AI in Medicine
~Recent Progress in iPS Cell Research and Application~

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Gladstone Institute of Cardiovascular Disease, San Francisco
Takeda - CiRA Joint Program, Shonan, Japan
Generation of iPS cells

Oct3/4  Sox2  Klf4  c-Myc

Skin cells

iPS Cells
(induced Pluripotent Stem cells)

Human 2007
Mouse 2006

Human 2007  Mouse 2006

Skin cells
Applications of iPS cells

Skin cells
Blood cells

iPS cells

Neurons
Heart cells
Muscle cells
Hepatic cells

Regenerative Medicine
Drug Development
Autologous Induced Stem-Cell–Derived Retinal Cells for Macular Degeneration

No rejection
No tumors
Vision: stabilized
Autologous iPS Cells

iPS cells

Differentiated cells

Sample collection

Quality check

Quality check

Transplantation

Autograft: Too expensive and time-consuming

iPS Cell Stock for Regenerative Medicine
HLA Homozygous “Super” Donors

To reduce the cost & time of autologous iPSC
iPS Cell Stock for Regenerative Medicine

Japanese Red Cross Society

Platelet / Bone Marrow Donors

Informed Consent & Blood Sampling

"HLA Super Donors"

7 donors
(Top 4 frequent HLA haplotypes among Japanese)
- Covering ~40% of Japanese population

Cord Blood Banks

Cell Processing Facility at CiRA

Clinical-grade iPS Cells

Quality Check

Stock

Distribution started from 2015
Center for iPS Cell Research and Application (CiRA)

Goal: To realize medical applications of iPS Cells

Started in April, 2010

14 Cell Processing Rooms
Clinical Application Using iPS Cell Stock

**Clinical Research**

- **Masayo Takahashi Lab. (RIKEN)**
  Age-related Macular Degeneration

- **Kohji Nishida Lab. (Osaka Univ.)**
  Cornea Epithelial Stem Cell Exhaustion

**Clinical Trial**

- **Jun Takahashi Lab. (CiRA)**
  Parkinson’s Disease

- **Yoshiki Sawa Lab. (Osaka Univ.)**
  Ischemic cardiomyopathy
Clinical Application Using iPS Cell Stock

Approved by MHLW

Hideyuki Okano Lab. (Keio Univ.)
Spinal Cord Injury

Noriyuki Tsumaki Lab. (CiRA)
Articular Cartilage Injury

Keiichi Fukuda Lab. (Keio Univ.)
Dilated cardiomyopathy

Osaka Univ.
Retinitis Pigmentosa
Regenerative Medicine Using iPS Cell Stock

- Neurons
- Retinal cells
- Corneal cells
- Platelets
- Heart Muscle cells
- Neural stem cells
- Liver cells
- Pancreatic cells
- Kidney cells
- Immune cells
- Cartilage

Applications:
- Parkinson’s Disease
- Macular degeneration
- Retinitis pigmentosa
- Corneal disorder
- Blood transfusion
- Ischemic cardiomyopathy
- Dilated cardiomyopathy
- Spinal cord injury
- Liver failure
- Type 1 Diabetes
- Renal failure
- Leukemia, Cancer
- Arthritic disorder

Clinical Study:
- Ongoing
- Approved
- Planned
How about the remaining 60%?

- 150 haplotypes would cover ~90% of Japanese population
- >1000 haplotypes would be required to cover most of the world population

Being distributed

- Top 4 frequent HLA haplotypes among Japanese:
  Covering ~40% of Japanese population

iPS Cell Stock for Regenerative Medicine
Alternative Approach ~ HLA-C Only

Class II MHC

Class I MHC

HLA-DP  HLA-DQ  HLA-DR

HLA-DP  HLA-DQ  HLA-DR

HLA-B  HLA-C  HLA-A

C2TA co-activator
(Essential for class II MHC expression)

Chr.6

Chr.16

Junior Associate Prof. Akitsu Hotta (CiRA)
<table>
<thead>
<tr>
<th></th>
<th>Current</th>
<th>Alternative (2020～)</th>
<th>Ultimate (2025～)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Super Donor</strong></td>
<td>Super Donor iPS Cell Stock</td>
<td>Genome-Editing iPS Cell Stock</td>
<td>My iPS Cells</td>
</tr>
<tr>
<td><strong>Cell Stock</strong></td>
<td>4 Types: Covering ~40% of Japanese population</td>
<td>10 lines would cover most of world population</td>
<td></td>
</tr>
</tbody>
</table>
Applications of iPS cells

Skin cells
Blood cells

iPS cells

Neurons
Heart cells
Muscle cells
Hepatic cells

Regenerative Medicine

Drug Development
iPS Cell Bank for Drug Discovery

10 diseases, 690 individuals, including 517 controls

231 diseases, 410 individuals, including 74 controls

EBiSC (EU)
NYSCF NIH
CIRM

19 diseases, 345 individuals, including 216 controls

CiRA/BRC (Japan)

63 diseases, 1195 individuals, including 199 controls

10 diseases, 690 individuals, including 517 controls

As of March, 2018

Assoc. Prof. M Saito (CiRA)
Drug Repurposing with Patient iPSCs

Two clinical trials are ongoing at Kyoto University Hospital

Ramamycin for FOP
(Fibrodysplasia Ossificans Progressiva)

Prof. Toguchida, Assoc. Prof. Ikeya (CiRA)

Bostinib for ALS
(Amyotrophic lateral sclerosis)

Prof. H Inoue (CiRA)
Applications of iPS cells

- Parkinson’s Disease
- Macular degeneration
- Corneal disorder
- Heart failure
- Spinal cord injury
- Platelet transfusion
- Type 1 Diabetes
- Leukemia, Cancer
- Arthritic disorder
- Alzheimer’s disease
- Pendred Syndrome
- ALS (2 trials)
- Fibrodysplasia Ossificans Progressiva (FOP)

On going  Approved  Planning

Regenerative Medicine

Drug Development
A trained neural network by multi-hierarchical data predicts iPSC properties.

**Good iPS cells**

Splicing patterns

Gene expression

Epigenetic states

**Bad iPS cells**

Splicing patterns

Gene expression

Epigenetic states

Untrained

Trained

iPS cells

Good

Bad
## Strategy for Epigenetic “identity” using AI

<table>
<thead>
<tr>
<th>Source</th>
<th>Recipe</th>
<th>Immuno-suppression</th>
<th>Culture condition</th>
<th>Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord blood</td>
<td>factors (OSKM etc.)</td>
<td>HLA homo</td>
<td>Temperature X Supplements X Hypoxic</td>
<td></td>
</tr>
<tr>
<td>PBMC (T-cell, B-cell, monocyte etc.)</td>
<td>vector X ncRNA X small molecules</td>
<td>Autologous engineered scATAC scRNA ATAC-seq RNA-seq Methylation</td>
<td>mesoderm endo derm ecto derm</td>
<td></td>
</tr>
<tr>
<td>fibroblast</td>
<td></td>
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</tbody>
</table>

**AI/Machine Learning Topological Data Analysis (powerful method for high dimensional data)**
Drug discovery using patient iPSCs and AI

Hit prediction from 2,000,000 compounds using AI based on iPSC screen data

- Hit prediction
- Extraction of predicted 5,000 active compounds
- Verification using patient iPSCs
- Prediction by AI
- Confirmation of the efficiency using patient iPSC panel

Screening using patient iPSCs
- Hit compound
- Predicted active
- Predicted inactive compound

Successful drug discovery
- New chemotypes
- Potent efficacy
- Broad-spectrum for various patients
Development of Precision Toxicology

New drug/chemical/food

(my) iPS cells

Prediction of Toxicity Target Organs

High Accuracy (95–100%) for Neurotoxins, Nephrotoxins, Hepatotoxicity, Carcinogens, etc.

Machine Learning + Genetic Networks

Stem Cell-based Chemical Risk Information Sharing Consortium (scChemRISC)

Gene Expression Database for 1,000 Chemicals

RNA-seq

Exposure to hESCs

Food

Chemical

Pharmaceutical

(aspirin, bisphenol-A, catechin)

(catechin, bisphenol-A, aspirin)

Thank you for your attention!