High-throughput Imaging and Kinetic Endpoints for Toxicity Testing in iPSC-derived (iCell) Cardiomyocytes and Hepatocytes in 2D and 3D Spheroid Cultures

Blake Anson, PhD and David Mann, PhD – CDI
Oksana Sirenko – Molecular Devices
Cellular Dynamics International

World’s largest producer of human iPS cells and iPS cell-derived tissue cells

**Infrastructure**

- **~170 total staff**
- Distinct R&D, Process Science, Manufacturing Teams
- **~800 yrs in cumulative human stem cell experience**
- Reprogramming, differentiation, terminal cell biology
- **Headquartered in Madison, WI**
- Serve and support the global market
- **>800 patents (owned or licensed)**

**Competencies**

- **Creation / culture of hiPS cells**
  Normal and disease phenotypes
- **Genetic engineering of hiPS cells**
  Gene editing, KO, SNP, indel etc
- **Developing new hiPS cell types**
  Across all three germ layers
- **Large-scale manufacture**
  Scalable production of highly purified cells
- **Application development and support**

Consistent delivery and support of robust, high quality human cellular models
iPSC Technology Enabling Toxicity – Discovery – Regenerative Medicine

iCell® Catalog Products
- iPSC Differentiated Cells From a Single Donor

Diversity and Disease Portfolio
- Diversity
  - Gender, Ethnicity, etc
- Disease Cohorts
  - Cardiac, hepatic, muscular, neuro, etc
- Cell Banks
  - CIRM, NHLBI, etc.

MyCell® Products
- Custom Reprogramming, Engineering, and Differentiation From Any Donor
# iCell Hepatocytes 2.0

## Key Characteristics

<table>
<thead>
<tr>
<th>Key Hepatocyte Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphology</strong></td>
</tr>
<tr>
<td><strong>Molecular Markers</strong></td>
</tr>
<tr>
<td><strong>Intrinsic Metabolism</strong></td>
</tr>
</tbody>
</table>
| **Phase I & II Metabolism** | - CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 (basal & induced)  
  - UGT, ST, GSTα activity |
| **Transporter Function** | Transport via uptake (e.g. OATP, NTCP) and efflux transporters (e.g. MDR-1/P-gp, BCRP, BSEP, MRP2) |
| **Infectivity** | - Expression of hepatitis virus receptors  
  - Viral infectivity (HCV, HBV)  
  - Malaria parasite infection (*P. falciparum; P. vivax*) |
iCell Hepatocytes
Morphological Characteristics

- Adherent monolayer
- Round nucleus
- Distinct nucleoli
- High cyto/nuclear ratio
- Bi-nucleation (circles)
- Bile canaliculi (arrows)
iCell Hepatocytes

Marker Expression

Mature Hepatocyte Marker

Liver Secreted Protease Inhibitor

Liver Specific Transcription Factor

Tight Junction Formation
iCell Hepatocytes
Long Term Culture Stability (No Matrigel)
Short vs Long Term Exposure in 2D Culture
Hepatotoxicity Assay Workflow

**Workflow**

- **Thaw & plate cells**
- **Feed with Plating Medium**
- **Feed (Maint. Medium) & Apply Compounds**

**Days in Culture**

0 1 2 3 4 5 6 7 8 9 10 11 12

**Assay Plate 1**

**Assay Plate 2**

**Multiplexed Readouts**

- **Calcein AM stain**
  - Cell viability (esterase activity)
  - Green fluorescence readout
  - Toxicity = loss-of-signal

- **CellTiter-Glo 2.0 Assay**
  - Cell viability (ATP levels)
  - Luminescence readout
  - Toxicity = loss-of-signal

- **YOYO-3 stain**
  - Cell death (impermeable DNA dye)
  - Red fluorescence readout
  - Toxicity = gain-of-signal
iCell Hepatocytes

Chronic Exposure - DMSO Tolerance Testing

Day 7
- Single dose
- 2 day exposure

CellTiter-Glo 2.0 Assay

Day 12
- 3 doses
- 7 day exposure

~90% viability at 0.5% DMSO

~90% viability at 0.5% DMSO
# iCell Hepatocytes

## Acute Vs Chronic Exposure – (Cell Titer Glo)

<table>
<thead>
<tr>
<th>Drug</th>
<th>2 Day EC50</th>
<th>7 Day EC50</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µM)</th>
<th>DILI category</th>
<th>DILI pattern</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>ND (&gt;5 mM)</td>
<td>3.1mM</td>
<td>165.38</td>
<td>3. Low Clinical DILI Concern</td>
<td>Hepatocellular</td>
<td>Regenthal et al. 1999</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>80µM</td>
<td>28µM</td>
<td>11.29</td>
<td>1. Severe Clinical DILI</td>
<td>Mixed; Black Box Warning</td>
<td>Regenthal et al. 1999</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>4.4µM</td>
<td>0.84µM</td>
<td>7.10</td>
<td>3. Low Clinical DILI Concern</td>
<td>Hepatocellular</td>
<td>Porceddu et al. 2012</td>
</tr>
</tbody>
</table>
### Drug Exposure in iCell Hepatocytes

#### Acute Vs Chronic Exposure - (Cell Titer Glo)

<table>
<thead>
<tr>
<th>Drug</th>
<th>2 Day EC50</th>
<th>7 Day EC50</th>
<th>( C_{\text{max}} ) (µM)</th>
<th>DILI category</th>
<th>DILI pattern</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan</td>
<td>ND (&gt;100 (µM))</td>
<td>ND (&gt;100 (µM))</td>
<td>0.79</td>
<td>5. No DILI</td>
<td></td>
<td>Market et al. 2013</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>ND (&gt;250 (µM))</td>
<td>~244µM</td>
<td>10.13</td>
<td>2. High Clinical DILI Concern</td>
<td>Mixed</td>
<td>Regenthal et al. 1999</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>58µM</td>
<td>46µM</td>
<td>4.26</td>
<td>1. Severe Clinical DILI</td>
<td>Mixed; Black Box Warning</td>
<td>Regenthal et al. 1999</td>
</tr>
</tbody>
</table>
iCell Hepatocytes
Formation of 3D Microtissues

➢ iCell Hepatocytes 2.0 Are Capable of Forming 3D Spheroids
➢ (A) An interconnected, confluent 2D culture
➢ (B) 3D spheroids are generated within 1 – 2 days from pre-plated cells
iCell Hepatocytes

3D Size vs Viability

- iCell Hepatocytes 2.0 Spheroid Size Can Be Easily Controlled
- (A) The spheroid size is tuned by the number of cells seeded into low-attachment wells
- (B, C) Viability correlates with cells number per aggregate, suggesting that the microtissues maintain cell health throughout
iCell Hepatocytes
P450 Induction

- iCell Hepatocytes 2.0 Spheroids Exhibit Highly Reproducible CYP3A4 and CYP1A2 Induction
- (A) CYP3A4 induction in response to a rifampicin titration
- (B) CYP1A2 induction in response to an omeprazole titration were measured by luminescent functional readout of activity (P450-Glo™ Promega).
iCell Hepatocytes
Toxicity Assay in 3D – Miniaturization (Cell Titer Glo 3D)

![Graphs showing RLU vs. FCCP concentration for different cell densities.](image)

<table>
<thead>
<tr>
<th>Cell Density</th>
<th>EC50 (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000 cells/well</td>
<td>7.663</td>
</tr>
<tr>
<td>1000 cells/well</td>
<td>4.755</td>
</tr>
<tr>
<td>500 cells/well</td>
<td>4.692</td>
</tr>
</tbody>
</table>

![Graph showing RLU vs. FCCP concentration for 500 cells/well.](image)
ImageXpress Micro - Confocal

- Automated Confocal + Widefield Imager
- 1X to 100X Magnification
- Large Field of View
  1.96mm² @ 10X
- 20,000 hour solid state light engine

- Compatible with any plate type (1-1536, round or flat bottom), transwell plates, and slides
- >3 log Dynamic Range
- <100 nm Stage Resolution
- High Speed Laser & Image Autofocus
Aims: Quantify the number of Dorsal Irridophores in Zebrafish embryos.

Requirements
Acquisition: Acquire the whole well to visualise all zebrafish embryos.
Analysis: Measure the number of Irridophores on a per Fish basis.
Identify distinct regions within each embryo.
iCell Hepatocytes in 3D
Optimized Staining Protocol

**Staining protocol:**
1-step addition of 3 dye mix
- Hoechst- blue, nuclei
- Calcein AM – green, viability
- EthD-1- red, dead cells
No wash

**Challenges:**
- Dye penetration
- Washes

**Images:**
- Hoechst – Nuclei
- CalceinAM – Viability
- EtHD – Dead Cells
- Composite Image
Staining protocol: 1-step addition of 3 dye mix - no wash

Control

Staurosporine

Filter Used: DAPI  FITC  Texas Red

Hoechst- nuclei
Calcein AM viability
EthD-1- dead cells

72h Compound Treatment
Representative images of liver spheroids treated with hepatotoxic compounds

**Hoechst- nuclei**
**Calcein AM viability**
**EthD-1- dead cells**
iCell Hepatocytes in 3D

Phenotypic Analysis of Compound Effects

- 10x or 20x objective allows segmentation of nuclei and cell count/cell scoring
- Multi-parametric analysis provides ability to characterize cells marked with different dyes

**Control**

**Ketoconazole**

**Image**

**Mask**

- Hoechst- nuclei
- Calcein AM viability
- EthD-1- dead cells
iCell Hepatocytes in 3D

Image Analysis

![Graph showing cells per spheroid and value as % of the control for different treatments.]

- **Cells per Spheroid**
  - All nuclei
  - Calcein AM pos
  - Calcein AM neg
  - EtH pos

- **Value as % of the control**
  - Sp volume
  - Diameter
  - Nuclear ave intensity
  - CalceinAM ave intensity

Legend:
- control
- ketoconazole
- staurosporine
- haloperidol
iCell Hepatocytes in 3D

Concentration Dependence for Selected Compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50s, μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (red)</td>
<td>10 +/- 0.49</td>
</tr>
<tr>
<td>Retinoic Acid (green)</td>
<td>4.0 +/- 0.92</td>
</tr>
<tr>
<td>TAB (purple)</td>
<td>3.9 +/- 0.77</td>
</tr>
<tr>
<td>Apigenin (blue)</td>
<td>37 +/- 10</td>
</tr>
<tr>
<td>Ketoconazole (red)</td>
<td>33 +/- 9.0</td>
</tr>
<tr>
<td>Doxorubicin (green)</td>
<td>5.7 +/- 0.40</td>
</tr>
<tr>
<td>Etoposide (blue)</td>
<td>350 +/- 173</td>
</tr>
<tr>
<td>Amiodarone (purple)</td>
<td>ND</td>
</tr>
</tbody>
</table>

Concentration, μM

Calcein AM Positive Celle
Summary

• iCell Hepatocytes have long term functional culturability enabling long term exposure toxicity in 2D
• iCell Hepatocytes can be readily cultured in 3D spheroids with enhanced function
• 3D culture enables miniaturization for high throughput assays – more wells per vial
• Confocal imaging of 3D hepatocyte spheroids affords multiplexed high content analyses
iCell Cardiomyocytes and Cardiac Spheroids
Cellular Dynamics and Molecular Devices
March, 2016
iCell Cardiomyocytes Overview

Cardiac Spheroids

- Formation
- Analysis
- Initial testing
iCell Cardiomyocytes

Human Cardiomyocytes

- >95% pure, cryopreserved, ready to use
- >4x10^6 cardiomyocytes per unit in unlimited volumes
- Normal human biology
- Industry Standard
  - Broad platform utility
  - More customer publications (>75) than all other commercial providers combined
  - Utilized by over 90 percent of top pharmaceutical companies
iCell Cardiomyocytes; Contextual Relevance

Functional Recapitulation

Primary Function – Rhythmic electrical activity at the membrane is translated to mechanical activity (action potentials to Ca2+ signaling to contraction)

Electrical

Ion channels, Action Potentials, GPCRs

Cell Signaling

• Ca2+ signaling (EC coupling)
• Biochemical

Mechanical

Contractility

Contextual relevance enables

- appropriate disease modeling,
- Valid target verification,
- predictive toxicity testing
iCell Cardiomyocytes Characterization
Gene Expression Analysis

Comparative Transcriptome Analysis of Cardiac Gene Expression
~200 cardiac genes identified through the Novartis GNF expression atlas

From Babiarz et al., 2011

iCell Cardiomyocytes expression is relevant and temporally stable

‘Primary’ cardiac cell models do not match native expression profiles
iCell Cardiomyocytes show expected protein profiles and subcellular localization

From Kattman et al., 2011
Similar to adult cardiomyocytes, iCell Cardiomyocytes can utilize glycolysis and mitochondrial oxidative phosphorylation.
iCell Cardiomyocytes Characterization

Electrophysiology

Ionic Currents

- $I_{Na}$
- $I_{Ca-L}$
- $I_{to}$
- $I_{Kr}$
- $I_{funny}$
- $I_{K1}$


Spontaneous Action Potentials

- Atrial-like
- Nodal-like
- Ventricular-like


Gqα – β1
Isoproterenol
Gqα – α1
Phenylephrine
Gq1 – m2
Carbachol

iCell Cardiomyocytes possess the appropriate ion channels, action potentials, and GPCR pathways expected of a relevant human cardiomyocyte model.
Contraction is driven by Ca\textsuperscript{2+} transients, is physiological relevant, and is modulatable in chemical space.

Adapted from Puppala et al., 2013
iCell Cardiomyocytes
Characterization Summary

Relevant & temporally stable in culture
Babiarz et al., 2012

Whole-Genome Gene Expression

Enables normal cardiomyocyte function
Kattman et al., 2011

Electrophysiology, E-C Coupling, Contractility

Substrate dependent, active mitochondria
Rana et al., 2012

Metabolism

iCell Cardiomyocytes:
- Native human biology
- Phenotypic and mechanistic interrogation of function
- Toxicity testing; disruption of normal processes
- Disease modeling; corruption of normal processes

A complete list of iCell Cardiomyocytes publications can be found at www.cellulardynamics.com

Ma et al., 2011, Puppala et al., 2012

Enables mechanistic toxicity testing

<table>
<thead>
<tr>
<th>HG</th>
<th>High Glucose</th>
<th>LG</th>
<th>Low Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>Fatty Acid</td>
<td>GAL</td>
<td>Galactose</td>
</tr>
</tbody>
</table>

Babiarz et al., 2012
Kattman et al., 2011
Rana et al., 2012
Ma et al., 2011, Puppala et al., 2012
iCell Cardiomyocytes; Contextual Relevance

Functional and Structural toxicity

**Functional Toxicity** - 1° effect is on electrical/mechanical function

- **Electrical**
  - Ion channels, Action Potentials, GPCRs

- **Cell Signaling**
  - \( \text{Ca}^{2+} \) signaling (EC coupling)
  - Biochemical

**Structural Toxicity**

1° effect is on general cellular processes

- **Viability**
- Lipid accumulation
- Mitochondrial function
- Oxidative stress
- Bioenergetics
- etc.....

- **Mechanical Contractility**

Contextual relevance should enable both functional and structural toxicity testing

March 30, 2016
Interrogating Biology
Energetics and mitochondria toxicity

Antimycin A Application
JC-10 Readout
Image Express Micro Reader

iCell Cardiomyocytes amenable to HTS screening platforms
FliPR with Calcium 5 Assay Kit

Surrogate for electrical activity at the membrane:
Chronotropy

Ca²⁺ transients pre/post epi

Positive/Negative Chronotropy

Surrogate measurements can provide HTS interrogation of physiological electrical activity

Surrogate for electrical activity at the membrane:
Ion Channel Block

No Treatment

0.14 µM Cisapride

Calcium 5 Response on FLIPR: Epinephrine High Dose (C06)

EC/IC₅₀ = 0.1446

Cisapride 15 min post addition

[Concentration, µM]
0.01 0.1 1 10 100

Peak Count (120 sec)
0
5

EC/IC₅₀ = 0.1446

No Treatment 0.14 mM Cisapride

Intracellular Ca²⁺ transients

Rise Time
Peak Width (FWHM)
Decay Time
Amplitude & Time

Surrogate for electrical activity at the membrane:
Chronotropes:
Positive
Negative

Ion Channel Block

Dopamine (Didoxine: Concentration vs Mean Value)
Epinephrine (Epinephrine: Concentration vs Mean Value)
Verapamil (Verapamil: Concentration vs Mean Value)
Doxazosine (Doxazosine: Concentration vs Mean Value)
Isoproterenol (Isoproterenol: Concentration vs Mean Value)

Ion Channel Block

Peak Width (FWHM)
Rise Time
Decay Time
Peak Count (120 sec)

Surrogate Measurements can provide HTS interrogation of physiological electrical activity

March 30, 2016
Comparisons between IonOptix-based measurements of dog cardiomyocytes (gold standard) to Ca\(^{2+}\) and impedance-based measurements of iCell Cardiomyocytes (higher throughput)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dog cardiomyocytes</th>
<th>iCell Cardiomyocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IonOptix(^1)</td>
<td>83%</td>
<td>77%</td>
</tr>
<tr>
<td>FLIPR(^2)</td>
<td>84%</td>
<td>74%</td>
</tr>
<tr>
<td>Impedance(^3)</td>
<td>82%</td>
<td>79%</td>
</tr>
<tr>
<td>sensitivity</td>
<td>83%</td>
<td>77%</td>
</tr>
<tr>
<td>specificity</td>
<td>84%</td>
<td>74%</td>
</tr>
<tr>
<td>accuracy</td>
<td>82%</td>
<td>74%</td>
</tr>
<tr>
<td>pos predict</td>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td>neg predict</td>
<td>76%</td>
<td>82%</td>
</tr>
</tbody>
</table>


iCell Cardiomyocytes
- Show potency correlation with gold standard model
- Demonstrate good to excellent assay validation parameters
- Provide a predictive surrogate model for measuring contractility
We are not two-dimensional organisms

Do 3d test systems make sense?
Introduction:

There is a substantial recent shift for more active use of complex 3D cell models and organoid models for biological research, drug screening, toxicity screening, and tissue engineering.

Increased complexity of cell models and organisms present challenges for the assay development, especially in the screening environment.

Here we present the development of 3D cardiac spheroid assay that uses calcium fluxes.

Courtesy of O. Sirenko
ImageXpress Micro - Confocal

Automated Confocal + Widefield Imager

1X to 100X Magnification

Large Field of View 1.96mm² @ 10X

20,000 hour solid state light engine

Courtesy of O. Sirenko
Cardiac Spheroid Assay Workflow

- CDI cardiomyocytes, or other cells
- Plate into 96w or 384 U-shape plates
- Spheroids formed in 3-4 days and start beating in the culture
- Spheroids loaded with Calcium 6 dye
- Automatic Image acquisition using time-lapses and WF: ~10 reads/sec; ~10 sec or longer

Courtesy of O. Sirenko
Modulation of beating patterns with selected compounds

Compounds cause changes in the beating profiles
- Beating rate and amplitude
- Rise/Decay Times
- Peak Spacing
Cardiac Assay Workflow: Analysis

After plate acquired:

- Open well vs time option,
- Make a stack,
- Find organoid,
- Assign ROI for organoid

Automatic image analysis and data export is available by journal

Measurements:
- Beats/min
- Amplitude
- Spacing
- Peak width 10% amp
- Raise/Decay time

Analysis currently available via SoftMaxPro program

Export Average Intensity vs time

<table>
<thead>
<tr>
<th>Elapsed Time</th>
<th>Average Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>00:00.0</td>
<td>1354.4</td>
</tr>
<tr>
<td>00:00.2</td>
<td>897.7</td>
</tr>
<tr>
<td>00:00.4</td>
<td>796.1</td>
</tr>
<tr>
<td>00:00.7</td>
<td>766.3</td>
</tr>
<tr>
<td>00:00.9</td>
<td>752.9</td>
</tr>
<tr>
<td>00:01.1</td>
<td>749.9</td>
</tr>
<tr>
<td>00:01.3</td>
<td>1457.5</td>
</tr>
<tr>
<td>00:01.5</td>
<td>1195.1</td>
</tr>
<tr>
<td>00:01.7</td>
<td>803.4</td>
</tr>
<tr>
<td>00:02.0</td>
<td>754.9</td>
</tr>
<tr>
<td>00:02.2</td>
<td>738.8</td>
</tr>
</tbody>
</table>
Spheroids can be formed from 3000-20000 cells.

The beating rate was not affected by Calcium 6 concentration or number of cells plated.

Assay has better performance with higher concentration of Calcium 6, at least 2h of incubation is required to allow efficient dye loading.
Beating Patterns Modulated by Cardioactive or Cardiotoxic Compounds

Typical qualitative effects are observed
IC50s calculated based on changes in beating rate

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoproterenol</td>
<td>0.077 +/- 0.03</td>
</tr>
<tr>
<td></td>
<td>0.084 +/- 0.091</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.084 +/- 0.091</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>30.3 +/- 14.7</td>
</tr>
<tr>
<td>Cisapride</td>
<td>2.82 +/- 14.2</td>
</tr>
<tr>
<td>Propranolol</td>
<td>5.49 +/- 5.43</td>
</tr>
<tr>
<td>Verapamil</td>
<td>20.9 +/- 17.5</td>
</tr>
<tr>
<td>Sotalol</td>
<td>29.8 +/- 16.1</td>
</tr>
<tr>
<td>Deltamethrin</td>
<td>8.10 +/- 10.5</td>
</tr>
<tr>
<td>Aspirin</td>
<td>n/d</td>
</tr>
</tbody>
</table>

Quantification is straight-forward
Making the assay platform-friendly

FliPR Tetra
Present in virtually all HTP labs
Optimization of the assay for FLIPR

Isoproterenol  Sotalol  Propranolol

FLIPR assay performed with 10000-20000 cells plated

2x concentration of Calcium 6 allows better result

Automatic data analysis is available by FLIPR SW
Examples of patterns changed by cardioactive or cardiotoxic compounds

Patterns consistent with previous studies (2D)
IC50s for compound effects derived from beating frequencies

3D model

2D model

<table>
<thead>
<tr>
<th>Compound</th>
<th>3D</th>
<th>2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoproterenol</td>
<td>0.002 +/- 0.0006</td>
<td>0.04 +/- 0.003</td>
</tr>
<tr>
<td>digoxin</td>
<td>0.31 +/- 0.042</td>
<td>0.027 +/- 0.042</td>
</tr>
<tr>
<td>verapamil</td>
<td>19.5 +/- 3</td>
<td>0.744 +/- 0.77</td>
</tr>
<tr>
<td>lidocaine</td>
<td>48.15 +/- 9.76</td>
<td>4.5 +/- 8.05</td>
</tr>
<tr>
<td>haloperidol</td>
<td>4.24 +/- 6.31</td>
<td>0.731 +/- 0.155</td>
</tr>
<tr>
<td>cizapride</td>
<td>0.027 +/- 0.01</td>
<td>0.339 +/- 0.194</td>
</tr>
</tbody>
</table>

- Compound effects were compared in parallel experiment in identical conditions, except shape of the plates that allowed formation of spheroids
- IC50s for 3D culture were significantly shifted toward greater concentrations for most of compounds tested
Testing across ‘safe’ and potentially toxic compounds

3D model allows testing compounds for potential cardiotoxicity

The effective concentrations for most of compounds shifted to the right
iCell Cardiomyocytes provides a rich, robust, and predictive biological model.

3d modeling may provide a model more closely aligned with native tissues (jury is still out)

Molecular Devices offers easy workflows, automated analysis, and commonly placed platforms