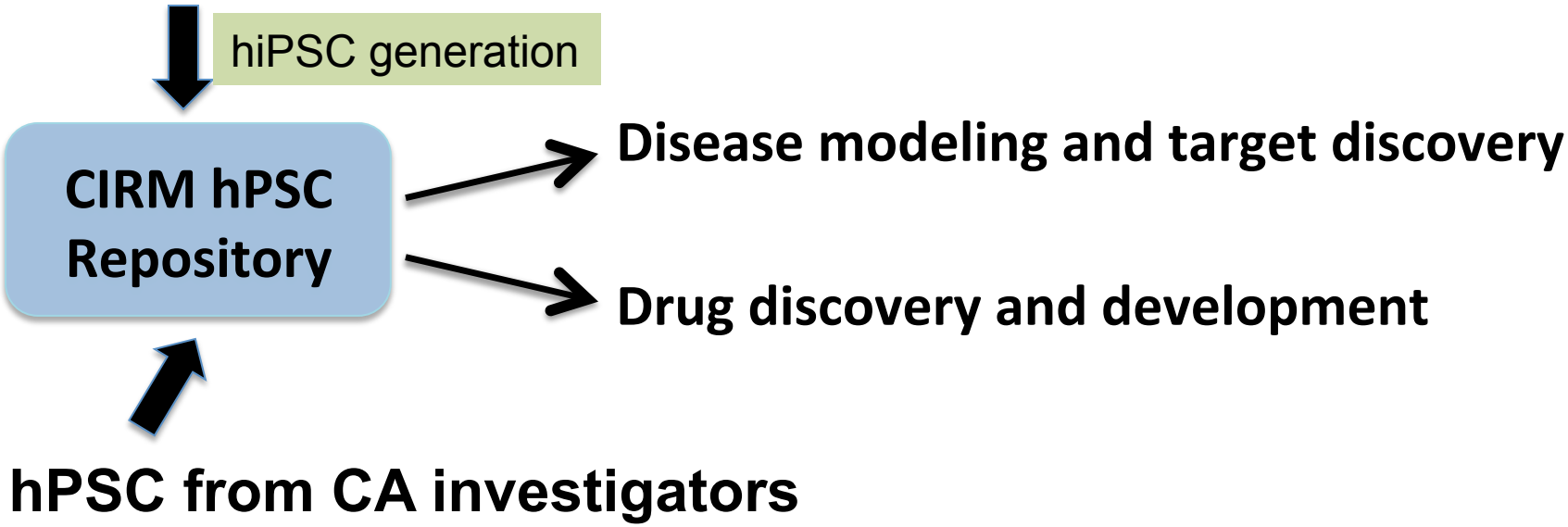
CIRM hiPSC Initiative - Goal

Establish a high quality disease-specific hiPSC resource in California

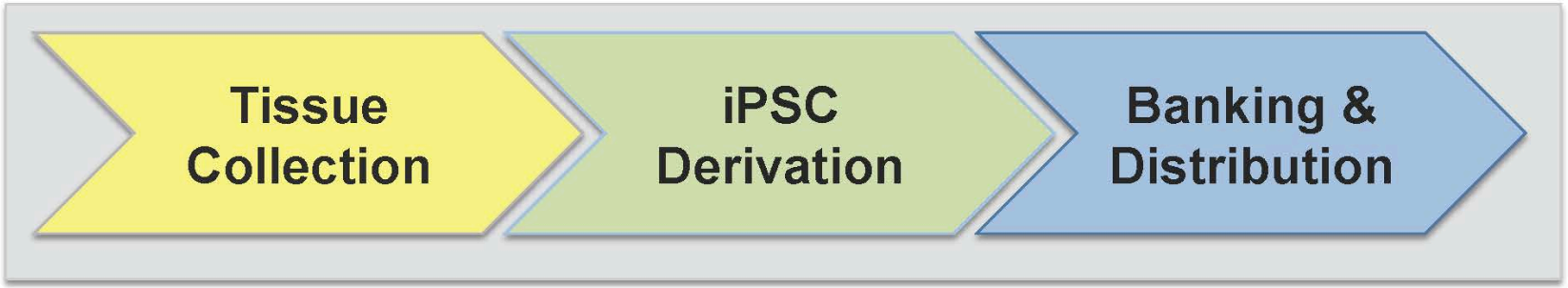
- **Prevalent, genetically complex diseases**
- **Tissue donor medical information**



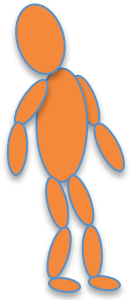
Potential Impact of Bank

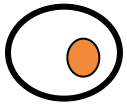
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- Disease modeling and target discovery
- Drug discovery and development
- Genomic analysis, Biomarker discovery



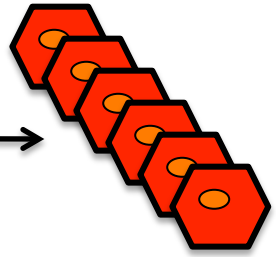
Affected individuals





iPSC

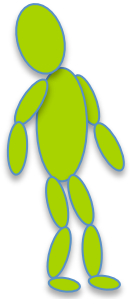
disease phenotype

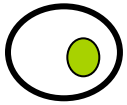


differentiated cells

- Demographic information
- Medical information

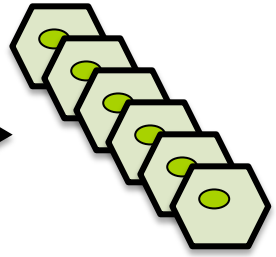
- Genome/exome sequence
- SNP profile





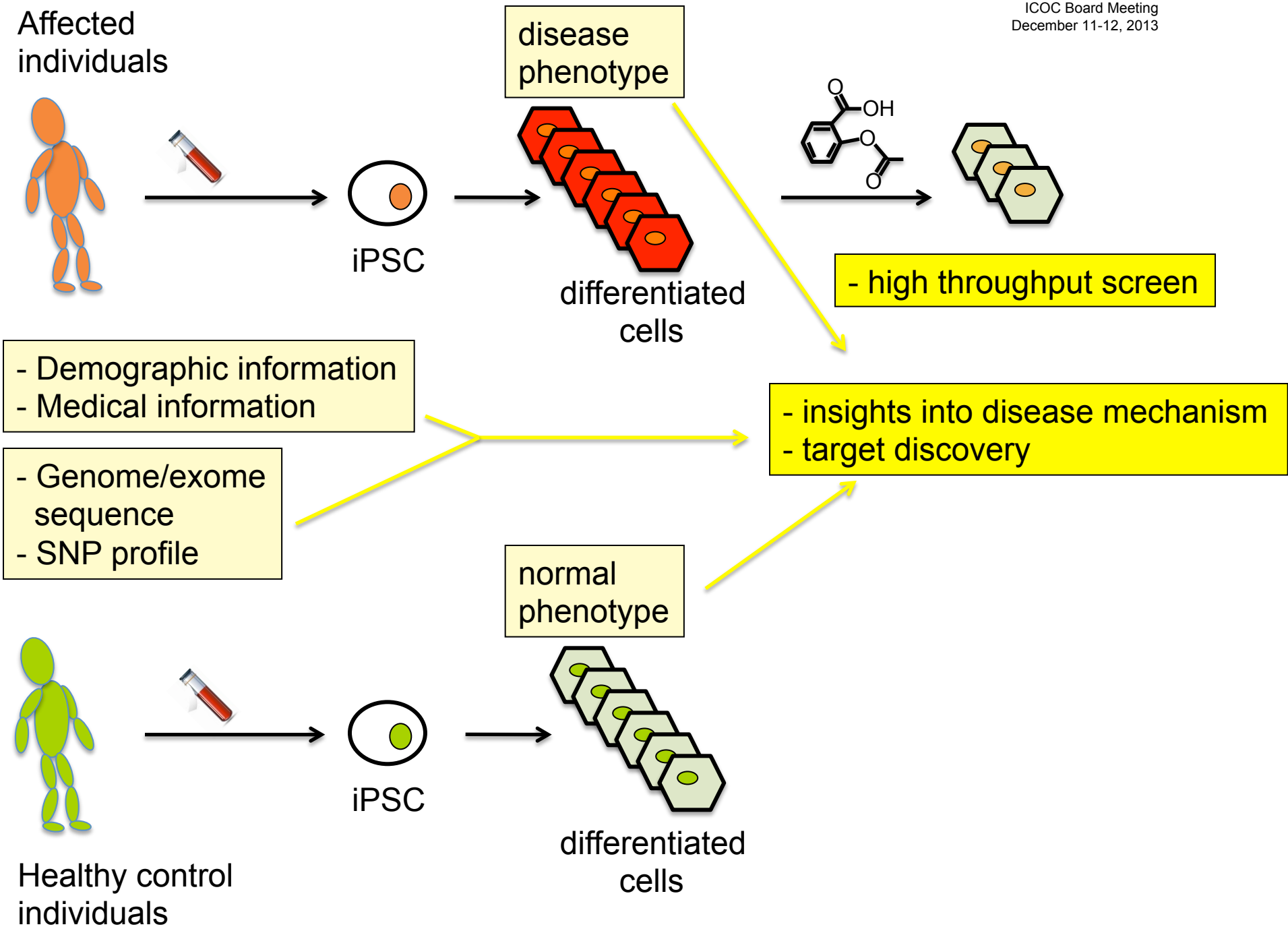
iPSC

normal phenotype



differentiated cells

Healthy control individuals


Affected individuals
disease phenotype
iPSC
differentiated cells
- high throughput screen
- Demographic information
- Medical information
- Genome/exome sequence
- SNP profile
- insights into disease mechanism
- target discovery
normal phenotype
iPSC
differentiated cells
Healthy control individuals

hiPSC Initiative - Awardees

Buck Institute

Tissue Collection for Disease Modeling	hiPSC Derivation Thomas Novak, CDI	hPSC Repository Steven Madore, Coriell

1	Joseph Gleeson	UCSD	Neurodevelopmental Disorders
2	Joachim Hallmayer	Stanford	Idiopathic Autism
3	Joseph Wu	Stanford	Idiopathic Familial Dilated Cardiomyopathy
4	Jacquelyn Maher	UCSF	Viral Hepatitis, NASH
5	Brigitte Gomperts	UCLA	Idiopathic Pulmonary Fibrosis
6	Kang Zhang	UCSD	Blinding Eye Diseases
7	Douglas Galasko	UCSD	Alzheimer's Disease

Total capacity: 3000 tissue donors
Total cases: 2450
Goal: specify 550 shared controls

Human stem cell transplantation

How to prevent immunological rejection

- Individualised iPSC
- Somatic-cell nuclear transfer
- Genetic manipulation of iPSC to reduce immunogenicity
- Induction of immunological tolerance
- HLA matching (create a bank of stem cell lines from which to find the best match)

Creation of national and international stem cell banks:

Comprised of hESC and hiPSC selected to be immunologically compatible with a large proportion of the potential recipient population

How large would a pluripotent stem cell bank need to be to make HLA matching a practical proposition ?

Populating an optimal iPSC bank to facilitate HLA matched stem cell therapy

- Determined all possible theoretical homozygous HLA-A, -B, -DR combinations
- Determined the utility of each theoretical homozygous HLA combinations to provide an HLA match for a representative sample of the Japan or UK populations
- Determine which of these ‘useful’ theoretical homozygous HLA combinations exist among the 22 million HLA typed volunteer HSC donors on the BMDW registry as donors for hiPSC derivation
- Identify the optimal potential iPSC donor panel to facilitate HLA matched stem cell transplantation

HLA haplotype banking and iPSC Japanese population

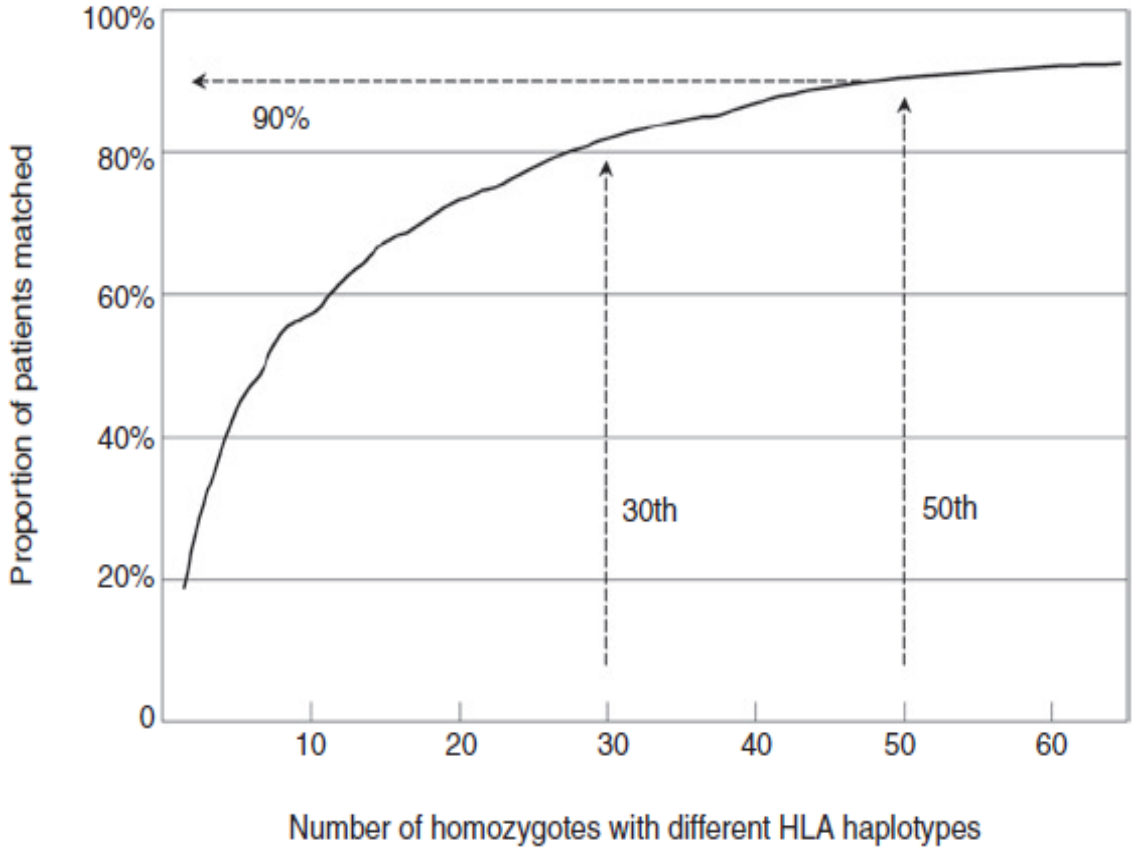
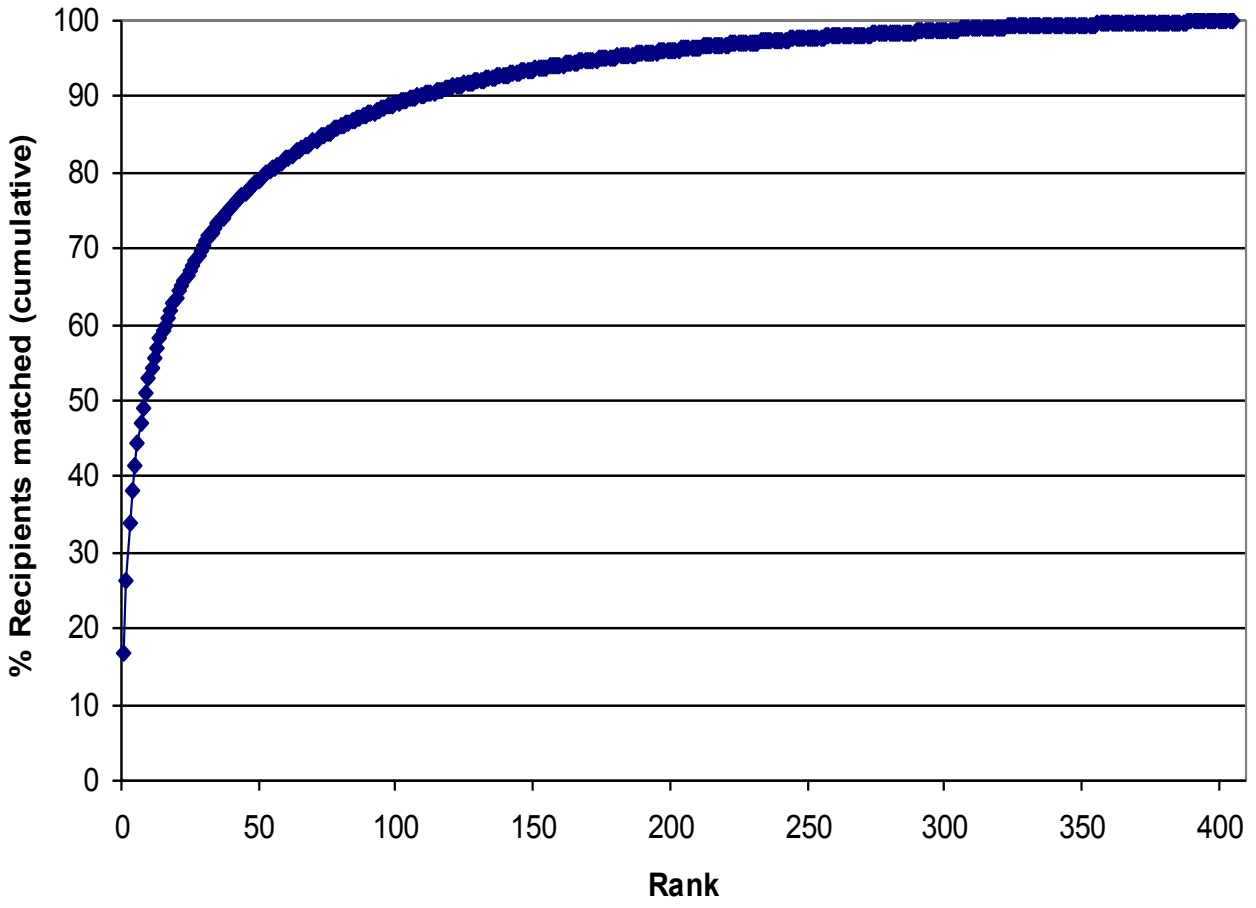


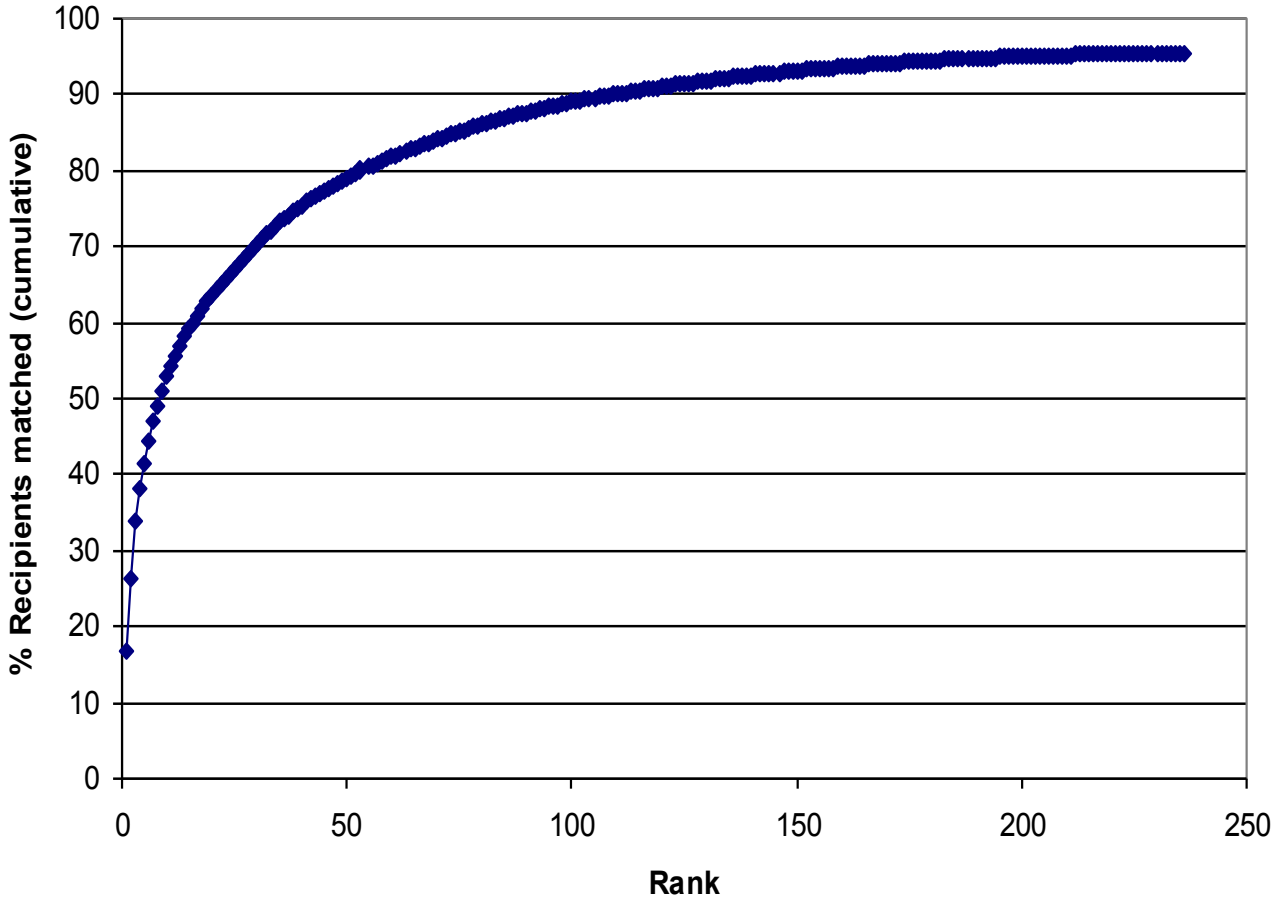
Figure 1 Cumulative proportion of patients with at least one HLA-A, HLA-B and HLA-DR–matched homozygous donor related to the number of homozygote donors with different HLA haplotypes, ordered according to their frequencies.

Nakatsuji et al, Nature Biotechnology 2008

Utility of matching using optimal theoretical homozygous HLA-A, -B, -DR combinations for the UK population



Utility of an optimal HLA homozygous iPSC panel identified among 17 million volunteers on BMDW for matching the UK population



Potential for HLA matching using a selected bank of iPSC

Bone Marrow Donors Worldwide registry (N=17 million)

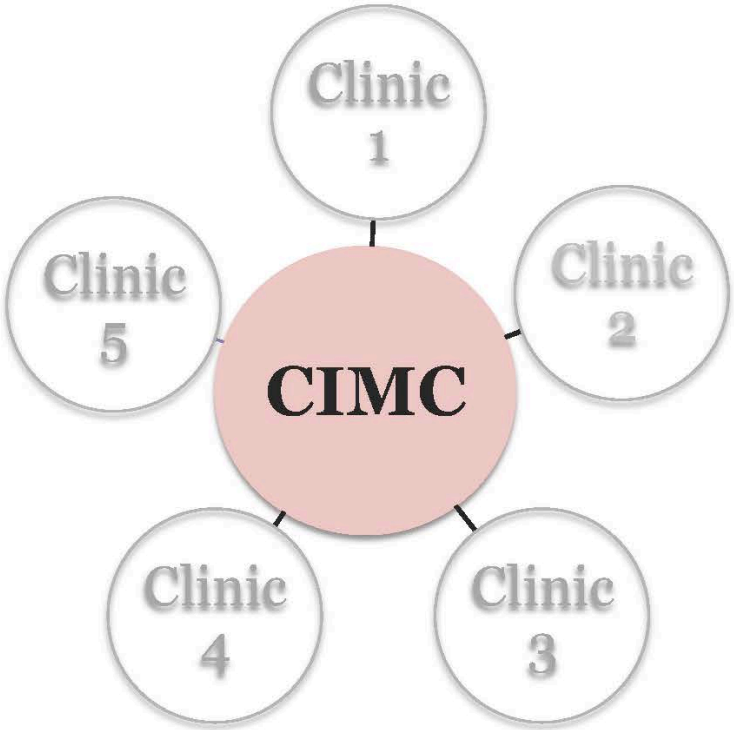
Conserved homozygous HLA haplotype	No. potential HLA matched donors	No. of HLA matched recipients	Cumulative No. of HLA matched recipients
A1, B8, C7, DR17, DQ2	>20,000	1,741 (17%)	1,741 (17%)
A2, B44, C5, DR4, DQ8	>2,500	1,074 (11%)	2,750 (27%)
A3, B7, C7, DR15, DQ6	>7,000	874 (9%)	3,540 (35%)

Utility of 15 highest ranked homozygous HLA-A, -B, -DR types identified on BMDW to provide a zero HLA mismatch for the UK population

Rank	HLA-A	HLA-B	HLA-DR	Recipients matched (%)	Recipients matched (cumulative %)
1	A1	B8	DR17(3)	16.87	16.87
2	A2	B44(12)	DR4	9.51	26.38
3	A3	B7	DR15(2)	7.45	33.83
4	A2	B7	DR15(2)	4.28	38.11
5	A2	B44(12)	DR7	3.41	41.52
6	A2	B62(15)	DR4	2.85	44.37
7	A1	B57(17)	DR7	2.54	46.91
8	A3	B35	DR1	2.10	49.01
9	A29(19)	B44(12)	DR7	2.04	51.05
10	A2	B60(40)	DR4	1.75	52.80
11	A2	B8	DR17(3)	1.60	54.40
12	A2	B27	DR1	1.28	55.68
13	A2	B44(12)	DR13(6)	1.23	56.91
14	A3	B7	DR4	1.20	58.11
15	A1	B8	DR4	0.94	59.05

CIRM Alpha Stem Cell Clinics

Coordinating and Information Management Center (CIMC)



- **Outreach, education and training (OET)**
- **Consulting services**
  - **Clinical**
  - **Regulatory**
  - **Biostatistics**
- **Patient Registry and Database**
- **Healthcare economics and business development**

• CIRM Collaboration for Global Haplotype iPSC Library

- **CIRM Alpha Clinic** Data Recovery Blood Banks, Cord Blood etc
- **CIRM Alpha Clinics** Patient Consent and Approval for iPSC storage and use
- **iPSC Derivation Methods and IP protection under GMP**

Transfer to CIRM Alpha C

- **Patient clinical data information stored under confidentiality**
- **Cell line genomics fidelity and differentiation capacity**

- **Data on haplotype, use, outcome data**
- **Connection with other haplotype banks**

Bio Bank for Distribution

Derivation in GMP Facilities

Possible $10-12M Additional Funding by CIRM through Alpha Clinics, iPSC derivation and Bio-Banking