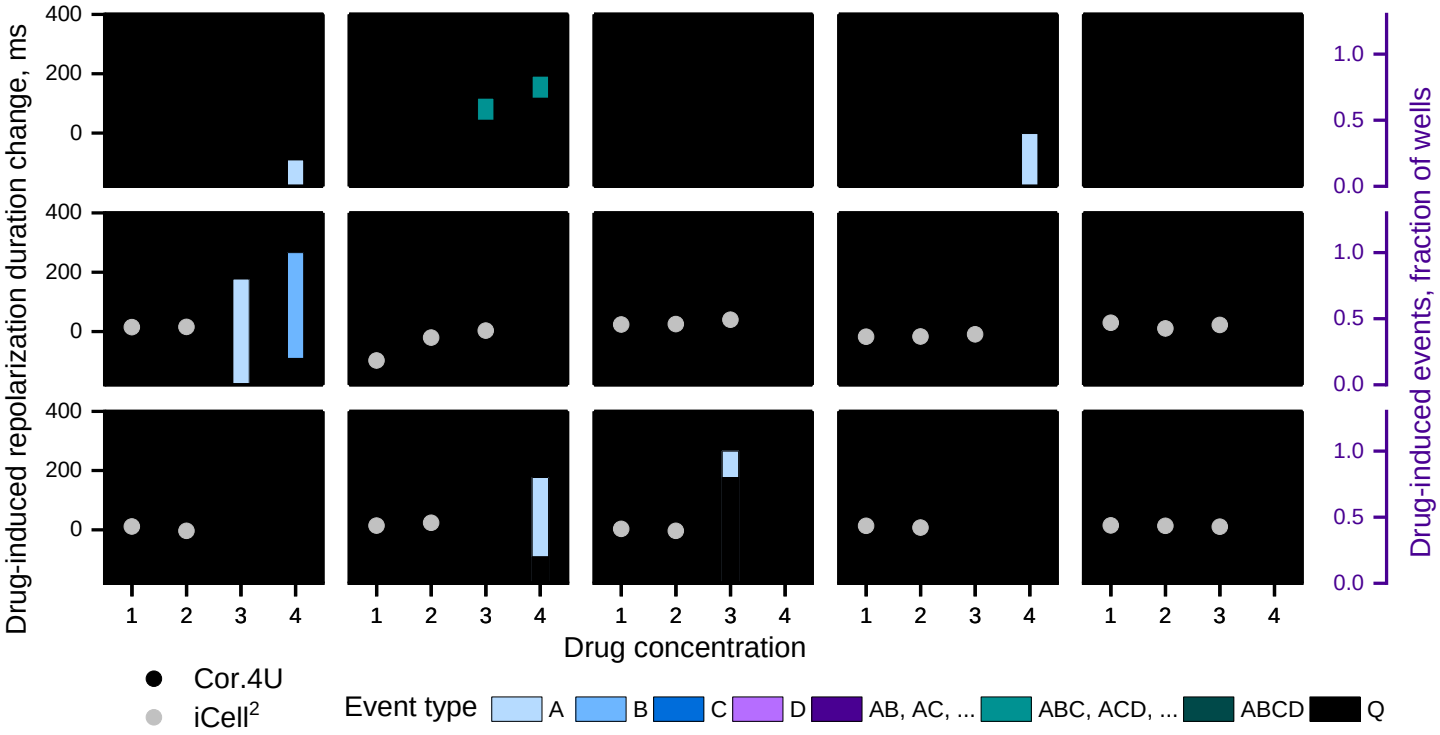
Low risk drug example: verapamil



Cmax, µM	Concentration	1	2	3	4
	µM	0.001	0.01	0.1	1
0.045	folds Cmax	0.02	0.22	2.22	22.2

Verapamil elicited shortening of repolarization (and no arrhythmia-like events) across all sites. Similarly to loratadine and verapamil, other low risk drugs (diltiazem, nifedipine, nitrendipine, and tamoxifen) did not induce arrhythmias or statistically significant prolongation at any concentrations (20- to 140-fold clinical Cmax).

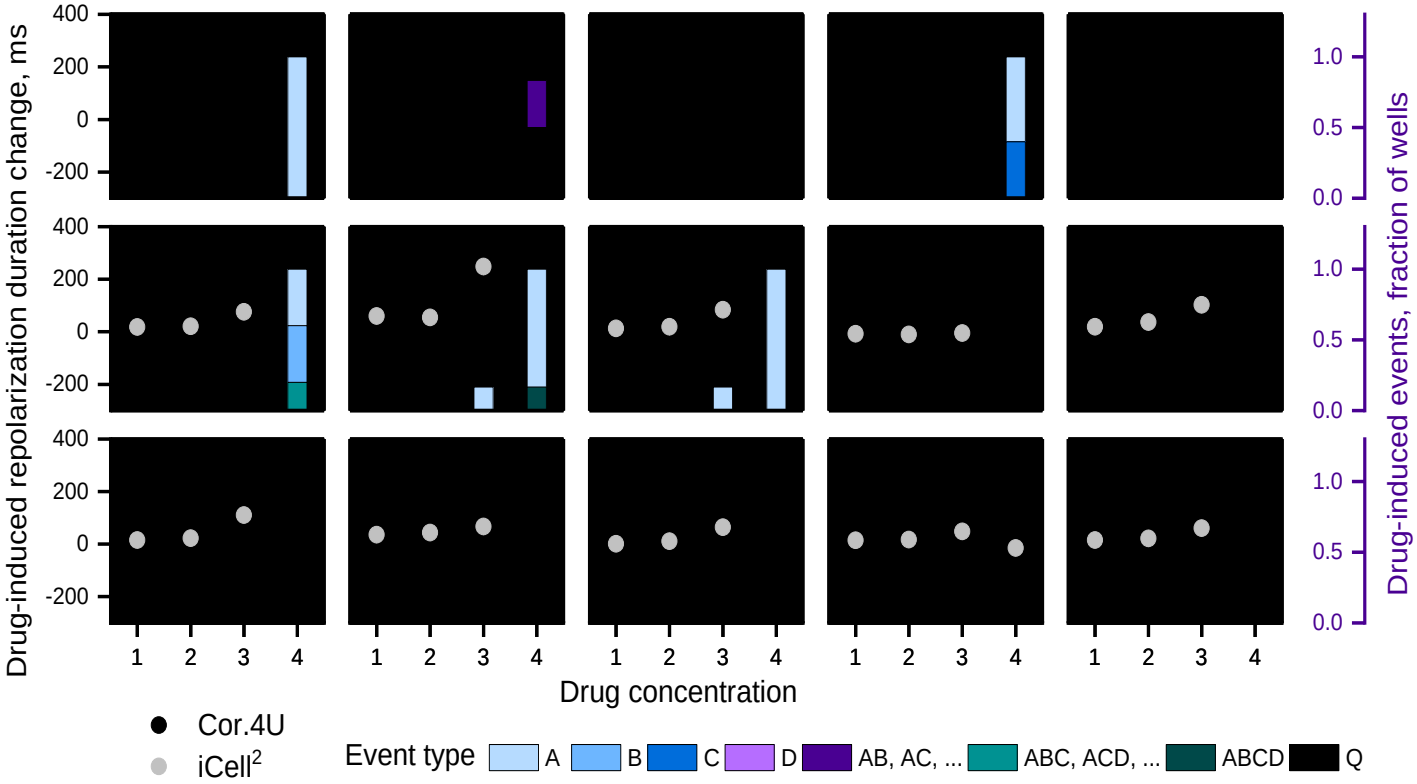
Low risk drug example: mexiletine



Cmax, µM	Concentration	1	2	3	4
2.5	µM	0.032	0.1	0.316	1
	folds Cmax	2	6.3	19.8	62.5

Mexiletine had no effect on myocytes up to 6x Cmax; arrhythmia-like events were recorded in 2/15 datasets at ~20x Cmax and 5/15 datasets at ~60x Cmax.

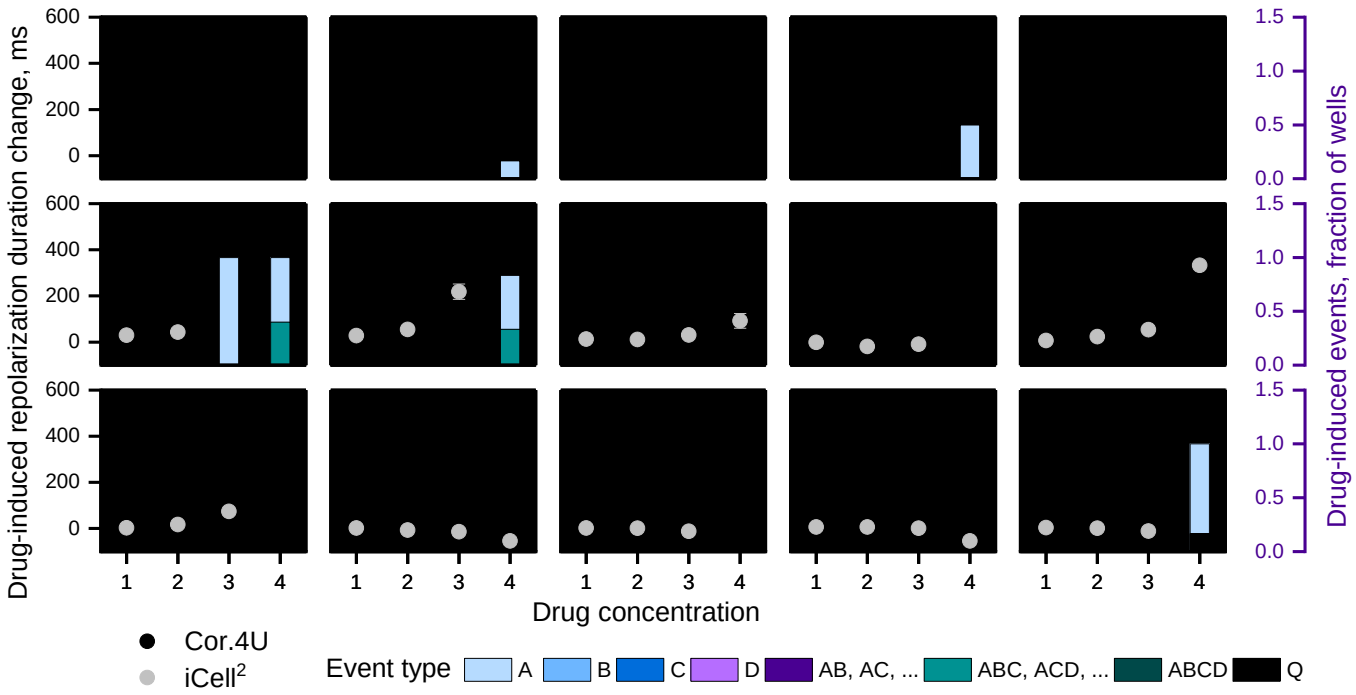
Low risk drug example: ranolazine



Cmax, µM	Concentration	1	2	3	4
1.948	µM	0.1	1	10	100
	folds Cmax	0.1	0.5	5.1	51.3

Ranolazine induced dose-dependent repolarization prolongation with a few drug-induced arrhythmia-like events recorded at 5x Cmax (1/5 wells in 2 datasets – iCell^2) and at 50x Cmax (6/15 datasets).

Low risk drug example: metoprolol



Cmax, µM	Concentration	1	2	3	4
1.8	µM	3.2	10	32	100
	folds Cmax	1.8	5.6	17.6	55.6

Metoprolol had no effect on iPSC-CMs at lower doses (up to 5.6 x Cmax) with drug-induced repolarization prolongation and a few arrhythmia-like events reported at ~20 Cmax (1/15 datasets) and at ~56x Cmax (5/15 datasets).

Low risk category results summary

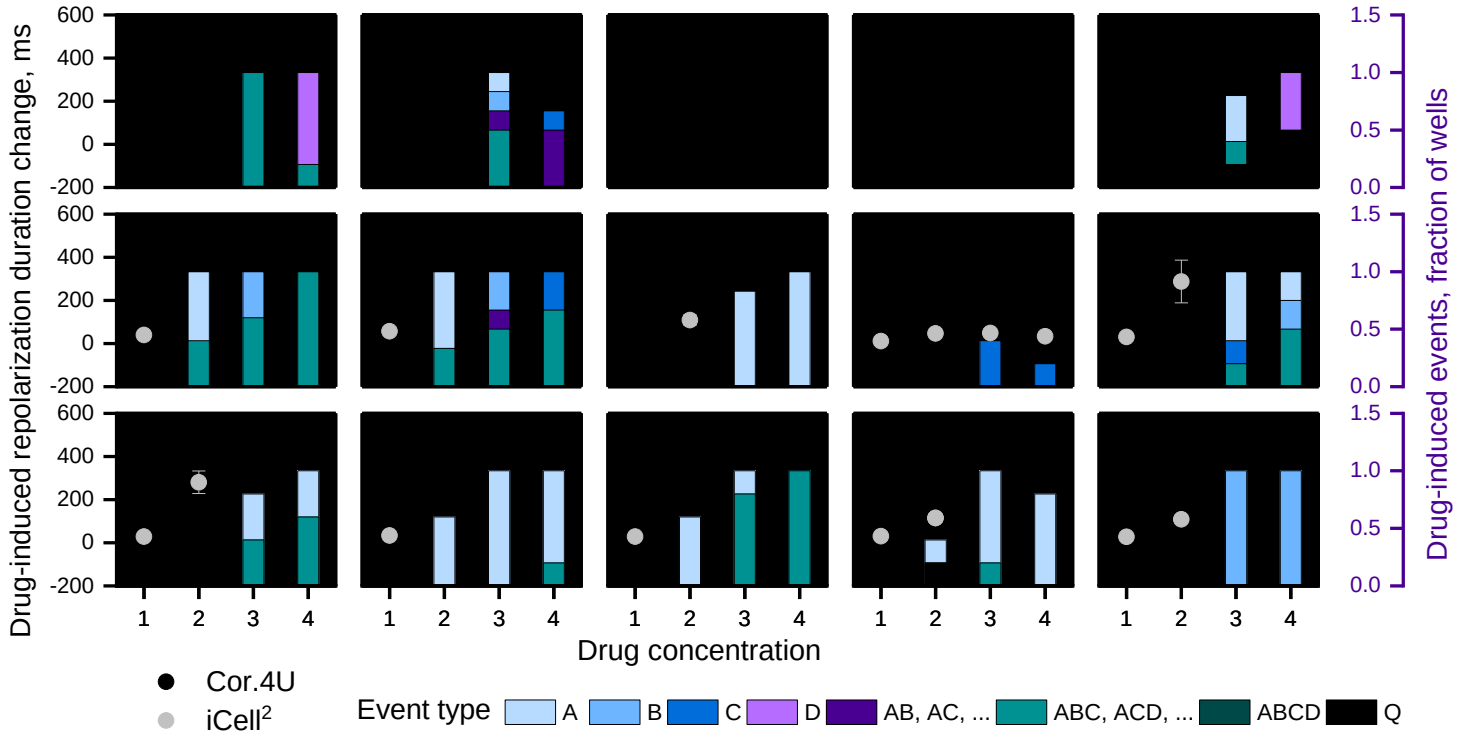
- None of the low TdP risk drugs induced statistically-significant repolarization prolongation or arrhythmia-like events in either iPSC-CMs line at or around Cmax (up to ~5X Cmax)

- 6/9 low risk drugs did not induce repolarization prolongation or arrhythmia-like events at any of studied concentrations (up to 20-140x Cmax, depending on the drug)

- Three drugs (Ranolazine, Mexiletine and Metoprolol) induced arrhythmia-like events at higher doses in a portion of datasets:
    - Ranolazine: 1/5 wells in 2 datasets – iCell^2 at 5xCmax and at 50xCmax (6/15 datasets)
    - Mexiletine: 2/15 datasets at ~20xCmax and 5/15 datasets at ~60xCmax.
    - Metoprolol: at ~20 Cmax (1/15 datasets) and at ~56xCmax (5/15 datasets)

- **Low risk category drug effects in iPSC-CMs were largely consistent with clinical safety record of these drugs**

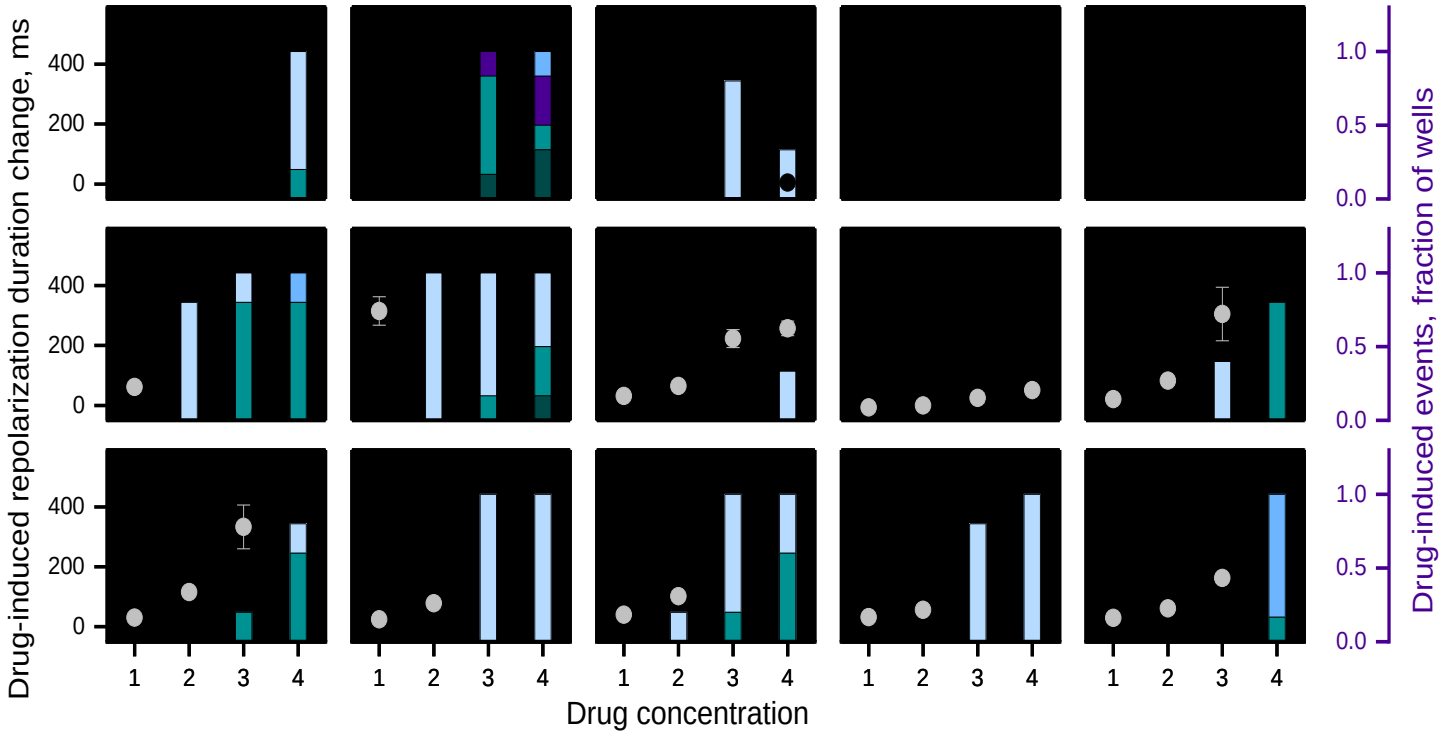
High risk drug example: ibutilide



Cmax, µM	Concentration	1	2	3	4
0.1	µM	0.0001	0.001	0.01	0.1
	folds Cmax	0.001	0.01	0.1	1

Ibutilide induced repolarization prolongation and arrhythmia-like events at concentration as low as 1/100 x Cmax in iCell^2 and at 1/10 x Cmax in both cell lines.

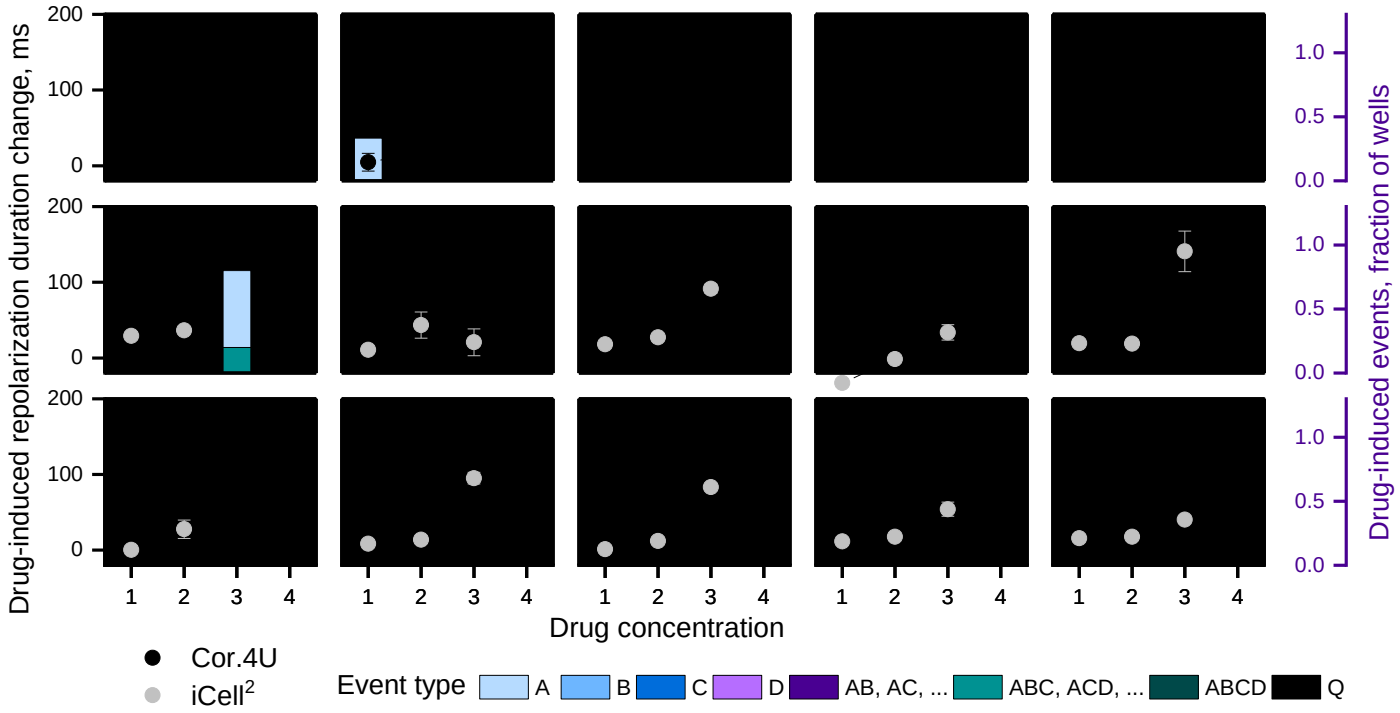
High risk drug example: dofetilide



Cmax, µM	Concentration	1	2	3	4
2	µM	0.0003	0.001	0.003	0.01
	folds Cmax	0.16	0.5	1.58	5

Dofetilide induced repolarization duration prolongation (all datasets) and arrhythmia-like events at concentrations as low as 1/2x Cmax and in 13/15 datasets at 5x Cmax (highest studied dose).

High risk drug example: bepridil



Cmax, µM	Concentration	1	2	3	4
0.032	µM	0.01	0.1	1	10
	folds Cmax	0.3	3.1	31.3	312.5

Bepridil induced repolarization prolongation, but no arrhythmia-like events were observed (with an exception of 2 datasets at one concentration) even at ~30x Cmax. Quiescence observed across many sites at higher conc's (3 &4). **Inconsistent with high TdP risk.**

High risk category results summary

- All of the high TdP risk drugs induced statistically significant repolarization prolongation and/or arrhythmia-like events in both hiPSC-CM lines in at least 10 out of 15 datasets.

- Drug-induced arrhythmia-like events were consistently observed at concentrations close to clinical Cmax for dofetilide, quinidine and d,l-sotalol and at concentrations well below Cmax for ibutilide.

- **High risk category drugs effects in iPSC-CMs were largely consistent with clinical safety record of these drugs (with an exception of bepridil)**

Good cross-site correlation

Pearson correlation in drug-induced ddFPD90c/APD90c reported for 28 drugs in iCell[2]

Test Site	1	2	3	4	5	6	7	8	9	10	Average
1	**1**	0.75	0.89	0.77	0.90	0.73	0.94	0.95	0.94	0.92	0.88
2	0.75	**1**	0.63	0.37	0.66	0.78	0.70	0.67	0.67	0.63	**0.69**
3	0.89	0.63	**1**	0.46	0.78	0.78	0.74	0.78	0.78	0.78	0.76
4	0.77	0.37	0.46	**1**	0.66	0.61	0.74	0.80	0.76	0.79	**0.70**
5	0.90	0.66	0.78	0.66	**1**	0.88	0.71	0.92	0.80	0.90	0.82
6	0.73	0.78	0.78	0.61	0.88	**1**	0.79	0.81	0.78	0.69	0.78
7	0.94	0.70	0.74	0.74	0.71	0.79	**1**	0.89	0.92	0.91	0.83
8	0.95	0.67	0.78	0.80	0.92	0.81	0.89	**1**	0.95	0.95	0.87
9	0.94	0.67	0.78	0.76	0.80	0.78	0.92	0.95	**1**	0.92	0.85
10	0.92	0.63	0.78	0.79	0.90	0.69	0.91	0.95	0.92	**1**	0.85

High correlation for most sites (average Pearson coefficients >75%), while Sites 2 and 4 had slightly lower correlation coefficients (69% and 70%, respectively). Site 2 was the only site using VSD platform and serum-free media, Site 4 reported lower response to dofetilide

– addition of **positive controls** should be considered for future studies!

Site-to-site variability compared to other variability sources

Site-to-site variability in drug-induced ddFPDc/APD90c averaged across all 28 drugs was compared to other sources of variability by treating site effects as either fixed or random effects and using square root of the mean squared error (SR MSE) for each contribution

Type of effects	Variability Source	Root of mean square error (ms)
Fixed	Test site	170
Fixed	Cell type	245
Fixed	Drug concentration	482
Random	Test site	36
Random	Other Errors	67

Site-induced variability is lower than hiPSC-CMs line-induced variability (iCell or Cor.4U)

Site-induced variability is lower than all other sources of random variability (well-to-well variability, plate-to-plate variability, human error etc.)

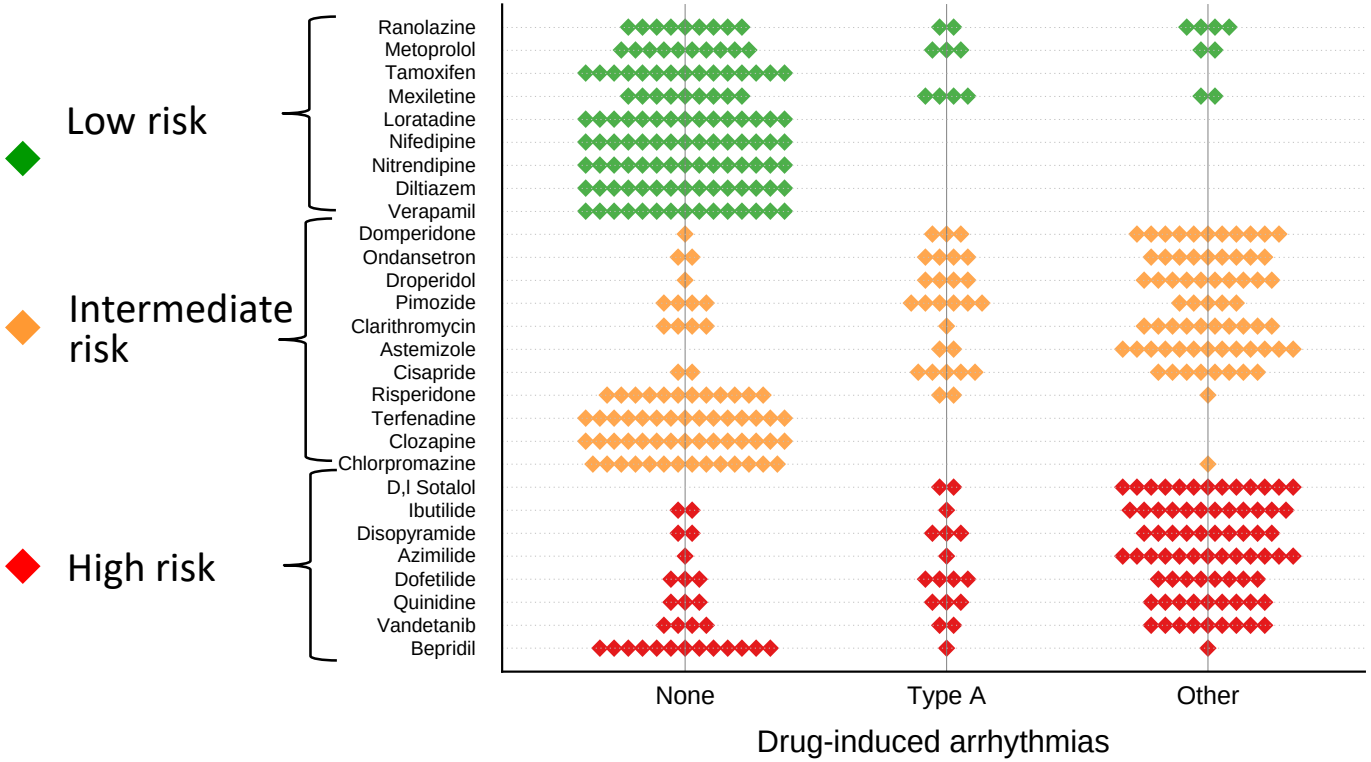
Low site-to-site variability

hiPSC-CM Assay Endpoints Evaluated in TdP Risk Categorization Models

#	Predictor Description	Predictor Type
1	**Did drug induced arrhythmias occur at any concentration? (0=no arrhythmia, 1=type A arrhythmia, 2=any other arrhythmia type)**	**Categorical**
2	Were drug-induced arrhythmias observed at any concentration in ≥40% wells (typically in at least 2 out of 5 replicate wells) (0=no, 1=yes)	Binary
3	Repolarization prolongation (ms) at the first drug concentration with statistically significant (p≤0.05) prolongation or shortening	Continuous
4	**Maximum repolarization change (ms) observed at any concentration**	**Continuous**
5	Drug concentration (folds over Cmax) at which the first statistically significant (p≤0.05) repolarization prolongation was first observed	Continuous
6	Drug concentration (folds over Cmax) when drug-induced arrhythmias were first observed	Continuous
7	**Drug-induced repolarization change (ms) at Cmax**	**Continuous**

Bolded predictors (1,4,7) most useful for drug categorization

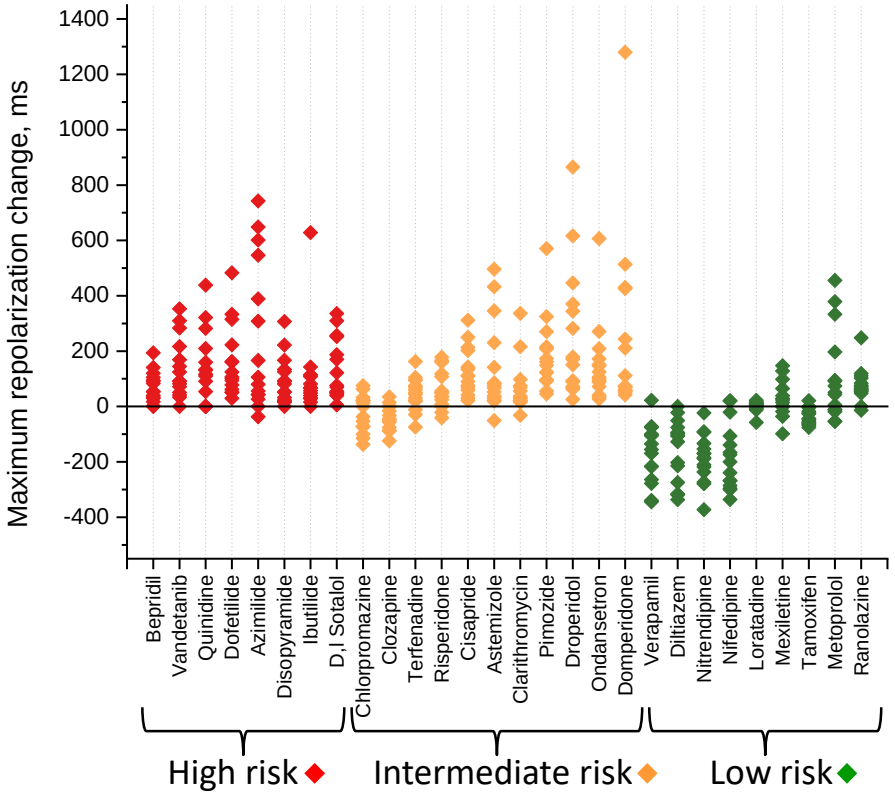
Predictor 1: Arrhythmia-like Events



Each data point represents an individual dataset (site/cell type combination)

- Most **low** risk drugs (green) did not induce any arrhythmias (None).
  A few sites showed arrhythmias (Type A or Other) for ranolazine, metoprolol and mexiletine.
- Few arrhythmias were reported for the following **intermediate** risk drugs (orange): risperidone, terfenadine, clozapine and chlorpromazine, but the majority of the datasets showed domperidone, ondansetron, droperidol, pimozide, clarithromycin, astemizole and cisapride-induced arrhythmias
- Most **high** risk drugs (except for bepridil) induced arrhythmia-like events in hiPSC-CMs
- The fraction of more severe drug-induced arrhythmias (Other) from the total arrhythmias (Type A and Other) is higher for high risk than intermediate risk drugs (77% high vs. 60% intermediate risk)

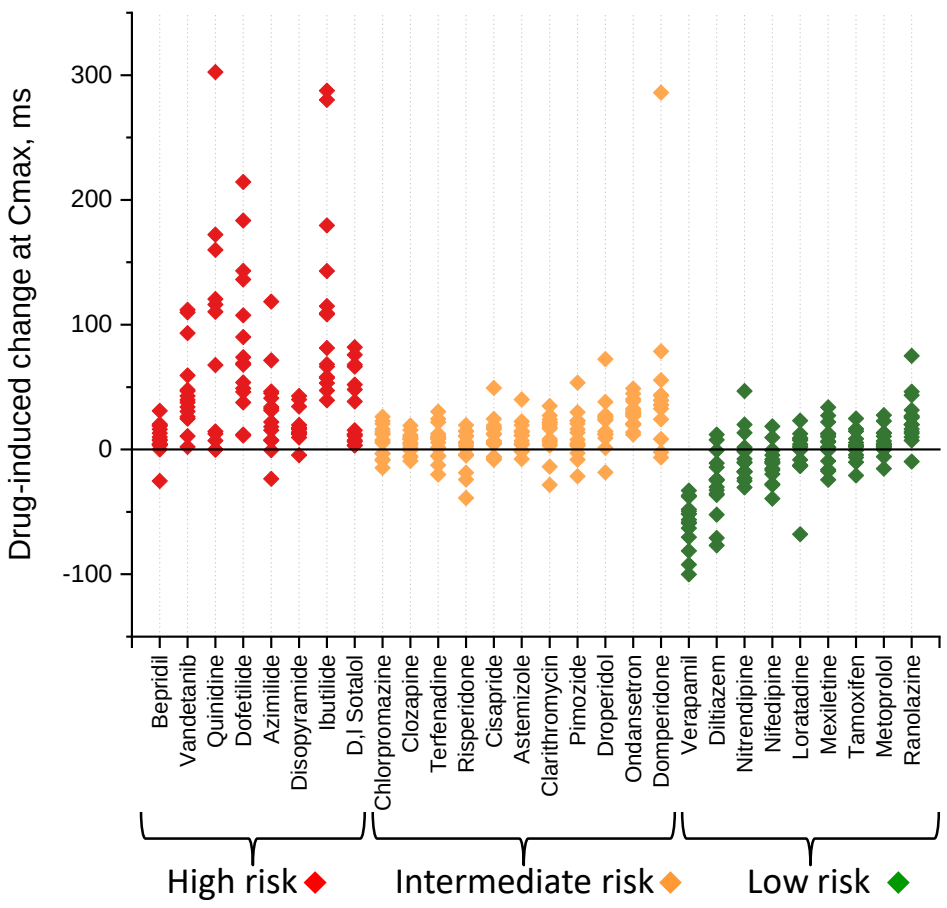
Predictor 4: Maximum Prolongation (at any concentration)



Each data point is an individual dataset (site/cell type combination)

- All **high** risk drugs (red) induced repolarization prolongation (range from 70 ms for bepridil to 250 ms for azimilide, average across all high risk drugs of **135** ms)
- **Intermediate** risk drug-induced change in repolarization duration ranged from negative 35 ms for clozapine to positive 255 ms for domperidone, average across all intermediate risk drugs **110** ms)
- 5/9 **low** risk drugs induced repolarization duration shortening, while maximum observed effect was positive for loratadine (~2 ms), mexiletine (26 ms), ranolazine (76 ms), and metoprolol (105 ms); Overall effect of low risk drugs was in a range from negative -187 ms to positive 105 ms (**-58** ms average across all drugs in this category

Predictor 7: Prolongation at Cmax



Each data point is an individual dataset (site/cell type combination)

- Estimated drug-induced repolarization prolongation at Cmax was the highest for ibutilide, dofetilide, quinidine and vandetanib in the **high** risk category with the average drug-induced prolongation at Cmax of **53 ms** in this category
- **Intermediate** risk drug induced moderate repolarization prolongation at Cmax with an average of **15 ms** across all drugs
- 5/9 drugs in the **low** risk category shorten repolarization duration at Cmax, while drug-induced prolongation was observed for tamoxifen (2 ms), mexiletine (4 ms), metoprolol (6 ms) and ranolazine (24 ms). The averaged across drugs change in repolarization duration was **-7 ms**

Risk Category Prediction Models

Model 1

Logistic Regression (High or Intermediate) vs. Low Risk

$$Logit(P1) = (Predictor1) + (Predictor4) + (Predictor7)$$

P1 is a probability of a drug to be high or intermediate risk

Model 2

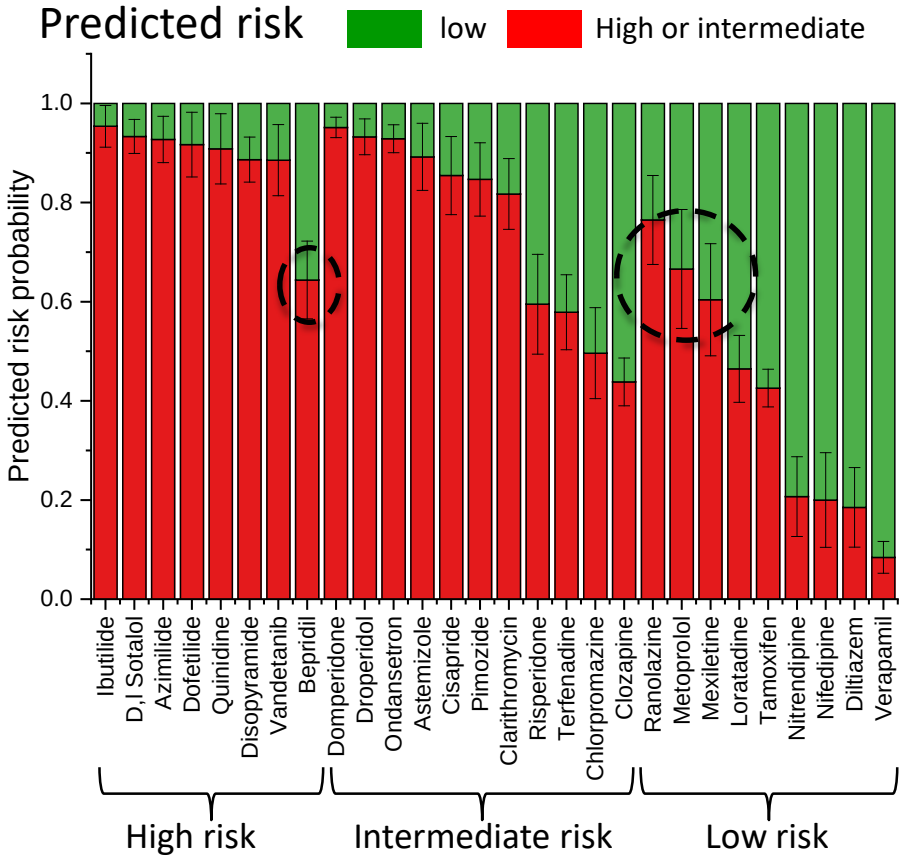
Ordinal Regression: High vs. Low or Intermediate vs. Low

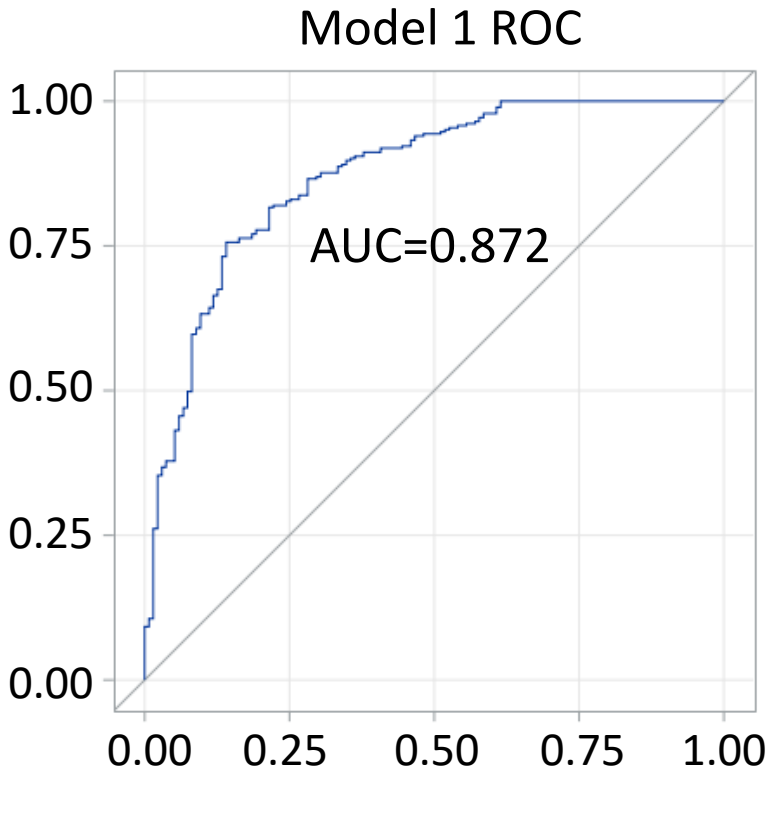
$$Logit(P2a) = (Cell\ Type) + (Predictor1) + (Predictor4) + (Predictor7)$$

$$Logit(P2b) = (Cell\ Type) + (Predictor1) + (Predictor4) + (Predictor7)$$

P2a and P2b are probabilities of a drug to be high versus low risk or intermediate versus low risk, respectively.

Model 1 TdP Risk Prediction: (high + Intermediate) vs. low risk drugs

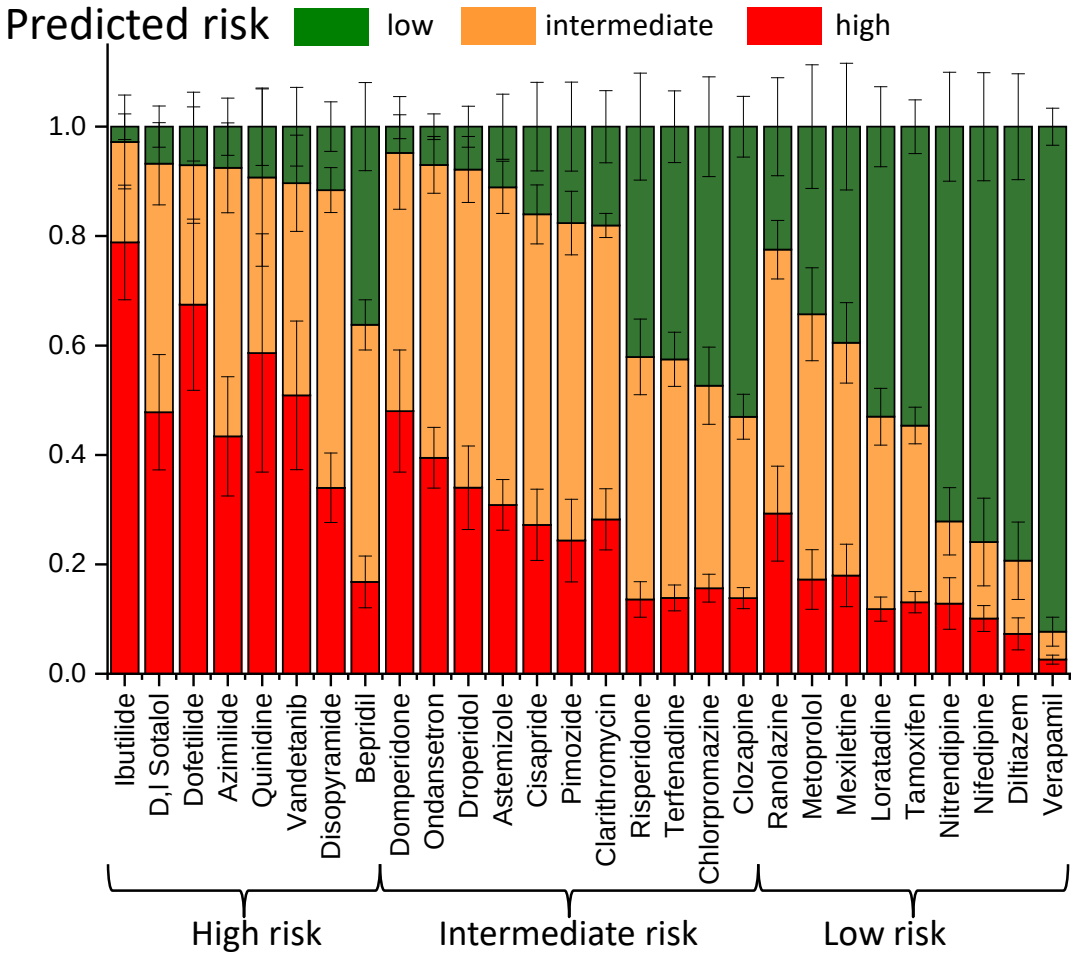




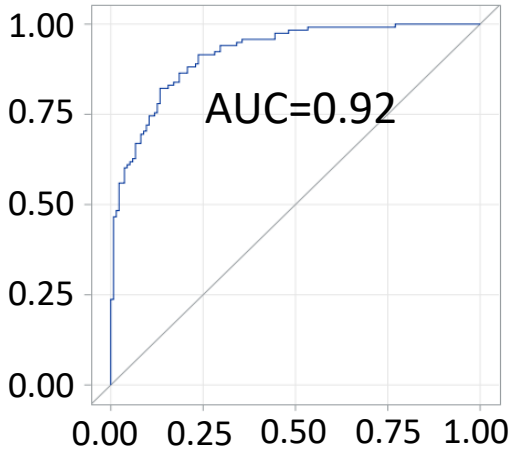
outliers: high risk – bepridil; low risk – ranolazine, metropolol, mexiletine (late Na current block)

Good AUC value from ROC curve for 28 drugs: 0.87 (close to excellent!)

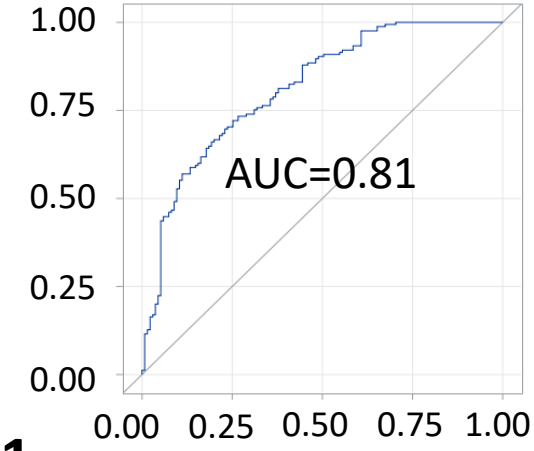
Model 2 TdP Risk Prediction: high vs. low and intermediate vs. low



Model 2 ROC: high vs. low



Model 2 ROC: intermediate vs. low

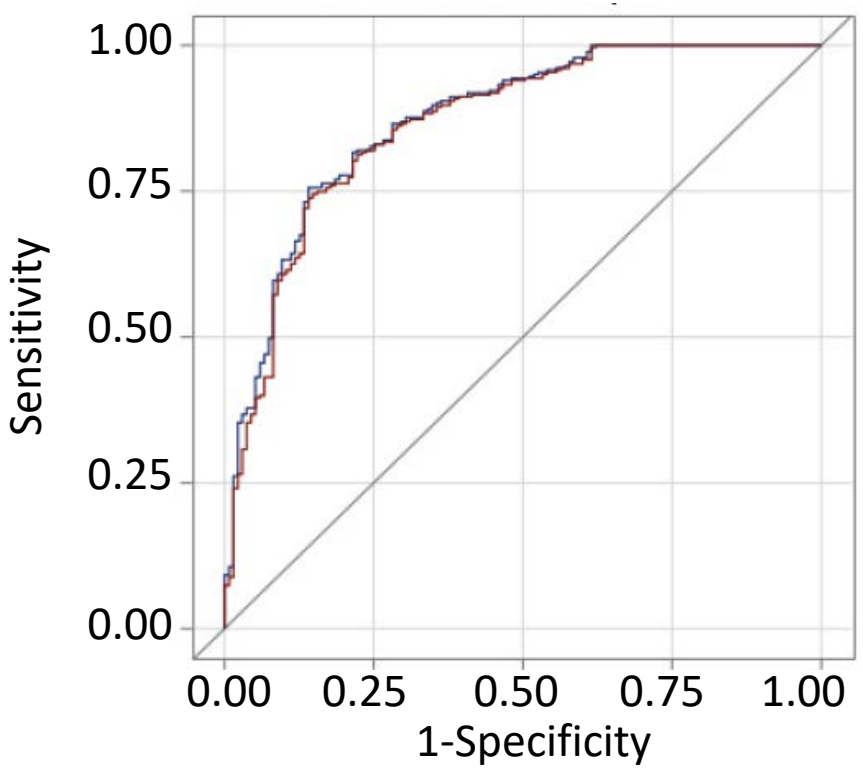


Good AUC value for intermediate vs. low: 0.81

Excellent AUC value from high vs. low ROC curve : 0.92

Model Validation

Cross-validation **Bootstrapping**

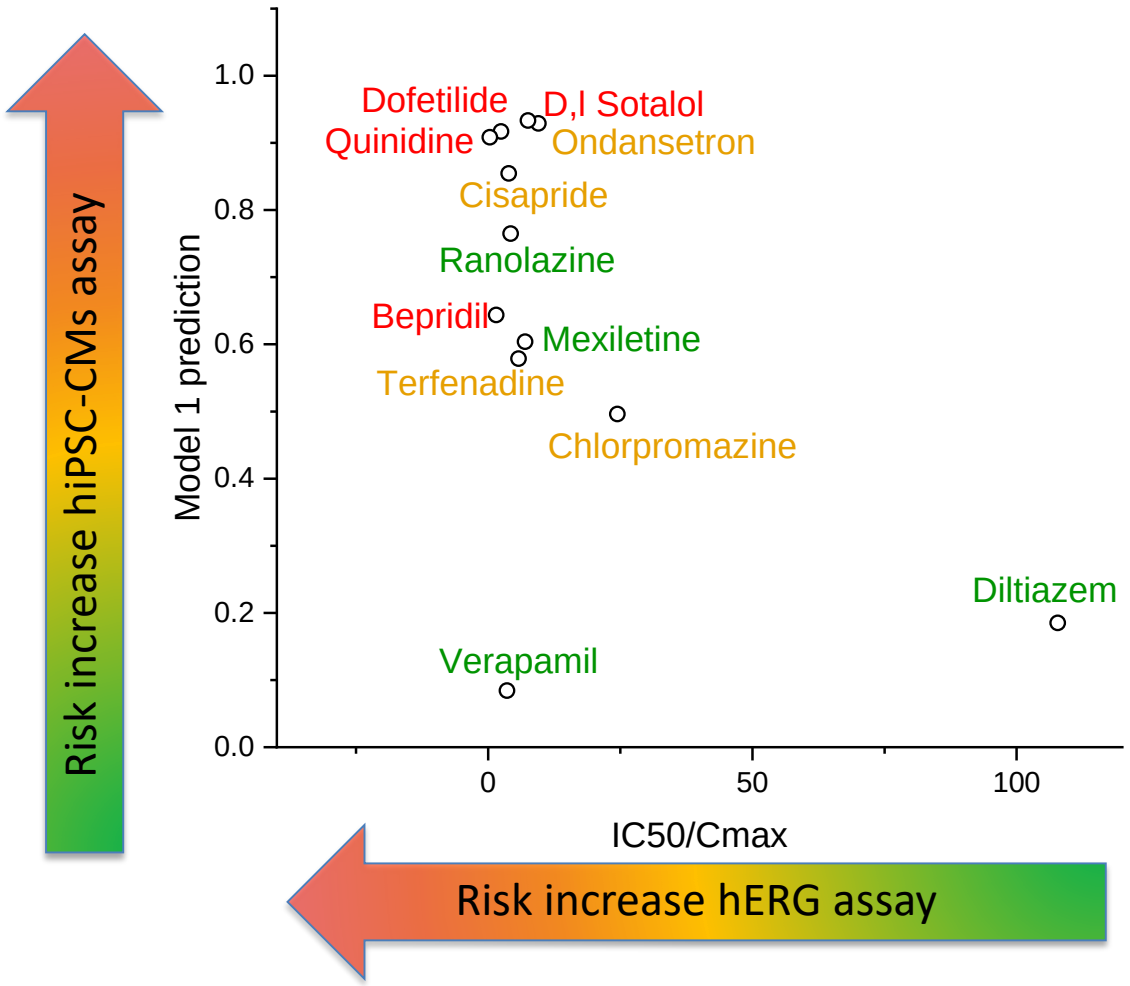


Cross-validation (k=10):
AUC change from 0.872 to 0.865

Bootstrapping (500 runs):
AUC change from 0.872 to 0.862

Reliable model expected to perform for a new independent dataset

Better Accuracy than hERG Assay



- hERG assay would classify verapamil as a high TdP risk drug
- iPSC-CMs assays correctly categorize verapamil as a low risk drug

hiPSC-CMs assays are likely to be superior to the current hERG assays – methodical comparative study of the two assays is yet to be done

Summary: Myocyte Validation Study

- First large scale multi-site study evaluating hiPSC-CMs assay variability
    - hiPSC-CM line, test site, and experimental platform had minimal influence on drug categorization

- A statistical model built based on the study data, predicting drug TdP risk based on its effects in hiPSC-CMs
    - Three of 7 predictors (drug-induced arrhythmia-like events, and prolongation of repolarization at either maximum tested or maximal clinical exposures) categorized drugs with reasonable accuracy to high, intermediate, or low risk proarrhythmic risk (AUC ~0.8)
    - Limited predictivity for late sodium current blocking drugs

- Protocols and approach set standards for “fit-for-purpose” applications of hiPSC-CMs
    - Appropriate on-plate controls are recommended

Role of hiPSC-CMs under CiPA

- **Drug discovery**
  - Early assessment of risk over wide exposures
- **Regulatory**
  - iPSC-myocytes may be considered as follow-up studies under S7B
  - iPSC-myocytes may be useful
    - When high clinical exposure is not possible in human ECG studies
    - When there is a discordance between ion channel/in silico and clinical ECG findings
- **Potential future roles (requires further validation)**
  - Longer exposures
  - Assessment of drug combinations

Contributors

CiPA myocyte team

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Daniel Millard, Axion
Godfrey Smith, Clyde
Liang Guo, NIH
Mathew Brock, Genentech
Hua Rong Lu, JNJ
Udo Kraushaar, NMI
Haoyu Zeng, Merck
Hong Shi, BMS
Xiaoyu Zhang, ACEA
Kohei Sawada, Eisai
Tomoharu Osada, LSI
Yasunari Kanda, NIHS
Yuko Sekino, NIHS
Tromondae K. Feaster, CDI
Ralf Kettenhofen, NCardia

And a host of support crew

Backup slides

Experimental conditions: validation study

iCell² | Cor.4U

Parameter/Site	1	2	3	4	5	6	7	8	9	10
Cell lot #	11515	11515	11515	11515	11515	21573A	11515	11515	11515	11515
	CB434CL	CB434CL	CB434CL	CB434CL	CB434CL					
Platform	AXN	CLY	MCS	ECR	MCS	ECR	AXN	AXN	AXN	AMD
	AXN	CLY	AXN	ECR	MCS					
Plating density, 1000/well	50	25	36	30	36	50	72	50	70	30
	20	25	10	30	8					
Culture age on test day	6-10	7-8	7	7	7	7-8	7-8	7	7-8	6-8
	7-10	6-7	5	7	6					
Antibiotics used	none/gent/pen-str-amp	gent	gent	gent	none	none	pen-str	none	pen-str	pen-str
	cipro	cipro	cipro	cipro	none					
Dosing scheme	single	single	single	single	single	single	single	single	single	seq
	single	single	single	single	single					
Recording media	CDI	SF	CDI	CDI	CDI	CDI	CDI	CDI	CDI	CDI
	AXG	SF	AXG	AXG	AXG					
Hours in recording media	19-25		4	18-24	4	18	4	4.5	4	2
	5-26		4	24	4					

Drug concentrations, validation study (µM)

Compound	Cmax	1	2	3	4	Interval
Loratadine	0.00045	0.001	0.003	0.009	0.03	1/2 log
Ibutilide	0.1	0.0001	0.001	0.01	0.1	log
Metoprolol	1.8	3.169	10.014	31.646	100	1/2 log
Droperidol	0.016	0.032	0.1	0.316	1	1/2 log
Mexiletine	2.5	0.1	1	10	100	log
Domperidone	0.02	0.003	0.03	0.3	3	log
Nifedipine	0.0077	0.001	0.01	0.1	1	log
Dofetilide	0.002	0.0003	0.001	0.003	0.01	1/2 log
Nitrendipine	0.003	0.01	0.03	0.095	0.3	1/2 log
Disopyramide	0.7	0.1	1	10	100	log
Ondansetron	0.372	0.03	0.3	3	30	log
Diltiazem	0.128	0.01	0.1	1	10	log
Pimozide	0.00043	0.001	0.003	0.009	0.03	1/2 log
Chlorpromazine	0.0345	0.095	0.3	0.949	3	1/2 log
Quinidine	3	0.95	3	9.49	30	1/2 log
Clozapine	0.071	0.095	0.3	0.949	3	1/2 log
Ranolazine	1.948	0.1	1	10	100	log
Clarithromycin	1.206	0.1	1	10	100	log
Vandetanib	0.3	0.01	0.1	1	10	log
Cisapride	0.00258	0.003	0.01	0.032	0.1	1/2 log
Tamoxifen	0.021	0.095	0.3	0.949	3	1/2 log
D,l Sotalol	15	0.1	1	10	100	log
Terfenadine	0.000286	0.001	0.01	0.1	1	log
Bepridil	0.032	0.01	0.1	1	10	log
Risperidone	0.0018	0.0032	0.01	0.032	0.1	1/2 log
Azimilide	0.07	0.01	0.1	1	10	log
Verapamil	0.045	0.001	0.01	0.1	1	log
Astemizole	0.0003	0.0001	0.001	0.01	0.1	log

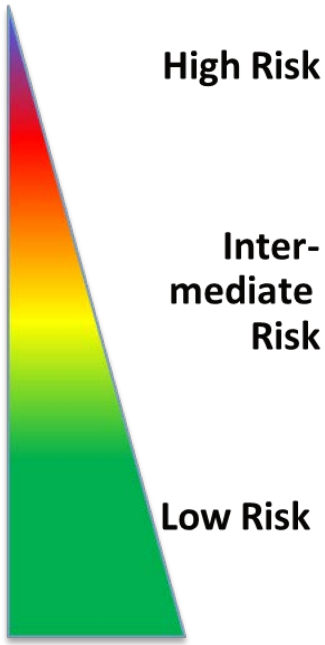
Drug concentrations, validation study (multiples of clinical free Cmax values)

Compound	1	2	3	4
Loratadine	2.1	6.7	21.1	66.7
Ibutilide	0.001	0.01	0.1	1
Metoprolol	1.8	5.6	17.6	55.6
Droperidol	2	6.3	19.8	62.5
Mexiletine	0.04	0.4	4	40
Domperidone	0.2	1.5	15	150
Nifedipine	0.1	1.3	13	129.9
Dofetilide	0.16	0.5	1.58	5
Nitrendipine	3.1	9.9	31.4	99.3
Disopyramide	0.1	1.4	14.3	142.9
Ondansetron	0.1	0.8	8.1	80.6
Diltiazem	0.1	0.8	7.8	78.1
Pimozide	2.2	7	22.1	69.8
Chlorpromazine	2.8	8.7	27.5	87
Quinidine	0.3	1	3.2	10
Clozapine	1.3	4.2	13.4	42.3
Ranolazine	0.1	0.5	5.1	51.3
Clarithromycin	0.1	0.8	8.3	82.9
Vandetanib	0.03	0.33	3.33	33.33
Cisapride	1.2	3.9	12.3	38.8
Tamoxifen	4.5	14.3	45.2	142.9
D,l Sotalol	0.01	0.07	0.67	6.67
Terfenadine	3.5	35	349.7	3496.5
Bepridil	0.3	3.1	31.3	312.5
Risperidone	1.8	5.6	17.6	55.6
Azimilide	0.1	1.4	14.3	142.9
Verapamil	0.02	0.22	2.22	22.22
Astemizole	0.3	3.3	33.3	333.3

Proarrhythmic Clinical Risk Categorization: Three-Tier Ranking of TdP Risk (CiPA 28)

High TdP Risk	Intermediate TdP Risk	Low TdP Risk
Training Set:	**Training Set:**	**Training Set:**
Bepridil	Chlorpromazine	Diltiazem
Dofetilide	Cisapride	Mexiletine
Quinidine	Terfenadine	Ranolazine
D,l Sotalol	Ondansetron	Verapamil
Validation:	**Validation:**	**Validation:**
Azimilide	Astemizole	Loratadine
Ibutilide	Clarithromycin	Metoprolol
Vandetanib	Clozapine	Nifedipine
Disopyramide	Domperidone	Nitrendipine
	Droperidol	Tamoxifen
	Pimozide	
	Risperidone	

Clinical Translational Working Group



Predictors 4 and 7 descriptive statistics

Predictor 4
(maximum drug-induced change at any dose)

		N total	Mean	Standard Deviation	Sum	Minimum	Median	Maximum
pred4	Bepridil	15	70.57669	54.80418	1058.65028	0	54.04425	193.5898
	Vandetanib	15	137.58296	107.83884	2063.74441	0	91.62312	352.52098
	Quinidine	15	136.55721	130.15219	2048.35811	0	116.7651	438.69456
	Dofetilide	15	158.45846	128.46125	2376.87694	29.93794	106.67475	483.09685
	Azimilide	15	247.98845	268.6889	3719.8268	-37.30518	106.08127	742.6194
	Disopyramide	15	94.37101	85.67152	1415.56509	0	81.45379	307.17286
	Ibutilide	15	102.61934	150.85478	1539.29008	0	66.44711	628.02049
	D,l Sotalol	15	135.05405	108.92007	2025.81072	5.43222	75.9043	335.95127
	Chlorpromazine	15	-22.66542	66.2334	-339.98137	-136.8514	0	75.73441
	Clozapine	15	-35.01505	45.14085	-525.22581	-124.37043	-32.3018	34.7278
	Terfenadine	15	47.52972	58.78089	712.94576	-74.34968	49.6482	162.4638
	Risperidone	15	61.72988	69.04771	925.94824	-40.96868	48.56162	178.00785
	Cisapride	15	124.18798	85.66818	1862.81977	21.76233	110.10288	311.48929
	Astemizole	15	138.11764	163.28106	2071.76457	-50.95336	75.92331	496.29928
	Clarithromycin	15	68.02548	92.67986	1020.38221	-31.66613	31.96816	336.78349
	Pimozide	15	180.21089	132.8281	2703.16331	45.44833	148.5882	570.6456
	Droperidol	15	255.85675	238.58647	3837.85119	25.84919	171.27396	865.40079
	Ondansetron	15	149.5488	142.93631	2243.23197	26.9267	106.27326	606.74477
	Domperidone	15	246.38055	327.70112	3695.70827	41.84103	73.77358	1279.76545
	Verapamil	15	-170.21034	105.16027	-2553.15509	-344.74968	-155.62522	22.52566
	Diltiazem	15	-156.20389	112.46508	-2343.0583	-336.40413	-106.38853	0
	Nitrendipine	15	-186.49715	86.0985	-2797.45718	-372.569	-184.72002	-23.17445
	Nifedipine	15	-183.92853	118.22443	-2758.9279	-336.31153	-199.78655	20.27606
	Loratadine	15	1.65634	18.50925	24.84511	-57.10365	5.15831	22.45601
	Mexiletine	15	26.20128	63.36696	393.01914	-98.519	14.76658	147.31169
	Tamoxifen	15	-34.73657	29.52138	-521.04862	-76.00426	-44.31437	21.28722
	Metoprolol	15	104.87528	162.40097	1573.1292	-54.02096	50.65753	455.61274
	Ranolazine	15	76.57345	59.39431	1148.60182	-13.34006	66.78254	248.29224

Averages: high **135.4** ms
intermediate **110.4** ms
low **-58.0** ms

Predictor 7
(estimated drug-induced change at Cmax)

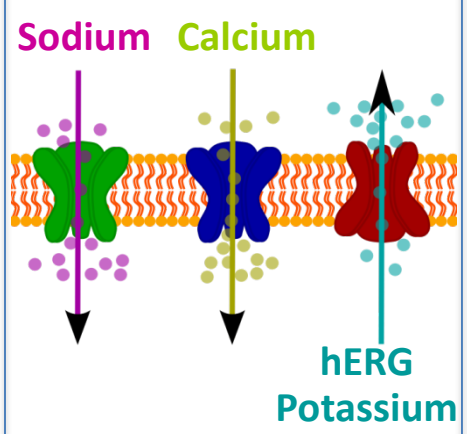
		N total	Mean	Standard Deviation	Sum	Minimum	Median	Maximum
pred7	Bepridil	15	8.97246	12.649	134.58687	-25.27321	7.83132	30.9584
	Vandetanib	15	47.84636	33.05424	717.69533	2.0743	39.76969	111.96512
	Quinidine	13	83.34937	92.0283	1083.54182	0	67.6505	302.50999
	Dofetilide	15	86.3795	60.03469	1295.69243	11.13584	69.12442	214.43468
	Azimilide	15	31.13711	33.20324	467.0567	-23.51567	31.19722	118.53756
	Disopyramide	15	18.36277	12.19022	275.44156	-4.47335	15.99132	42.95172
	Ibutilide	15	112.92862	79.45121	1693.92931	39.42357	81.36009	287.56498
	D,l Sotalol	15	33.43896	29.25922	501.58441	3.16876	15.42981	81.9414
	Chlorpromazine	15	7.09457	12.41679	106.41851	-14.771	7.66092	26.20647
	Clozapine	15	5.02505	8.0123	75.37576	-9.20108	5.29527	19.10871
	Terfenadine	15	6.08829	13.63729	91.32435	-20.10627	8.23356	30.36258
	Risperidone	15	0.32646	16.23572	4.89694	-38.83171	4.70142	19.44744
	Cisapride	15	10.48733	14.4532	157.30997	-8.22919	6.80648	49.28108
	Astemizole	15	10.13162	11.85714	151.97423	-7.69344	11.21433	39.97698
	Clarithromycin	15	11.44357	16.27525	171.65358	-28.44439	16.6029	34.88671
	Pimozide	15	11.33899	17.74014	170.08487	-21.50103	7.93834	53.46986
	Droperidol	15	20.47195	19.67173	307.07918	-18.30023	23.35517	72.41976
	Ondansetron	15	29.06673	10.80811	436.00098	12.02456	28.8318	48.87042
	Domperidone	15	50.48535	68.60213	757.28025	-6.44682	39.26344	285.93451
	Verapamil	15	-59.29232	19.60079	-889.38479	-100.03039	-56.30604	-32.85132
	Diltiazem	15	-27.59612	25.48501	-413.94183	-76.85703	-24.78048	11.90932
	Nitrendipine	15	-5.40378	20.11329	-81.05675	-30.37028	-10.20251	46.84866
	Nifedipine	15	-10.9198	14.82116	-163.79699	-39.34339	-10.07559	18.4753
	Loratadine	15	-2.52108	20.84662	-37.81621	-67.90304	2.75261	23.16017
	Mexiletine	15	4.43715	16.49209	66.55725	-24.3115	6.00628	33.81692
	Tamoxifen	15	2.77628	11.12103	41.64419	-20.78577	2.80941	24.82595
	Metoprolol	15	5.98338	10.62001	89.75067	-15.40087	4.20141	27.49564
	Ranolazine	15	24.37843	19.77448	365.67652	-9.70143	20.02838	74.99154

Averages: high **52.8** ms
intermediate **14.7** ms
low **-7.6** ms

Role of Myocytes in CiPA

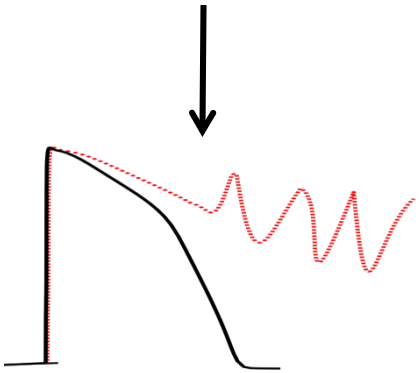
FDA

1. *In vitro* Assessment of Ion Channels

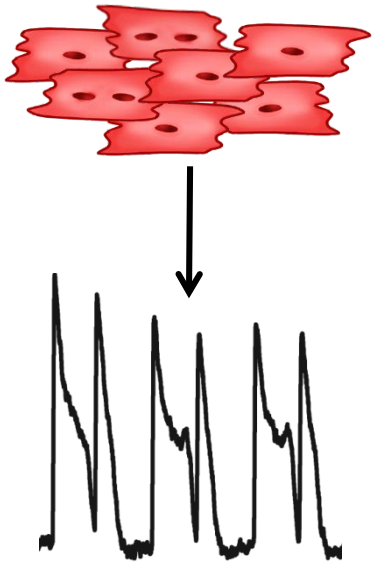


2. *In silico* Computer Modeling to Predict Risk

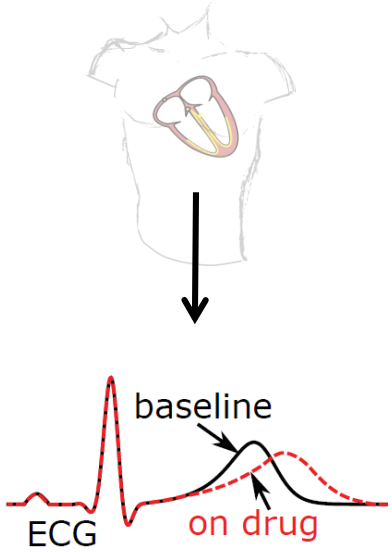
$$I_{stim} = C\frac{dV_m}{dt} + I_m$$



3. *In vitro* Stem Cell Derived Cardiomyocytes



4. *In vivo* ECG Biomarker in Phase 1 Clinical Trials



Define Proarrhythmic Risk (beyond QTc)

Check for Missed or Unanticipated Effects Increase Confidence in Risk Assessment