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



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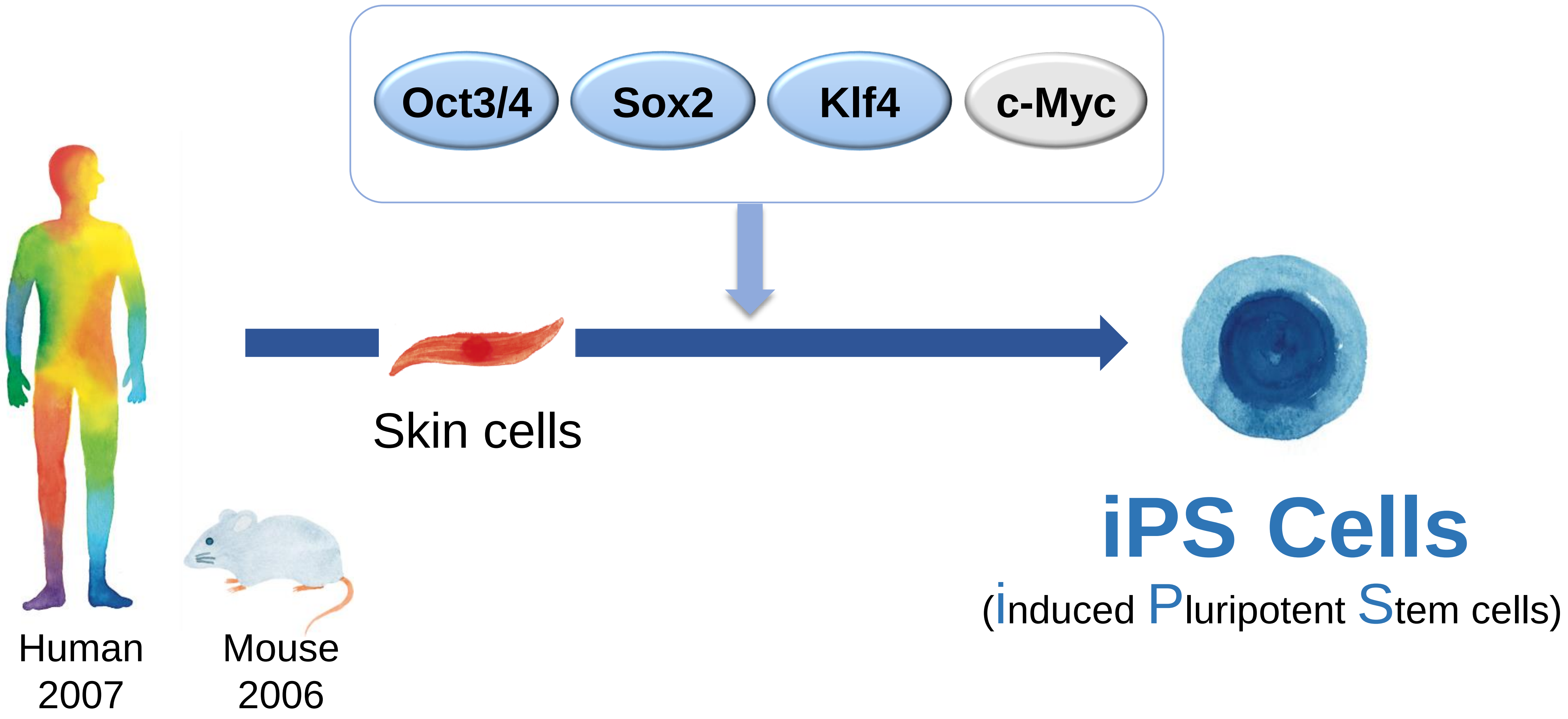
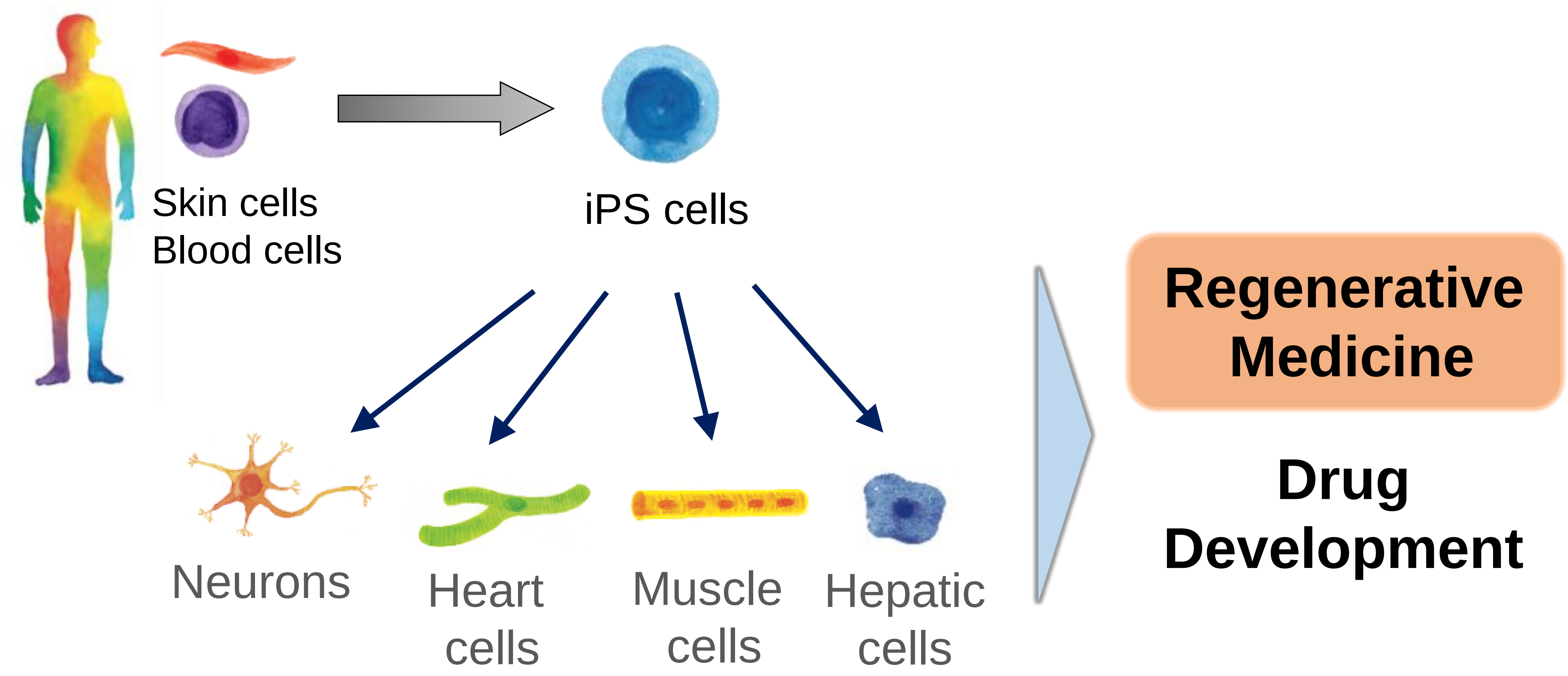
Center for iPS Cell Research and Application (CiRA), Kyoto University, Japan
Gladstone Institute of Cardiovascular Disease, San Francisco
Takeda - CiRA Joint Program, Shonan, Japan

Generation of iPS cells

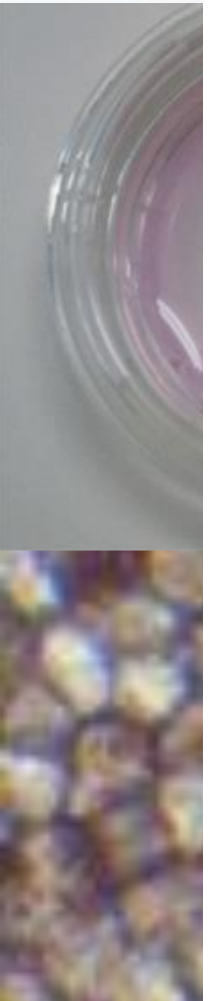


Applications of iPS cells



iPS Cell-Based Cell Therapy For Age-related Macular Degeneration (2014)

Retir



(Photo by F

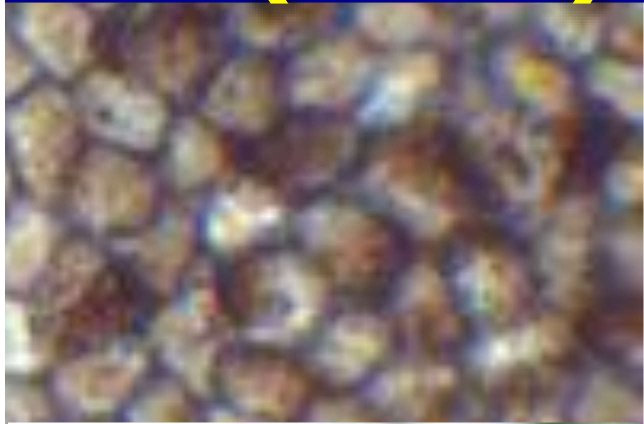
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Autologous Induced Stem-Cell–Derived Retinal Cells for Macular Degeneration

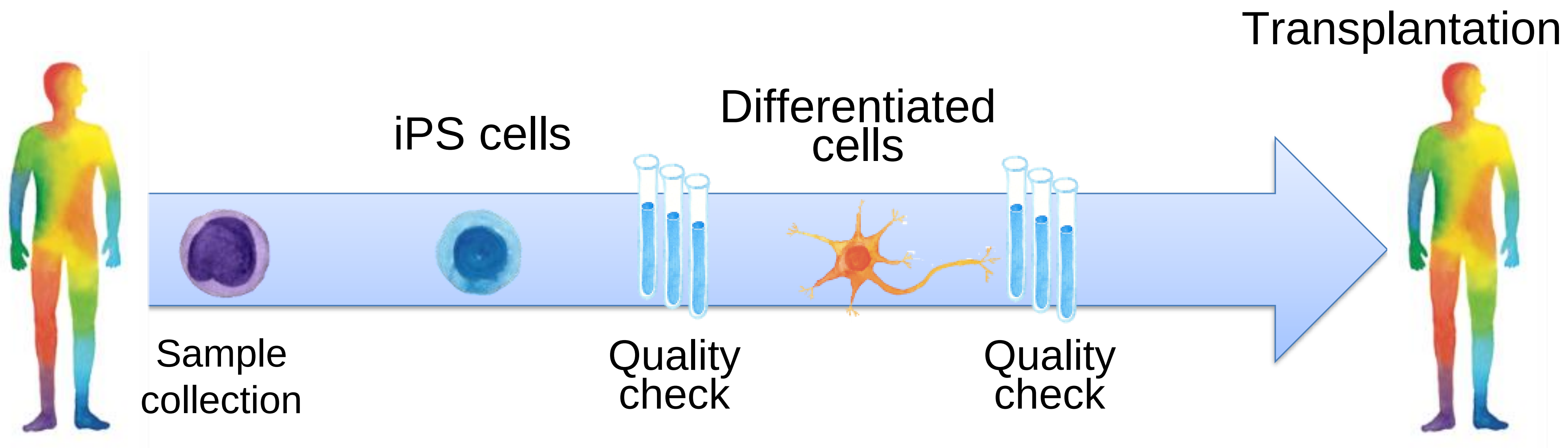
M. Man
M. F
S. Tanish
S. Kawamat
Y. Ohara, K
A. Tanak

No rejection
No tumors
Vision: stabilized



Dr. Masayo Takahashi
（RIKEN, BDR）

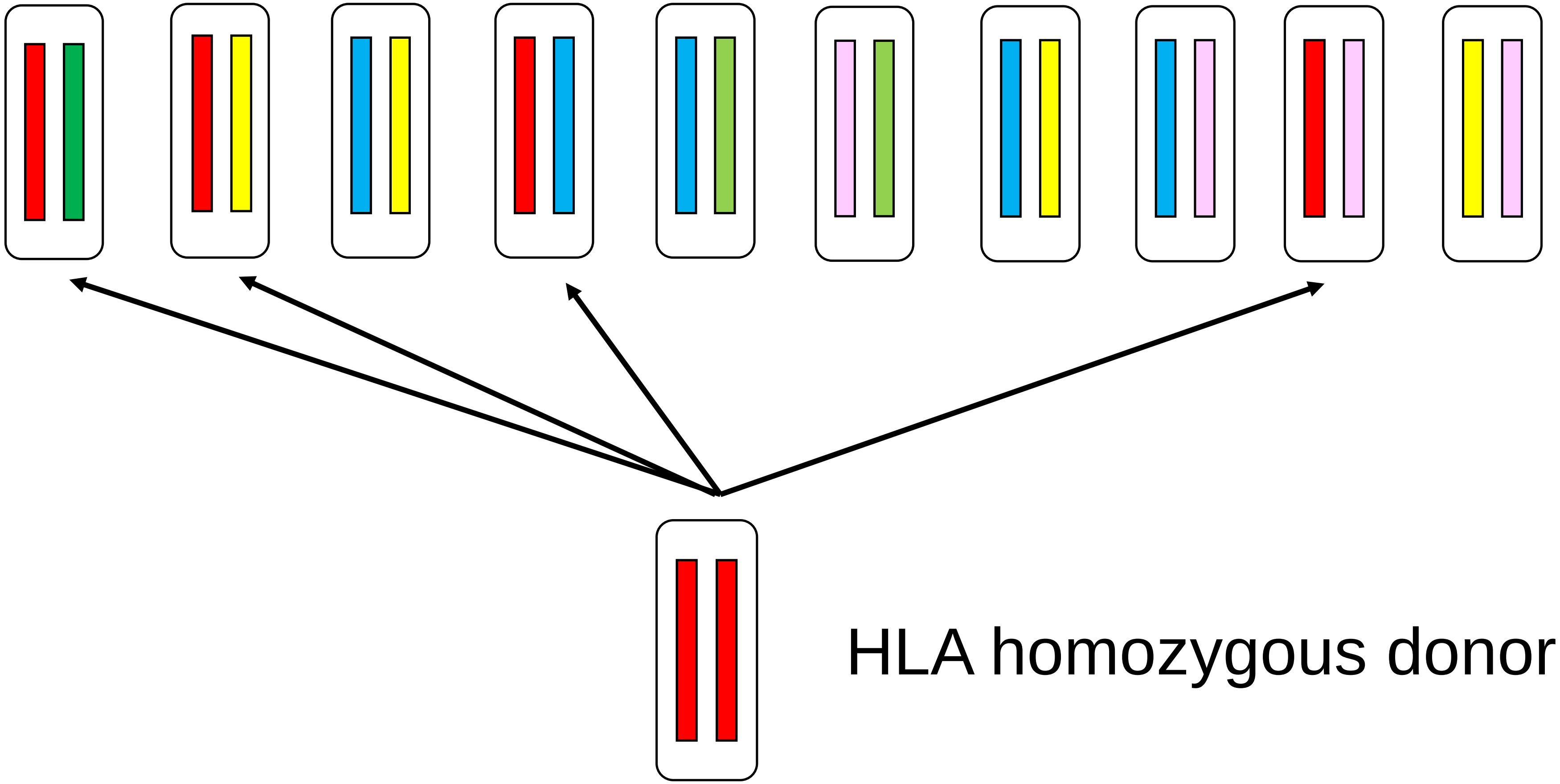
Autologous iPS Cells



Autograft: Too expensive and time-consuming

iPS Cell Stock for Regenerative Medicine

HLA Homozygous “Super” Donors



HLA homozygous donor

<u>To reduce the cost & time of autologous iPSC</u>

iPS Cell Stock for Regenerative Medicine

Japanese Red Cross Society

日本赤十字社

Platelet / Bone Marrow Donors

Informed Consent & Blood Sampling

Cell Processing Facility at CiRA

Clinical-grade iPS Cells → Quality Check → Stock

"HLA Super Donors"

Cord Blood Banks

Informed Consent

Distribution started from 2015

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

Center for iPS Cell Research and Application (CiRA)

Goal: To realize medical applications of iPS Cells

CiRA

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

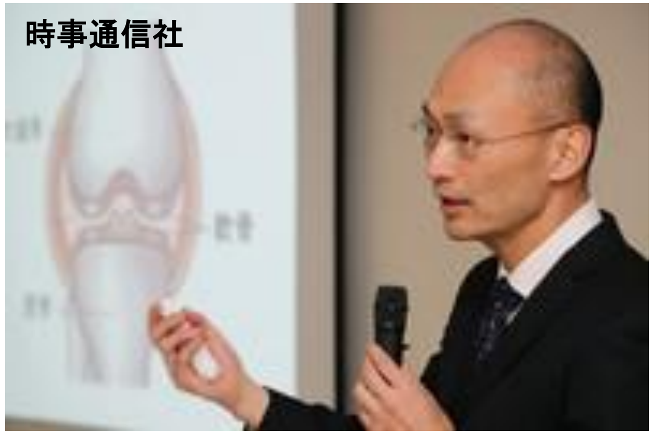
Yoshiki Sawa Lab. (Osaka Univ.)

Ischemic cardiomyopathy

Clinical Application Using iPS Cell Stock

Approved by MHLW

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



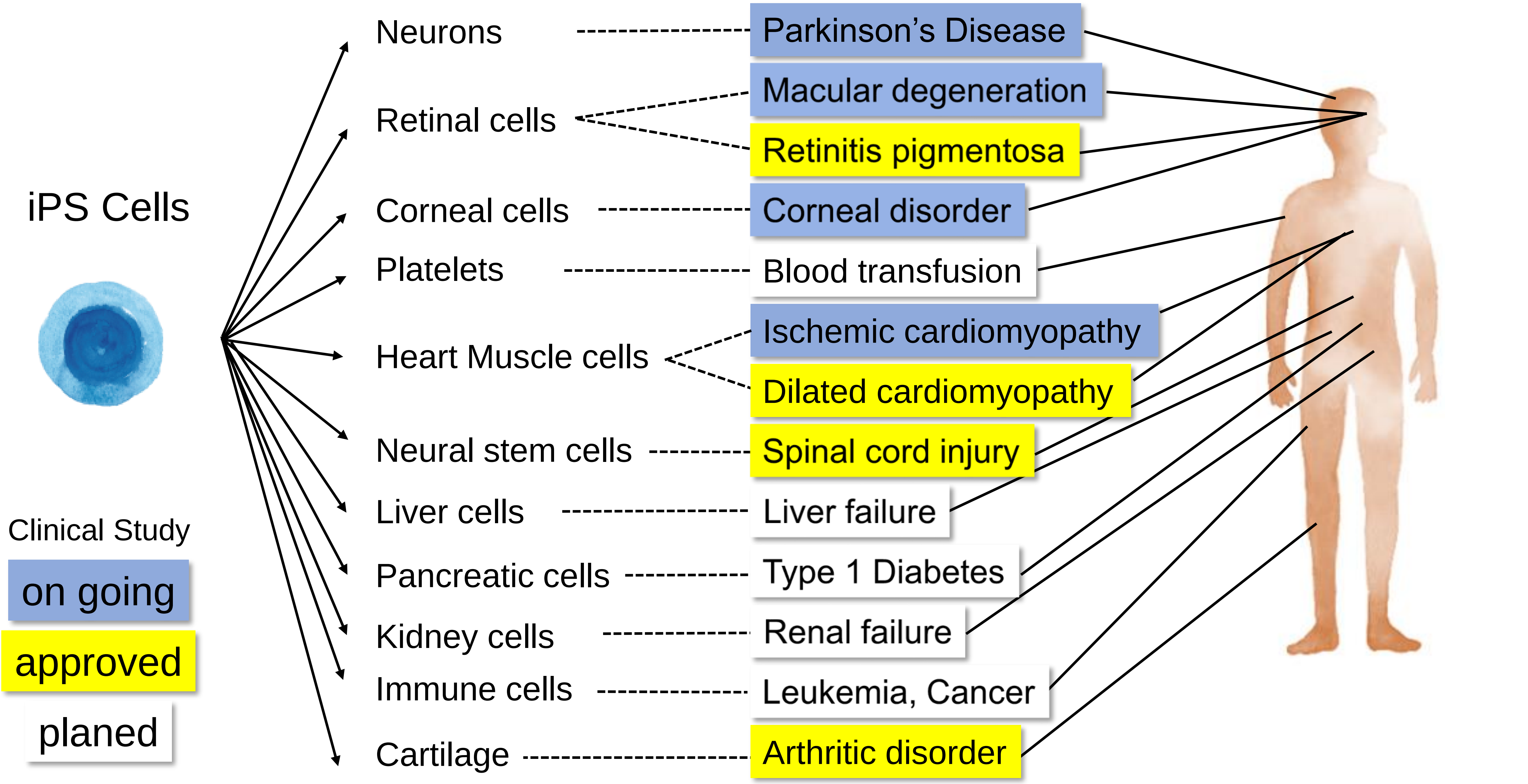
Noriyuki Tsumaki Lab. (CiRA)
Articular Cartilage Injury

University approved

Osaka Univ.
Retinitis Pigmentosa

Keiichi Fukuda Lab. (Keio Univ.)
Dilated cardiomyopathy

Regenerative Medicine Using iPS Cell Stock



iPS Cell Stock for Regenerative Medicine

Being distributed

- Top 4 frequent HLA haplotypes among Japanese

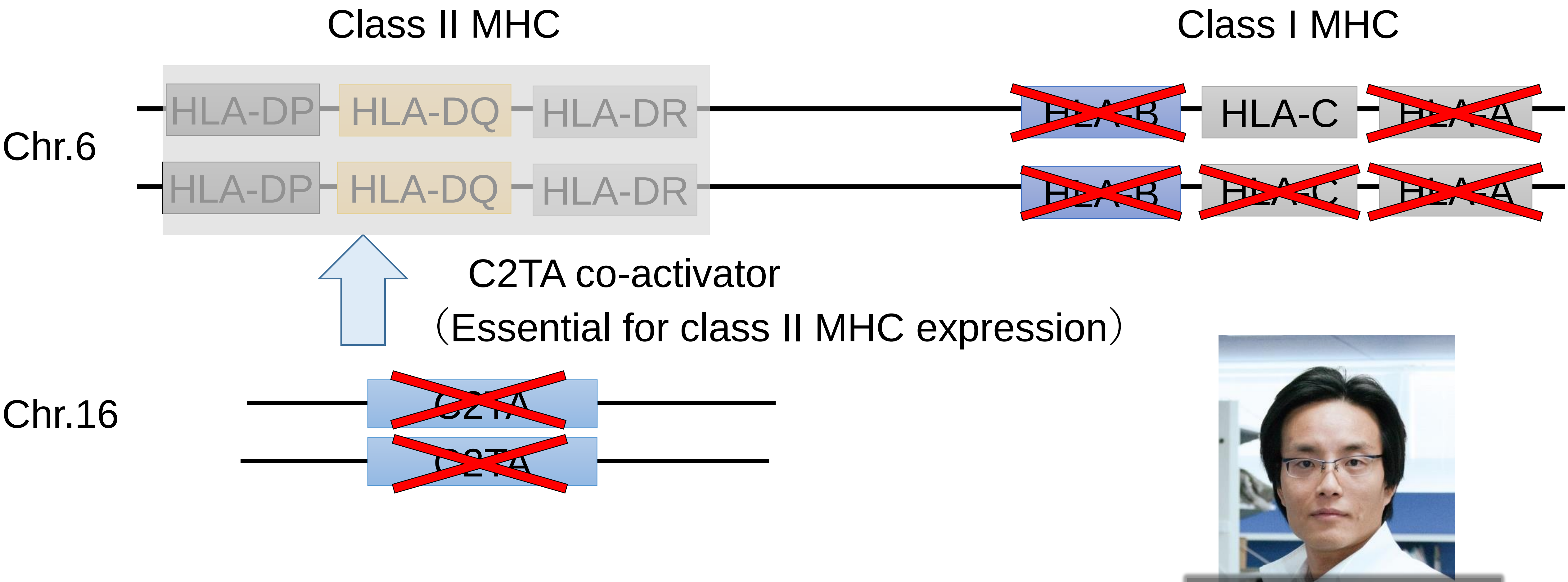
  ：**Covering ~40% of Japanese population**

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

Alternative Approach ~ HLA-C Only

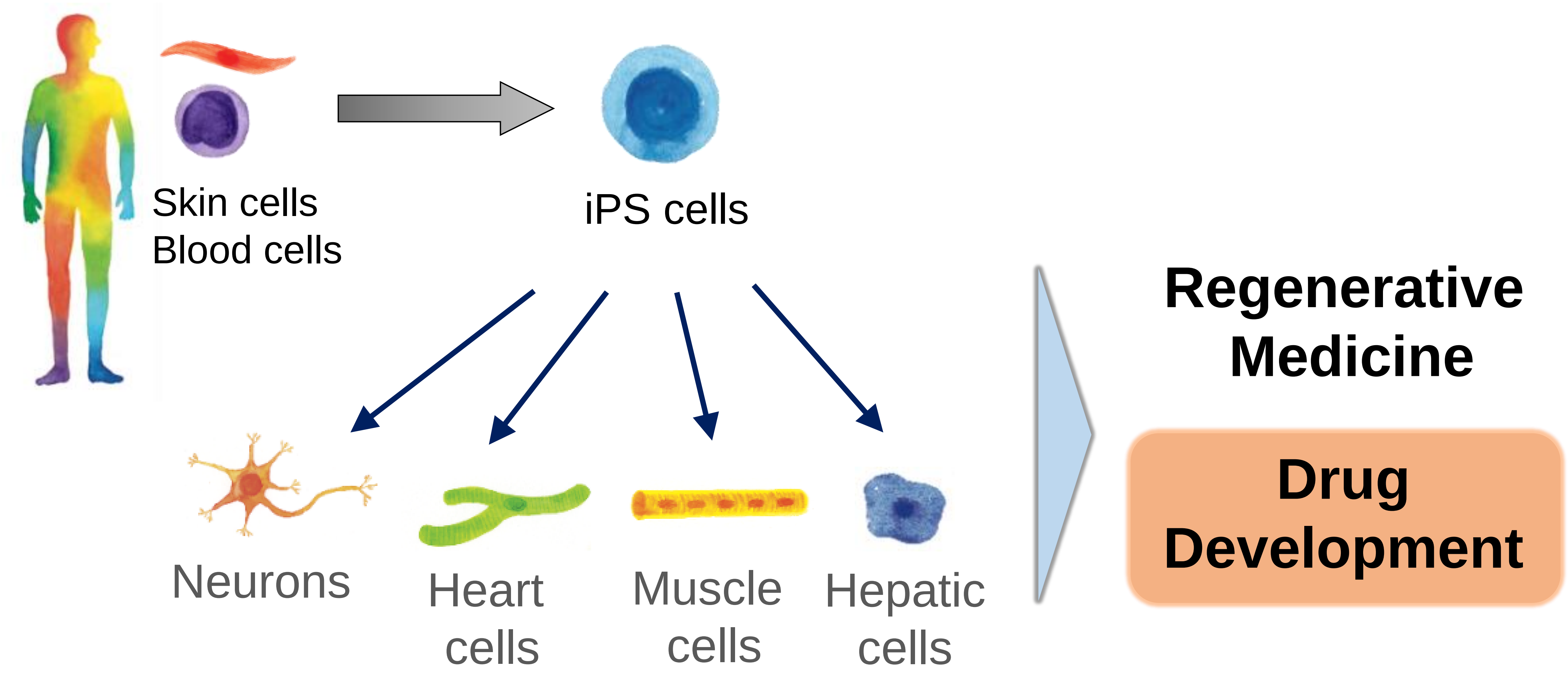


Junior Associate Prof.
Akitsu Hotta
(CiRA)

Future Plan of iPS Cell Therapy

Current	Super Donor iPS Cell Stock 4 Types: Covering ~40% of Japanese population
Alternative （2020～）	Genome-Editing iPS Cell Stock 10 lines would cover most of world population
Ultimate （2025～）	My iPS Cells

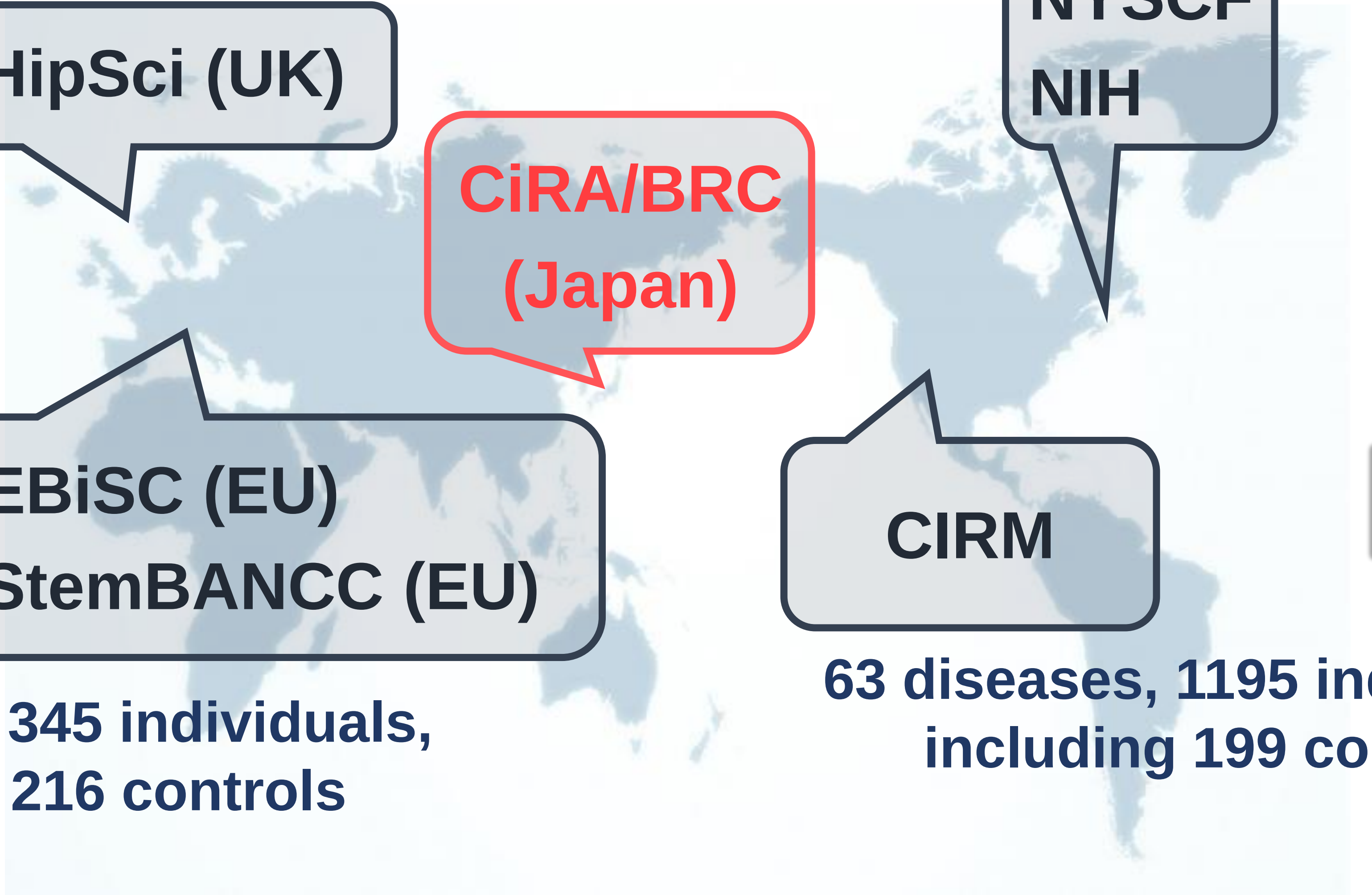
Applications of iPS cells

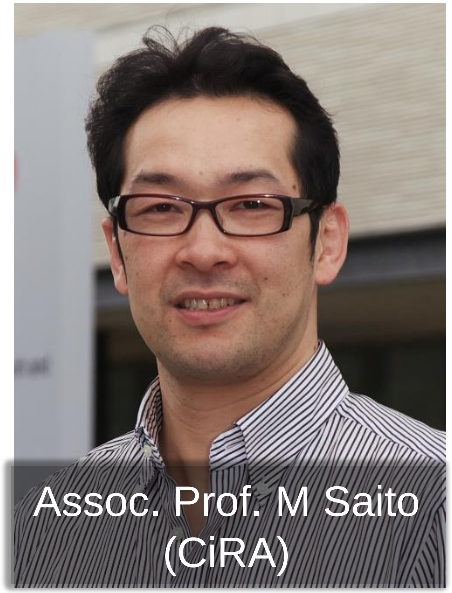


iPS Cell Bank for Drug Discovery

10 diseases,690 individuals, including 517 control

231 diseases, 410 individuals, including 74 control





19 diseases, 345 individuals, including 216 controls

63 diseases, 1195 individuals, including 199 controls

As of March, 2018

Drug Repurposing with Patient iPSCs

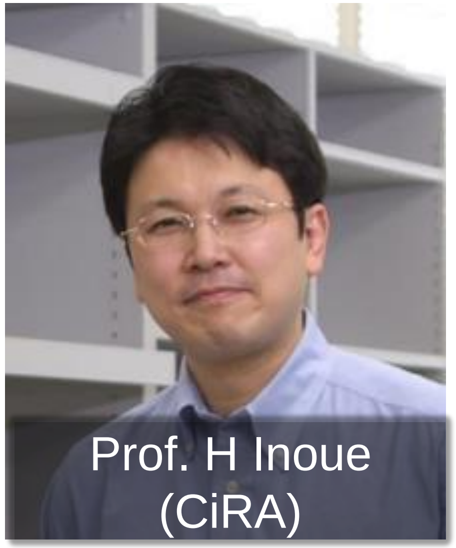
<u>Two clinical trials are ongoing at Kyoto University Hospital</u>

Ramamycin for FOP

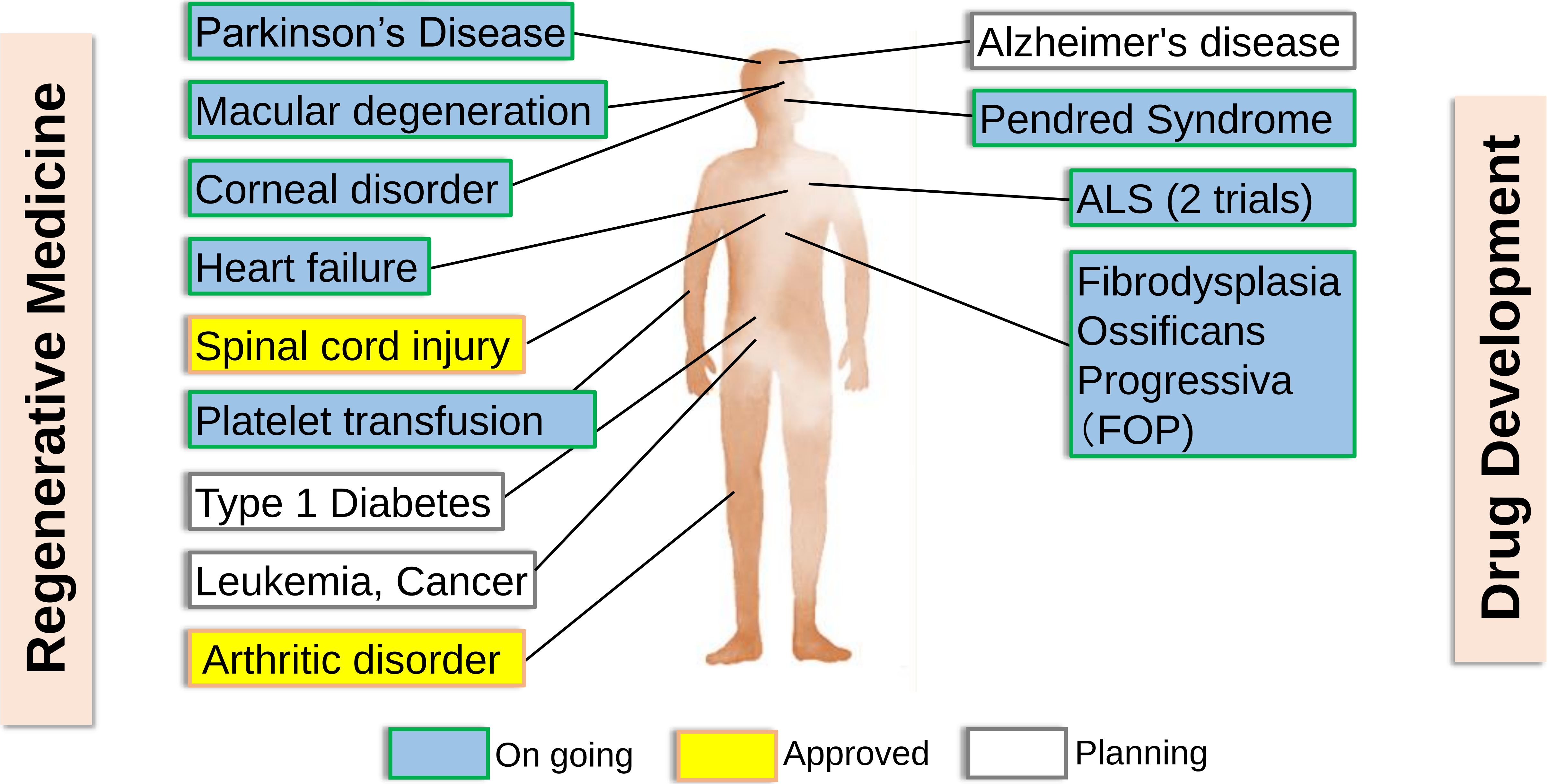
(Fibrodysplasia Ossificans Progressiva)

Bostinib for ALS

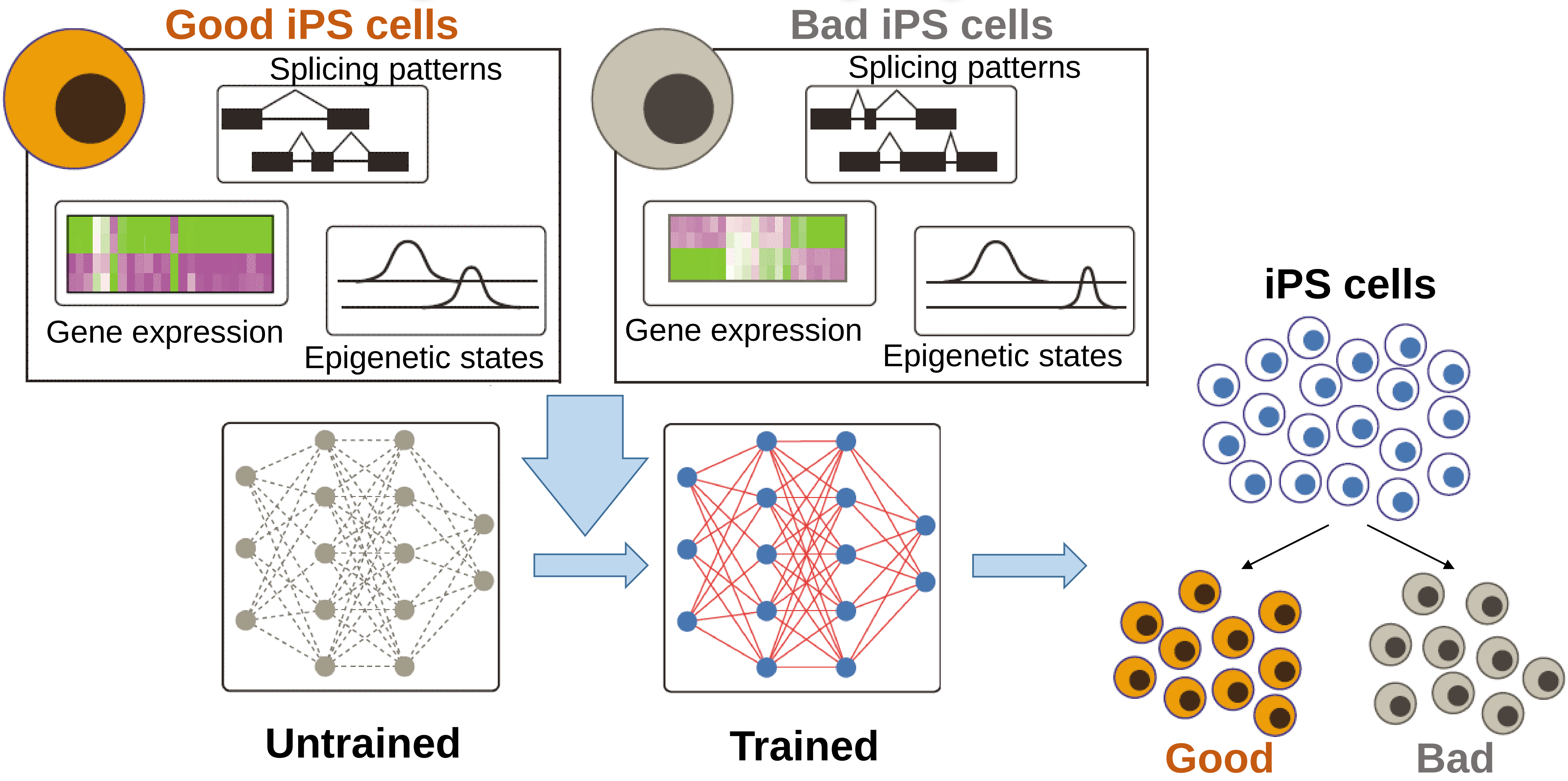
(Amyotrophic lateral sclerosis)



Applications of iPS cells



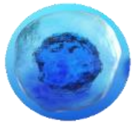
A trained neural network by multi-hierarchical data predicts iPSC properties



Strategy for Epigenetic "identity" using AI

Source	Recipe	Immuno-suppression	Culture condition
Cord blood PBMC (T-cell, B-cell, monocyte etc.) fibroblast	factors (OSKM etc.) X vector X ncRNA X small molecules	HLA homo Autologous engineered	Temperature X Supplements X Hypoxic

iPSC

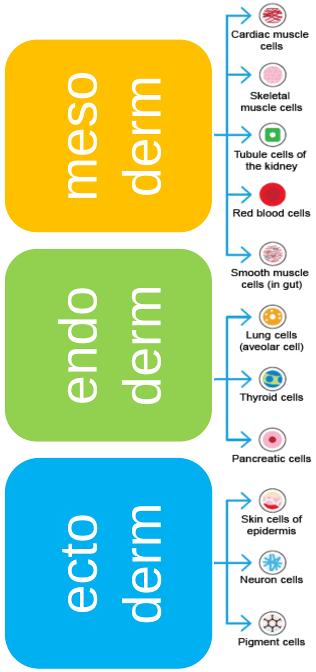


scATAC
scRNA
ATAC-seq
RNA-seq
Methylation

zygote

hESC

Differentiation

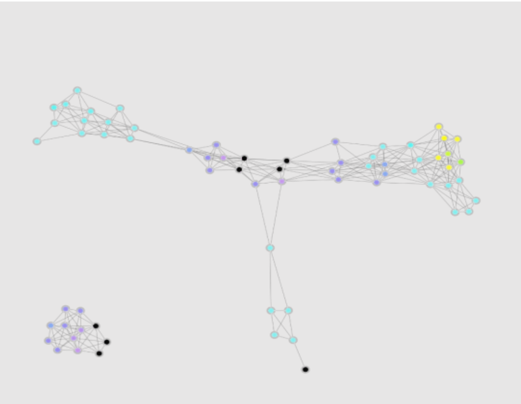


ATAC -seq

RNA-seq

GEO Gene Expression Omnibus

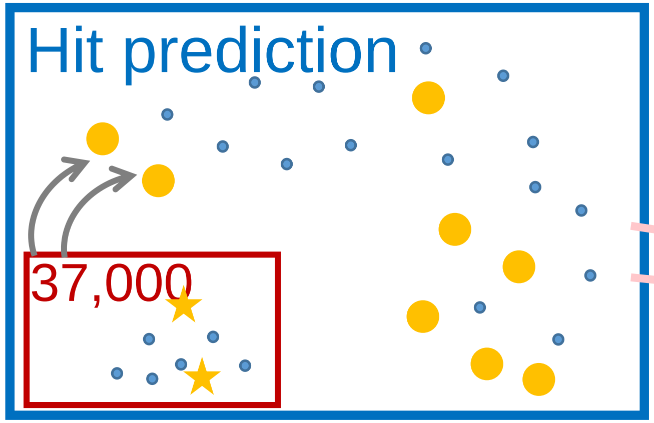
GTEx



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

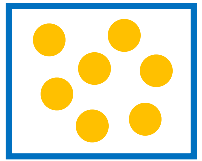


Screening using patient iPSCs

★ Hit compound

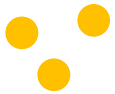
● Predicted active
• Predicted inactive compound

Extraction of predicted 5,000 active compounds

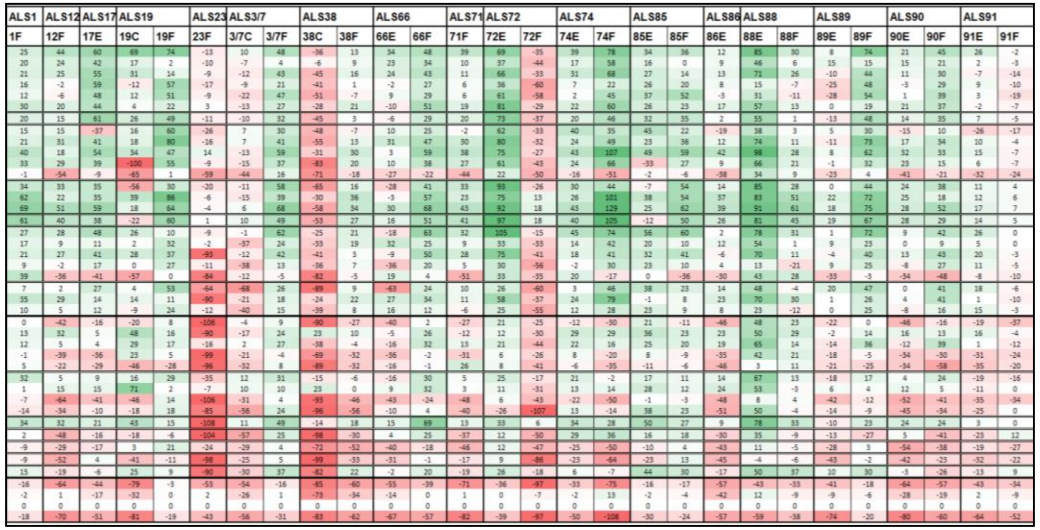


Prediction by AI

Verification using patient iPSCs



Confirmation of the efficiency using patient iPSC panel

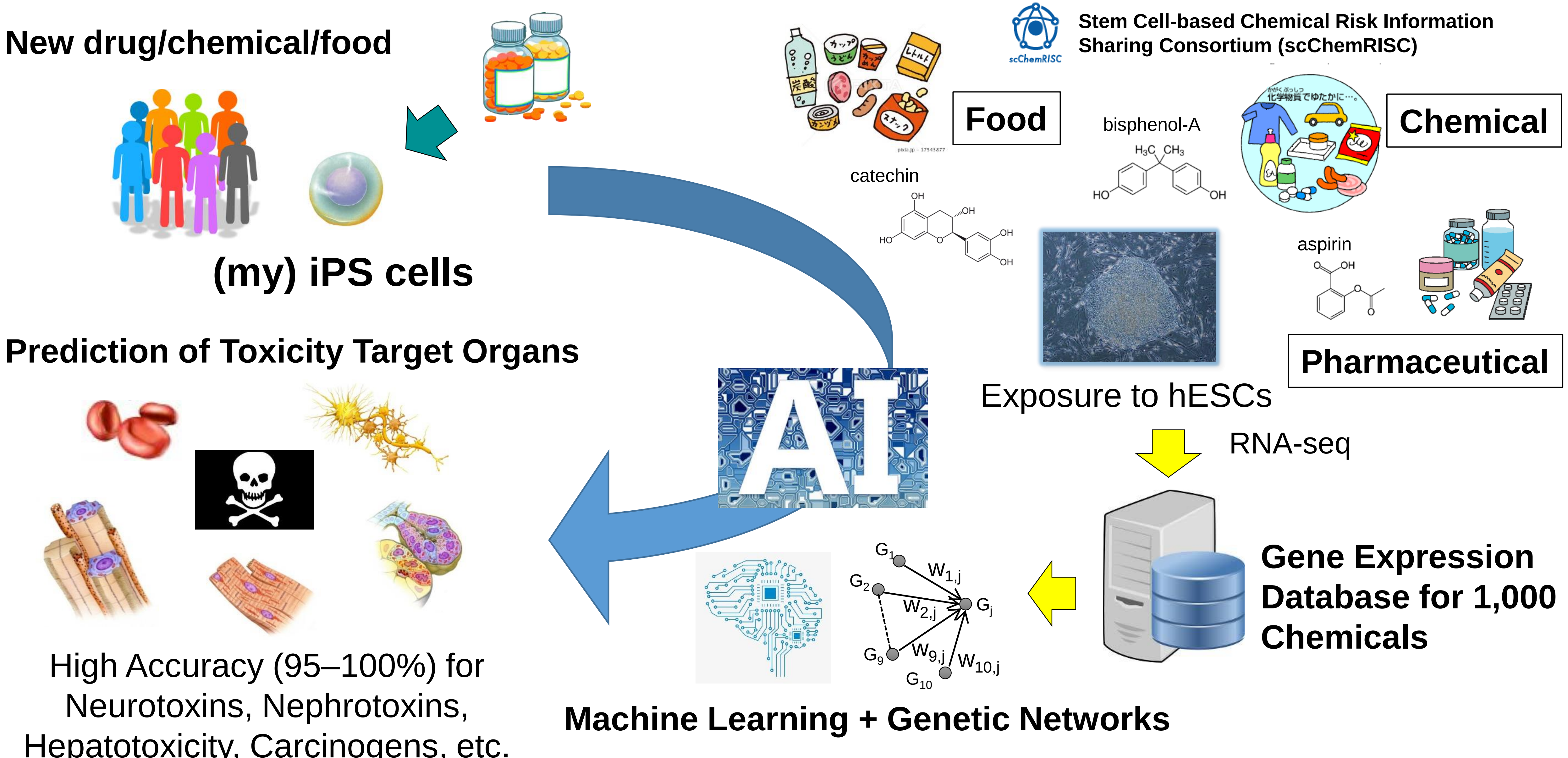


Successful drug discovery

- New chemotypes
- Potent efficacy
- Broad-spectrum for various patients

T-CiRA

Development of Precision Toxicology



(cf. Yamane *et al*. Nucleic Acids Res. 44:5515-28, 2016)

Thank you for your attention!