

AI in Medicine

~Recent Progress in iPS Cell Research and Application~



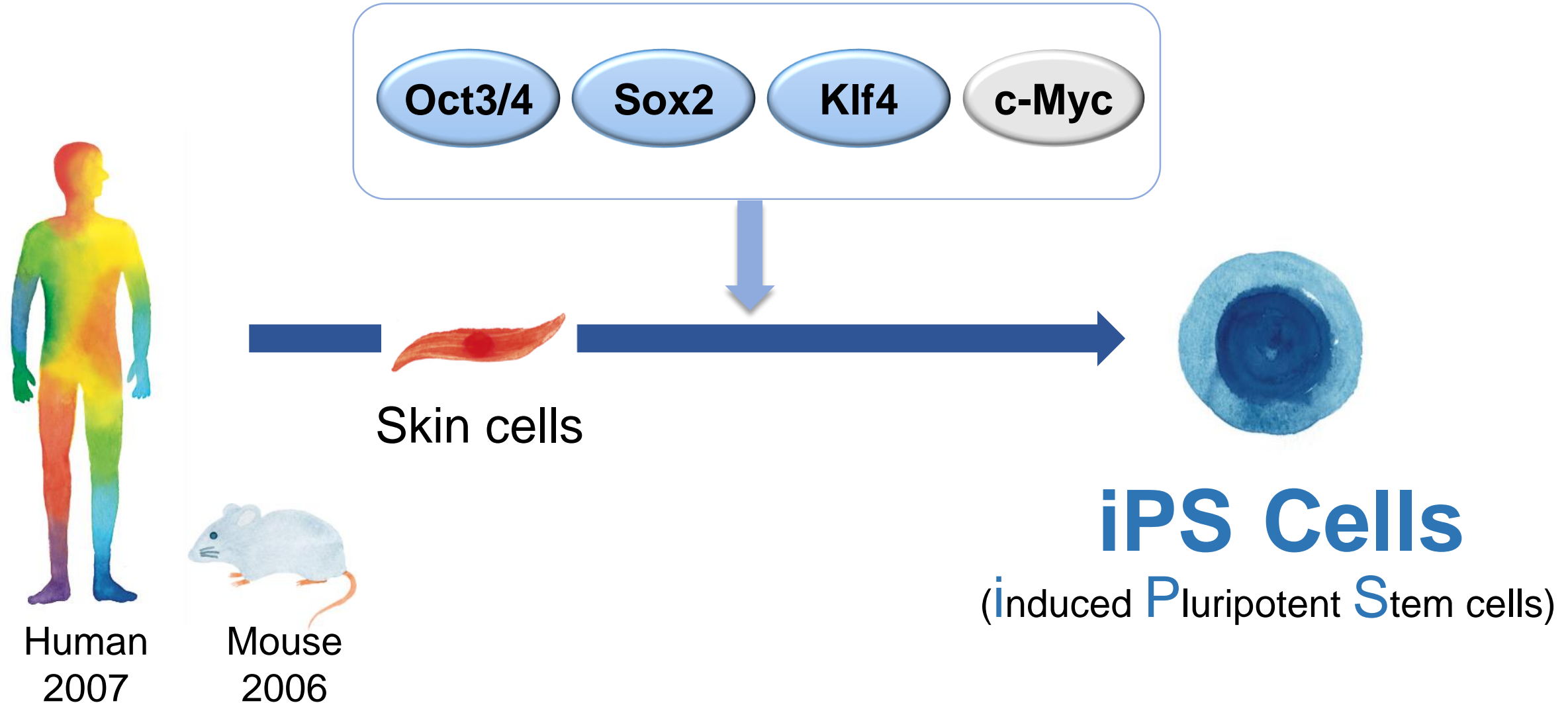
Shinya Yamanaka

Center for iPS Cell Research and Application (CiRA), Kyoto University, Japan

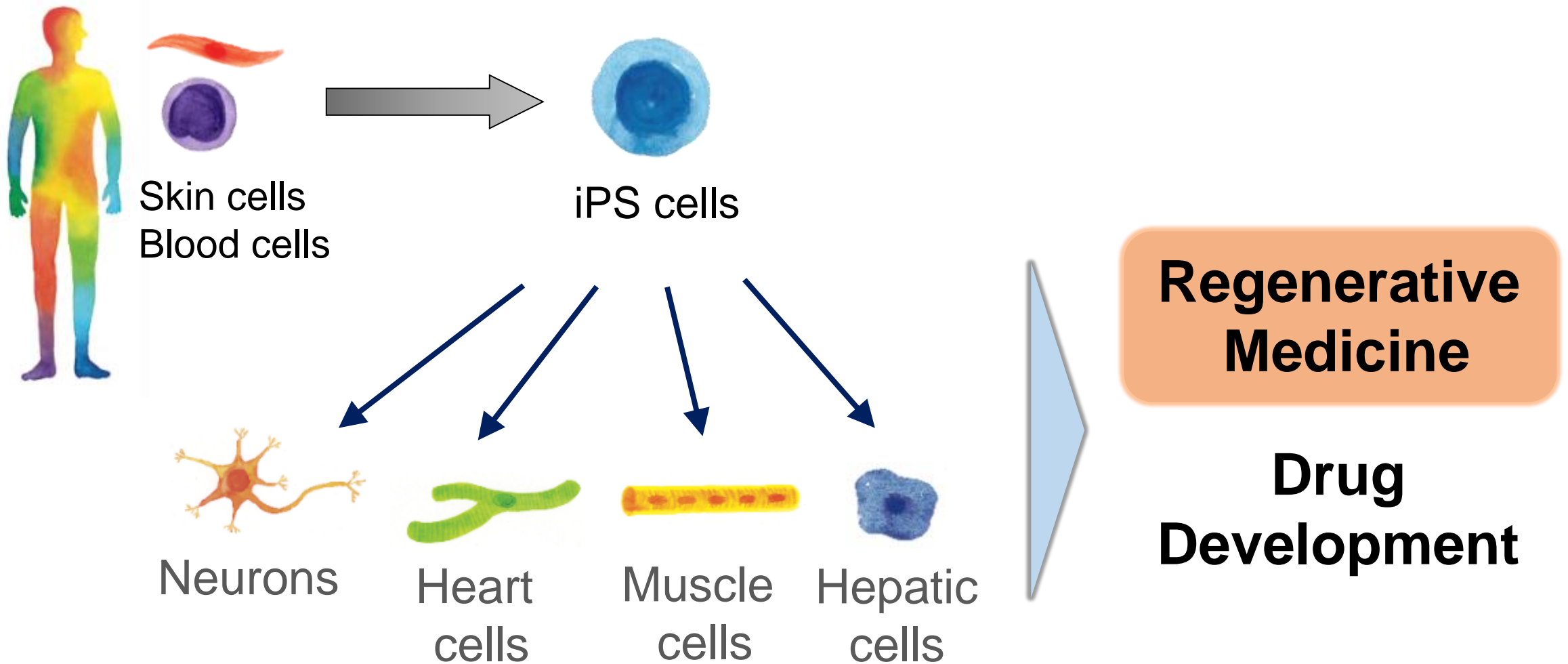
Gladstone Institute of Cardiovascular Disease, San Francisco

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)

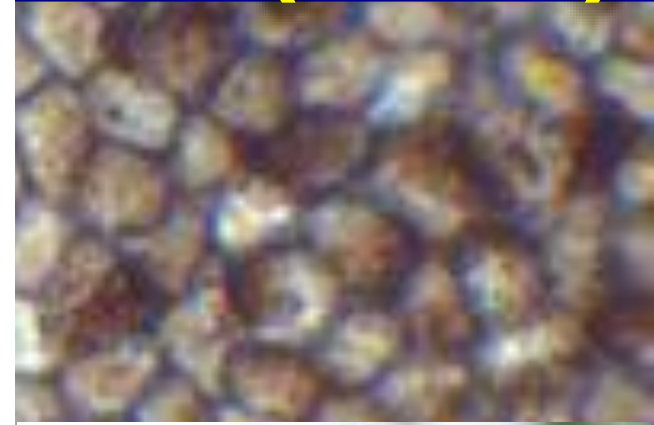
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

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

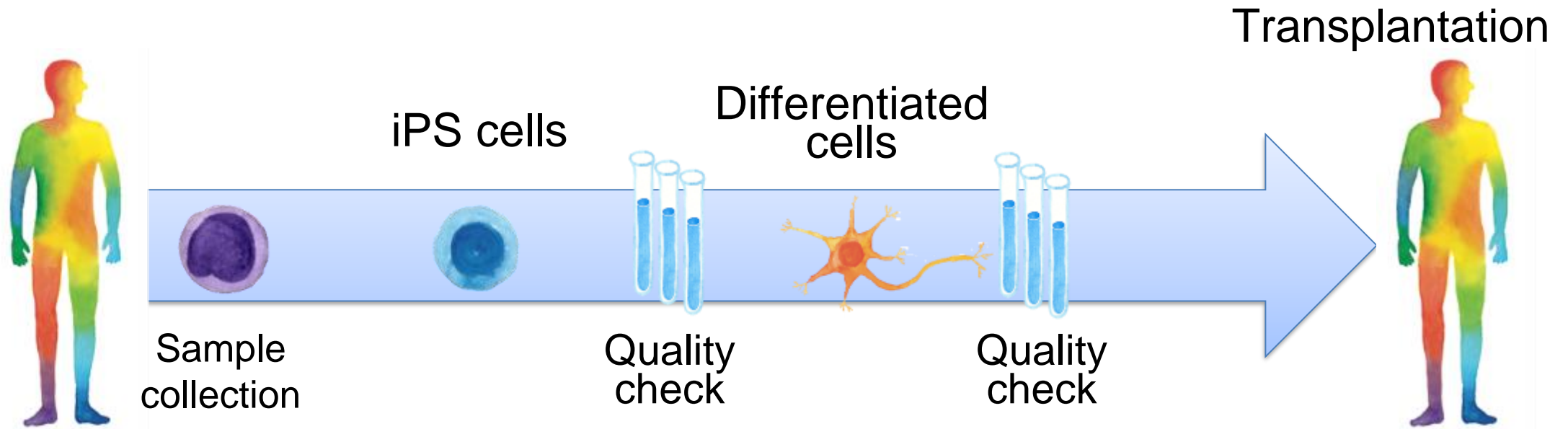
M. Mar
M. F
S. Tanish
S. Kawama
Y. Ohara, K
A. Tanal

No rejection
No tumors
Vision: stabilized



Dr. Masayo Takahashi
(RIKEN, BDR)

Autologous iPS Cells

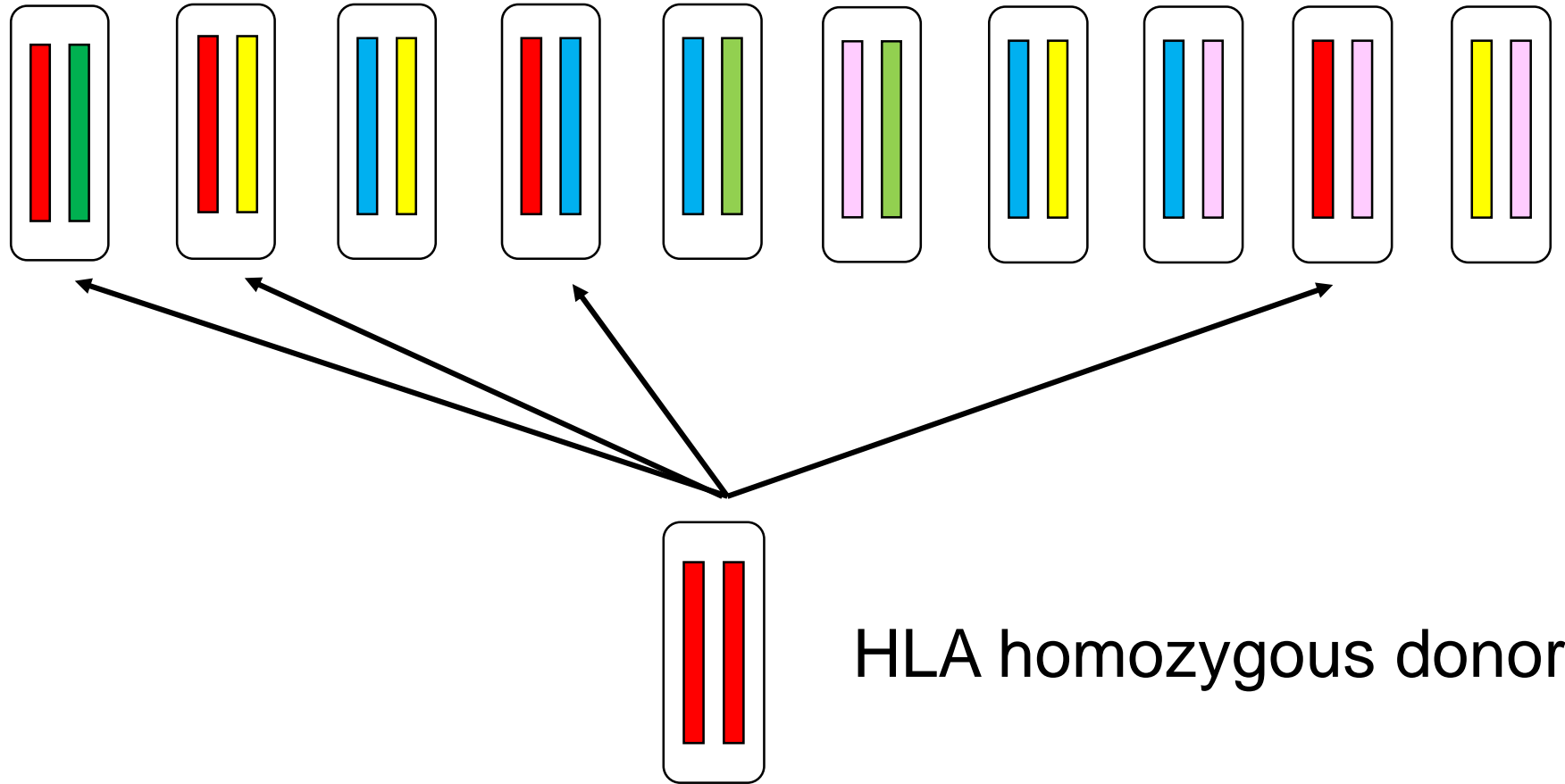


Autograft: Too expensive and time-consuming



iPS Cell Stock for Regenerative Medicine

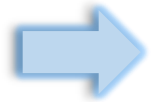
HLA Homozygous “Super” Donors



To reduce the cost & time of autologous iPSC

iPS Cell Stock for Regenerative Medicine

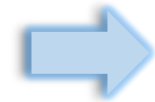
Japanese Red Cross Society



Platelet / Bone Marrow Donors



Informed Consent & Blood Sampling



Cell Processing Facility at CiRA



Clinical-grade iPS Cells



Quality Check



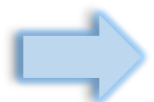
Stock



“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



Started in April, 2010



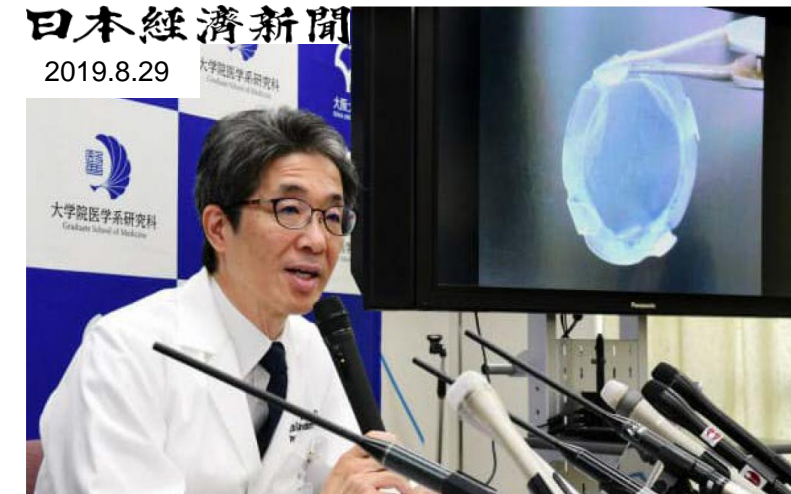
14 Cell Processing Rooms

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

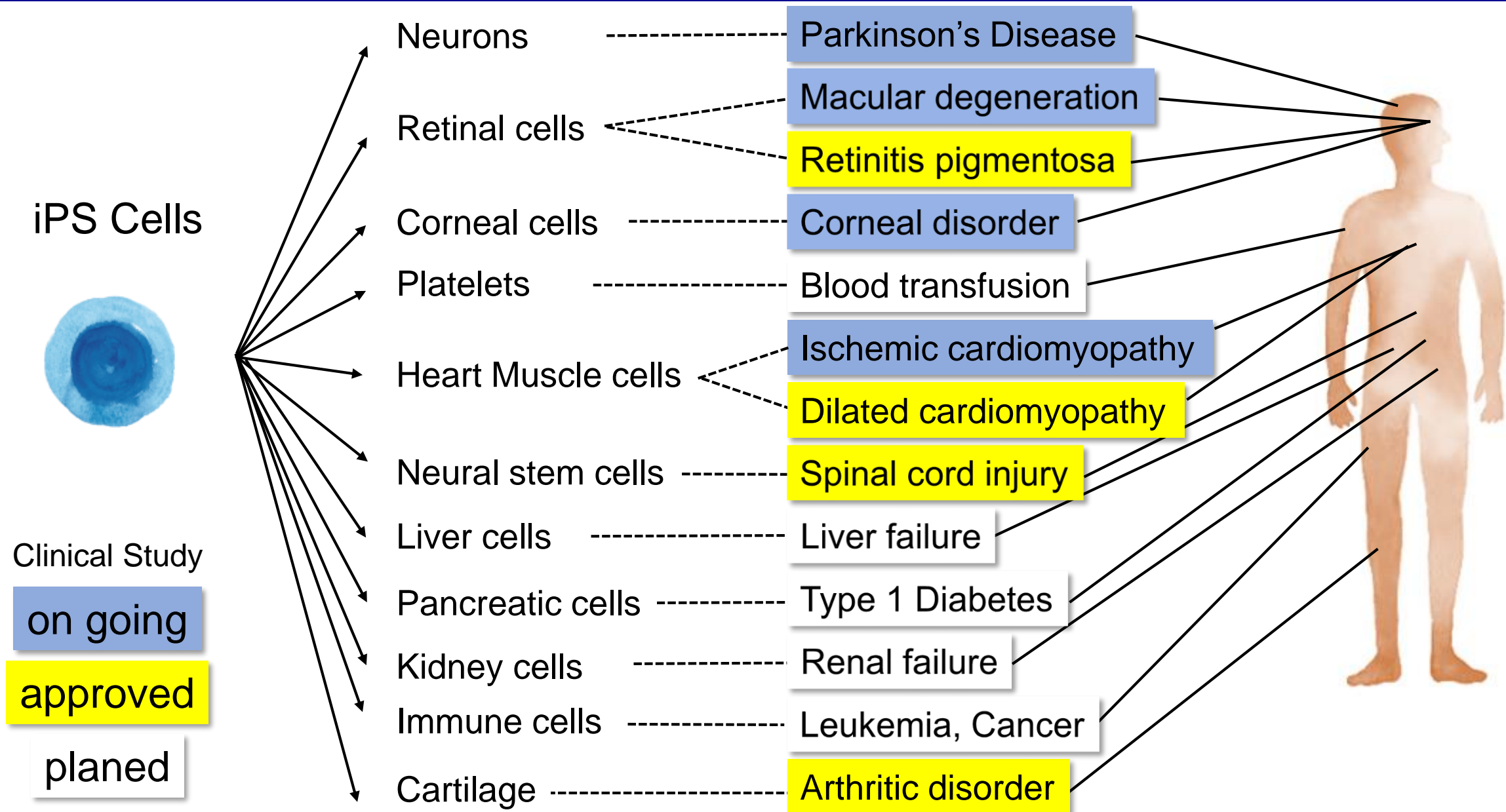


Osaka Univ.
Retinitis Pigmentosa



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%?

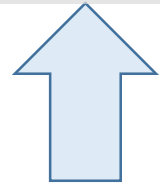
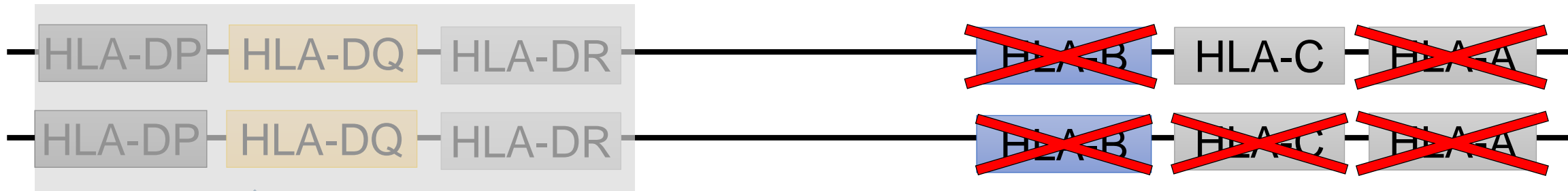
- 150 haplotypes would cover ~90% of Japanese population
- >1000 haplotypes would be required to cover most of the world population

Alternative Approach ~ HLA-C Only

Class II MHC

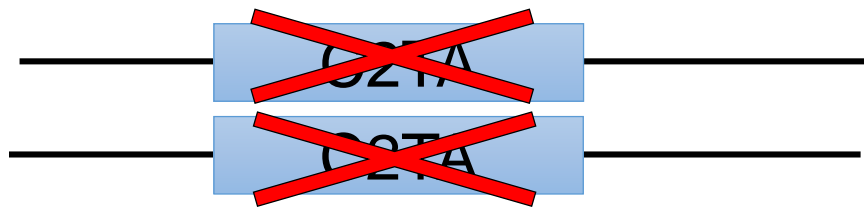
Class I MHC

Chr.6



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

Chr.16



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

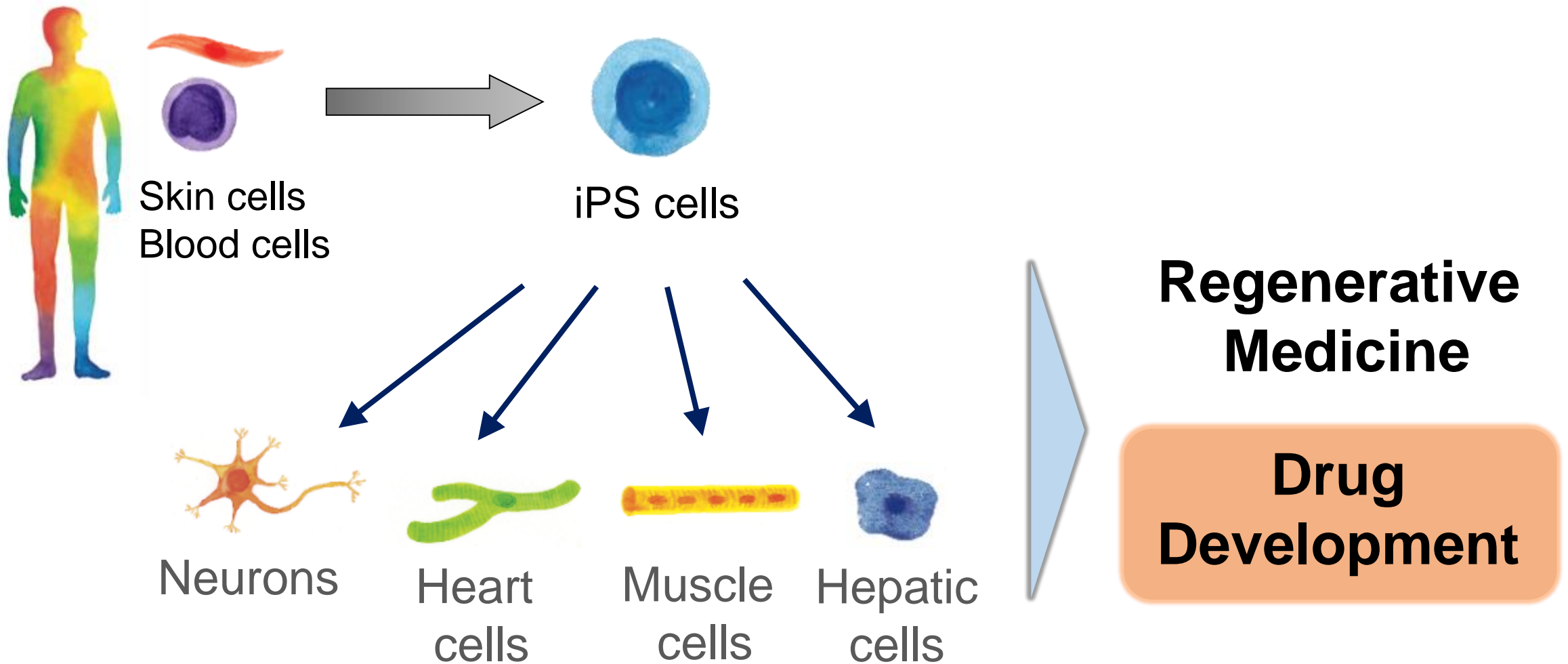
10 lines would cover most of world population

Ultimate

(2025~)

My iPS Cells

Applications of iPS cells



iPS Cell Bank for Drug Discovery

10 diseases, 690 individuals,
including 517 control

HipSci (UK)

EBiSC (EU)
StemBANCC (EU)

19 diseases, 345 individuals,
including 216 controls

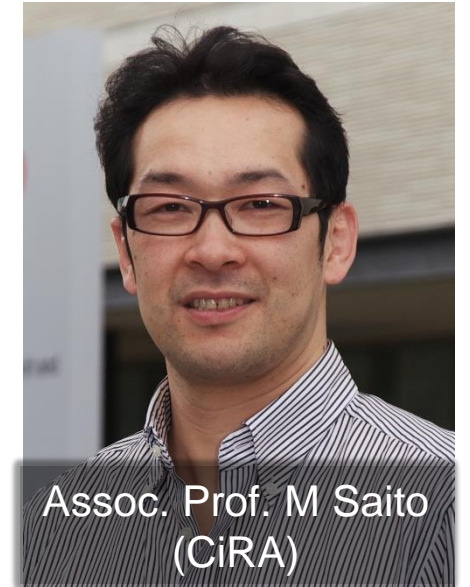
231 diseases, 410 individuals,
including 74 control

CiRA/BRC
(Japan)

NYSCF
NIH

CIRM

63 diseases, 1195 individuals,
including 199 controls



As of March, 2018

Drug Repurposing with Patient iPSCs

Two clinical trials are ongoing at Kyoto University Hospital

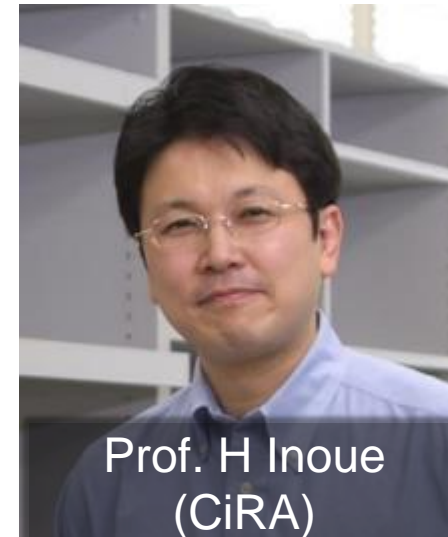
Ramamycin for FOP

(Fibrodysplasia Ossificans Progressiva)



Bostinib for ALS

(Amyotrophic lateral sclerosis)



Applications of iPS cells

Regenerative Medicine

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

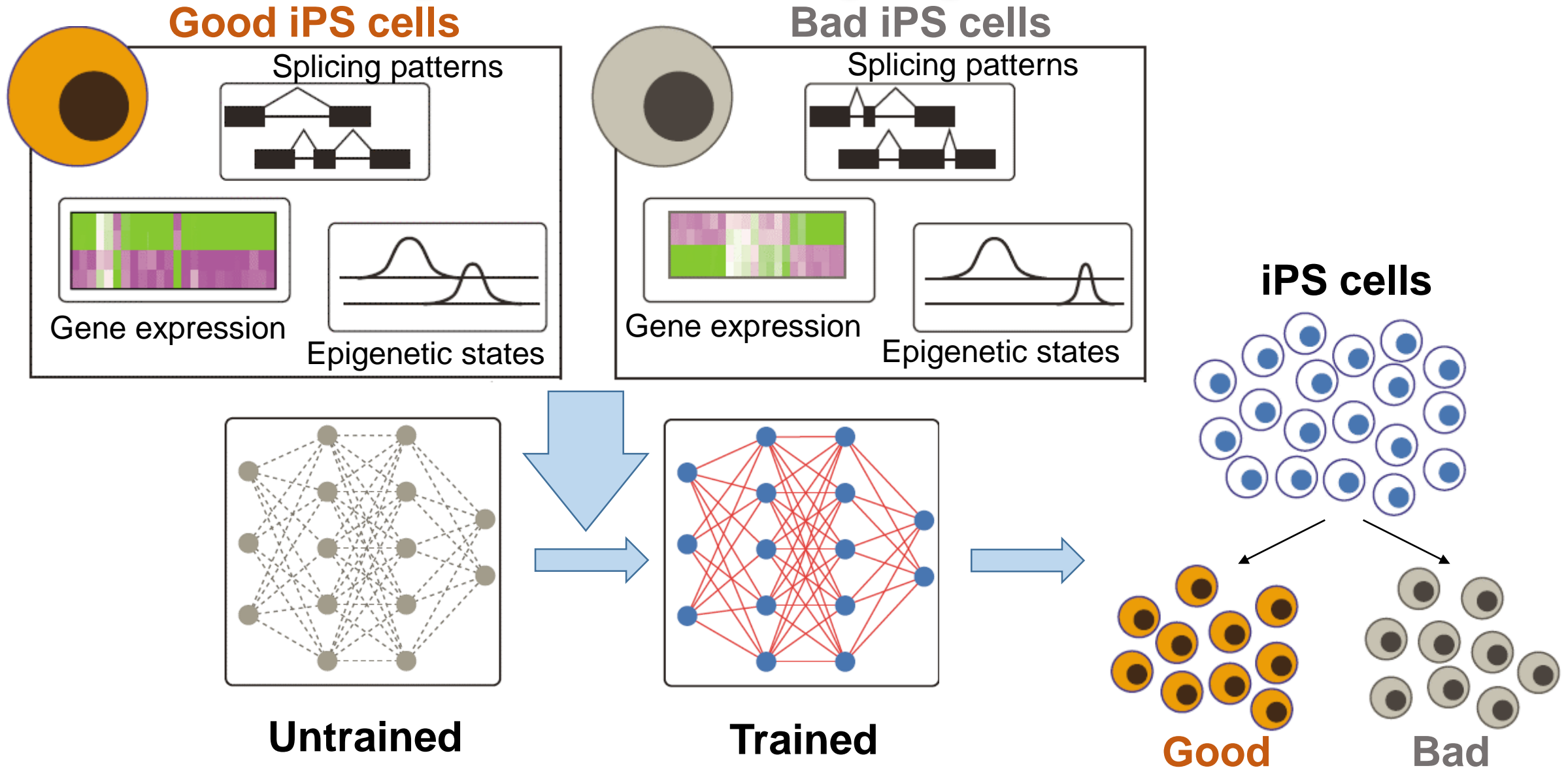
ALS (2 trials)

Fibrodysplasia
Ossificans
Progressiva
(FOP)

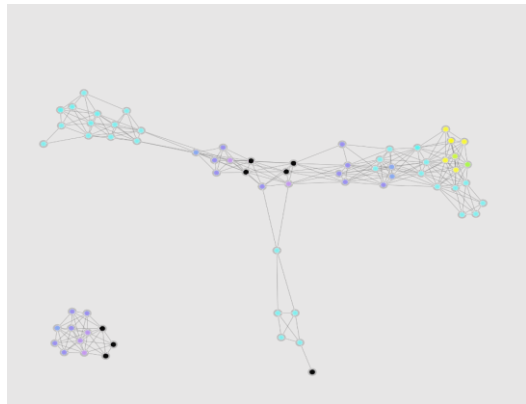
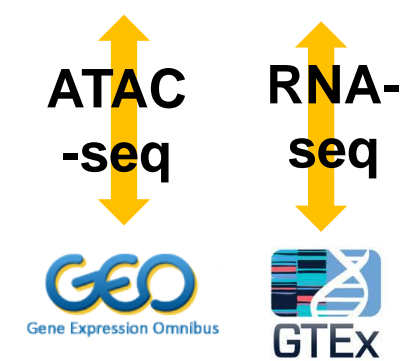
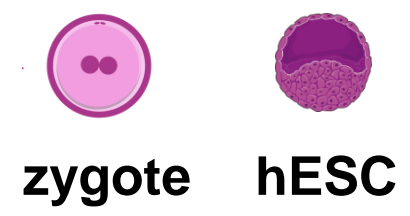
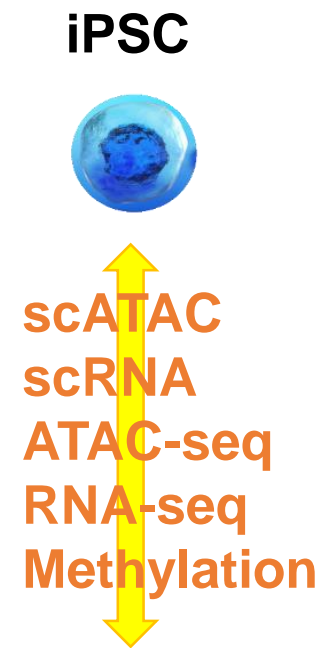
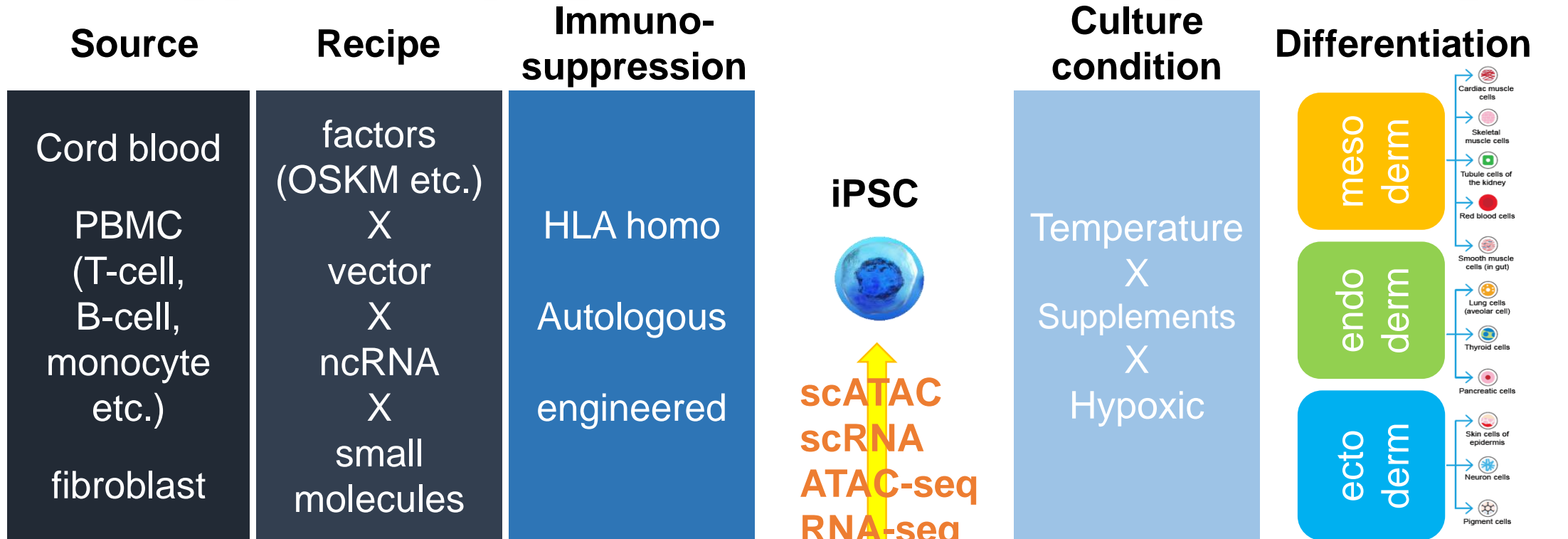
Drug Development

 On going  Approved  Planning

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



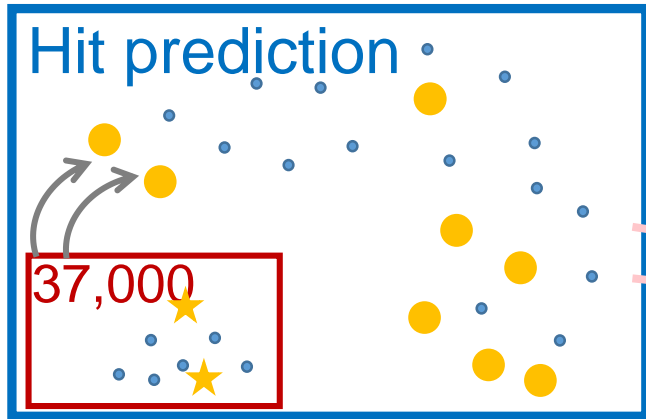
Strategy for Epigenetic “identity” using AI



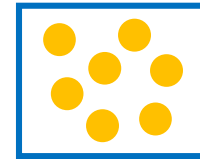
AI/Machine Learning
Topological Data Analysis (powerful method for high dimensional data)

Drug discovery using patient iPSCs and AI

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



Extraction of predicted 5,000 active compounds



Prediction by AI

Verification using patient iPSCs



Confirmation of the efficiency using patient iPSC panel

Screening using patient iPSCs

- Predicted active
- Predicted inactive compound
- ★ Hit compound

Successful drug discovery

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

| ALS1 | ALS12 | ALS17 | ALS19 | ALS23 | ALS37 | ALS38 | ALS66 | ALS71 | ALS72 | ALS74 | ALS85 | ALS88 | ALS89 | ALS90 | ALS91 | | | | | | | | | | | | | |
|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|
| 1F | 2F | 17E | 19C | 19F | 23F | 37C | 37F | 38C | 38F | 66E | 66F | 71F | 72E | 72F | 74E | 74F | 85E | 85F | 86E | 88E | 88F | 89E | 89F | 90E | 90F | 91E | 91F | |
| 25 | 44 | 60 | 69 | 74 | -23 | 10 | 48 | -28 | 13 | 34 | 48 | 39 | 49 | -25 | 39 | 74 | 34 | 36 | 22 | 61 | 30 | 9 | -54 | 21 | -45 | 26 | -2 | |
| 20 | 24 | 42 | 17 | 2 | -10 | -7 | 4 | -6 | 9 | 23 | 34 | 10 | 37 | -44 | 17 | 58 | 16 | 0 | 9 | 46 | 6 | 15 | 15 | 15 | 21 | 2 | -3 | |
| 21 | 25 | 55 | 31 | 14 | -9 | -12 | 43 | -45 | 16 | 24 | 43 | 11 | 66 | -33 | 31 | 88 | 27 | 14 | 13 | 73 | 26 | -10 | 44 | 11 | 30 | -7 | -34 | |
| 16 | -2 | 59 | -12 | 37 | -37 | -9 | 21 | -41 | 1 | -2 | 27 | 6 | 36 | -60 | 7 | 22 | 26 | 25 | 8 | 15 | -7 | -25 | 48 | -8 | 29 | 9 | -10 | |
| 12 | -4 | 48 | 12 | 91 | -9 | -22 | 47 | -51 | -7 | 9 | 29 | 6 | 61 | -58 | 2 | 45 | 37 | 52 | -3 | 31 | -11 | -38 | 54 | 1 | 39 | 3 | -19 | |
| 30 | 20 | 44 | 4 | 22 | 3 | -13 | 27 | -28 | 21 | -10 | 51 | 19 | 81 | -29 | 22 | 60 | 26 | 23 | 17 | 57 | 13 | 0 | 19 | 21 | 37 | -2 | -7 | |
| 20 | 15 | 41 | 26 | 49 | -11 | -10 | 32 | -45 | 3 | -6 | 29 | 20 | 73 | -17 | 20 | 46 | 32 | 35 | 7 | 55 | 1 | -13 | 48 | 14 | 35 | 7 | -5 | |
| 15 | 15 | -17 | 16 | 60 | -26 | 7 | 30 | -48 | -7 | 10 | 25 | -2 | 62 | -33 | 40 | 15 | 48 | 22 | -19 | 18 | 3 | 5 | 10 | -15 | 10 | -26 | -17 | |
| 21 | 31 | 41 | 18 | 80 | -16 | 7 | 41 | -55 | 15 | 31 | 47 | 30 | 80 | -52 | 24 | 49 | 23 | 36 | 12 | 74 | 11 | -11 | 79 | 17 | 34 | 10 | -4 | |
| 40 | 18 | 54 | 24 | 47 | 14 | -13 | 59 | -31 | 30 | 3 | 59 | 38 | 75 | -27 | 43 | 107 | 49 | 59 | 42 | 98 | 28 | 8 | 62 | 32 | 35 | 15 | -7 | |
| 38 | 29 | 39 | 106 | 36 | -9 | -15 | 37 | 48 | 20 | 10 | 36 | 27 | 61 | -43 | 24 | 66 | -18 | 27 | 9 | 66 | 21 | -1 | 32 | 23 | 13 | 6 | -7 | |
| 1 | -54 | -9 | -65 | 1 | -39 | -44 | 16 | -71 | -18 | -27 | -23 | 44 | -2 | -50 | -16 | 51 | -2 | -4 | -38 | 34 | 8 | -23 | 4 | -41 | -21 | 32 | -24 | |
| 34 | 33 | 35 | -56 | 30 | -20 | -11 | 58 | -89 | 16 | -28 | 41 | 33 | 93 | -26 | 30 | 44 | -7 | 54 | 14 | 85 | 28 | 0 | 44 | 24 | 38 | 11 | 4 | |
| 62 | 22 | 35 | 39 | 86 | -6 | -15 | 39 | -35 | -3 | 57 | 23 | 75 | 13 | 28 | 101 | 38 | 54 | 37 | 83 | 51 | 22 | 72 | 25 | 18 | 12 | 6 | | |
| 89 | 51 | 59 | 18 | 64 | -4 | 6 | 68 | -58 | 34 | 30 | 68 | 43 | 62 | 18 | 43 | 129 | 25 | 62 | 39 | 82 | 61 | 18 | 75 | 28 | 52 | 17 | 7 | |
| 61 | 40 | 38 | -22 | 60 | 1 | 10 | 49 | -53 | 27 | 16 | 51 | 41 | 97 | -18 | 40 | 105 | -12 | 80 | 26 | 82 | 45 | 19 | 67 | 28 | 29 | 14 | 5 | |
| 27 | 28 | 48 | 26 | 10 | -9 | -1 | 62 | -25 | 21 | -18 | 83 | 32 | 105 | -15 | 45 | 74 | 56 | 80 | 2 | 78 | 31 | 3 | 72 | 9 | 42 | 26 | 0 | |
| 17 | 9 | 21 | 2 | 32 | -2 | 397 | 24 | -15 | 19 | 32 | 25 | 9 | 33 | -25 | 14 | 42 | 20 | 15 | 12 | 54 | 1 | 9 | 23 | 0 | 9 | 5 | 0 | |
| 21 | 27 | 41 | 28 | 37 | -30 | -12 | 42 | -41 | 3 | -9 | 50 | 28 | 75 | -41 | 18 | 41 | 32 | 41 | -6 | 70 | 11 | -4 | 40 | 13 | 43 | 20 | -3 | |
| 9 | -2 | 17 | 0 | 27 | -11 | -18 | 13 | -36 | 7 | 36 | 20 | 5 | 30 | -56 | -2 | 30 | 23 | 10 | 4 | 13 | -21 | 9 | 25 | -8 | 27 | 11 | -5 | |
| 39 | -6 | -41 | 257 | 0 | 46 | -12 | -5 | 12 | 0 | -36 | 12 | 4 | 43 | 33 | 4 | 20 | 17 | 0 | -20 | 43 | 28 | -33 | -3 | -24 | -6 | -10 | | |
| 7 | 2 | 27 | 4 | 53 | -44 | 68 | 26 | 89 | 9 | -83 | 24 | 10 | 26 | -60 | 20 | 48 | 38 | 23 | 14 | 48 | -4 | 20 | 47 | 0 | 41 | 18 | -6 | |
| 35 | 29 | 14 | 14 | 11 | -90 | -21 | 18 | -24 | 22 | 27 | 34 | 11 | 58 | -57 | 24 | 79 | -1 | 8 | 23 | 70 | 30 | 1 | 26 | 4 | 41 | 1 | -10 | |
| 10 | 5 | 12 | -8 | 24 | -12 | -60 | 15 | -39 | 8 | 16 | 12 | -35 | 11 | 28 | 23 | 8 | 23 | -12 | 5 | 23 | -12 | 5 | 25 | -8 | 16 | 15 | 9 | |
| 9 | -42 | -16 | -20 | 8 | -206 | -4 | 9 | -26 | -17 | -62 | 2 | -57 | 21 | -25 | -12 | 30 | 21 | -11 | -66 | 48 | 23 | -22 | 9 | -42 | -26 | -19 | | |
| 13 | 32 | 5 | 48 | 16 | -90 | -17 | 24 | 23 | 10 | -5 | 26 | -12 | 12 | -30 | 29 | 29 | 36 | 23 | 23 | 30 | 29 | -2 | 14 | 16 | 13 | 16 | -4 | |
| 12 | 5 | 4 | 29 | 17 | -16 | 2 | 27 | -38 | -4 | -16 | 32 | 13 | 21 | -44 | 22 | 16 | 25 | 20 | 19 | 65 | 14 | -14 | 86 | -12 | 39 | 1 | -12 | |
| -1 | -39 | -69 | 23 | 5 | 4 | -69 | -12 | -6 | -20 | -36 | -2 | -31 | 4 | -26 | 6 | 4 | 30 | 8 | 6 | -56 | -20 | -43 | -5 | -24 | -20 | -24 | | |
| 5 | -22 | -29 | -46 | -28 | -66 | 32 | 8 | 89 | -32 | -16 | -1 | 26 | 8 | 41 | -6 | -35 | -11 | -4 | 46 | 3 | 11 | -21 | 25 | -34 | -58 | -35 | -20 | |
| 32 | 5 | 9 | 16 | 29 | -55 | 12 | 31 | -15 | -6 | -16 | 30 | 5 | 25 | -17 | 21 | -2 | 17 | 11 | 14 | 67 | 13 | -18 | 17 | 4 | 24 | -19 | -16 | |
| 16 | -64 | -44 | 79 | -9 | -13 | 24 | -16 | -61 | -60 | -16 | -19 | -11 | 11 | 11 | 11 | 16 | -16 | -12 | -37 | -42 | -18 | -42 | -18 | -64 | -27 | -43 | -34 | |
| -7 | -64 | -41 | -46 | 14 | -106 | 91 | 4 | 63 | -46 | -43 | -24 | -48 | 6 | -43 | -22 | -50 | -1 | -3 | -48 | 8 | 4 | -42 | 12 | -52 | -41 | -35 | -34 | |
| -14 | -30 | -10 | -18 | 18 | -35 | -56 | 24 | -36 | -16 | -10 | 4 | -40 | -26 | -377 | 13 | -40 | -26 | 377 | 13 | -40 | -26 | 377 | 13 | -40 | -26 | 377 | 13 | 0 |
| 34 | 32 | 21 | -43 | 15 | -108 | 11 | 49 | -14 | 18 | 15 | 69 | 13 | 33 | 6 | 34 | 28 | 50 | 27 | 9 | 79 | 33 | -10 | 23 | 24 | 24 | 3 | 0 | |
| 1 | 48 | 18 | 18 | -6 | -104 | 37 | 25 | 66 | 10 | 4 | 21 | -47 | 12 | -52 | 29 | 36 | 16 | 18 | -30 | 37 | -9 | -13 | 37 | 5 | -41 | -13 | 17 | |
| -9 | -25 | -17 | 3 | 21 | -24 | -29 | 4 | -72 | -32 | -40 | -18 | -46 | 12 | -47 | -25 | -50 | -10 | 4 | -43 | 11 | -5 | -28 | 3 | -54 | -38 | -19 | -27 | |
| -9 | -52 | 4 | -41 | -11 | -98 | -25 | 5 | -99 | -33 | -31 | -1 | -17 | 9 | 85 | -23 | 64 | -23 | 13 | -45 | -4 | -6 | -3 | -2 | -42 | -23 | -32 | -22 | |
| 15 | -19 | -6 | 25 | 8 | 80 | 30 | 37 | 82 | 27 | -2 | 20 | -19 | 26 | -18 | 8 | -7 | 44 | 30 | -17 | 50 | 37 | 10 | 10 | -3 | -26 | -13 | 9 | |
| -2 | 1 | -17 | -32 | 0 | 2 | -28 | 1 | -73 | -34 | -14 | 0 | 1 | 0 | -7 | -2 | 13 | -2 | 4 | -42 | 12 | 9 | -9 | -6 | -28 | -19 | 2 | 9 | |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 18 | 70 | -61 | -81 | -19 | -43 | -16 | -31 | 83 | -43 | -87 | 53 | 43 | 39 | 89 | 40 | -28 | 30 | -24 | -43 | -39 | 34 | -24 | 30 | 86 | 40 | 44 | -32 | |



Development of Precision Toxicology

New drug/chemical/food



(my) iPS cells

Prediction of Toxicity Target Organs

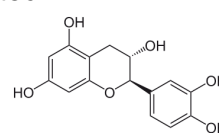


High Accuracy (95–100%) for Neurotoxins, Nephrotoxins, Hepatotoxicity, Carcinogens, etc.



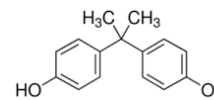
Food

catechin

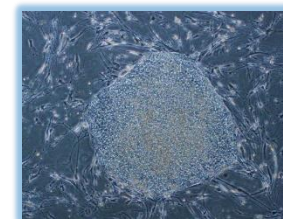


Stem Cell-based Chemical Risk Information Sharing Consortium (scChemRISC)

bisphenol-A

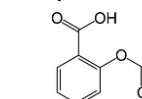


Chemical



Exposure to hESCs

aspirin



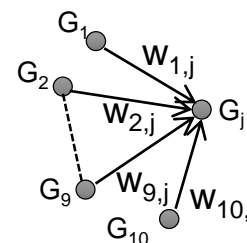
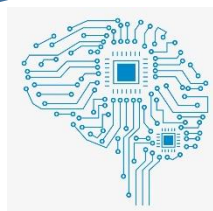
Pharmaceutical

RNA-seq



Gene Expression Database for 1,000 Chemicals

AI



Machine Learning + Genetic Networks



CiRA, Kyoto

Thank you for your attention!



T-CiRA Program



Gladstone Institutes,
San Francisco