Regulatory Research at FDA

FDA Small Business
Regulatory Education for Industry (REdI)
May 9, 2017

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Induced Pluripotent Stem Cells for Cardiac Safety Assessment

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Technology for Assessing the Risk of Drugs

1930s

2017

Division of Applied Regulatory Science

Vision

- To move new science into the CDER review process and close the gap between scientific innovation and product review

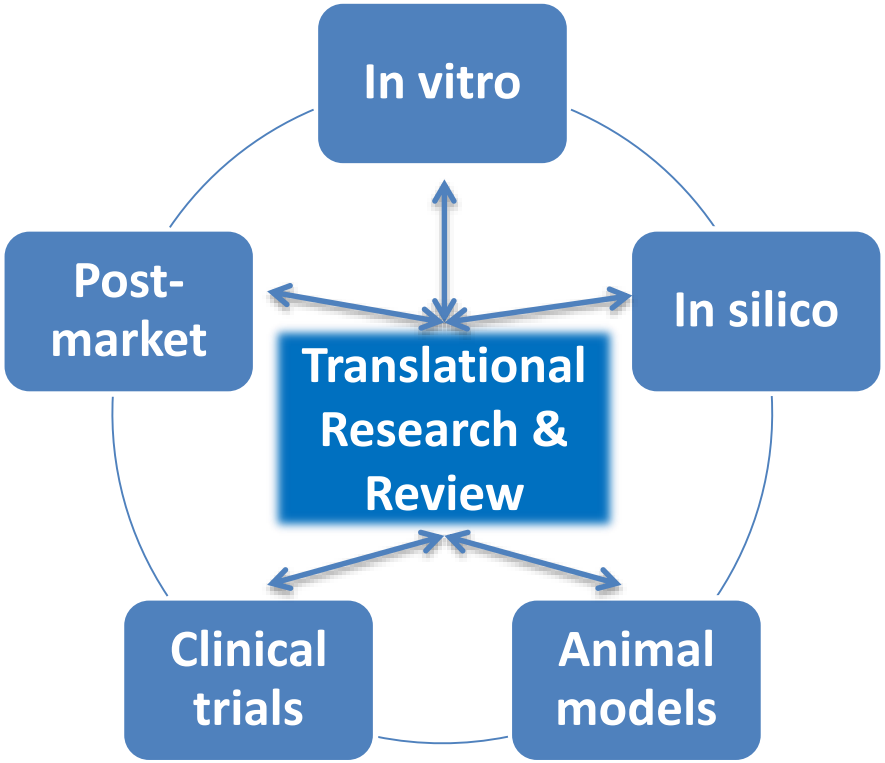
What does DARS do?

- Performs mission-critical applied research to develop and evaluate tools, standards and approaches to assess the safety, efficacy, quality and performance of drugs

- Performs expert regulatory review consultations for mechanistic safety evaluation for immediate regulatory needs combining
  - Critical review of existing knowledge
  - Computational analyses with informatics tools and disease-pharmacology models
  - In vitro and in vivo laboratory studies
  - Translational analysis of preclinical studies, clinical trials and postmarket data

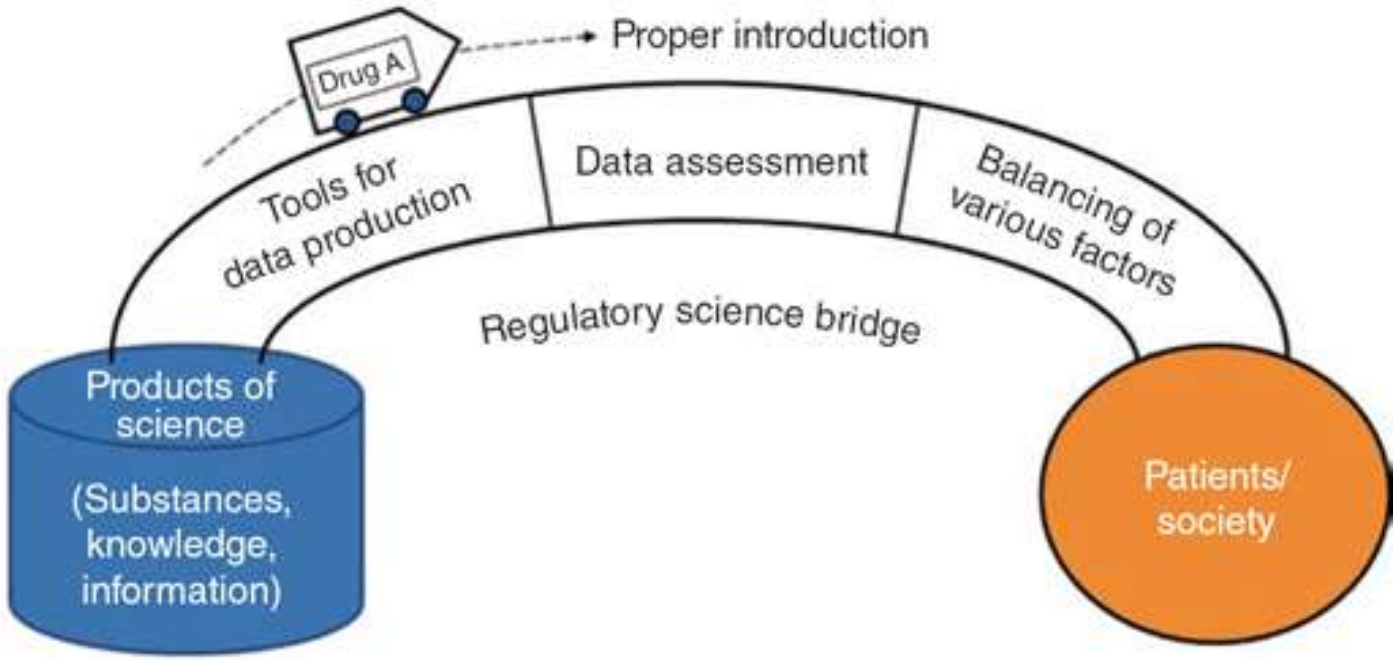
Division of Applied Regulatory Science
Priority Areas

- Translational research
- Collaboration and interdisciplinary team approaches
- Implementation of new regulatory review methods and programs



Collaboration: Office of New Drugs, Office of Surveillance and Epidemiology, Office of Generic Drugs, Center for Devices and Radiological Products, Center for Biologics Evaluation and Research, National Center for Toxicological Research, National Insititute of Health, Industry, Universities/Academia

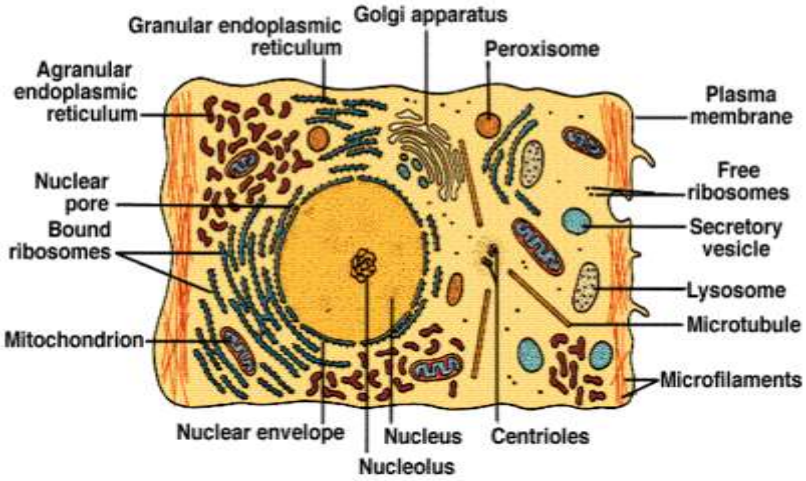
Use science to improve the drug regulatory process



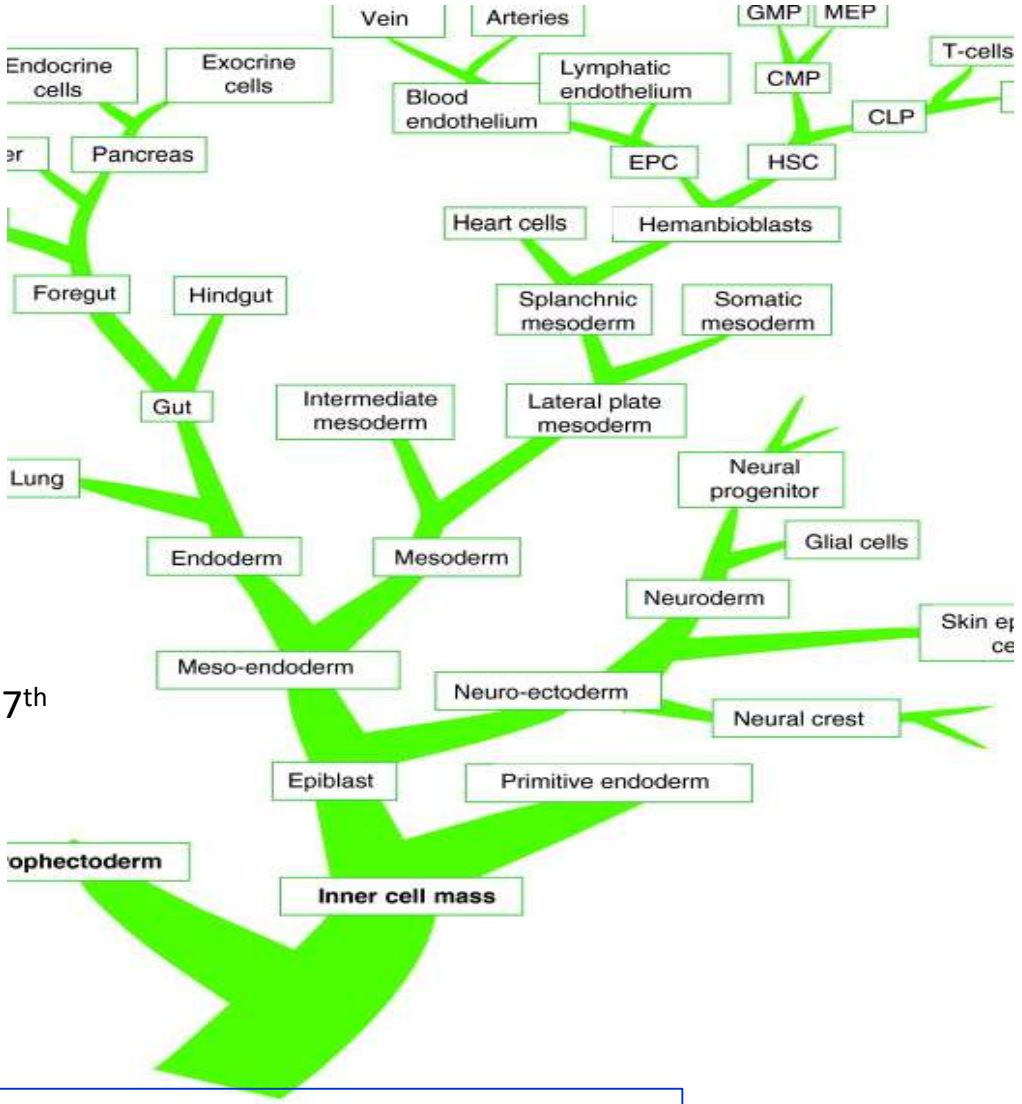
We predict the clinical toxicity of drugs with pluripotent stem cells

Tominaga, T et al, Clin Pharmacol Ther, 2011

Pluripotent stem cells can differentiate into any cell type in the body



Vander/Sherman/Luciano Human Physiology. 7th Edition. 1998 McGraw-Hill



Pluri = several

Potent = being able

Pluripotent Stem Cells

Key takeaways today

1. Pluripotent stem cells have high potential for predicting clinical drug toxicity

2. Engineered microfabricated systems can address the main problems of using pluripotent stem cells:

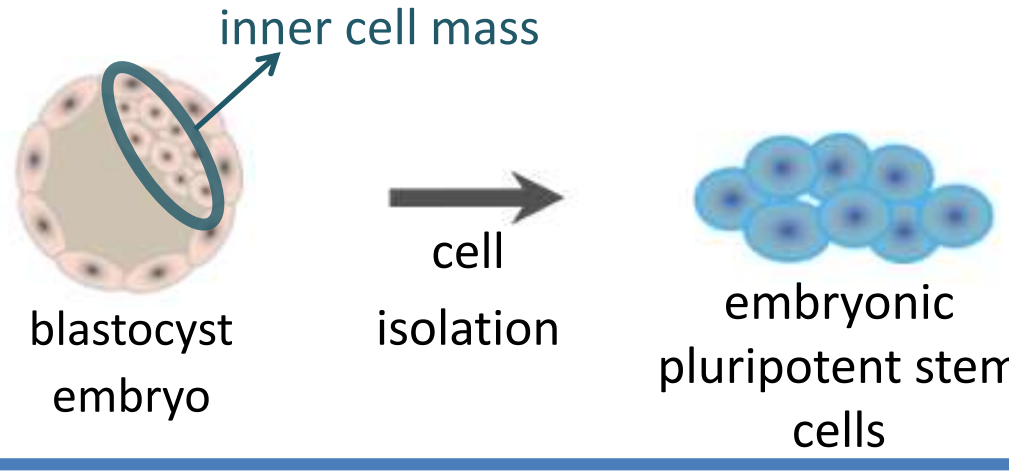
    a) Physiological immaturity

    b) Variability

Main focus of presentation:

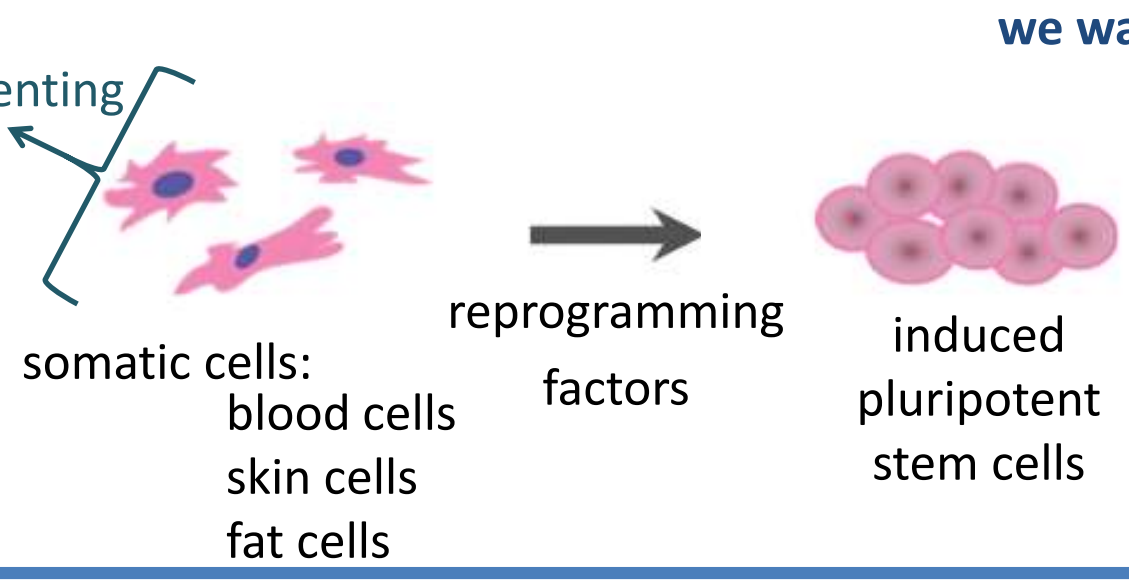
- Structural maturity
- Genetic variability

Two types of pluripotent stem cells: embryonic cells and induced pluripotent stem cells

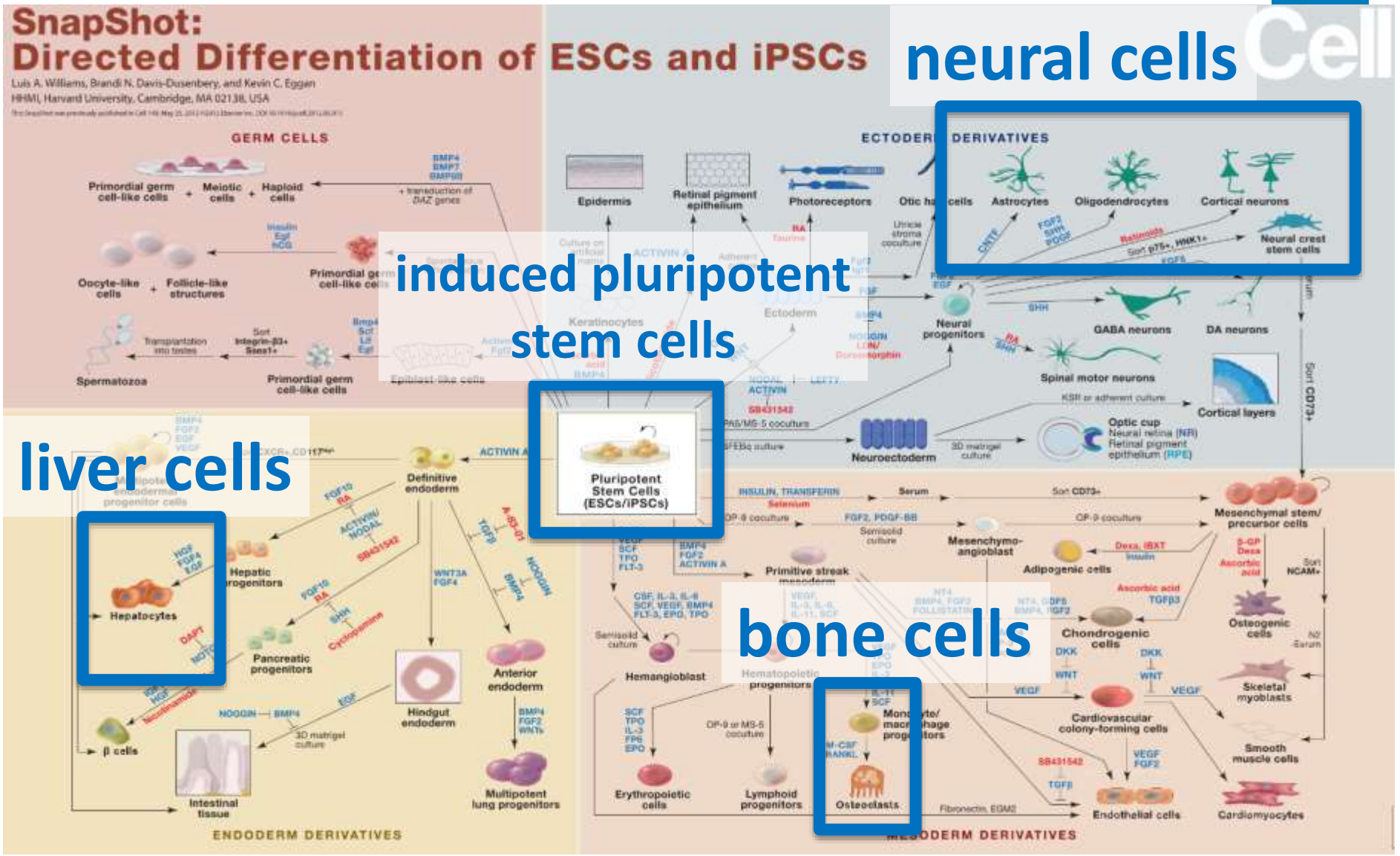


we want this!

- Can model patient specific features
- Potential for precision medicine



Protocols to differentiate into different tissues



Poll Question

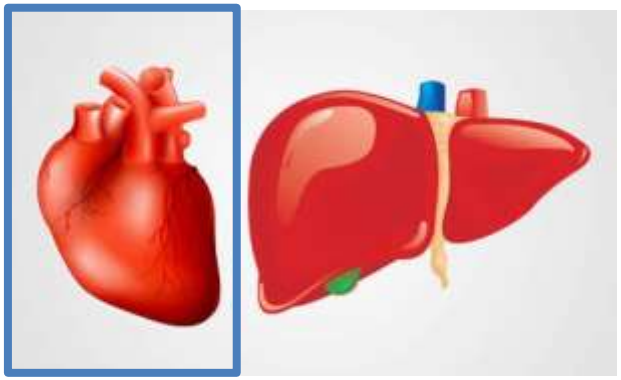
What is the type of tissue more affected by drug adverse effects?

(*Pick three choices*)

Poll Question

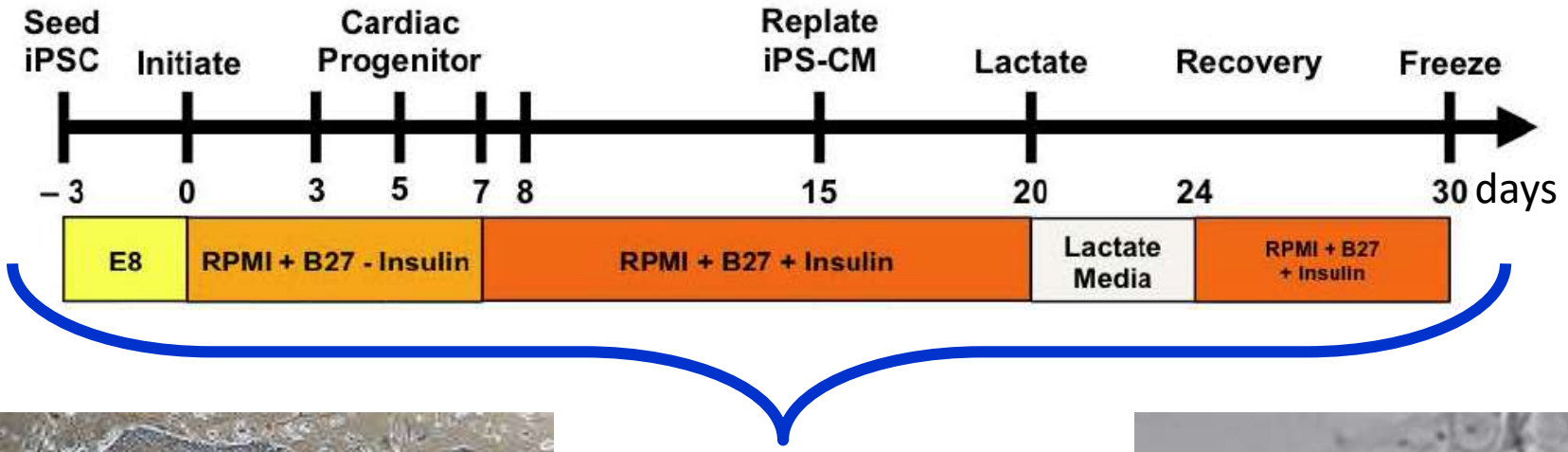
What is the type of tissue more affected by drug adverse effects?

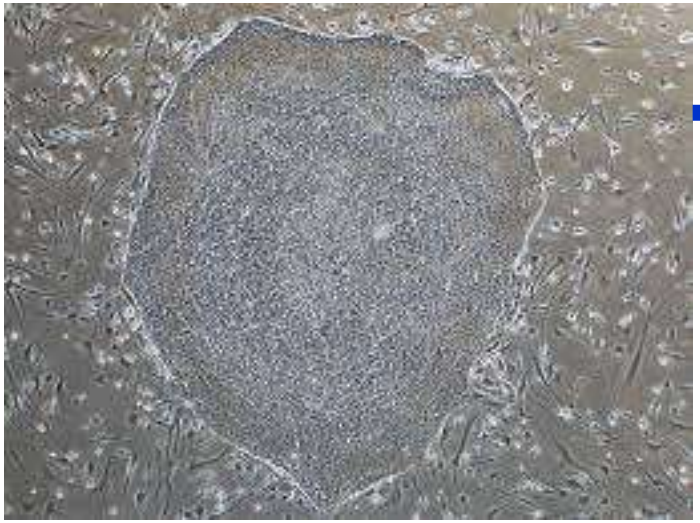
1. Brain
2. Liver
3. Heart
4. Bone
5. Kidney
6. Pancreas
7. Lung
8. Blood



I focus my research in heart cells

We differentiate heart muscle cells: cardiomyocytes

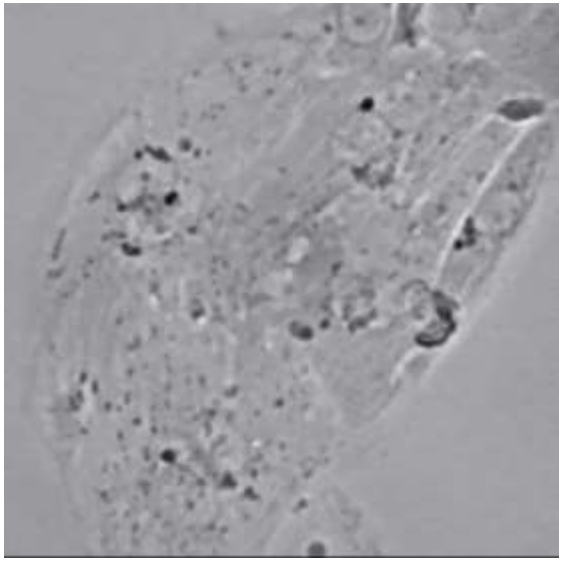




Pluripotent stem cell colony (iPSCs)

Involves:

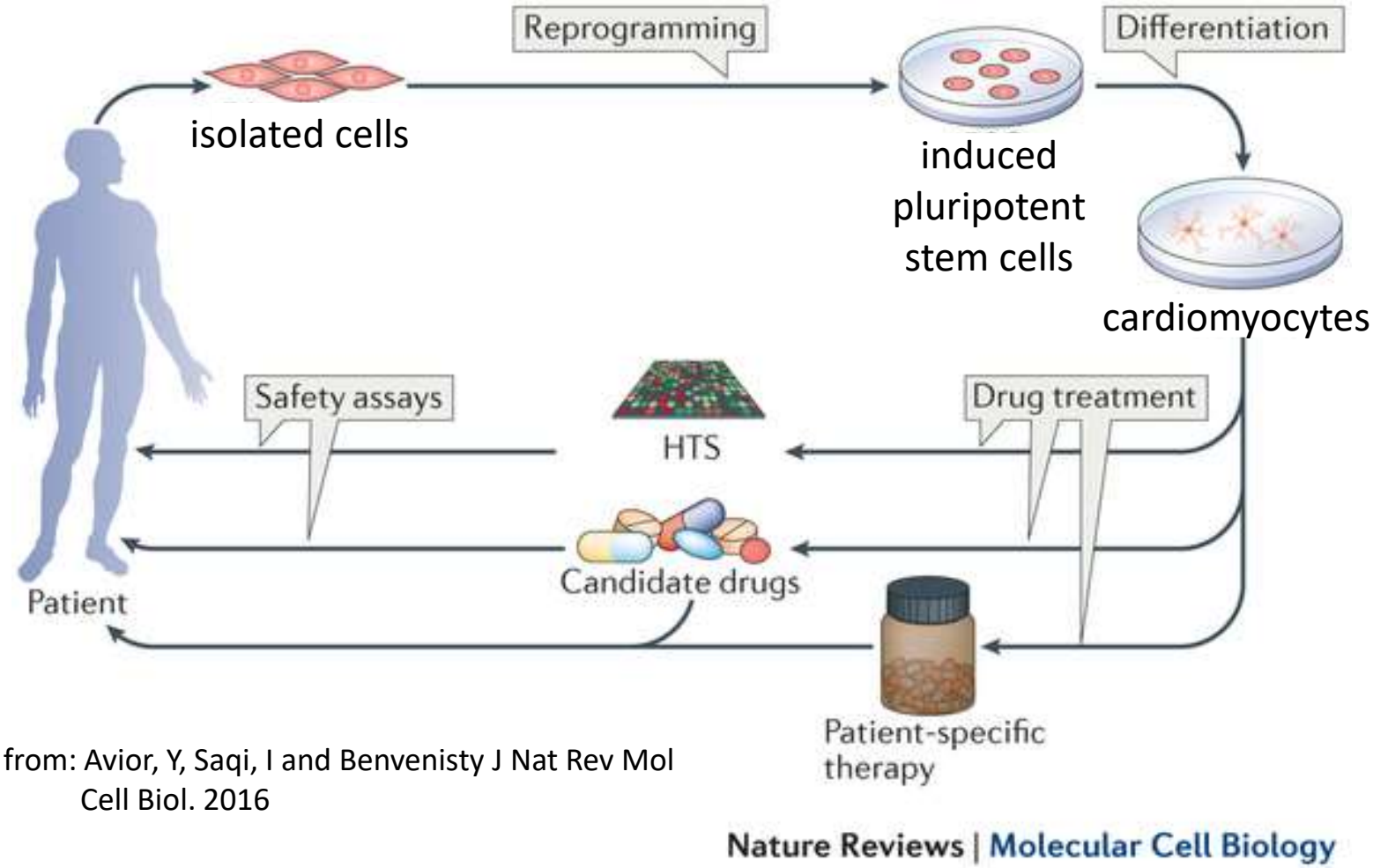
- Changes in culture media
- Different small molecules
- Purification steps



Differentiated cardiomyocytes (iPS-CMs)

30 day process

Ultimate goal: assay human heart function in a dish



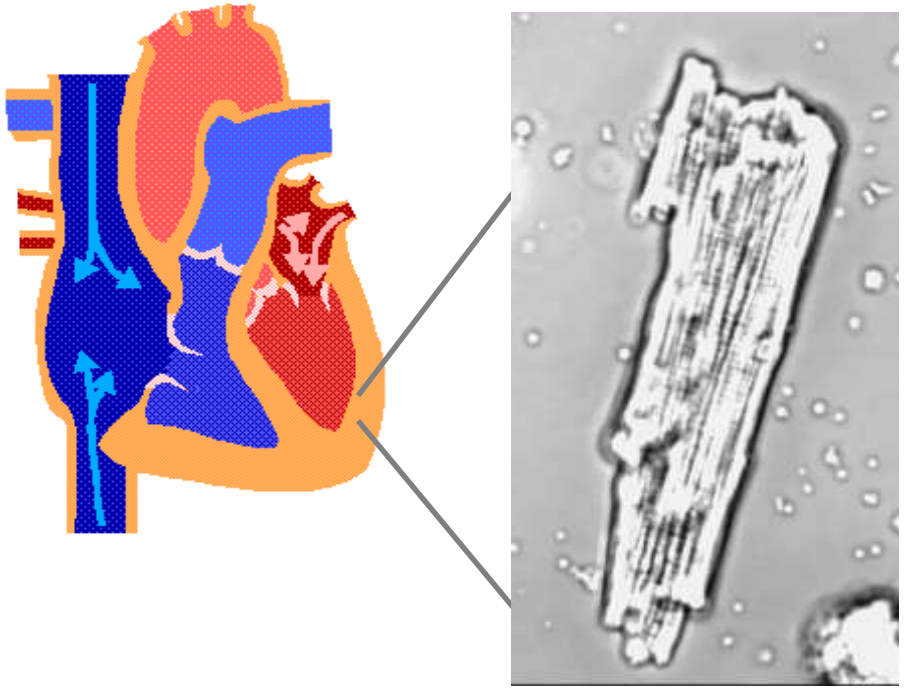
Adapted from: Avior, Y, Saqi, I and Benvenisty J Nat Rev Mol Cell Biol. 2016

Our goal is to assay drug toxicity

How do we assay heart function *in a dish*?

- Physiological function
  - beating activity: contractility
  - electrophysiology
  - calcium flow
  - metabolism
- Expression of genes that encode for proteins that regulate function

Cardiomyocyte
Isolated from a Mouse

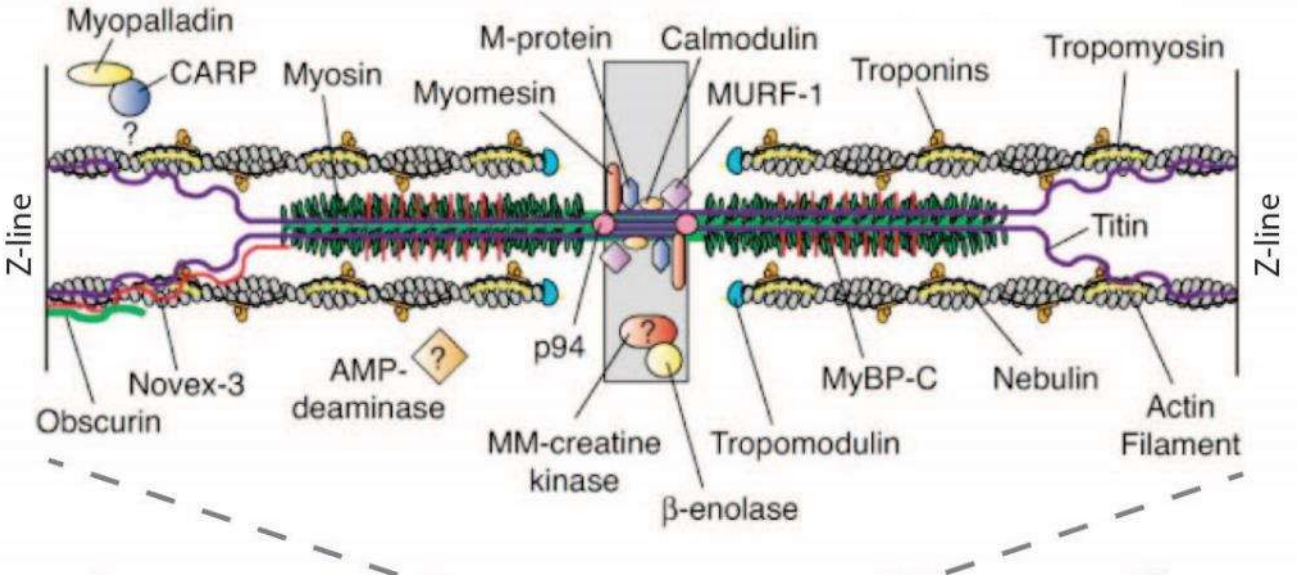


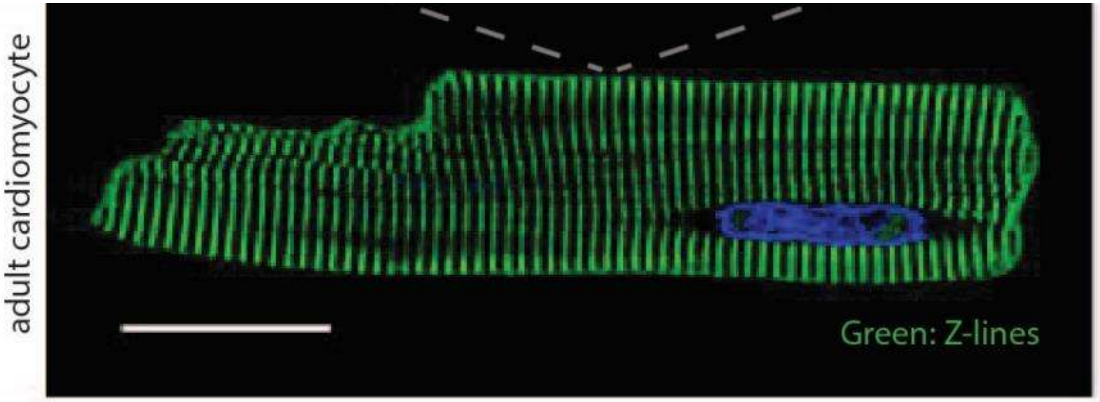
Braunwald's Heart Disease - A Textbook of Cardiovascular Medicine, 9th ed. - 2011

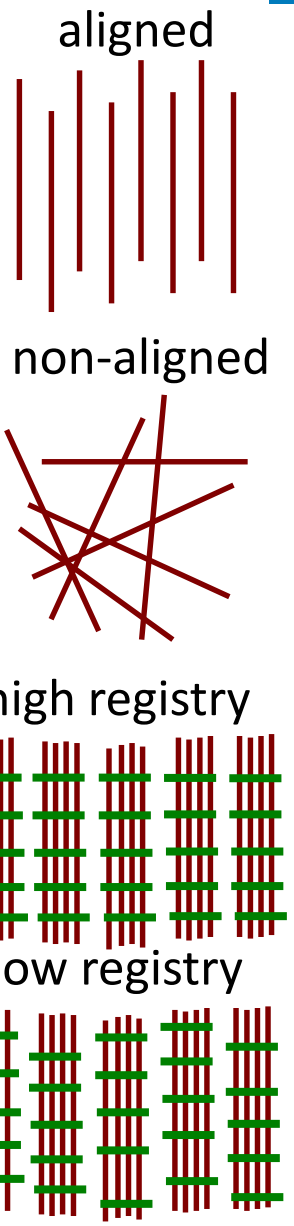
Differentiated cardiomyocytes must be mature

Mature cardiomyocytes have aligned contractile fibers and well registered Z-lines

Between Z-lines



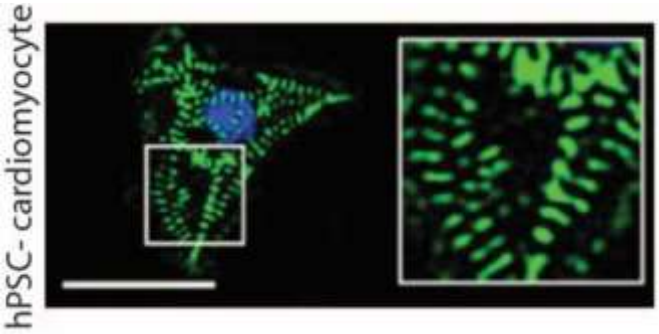




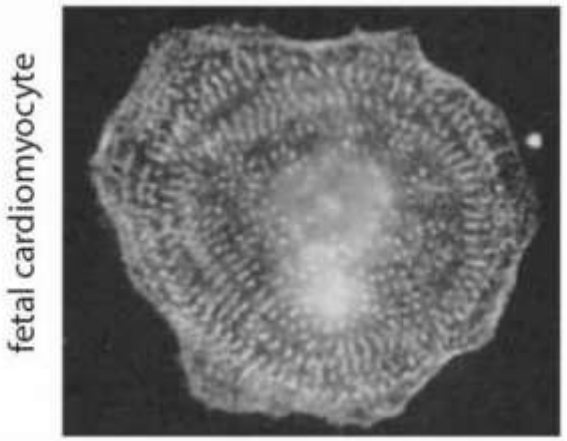
Clark, KA et al. Annu Rev Cell Dev Biol 2002

Yang, X et al. Circ Res 2014

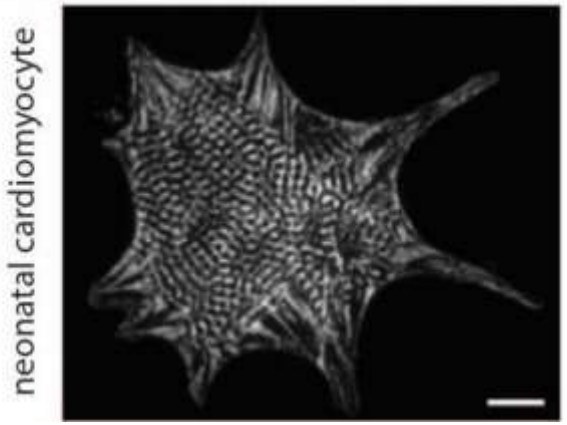
1st problem: immature physiological function in stem cell derived cardiomyocytes



Yang, X et al. Circ Res 2014



Rhee, D et al. Cell Motil Cytoskeleton 1994

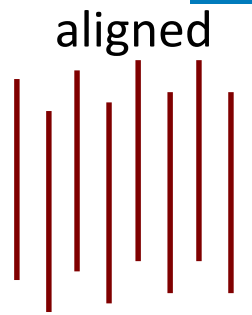


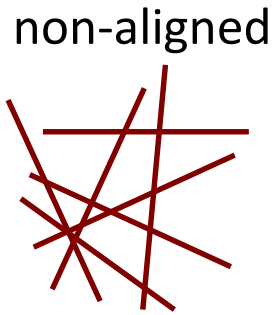
Bray, MA et al. Cell Motil Cytoskeleton 2008

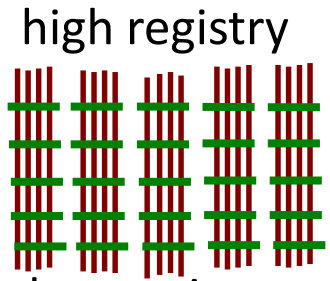
Stem cell derived cardiomyocytes have:

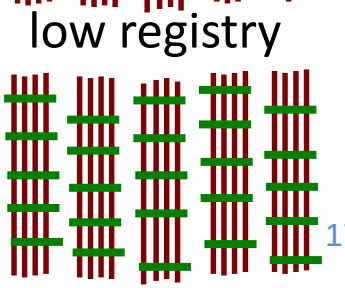
- Non-aligned fibers
- Low registry of Z-lines

immature







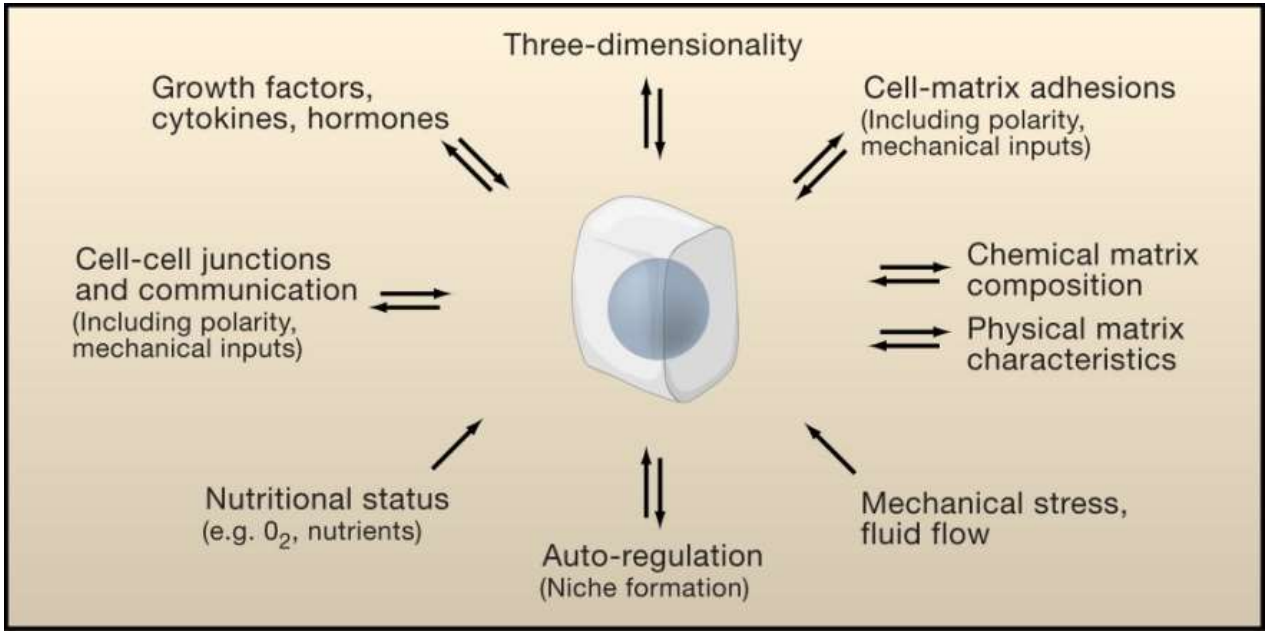


Microfabricated devices can mature cardiomyocytes differentiated from stem cells

Microfabrication of cell culture platforms:

- Polymer chemistry
- Material sciences
- Surface chemistry
- Lithography
- Etching
- Microforming
- Photochemistry
- Patterning
- Microinjection
- Microelectronics

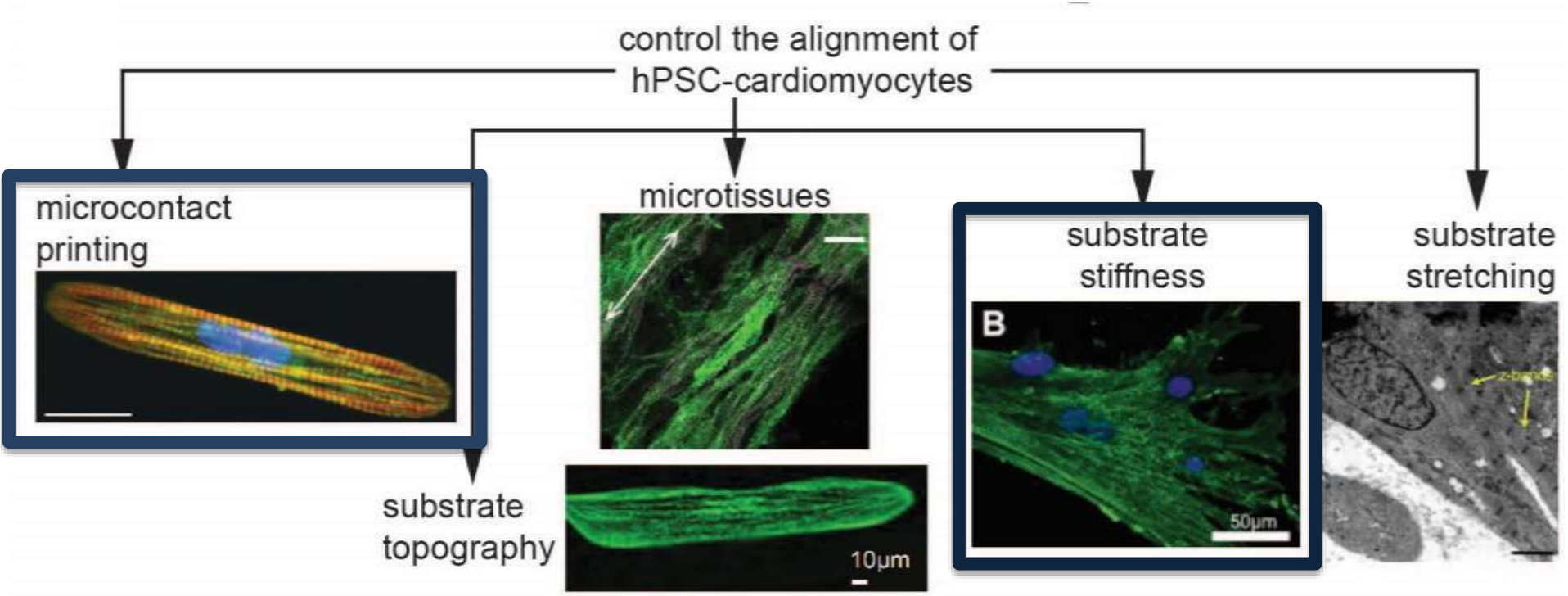
Cell culture platforms that replicate physiological cues *in vitro*



Santos, E et al, Cell-Biomaterial Interactions: Strategies to Mimic the Extracelular Matrix, 2011

Build physiological settings in a dish to engineer cell maturity

Cell and fiber alignment is central for enhancing the physiology of hiPSC-cardiomyocytes



Aligned cells:

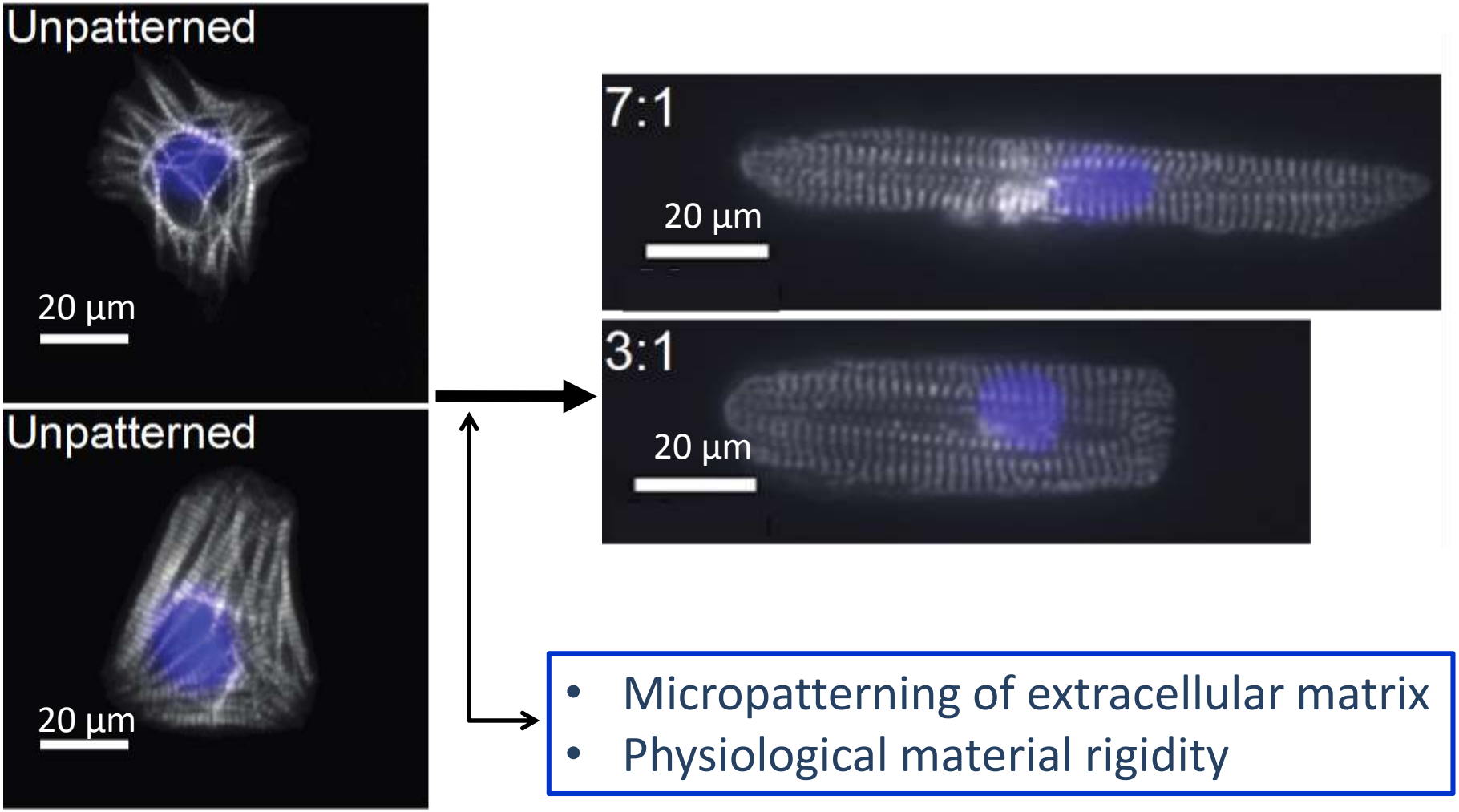
- have a more physiological structural organization,
- have a more mature function,
- are more suitable for toxicity assays.

Nunes SS et al. Nat Methods 2013

Jung J et al. FASEB J 2015

Ribeiro AJS et al. Proc Natl Acad Sci USA 2015

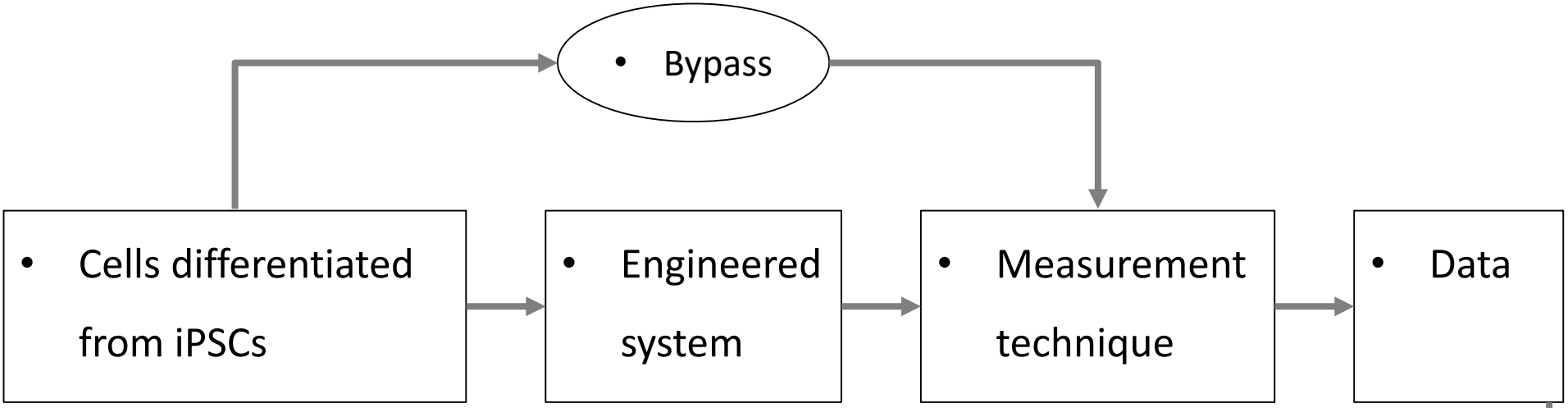
Disorganized cell becomes more mature with combined micropatterning and physiological rigidity



- Micropatterning of extracellular matrix
- Physiological material rigidity

Ribeiro AJS et al. Proc Natl Acad Sci USA 2015

Engineered microfabricated systems for designing stem cell assays



Engineered systems :

- improve physiological relevance of measurements
- mature cells by delivering different types of stimuli:
  - chemical
  - electrical
  - mechanical
  - biological

Problem number 2: Genetic Variability

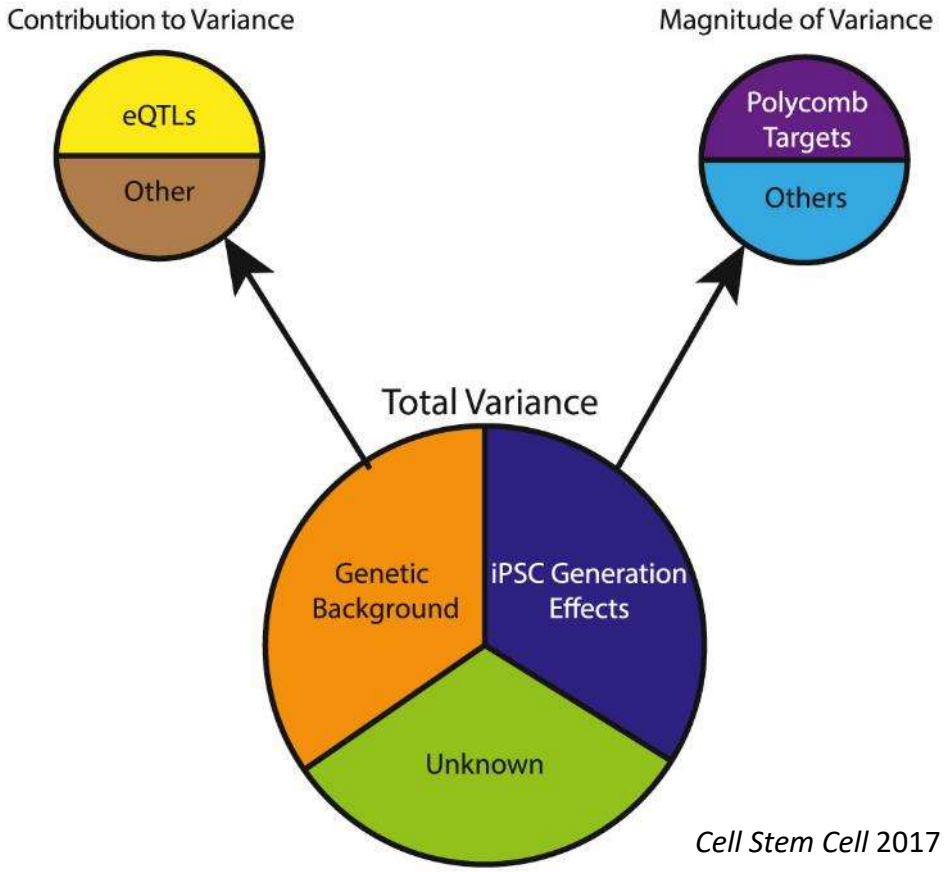
Type of variability	Occurrence: Among ESC	Among iPSC	Between ESC, iPSC	Heterogeneity within PSC line
Functional • in vitro differentiation	+	+	+	+
RNA • mRNA	-	+	+	+
Epigenetic • DNA methylation	?	+	+	?
Genetic • Germline (background)	+	+	+	?
• Result of derivation • selection • induced	?	+	na	?

+ high - low ? unclear

Cahan, P, Daley, GQ J Nat Rev Mol Cell Biol. 2013

- Gene expression is highly variable
- Function is affected by gene expression

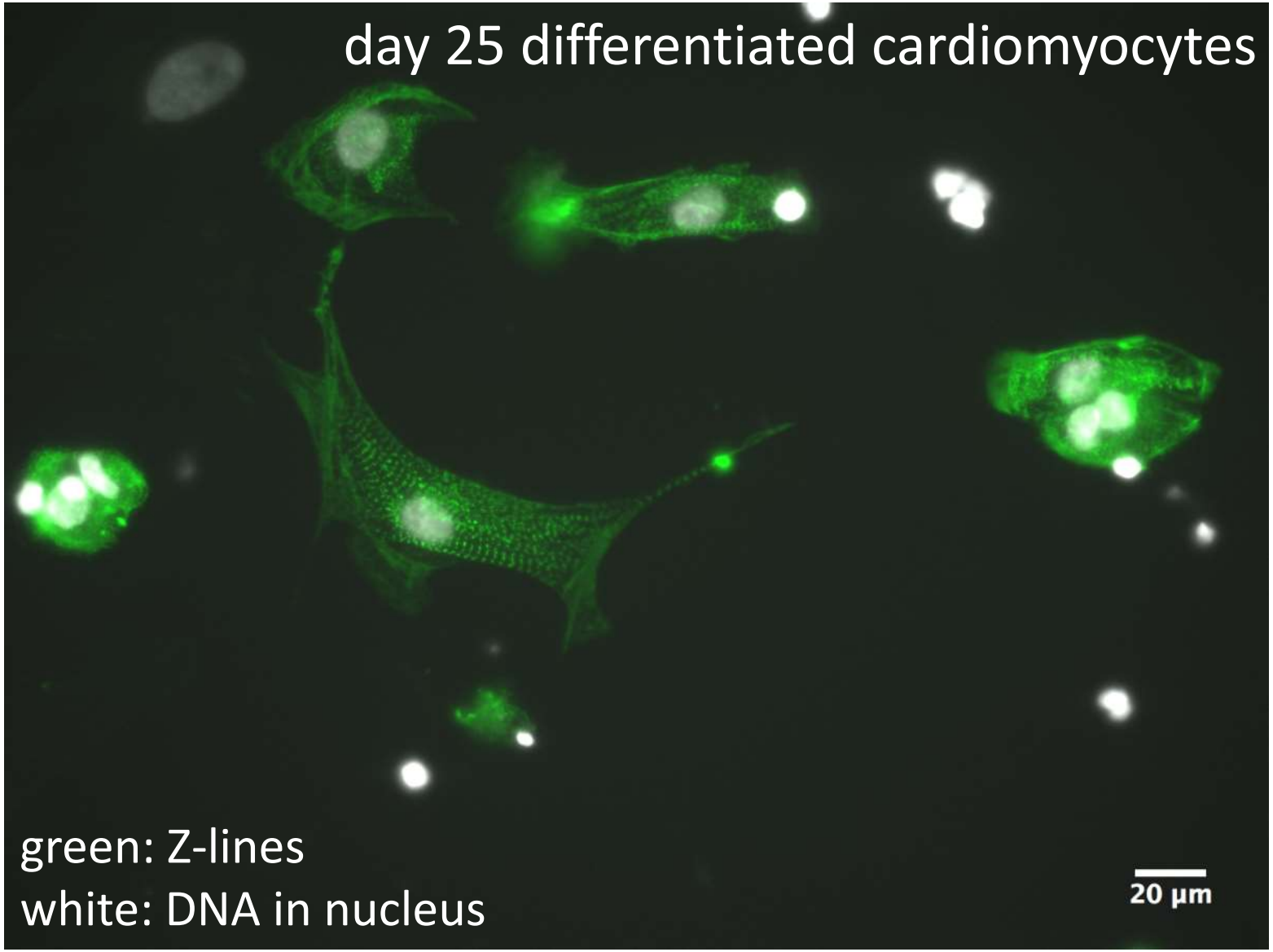
Only 50% of genetic variability is explained by variation across individuals



- A set of genes regulates variance
- Another set of genes regulates magnitude of variance
- Differentiation is affected by the variability of pluripotent stem cells

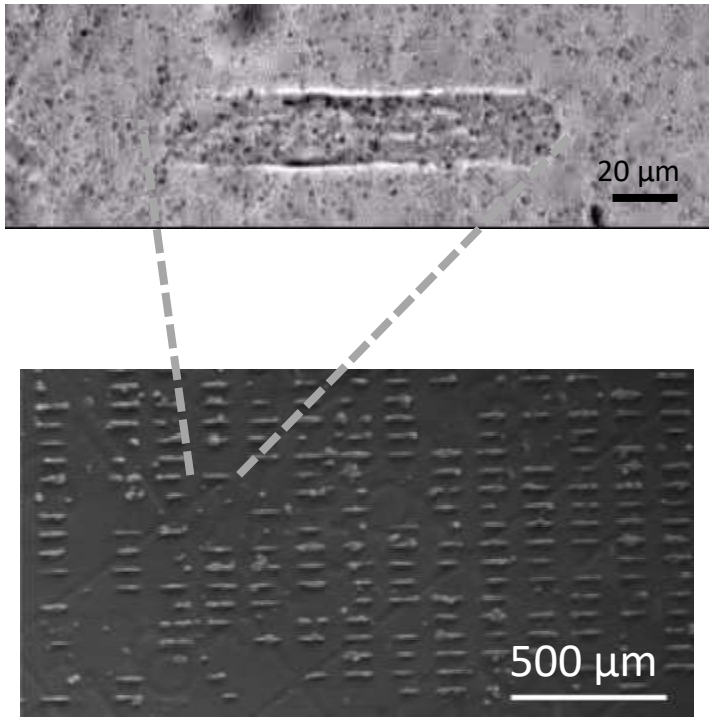
Cell Stem Cell 2017 20, 518-532.e9DOI: (10.1016/j.stem.2016.11.005

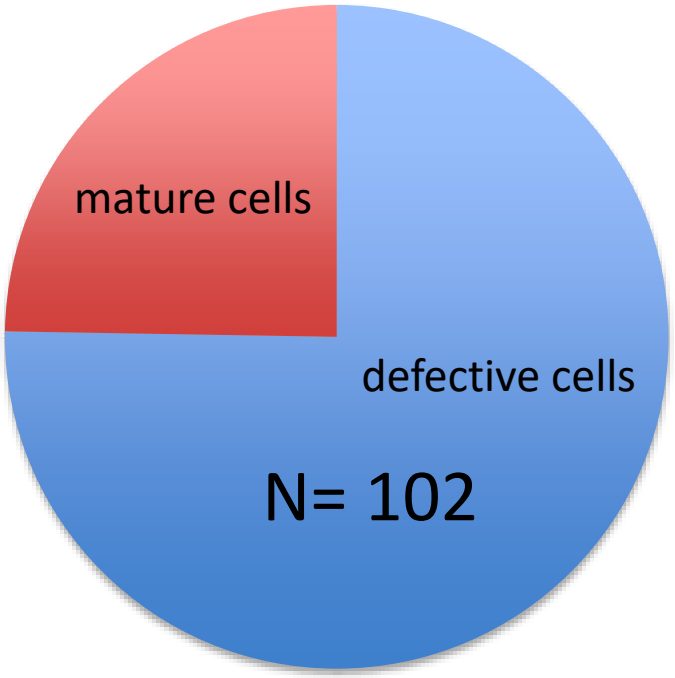
Populations of differentiated cardiomyocytes are highly variable



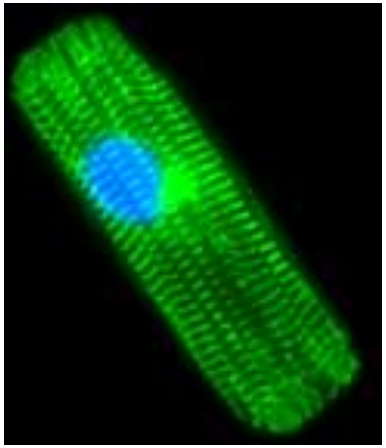
- Some cells have well developed Z-lines
- Some cells have poorly developed Z-lines
- Some cells have no Z-lines

How can microfabrication help study variability?

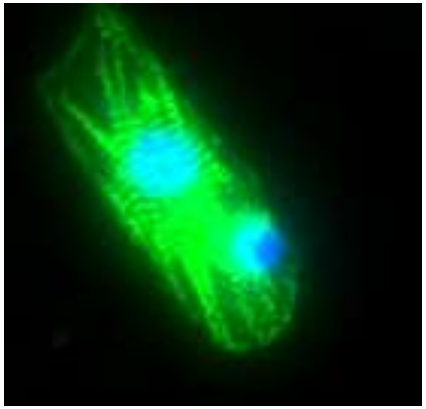




mature cells



defective cells



The way of the future:

single cell studies

- function (contractility, electrophysiology, calcium)
- omics (genomics, proteomics, metabolomics, etc)

Goal: Learn how to select for more mature cells

Key Takeaways

1. Induced pluripotent stem cells have high potential for modeling heart function *in vitro*

2. Engineered microfabricated systems can solve the main limitations of these cells:

    1. Lack of Structural Maturity
    2. High Genetic Variability

Case Study: Prevention of drug-induced cardiac arrhythmias

Ksenia Blinova, PhD
Staff Fellow
Division of Biomedical Physics
Office of Science and Engineering Laboratories
Center for Devices and Radiological Products
U.S. Food and Drug Administration

Regulatory research at CDRH

Center for Devices and Radiological Health (CDRH)

- oversees **175,000 medical devices** on US market
- **22,000 premarket submissions** each year
- **1.4 M adverse events** and **malfunctions** reports each year

Office of Science and Engineering Laboratories

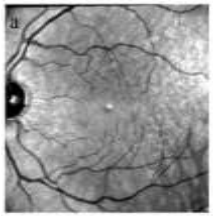
- Ensures readiness for **emerging and innovative** medical technologies
- **Develops** appropriate evaluation **strategies and testing standards**

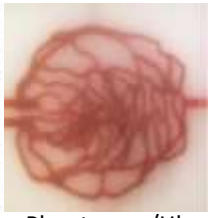
Division of Biomedical Physics (DBP)

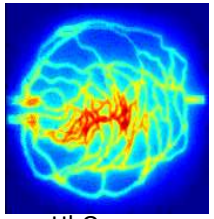
- 38 full time employees (71% Ph.D.)
- 34 fellows, 2 contractors, 12 volunteers (March 2017)

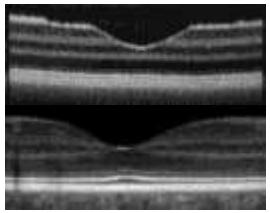
Division of Biomedical Physics

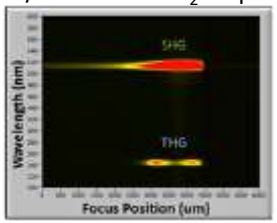
Optical Physics


Retina image


Phantom w/Hb

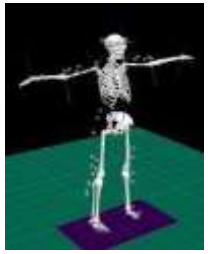

HbO_2 map

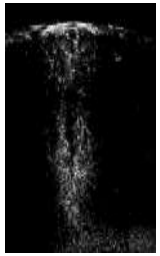

Biomimetic retina phantom

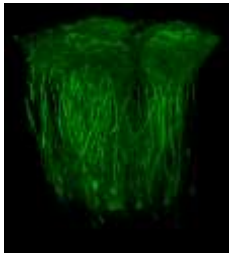


SHG and THG in ex-vivo corneas

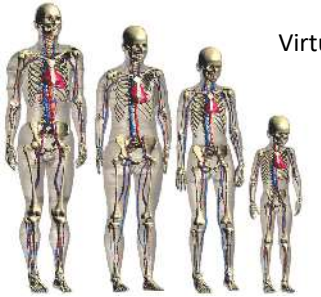
Neuroscience



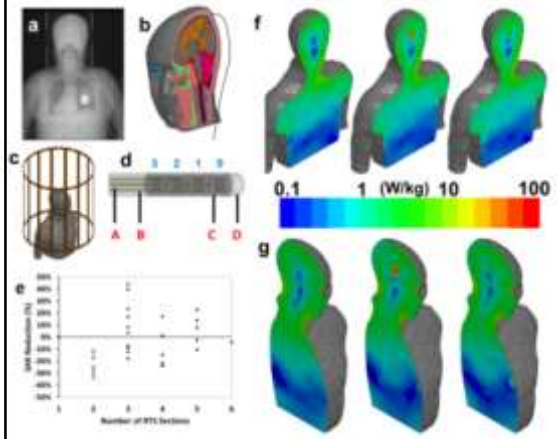




Electromagnetics and MRI


Virtual Family 2.0


MIDA
head model



Modeling of heating from DBS leads during MRI

3-D Printing


3D-printed skull


Patient matched
cutting guide

Cardiac Modeling

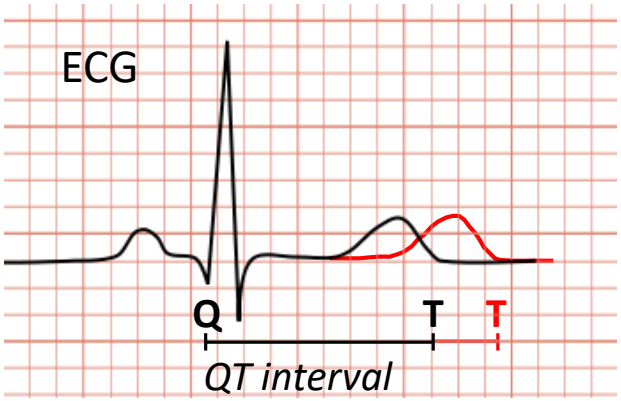

High-throughput devices for cardiac
electrophysiology testing

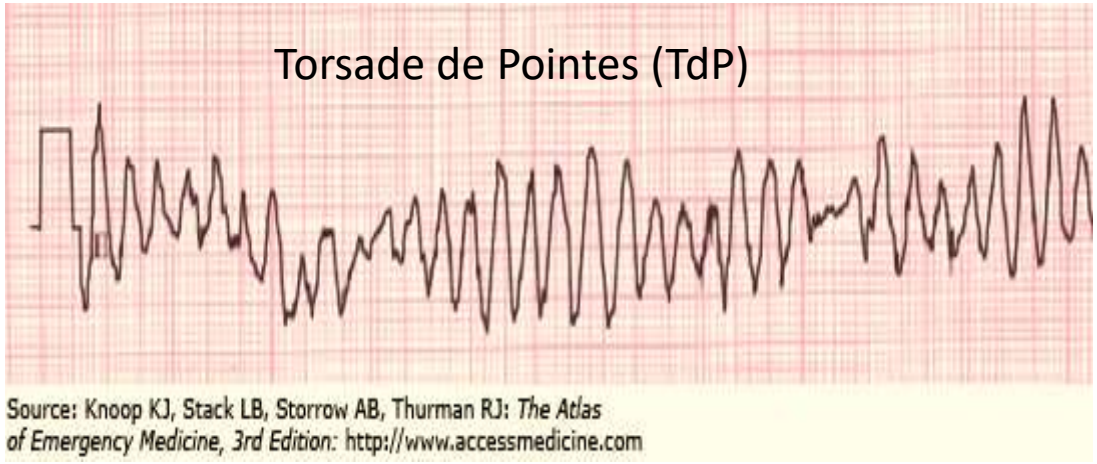
Learning Objectives

- Review current regulatory approach to prevent drug-induced arrhythmias
- Why and how it can be improved
    - **C**omprehensive ***I****n vitro* **P**roarrhythmia **A**ssay (CiPA)
- Role of induced pluripotent stem cells in CiPA
- Stem cells for individual risk assessment

Drug-induced Arrhythmia

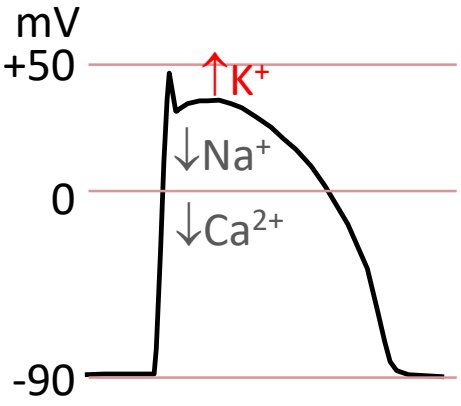
Whole heart



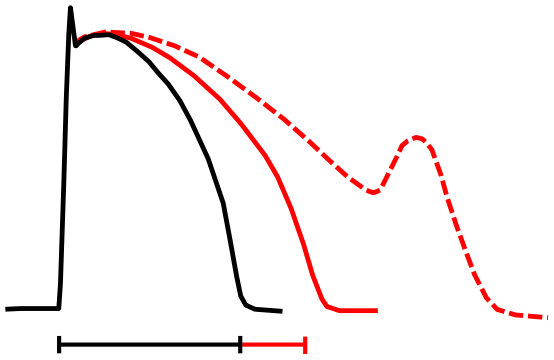


Single cell

Action potential

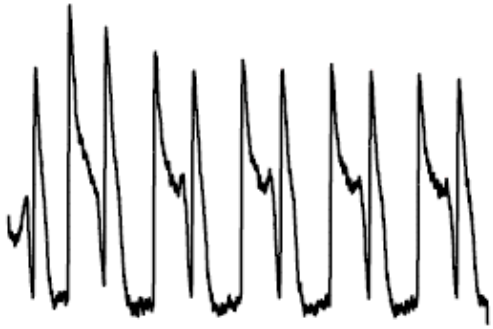


hERG potassium (K^+) block

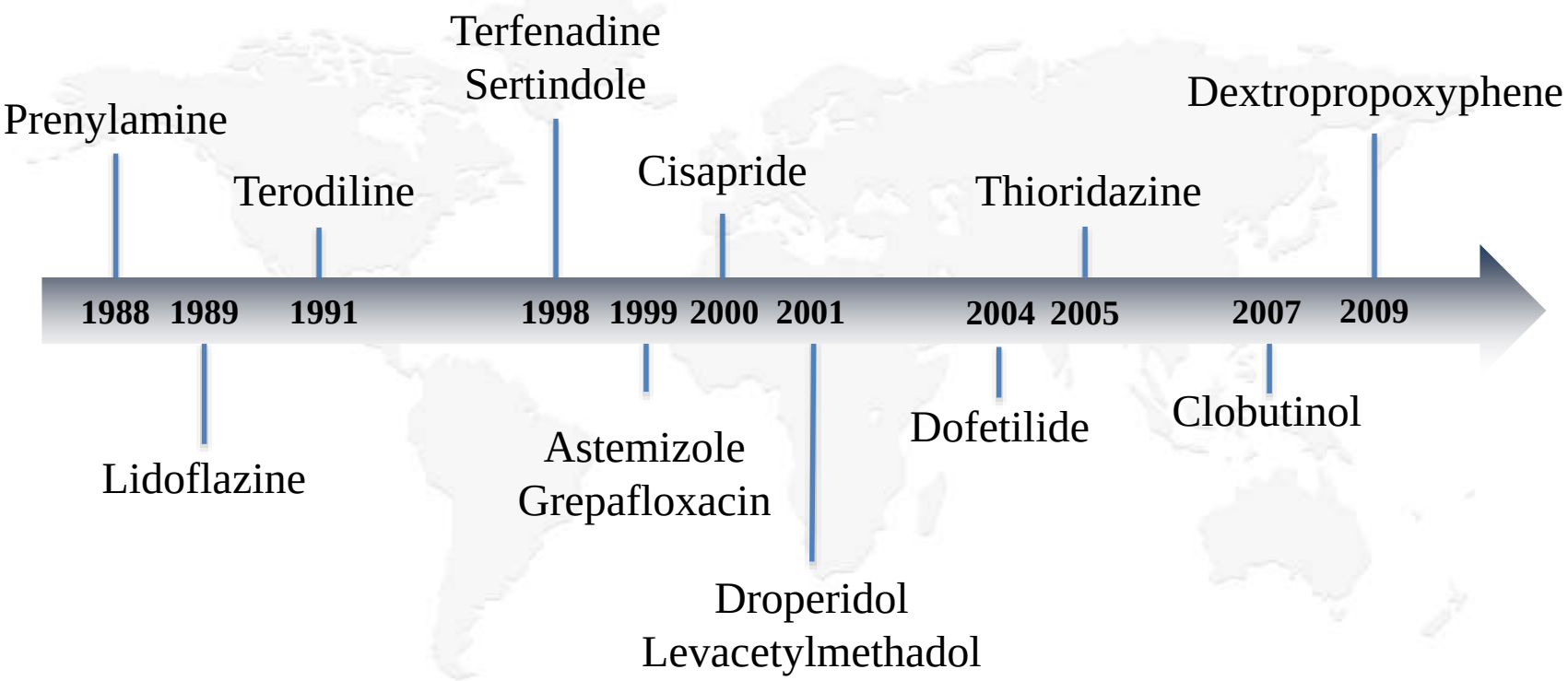


Action potential duration

Arrhythmia in iPSC-CM



Drugs withdrawn from market



Adapted from Table 1
N. Stockbridge et al
Drug Saf 2013

Regulatory Guidelines

- International Conference on Harmonization (ICH)

- ICH S7B: The nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (focus on hERG)

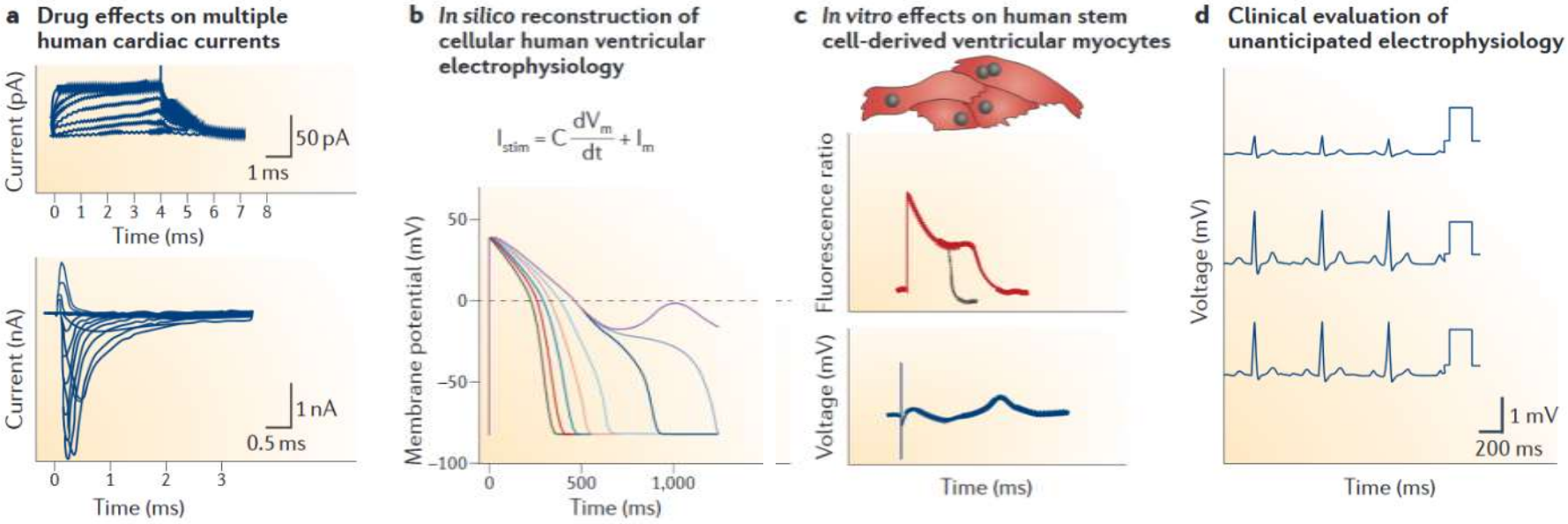
- ICH E14: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs

Why to improve current approach?

- ICH S7B/E14 have resulted in **no drugs** with unrecognized TdP risk being approved or removed from the market
- However,
    - hERG block and QT prolongation are not perfect predictors of Torsade
        - » Verapamil, ranolazine
    - Many sponsors chose to terminate drug development if hERG or QT “signal” observed
    - Potentially useful drugs never get evaluated in humans due to hERG effect

How to improve current approach?

Comprehensive *in Vitro* Proarrhythmia Assay (CiPA)

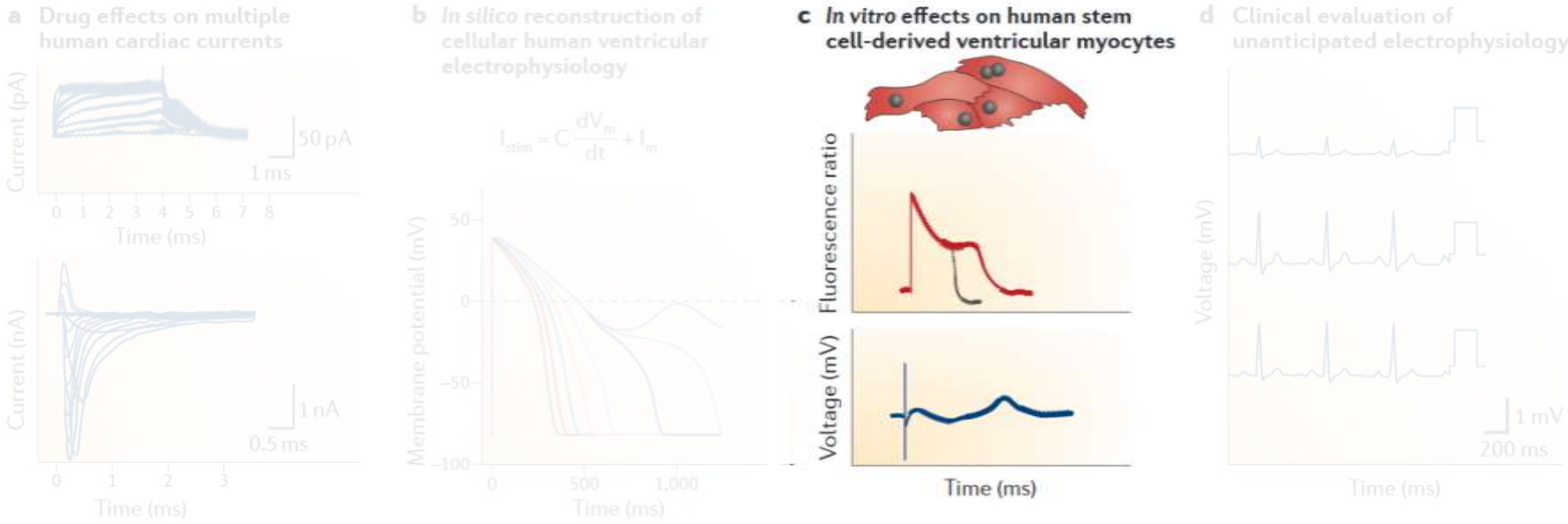


Gintant et al. *Nat Rev Drug Discov*. 2016 Jul;15(7):457-71

Goal: Develop a new *in vitro* paradigm for cardiac safety evaluation of new drugs that provides a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential

Induced Pluripotent Stem Cells (iPSC)

Comprehensive *in Vitro* Proarrhythmia Assessment (CiPA)



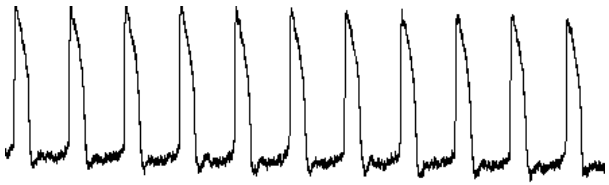
Role in CiPA: to identify potential gaps in cellular electrophysiologic effects, not detected from ionic current/*in silico* reconstructions that may impact TdP risk assessment

Proof of Concept Study at FDA

- 26 drugs (blinded)
- 2 commercially-available stem cell lines
  - iCell cardiomyocytes (Cellular Dynamics)
  - Cor.4U cardiomyocytes (Axiogenesis)
- 2 plate-based platforms selected for CiPA myocyte studies:
  - Microelectrode arrays (MEA)
  - Voltage-sensitive dyes (VSD)
- Acute (30 min) and chronic (72 h) drug effects
- 4 ion currents effects with manual patch clamp
  - hERG potassium, sodium and calcium

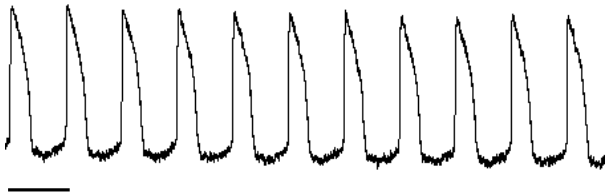
Optical imaging of stem cell derived cardiomyocytes

Baseline action potential

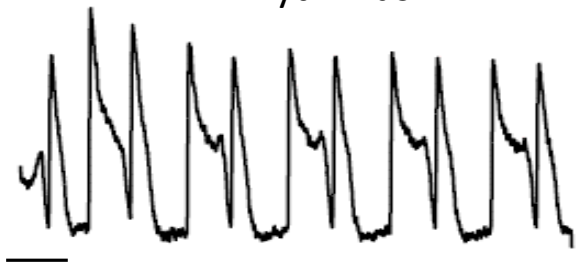


Drug addition

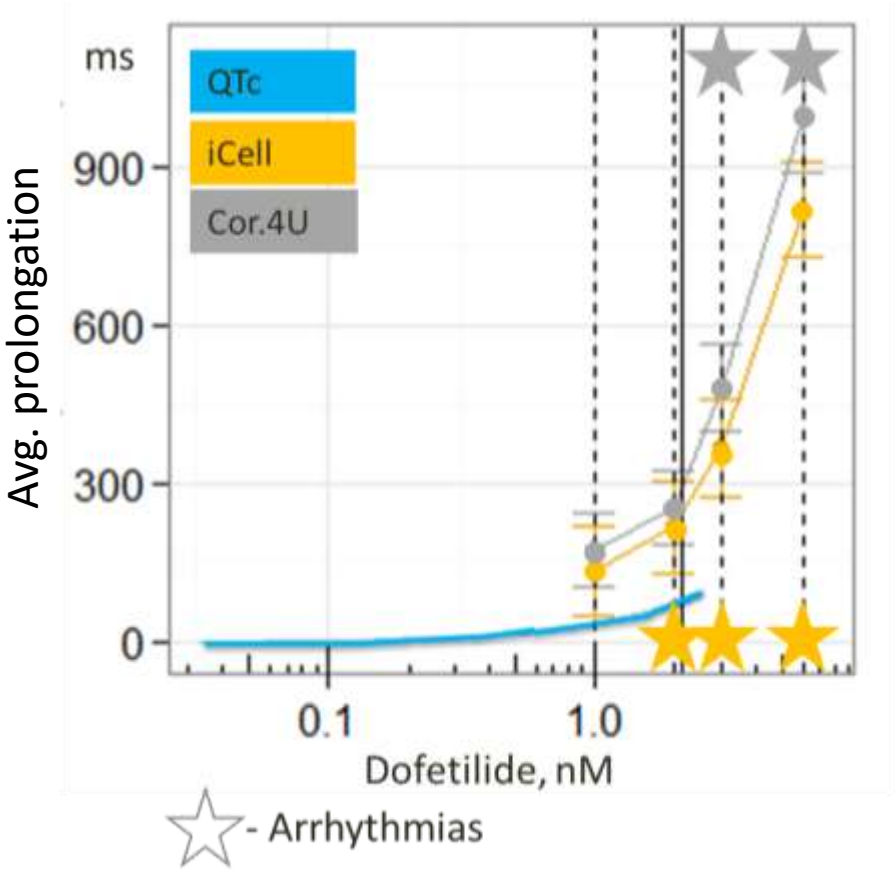
Action potential prolongation



Arrhythmias



Comparison to clinical data



FDA Study Drugs

QT prolongation (20)

Quinidine	Amiodarone
Dofetilide	Azithromycin
Quinine	Sertindole
Propafenone	Pentamidine
Moxifloxacin	Ranolazine
Chloroquine	Ritonavir
Bepridil	Amitriptyline
Chlorpromazine	Nilotinib
Terfenadine	Toremifene
Cisapride	Cibenzoline

TdP risk (14)

No arrhythmia risk (6)

- Lidocaine
- Mexiletine
- Licarbazepine
- Diltiazem
- Verapamil
- Mibefradil

iPSC-CMs Results in FDA Study

QT prolongation

Quinidine	*Amiodarone*
Dofetilide	Azithromycin
Quinine	***Sertindole***
Propafenone	***Pentamidine***
Moxifloxacin	Ranolazine
Chloroquine	Ritonavir
Bepridil	Amitriptyline
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Terfenadine	Toremifene
Cisapride	Cibenzoline

TdP risk

No arrhythmia risk (6)

Lidocaine
Mexiletine
Licarbazepine
Diltiazem
Verapamil
Mibefradil

Of 20 drugs associated with QT↑ in iPSC-CMs induced repolarization↑
- **17 in VSD platform (bold)** and - *16 in MEA platform (italic)*

iPSC-CMs Results in FDA Study

QT prolongation

Quinidine	*Amiodarone*
Dofetilide	Azithromycin
Quinine	***Sertindole***
Propafenone	***Pentamidine***
Moxifloxacin	Ranolazine
Chloroquine	Ritonavir
Bepridil	Amitriptyline
Chlorpromazine	Nilotinib
Terfenadine	Toremifene
Cisapride	Cibenzoline

TdP risk

No arrhythmia risk (6)

Lidocaine
Mexiletine
Licarbazepine
Diltiazem
Verapamil
Mibefradil

Of 14 drugs associated with TdP, induced arrhythmias in iPSC-CMs (any device) 10 (**red**)

iPSC-CMs Results in FDA Study

QT prolongation

Quinidine	*Amiodarone*	**TdP risk**
Dofetilide	Azithromycin	
Quinine	***Sertindole***	
Propafenone	***Pentamidine***	
Moxifloxacin	Ranolazine	
Chloroquine	Ritonavir	
Bepridil	Amitriptyline	
Chlorpromazine	Nilotinib	
Terfenadine	Toremifene	
Cisapride	Cibenzoline	

No arrhythmia risk (6)

Lidocaine

Mexiletine

Licarbazepine

Diltiazem

Verapamil

Mibefradil

No repolarization prolongation was observed in iPSC-CMs with any of the 6 drugs with no arrhythmia risk on the label

FDA Study Results

OXFORD
SOT | Society of Toxicology
www.toxsci.oxfordjournals.org

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

doi: 10.1093/toxsci/kfw200
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[*,#]

Overall, iPSC-CMs assay demonstrated 100% specificity,
79% sensitivity for Cor.4U cardiomyocytes on both platforms,
63% for iCells on VSD, and 47% for iCells on MEA platform

This is one site study – need to assay site-to-site variability

CiPA myocyte working group

- Led by health and environmental sciences institute (HESI)
- 10 core sites, 20+ non-core from US, Europe and Japan
- 5 devices (MEA, VSO) ; 2 iPSC–CMs providers

CiPA Validation Study Drugs

High TdP Risk	Intermediate Risk	Low/No risk
Dofetilide Quinidine D,l Sotalol Bepridil Ibutilide Vandetanib Azimilide Disopyramide	Ondansetron Chlorpromazine **Cisapride** **Terfenadine** **Droperidol** Domperidone Pimozide Clozapine Clarithromycin Risperidone **Astemizole**	Mexiletine Diltiazem Ranolazine Verapamil Loratadine Metoprolol Nifedipine Nitrendipine Tamoxifen
8	11	9

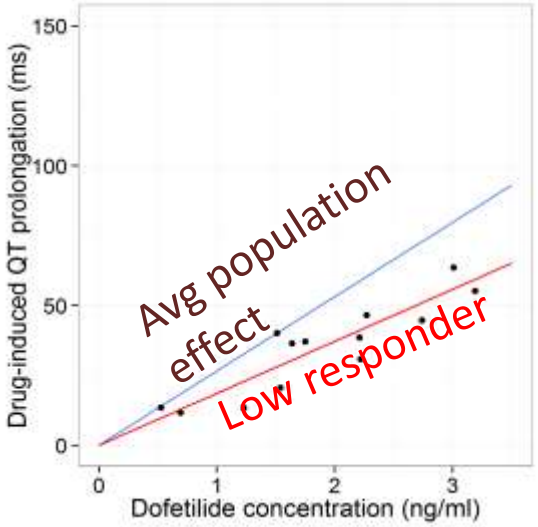
CiPA myocyte studies

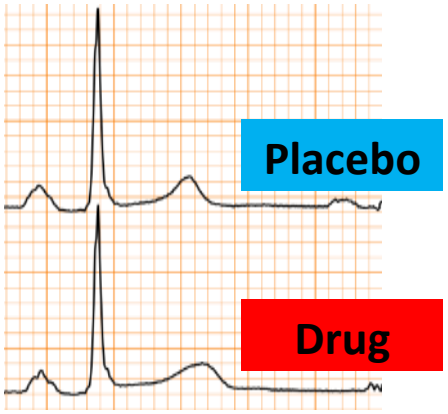
- Pilot multisite study with 8 drugs completed, manuscript in preparation
- Phase II validation study with all 28 CiPA drugs is completed by core sites, data submitted and unblinded (Apr 2017)
- Statistical analysis of the data/model development is ongoing at FDA
- Results will be compared with prospective *in silico* reconstructions and categories of high-, intermediate- and low-risk of torsade de points
- Role of myocytes in regulatory pro-arrhythmia risk assessment will be defined

Beyond CiPA: stem cells in personalized medicine

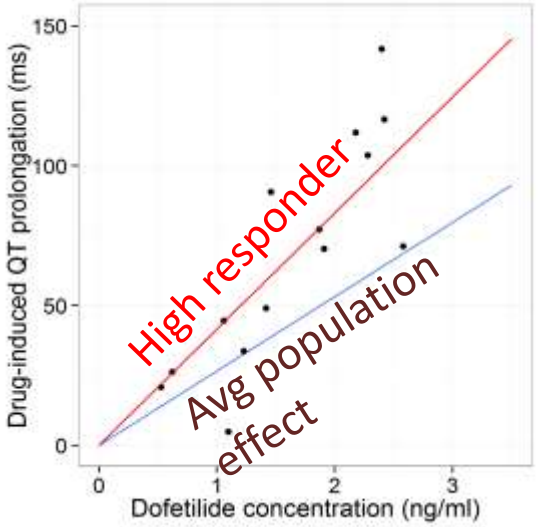
Personalized Drug Response in FDA clinical trial

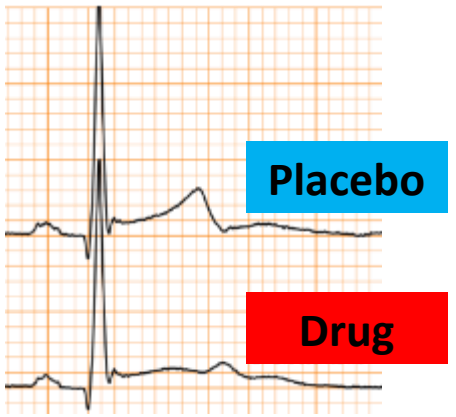
Subject 1 – "Low responder"





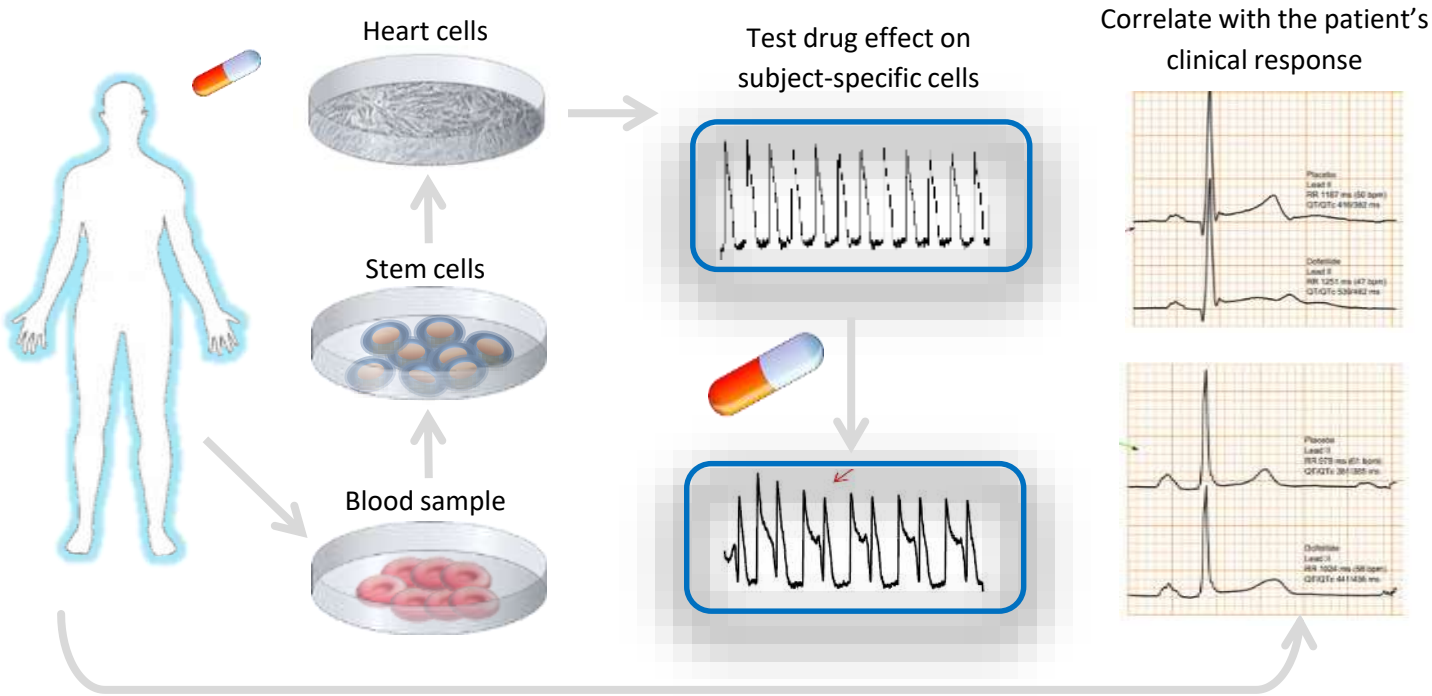
Subject 2 – "High responder"





Ongoing FDA study

Can individual drug response be predicted using subject-specific stem cells?



20 subjects

2 stem cell labs:
Stem Cell Theranostics
Cellular Dynamics

2 devices:
Microelectrode arrays
Voltage-sensitive dyes

2 QT-prolonging drugs
dofetilide
moxifloxacin

Published studies on subject-specific iPSC-CMs

1. Stillitano et al. eLife 2017;6:e19406.
Modeling susceptibility to drug-induced long QT with a panel of subject-specific induced pluripotent stem cells

2. Burridge et al. Nat Med. 2016 May;22(5):547-56
Human induced pluripotent stem cell-derived cardiomyocytes recapitulate the predilection of breast cancer patients to doxorubicin-induced cardiotoxicity.

Results from FDA study on subject-specific iPSC-CMs will be published soon

Key Takeaways

- FDA regulatory research supports review of emerging and innovative products, including induced pluripotent stem cells
- FDA develops new alternative approaches to measuring electrophysiology in these cells
- Pro-arrhythmic assessment of new drugs may soon become more accurate under CiPA
- Stem cell potential to predict individual clinical response is currently being assessed at FDA

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FDA Office of Women's Health Grant
FDA CDER
FDA CDRH

BMES
BIOMEDICAL ENGINEERING SOCIETY

BMES Medical Devices
SPECIAL INTEREST GROUP

FDA

2017 BMES/FDA

Frontiers in Medical Devices Conference

Innovations in Modeling and Simulation: Advancing Translational Science

May 16–18, 2017, Washington DC

The College Park Marriott Hotel and
Conference Center at the University of Maryland

The Biomedical Engineering Society and the US Food and Drug Administration have formed a partnership to co-host the BMES/FDA Frontiers in Medical Devices Conference, a meeting for researchers, engineers, clinicians and other professionals in the fields of designing, building and using medical devices.

Questions

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