Human Stem Cells & Genomics for Precision Medicine

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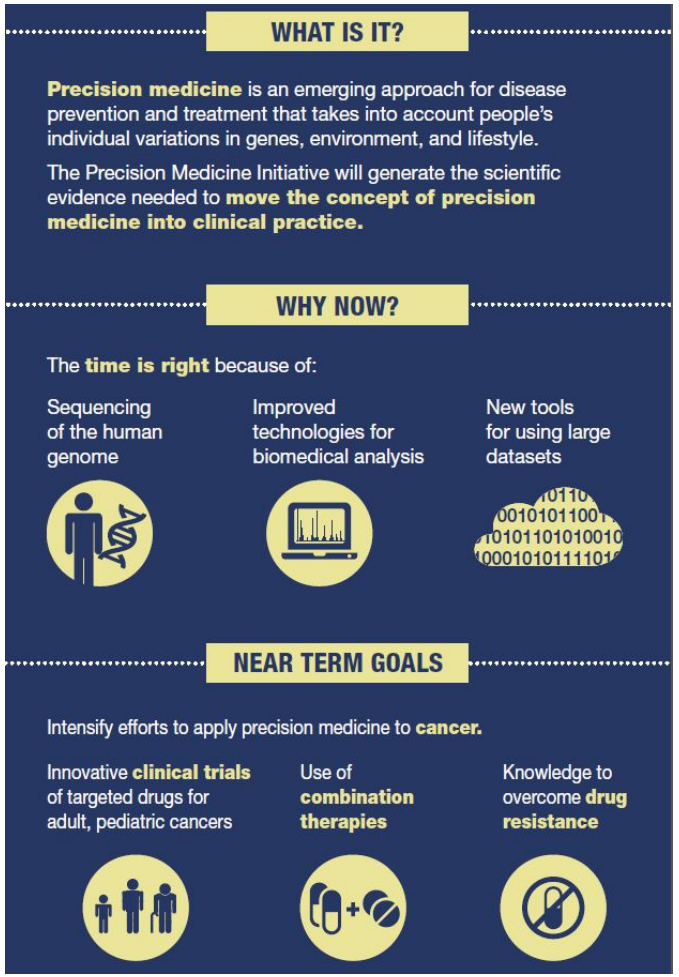
STANFORD SCHOOL OF MEDICINE

Disclosure Statement of Financial Interest

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

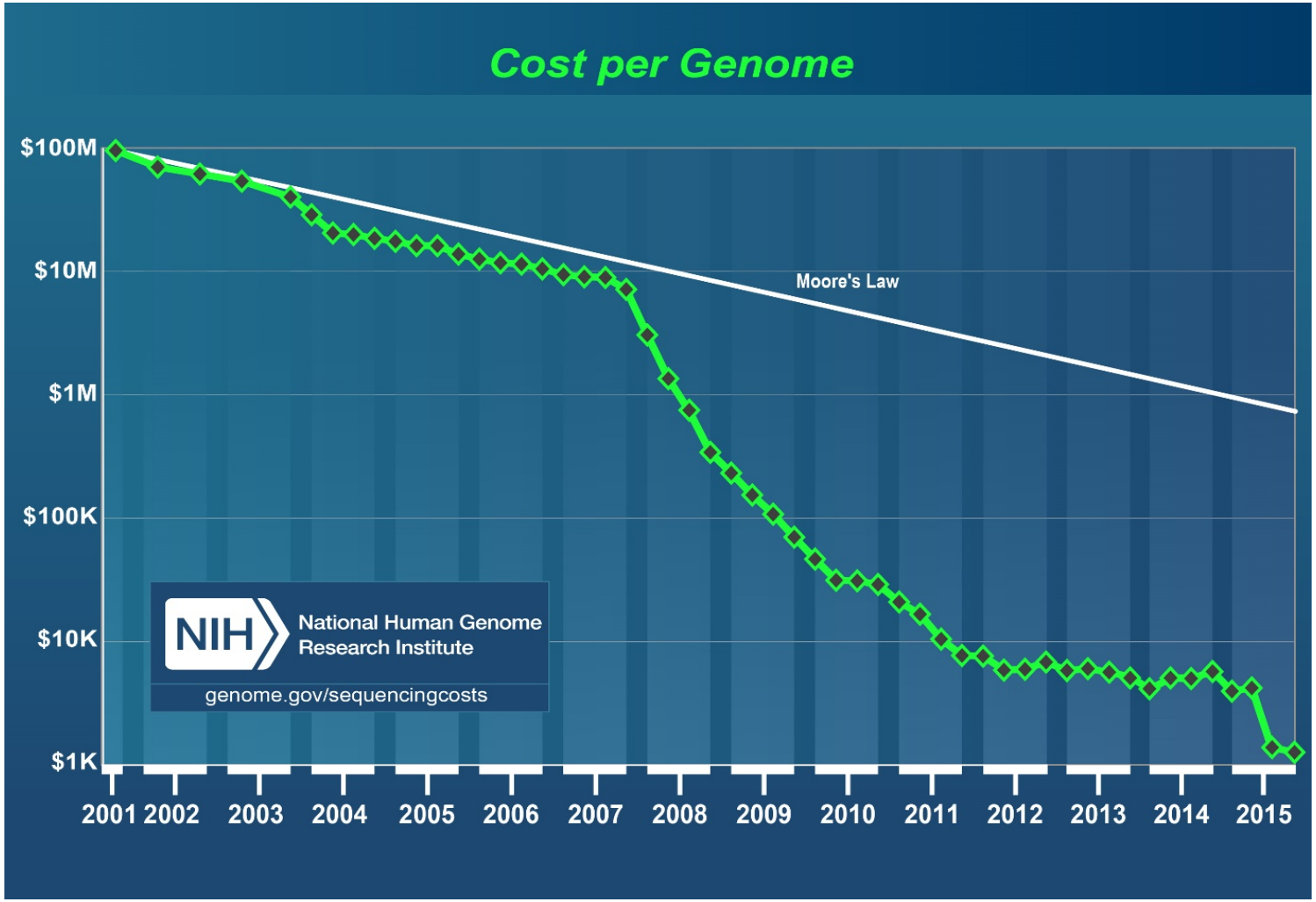
Affiliation/Financial Relationship	Company
• Grant/Research Support	• AztraZeneca, Astellas
• Consulting Fees/Honoraria	• Novartis, Merck, BMS
• Scientific Advisory Board	• Juvena, LifeVault
• Co-founder	• Khloris Biosciences

Precision Medicine Initiative (PMI)



President Obama (2015): *"delivering the right treatment at the right time, every time, to the right person"*

Promise of NGS for Patient Stratification (4P):
Predictive, Preventive, Personalized, Participatory



Next Gen Sequencing

Low-cost

Low-error rate

Rapid

Precision Medicine

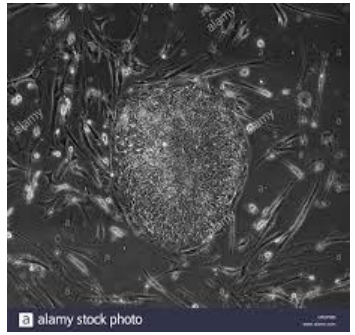
"NGS presents a great opportunity to detect or prevent many serious early-onset health conditions before they occur"

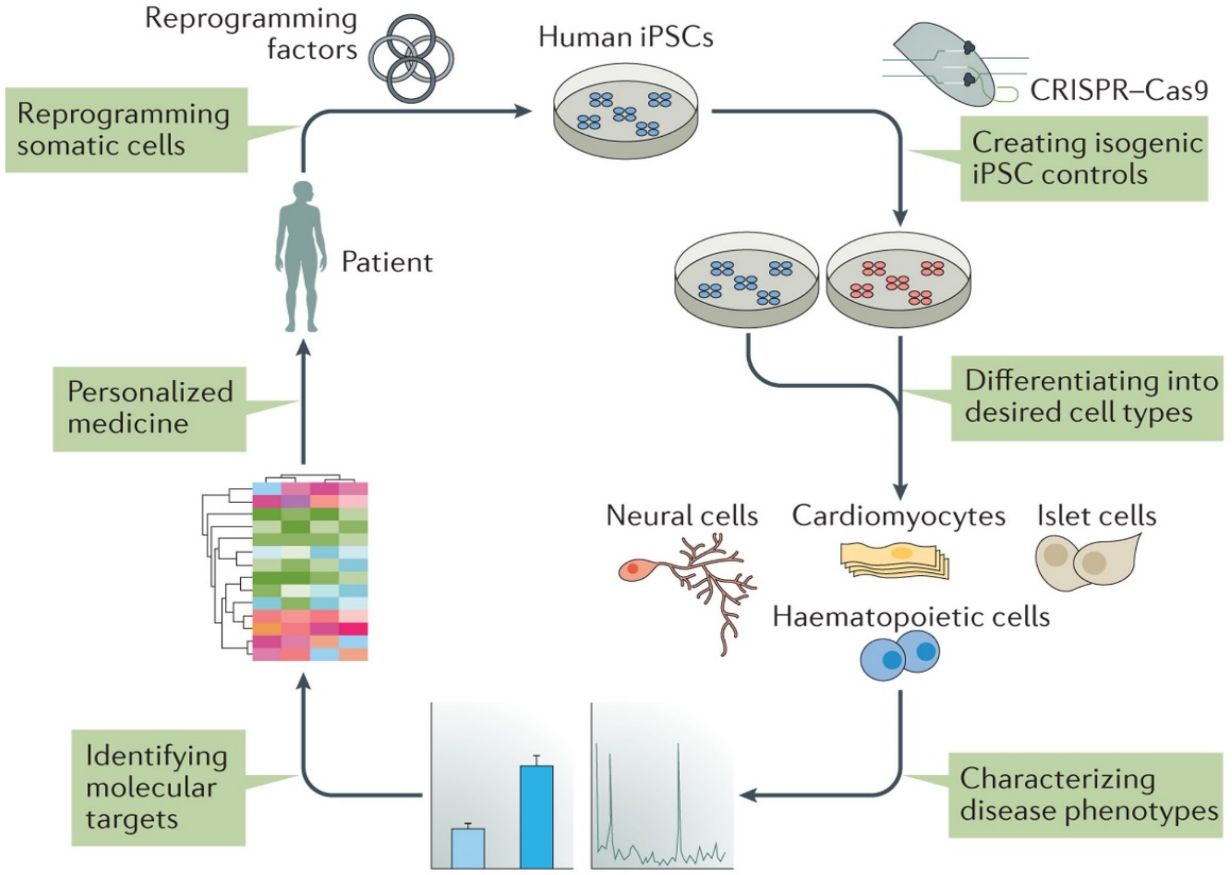
Human Induced Pluripotent Stem Cells

Shinya Yamanaka at the Kyoto University in Japan created the first iPSCs from mouse in **2006 and from human in **2007**. He shared the Nobel Prize in Medicine & Physiology in **2012** with Sir John Gurdon.

**iPSCs can be generated from the patient's blood, skin, hair, fat or other somatic cell types.

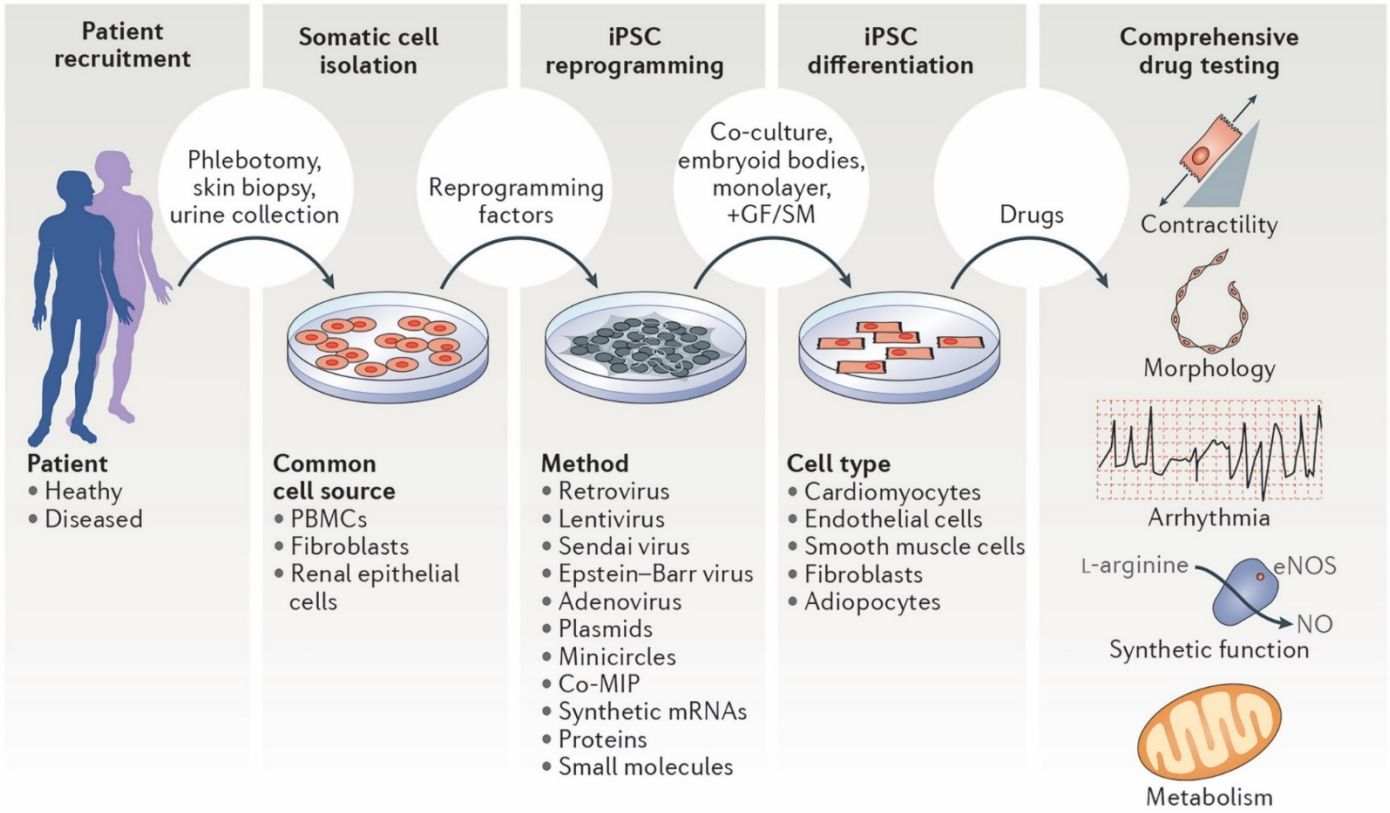
**Similar to human embryonic stem cells (ESCs), human iPSCs can *"self-renew"* and are *"pluripotent"*.

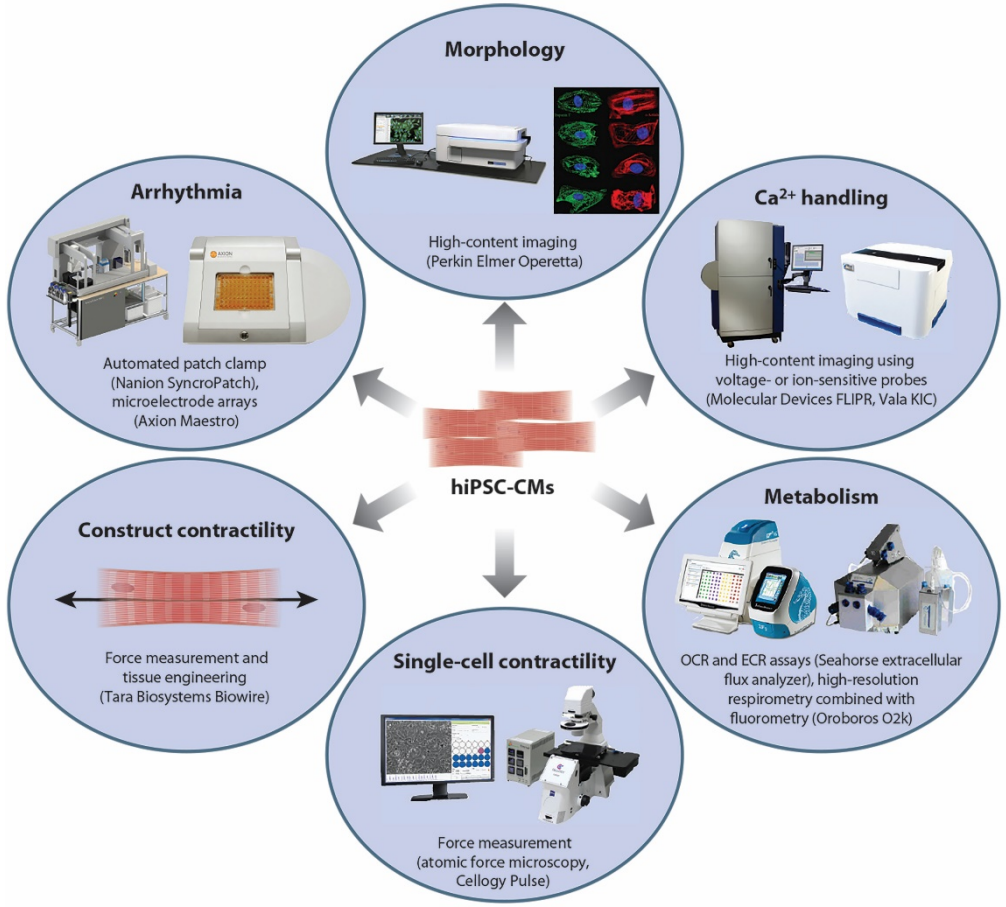




Wilson, Wu. *JAMA* 2015
Shi, Inoue, Wu, Yamanaka. *Nat Rev Drug Discov* 2016

Workflow for Generating & Testing Patient-Specific iPSC-CMs at Stanford Cardiovascular Institute





Chen IY et al. *Nat Rev Cardiol* 2017
Magdy T et al. *Ann Rev Pharm & Tox* 2018

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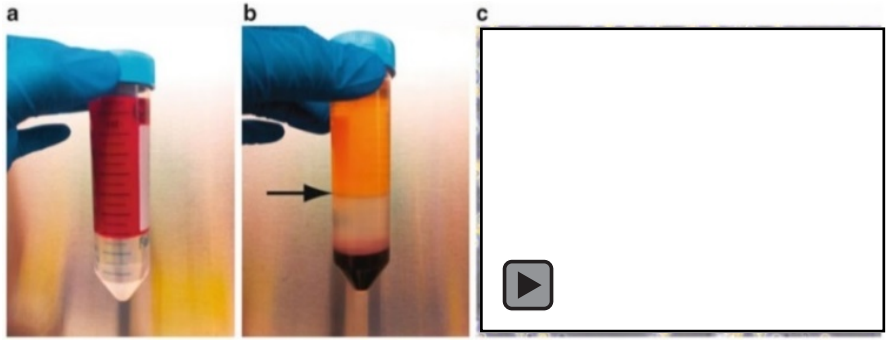
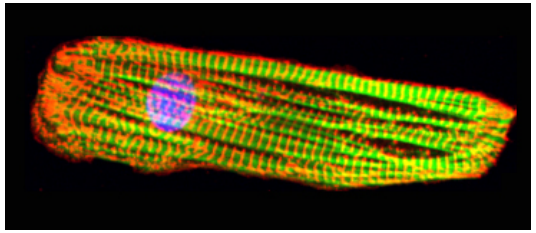
Diverse Population of Human iPSC-CMs (2D & 3D) as Alternative Toxicological Methods?

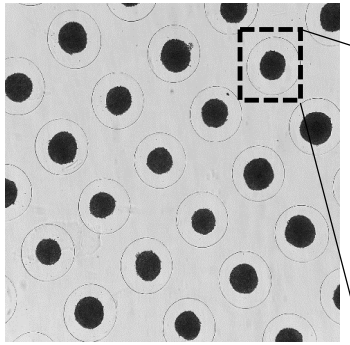
Diverse population



Patient- and disease-specific iPSC lines

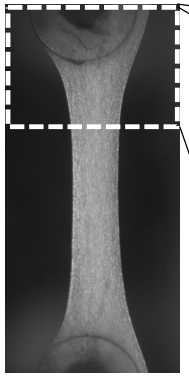


Differentiate heart cells



Microtissues Inc

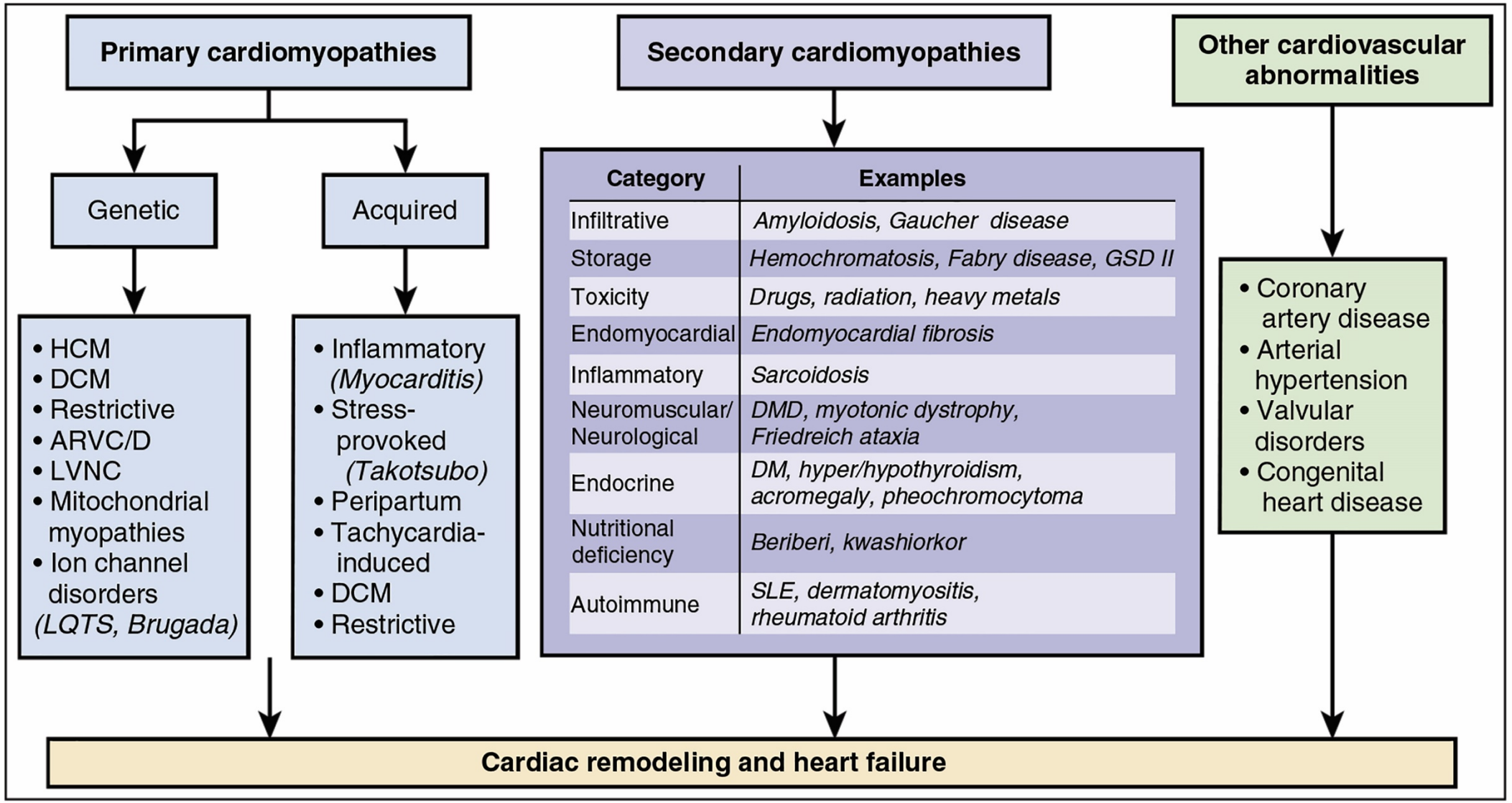
3D Cardiac Organoids



EHT Technologies GmbH

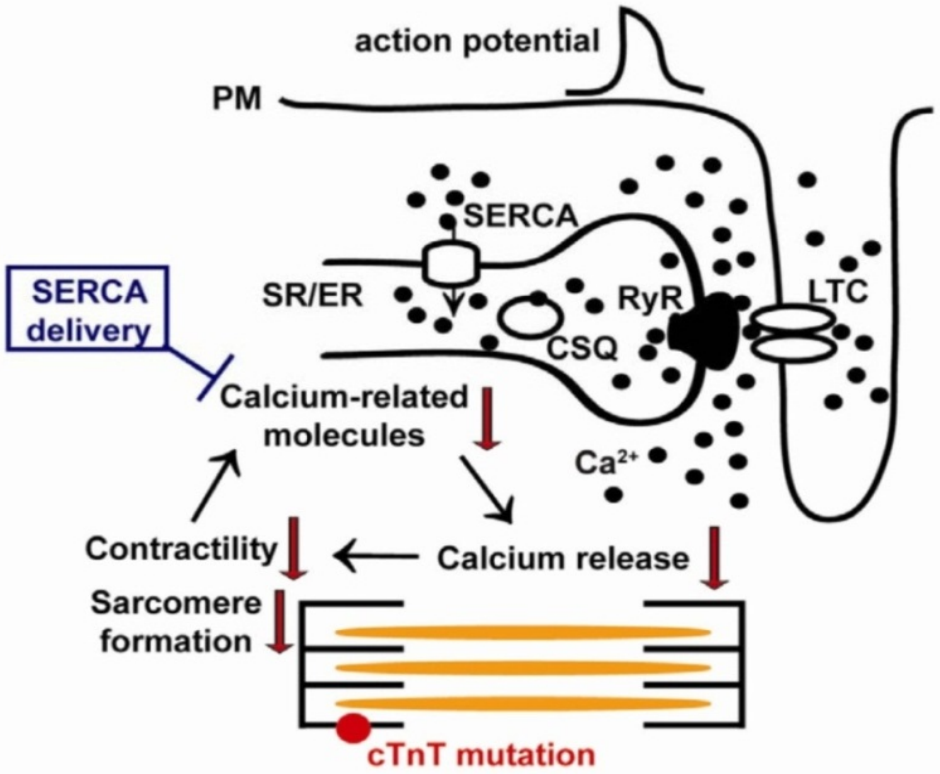
3D Engineered Heart Tissues

(1) Elucidating CV Disease Mechanisms



Patient-Specific Induced Pluripotent Stem Cells as a Model for Familial Dilated Cardiomyopathy

Ning Sun,[1,2,3]* Masayuki Yazawa,[4]* Jianwei Liu,[5] Leng Han,[1,2] Veronica Sanchez-Freire,[1,2] Oscar J. Abilez,[6] Enrique G. Navarrete,[2] Shijun Hu,[1,2] Li Wang,[1,2,3] Andrew Lee,[1,2,3] Aleksandra Pavlovic,[1] Shin Lin,[1] Rui Chen,[7] Roger J. Hajjar,[8] Michael P. Snyder,[7] Ricardo E. Dolmetsch,[4] Manish J. Butte,[5] Euan A. Ashley,[1] Michael T. Longaker,[3,9] Robert C. Robbins,[10] Joseph C. Wu[1,2,3,10†]



- **Summary:** Generated iPSC-CMs from a 7-member family with DCM. DNA-seq confirmed point mutation in TNNT2 (R173W). Compared to healthy control iPSC-CMs, diseased DCM iPSC-CMs showed altered regulation of calcium ion, decreased contractility, and abnormal distribution of sarcomeric α-actinin.

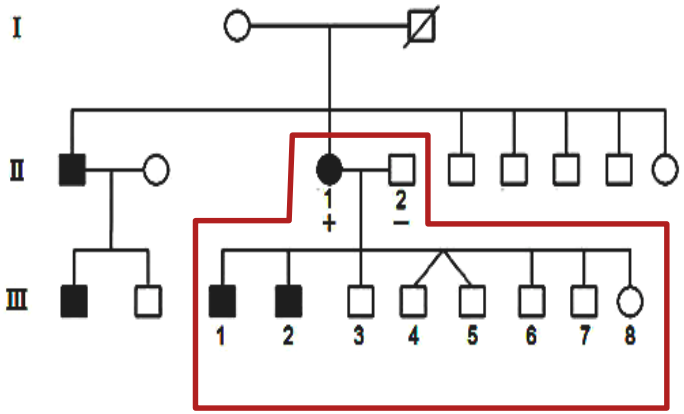
- **Clinical Relevance:** Treatment w/ β-adrenergic agent causes increased cellular stress. Treatment with beta blocker (metoprolol) improved function of DCM iPSC-CMs, recapitulating results from multiple large beta blocker clinical trials.

Sci Transl Med 2012

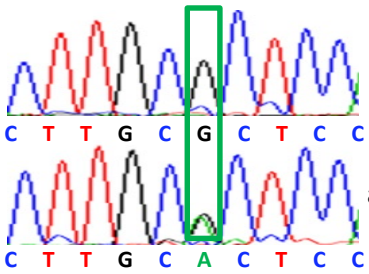
Abnormal Calcium Handling Properties Underlie Familial Hypertrophic Cardiomyopathy Pathology in Patient-Specific Induced Pluripotent Stem Cells

Feng Lan,[1,2,3,12] Andrew S. Lee,[1,2,3,12] Ping Liang,[1,2,3,12] Veronica Sanchez-Freire,[1,2,3] Patricia K. Nguyen,[1] Li Wang,[1,2] Leng Han,[1,2] Michelle Yen,[4] Yongming Wang,[1,2,3] Ning Sun,[1,2] Oscar J. Abilez,[5] Shijun Hu,[1,2,3] Antje D. Ebert,[1,2,3] Enrique G. Navarrete,[2] Chelsey S. Simmons,[9] Matthew Wheeler,[1] Beth Pruitt,[9] Richard Lewis,[4] Yoshinori Yamaguchi,[10] Euan A. Ashley,[1] Donald M. Bers,[11] Robert C. Robbins,[2,6] Michael T. Longaker,[3,8] and Joseph C. Wu[1,2,3,7,*]

Family Pedigree

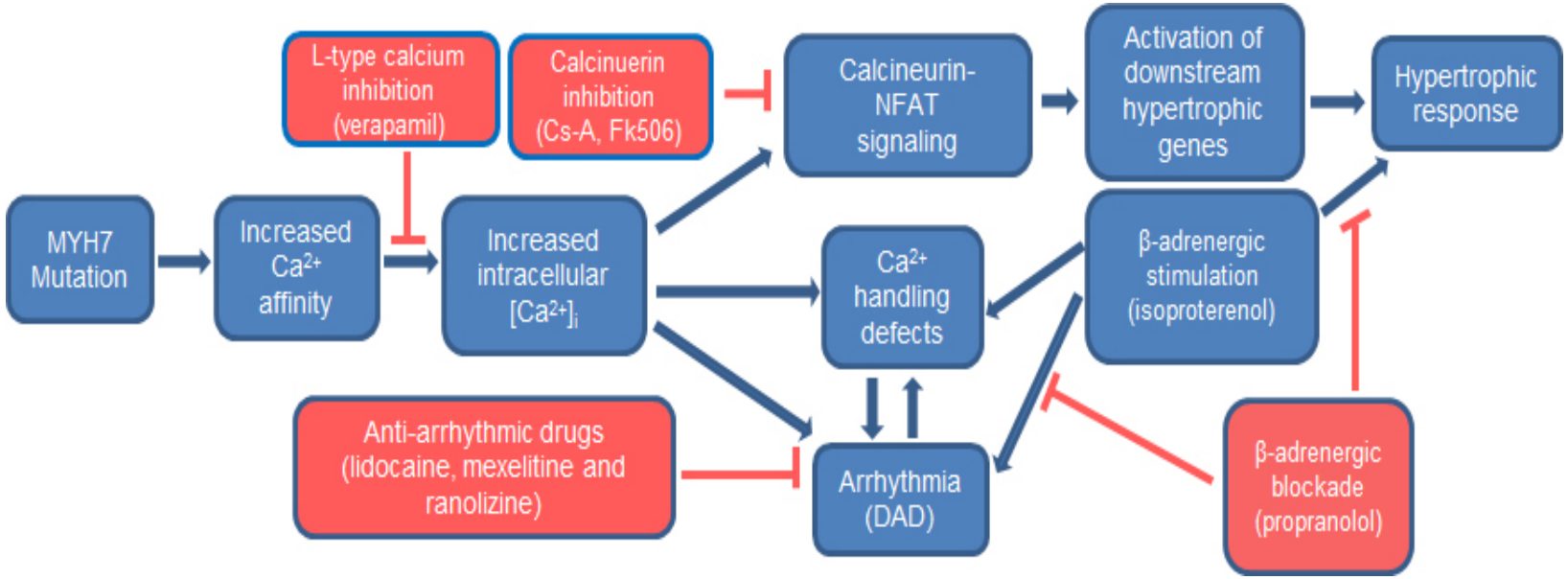


MYH7 Arg663His MUTATION



codon change: CGC>CAC

amino acid change: Arg>His



Summary: We generated iPSC-CMs from a 10-member family cohort, half carry HCM missense mutation (MYH7 Arg663His). Patient-specific iPSC-CMs recapitulated numerous characteristics of HCM. Pharmacological treatment with calcium-channel blocker (verapamil), β-blocker (propranolol), and calcineurin inhibitors (Cs-A, FK506) prevented development of cellular hypertrophy and electrophysiological irregularities.

Cell Stem Cell 2013

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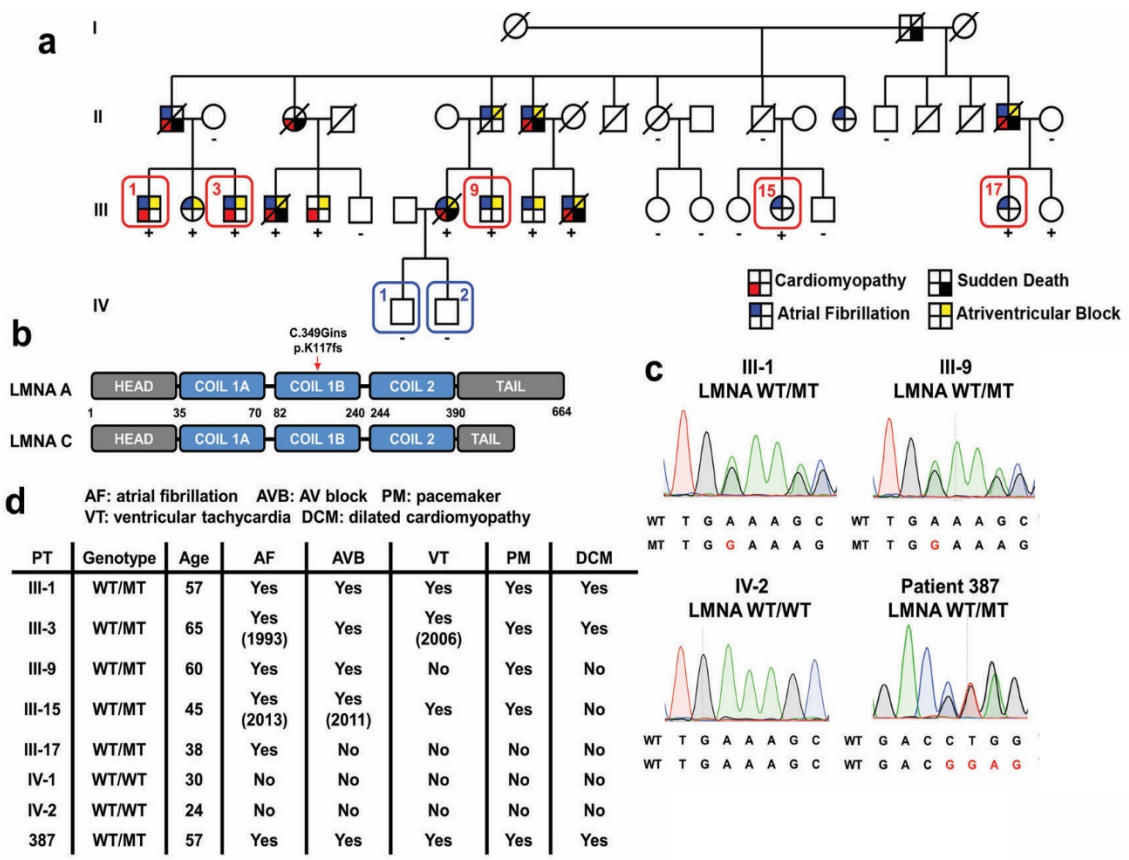
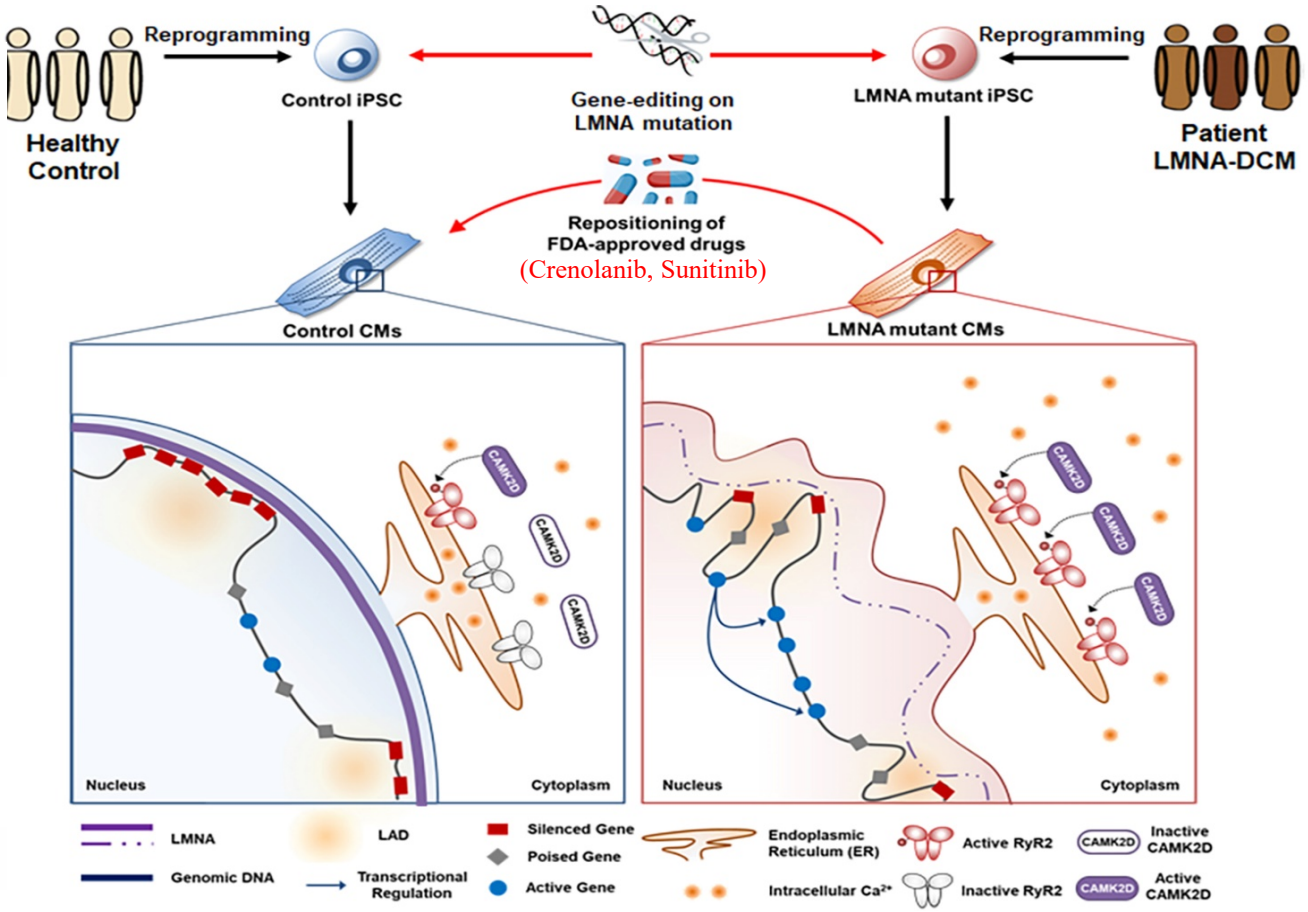
Activation of PDGF pathway links *LMNA* mutation to dilated cardiomyopathy

Jaecheol Lee[1,2,3,4,1,2*], Vittavat Termglinchan[1,2,3,12], Sebastian Diecke[5,6,7,12], Ilanit Itzhaki[1,2,3], Chi Keung Lam[1,2,3], Priyanka Garg[1,2,3], Edward Lau[1,2,3], Matthew Greenhaw[8], Timon Seeger[1,2,3], Haodi Wu[1,2,3], Joe Z. Zhang[1,2,3], Xingqi Chen[9], Isaac Perea Gil[1,8], Mohamed Ameen[1,2,3], Karim Sallam[1,2,3], June-Wha Rhee[1,2,3], Jared Churko[1,2,3], Rinkal Chaudhary[1,2,3], Tony Chour[1,2,3], Paul J. Wang[2], Michael P. Snyder[1,10], Howard Y. Chang[9,11], Ioannis Karakikes[1,8*] & Joseph C. Wu[1,2,3*]



PT	Genotype	Age	AF	AVB	VT	PM	DCM
III-1	WT/MT	57	Yes	Yes	Yes	Yes	Yes
III-3	WT/MT	65	Yes (1993)	Yes	Yes (2006)	Yes	Yes
III-9	WT/MT	60	Yes	Yes	No	Yes	No
III-15	WT/MT	45	Yes (2013)	Yes (2011)	Yes	Yes	No
III-17	WT/MT	38	Yes	No	No	No	No
IV-1	WT/WT	30	No	No	No	No	No
IV-2	WT/WT	24	No	No	No	No	No
387	WT/MT	57	Yes	Yes	Yes	Yes	Yes



Nature 2019

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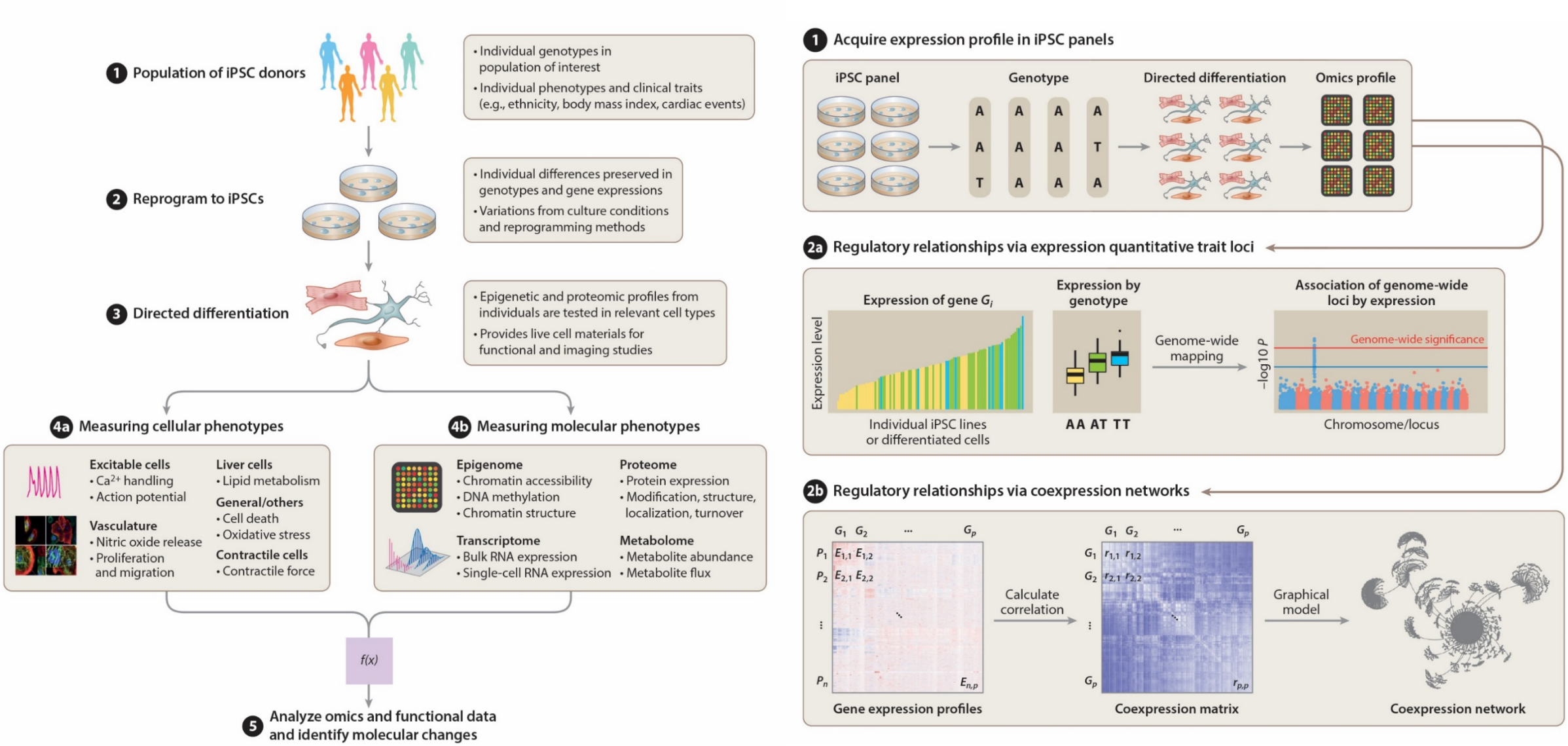
Multi-Omics of Human Population Using iPSC Lines



Lau E et al. *Annu Rev Pathol Mech Dis* 2019

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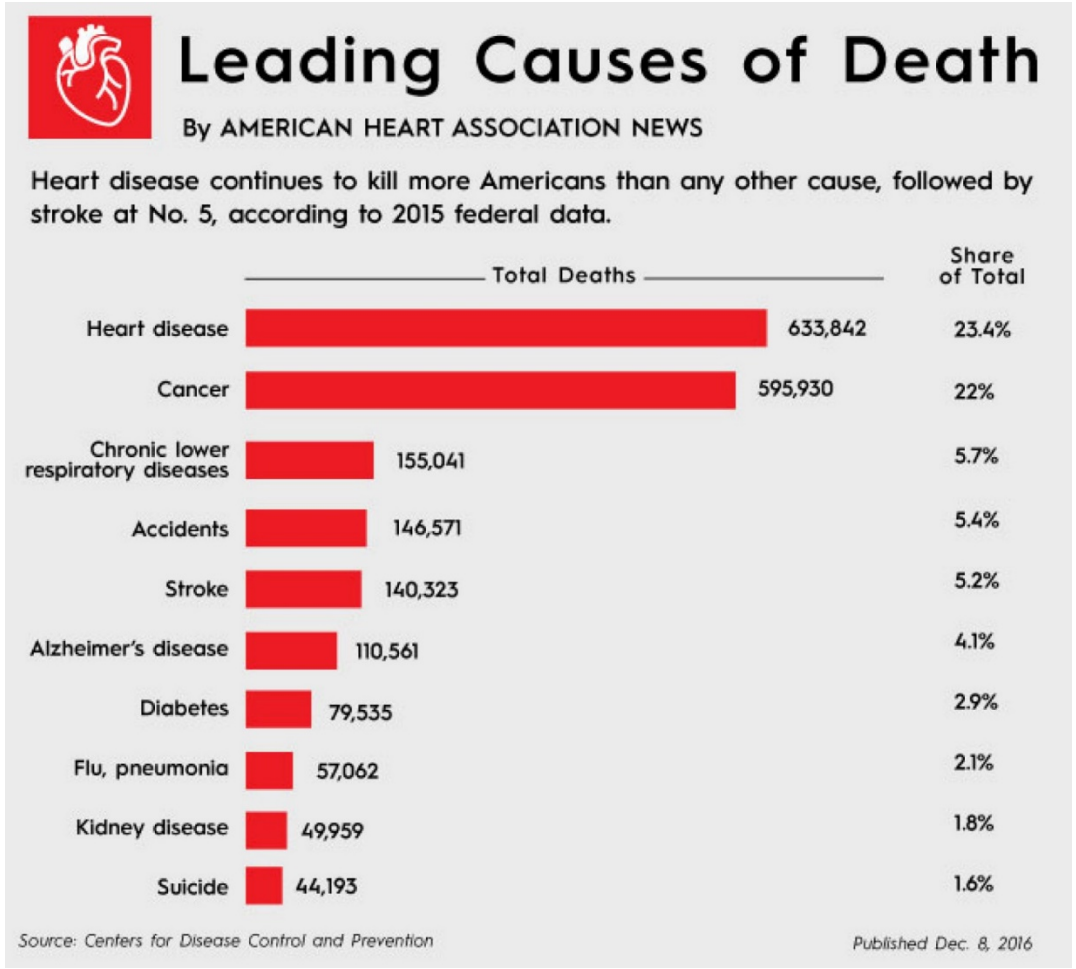
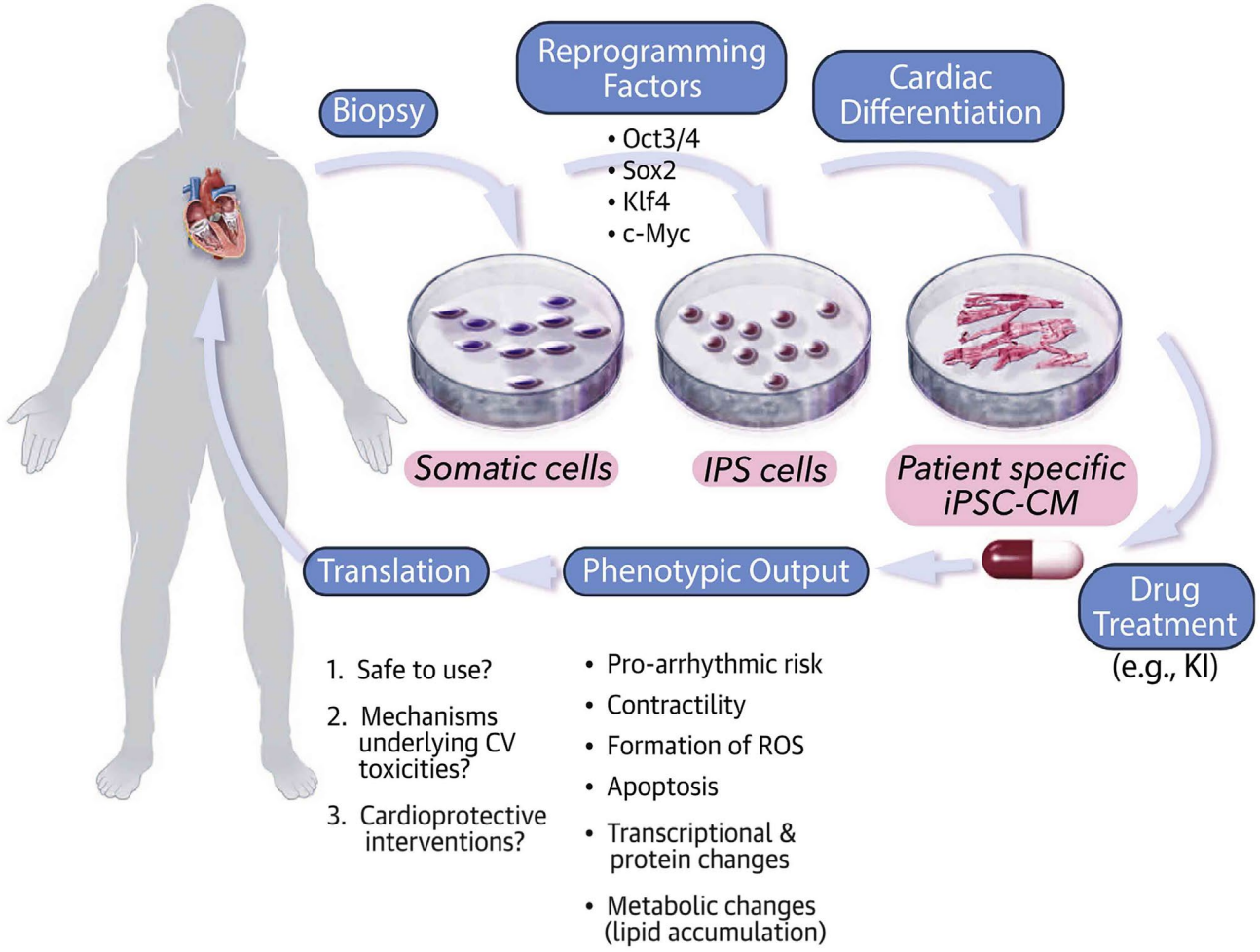
(2) Cardio-Oncology: Personalized iPSC for Assessing Chemotherapy-Induced Cardiotoxicity?





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Sheng CS et al, *JACC BTS* 2017

Human induced pluripotent stem cell–derived cardiomyocytes recapitulate the predilection of breast cancer patients to doxorubicin-induced cardiotoxicity

Paul W Burridge[1–5], Yong Fuga Li[6,7], Elena Matsa[1–3], Haodi Wu[1–3], Sang-Ging Ong[1–3], Arun Sharma[1–3], Alexandra Holmström[1–3], Alex C Chang[1,2,8], Michael J Coronado[9], Antje D Ebert[1–3], Joshua W Knowles[1,3], Melinda L Telli[10], Ronald M Witteles[1,3], Helen M Blau[1,2,8], Daniel Bernstein[1,9], Russ B Altman[7,11] & Joseph C Wu

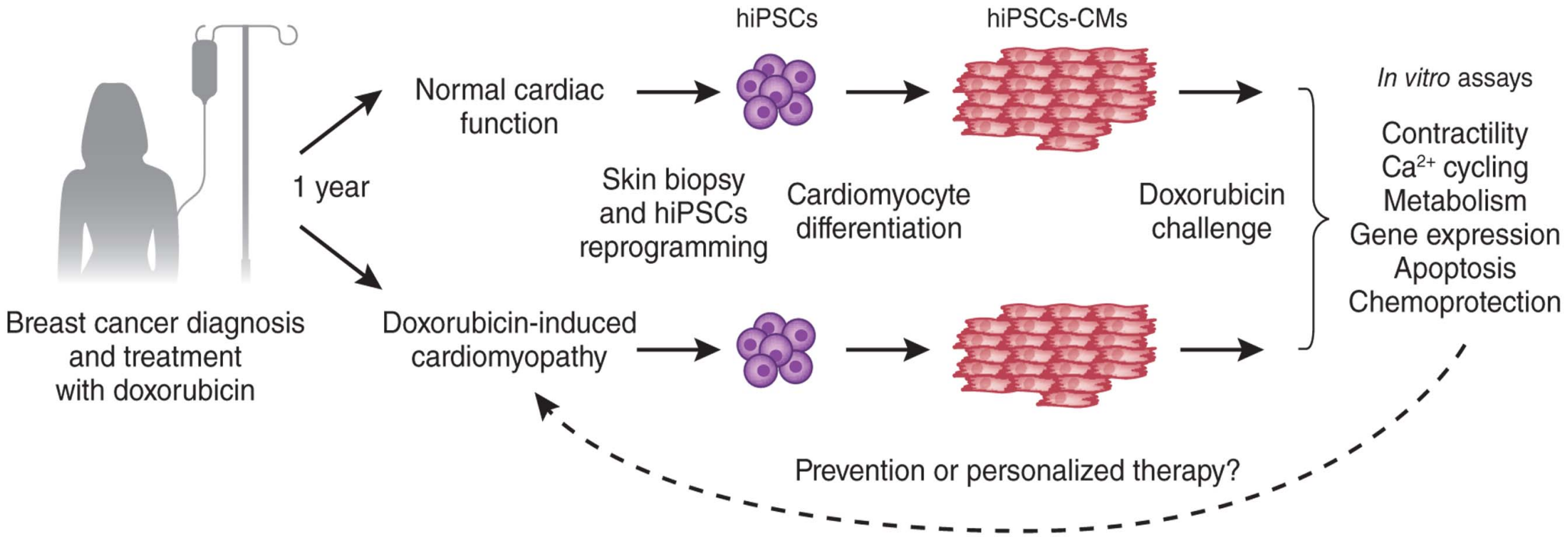

Figure 1 Cardiac hiPSCs can give indications as to the cardiotoxicity of doxorubicin. Burridge *et al.*[2] derive hiPSCs from the tumors of individuals with breast cancer who do and do not experience doxorubicin-induced toxicity. They find that these cells respond differently to doxorubicin. Hence, they can be used to investigate the cause of toxicity and, in the future, potentially to tailor relevant treatments.

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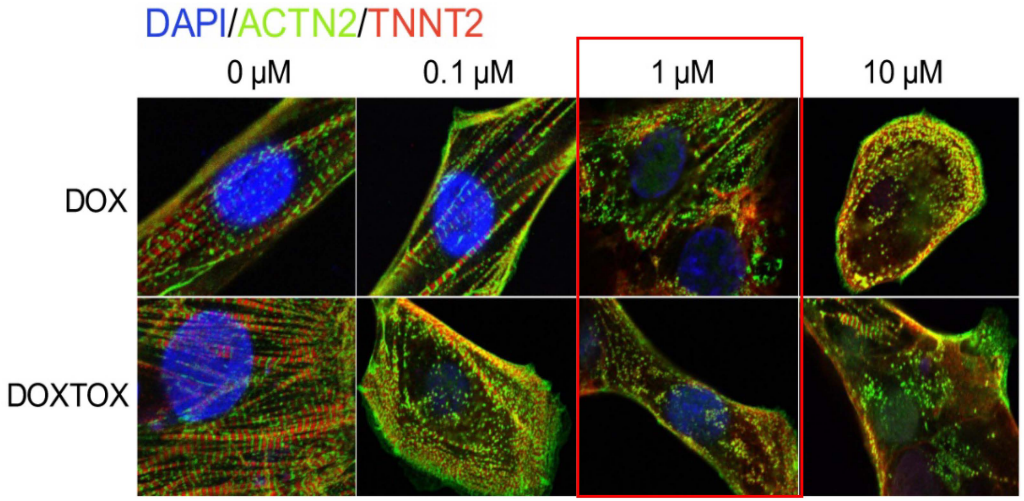
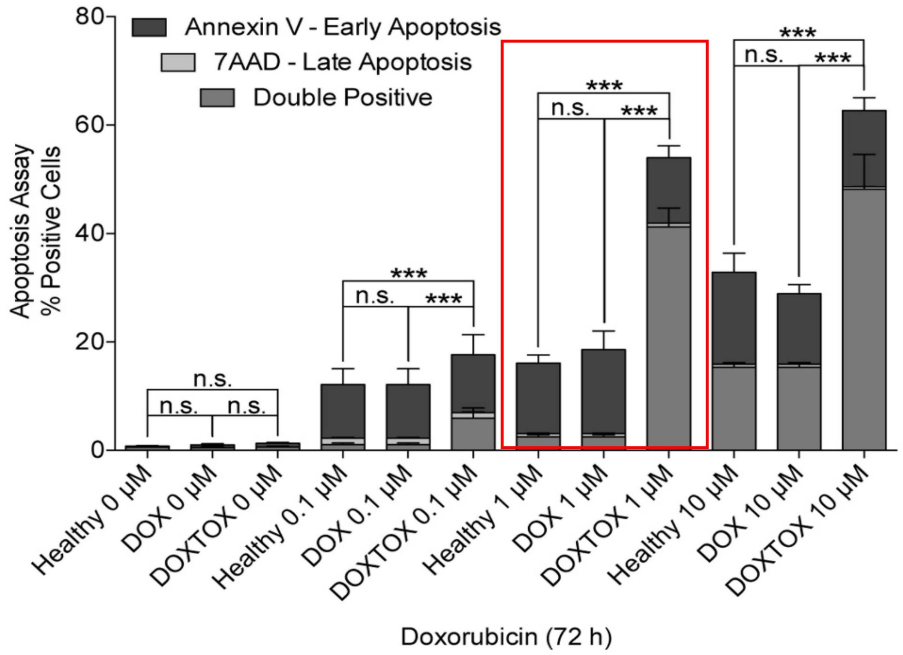
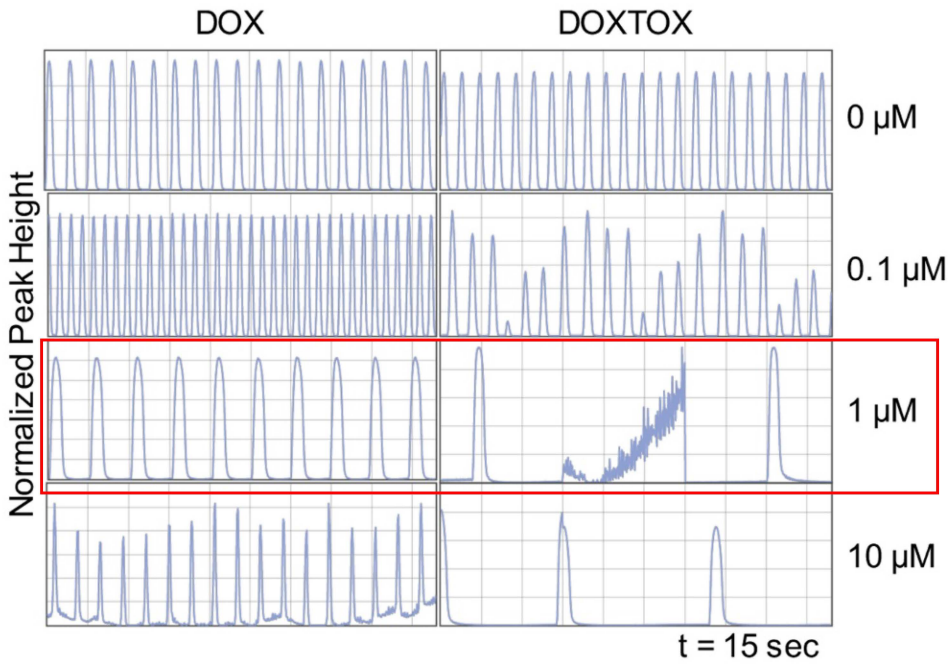
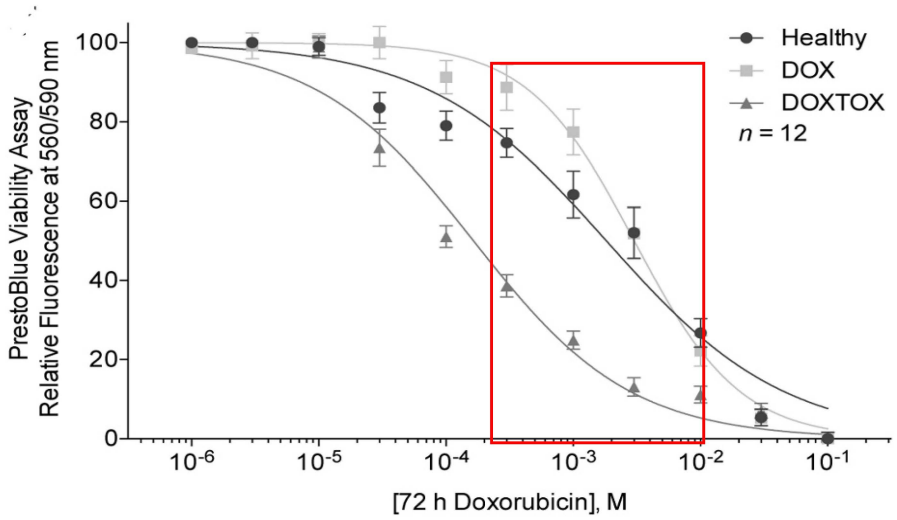
Kamp. Cardiotoxicity in a dish: new insights for personalized therapy. *Nature Medicine* 2016

Line code	Patient #	Sex	Age	Treatment	Pre LVEF (%)	Post LVEF (%)	BMI
Healthy1	62	F	57	None	67	NA	29.1
Healthy2	72	F	45	None	61	NA	25.2
Healthy3	78	F	64	None	55	NA	22.7
Healthy4	202	F	30	None	71	NA	24.5
DOX1	59	F	59	4 cycles 2000 mg/m^2 epirubicin + cyclophosphamide then trastuzumab + docetaxel	80	71-77	27.2
DOX2	60	F	66	4 cycles 240 mg/m^2 doxorubicin + cyclophosphamide then trastuzumab + docetaxel	60	62-70	27.6
DOX3	64	F	52	4 cycles 240 mg/m^2 doxorubicin + cyclophosphamide then trastuzumab + docetaxel	58	56-58	25.3
DOX4	65	F	66	4 cycles 240 mg/m^2 doxorubicin + cyclophosphamide then trastuzumab + docetaxel	68	62-70	33.8
DOXTOX1	31	F	40	4 cycles 240 mg/m^2 doxorubicin + cyclophosphamide	77	36-50	28.2
DOXTOX2	40	F	66	3 cycles 240 mg/m^2 doxorubicin + cyclophosphamide	67	10-57	28.6
DOXTOX3	51	F	52	4 cycles 240 mg/m^2 doxorubicin + cyclophosphamide	62	44-55	26
DOXTOX4	79	F	31	4 cycles 240 mg/m^2 doxorubicin + cyclophosphamide	70	45-49	26.4


DAPI/ACTN2/TNNT2
0 μM
0.1 μM
1 μM
10 μM
DOX
DOXTOX

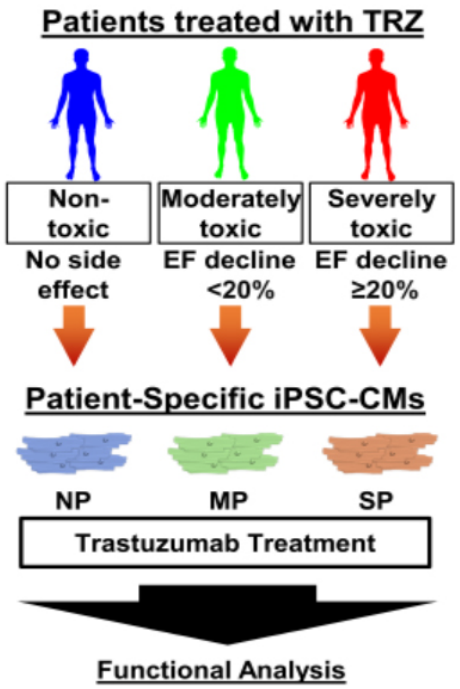

Annexin V - Early Apoptosis
7AAD - Late Apoptosis
Double Positive
Apoptosis Assay
% Positive Cells
n.s.
***
Healthy 0 μM
DOX 0 μM
DOXTOX 0 μM
Healthy 0.1 μM
DOX 0.1 μM
DOXTOX 0.1 μM
Healthy 1 μM
DOX 1 μM
DOXTOX 1 μM
Healthy 10 μM
DOX 10 μM
DOXTOX 10 μM
Doxorubicin (72 h)


DOX
DOXTOX
Normalized Peak Height
0 μM
0.1 μM
1 μM
10 μM
t = 15 sec


Healthy
DOX
DOXTOX
n = 12
PrestoBlue Viability Assay
Relative Fluorescence at 560/590 nm
[72 h Doxorubicin], M

Human-Induced Pluripotent Stem Cell Model of Trastuzumab-Induced Cardiac Dysfunction in Patients With Breast Cancer

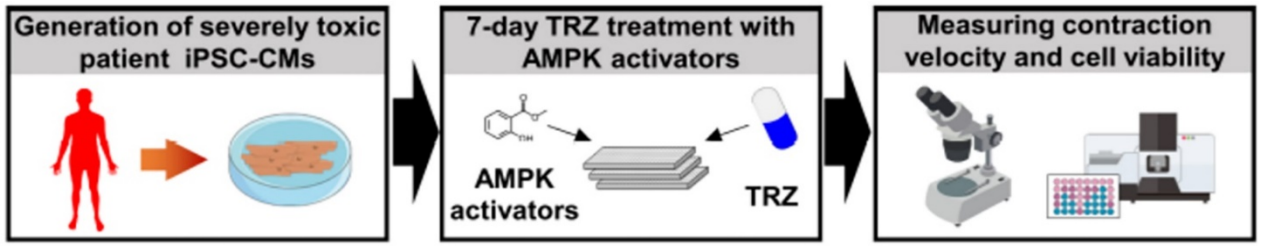
A



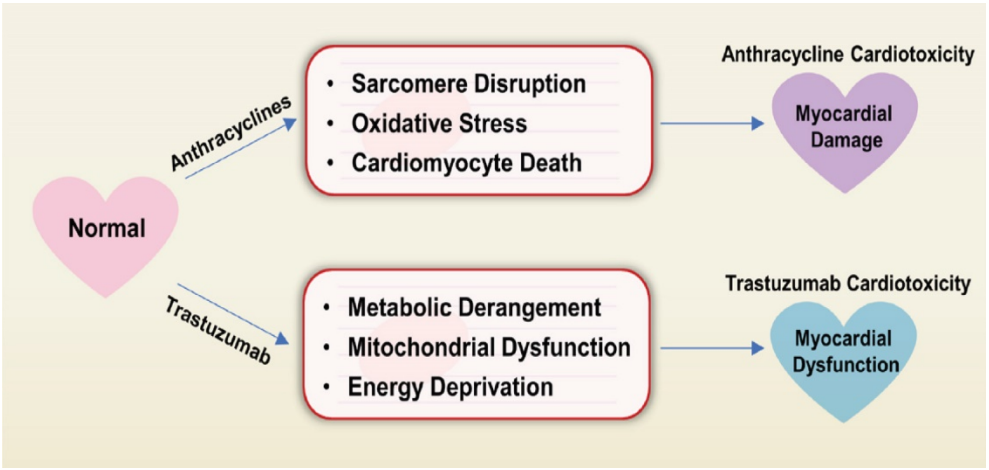
B

	iPS Lines	LVEF Decline (%)	Age (yr)	Sex (F/M)	LVEF Recovery	Duration of TRZ
Severely toxic	SP 1	35	57	F	Yes	1 mo
	SP 2	21	48	F	Yes	1 mo
	SP 3	21	42	F	Yes	2 mo
Moderately toxic	MP 1	12	64	F	Yes	4 mo
	MP 2	14	76	F	Yes	3 mo
Non-toxic	NP 1	-	52	F	-	>1 yr
	NP 2	-	66	F	-	>2 yr

C



D

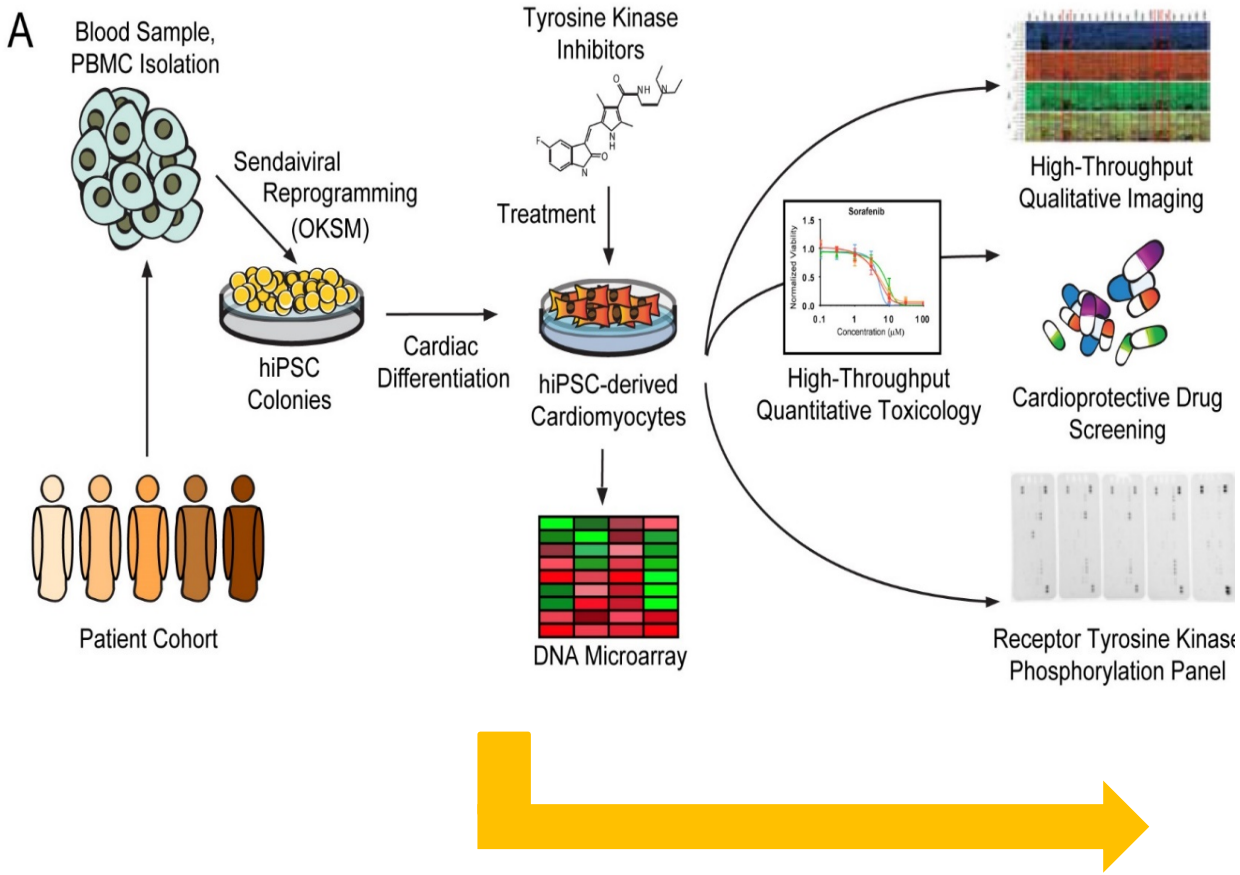


Note: Herceptin-induced cardiac dysfunction in iPSC-CMs can be improved by AMPK activators (e.g., metformin)

Kitani T et al, *Circulation* 2019

High-throughput screening of tyrosine kinase inhibitor cardiotoxicity with human induced pluripotent stem cells

Arun Sharma,[1,2,3]* Paul W. Burridge,[1,2,4]* Wesley L. McKeithan,[1,5,6] Ricardo Serrano,[7] Praveen Shukla,[1,2,3] Nazish Sayed,[1,2,3] Jared M. Churko,[1,2,3] Tomoya Kitani,[1,2,3] Haodi Wu,[1,2,3] Alexandra Holmström,[1,2,3] Elena Matsa,[1,2,3] Yuan Zhang,[1,2,3] Anusha Kumar,[1,2,3] Alice C. Fan,[8] Juan C. del Álamo,[7] Sean M. Wu,[1,2,3] Javid J. Moslehi,[9] Mark Mercola,[1,3,5] Joseph C. Wu[1,2,3†]



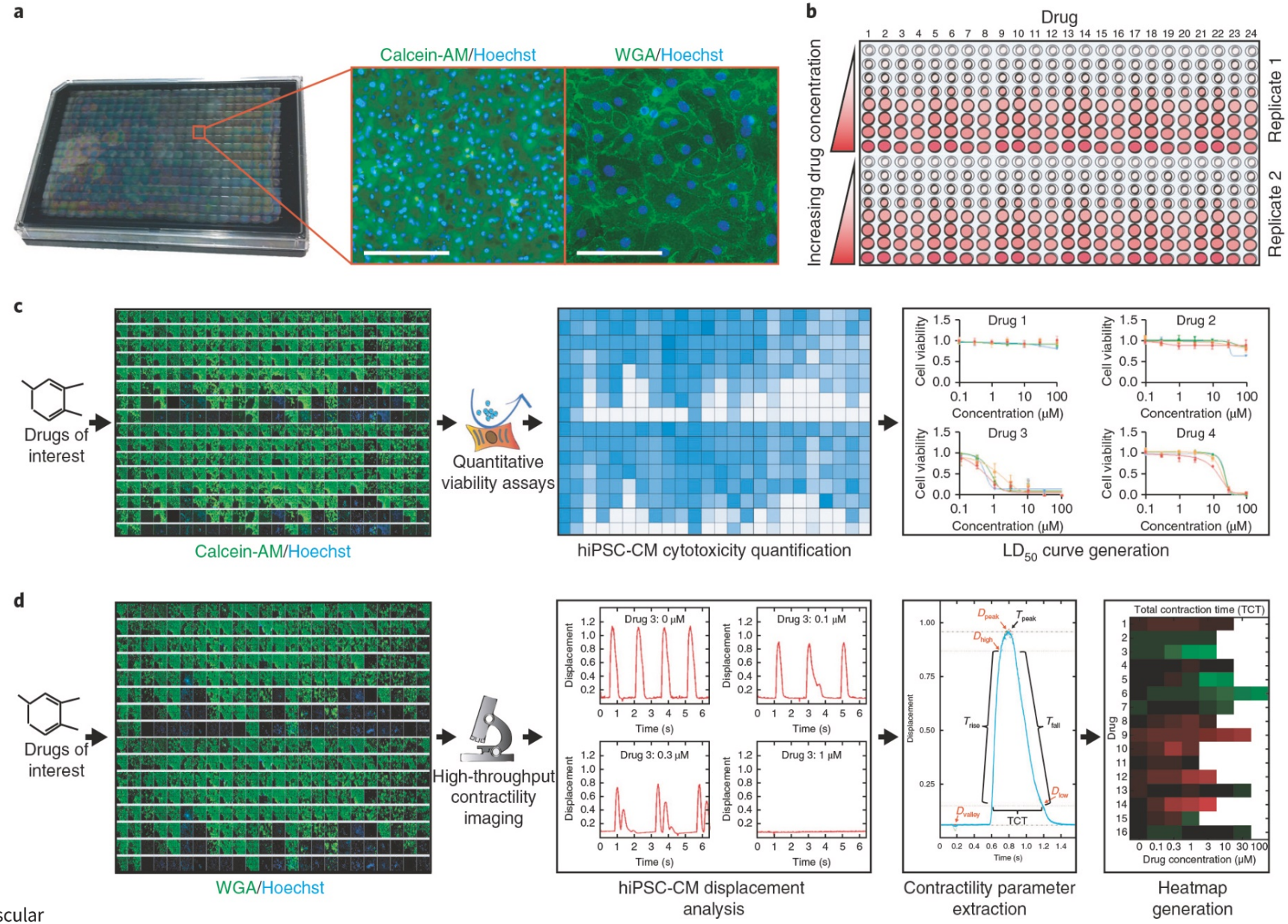
B

"Cardiac Safety Index"

	Drug	Cessation of Beating (μM)	Effective Concentration (μM)	Amplitude of Effect	LD50 (μM)	Cmax (μM)	Cardiac Safety Index	Clinically-Reported Cardiotoxicity
	Vemurafenib	33	11.00	0.34	32.10	126.04	0.003	QT
	Sorafenib	3.7	2.51	1.03	3.40	8.43	0.004	QT, LV, HF, MI, Hy
	Doxorubicin	3.7	1.20	0.60	0.78	2.93	0.010	**HF, LV
	Regorafenib	11	3.70	0.84	7.10	8.08	0.010	#MI, Hy
QT	Vandetanib	33	5.68	2.47	20.60	4.26	0.041	**QT, TdP, SCD, HF, Hy
	Crizotinib	11	1.91	0.59	8.60	1.24	0.063	QT, Brady
QT	Nilotinib	100	8.31	2.65	29.00	4.27	0.104	**QT, LV, Vas
	Imatinib	100	33.00	1.59	78.20	5.11	0.126	LV (rare)
	Lapatinib	33	11.00	0.40	100.76	2.30	0.209	#LV, QT
	Sunitinib	3.7	0.81	1.33	12.70	0.18	0.218	#HF, LV, MI, QT, Hy
	Bosutinib	33	4.73	1.92	12.39	0.51	0.315	PE
	Gefitinib	33	3.11	1.24	26.30	0.45	0.409	None
	Afatinib	3.7	1.65	1.11	12.30	0.10	0.444	None
	Dabrafenib	100	36.75	0.71	100.68	4.16	0.459	LV
	Ponatinib	3.7	3.70	0.54	4.30	0.14	0.483	**Vas, HF, LV, Hy
	Ibrutinib	33	10.01	1.54	11.90	0.37	0.507	Afib
	Dasatinib	3.7	1.20	0.31	42.00	0.21	0.524	QT, PE, Hy
	Erlotinib	N/A	63.38	0.51	87.60	3.11	0.653	MI (Rare)
	Pazopanib	N/A	73.86	1.19	N/A	103.08	0.671	#QT, LV (Rare)
	Cabozantinib	N/A	91.14	1.37	N/A	4.43	0.769	#None
	Trametinib	100	33.00	2.37	66.80	0.02	1.000	LV
	Axitinib	N/A	71.79	0.44	N/A	0.07	1.000	HF (Rare), Hy
	DMSO	N/A	100.00	0.58	N/A	N/A	1.000	None

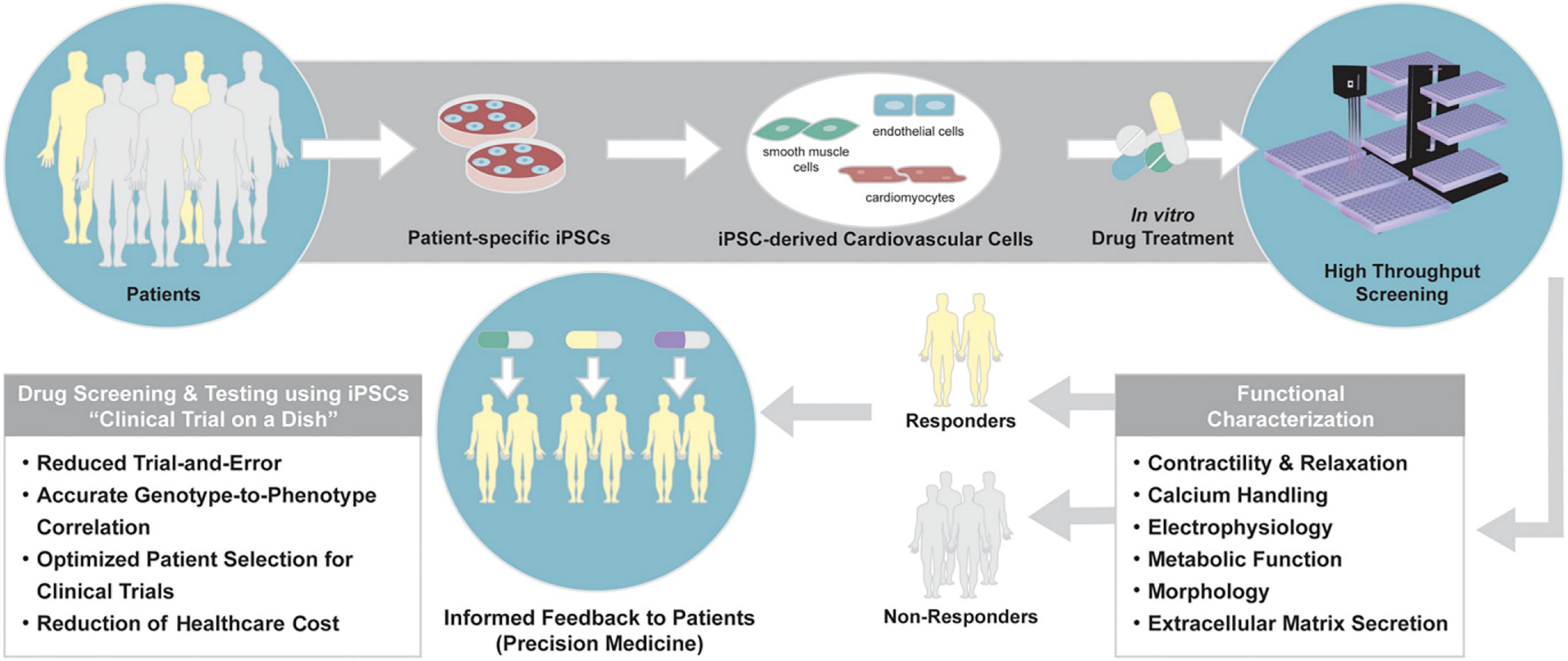
Sci Transl Med 2017

iPSC-CM Platform for Assessing Cardiac Safety Index



Sharma A et al, *Nat Protocol* 2018

(3) "Clinical Trial in a Dish"



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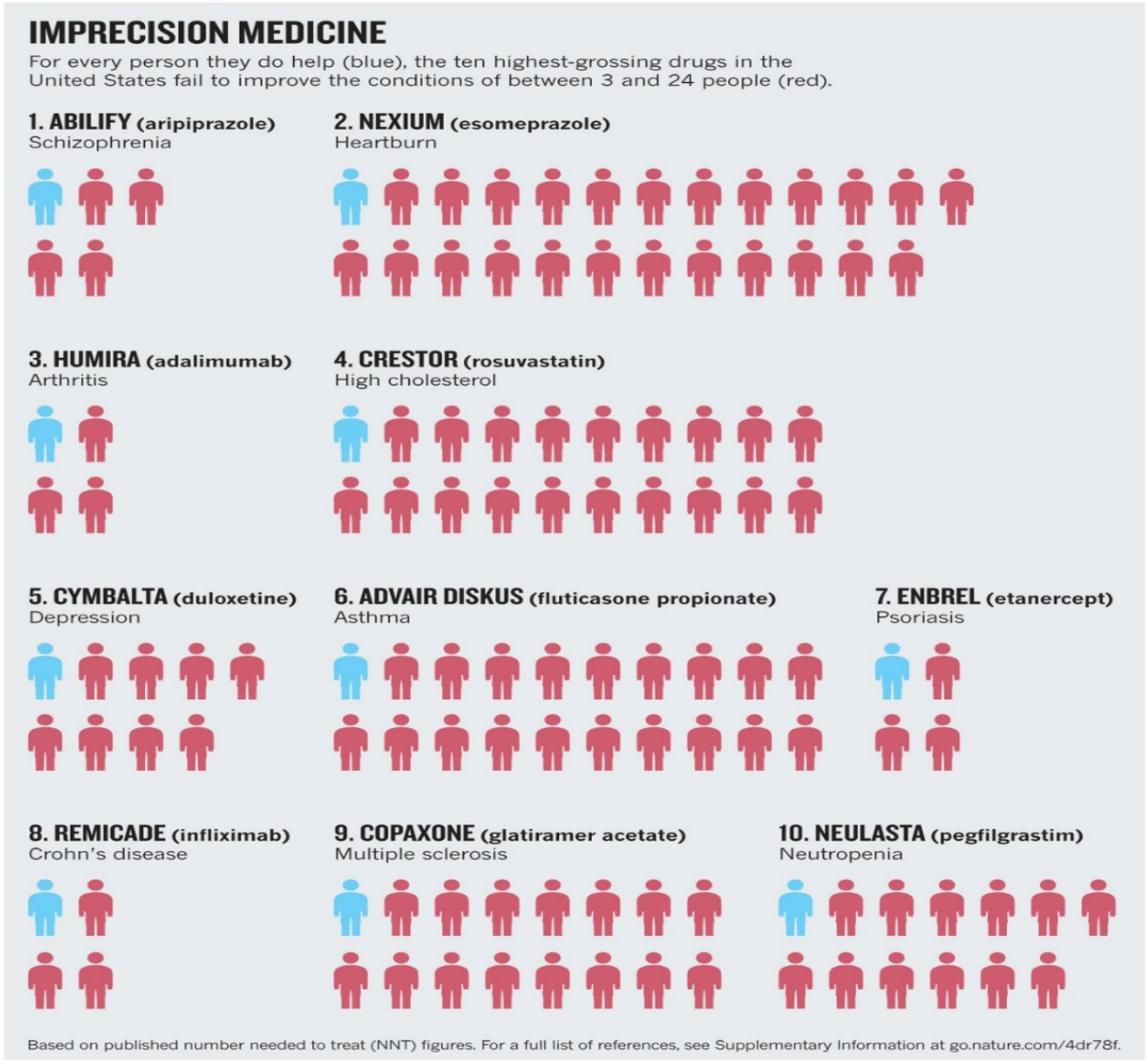
Paik DT et al. Patient-specific iPSCs for personalized therapeutics. ***Pharmacologic Reviews*** 2020

Imprecision Medicine: Many Drugs Do Not Work!



Note: the top 10 highest-grossing drugs in the US fail to improve the conditions of treated patients (red) more than they help (blue).

1) Abilify (1/5)
2) Nexium (1/25)
3) Humira (1/4)
4) Crestor (1/20)
5) Cymbalta (1/9)
6) Advair Diskus (1/20)
7) Enbrel (1/4)
8) Remicade (1/4)
9) Copaxone (1/16)
10) Neulasta (1/13)

Schork NJ. **Time for one-person clinical trial.** *Nature* 2016

Takeda, CiRA Launch $268.5M iPS Collaboration

Apr 17, 2015

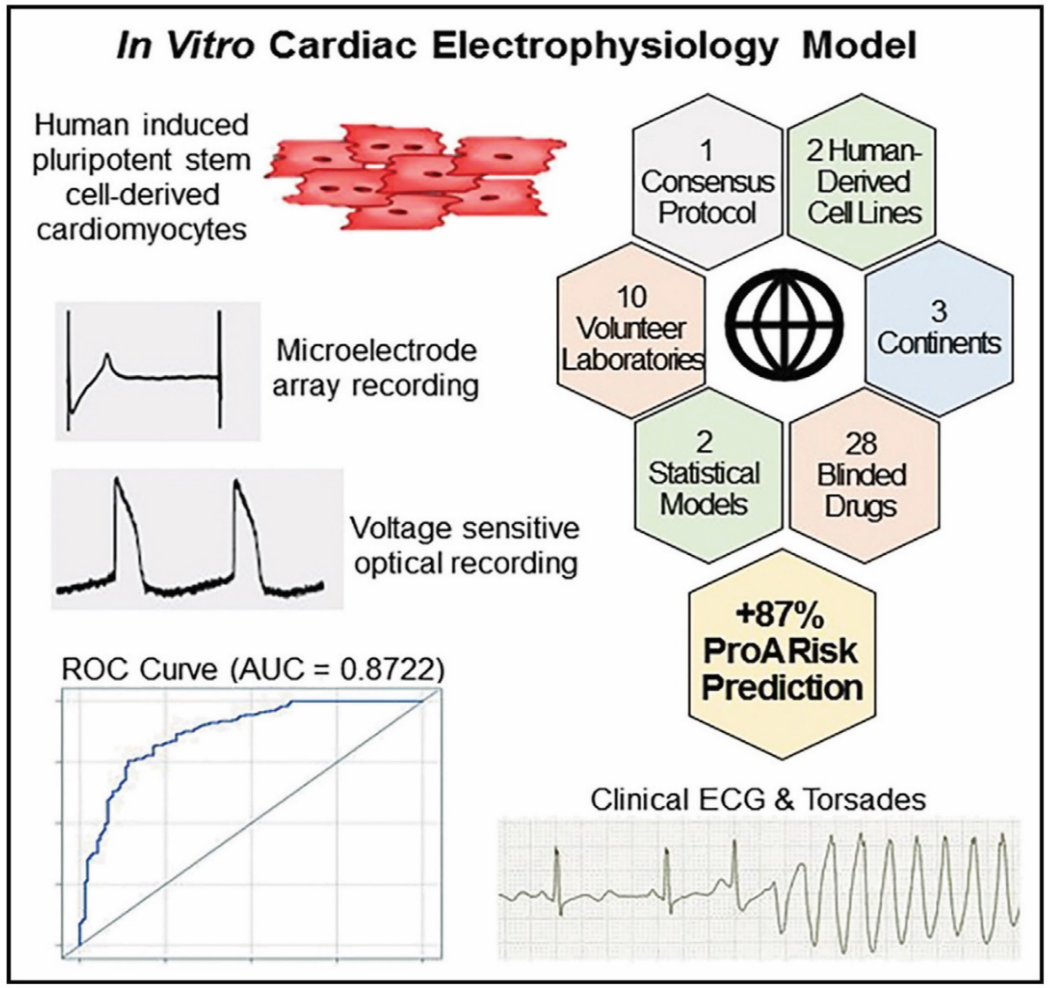
Takeda Pharmaceutical and Kyoto University's Center for iPS Cell Research Application (CiRA) said today they have will launch a ¥32 billion (nearly $268.5 million) collaboration to develop clinical applications of induced pluripotent stem cells.

The partners said their Takeda-CiRA Joint Program for iPS Cell Applications (T-CiRA) is expected to make "significant" contributions to the science and application of iPS cell technology into clinical practice, by expediting multiple research projects for drug discovery and cell therapy using iPS cells. During the collaboration's 10-year timeframe, Takeda and CiRA will jointly run projects led by research experts from CiRA.

Potential initial research projects, according to the partners, will involve the use of iPS cells in areas such as heart failure, diabetes, neuro-psychiatric disorders, and cancer immunotherapy. Additional projects will be launched over time, with the collaboration ramping up to pursue "around 10" projects concurrently.

International Multisite Study of Human-Induced Pluripotent Stem Cell-Derived Cardiomyocytes for Drug Proarrhythmic Potential Assessment

Graphical Abstract



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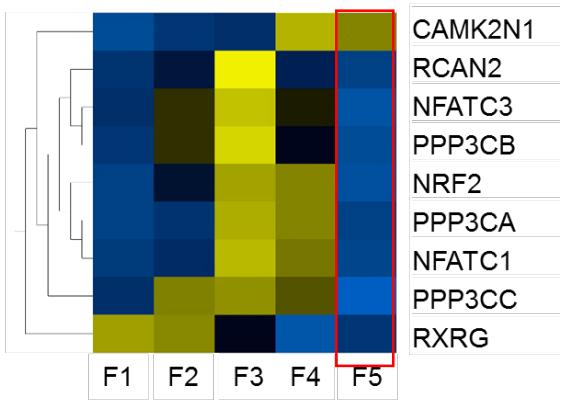
In Brief

Blinova et al. tested human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) for improving torsades de pointes arrhythmia risk prediction of drugs in the Comprehensive *In Vitro* Proarrhythmia Assay (CiPA) initiative. This validation study confirms their utility based on electrophysiologic responses to 28 blinded drugs, with minimal influence from cell lines, test sites, and electrophysiological platforms.

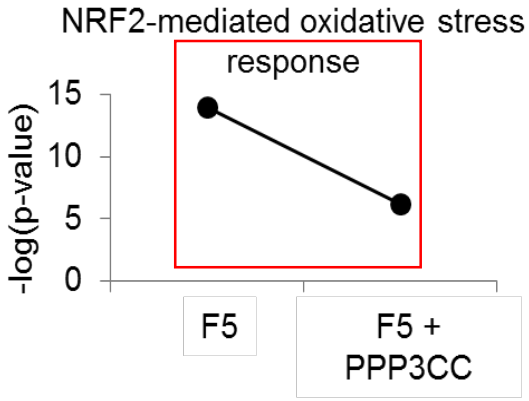
Transcriptome Profiling of Patient-Specific Human iPSC-Cardiomyocytes Predicts Individual Drug Safety and Efficacy Responses In Vitro

Elena Matsa,[1,2,3,*] Paul W. Burridge,[1,2,3,4,5] Kun-Hsing Yu,[6,7] John H. Ahrens,[1] Vittavat Termglinchan,[1,2,3] Haodi Wu,[1,2,3] Chun Liu,[1,2,3] Praveen Shukla,[1,2,3] Nazish Sayed,[1,2,3] Jared M. Churko,[1,2,3] Ningyi Shao,[1,2,3] Nicole A. Woo,[1] Alexander S. Chao,[1] Joseph D. Gold,[1] Ioannis Karakikes,[1,2] Michael P. Snyder,[6] and Joseph C. Wu[1,2,3,*]

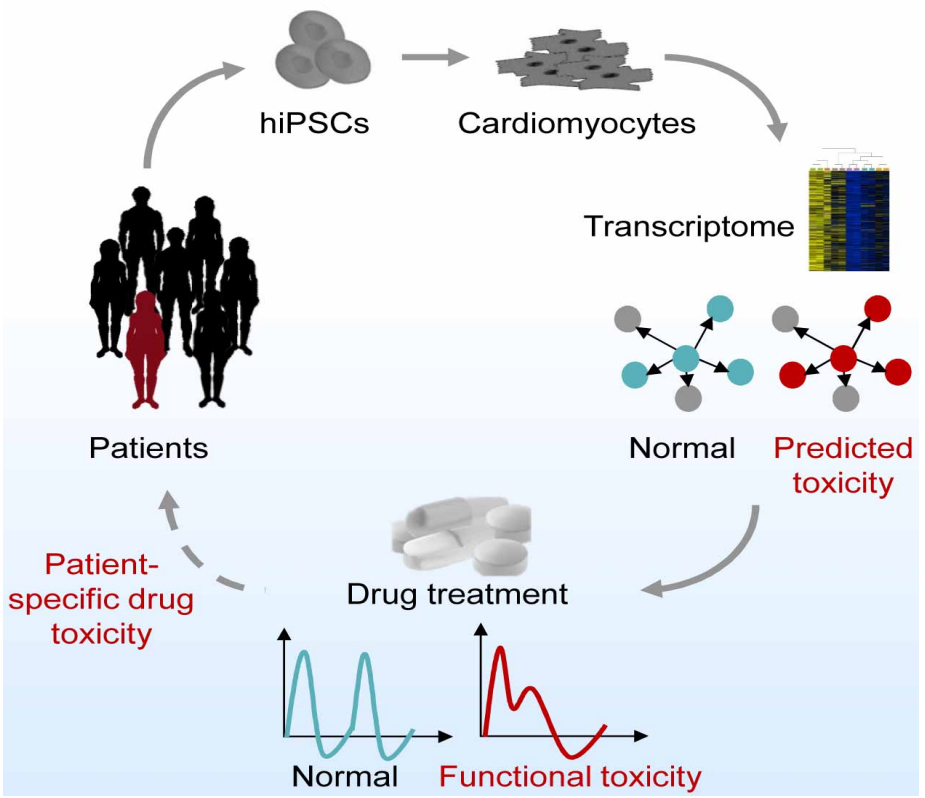
A Toxicology analysis



B CRISPR genome editing



C Prediction of drug responses



- Drug-induced cardiotoxicity (e.g., rosiglitazone & tacrolimus) can be functionally evaluated *in vitro* using iPSC-CMs and genome editing.
- Bioinformatics analysis can be used to predict and risk-stratify patient-specific drug response.

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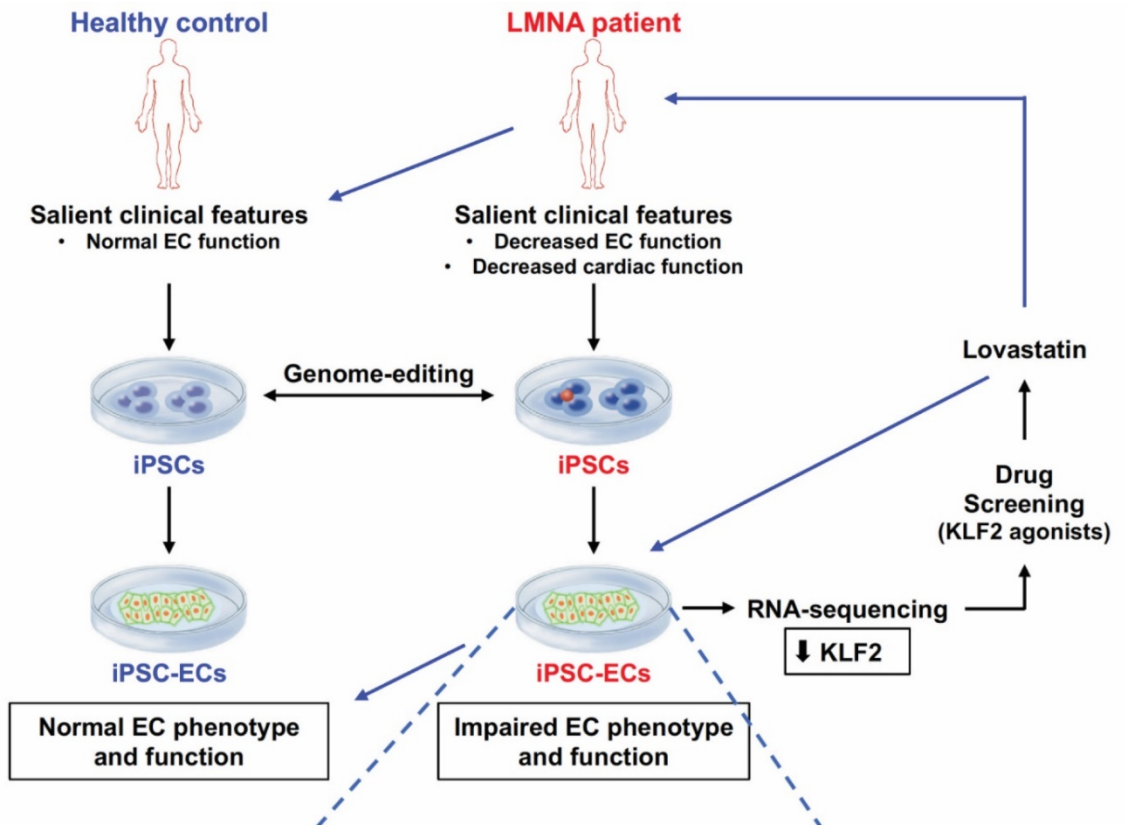
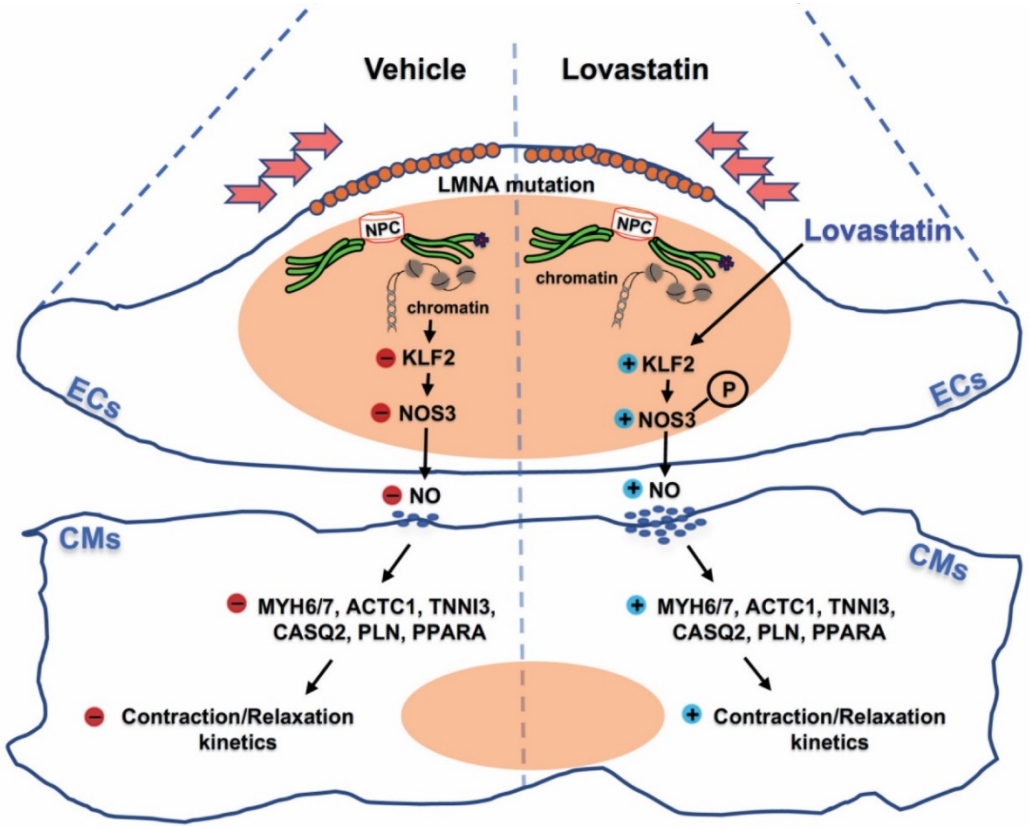
Cell Stem Cell 2016

Clinical trial in a dish using iPSCs shows lovastatin improves endothelial dysfunction and cellular cross-talk in LMNA cardiomyopathy

Nazish Sayed[1,2,3*†], Chun Liu[1,2,3*], Mohamed Ameen[1,2], Farhan Himmati[1,2], Joe Z. Zhang[1,2], Saereh Khanamiri[1,2], Jan-Renier Moonen[1,4,5], Alexa Wnorowski[1,6], Linling Cheng[1], June-Wha Rhee[1,2,3], Sadhana Gaddam[7], Kevin C. Wang[7], Karim Sallam[1,2,3], Jack H. Boyd[1,8], Y. Joseph Woo[1,8], Marlene Rabinovitch[1,4,5], Joseph C. Wu[1,2,3,9†]





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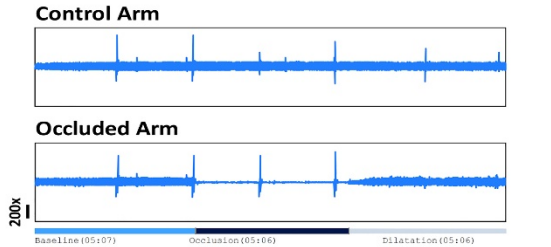
Sci Transl Med 2020

EndoPAT assesses digital flow-mediated dilation during reactive hyperemia using measurements from both arms – occluded side and control side.

RHI (Reactive Hyperemia Index) is the post-to-pre occlusion PAT™ signal ratio in the occluded side, normalized to the control side and further corrected for baseline vascular tone.
Normal: RHI > 1.67
Abnormal: RHI ≤ 1.67

A

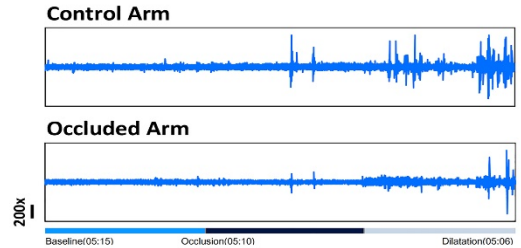
LMNA Pt. 2



RHI	Heart Rate	
0.48 ± 0.07	78 ± 7 bpm	Endothelial Dysfunction

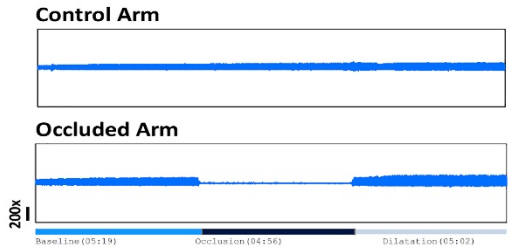
B

LMNA Pt. 3



RHI	Heart Rate	
0.61 ± 0.07	65 ± 6 bpm	Endothelial Dysfunction

LMNA Pt. 2 (Lovastatin, 6 months)

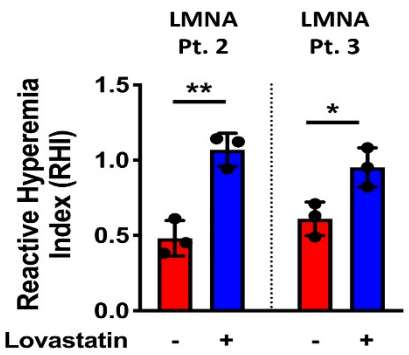


RHI	Heart Rate	
1.06 ± 0.06	61 ± 3 bpm	Improved Endothelial Function

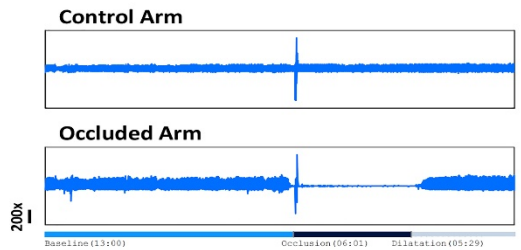
LMNA Pt. 3 (Lovastatin, 6 months)

RHI	Heart Rate	
0.95 ± 0.09	60 ± 11 bpm	Improved Endothelial Function

C



LMNA Pt. 3 (Lovastatin, 18 months)



RHI	Heart Rate	
1.50	85 bpm	Improved Endothelial Function

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Stanford Cardiovascular Institute iPSC Biobank: 1,000+ iPSC Lines to Accelerate Drug Discovery

1) A biorepository of >1,000 iPSC lines from patients with different CV history, ethnicity, sex, and also isogenic lines using CRISPR genome editing.

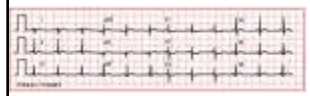
2) Perform multi-omics of human population using iPSC derivatives

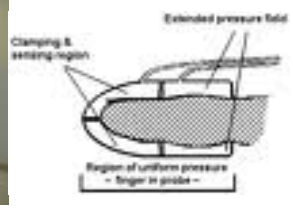
3) Use PharmGK (http://www.pharmgkb.org) to create a database on how human genetic variation impacts drug response phenotypes.

4) Link to medical information using clinical database *(STRIDE: Stanford Translational Research Integrated Database Environment)*

5) Working with the NIH on iPSC biobanking and with the FDA on drug safety testing.

6) Established robust sharing resource plan with many investigators.





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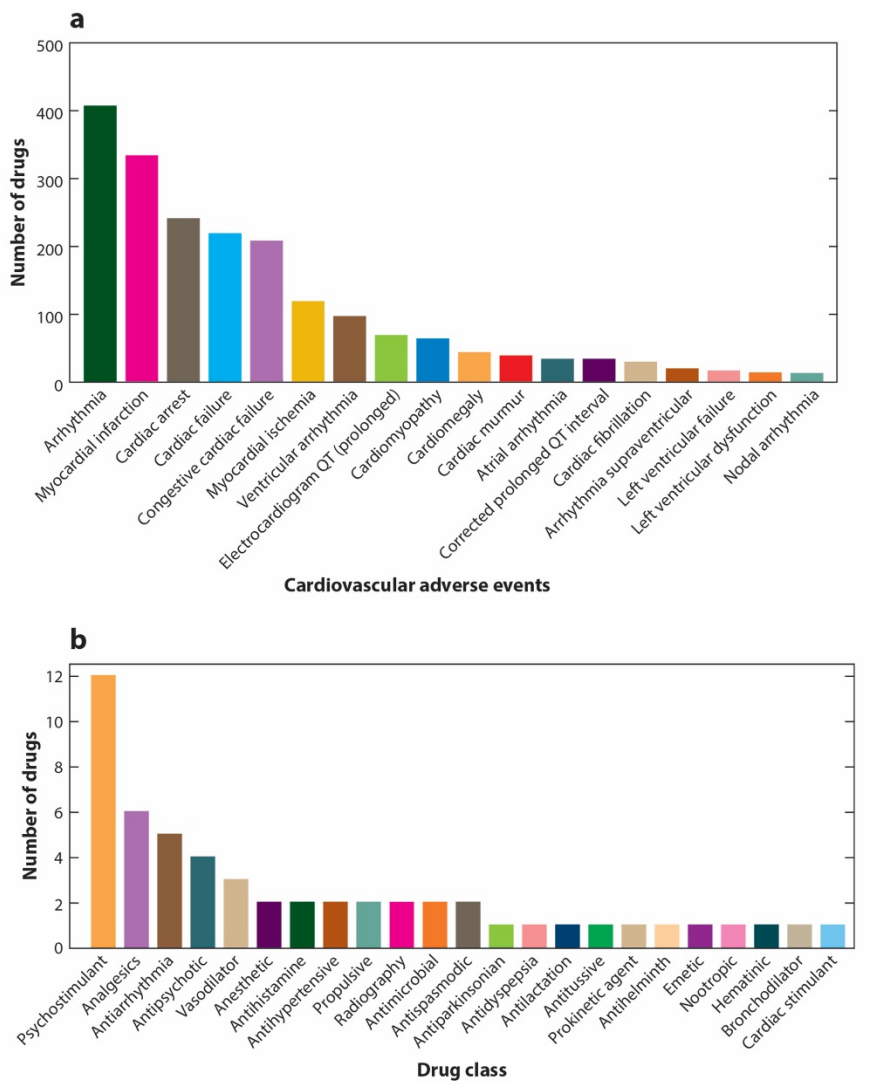
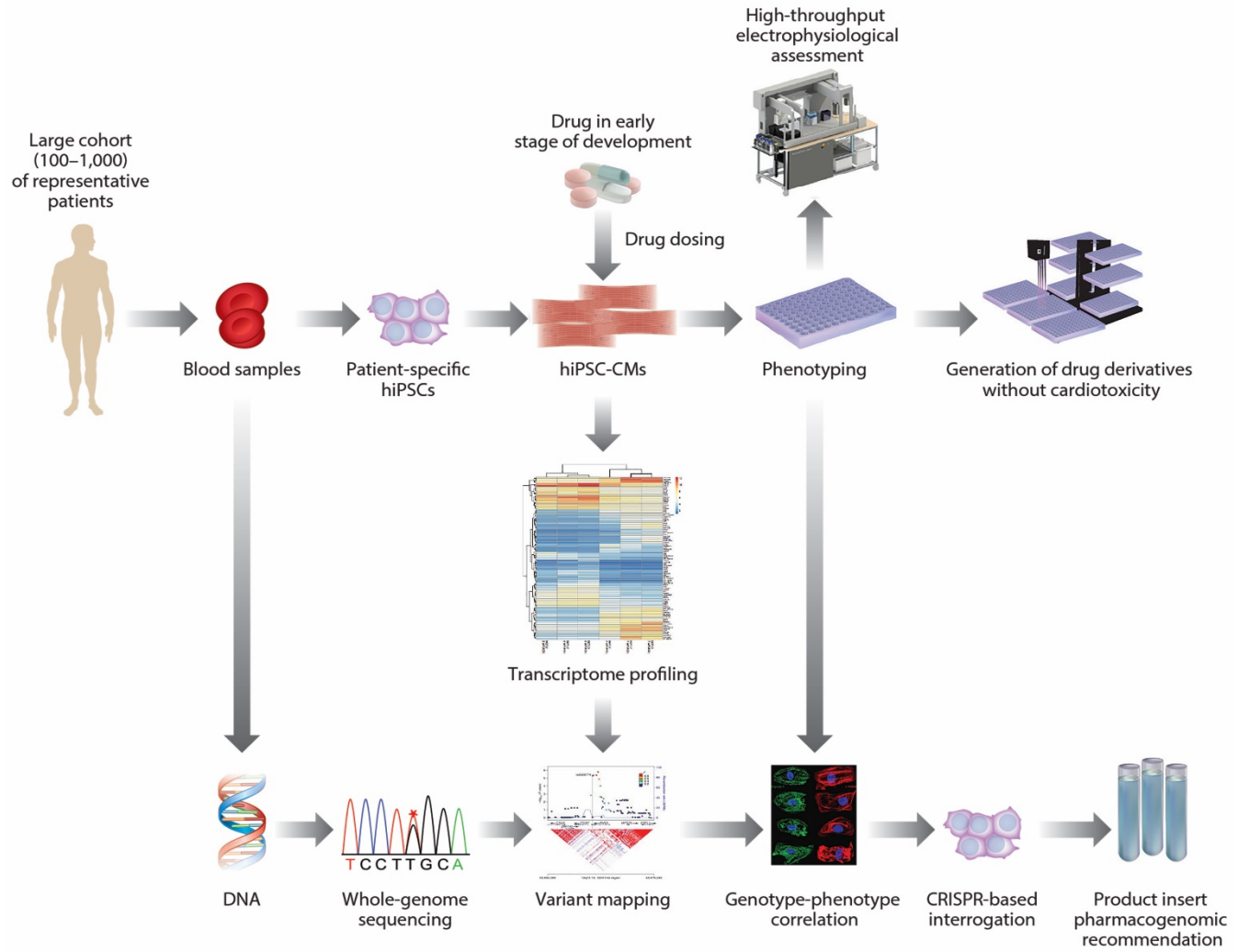
Potential Application of Large Cohort of Patient iPSCs as Alternative Toxicological Methods?





Magdy T et al. *Ann Rev Pharm & Tox* 2018

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