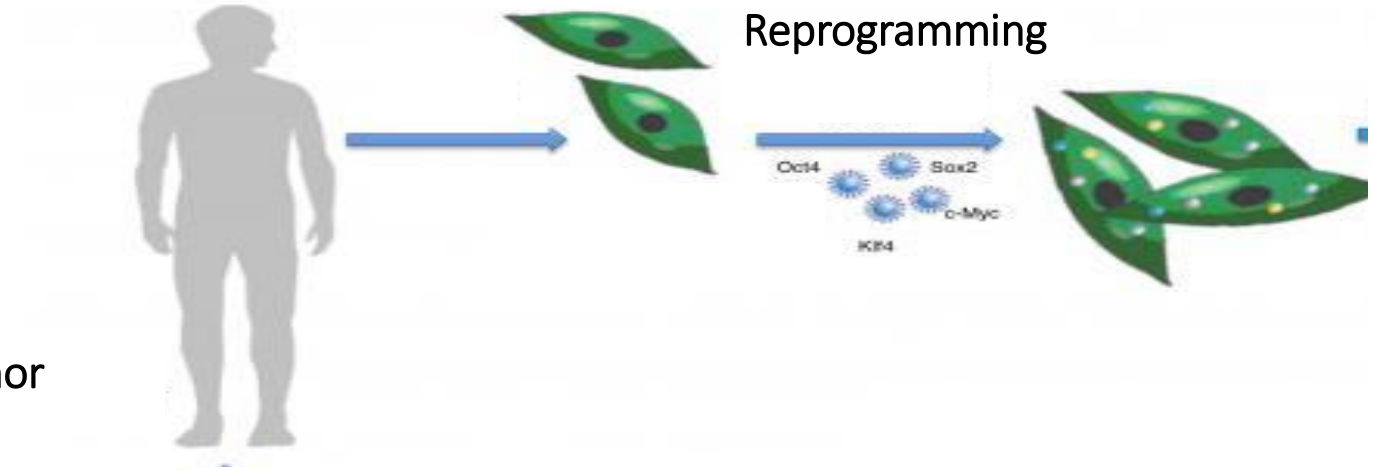
Use of Stem Cell-derived Cardiomyocytes in Safety Assessment and Drug Discovery

Kyle Kolaja

The Potential of iPS Cells: Genetic Diversity

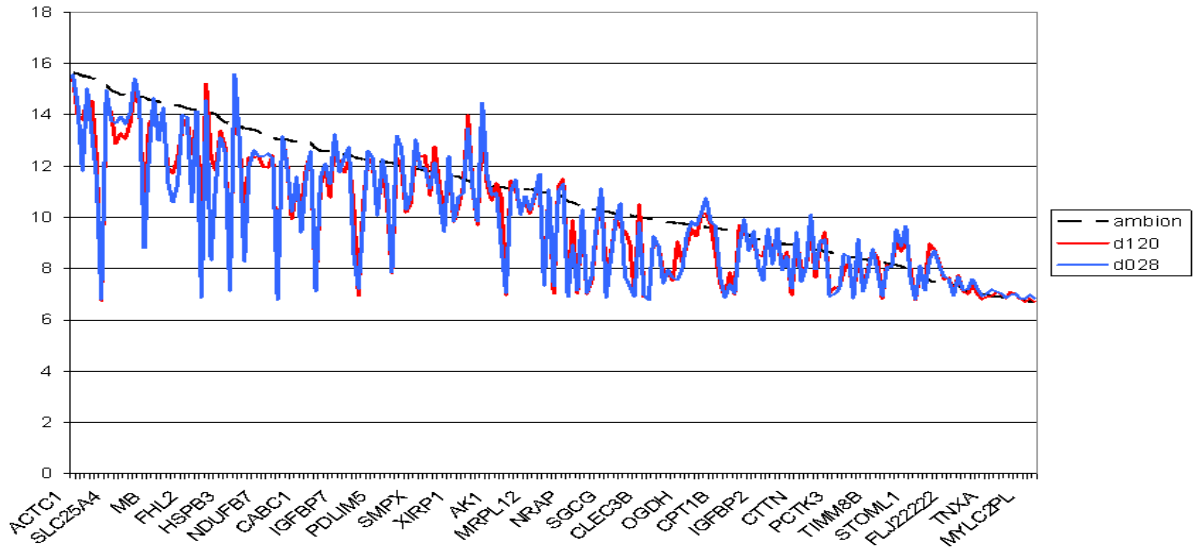


Human
Footprint free method
Gene editing/engineering
Made from anyone

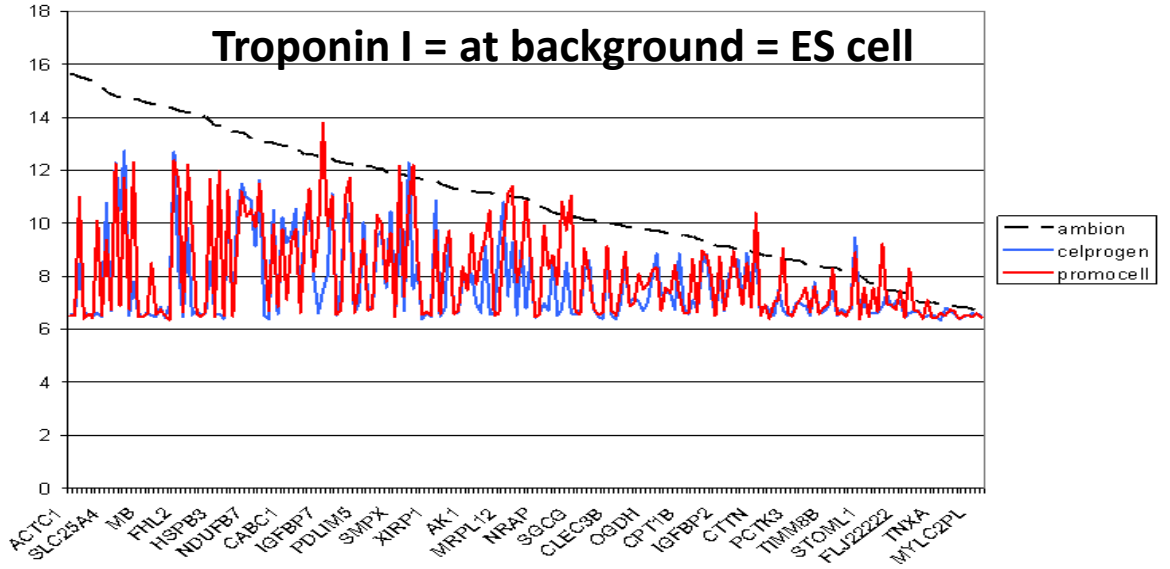
M. Rossbach

iCell Cardiomyocytes are more similar to Adult Human Heart Samples than Primary Cultures

CDI cells d28 and d120



Primary Heart cultures

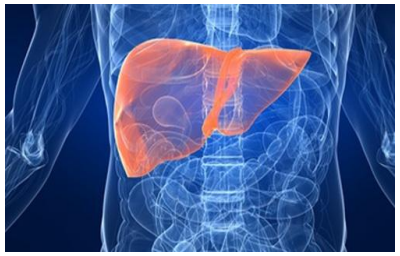


Primary isolation of organs/tissues/cells

- >100 years since Harrison first cultured frog neurons
- >60 years since Gey first immortalized human cell line (HeLa)
- Immeasurable innovations, advancements, and knowledge

Yet, cell culture limitations havent changed much and prevented the ultimate potential of replacing animal and human experiments

- Variability of isolation, timing, etc
- Degeneration of phenotype with time



Primary Human Cells

Transformed Cell Lines

Quality Manufacturing and Broad Access Lead to Scientific Progress

- **Robust manufacturing = enterprise wide quality management system**
  - Defined media and control of components
  - Substrate shift from feeder layers to recombinant proteins
  - Control of process from start to finish
  - Automation
- **Successful, broadly used items become commercialized → ACCESS**
  - Media and substrates above
  - Micro-arrays great example
    - Academia – Govt – Industry
    - Homemade to QC product

Key Systems	Objectives
QA/QC	**Compliance and product consistency**
Standard Operating Procedures	**Consistent procedures**
Calibration/Qual/Val	**Equipment/facilities/processes fit for intended use**
Change Management	**Changes are documented, assessed for risk, and tested**
CAPA	**Report, correct, and prevent product quality issues**
Supplier Qual & Mgmt	**Quality and reliability of raw materials**
Materials Management	**Control, trace, and monitor stock inventory**
Training	**Education and proficiency**
Complaint Handling	**Customer satisfaction and continuous improvement**
New Product Introduction	**Improve likelihood that product meets market need**


Journal of Biomedical Discovery and Collaboration

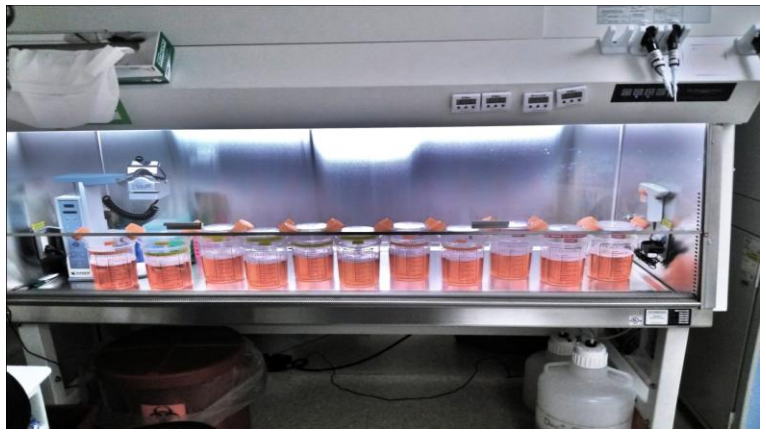
BioMed Central

Case Study

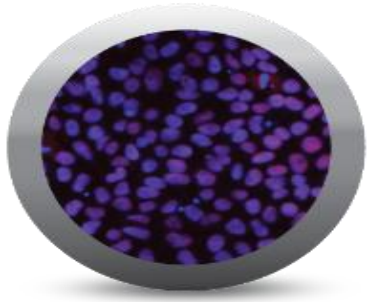
Open Access

The emergence and diffusion of DNA microarray technology

Tim Lenoir*† and Eric Giannella†



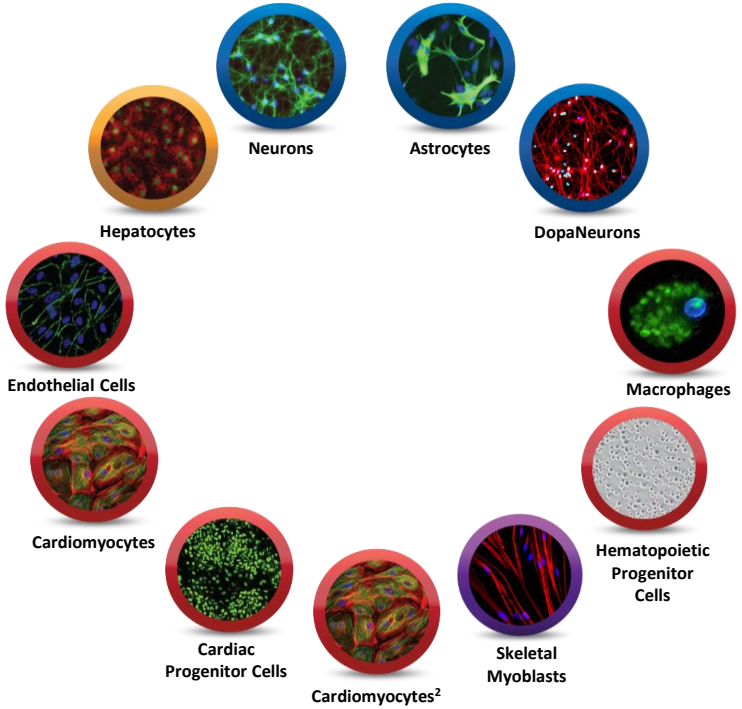
Standardization through Quality, Quantity and Purity:



Induced Pluripotent Stem Cells

Scale-Up Manufacturing

- Quality
- Quantity
- Purity



Scale-Out Manufacturing

- 1000's of individuals
- Billions of cells

CIRM
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
The State Stem Cell Agency

NIH
National Heart, Lung, and Blood Institute

Stem Cell Derived Cardiomyocytes Are the Standard for In Vitro Cardiac Research

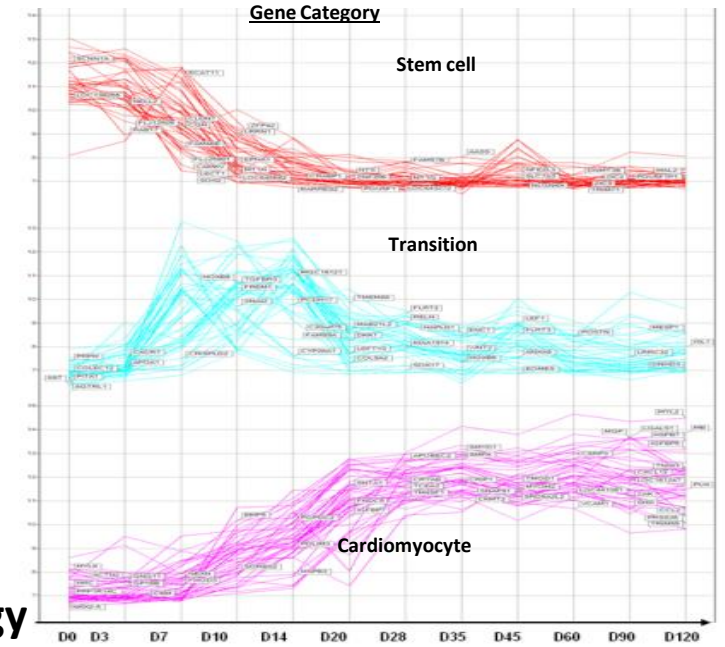
- **First stem cell derived cell type**
  - Used in regulatory filings to support claims

- **Proof of comparability (+) established**
  - Gene expression
  - Morphology
  - Electrophysiology and contractility
  - Biochemical properties
  - Functional (pharm and tox)

- **Major opportunity in arrhythmia detection, but ample applications in pharmacology, toxicology, and disease biology research**

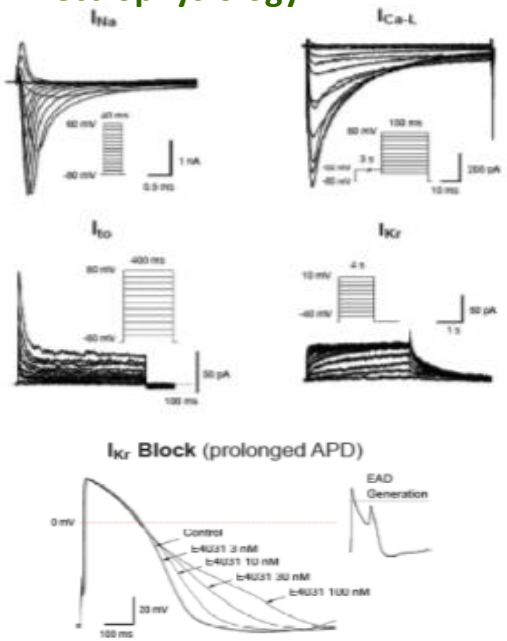
Endpoint	Platform(s)
Viability	Cell-based assays, HCI
Mitochondrial health	Cell-based assays, HCI
Oxidative stress	Cell-based assays
Bioenergetics	Seahorse XF-Analyzer

Gene Expression



Babiarz, et al. (2012) Stem Cells & Development.

Electrophysiology



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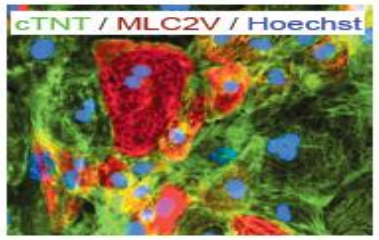
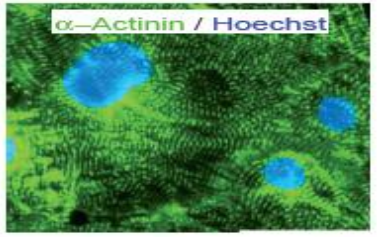
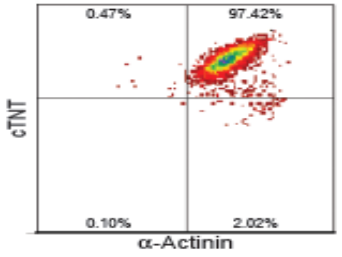
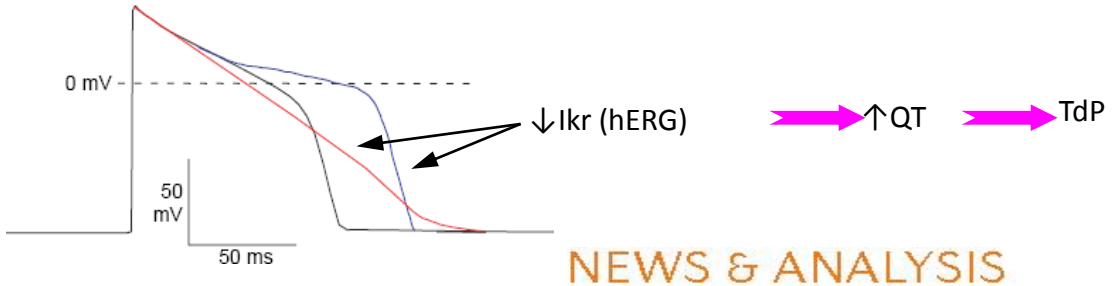






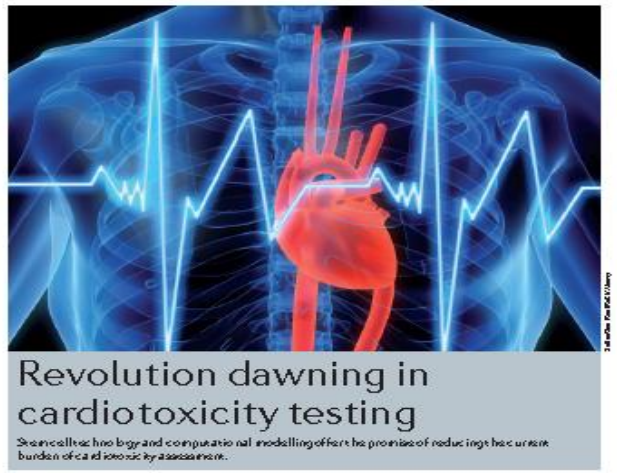
Fear of Arrhythmia
#1 reason for discovery and development attrition

- **~10 drugs pulled from market based on torsades de pointe**
- **Regulatory Guidance documents ICH7A and 7B proscribe a new host of cardiovascular safety approaches**
  - hERG screening – ex vivo preps – in vivo animal models – ECGs – Thorough QTc trials
- **Two consequences –**
  - no drug induced torsades
  - a lot of beneficial drugs not marketed

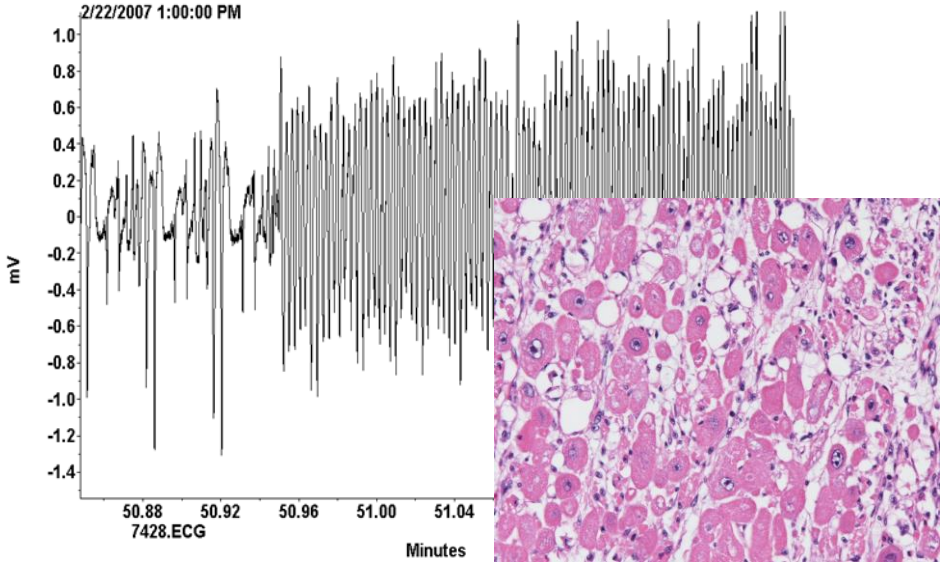


- **Early screening relies heavily on hERG**
  - hERG block ≠ QT prolongation
  - hERG block ≠ arrhythmia
  - QT prolongation ≠ arrhythmia
  - Arrhythmia can be independent of hERG

- **Cardiovascular safety and regulations could be better**
  - HESI and CIPA



Torsades induction in Cynomolgus Monkey reproduced in Vitro



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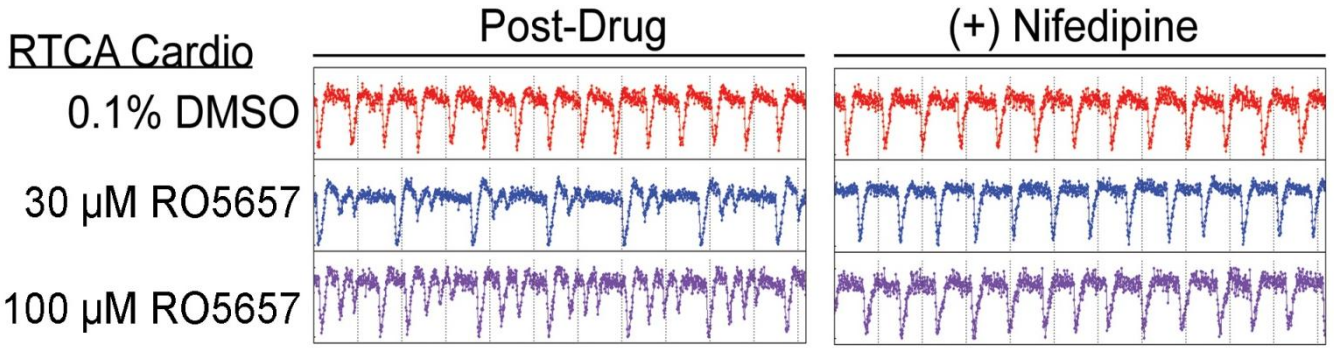
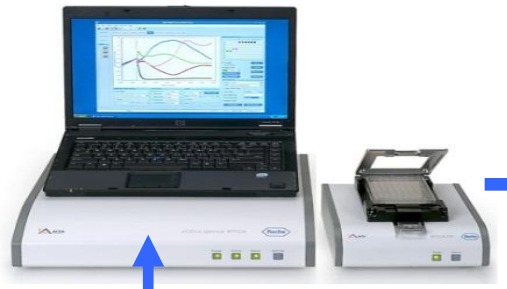
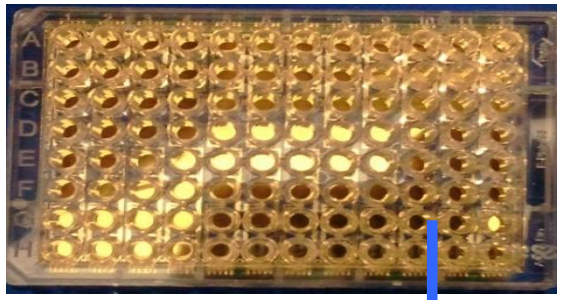
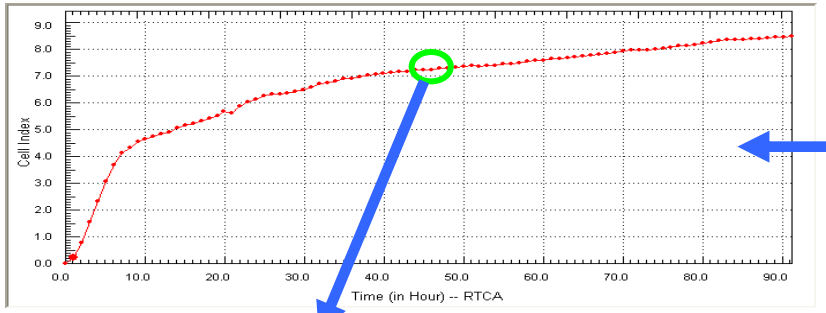


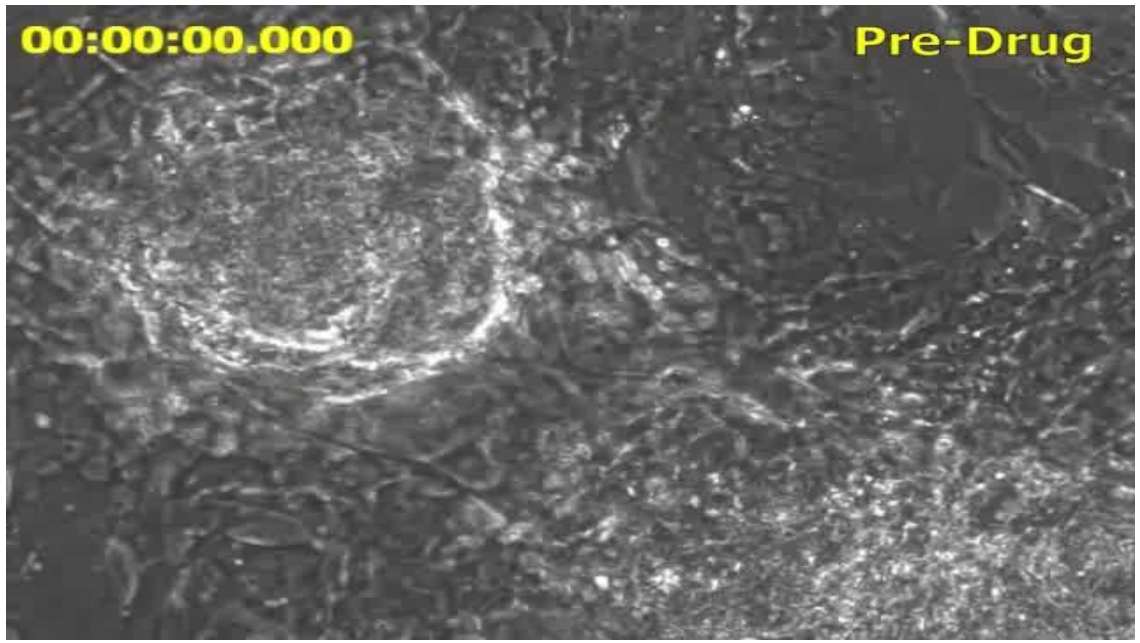
Guo et al. Toxicol Sci. 2011 Sep;123(1):281-9.

Human Cardiomyocytes Arrhythmia Risk (hCAR) Model *with iCell CMs*

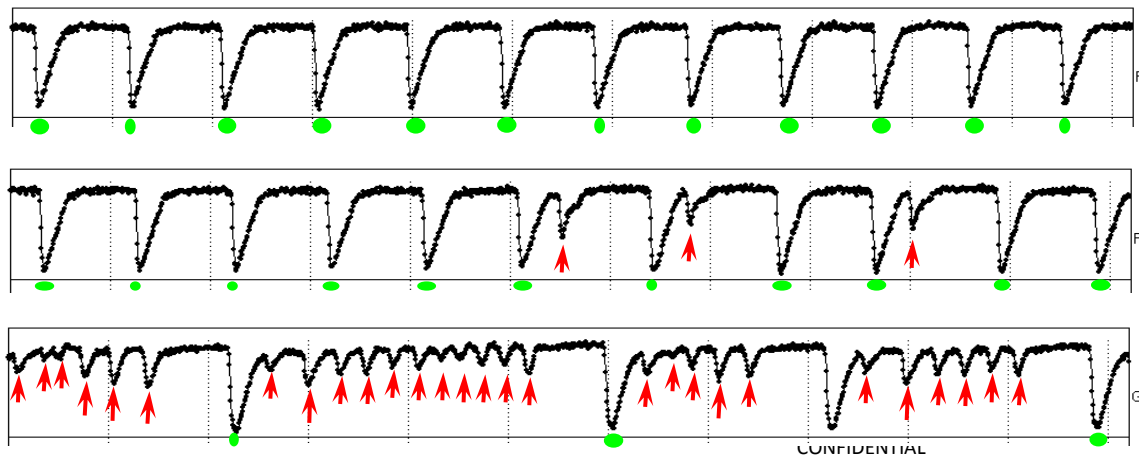








R	I	T	IBR
12	0	12	0
11	3	14	0.21
4	28	32	0.88



IB20= lowest tested concentration resulting in 20% irregular beats

hCAR Assay Validation:
23 Commercially available compounds with know in vivo effect

- 12 Pro-arrhythmic
- 11 Non-arrhythmic
- IB20 30 uM
  - One False Positive
  - No False Negatives

- IB20= lowest tested concentration resulting in 20% irregular beats

Drug	IB20 (µM)	hERG	QT	Clinical arrhythmia
Dofetilide	0.003	(+)	(+)	(+)
Ouabain	0.03	(-)	(-)	(+)
Aconitine	0.03	(-)	(-)	(+)
Cisapride	0.03	(+)	(+)	(+)
E-4031	0.03	(+)	(+)	(+)
Astemizole	0.03	(+)	(+)	(+)
Terfenadine	0.3	(+)	(+)	(+)
Flecainide	1	(+)	(+)	(+)
Alfuzosin	1	(-)	(+)	(-)
Thioridazine	3	(+)	(+)	(+)
Quinidine	10	(+)	(+)	(+)
Erythromycin	30	(+)	(+)	(+)
Sotalol	30	(+)	(+)	(+)
Fluoxetine	>30	(+)	(+)	(-)
Verapamil	>30	(+)	(±)	(-)
Moxifloxacin	>100	(+)	(+)	(+)
Amiodarone	>100	(+)	(+)	(±)
Ranolazine	>100	(+)	(+)	(-)
Captopril	>100	(-)	(-)	(-)
Rofecoxib	>100	(-)	(-)	(-)
Amoxicillin	>1000	(-)	(-)	(-)
Aspirin	>1000	(-)	(-)	(-)
Nifedipine	>3	(-)	(-)	(-)

Guo et al. Toxicol Sci. 2011 Sep;123(1):281-9.

Human Cardiomyocytes Arrhythmia Risk (hCAR) Model
2nd Paper - *Next Round of Validation*

Drug	C_{max} (nM)	IB_{50} (μM)	↓hERG	↑QT	TdP
Digitoxin	33	0.003	(-)*	(-)	(+)*
Dofetilide	6	0.003	(+)	(+)	(+)
Digoxin	3	0.01	(-)*	(-)	(+)*
Ouabain	170	0.01	(-)*	(-)	(+)*
Aconitine	77	0.03	(-)	(-)	(+)*
Astemizole	8	0.03	(+)	(+)	(+)
E-4031	13	0.03	(+)	(+)	(+)
Pimozide	217	0.1	(+)	(+)	(+)
Sertindole	3.18	0.1	(+)	(+)	(+)
Cisapride	129	0.3	(+)	(+)	(+)
Geldanamycin	16,800	0.3	(-)*	(-)	(+)*
Idarubicin	123	0.3	(-)	(+)	(+)*
Terfenadine	300	0.3	(+)	(+)	(+)
Alfuzosin	56	1	(-)	(+)	(-)
Dobutamine	3,819	1	(+)	(-)	(-)
Doxorubicin	15,344	1	(-)	(+)	(+)*
Flecainide	1,931	1	(+)	(+)	(+)
Pentamidine	2,181	1	(-)*	(+)	(+)
Tacrine	100	1	(-)	(-)	(-)
Amphotericin B	89.818	3	(-)	(+)	(+)*
Arsenic Trioxide	12,132	3	(-)*	(+)	(+)
Clozapine	1	3	(-)	(+)	(±)
Mitoxantrone	3,311	3	(-)	(+)	(+)*
Prenylamine	70	3	(-)	(+)	(+)
Sunitinib	253	3	(+)	(+)	(+)
Thioridazine	1,781	3	(+)	(+)	(+)
Zimelidine	328	3	(+)	(±)	(±)
Ajmaline (I.v.)	105	10	(+)	(+)	(+)
Chlorpromazine	2,630	10	(+)	(+)	(+)
Clarithromycin	6,025	10	(+)	(+)	(+)
Dantrolene	7,900	10	(-)	(-)	(-)
Desipramine	601	10	(+)	(+)	(+)
Epirubicin	16,036	10	(-)	(+)	(+)*
Netazodone	4,858	10	(+)	(+)	(-)
Phentolamine	100	10	(-)	(-)	(-)
Quinidine	21,578	10	(+)	(+)	(+)
Erythromycin (I.v.)	34,064	30	(+)	(+)	(+)
Fluvoxamine	1,257	30	(+)	(-)	(-)
Imatinib	3,541	30	(-)	(+)	(-)
Mesoridine	11,161	30	(+)	(-)	(-)
Propafenone	4,827	30	(+)	(+)	(+)
Propranolol (I.v.)	193	30	(-)	(+)	(-)
Sotalol	14,733	30	(+)	(+)	(+)

	in vivo ECG		hERG		
Cyclosporin A	1,458	100	(-)	(-)	(-)
Lidocaine (I.v.)	36,000	100	(+)	(-)	(-)
Pimobendan	164	100	(-)	(-)	(-)
Ranolazine	6,005	100	(+)	(+)	(-)
Nifedipine	194	>3	(-)	(-)	(-)
Amitriptyline	793	>30	(-)	(+)	(±)
Bepridil	3,258	>30	(+)	(+)	(+)
Cetirizine	800	>30	(-)	(-)	(-)
Cibenzoline	2,168	>30	(+)	(+)	(-)
Delta mpridine	493	>30	(-)	(-)	(-)
Diltiazem	552	>30	(-)	(-)	(-)
Diphenhydramine	157	>30	(-)	(+)	(+)
Fluorouracil	4,613	>30	(-)	(-)	(+)*
Fluoxetine	485	>30	(+)	(+)	(+)
Imipramine	1,070	>30	(+)	(+)	(±)
Ketoconazole	17,689	>30	(+)	(+)	(±)
Loratadine	23	>30	(-)	(-)	(-)
Nitrendipine	150	>30	(-)	(-)	(-)
Olanzapine	74	>30	(-)	(±)	(-)
Rosiglitazone	1,673	>30	(-)	(-)	(-)
Troglitazone	6,387	>30	(-)	(-)	(-)
Verapamil	815	>30	(+)	(-)	(-)
Acetamidophenol	130,000	>100	(-)	(-)	(-)
Alpidem	284	>100	(-)	(-)	(-)
Amiodarone	3,874	>100	(+)	(+)	(±)
Atenolol	1,284	>100	(-)	(-)	(-)
Captopril	2,466	>100	(-)	(-)	(-)
Colchicine	16	>100	(-)	(-)	(-)
Cyclophosphamide	153,200	>100	(-)	(±)	(-)
Dextrazotane	136,052	>100	(-)	(-)	(-)
Levosimendan	136	>100	(-)	(-)	(-)
Mechlorethamine	?	>100	(-)	(-)	(-)
Moxifloxacin	10,276	>100	(+)	(+)	(+)
Nimesulide	15,000	>100	(-)	(-)	(-)
Pemoline	6,925	>100	(-)	(-)	(-)
Rofecoxib	1,021	>100	(-)	(-)	(-)
Tolcapone	21,959	>100	(-)	(-)	(-)
Zalcitabine	119	>100	(-)	(-)	(-)
Amoxicillin	17,036	>1000	(-)	(-)	(-)
Aspirin	10,000	>1000	(-)	(-)	(-)

30	-	-	-	4.9
00	-	-	-	30
27	>100	>100	-	-	-	4.0
28	>100	>100	-	-	-	4.3
29	>100	>100	-	-	-	30
30	>100	>100	-	-	-	>300

83 Compounds

~82% -- arrhy. prediction
>90% -- QT prediction

30 Internal Compounds

80% -- arrhy. prediction
95% -- QT prediction

Comprehensive In Vitro Proarrhymia Assay

Objective:

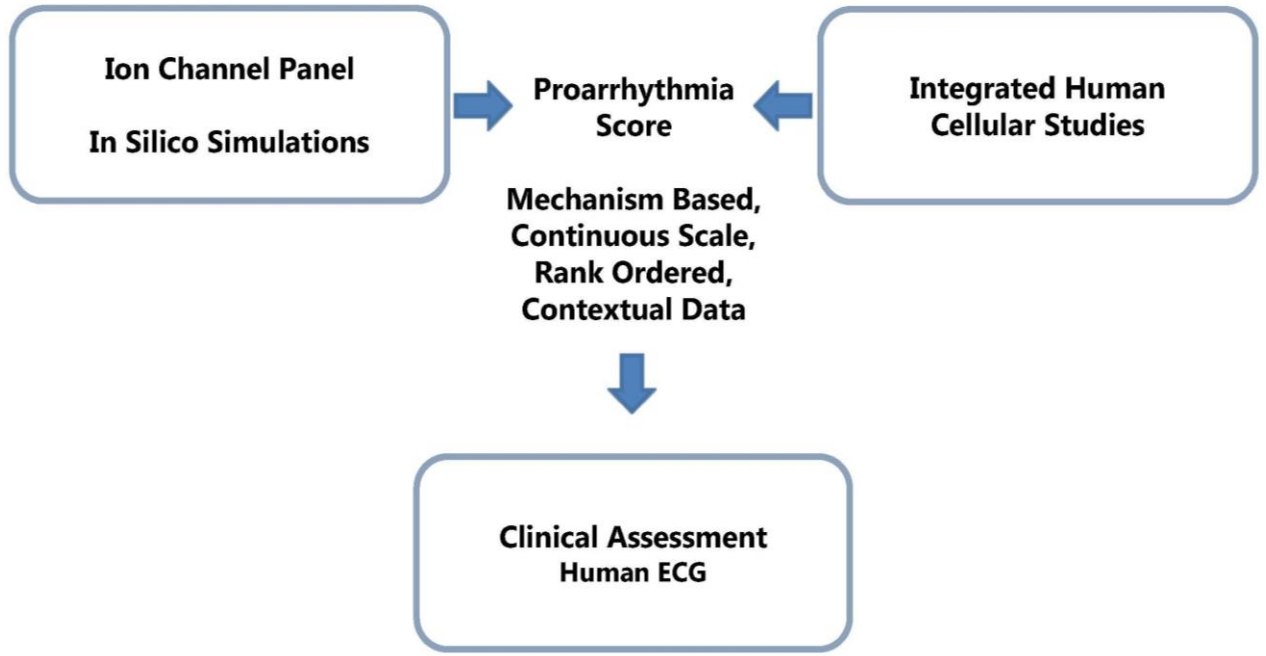
- Facilitate the adoption of a new paradigm for assessment of clinical potential of TdP that is not measured exclusively by potency of hERG block and not at all by QT prolongation.
- CIPA is envisioned to ultimately require modification or replacement of the existing ICH S7a/b guidelines and elimination of E14 guidelines.

Anticipated Final Outcome:

- Eliminate the need for a TQT study for compounds entering clinical development with a negative dataset based on the newly proposed in vitro and in silico paradigm

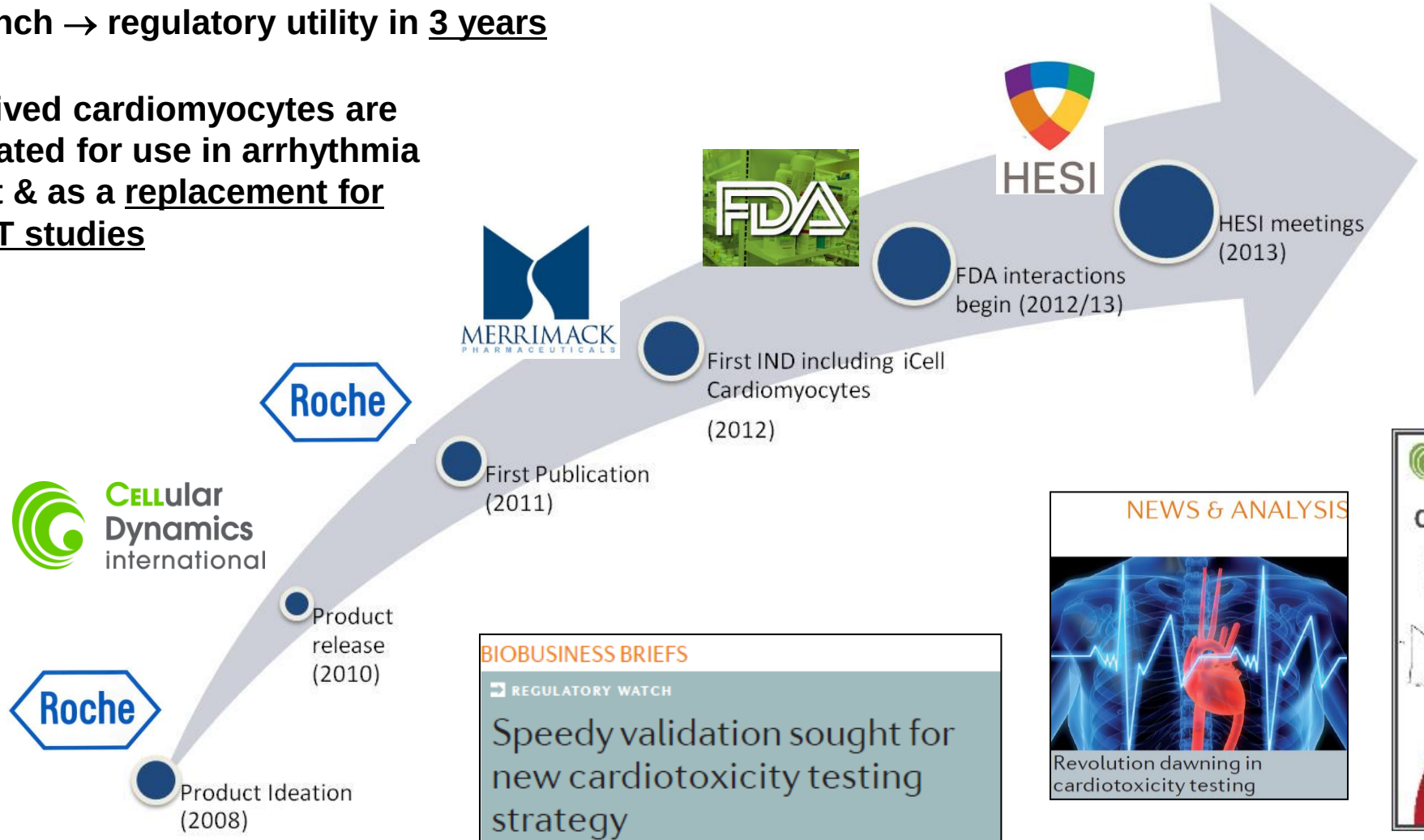
CIPA Partners:

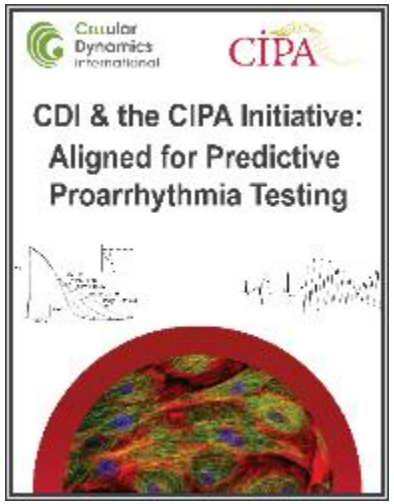
- USU FDA, HESI, CSRC, SPS, EMA, Health Canada, Japan NIHS, PMDA



iCell Cardiomyocytes:
Development → Regulatory Guidance

- **Product launch → regulatory utility in 3 years**
- **iPS cell-derived cardiomyocytes are being evaluated for use in arrhythmia assessment & as a replacement for thorough QT studies**





Nature Reviews Drug Discovery (Aug, Sept 2013)

Nature Reviews Drug Discovery (Aug, Sept 2013)

Electrical and Structural Toxicity are Inter-related – Key is to Determine Mechanistic Driver

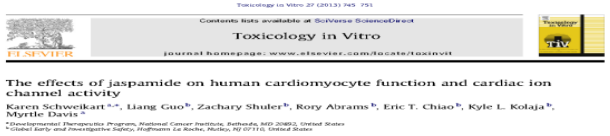
- **Jaspamide** - potential cancer therapeutic agent
  - a cyclodepsipeptide (marine sponge Jaspis johnstoni)
  - Affects actin binding to cytoskeleton
  - Pulmonary edema /cardiac hemorrhage /congestion in tox species
  - inhibited Kv1.5 activity by 98.5%. inhibited Cav1.2, Cav3.2, and HCN2;
  - but not a hERG blocker
  - Induced arrhythmic beats in vitro in stem cell derived CMs

- **Sunitinib -** multi-targeted inhibitor – oncology
  - cardiac dysfunction and cardiotoxicity (CHF)
  - potently cardiotoxic in stem cell derived cardiomyocytes
  - **AMPK inhibited but no attenuation**
  - Inhibit hERG, Ca++ cycling and NaV1.5 -> arrhythmia
  - arrhythmia and cytotoxicity in stem cell dervied CMs

hIPSC- CMs ideal model to assess cardiotoxicity, electrophysiology and contractility effects in parallel

- **R5657**
  - CCR5 antagonist, mild hERG inhibitor (IC 50 = 12 uM)
  - Myofiber loss and morbundity in 2 monkeys
  - Expanded telemetry study showed only torsades, no cardiac tox.
  - Stem cell derived CMs show arrhythmia and no cytotoxicity

- **Multi-factorial combination of cytotoxicity, cardiac conduction abnormalities, hypoxia, suppressed response/accommodation mechanisms**



Off Target Cellular Gene Therapy Targeting MAGE A3 – Toxicity due to Titin-cross reactivity

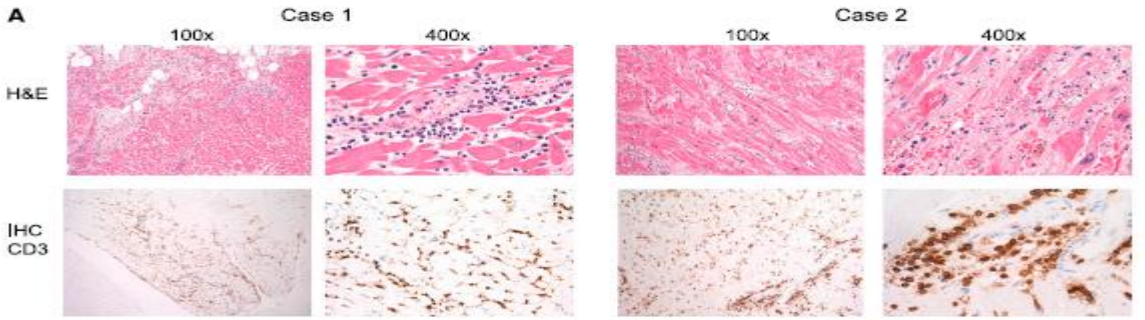
- **Modified T cell to increase affinity to MAGE 3A receptor, a putative tumor antigen**

- **Phase I trial – 2 patients died of cardiogenic shock and fever**
  - Ventricular myofiber loss with infiltrate
  - MAGE 3A not expressed on heart samples
  - No toxicity in preclinical toxicity studies

- **Bioinformatic modeling to detect - off target recognition of titin, a protein that is a component of striated muscle**
  - only expressed in beating cells
  - not expressed in static primaries
  - 1uM long, largest protein in body, 3rd most abundant, 0.5 kg/person

- **T cells expressing the affinity-enhanced TCR but not wild type were toxic to IPSC-CMs**

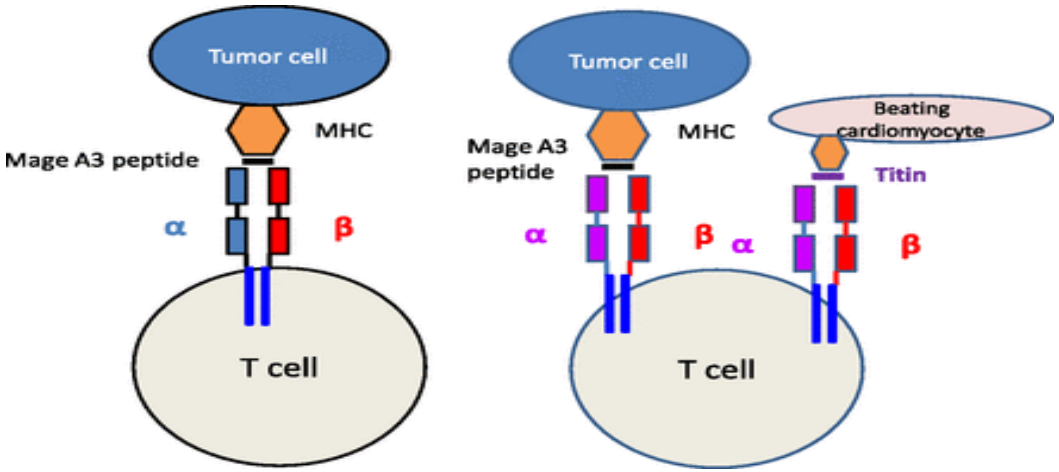
- **2 Main points**
  - Affinity enhancing T cells may create unintended targets
  - Complex development programs need to test toxicity in human models



Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma

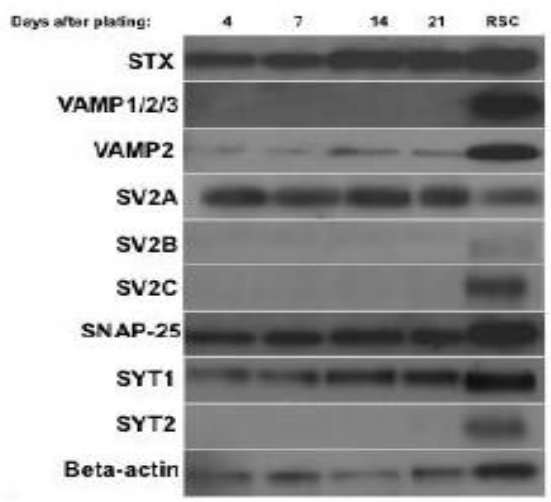
Gerald P. Linette,[1] Edward A. Stadtmauer,[2] Marcela V. Maus,[2] Aaron P. Rapoport,[3] Bruce L. Levine,[2] Lyndsey Emery,[2] Leslie Litzky,[2] Adam Bagg,[2] Beatriz M. Carreno,[1] Patrick J. Cimino,[1] Gwendolyn K. Binder-Scholl,[4] Dominic P. Smethurst,[4] Andrew B. Gerry,[4] Nick J. Pumphrey,[4] Alan D. Bennett,[4] Joanna E. Brewer,[4] Joseph Dukes,[5] Jane Harper,[5] Helen K. Tayton-Martin,[4] Bent K. Jakobsen,[4,5] Namir J. Hassan,[5] Michael Kalos,[2] and Carl H. June[2]

[1]Siteman Cancer Center and Departments of Medicine and Pathology and Immunology, Washington University School of Medicine, St. Louis, MO; [2]Abramson Cancer Center, Department of Medicine, and Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA; [3]The Greenebaum Cancer Center, University of Maryland, Baltimore, MD; [4]Adaptimmune Ltd, Philadelphia and Abingdon, United Kingdom; and [5]Immunocore Ltd, Abingdon, United Kingdom

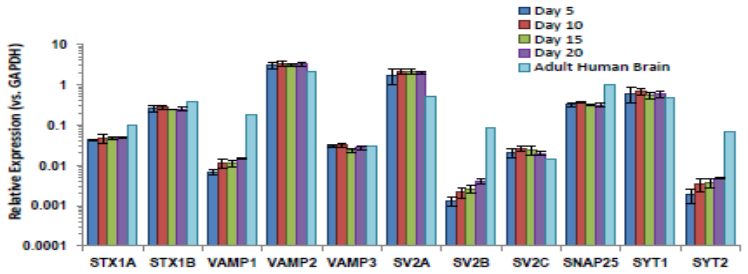


Stem Cell Derived Cortical Neurons and Toxicology – Potency Release Assay

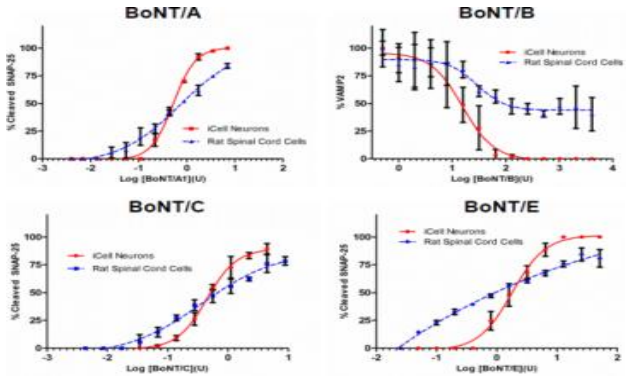
BoNT Receptor Protein Expression



BoNT Receptor Gene Expression



BoNT Receptor Cleavage



- Assess the potency of botulinum neurotoxin (BoNT) better than rat spinal cord neurons or mouse LD50.
- a consortium of BoNT manufacturers is in the process of validating the use of Stem Cell derived Neurons to replace the current industry "gold" standard, a high-cost and labor-intensive in vivo bioassay.

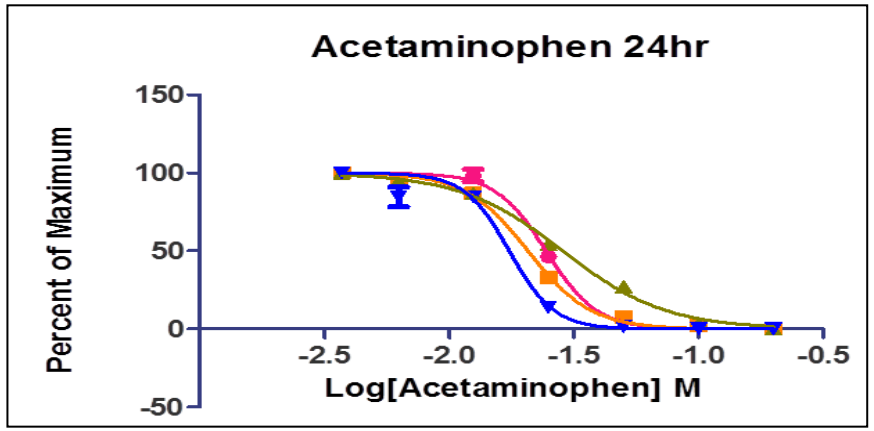
- iCell Neurons express the receptors and enzymatic targets necessary for BoNT cell entry and catalytic activity
- iCell Neurons reproducibly show equivalent or greater sensitivity to BoNT activity vs. rat spinal cord cells

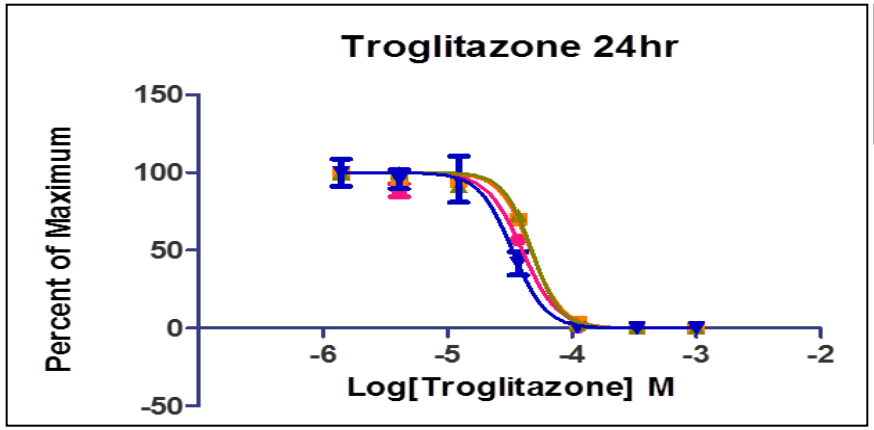
Novel Application of Human Neurons Derived from Induced Pluripotent Stem Cells for Highly Sensitive Botulinum Neurotoxin Detection

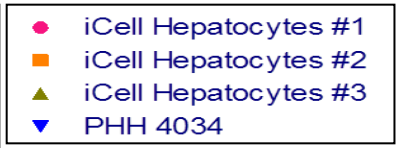
Regina C. M. Whitemarsh,* Monica J. Strathman,† Lucas G. Chase,* Casey Stankewicz,† William H. Tepp,* Eric A. Johnson,* and Sabine Pellett*,1

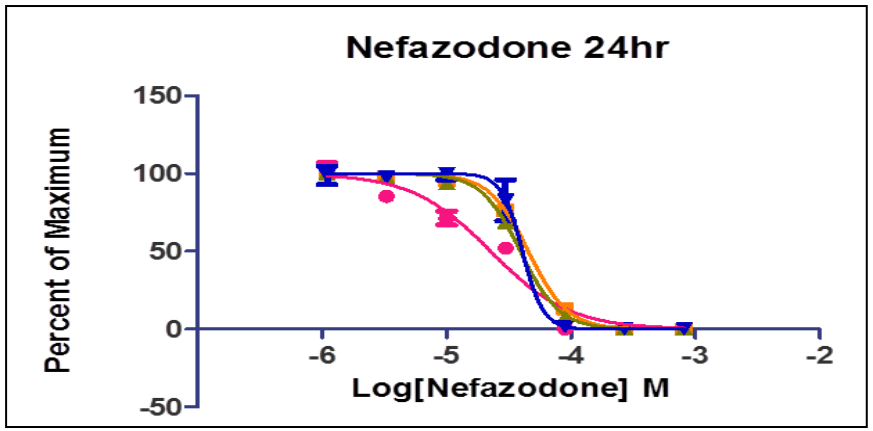
*Department of Bacteriology, University of Wisconsin, Madison, Madison, Wisconsin 53706 and †Cell Biology Group, Cellular Dynamics International, Inc., Madison, Wisconsin 53711

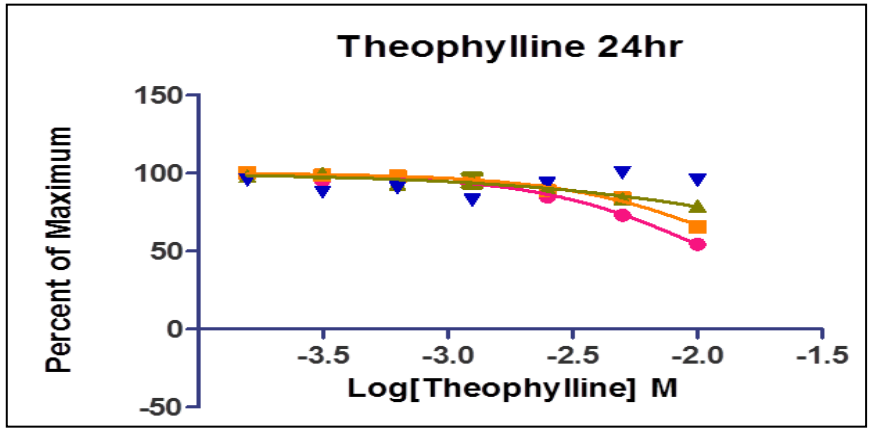
Stem Cell Derived Hepatocytes and Toxicology









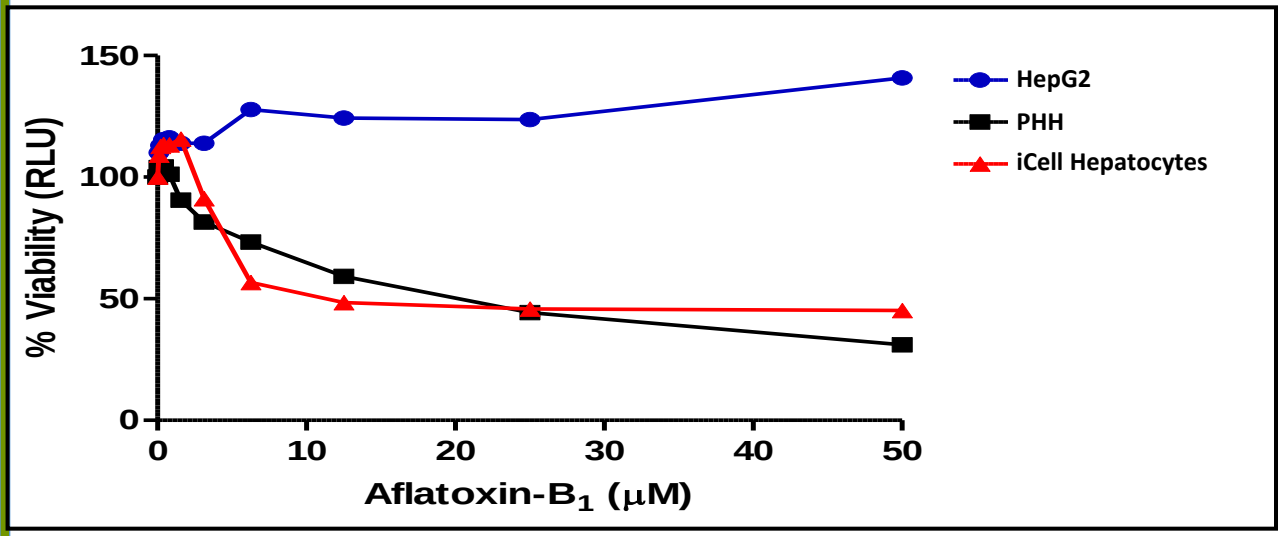


	iCell HCs		PHH	
Compound	**EC50 (AVG mM)**	**EC50/CMax**	**EC50 (mM)**	**EC50/CMax**
Acetaminophen	25	55.4	17.4	39.3
Troglitazone	0.045	2.0	0.033	1.5
Nefazodone	0.036	4.2	0.041	4.8
Theophylline	>10	>100	>10	>100

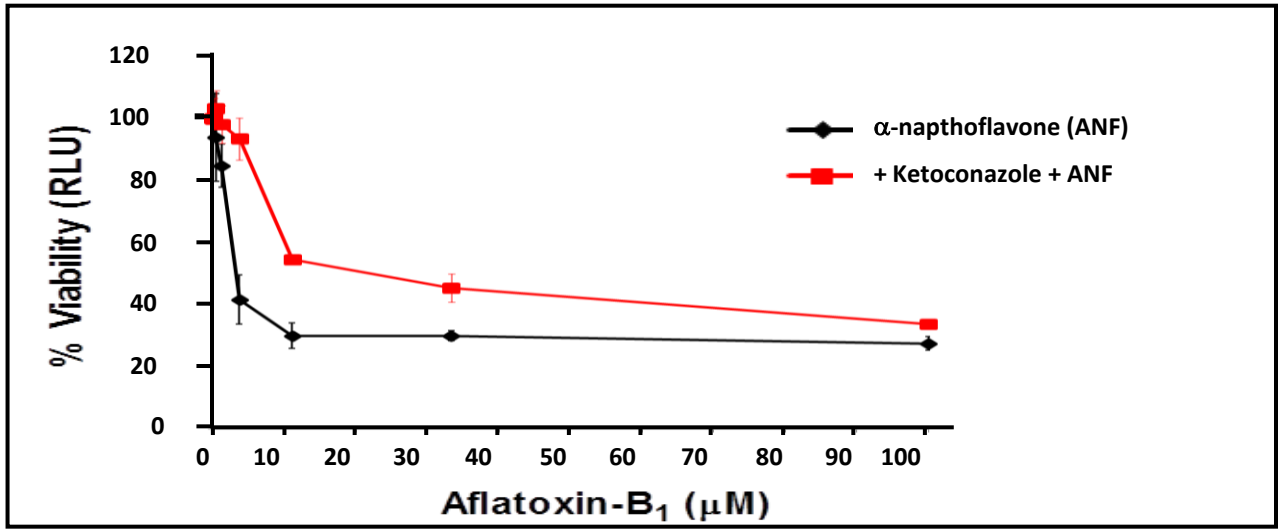
iCell Hepatocytes

Hepatoxtocity via Metabolic Activation - Aflatoxin

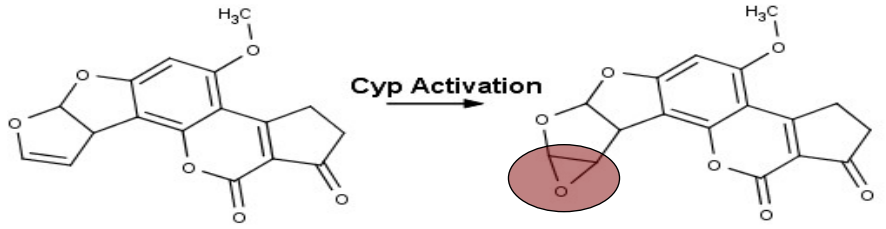
Cytotoxic Response to Aflatoxin-B_1



CYP Inhibitors Potentiate Sensitivity to Aflatoxin-B_1

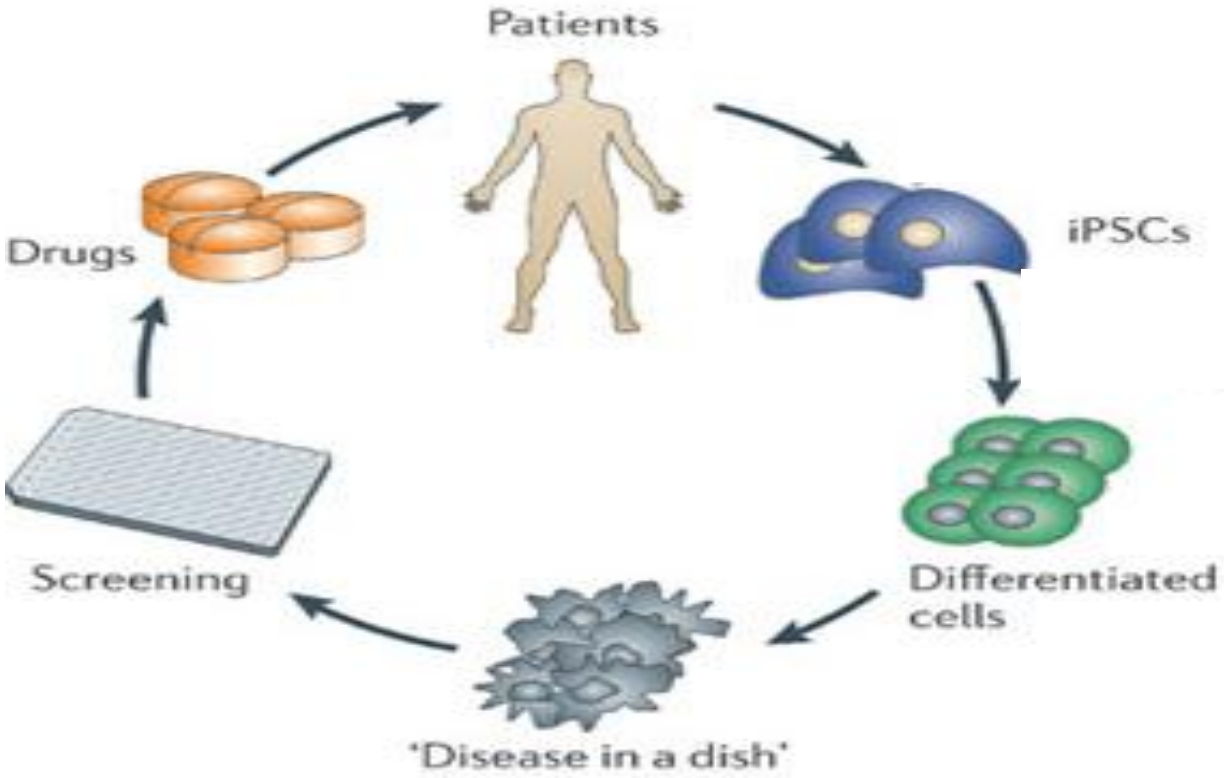


Evidence of CYP Mediated Conversion to Reactive Toxic Aflatoxin Epoxide



‘Disease in a Dish”

Modeling Human Disease using iPSCs



Adapted from Grskovic, et al. (2011)

iPSC technology can be used to model human **Innate**, **Induced** and **Infectious** diseases that cannot be interrogated using conventional cell lines, primary cells or animal models

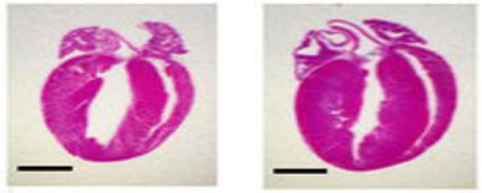
Reviews & summaries of disease-specific iPSCs created:

- Grskovic, et al. (2011) *Nature Reviews Drug Discovery*
- Rajamohan, et al. (2012) *Bioessays*
- Trounson, et al. (2012) *Current Opinion Genetics & Development*

Induced Disease Modeling

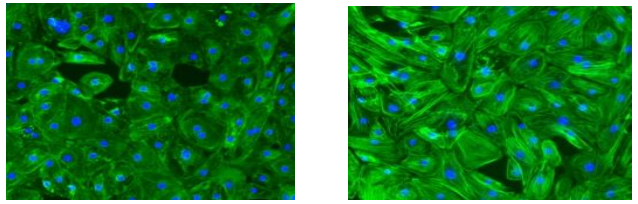
Cardiac Hypertrophy

Mouse Phenotype
(increased cell size)

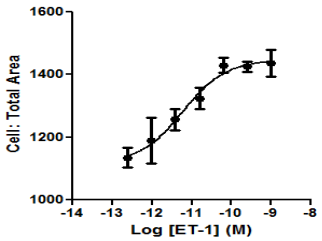


Normal Disease

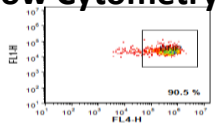
Endothelin Induced iCell CM



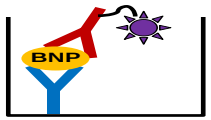
Control ET-1 (10 nM)



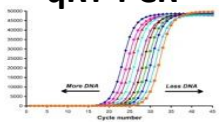
Flow Cytometry



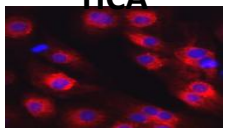
ELISA



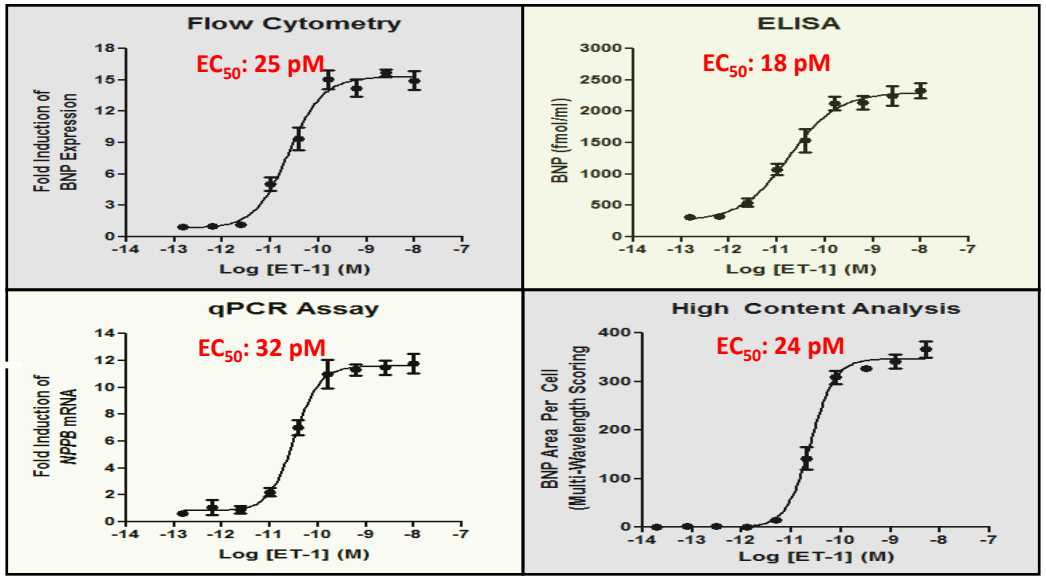
qRT-PCR



HCA

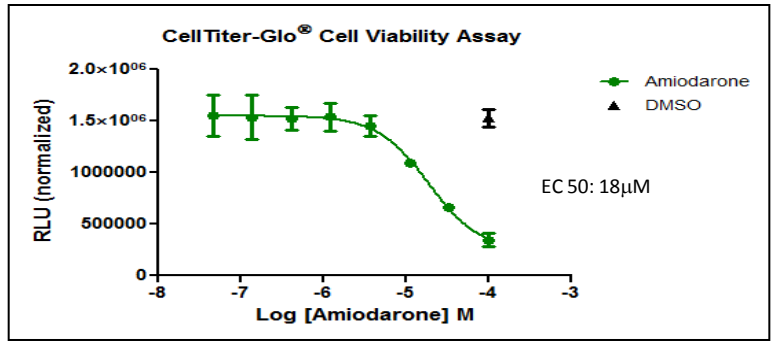


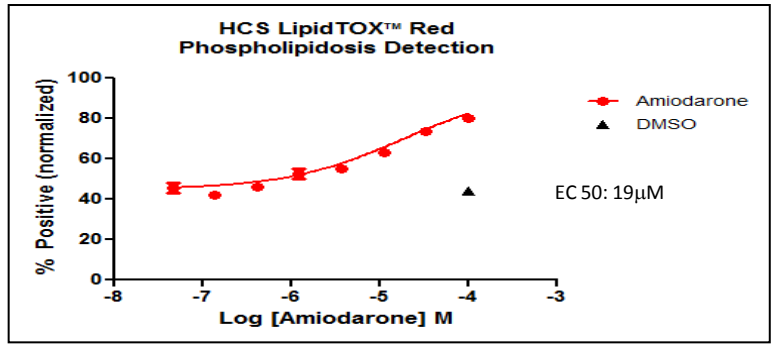
Robust and Reproducible in-vitro assays
(BNP-based readouts)

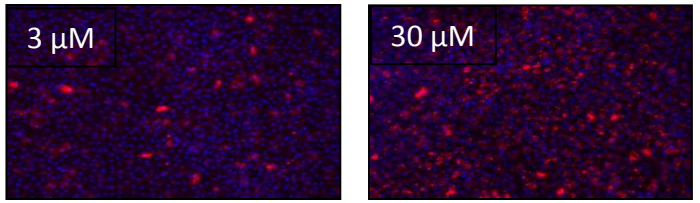


Steatohepatitis

Amiodarone Induced iCell HC



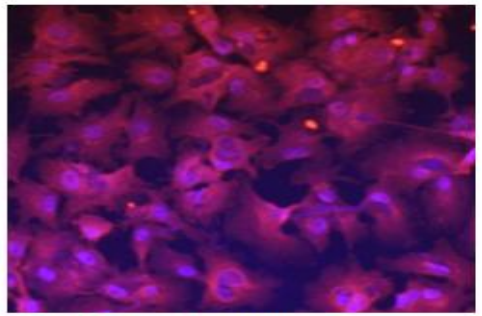




Infectious Disease Modeling

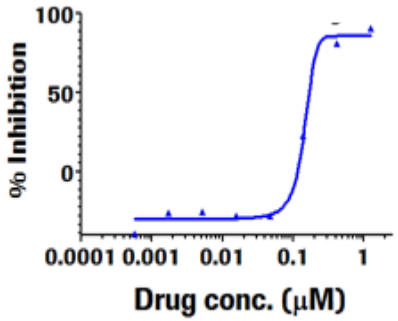
iCell Hepatocytes
HCV Infection (Clinical Genotypes)

Luc Expressing HCV pseudoparticle (HCVpp) uptake

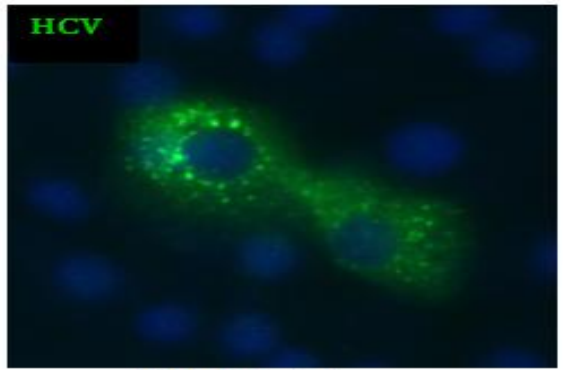


HCVpp encoding Firefly luciferase

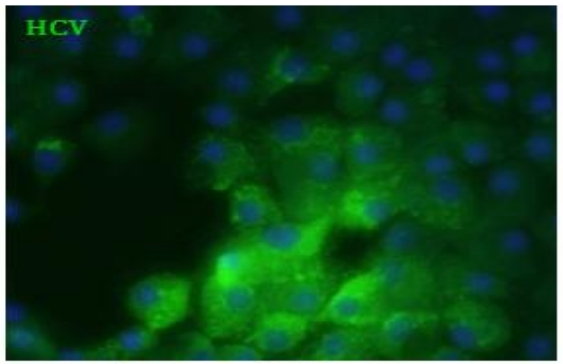
Inhibition of HCVpp Uptake by anti-CD81 Ab



iCell Hepatocytes are Susceptible to Multiple HCV Genotypes

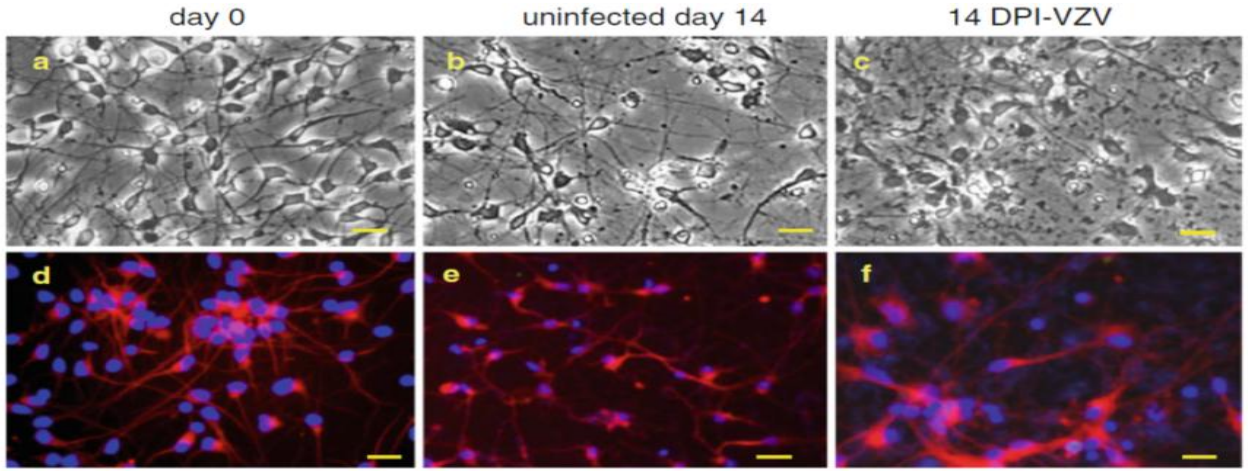


HCVcc - Cell Culture Passaged Virus (Genotype 1a/2a)

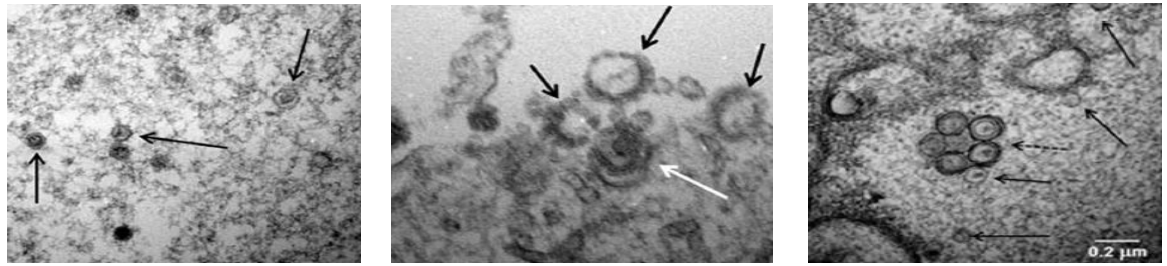


Patient Serum HCV (Genotype 1a)

iCell Neurons
Physiologic VZV Latent Infection



VZV infection did not produce a cytopathic effect



Viral Particles and Capsids in iCell Neurons

Yu, et al. (2013) J Neurovirology

iPS Cell Disease Lines with Phenotypes

Neuronal Diseases
Amyotrophic lateral sclerosis
Spinal muscular atrophy
Olivopontocerebellar atrophy
Parkinson's disease
Huntington's disease
Down's syndrome
Fragile X syndrome
Friedrichs Ataxia
Familial dysautonomia
Rett's syndrome
Mucopolysaccharidosis type IIIB
Schizophrenia
X-linked adrenoleukodystrophy
childhood cerebral ALD
Adrenomyeloneuropathy
Autism spectrum disorders
Angelman syndrome
Pradder-Willi

Skin
Recessive dystrophic epidermolysisbullosa

Eye
Retinitis pigmentosa
Age-related cataract
Gyrate atrophy

Multi-organ
Down syndrome - Trisomy 21
Shwachman-Bodian-Diamond syndrome
Dyskeratosiscongenita

Current status of drug screening and disease modelling in human pluripotent stem cells

*Divya Rajamohan, Elena Matsa, Spandan Kalra, James Crutchley, Asha Patel, Vinoj George and Chris Denning**

Bioessays 35: 281–298,© 2012 WILEY Periodicals, Inc.

Muscle
Duchene Muscular Dystroph
Becker muscular dystrophy
Hutchinson-Gilford progeria syndrome

Metabolic
Gaucher disease type III
Lesch-Nyhan syndrome
Juvenile Diabetes
Type 2 diabetes
Familial hypercholesterolemia
Alpha1-antitrypsin deficiency
Glycogen storage disease type 1a

Immune
Adenosine deaminase deficiencyassociated severe combined immunodeficiency (ADA-SCID)
Multiple Sclerosis

Cardiovascular Diseases
Flavors of long QT syndrome
CPTV
LEOPARD syndrome
Timothy Syndrome
Diabetes

Haematological
Sickle cell anaemia b-Globin alleles
Fanconi anaemia
Acquired myeloproliferativedisordes
b-Thalassaemia major (Cooley's anaemia)

Worlds Largest iPS Cell Research Repository

- **California Institute for Regenerative Medicine (CIRM)**

- **Human iPS Cell Initiative – 3 Awards (Total $32M)**
  - Sample Collection
  - iPS Cell Derivation
  - iPS Cell Banking

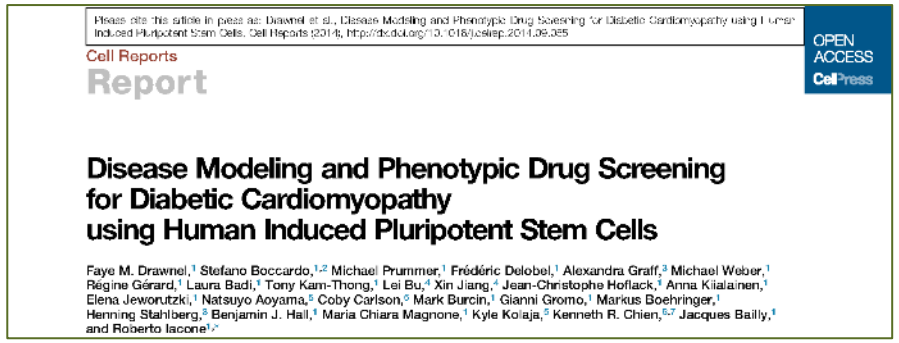
- **iPS Cell Derivation**
  - 3000 donors (healthy & disease phenotypes)
  - 3 iPS cell clones per donor
  - Disease categories: epilepsy, autism, cerebral palsy, cardiomyopathy, Alzheimer's disease, eye diseases, hepatitis (HCV), non-alcoholic steatohepatitis (NASH), pulmonary fibrosis
  - Derived from peripheral blood (preferred) or skin fibroblasts
  - Episomal "footprint-free" method

- **CDI – Coriell Partnership**
  - Brings together expertise in electronic record-keeping, sample tracking, iPS cell derivation & characterization, cell banking & distribution

First few hundred samples available via Coriell's Website in September

iCell and Patient-derived Cardiomyocytes in Drug Discovery

Drawnel et al, 2014 Cell Reports


Please cite this article in press as: Drawnel et al., Disease Modeling and Phenotypic Drug Screening for Diabetic Cardiomyopathy using Human Induced Pluripotent Stem Cells, Cell Reports (2014), http://dx.doi.org/10.1016/j.celrep.2014.09.015

Cell Reports
Report

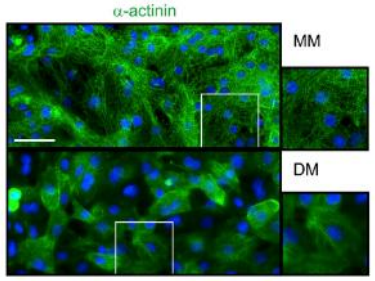
OPEN ACCESS
CellPress

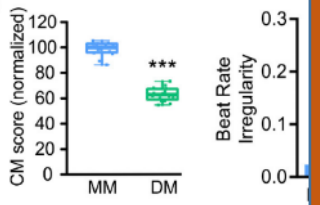
Disease Modeling and Phenotypic Drug Screening for Diabetic Cardiomyopathy using Human Induced Pluripotent Stem Cells

Faye M. Drawnel,[1] Stefano Boccardo,[1,2] Michael Prummer,[1] Frédéric Delobel,[1] Alexandra Graff,[3] Michael Weber,[1] Régine Gérard,[1] Laura Badi,[1] Tony Kam-Thong,[1] Lei Bu,[4] Xin Jiang,[4] Jean-Christophe Hoflack,[1] Anna Kiialainen,[1] Elena Jeworutzki,[1] Natsuyo Aoyama,[5] Coby Carlson,[5] Mark Burcin,[1] Gianni Gromo,[1] Markus Boehringer,[1] Henning Stahlberg,[5] Benjamin J. Hall,[1] Maria Chiara Magnone,[1] Kyle Kolaja,[5] Kenneth R. Chien,[6,7] Jacques Bailly,[1] and Roberto Iacone[1,*]

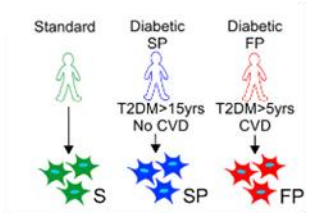
- **Diabetes causes pathological remodeling of cardiac muscle, which impairs heart function**
- **Diabetic media induces hallmarks of in vivo diabetic cardiomyopathy**
  - **Sarcomeric disorganization, altered Ca^{2+} transients, cellular hypertrophy, lipid accumulation, oxidative stress, BNP release, gene expression**
- **iCell diabetic patient-specific CMs mimic diabetes**
  - **Severity dependent on their original clinical status**

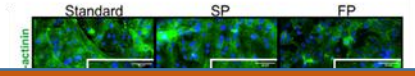
Diabetic media induces disease phenotype



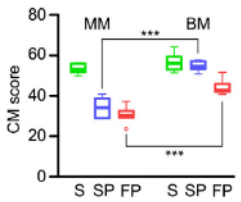


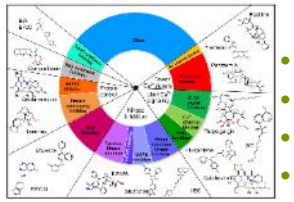
Patient-derived CMs show baseline pathology



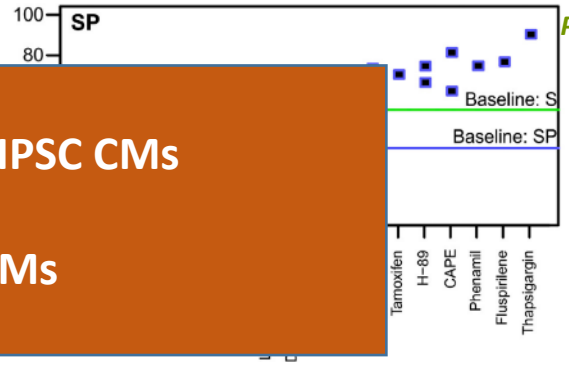


Tiered phenotypic screens identified functionally diverse hits





- *480 compounds*
- *47 hits*
- *28 confirmed DR*
- *Across a wide MOA*



Phenotypic screen enabled large diversity of hits

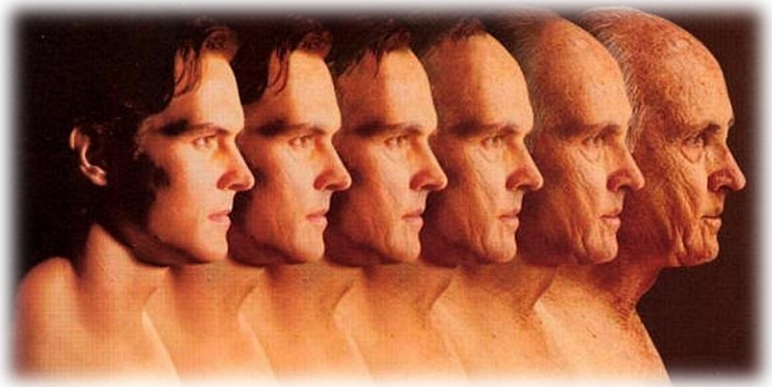
"Induced" diabetes model in normal hIPSC CMs
=
"Innate" diabetes patient iPSC CMs

Drawnel et al, Cell Reports, 2

CDI Therapeutics

Why cell therapy?

- Many human diseases caused by loss of cells/function
- Traditional drugs do not replace cells or restore function
- Cell therapy offers a potential cure



Why CDI?

- Leverages our success in commercializing cells for the research market
  - Cell manufacturing expertise
  - iPSc bank of common HLA homozygous variants
    - *Tissue matching strategy for beneficial allogeneic therapy*
  - Extensive KOL network
  - Active Programs
    - *DA Neurons*
    - *RPE/PR*
    - *CMs*

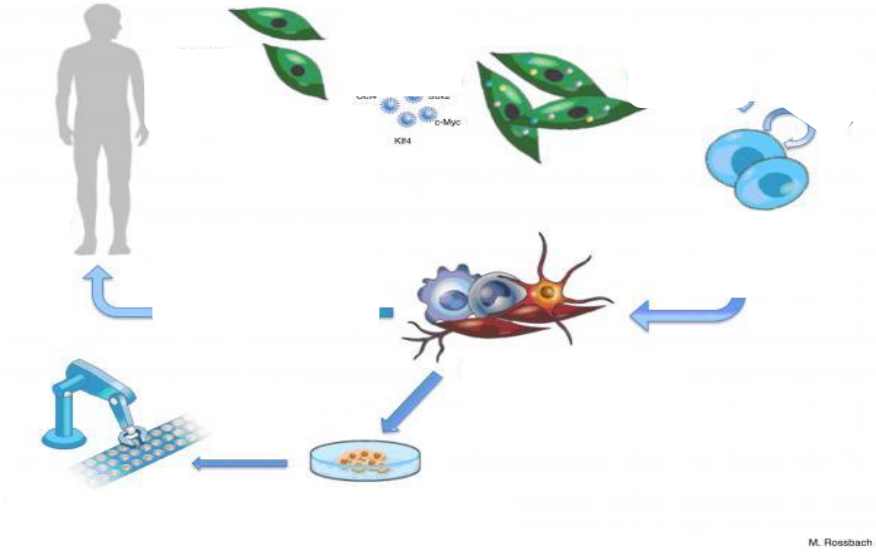
Cellular Dynamics international
a FUJIFILM company

iPS cell-derived Tissues and the Potential

- **IPS-derived cells improvement over primary culture**
  - Amenable to genetic engineering
  - Maturing phenotype
  - Relevant disease models can be induced or derived

  Improved functionality → Ask better questions

  Robust manufacturing a necessity



- **iPS cells allow direct control over genetic diversity**
  - Patient disease phenotype recapitulation in vitro
  - Retrospective clinical trials
  - Prospective clinical trials ?

- Clinical applications have potential to completely change medicine