Human Stem Cells & Genomics for Precision Medicine

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2020 SACATM
Sept 3, 2020
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.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Grant/Research Support</td>
<td>• AztraZeneca, Astellas</td>
</tr>
<tr>
<td>• Consulting Fees/Honoraria</td>
<td>• Novartis, Merck, BMS</td>
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<td>• Scientific Advisory Board</td>
<td>• Juvena, LifeVault</td>
</tr>
<tr>
<td>• Co-founder</td>
<td>• Khloris Biosciences</td>
</tr>
</tbody>
</table>
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

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

- Genetic
  - HCM
  - DCM
  - Restrictive
  - ARVC/D
  - LVNC
  - Mitochondrial myopathies
  - Ion channel disorders (LQTS, Brugada)

- Acquired
  - Inflammatory (Myocarditis)
  - Stress-provoked (Takotsubo)
  - Peripartum
  - Tachycardia-induced
  - DCM
  - Restrictive

Secondary cardiomyopathies

- Infiltrative: Amyloidosis, Gaucher disease
- Storage: Hemochromatosis, Fabry disease, GSD II
- Toxicity: Drugs, radiation, heavy metals
- Endomyocardial: Endomyocardial fibrosis
- Inflammatory: Sarcoidosis
- Neuromuscular/Neurological: DMD, myotonic dystrophy, Friedreich ataxia
- Endocrine: DM, hyper/hypothyroidism, acromegaly, pheochromocytoma
- Nutritional deficiency: Beriberi, kwashiorkor
- Autoimmune: SLE, dermatomyositis, rheumatoid arthritis

Cardiac remodeling and heart failure

Other cardiovascular abnormalities

- Coronary artery disease
- Arterial hypertension
- Valvular disorders
- Congenital heart disease

(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. Wu1,2,3,10†

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.
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,9 Yoshinori Yamaguchi,10 Euan A. Ashley,1 Donald M. Bers,11 Robert C. Robbins,2,6 Michael T. Longaker,3,8 and Joseph C. Wu1,2,3,7

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.
Activation of PDGF pathway links LMNA mutation to dilated cardiomyopathy


Stanford Cardiovascular Institute

Nature 2019
Multi-Omics of Human Population Using iPSC Lines

1. Population of iPSC donors
   - Individual genotypes in population of interest
   - Individual phenotypes and clinical traits (e.g., ethnicity, body mass index, cardiac events)

2. Reprogram to iPSCs
   - Individual differences preserved in genotypes and gene expressions
   - Variations from culture conditions and reprogramming methods

3. Directed differentiation
   - Epigenetic and proteomic profiles from individuals are tested in relevant cell types
   - Provides live cell materials for functional and imaging studies

4a. Measuring cellular phenotypes
   - Excitable cells: Ca²⁺ handling, Action potential
   - Vasculature: Nitric oxide release, Proliferation and migration

4b. Measuring molecular phenotypes
   - Epigenome: Chromatin accessibility, DNA methylation, Chromatin structure
   - Transcriptome: Bulk RNA expression, Single-cell RNA expression
   - Proteome: Protein expression, Modification, structure, localization, turnover
   - Metabolome: Metabolite abundance, Metabolite flux

5. Analyze omics and functional data and identify molecular changes

1. Acquire expression profile in iPSC panels

2a. Regulatory relationships via expression quantitative trait loci
   - Expression of gene G₁
   - Expression by genotype
   - Association of genome-wide loci by expression

2b. Regulatory relationships via coexpression networks
   - Calculate correlation
   - Graphical model

Lau E et al. Annu Rev Pathol Mech Dis 2019
(2) Cardio-Oncology: Personalized iPSC for Assessing Chemotherapy-Induced Cardiotoxicity?

Leading Causes of Death

- Heart disease continues to kill more Americans than any other cause, followed by stroke at No. 5, according to 2015 federal data.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Total Deaths</th>
<th>Share of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>633,842</td>
<td>23.4%</td>
</tr>
<tr>
<td>Cancer</td>
<td>595,930</td>
<td>22%</td>
</tr>
<tr>
<td>Chronic lower respiratory diseases</td>
<td>155,041</td>
<td>5.7%</td>
</tr>
<tr>
<td>Accidents</td>
<td>146,571</td>
<td>5.4%</td>
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<tr>
<td>Stroke</td>
<td>140,323</td>
<td>5.2%</td>
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<tr>
<td>Alzheimer’s disease</td>
<td>110,561</td>
<td>4.1%</td>
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<tr>
<td>Diabetes</td>
<td>79,533</td>
<td>2.9%</td>
</tr>
<tr>
<td>Flu, pneumonia</td>
<td>57,062</td>
<td>2.1%</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>49,959</td>
<td>1.8%</td>
</tr>
<tr>
<td>Suicide</td>
<td>44,193</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention

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 Burridge¹⁻⁵, Yong Fuga Li⁶,⁷, Elena Matsa¹⁻³, Haodi Wu¹⁻³, Sang-Ging Ong¹⁻³, Arun Sharma¹⁻³, Alexandra Holmström¹⁻³, Alex C Chang¹,²,⁸, Michael J Coronado⁹, Antje D Ebert¹⁻³, Joshua W Knowles¹,³, Melinda L Telli¹⁰, Ronald M Witteles¹,³, Helen M Blau¹,²,⁸, Daniel Bernstein¹,⁹, Russ B Altman⁷,¹¹ & Joseph C Wu

Breast cancer diagnosis and treatment with doxorubicin

1 year

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.

<table>
<thead>
<tr>
<th>Line code</th>
<th>Patient #</th>
<th>Sex</th>
<th>Age</th>
<th>Treatment</th>
<th>Pre LVEF (%)</th>
<th>Post LVEF (%)</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy1</td>
<td>62</td>
<td>F</td>
<td>57</td>
<td>None</td>
<td>67</td>
<td>NA</td>
<td>29.1</td>
</tr>
<tr>
<td>Healthy2</td>
<td>72</td>
<td>F</td>
<td>45</td>
<td>None</td>
<td>61</td>
<td>NA</td>
<td>25.2</td>
</tr>
<tr>
<td>Healthy3</td>
<td>78</td>
<td>F</td>
<td>64</td>
<td>None</td>
<td>55</td>
<td>NA</td>
<td>22.7</td>
</tr>
<tr>
<td>Healthy4</td>
<td>202</td>
<td>F</td>
<td>30</td>
<td>None</td>
<td>71</td>
<td>NA</td>
<td>24.5</td>
</tr>
<tr>
<td>DOX1</td>
<td>59</td>
<td>F</td>
<td>59</td>
<td>4 cycles 2000 mg/m² epirubicin + cyclophosphamide then trastuzumab + docetaxel</td>
<td>80</td>
<td>71-77</td>
<td>27.2</td>
</tr>
<tr>
<td>DOX2</td>
<td>60</td>
<td>F</td>
<td>66</td>
<td>4 cycles 240 mg/m² doxorubicin + cyclophosphamide then trastuzumab + docetaxel</td>
<td>60</td>
<td>62-70</td>
<td>27.6</td>
</tr>
<tr>
<td>DOX3</td>
<td>64</td>
<td>F</td>
<td>52</td>
<td>4 cycles 240 mg/m² doxorubicin + cyclophosphamide then trastuzumab + docetaxel</td>
<td>58</td>
<td>56-58</td>
<td>25.3</td>
</tr>
<tr>
<td>DOX4</td>
<td>65</td>
<td>F</td>
<td>66</td>
<td>4 cycles 240 mg/m² doxorubicin + cyclophosphamide then trastuzumab + docetaxel</td>
<td>68</td>
<td>62-70</td>
<td>33.8</td>
</tr>
<tr>
<td>DOXTOX1</td>
<td>31</td>
<td>F</td>
<td>40</td>
<td>4 cycles 240 mg/m² doxorubicin + cyclophosphamide</td>
<td>77</td>
<td>36-50</td>
<td>28.2</td>
</tr>
<tr>
<td>DOXTOX2</td>
<td>40</td>
<td>F</td>
<td>66</td>
<td>3 cycles 240 mg/m² doxorubicin + cyclophosphamide</td>
<td>67</td>
<td>10-57</td>
<td>28.6</td>
</tr>
<tr>
<td>DOXTOX3</td>
<td>51</td>
<td>F</td>
<td>52</td>
<td>4 cycles 240 mg/m² doxorubicin + cyclophosphamide</td>
<td>62</td>
<td>44-55</td>
<td>26</td>
</tr>
<tr>
<td>DOXTOX4</td>
<td>79</td>
<td>F</td>
<td>31</td>
<td>4 cycles 240 mg/m² doxorubicin + cyclophosphamide</td>
<td>70</td>
<td>45-49</td>
<td>26.4</td>
</tr>
</tbody>
</table>
Human-Induced Pluripotent Stem Cell Model of Trastuzumab-Induced Cardiac Dysfunction in Patients With Breast Cancer

A. Patients treated with TRZ
   - Non-toxic: No side effect, EF decline <20%
   - Moderately toxic: EF decline 20% – 40%
   - Severe toxic: EF decline ≥40%

B. Generation of severely toxic patient iPSC-CMs
   - 7-day TRZ treatment with AMPK activators
   - Measuring contraction velocity and cell viability

C. Patient-Specific iPSC-CMs
   - SP 1: 35, 57, F, Yes, 1 mo
   - SP 2: 21, 48, F, Yes, 1 mo
   - SP 3: 21, 42, F, Yes, 2 mo
   - MP 1: 12, 64, F, Yes, 4 mo
   - MP 2: 14, 76, F, Yes, 3 mo
   - NP 1: - , 52, F, -, >1 yr
   - NP 2: - , 66, F, -, >2 yr

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 Alamo,7 Sean M. Wu,1,2,3 Javid J. Moslehi,9 Mark Mercola,1,3,5 Joseph C. Wu1,2,3†

Tyrosine Kinase Inhibitors

Drug Cessation of Beating (µM) Concentration (µM) Amplitude of Effect LD50 (µM) Cmax (µM) Cardiac Safety Index Clinically-Reported Cardiotoxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cessation of Beating (µM)</th>
<th>Concentration (µM)</th>
<th>Amplitude of Effect</th>
<th>LD50 (µM)</th>
<th>Cmax (µM)</th>
<th>Cardiac Safety Index</th>
<th>Clinically-Reported Cardiotoxicity</th>
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</thead>
<tbody>
<tr>
<td>Vemurafenib</td>
<td>33</td>
<td>11.00</td>
<td>0.34</td>
<td>32.10</td>
<td>126.04</td>
<td>0.003</td>
<td>QT</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>3.7</td>
<td>2.51</td>
<td>1.03</td>
<td>3.40</td>
<td>8.43</td>
<td>0.004</td>
<td>QT, LV, HF, MI, Hy</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>3.7</td>
<td>1.20</td>
<td>0.60</td>
<td>0.78</td>
<td>2.93</td>
<td>0.010</td>
<td>**HF, LV</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>11</td>
<td>3.70</td>
<td>0.84</td>
<td>7.10</td>
<td>8.08</td>
<td>0.010</td>
<td>#MI, Hy</td>
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<tr>
<td>Vandetanib</td>
<td>33</td>
<td>5.68</td>
<td>2.47</td>
<td>20.60</td>
<td>4.26</td>
<td>0.041</td>
<td>**QT, TdP, SCD, HF, Hy</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>11</td>
<td>1.91</td>
<td>0.59</td>
<td>3.80</td>
<td>1.24</td>
<td>0.083</td>
<td>QT, Brady</td>
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<tr>
<td>Nilotinib</td>
<td>100</td>
<td>8.51</td>
<td>2.85</td>
<td>29.00</td>
<td>4.27</td>
<td>0.104</td>
<td>**QT, LV, Vas</td>
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<tr>
<td>Imatinib</td>
<td>100</td>
<td>33.00</td>
<td>1.59</td>
<td>78.20</td>
<td>5.11</td>
<td>0.126</td>
<td>LV (rare)</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>33</td>
<td>11.00</td>
<td>0.40</td>
<td>100.76</td>
<td>2.30</td>
<td>0.209</td>
<td>#LV, QT</td>
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<tr>
<td>Sunitinib</td>
<td>3.7</td>
<td>0.81</td>
<td>1.33</td>
<td>12.70</td>
<td>0.18</td>
<td>0.218</td>
<td>#HF, LV, MI, QT, Hy</td>
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<tr>
<td>Bosutinib</td>
<td>33</td>
<td>4.73</td>
<td>1.92</td>
<td>12.39</td>
<td>0.51</td>
<td>0.315</td>
<td>PE</td>
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<td>Gefitinib</td>
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<td>3.11</td>
<td>1.24</td>
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<td>0.409</td>
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<td>Aftinib</td>
<td>3.7</td>
<td>1.65</td>
<td>1.11</td>
<td>12.30</td>
<td>0.10</td>
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<td>Dabrafenib</td>
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<td>Ponatinib</td>
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<td>3.70</td>
<td>0.54</td>
<td>4.30</td>
<td>0.14</td>
<td>0.483</td>
<td>**Vas, HF, LV</td>
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<td>Brinobin</td>
<td>33</td>
<td>10.01</td>
<td>1.54</td>
<td>11.90</td>
<td>0.37</td>
<td>0.507</td>
<td>AfiB</td>
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<tr>
<td>Dasatinib</td>
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<td>1.20</td>
<td>0.31</td>
<td>42.00</td>
<td>0.21</td>
<td>0.524</td>
<td>QT, PE, Hy</td>
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<td>Erlotinib</td>
<td>N/A</td>
<td>63.38</td>
<td>0.51</td>
<td>87.60</td>
<td>3.11</td>
<td>0.653</td>
<td>MI (Rare)</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>N/A</td>
<td>73.86</td>
<td>1.19</td>
<td>N/A</td>
<td>103.08</td>
<td>0.671</td>
<td>#QT, LV (Rare)</td>
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<tr>
<td>Cabozantinib</td>
<td>N/A</td>
<td>91.14</td>
<td>1.37</td>
<td>N/A</td>
<td>4.43</td>
<td>0.769</td>
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<tr>
<td>Trametinib</td>
<td>100</td>
<td>33.00</td>
<td>2.37</td>
<td>66.80</td>
<td>0.02</td>
<td>1.000</td>
<td>LV</td>
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<tr>
<td>Axitinib</td>
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<td>71.79</td>
<td>0.44</td>
<td>N/A</td>
<td>0.07</td>
<td>1.000</td>
<td>HF (Rare), Hy</td>
</tr>
<tr>
<td>DMSO</td>
<td>N/A</td>
<td>100.00</td>
<td>0.58</td>
<td>N/A</td>
<td>N/A</td>
<td>1.000</td>
<td>None</td>
</tr>
</tbody>
</table>

A: Blood Sample, PBMC Isolation
B: “Cardiac Safety Index”
iPSC-CM Platform for Assessing Cardiac Safety Index

Sharma A et al, *Nat Protocol* 2018
(3) “Clinical Trial in a Dish”

Drug Screening & Testing using iPSCs “Clinical Trial on a Dish”
- Reduced Trial-and-Error
- Accurate Genotype-to-Phenotype Correlation
- Optimized Patient Selection for Clinical Trials
- Reduction of Healthcare Cost

Informed Feedback to Patients (Precision Medicine)
- Responders
- Non-Responders

Functional Characterization
- Contractility & Relaxation
- Calcium Handling
- Electrophysiology
- Metabolic Function
- Morphology
- Extracellular Matrix Secretion

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

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.

Authors
Ksenia Blinova, Qianyu Dang, Daniel Millard, ..., Norman Stockbridge, David G. Strauss, Gary Gintant

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

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NRF2-mediated oxidative stress

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

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Salient clinical features
- Decreased EC function
- Decreased cardiac function

Lovastatin
- Improves endothelial dysfunction
- Improves cellular cross-talk

LMNA patient
- Normal EC function
- Decreased EC function
- Decreased cardiac function

Healthy control
- Normal EC function
- Normal cardiac function

iPSCs
- Genome-editing
- Drug screening
- RNA-sequencing

iPSC-ECs
- Normal EC phenotype and function
- Impaired EC phenotype and function

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

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