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- Work: laboratory at the SiSCR to pursue her interest in targeting cancer stem cells in cancer therapeutic
- Area Interest: cellular and molecular mechanisms of gene regulation and targeted therapy for cancer
- Qualification & Education:
  - Ph.D. in Pharmaceutical Technology from Chulalongkorn University (2009)
  - B.Sc. in Pharmacy, Chulalongkorn University

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SiSCR
Siriraj Center of Excellence
for Stem Cell Research

# FROM STEM CELL TO STEM CELL THERAPY

Surapol Issaragrisil
Division of Hematology, Department of Medicine
Siriraj Center of Excellence for Stem Cell Research
Faculty of Medicine Siriraj Hospital
Mahidol University, Thailand

Presented by: Dr. Sudjit Luanpitpong

# Outline of The Talk

- Introduction to stem cell
- PNH and generation of iPS cell
- Thalassemia and genetic correction
- Transdifferentiation of erythroblasts to megakaryocytes
- HaploES cell banking
- EPC in DM

“All blood elements develop from one origin cell – stem cell”

Monophyletic theory, A. A. Maksimov

The term **"stem cell"** Maksimov proposed in 1908.

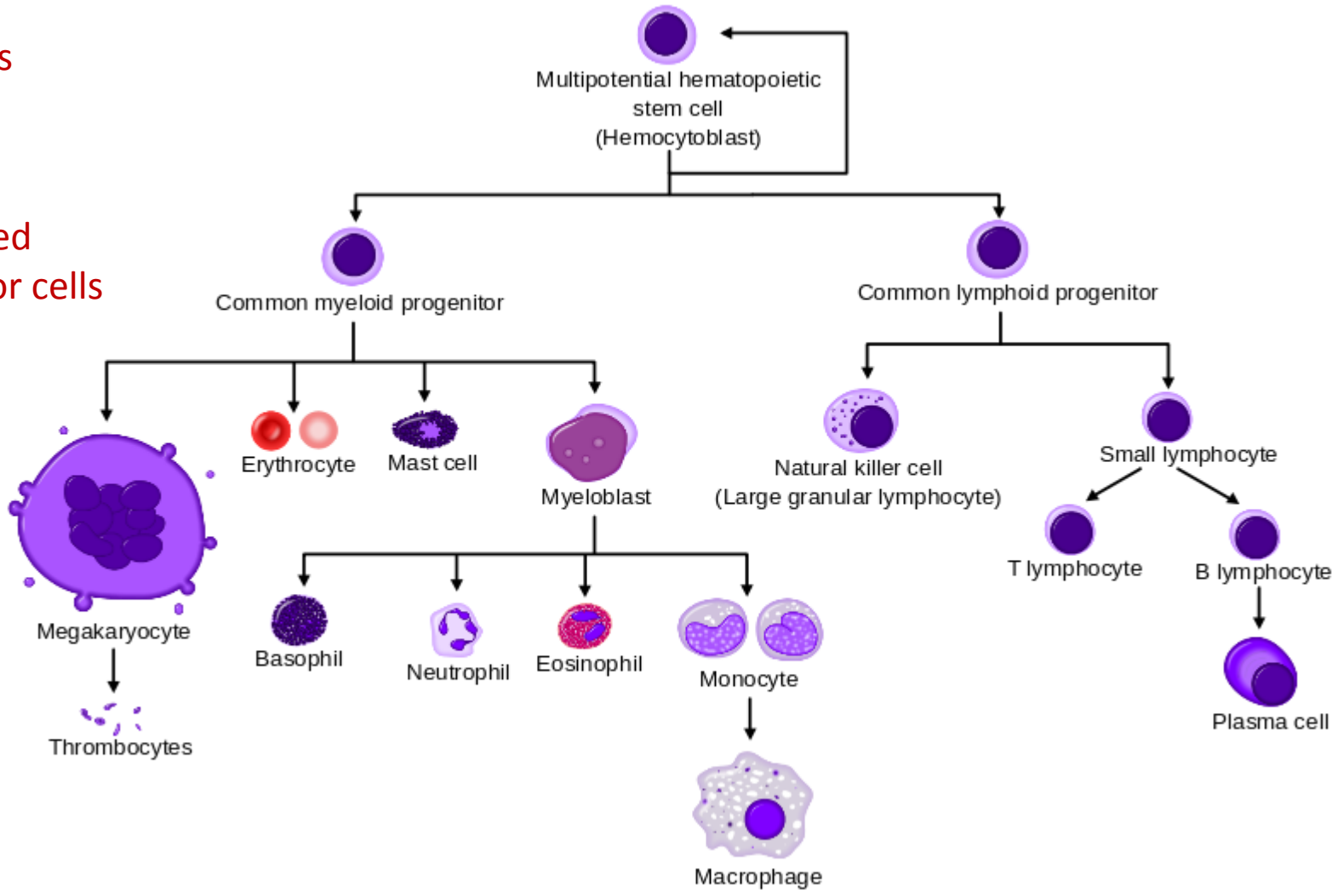
**Alexander A. Maximow**
1874 - 1928

- Developed and proved the “Unitarian theory of hematopoiesis”

# Diagram of Hematopoiesis

Stem cells

Committed progenitor cells



# What is Stem Cell?

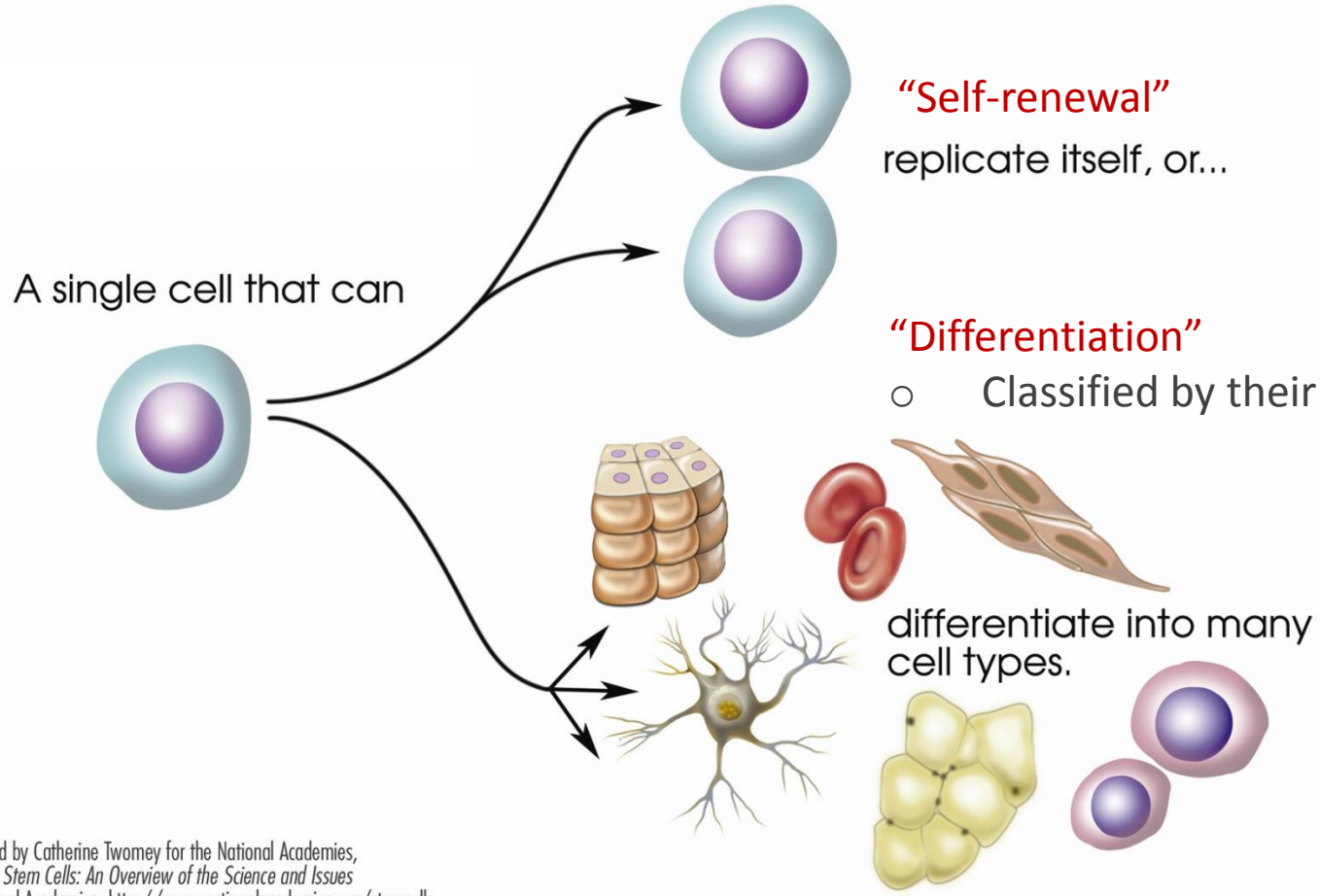
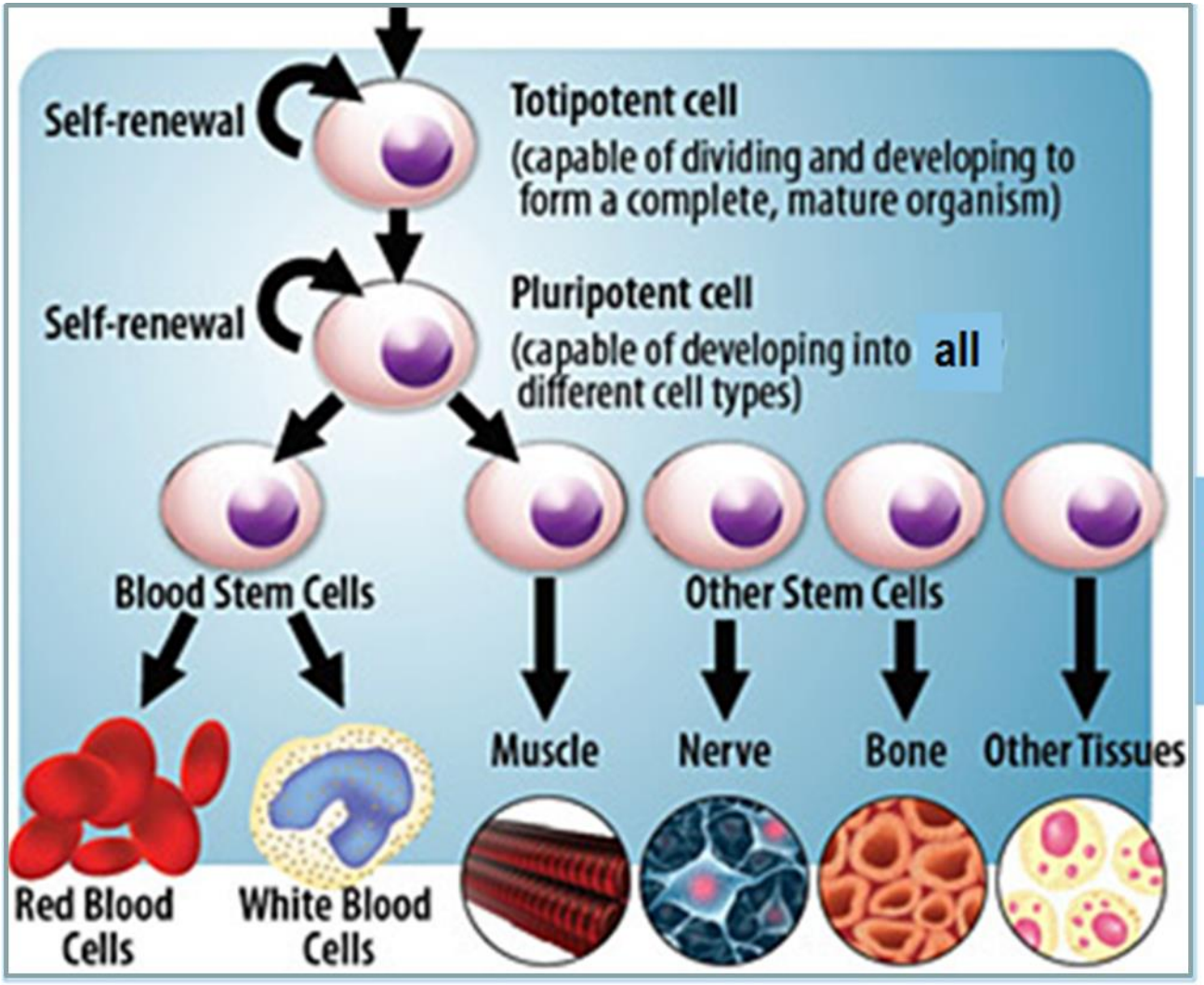


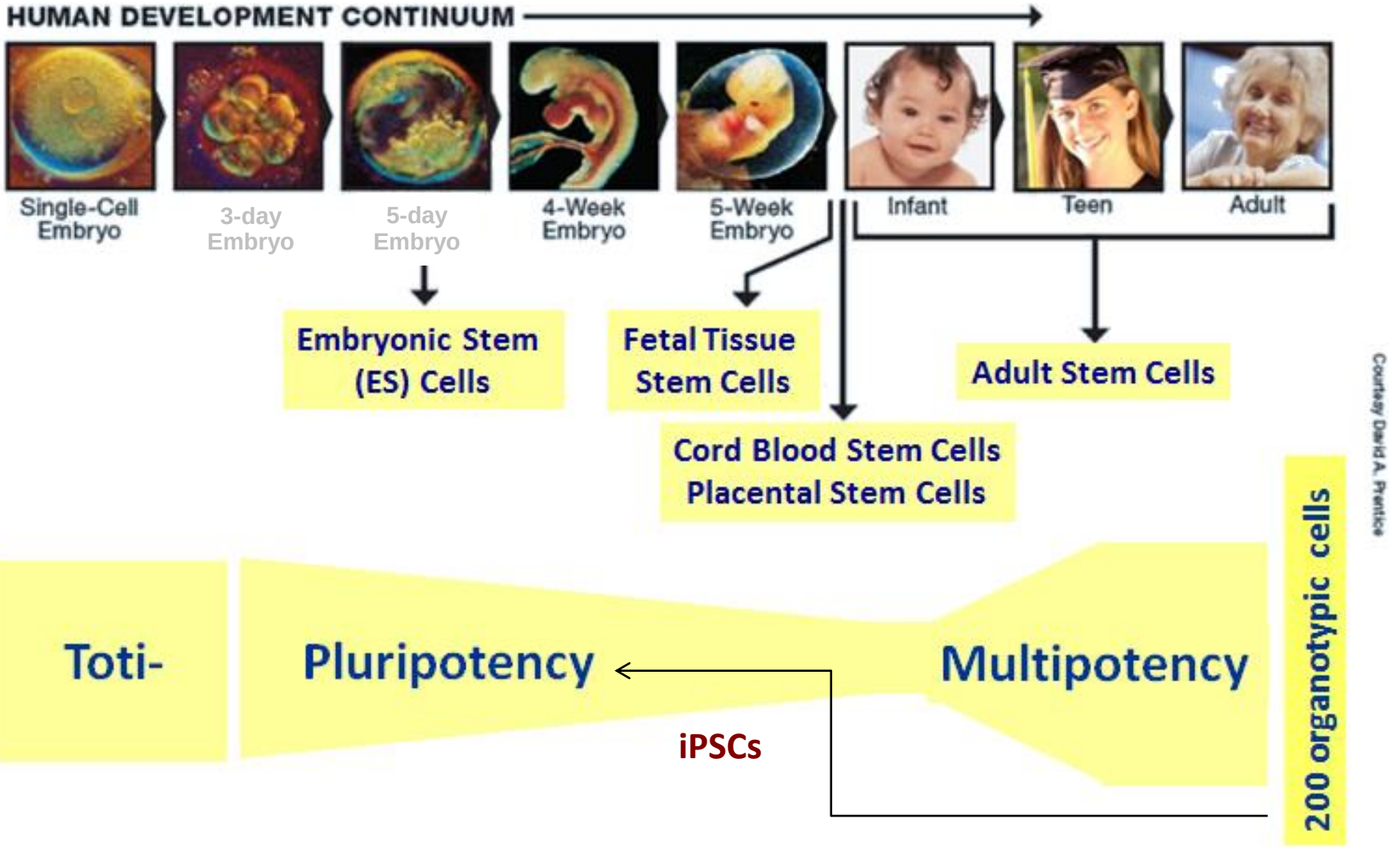

Image prepared by Catherine Twomey for the National Academies, *Understanding Stem Cells: An Overview of the Science and Issues* from the National Academies, http://www.nationalacademies.org/stemcells. Academic noncommercial use is permitted.

# Hierarchy of Stem Cells and Progenitor Cells




**Multipotent cell**
(capable of developing into many cell types)

# Where Can We Find Stem cells?



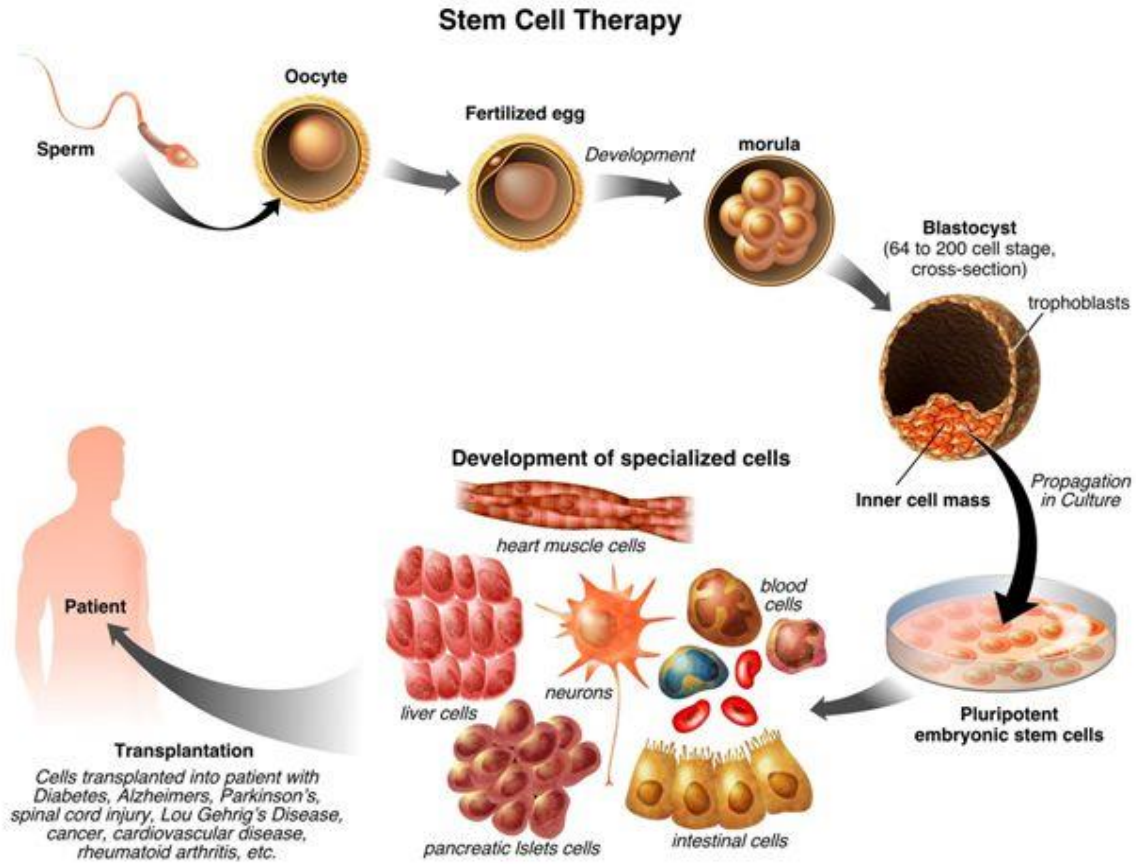
Embryonic stem cell research will prolong life, improve life and give hope for life to millions of people.

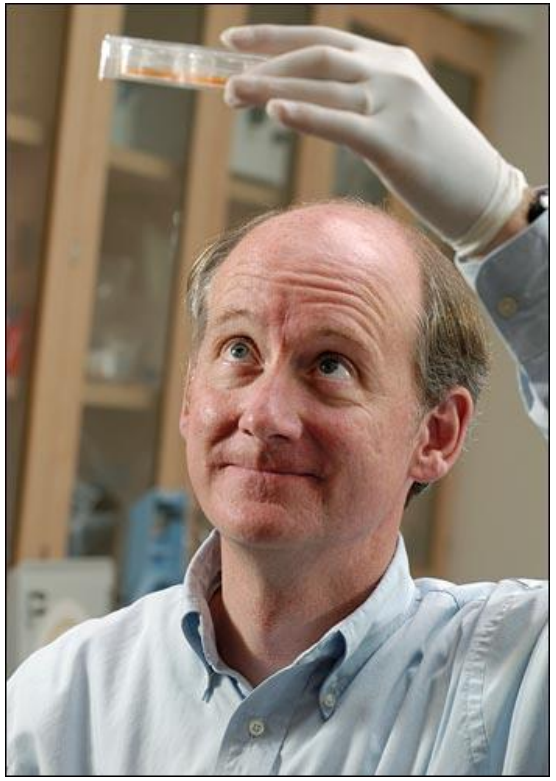
(Jim Ramstad)

"STEM CELL RESEARCH HOLDS OUT THE PROMISE OF FINDING CURES AND TREATMENTS FOR A WIDE RANGE OF DISEASES."

TOM ALLEN

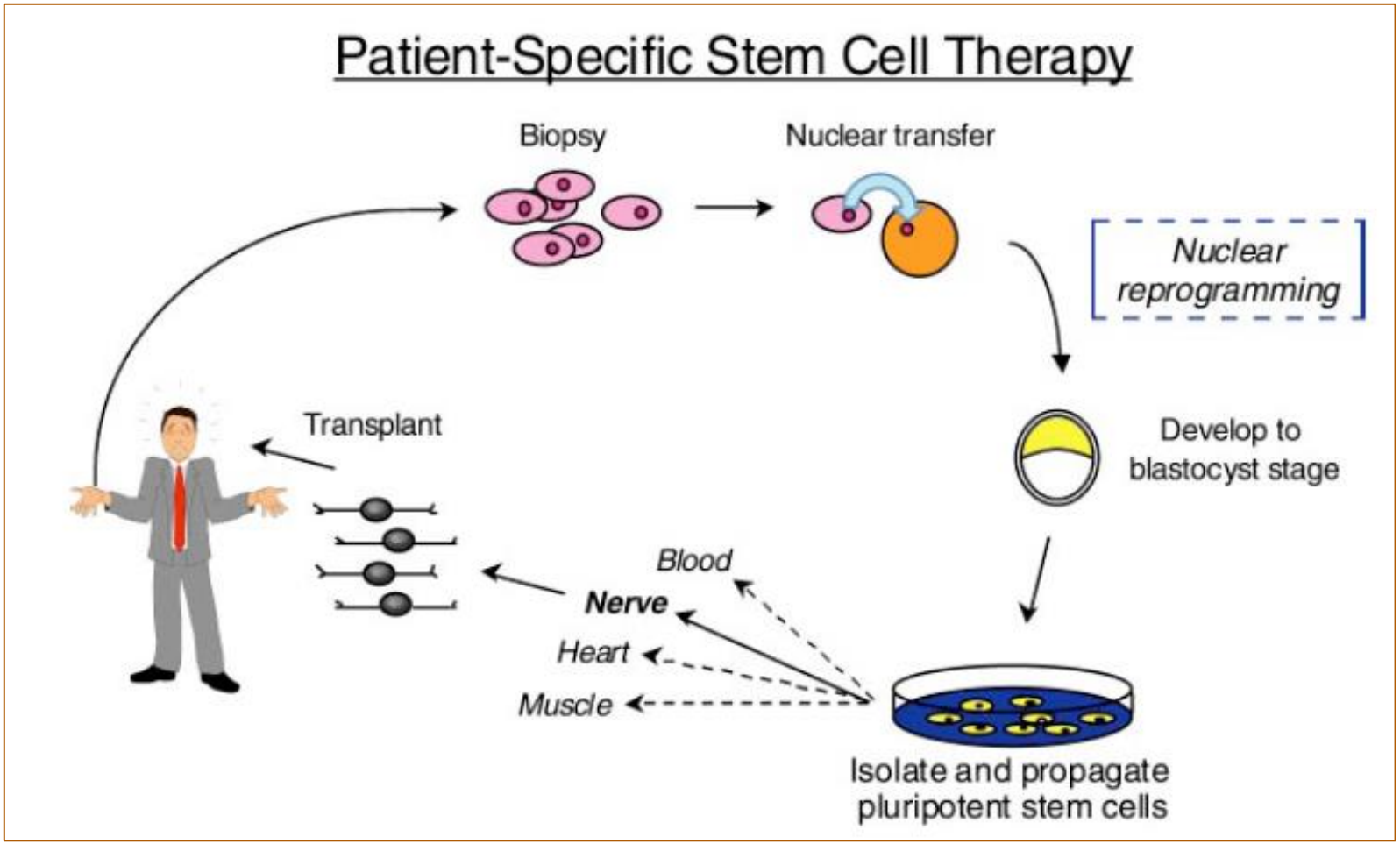
# Human Embryonic Stem Cells



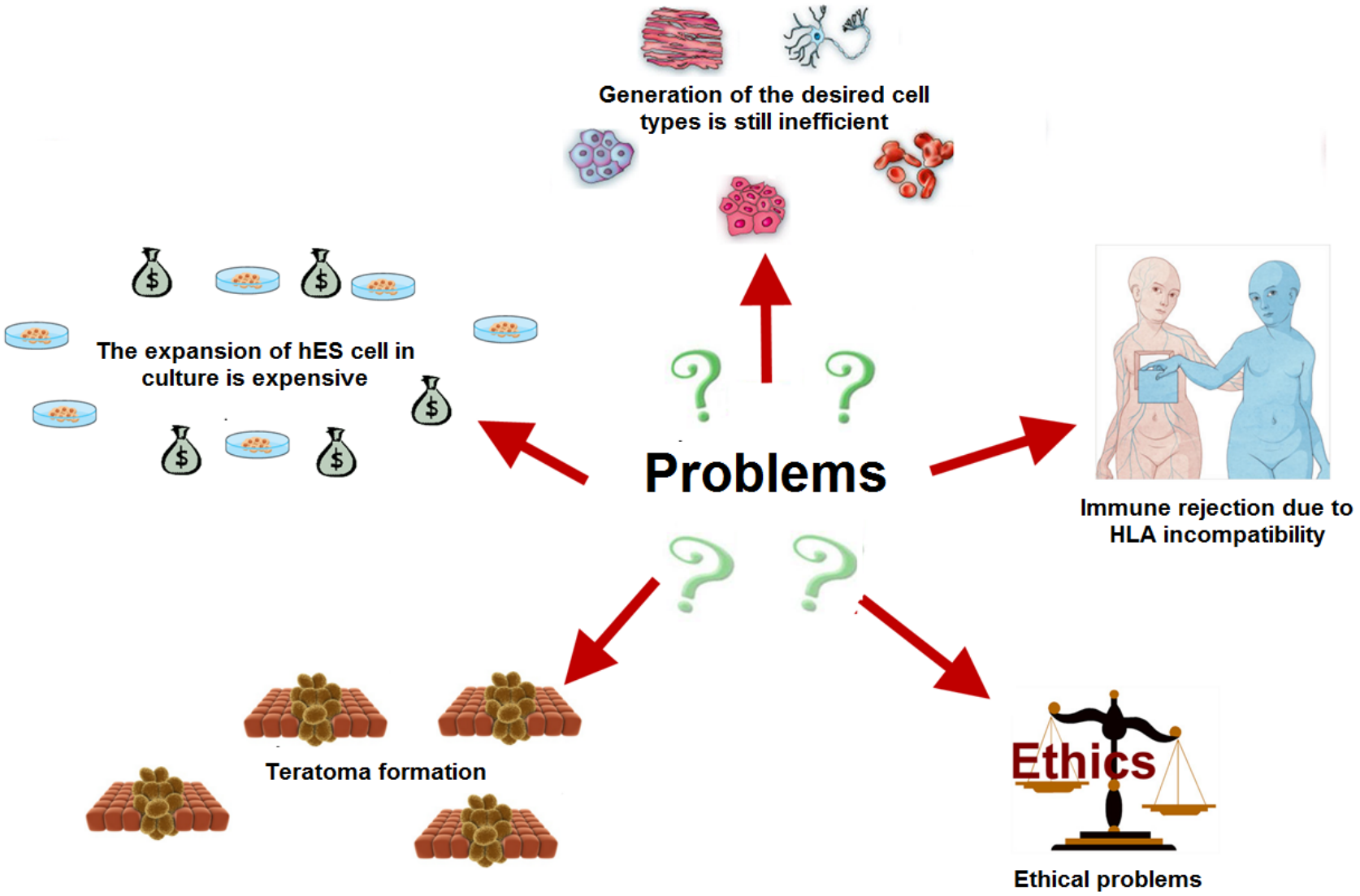
**James Thomson,** 1998
University of Wisconsin-Madison

# THERAPEUTIC CLONING

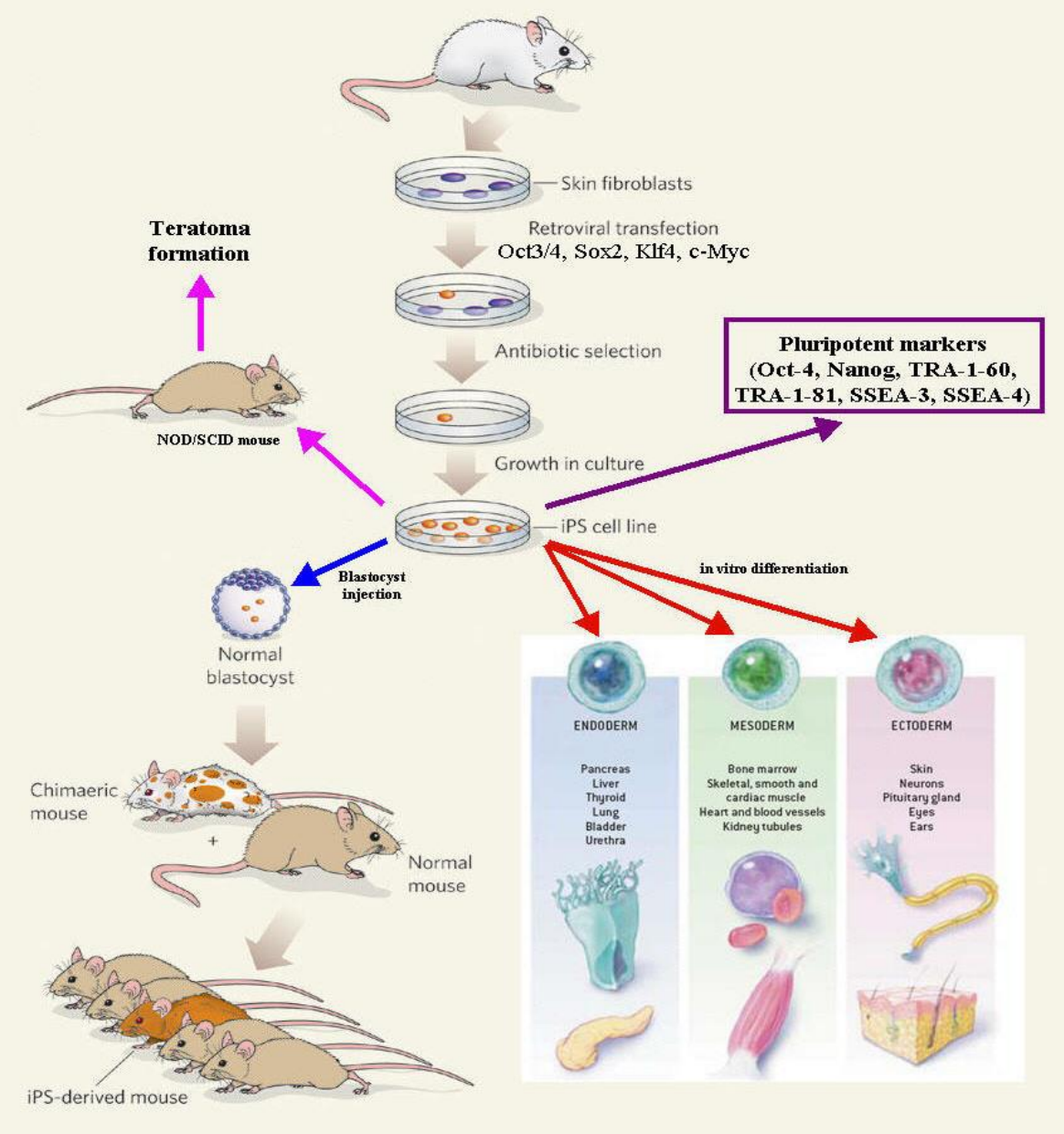


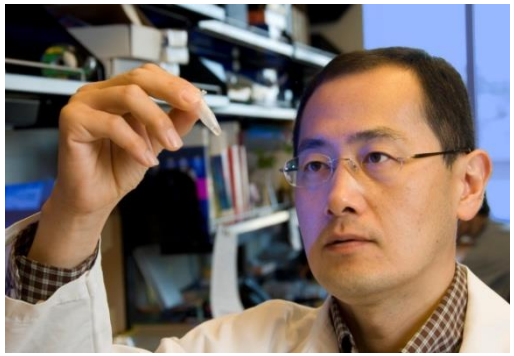

Smith *et al*., 2001

# Problems Associated with The Use of human ESCs in Clinical Applications



# Induced Pluripotent Stem Cells (iPSCs)



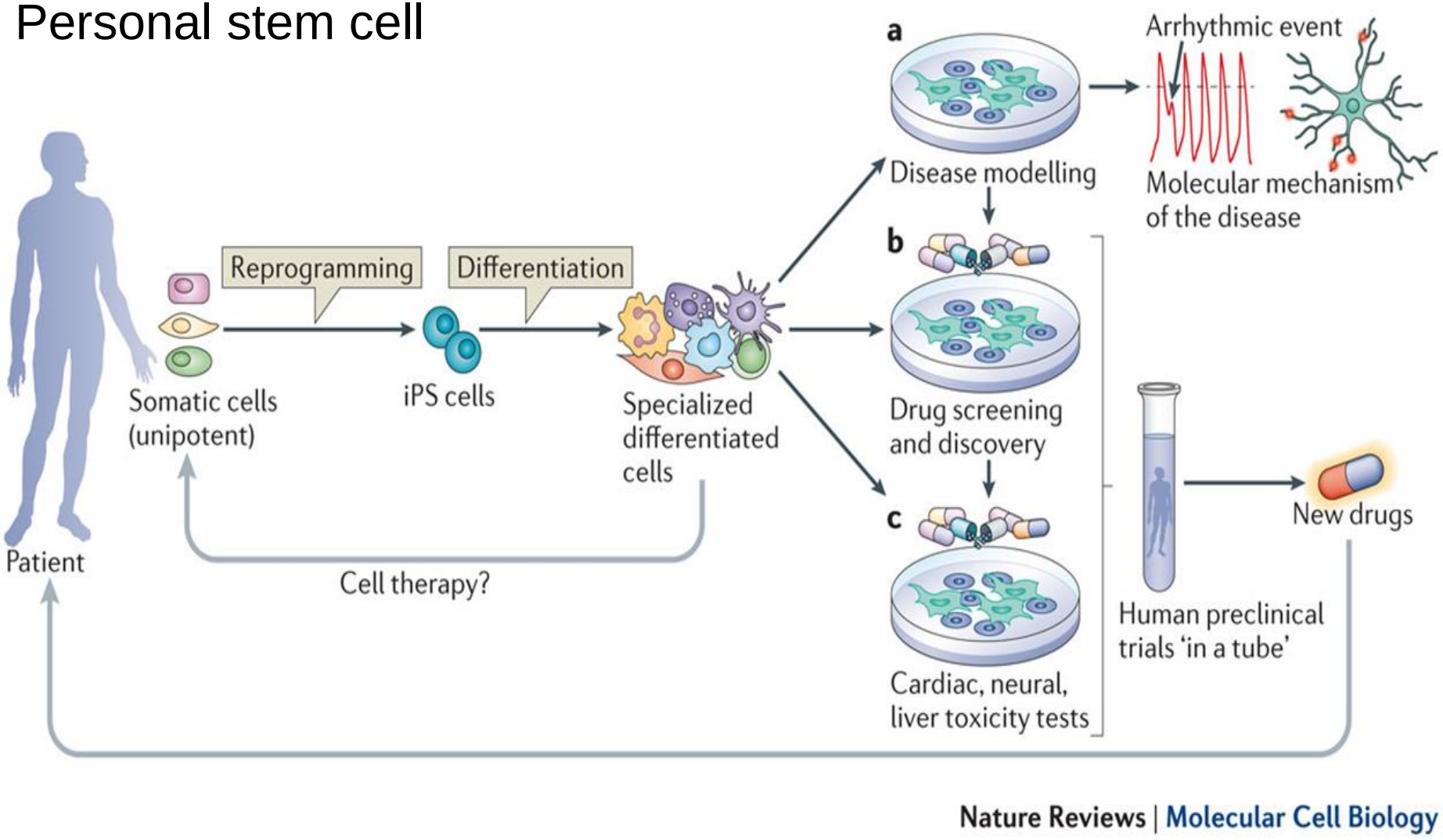



Dr. Shinya Yamanaka
Kyoto University
Nobel prize 2012 in Physiology or Medicine

Takahashi *et al*, 2006, 2007

# IPSC Therapeutic Applications

Personal stem cell

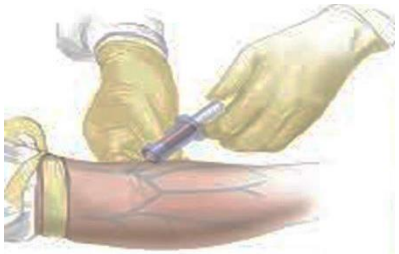



Nature Reviews | Molecular Cell Biology

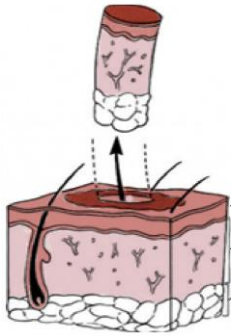
# PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

- Non-malignant, clonal disorder of hematopoietic stem cells
- Hemoglobinuria (Intravascular hemolysis) , cytopenia, thrombosis
- *PIG-A* gene mutation in HSCs → decreased or absent CD55 and CD59 expressions
- CD55 & CD59 → complement regulatory molecules

# Experimental Overview



Peripheral blood



Punched skin biopsy

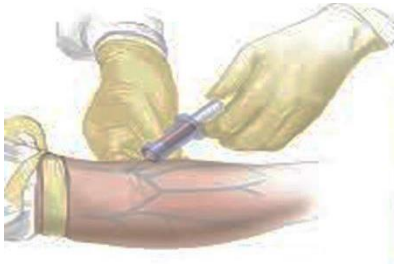
“ Diagnosis ”

“ PNH-specific iPSC generation ”

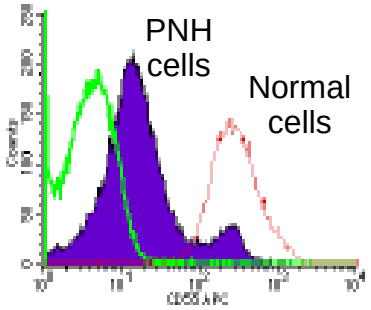
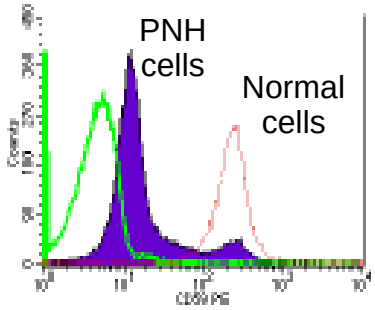
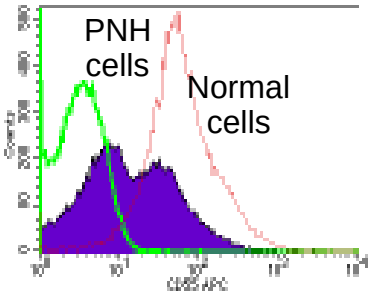
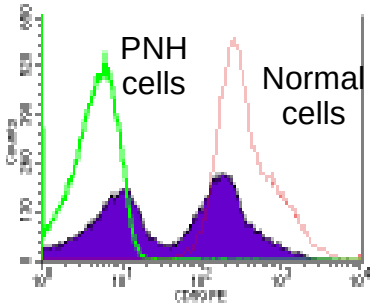
“ Characterization ”

“ Hematopoietic differentiation ”

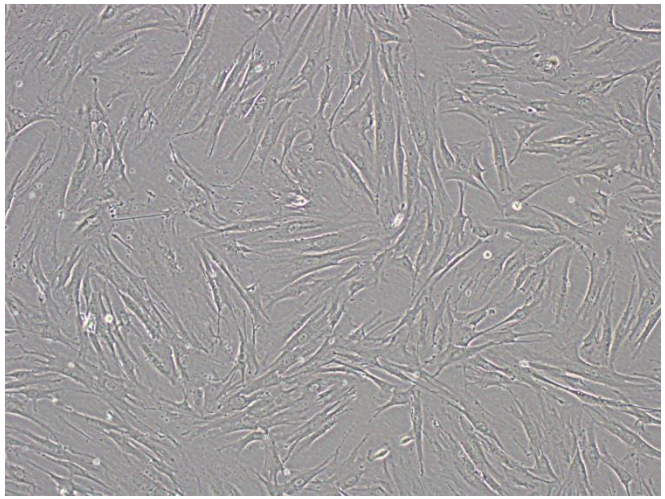
# PNH Diagnosis

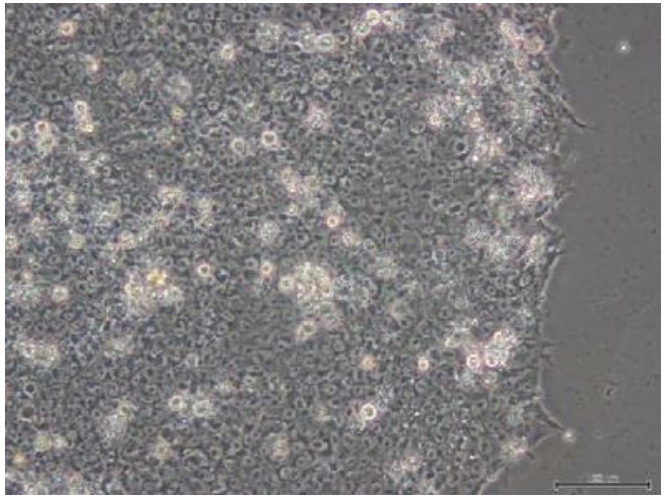


**CD55 and CD59 expressions by flow cytometry for PNH diagnosis**

| | **CD55** | **CD59** |
|---|---|---|
| **Granulocytes** |   |   |
| **Red blood cells** |   |   |

# IPSC GENERATION



**Patient's HDF**

- Spindle shape

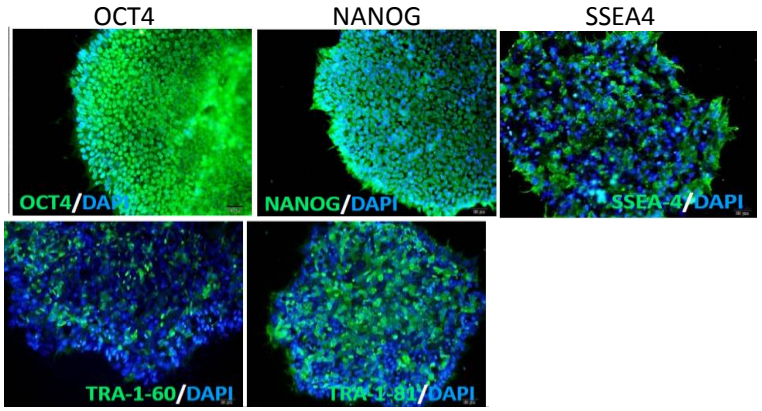
**iPS cells → hESC morphology**

- Round shape with high N/C ratio
- Compact colony with clear boundary

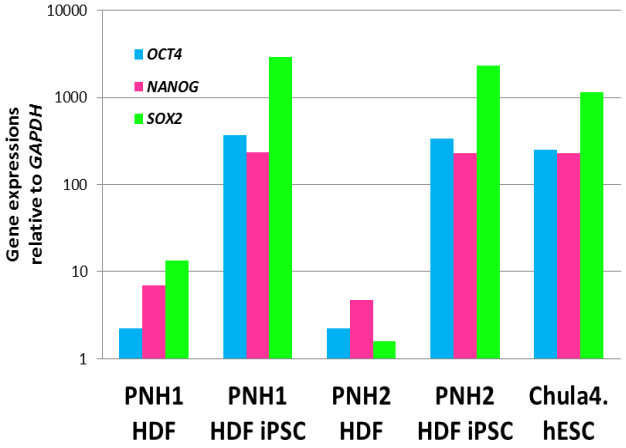
Phondeechareon, et al. Ann Hematol 2016; 95: 1617.

# IPSC CHARACTERIZATION

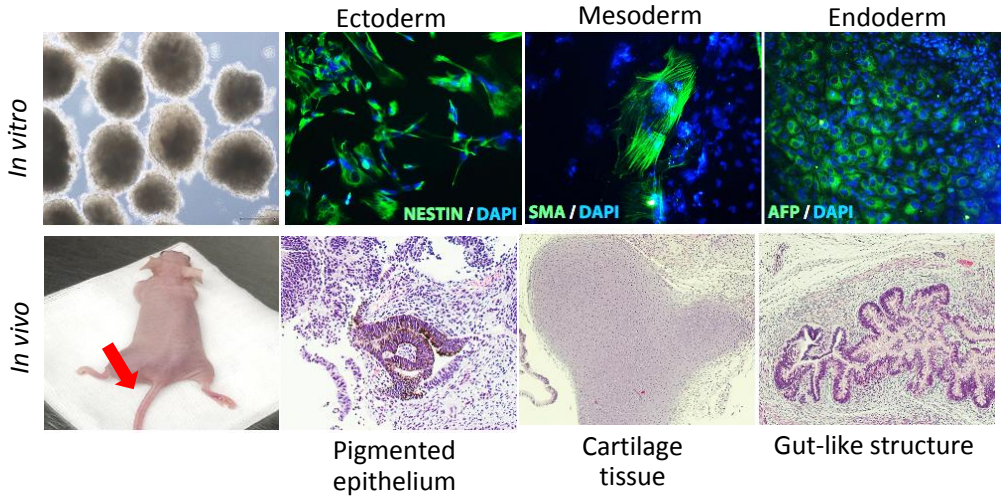
## Pluripotent marker



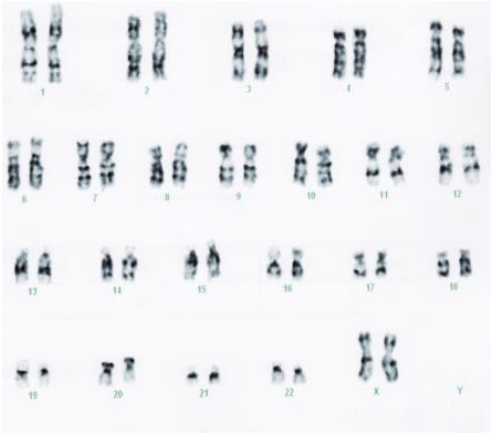

## Gene expression




## *In vitro* and *in vivo* differentiation



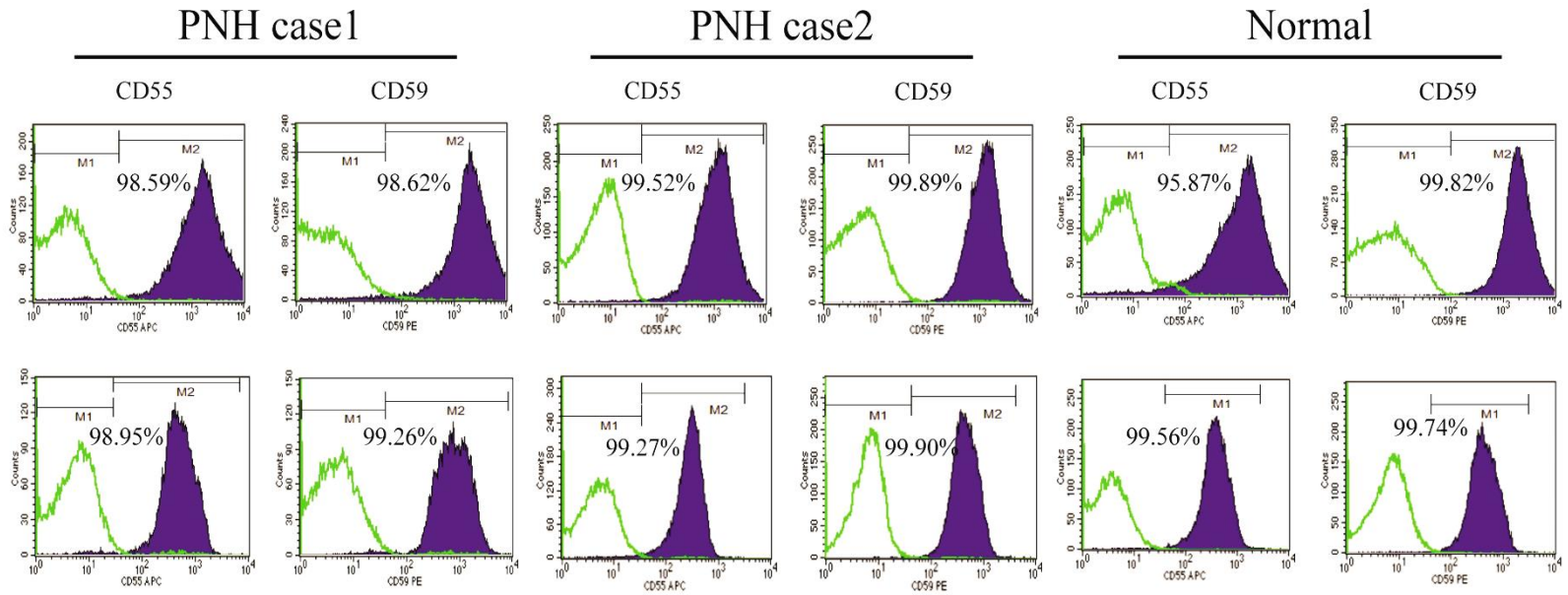

## Karyotypic analysis



Phondeechareon, et al. Ann Hematol 2016; 95: 1617.

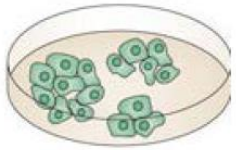
# EXPRESSION OF CD55 AND CD59

**CD55 and CD59 expression**




Phondeechareon, et al. Ann Hematol 2016; 95: 1617.

# HEMATOPOIETIC CELL DIFFERENTIATION



**PNH-specific iPSCs**

Differentiation

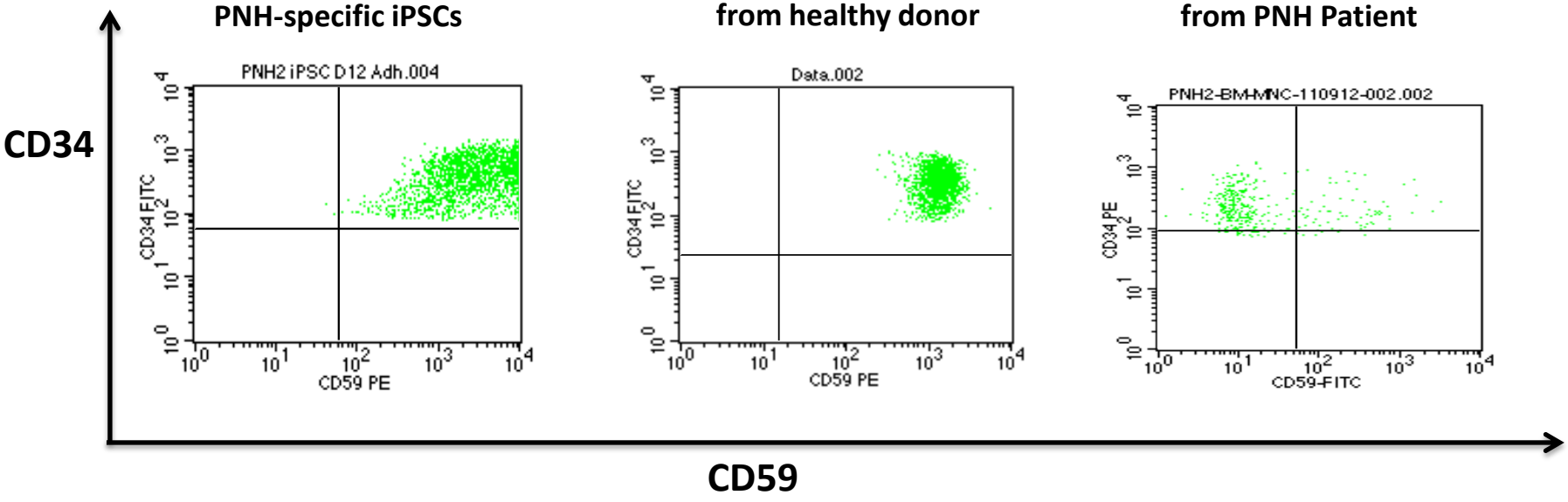
Cytokine cocktails

**CD34 and CD59 expressions by flow cytometry**

**CD34⁺ HSPCs derived from PNH-specific iPSCs**

**CD34⁺ HSPCs from healthy donor**

**CD34⁺ HSPCs from PNH Patient**




Phondeechareon, et al. Ann Hematol 2016; 95: 1617.

# CONCLUSION

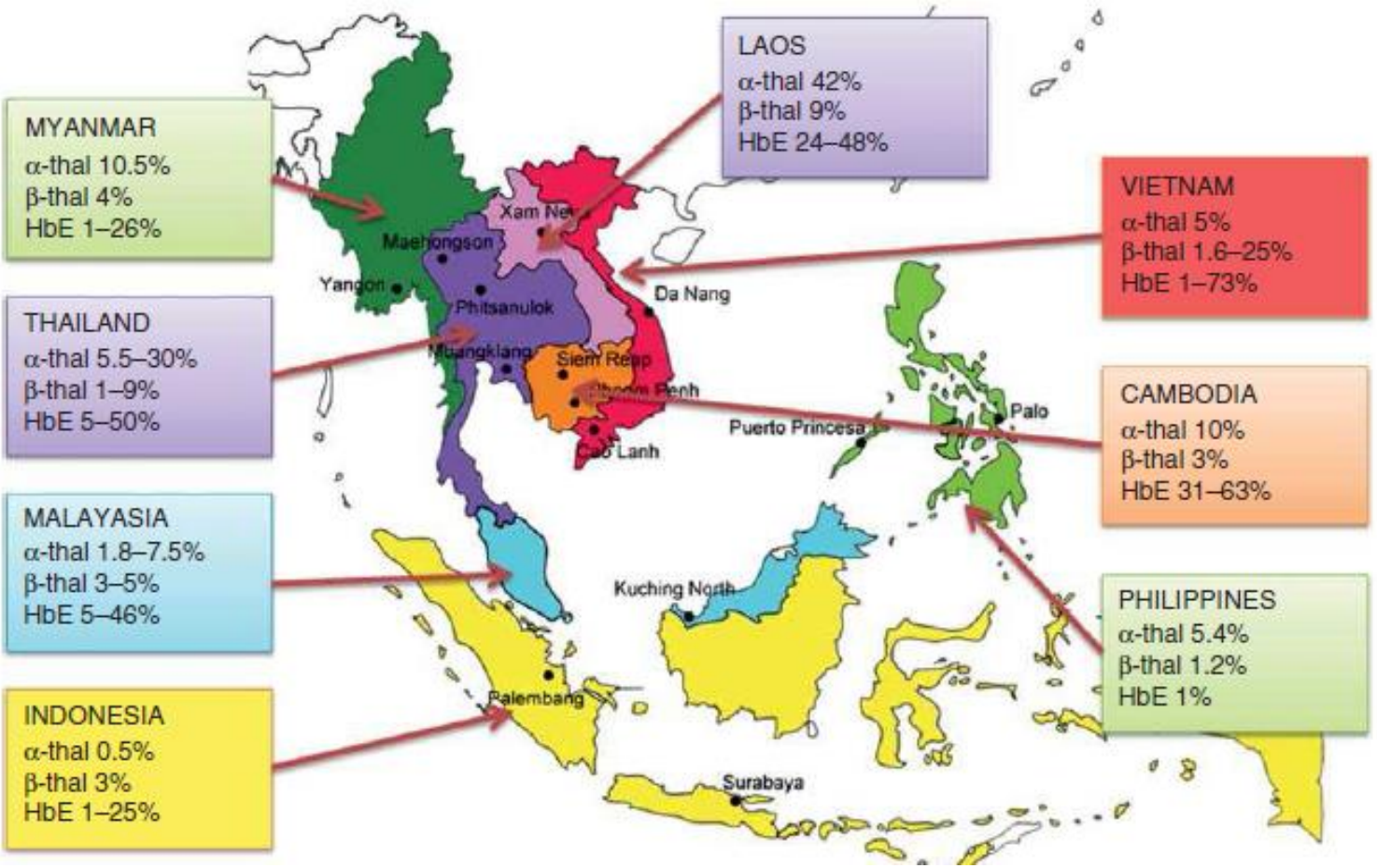
- Our PNH-specific iPSCs demonstrated pluripotency with normal karyotype.

- After reprogramming, PNH-specific iPSCs maintained expressions of CD55 and CD59 at the normal levels.

- $CD34^+$ HSPCs derived from PNH-specific iPSCs expressed CD59 at the normal level similar to those of healthy donor's $CD34^+$ HSPCs.

- PNH-specific iPSCs may provide a potential cell source for autologous transplantation in the future.

# Prevalence of Thalassemia and Hemoglobinopathies in Asia Pacific Region




Viprakasit V et al. *Expert Opinion on Orphan Drug 2014.*

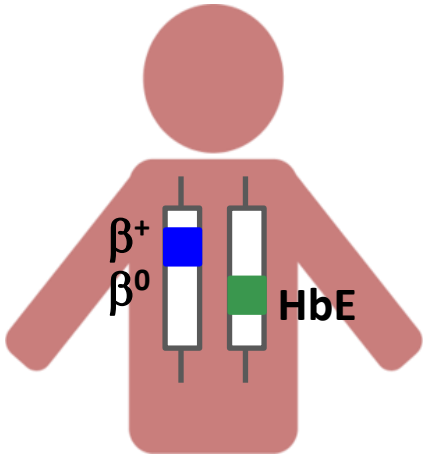
# EPIDEMIOLOGY OF THALASSEMIA SYNDROMES IN THAILAND

- At least 800,000 patients are thalassemia patients in Thailand
- At least 20 million with HbE trait worldwide and nearly 1 million are at risk of HbE/b-thalassemia


| Disease | Pregnancy at risk | New cases | Surviving cases |
|---|---|---|---|
| β-TM | 2,500 | 625 | 6,250 |
| Hb Bart's hydrops | 5,000 | 1,250 | 0 |
| β-Thal/HbE | 13,000 | 3,250 | 97,500 |
| HbH disease | 28,000 | 7,000 | 420,000 |
| Total | 48,500 | 12,125 | 523,750 |

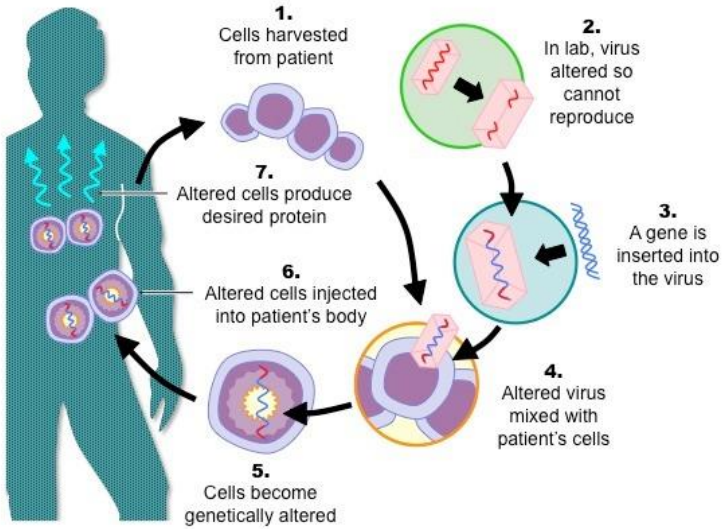
Source: thalassemia Foundation of Thailand 1998.
Thal, thalassemia.

# Beta Thalassemia/Hemoglobin E




- One allele produces decreased levels ($\beta^+$) or no beta globin ($\beta^0$), another allele produces abnormal HbE.
  - $\beta^+$or $\beta^0$ can result from various possible mutations.
  - HbE results from a single point mutation at codon 26 of the *HBB* gene, G → A substitution (glutamic acid → lysine).

# Standard Treatments




- Blood transfusions
- Iron chelation therapy
- Folic acid supplements

- Hematopoietic stem cell transplantation (HSCT)

Future treatments

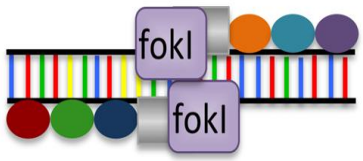
- γ-globin inducing agents
- Gene therapy in HSCs
- Genome editing in HSCs and iPSCs

http://landdestroyer.blogspot.com/2012/12/on-cusp-of-ending-big-pharma.html

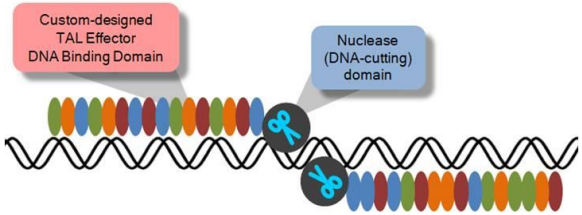
# GENOME EDITING TECHNOLOGIES

**Artificially engineered nucleases**

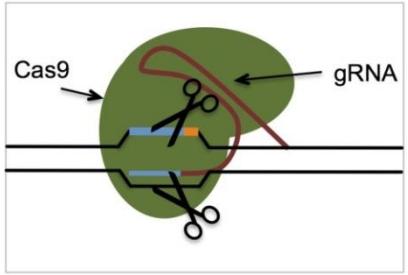
## Zinc finger nucleases (ZFNs)




## Transcription activator-like effector nucleases (TALENs)

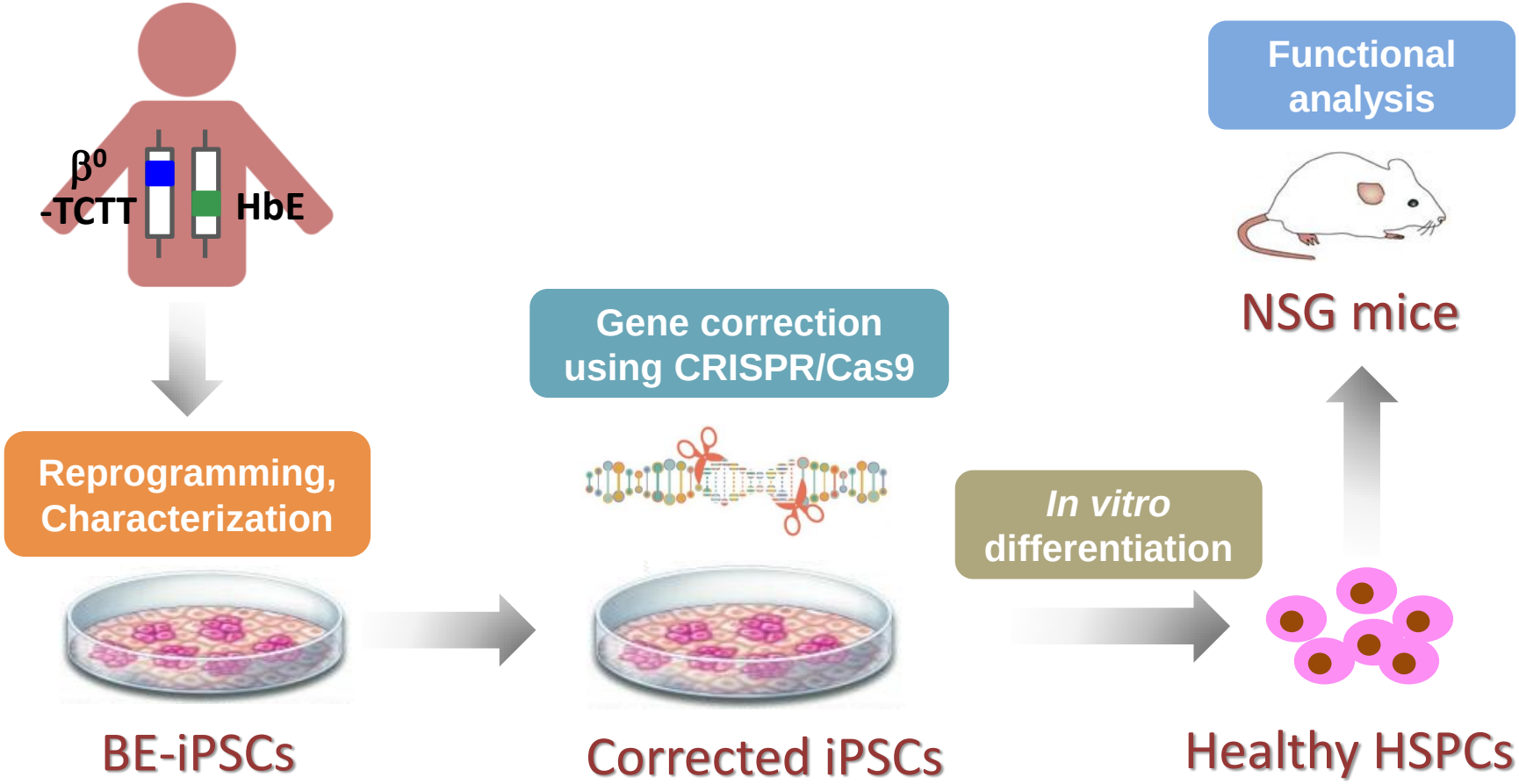



## RNA-guided CRISPR-Cas9 nuclease

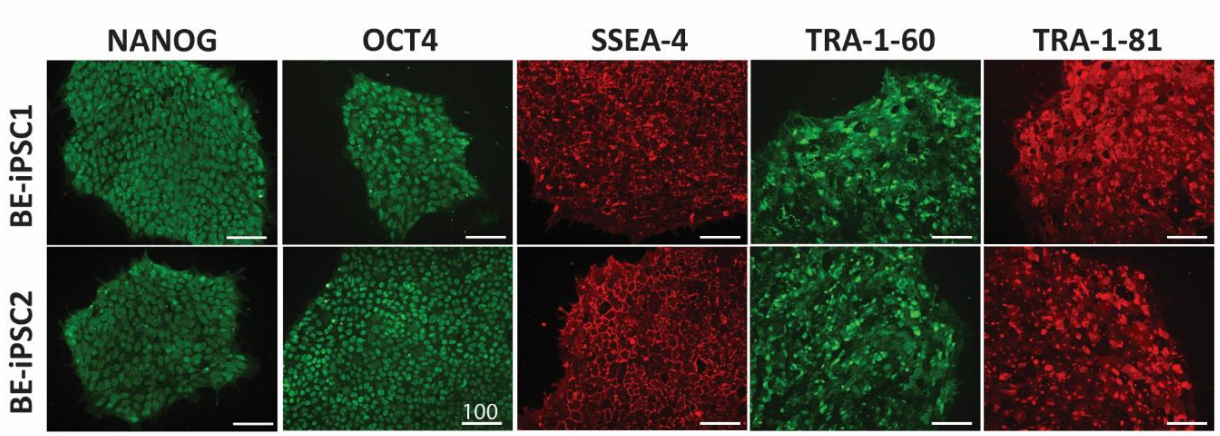


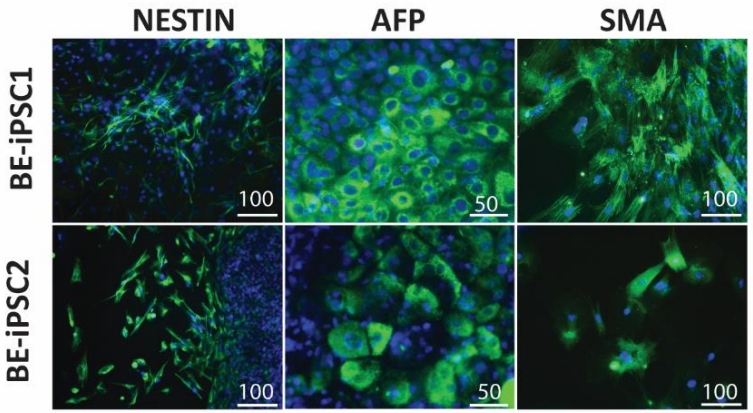
# Genetic Correction of Beta Thal/HbE iPSCs

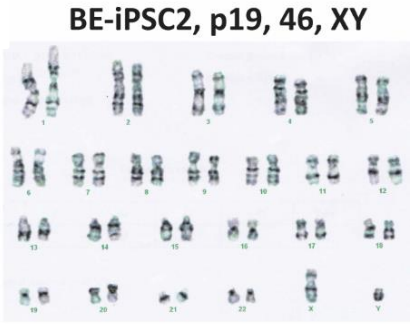
- To correct mutation (HbE: Codon 26 G→A) on HBB gene of beta-thalassemia/hemoglobin E iPSCs using CRISPR/Cas9.

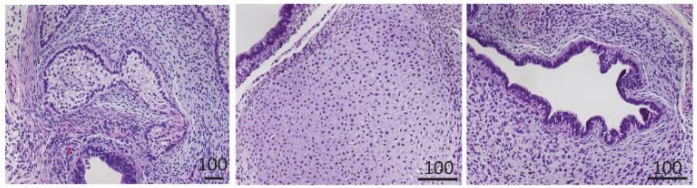


# Characterization of β-Thalassemia/HbE iPSCs



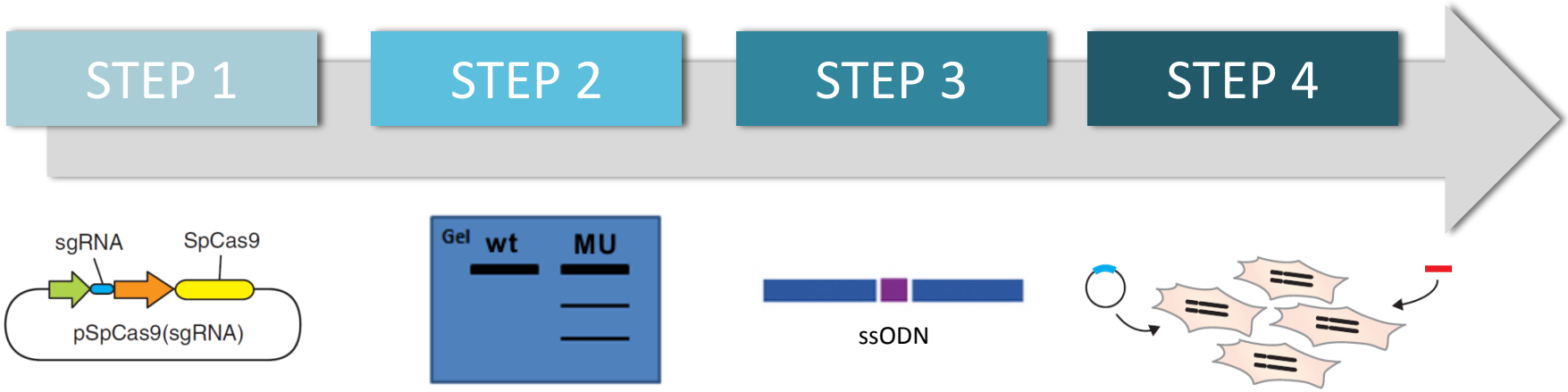




Wattanapanitch, et al. submission 2017

# Target Mutation Correction by CRISPR/Cas9

## Workflow



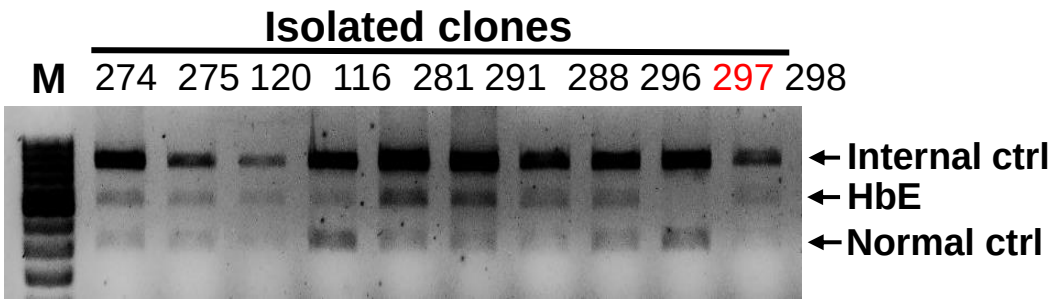

Construct Cas9 & sgRNA plasmids

Evaluate the function and efficiency of sgRNAs

Prepare a repair template

Genome edit the cells

# GENETIC CORRECTION OF BE-iPSCs




DNA sequencing of negative clones

**312 clones screened**

- **93 clones were transfected**
- **23 HbE negative clones** ***(7.4% DSB efficiency)***
- **14 clones showed indels** ***(4.5% NHEJ)***
- **9 clones showed successful seamless correction of HbE mutation.** ***(2.9% HDR)***

**DSB**

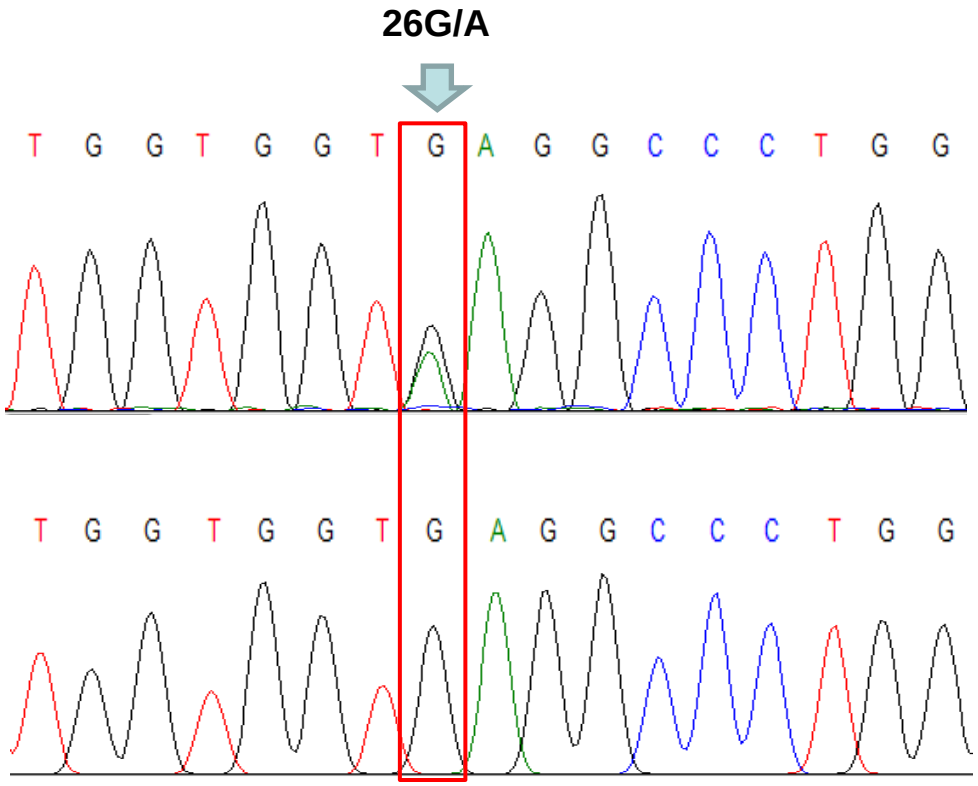
| | |
|---|---|
| **βE-iPSC2** | AAGTTGGTGGTAAGGCCCTGGGCAGGTTGGTATCAAGGTTACAAGACAGGTT |
| **Corrected** | AAGTTGGTGGTGAGGCCCTGGGCAGGTTGGTATCAAGGTTACAAGACAGGTT |
| **C297** | AAGTTGGTGGTGAGGCCCTGGGCAGGTTGGTATCAAGGTTACAAGACAGGTT |
| **Corrected** | AAGTTGGTGGTGAGGCC---------- |
| **C22** | AAG----------ACAGGTT |
| **C194** | AAG----------GGTT |
| **C292** | AAGTTGG----------GGTT |
| **C232** | AAGTTGGTGG----------GGTT |
| **C88** | |
| **C138** | |

Wattanapanitch, et al. submission 2017

# SEAMLESS CORRECTION OF HBE MUTATION

**βE-iPSC2**
**(Before genome editing)**

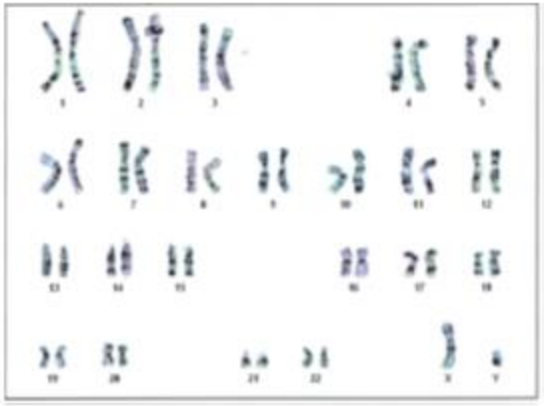
**C22**
**(After genome editing)**



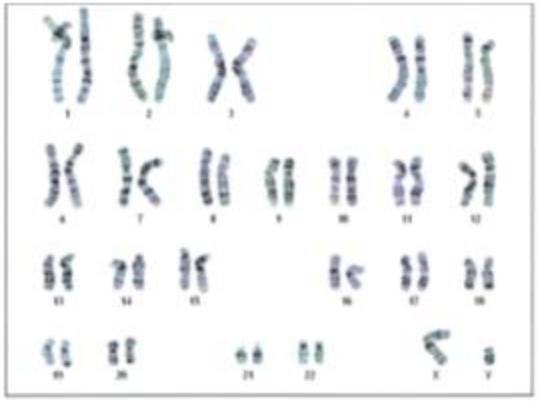

Wattanapanitch, et al. submission 2017

# All Corrected iPSCs Have Normal Karyotype

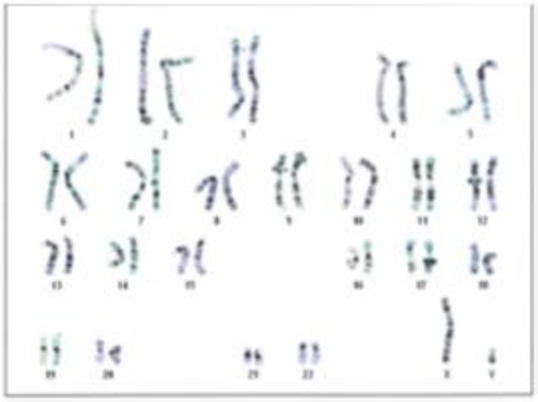
C22



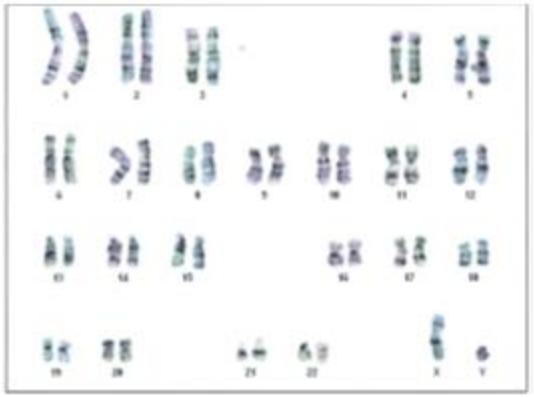
C46



C137

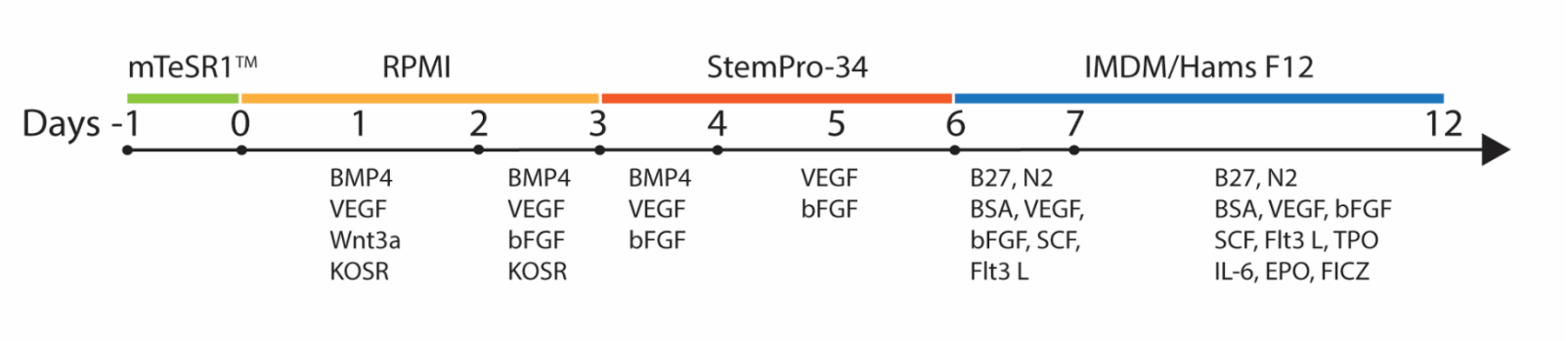


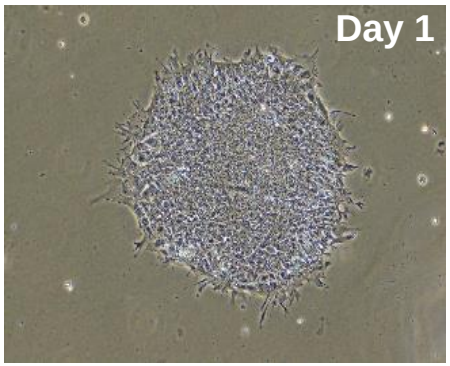
C297

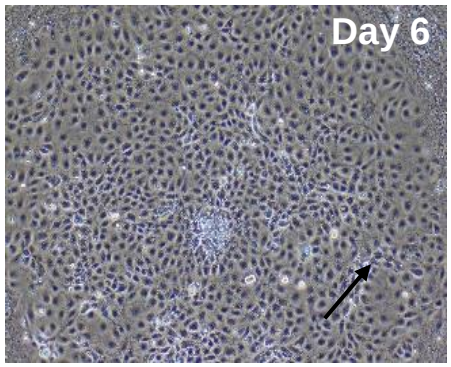


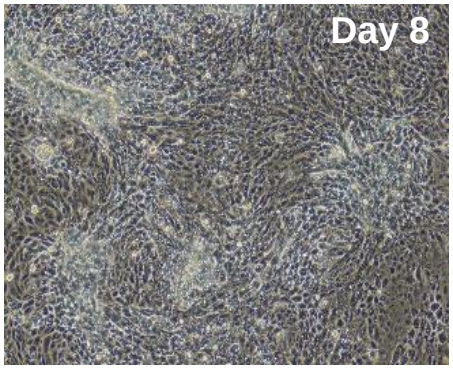
Wattanapanitch, et al. submission 2017

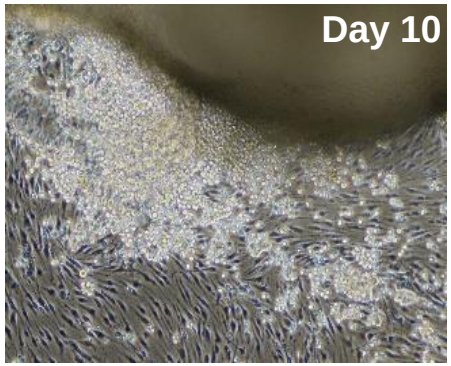
# Hematopoietic Differentiation

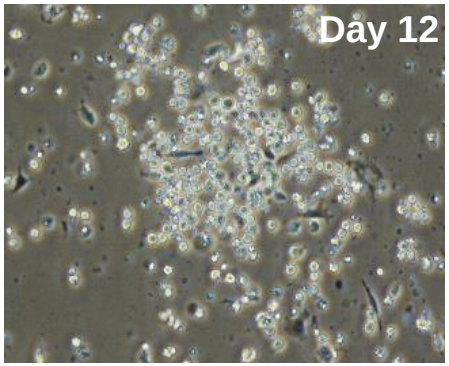


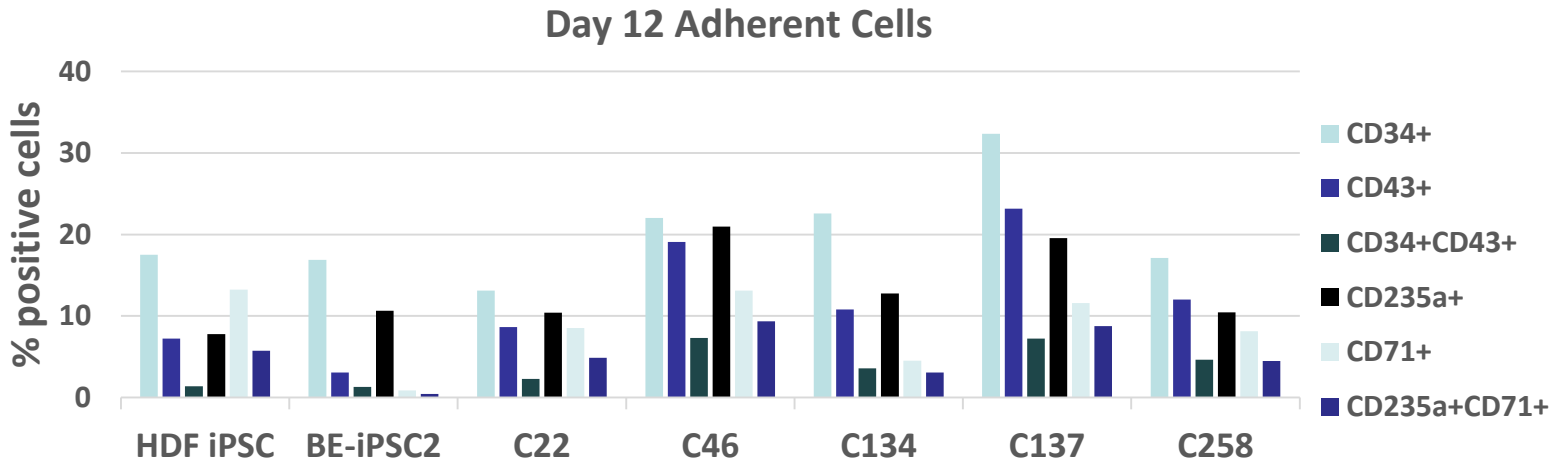



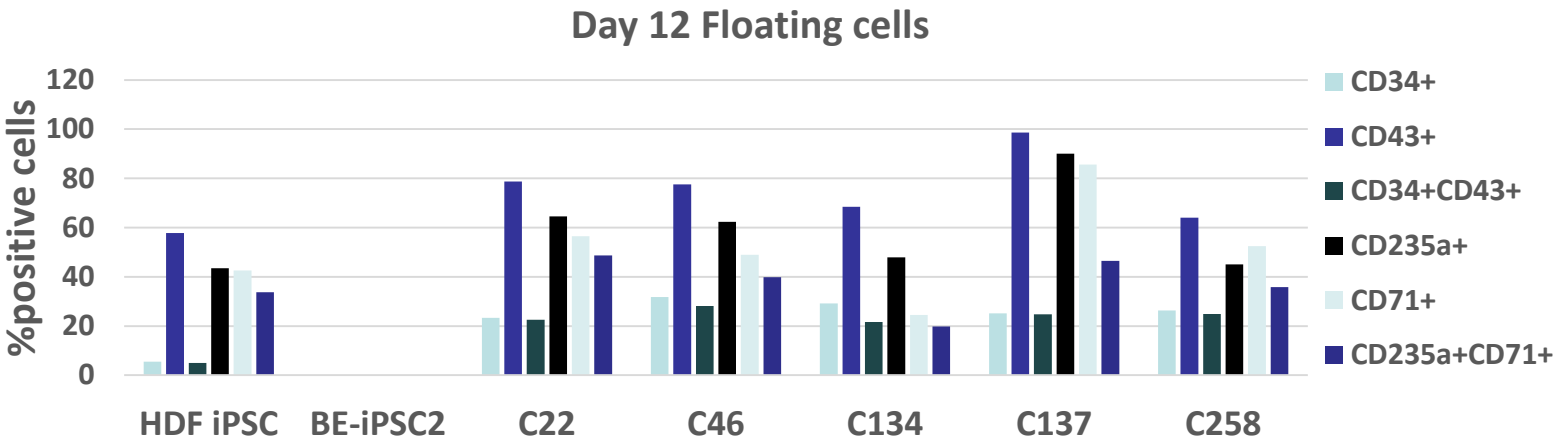




Smith *et al*, Blood, 2014

# HEMATOPOIETIC DIFFERENTIATION

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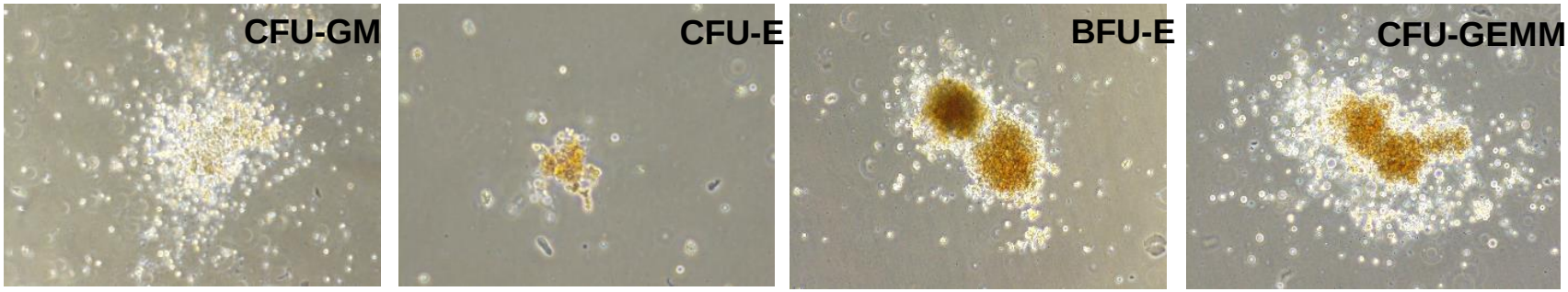
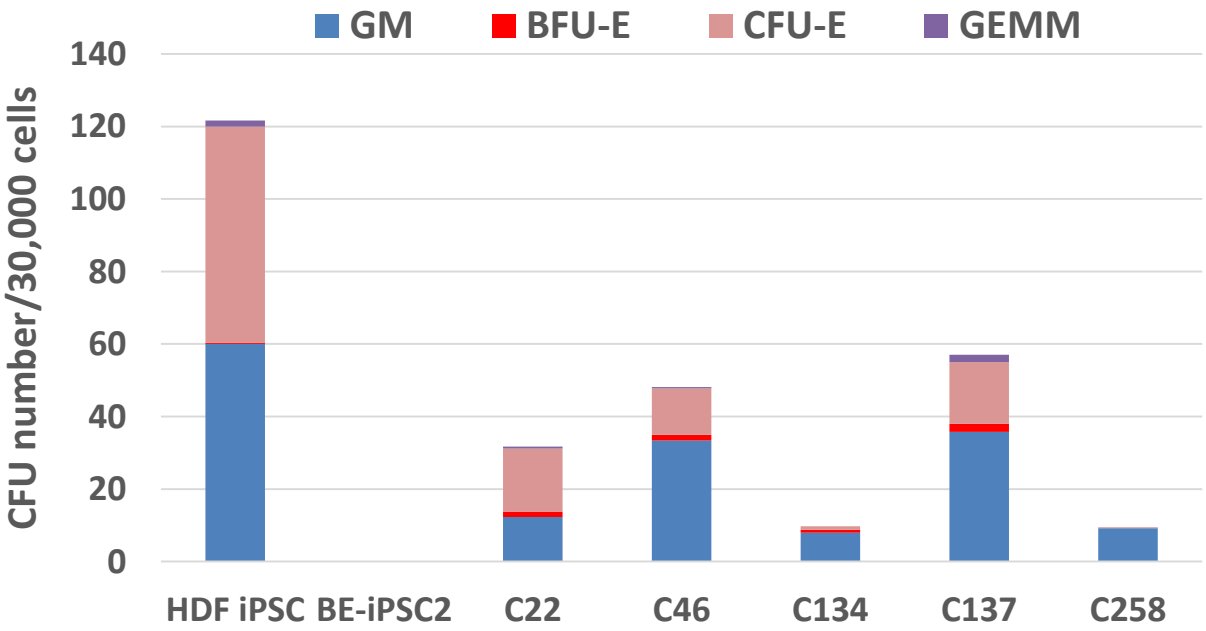
# CFU Assay




Wattanapanitch, et al. submission 2017

# CONCLUSION

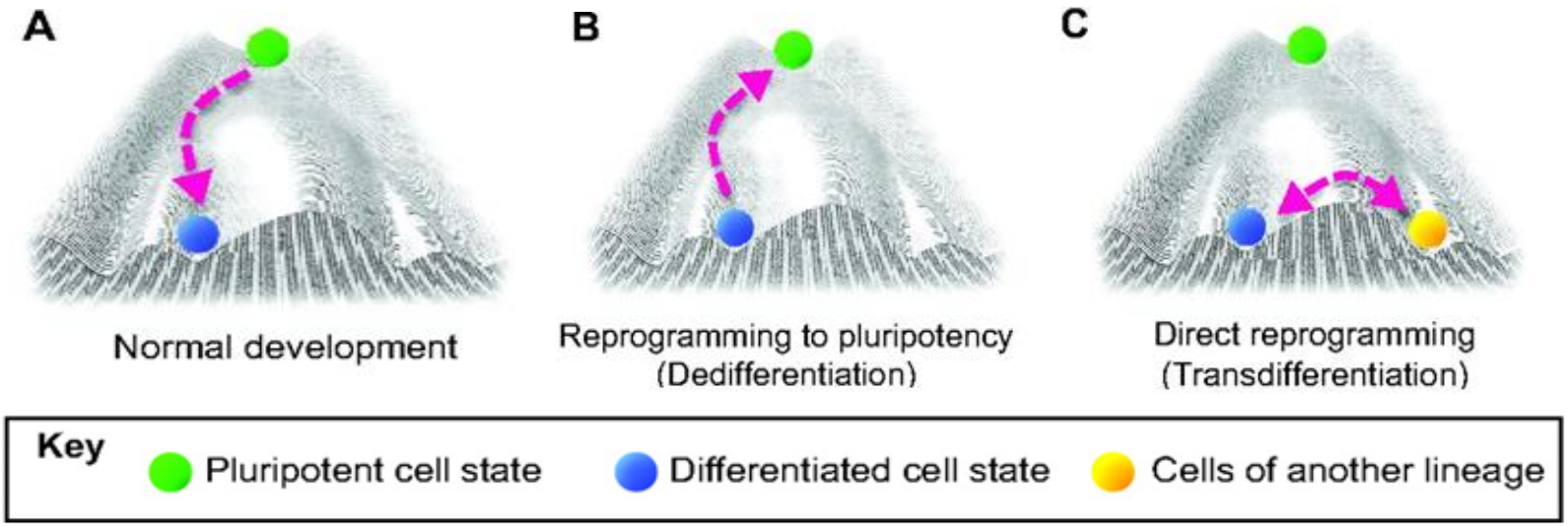
- Thalassemia patient-specific iPSCs were generated and genetic correction of HbE mutation was efficiently performed in one step using CRISPR/Cas9 system.

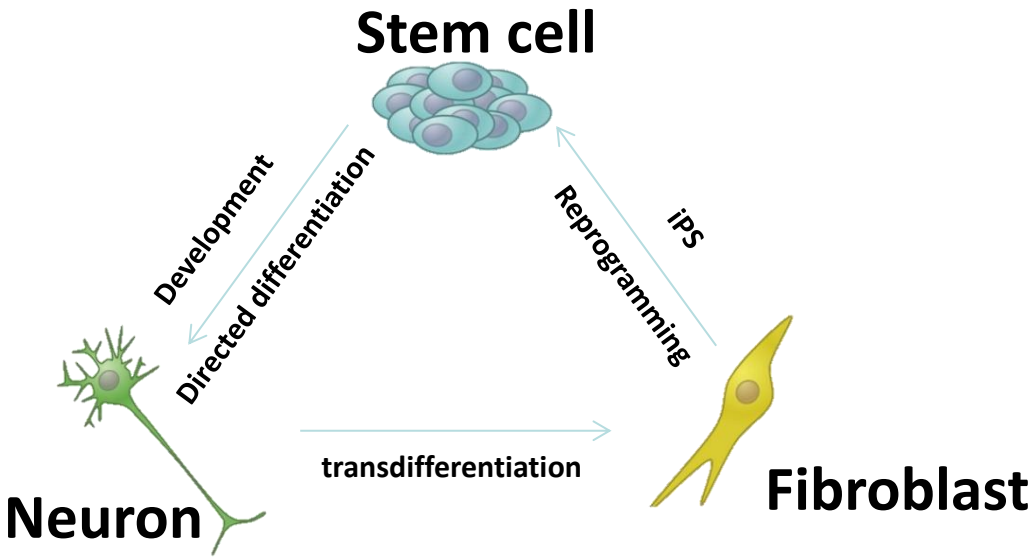
- Together with efficient hematopoietic differentiation protocol, the corrected iPSCs would provide an alternative renewable cell source for autologous transplantation to the patient.

- This gRNA design can also be applied to genome editing in HSCs for patients with beta thalassemia/HbE mutation.

- This strategy can be applied to other genetic diseases, in which the mutations are resulted from a single or a few nucleotide change(s) such as sickle cell disease, familial platelet disorder or SCID-X1.

# DIFFERENTIATION

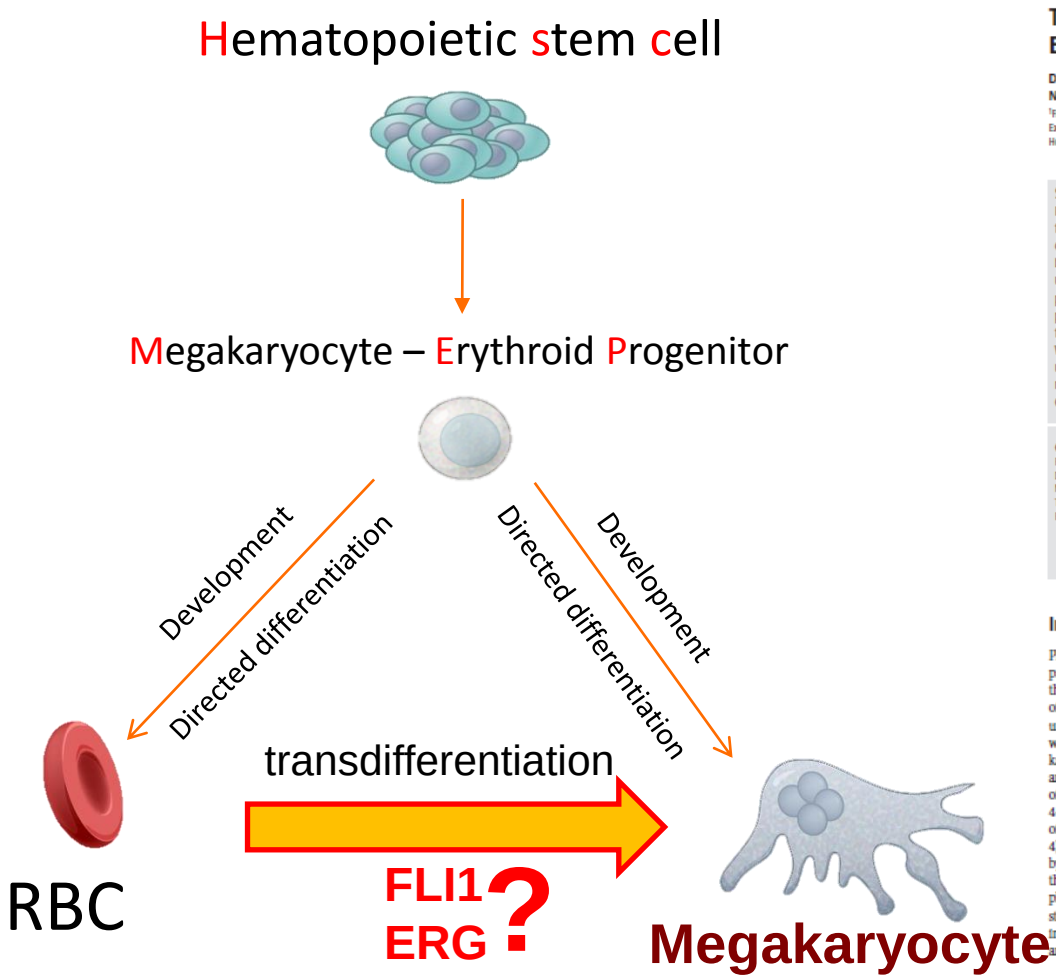



1. **Direct-differentiation**
2. **De-differentiation**
3. **Trans-differentiation**

Kazutoshi Takahashi. J Cell Sci. 2012

# TRANSDIFFERENTIATION OF ERYTHROBLASTS TO MEGAKARYOCYTES BY FLI1 AND ERG TRANSCRIPTION FACTORS






## Transdifferentiation of erythroblasts to megakaryocytes using FLI1 and ERG transcription factors

Darin Siripin[1,5]; Pakpoom Kheolamai[2,3,5]; Yaowalak U-Pratya[4,5]; Aungkura Supokawej[1]; Methichit Wattanapanitch[5]; Nuttha Klincumhom[5]; Chuti Laowtammathron[5]; Surapol Issaragrisil[4,5]

[1]Faculty of Medical Technology, Mahidol University, Bangkok, Thailand; [2]Division of Cell Biology, Faculty of Medicine, Thammasat University, Pathumthani, Thailand; [3]Center of Excellence in Stem Cell Research, Faculty of Medicine, Thammasat University, Pathumthani, Thailand; [4]Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [5]Siriraj Center of Excellence for Stem Cell Research, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

**Summary**

Platelet transfusion has been widely used to prevent and treat life-threatening thrombocytopenia; however, preparation of a unit of concentrated platelet for transfusion requires at least 4–6 units of whole blood. At present, a platelet unit from a single donor can be prepared using apheresis, but lack of donors is still a major problem. Several approaches to produce platelets from other sources, such as haematopoietic stem cells and pluripotent stem cells, have been attempted but the system is extremely complicated, time-consuming and expensive. We now report a novel and simpler technology to obtain platelets using transdifferentiation of human bone marrow erythroblasts to megakaryocytes with overexpression of the *FLI1* and *ERG* genes. The obtained transdifferentiated erythroblasts (both from CD71$^+$ and GPA$^+$ erythroblast subpopulations) exhibit typical features of megakaryocytes including morphology, expression of specific genes (*cMPL* and *TUBB1*) and a marker protein (CD41). They also have the ability to generate megakaryocytic CFU in culture and produce functional platelets, which aggregate with normal human platelets to form a normal-looking clot. Overexpression of *FLI1* and *ERG* genes is sufficient to transdifferentiate erythroblasts to megakaryocytes that can produce functional platelets.

**Keywords**

Transdifferentiation, erythroblast, megakaryocyte, platelet, transcription factors

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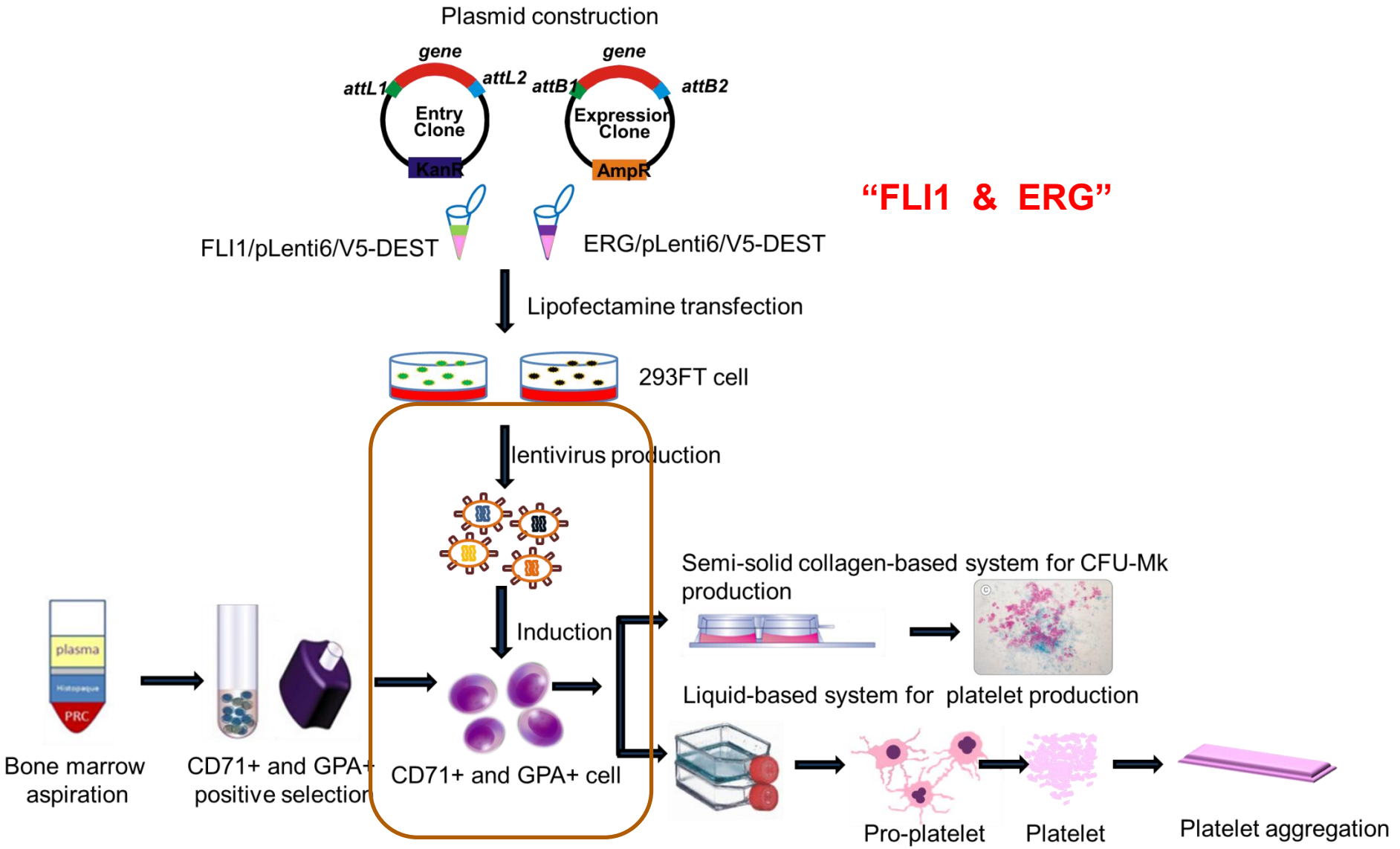
Thromb Haemost 2015; 114: ■■■

### Introduction

Platelets play a critical role in maintaining haemostasis by participating in blood coagulation and vascular repair processes (1). Life-threatening thrombocytopenia, a condition in which the number of platelets in blood is markedly decreased, can occur in patients undergoing chemotherapy or immunosuppression and patients with bone marrow failure such as aplastic anaemia and acute leukaemia (2). Platelet transfusion has been widely used to prevent and treat life-threatening thrombocytopenia; however, preparation of a unit of concentrated platelets for transfusion requires at least 4–6 units of whole blood thereby significantly increasing the risk of blood-borne infections and adverse immunologic reactions (3, 4). At present, a platelet unit from a single donor can be prepared by apheresis, but lack of donors is still a major problem. Despite the recent development of an *in vitro* culture system for producing platelets from various types of stem cells, such as haematopoietic stem cells (HSCs) (5–7), embryonic stem cell lines (ESCs) (8, 9) and induced pluripotent stem cells (iPSCs) (10, 11), these approaches are expensive, time-consuming and inappropriate for clinical use. Therefore, the development of a novel methodology which is less expensive and more efficient is required.

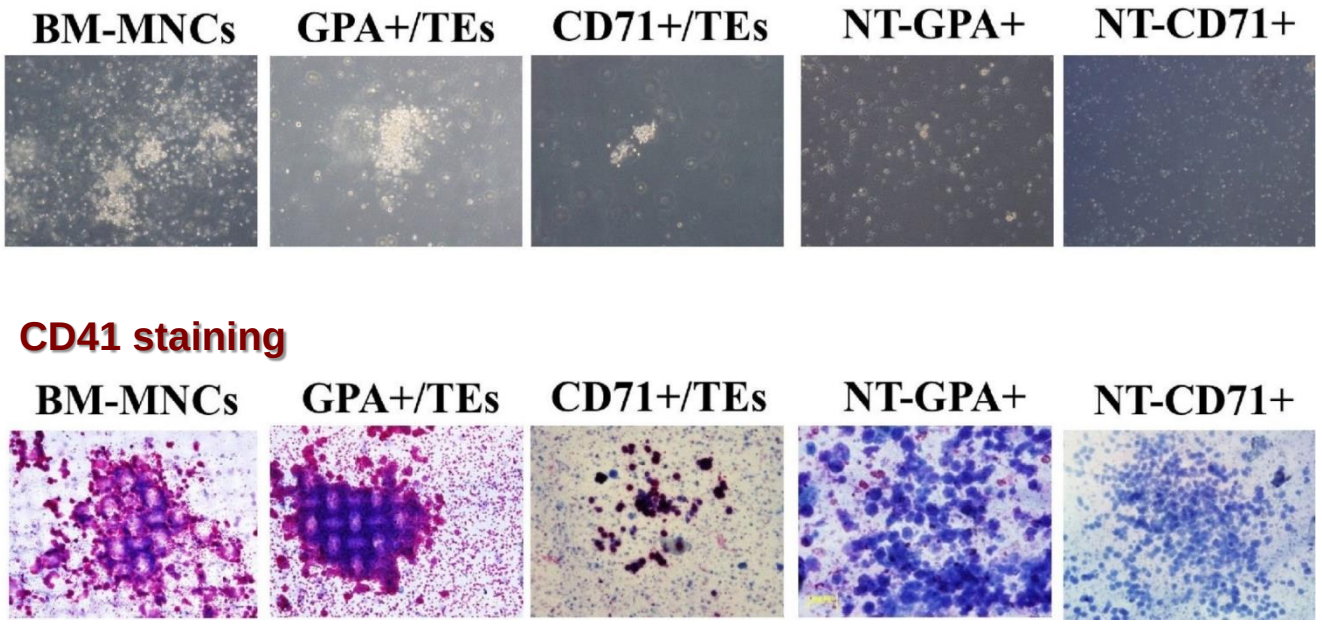
Several transcription factors and cytokines are essential for proliferation, survival, lineage commitment, and functional maturation of all haematopoietic lineages (12). Although erythroblasts and megakaryocytes are different from each other with regard to cell morphology, gene expression and function, they are derived from a common progenitor called the megakaryocyte-erythroid progenitor (MEP). Previous studies indicated that GATA1, GATA2, FOG1, TAL1/SCL, GFI1B, and NFE2 play important roles during the development of both erythroid and megakaryocyte lineages and three transcription factors including erythroid-specific KLF (EKLF1), Friend leukemia integration 1 transcription factor (FLI1), and ETS-related gene (ERG) are necessary for the lineage diversification process of the MEP (13–17). It has been shown that overexpression of *ERG* or *FLI1* genes in the K–562 cell line downregulated expression of erythroid-specific genes and upregulated the expression of megakaryocyte-specific genes (8, 18, 19). In fact, transdifferentiation of human somatic cells such as lymphocytes and fibroblasts to macrophages can be successfully

# A SCHEMATIC DIAGRAM OF THE EXPERIMENTAL SETUP



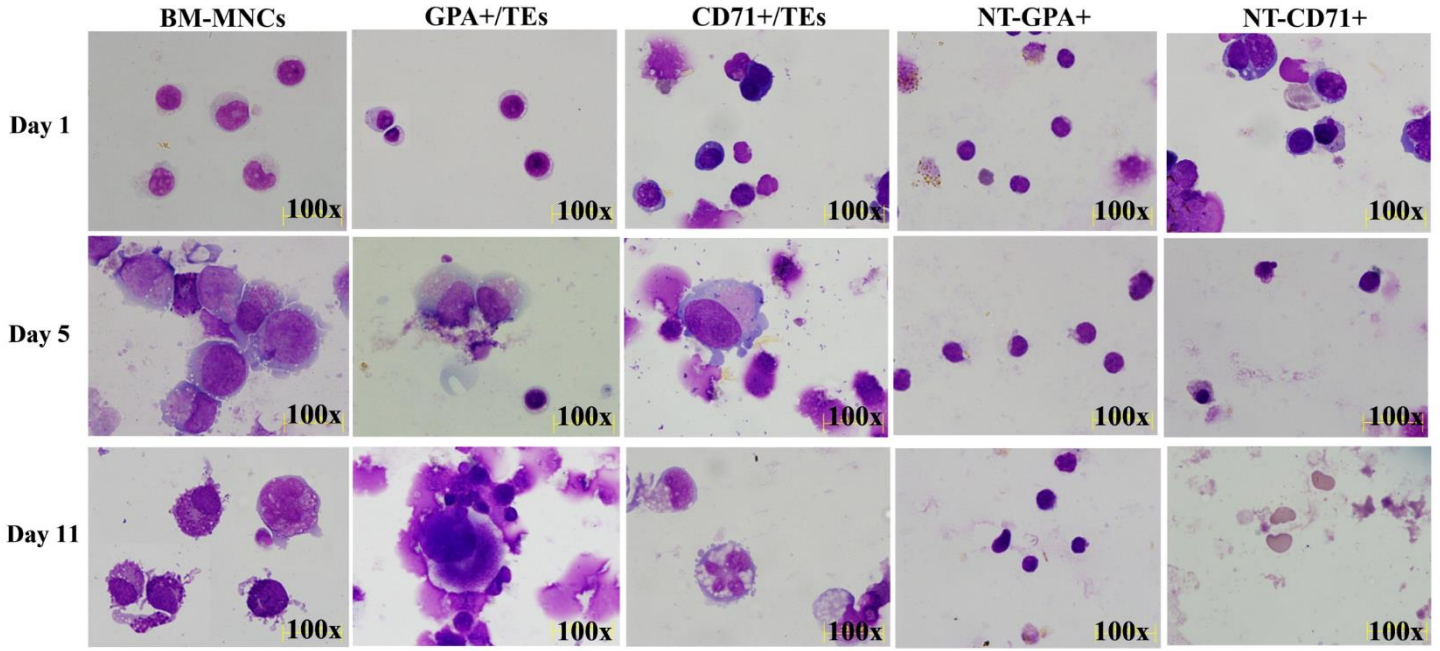

Siripin, et al. Thrombosis and Haemostasis 2015: 593.

# MEGAKARYOCYTE COLONY FORMING UNIT (CFU-MK) OF IMKS

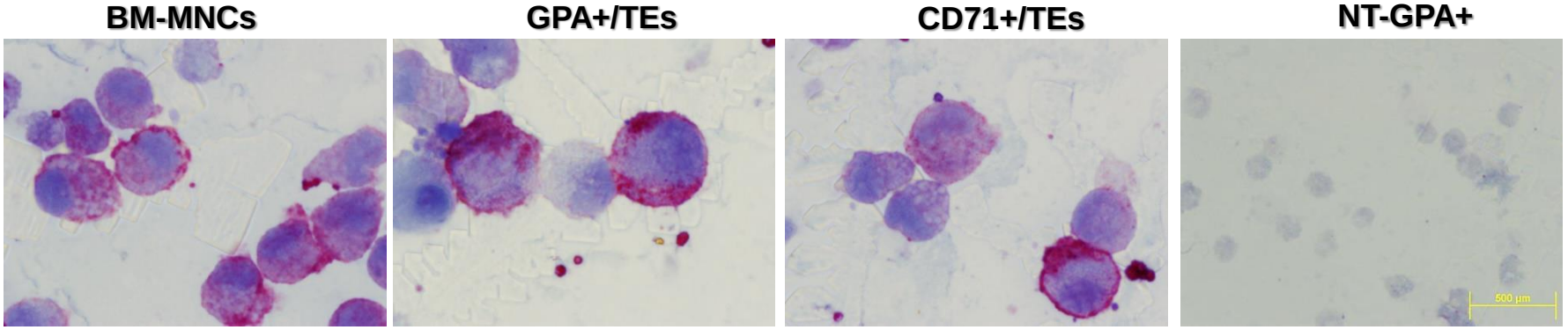



Siripin, et al. Thrombosis and Haemostasis 2015: 593.

# MORPHOLOGY OF THE CD71+/IMKS AND GPA+/IMKS (LIQ CULTURE)

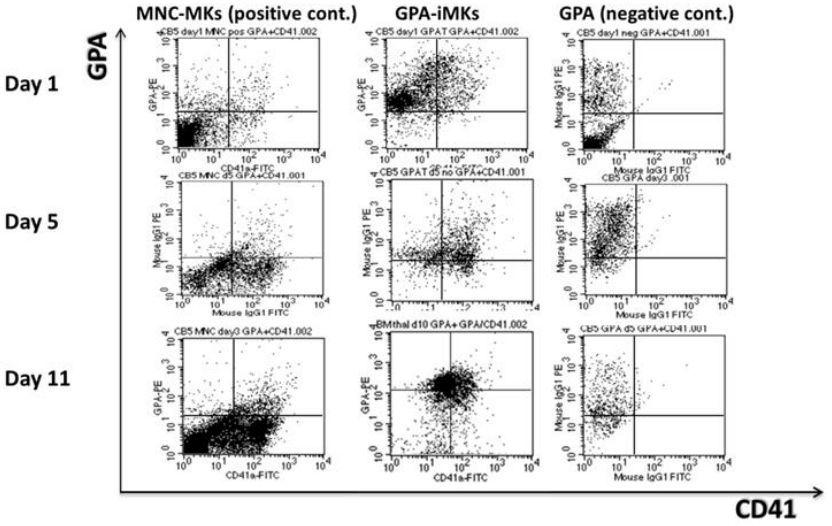


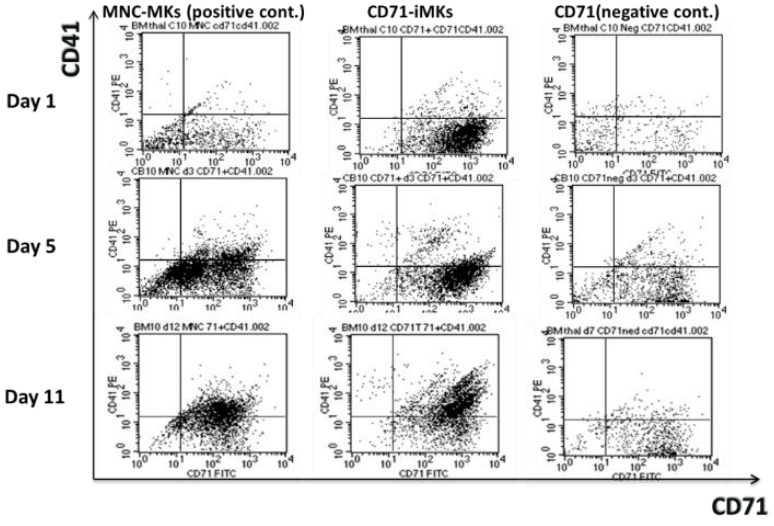

# IMMUNOCYTOCHEMICAL IDENTIFICATION OF MKS : CD41 STAINING

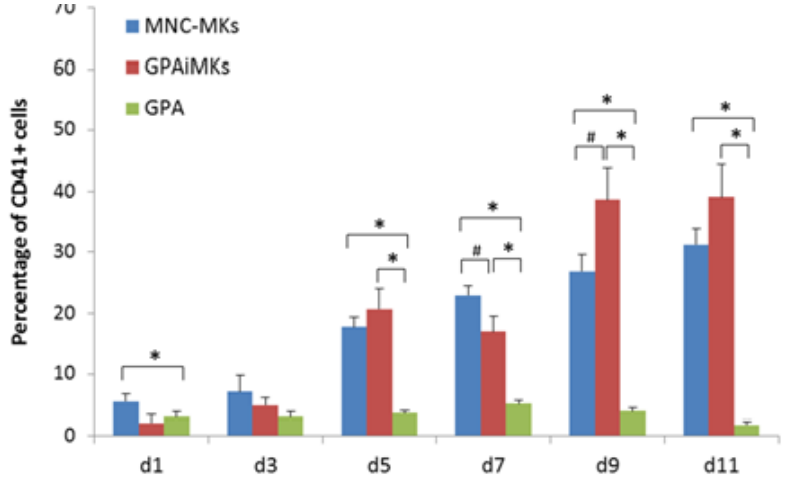


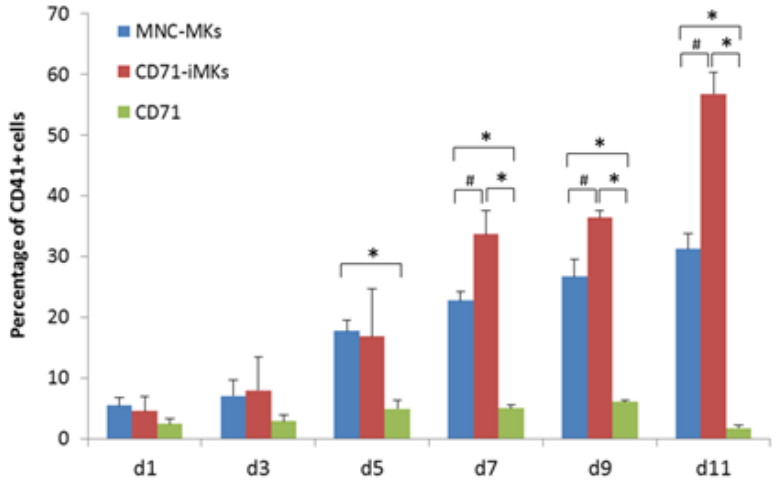

Siripin, et al. Thrombosis and Haemostasis 2015: 593.

# SURFACE MARKER EXPRESSION OF IMKS ANALYSIS



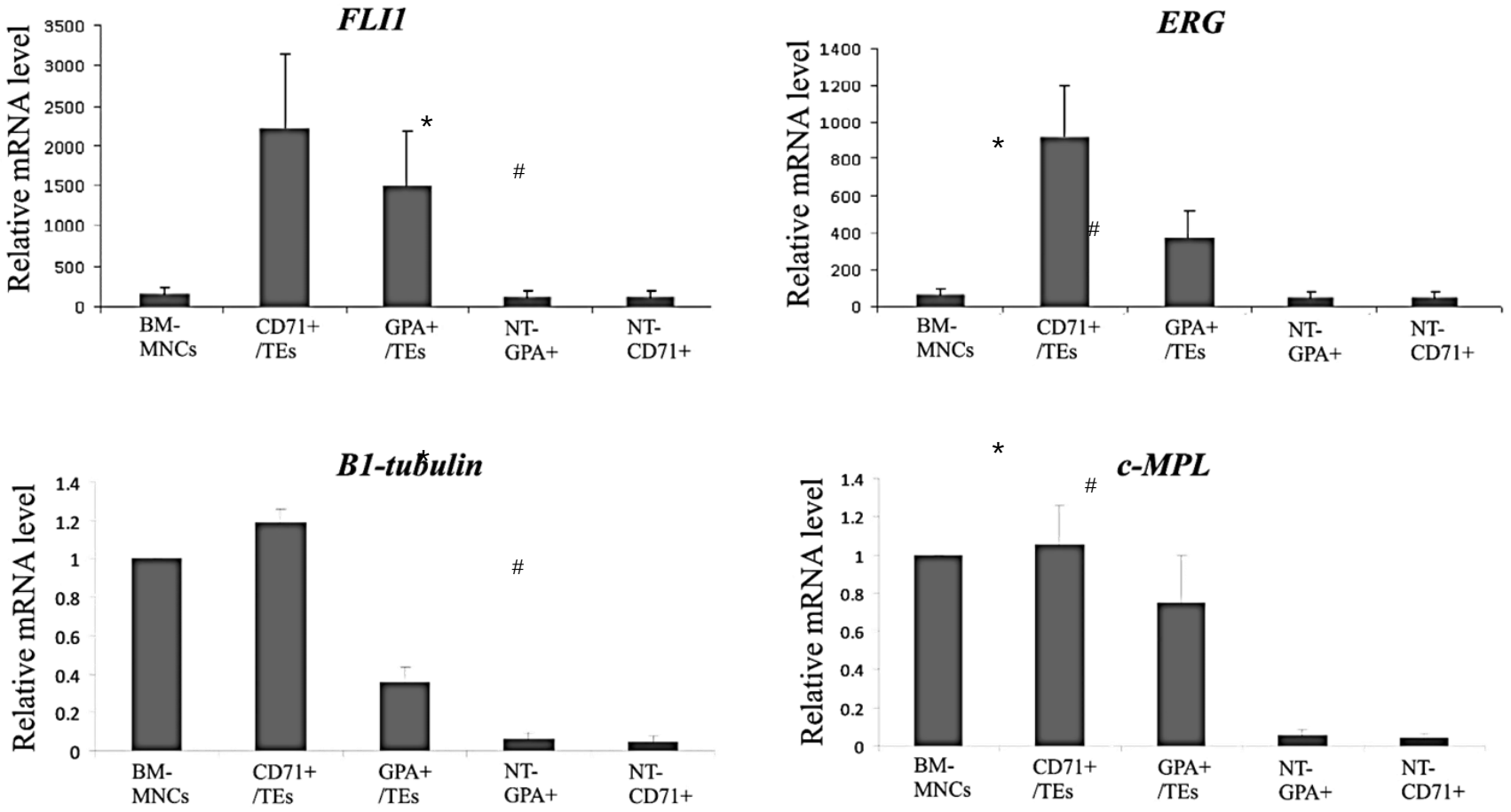



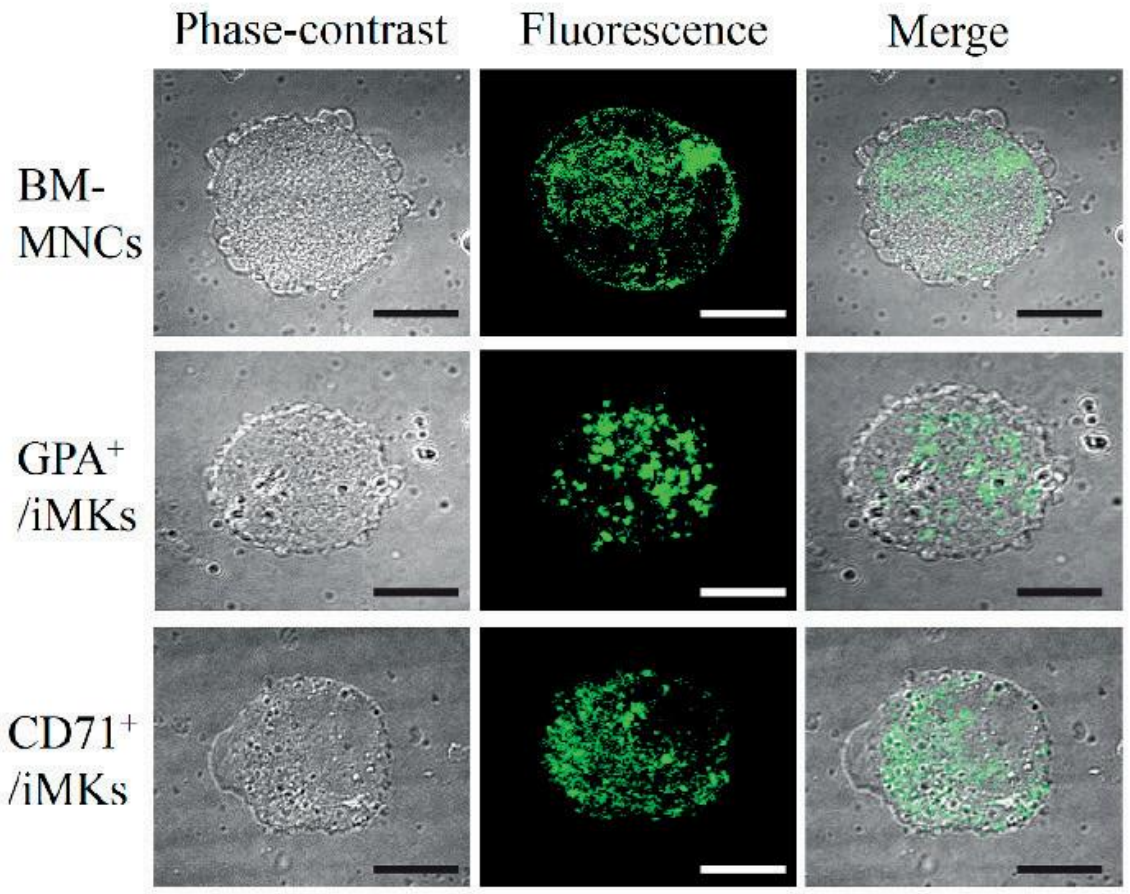

Siripin, et al. Thrombosis and Haemostasis 2015: 593.

# GENE EXPRESSION OF TES ANALYSIS BY USING QRT-PCR




Siripin, et al. Thrombosis and Haemostasis 2015: 593.

# Functional Characterization of iMK-derived Platelet *in vitro* by Aggregation Assay

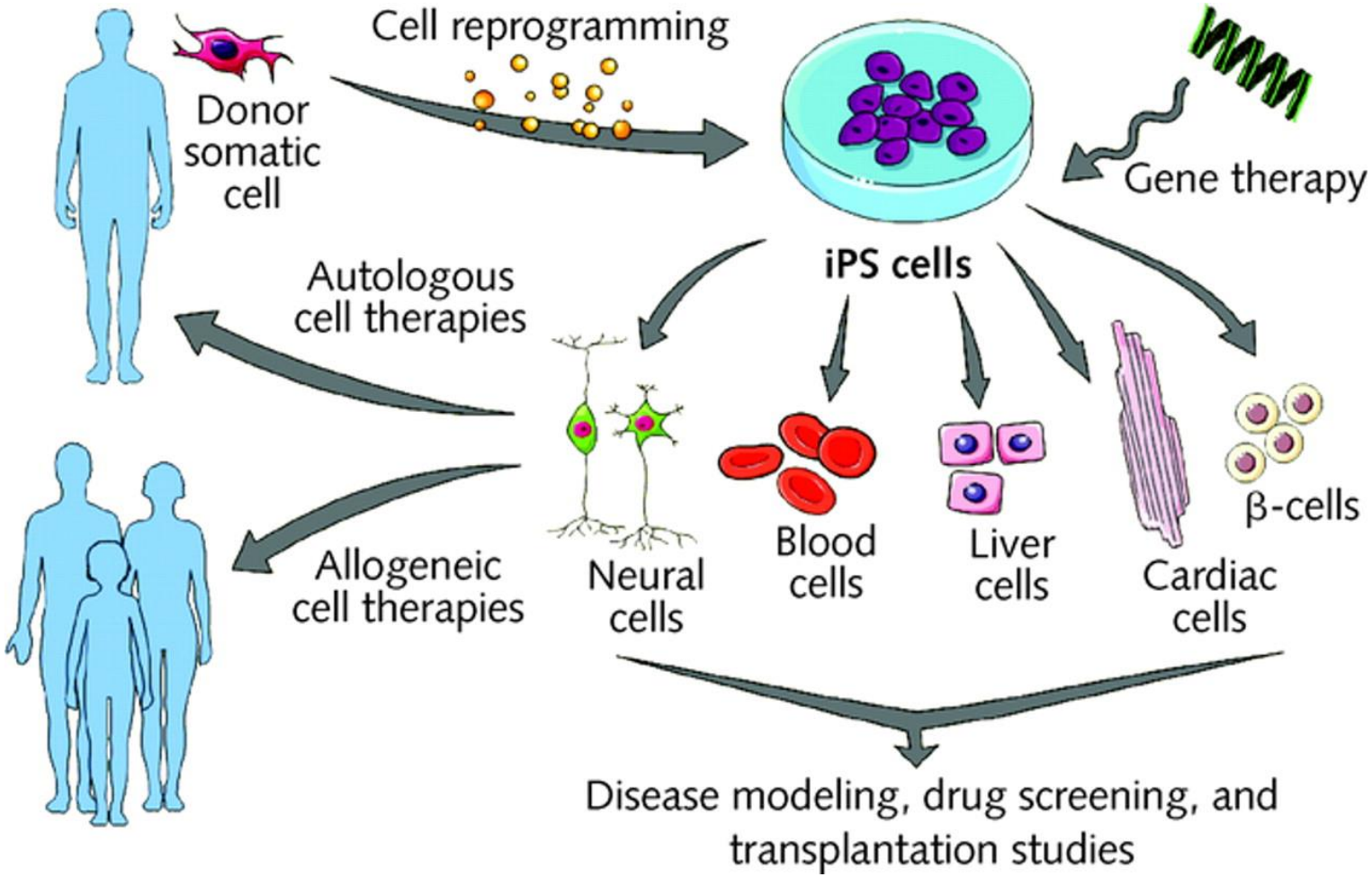



Siripin, et al. Thrombosis and Haemostasis 2015: 593.

# CONCLUSION

- Overexpression of *FLI1* and *ERG* genes can transdifferentiate erythroblasts to megakaryocytes which can produce functional platelets *in vitro.*
- This offers a novel sources of platelets for future clinical applications.

# iPSC Therapeutic Applications



# BANKING OF HUMAN PLURIPOTENT STEM CELL

## Banking iPSCs

- **Japan**
  - Yamanaka announces plan to establish global iPS cell bank on Jan 16, 2014
  - 140 types of homozygous iPS cells, which can cover 90 percent of all Japanese[1]
- **United Kingdom**
  - 150 types of homozygous iPSCs for common HLA types selected from 17 million individuals could provide an HLA antigen match for 93% of the UK population[2]

## Banking hESCs

Ten homozygous hESC lines would provide an HLA antigen match for 38% of recipients[3]

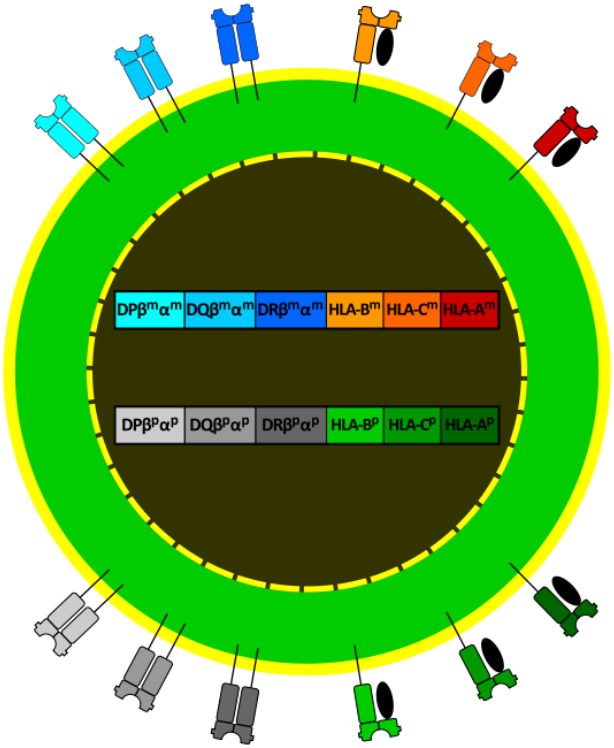
hESC lines that are homozygous for common HLA haplotypes would be a valuable resource in the establishment of a stem cell bank

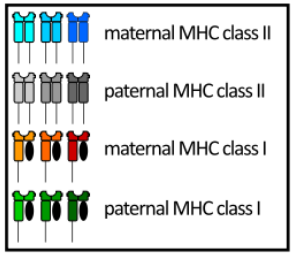
Haploid ESCs would be a valuable resource for a stem cell bank

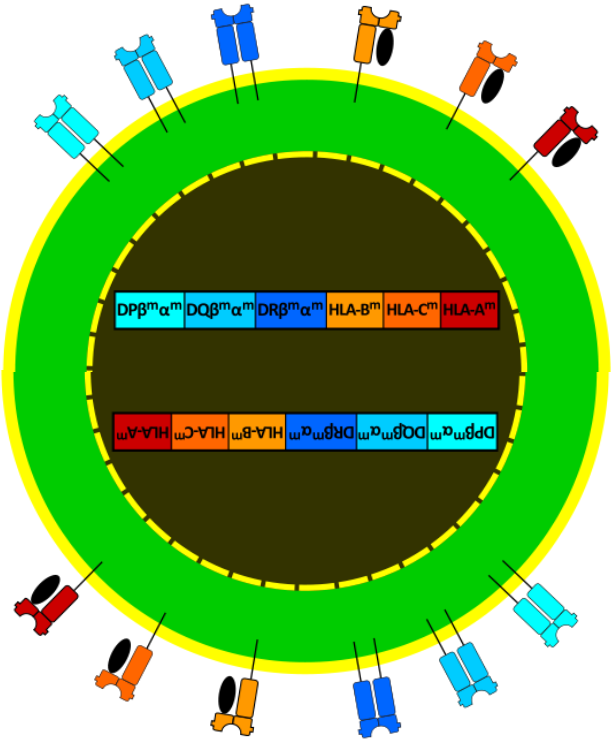
[1]Nat. Methods 2011, 8:409, [2]Cell Stem Cell 2012, 11: 147, [3]Lancet 2005, 366: 2019

# Haploid Application

*Half HLA express: high chance to match*




Diploid cells

Haploid cells
(& diploidized cells)

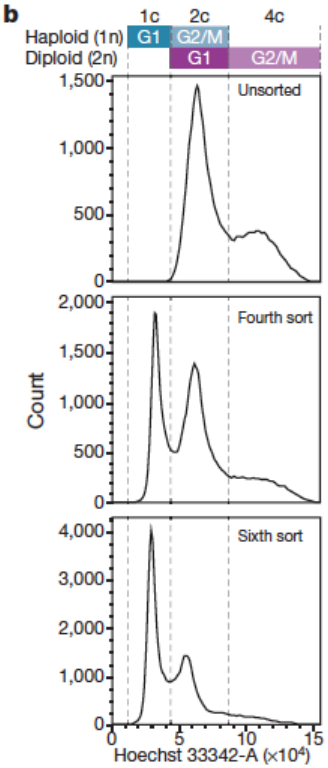
# HUMAN HAPLOID ESCs

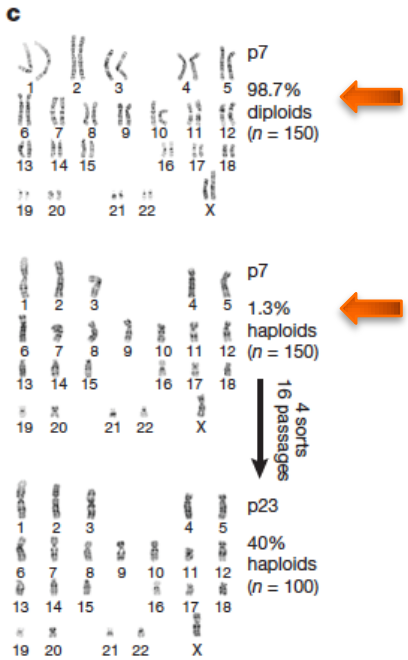
## Derivation and differentiation of haploid human embryonic stem cells

Ido Sagi[1], Gloryn Chia[2], Tamar Golan-Lev[1], Mordecai Peretz[1], Uri Weissbein[1], Lina Sui[2], Mark V. Sauer[3], Ofra Yanuka[1], Dieter Egli[2,4] & Nissim Benvenisty[1]

*Nature* (2016) | doi:10.1038/nature17408

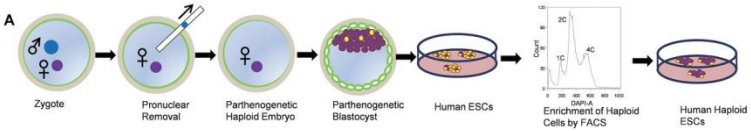
Received 30 July 2015 | Accepted 08 February 2016 | Published online 16 March 2016

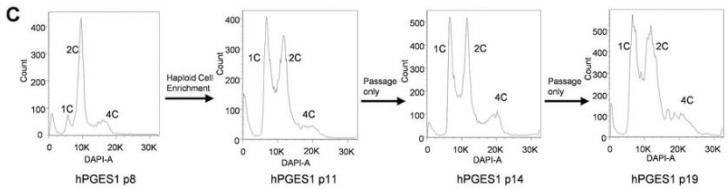



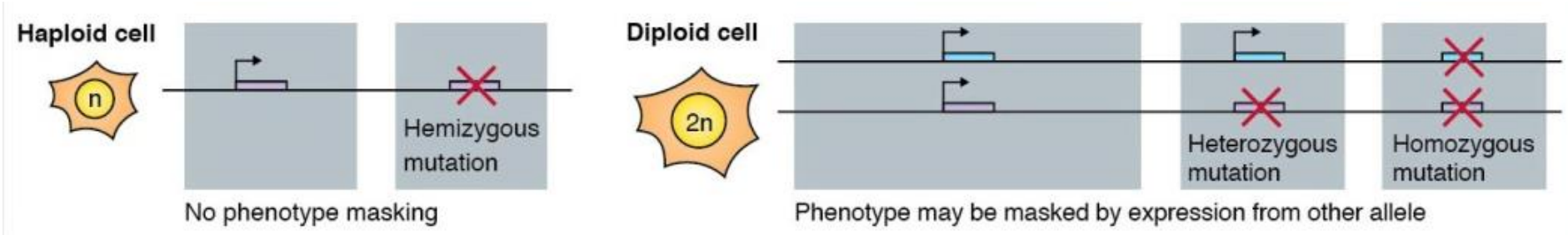

## Generation of human haploid embryonic stem cells from parthenogenetic embryos obtained by microsurgical removal of male pronucleus

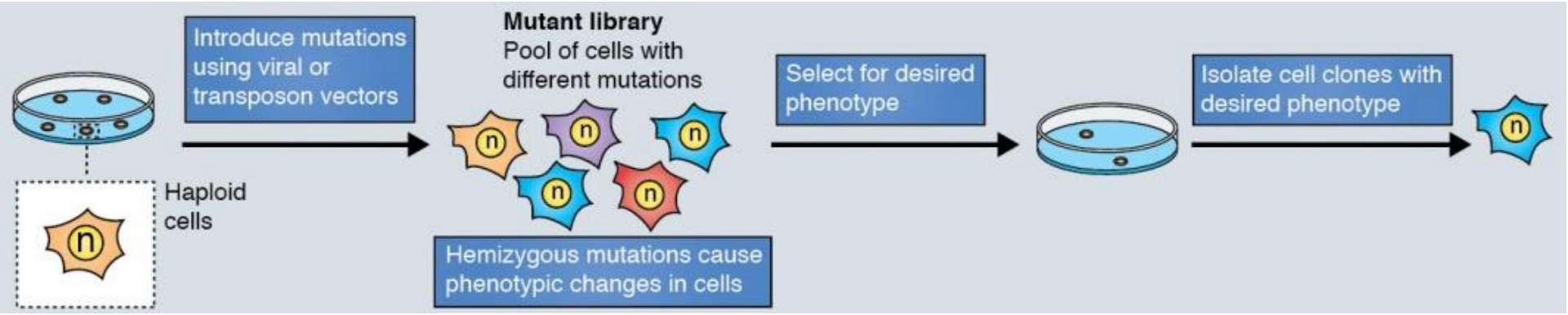
*Cell Research* (2016) **26**:743-746. doi:10.1038/cr.2016.59; published online 17 May 2016



# Application of Haploid Cells to Genetic Screening

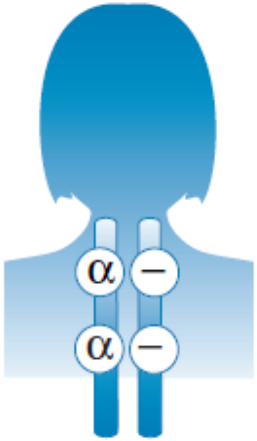


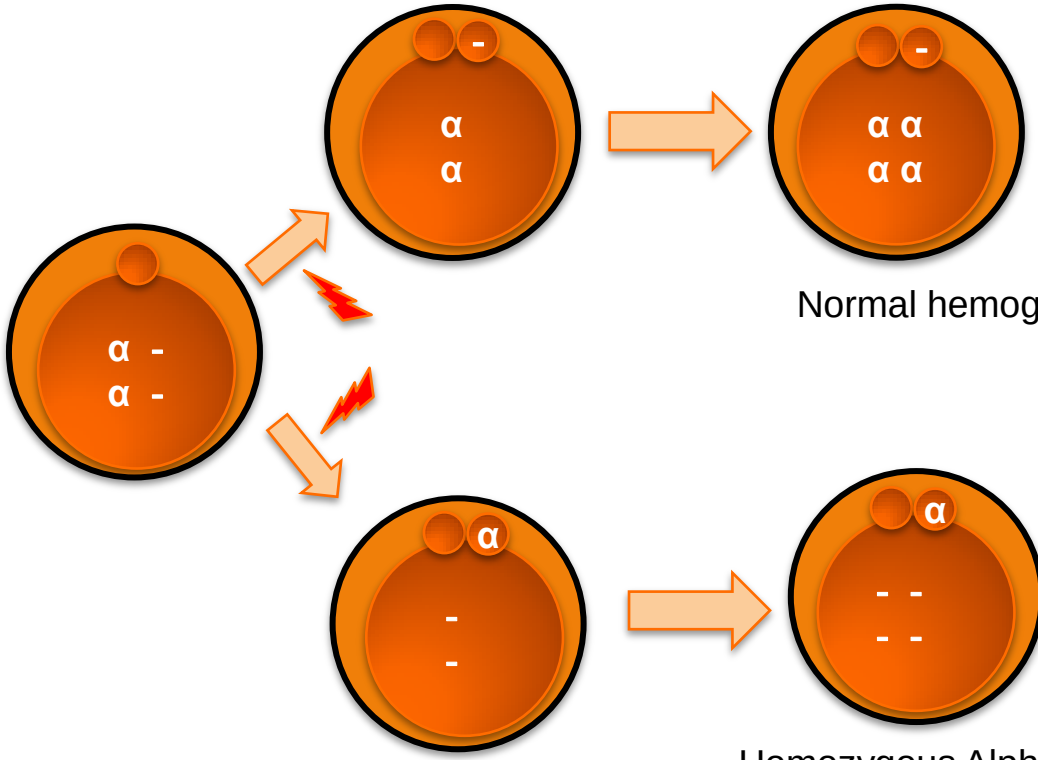

Development 2014 141: 1423

# HAPLOID APPLICATION

*Disease modelling:*




Alpha thalassemia trait



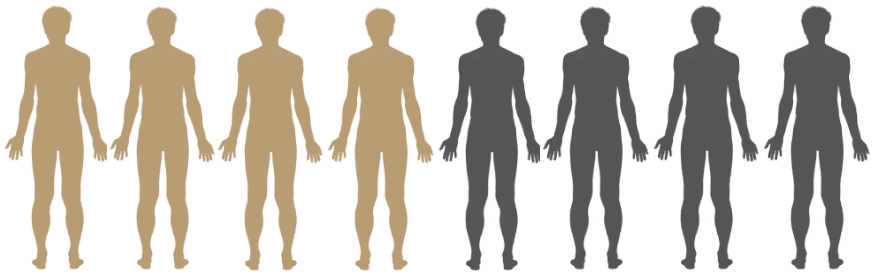

Normal hemoglobin

Homozygous Alpha Thalassemia1

It possible to establish human parthenogenetic disease-specific stem cell lines

# hpESCs FOR THERAPEUTIC APPLICATION

- Haploid ESCs only have half of HLA antigen → easy to set the match
- hpESC banking (Diploidized Bank)



# THE ADVANTAGE OF HAVING HAPLOID hESCs

1. For gene targeting

   Haploid hESCs → Sorting 1N→ Gene targeting → Diploidization

2. Homozygous hESCs banking for therapeutic propose (Clinical grade)

   Haploid hESCs → Diploidization → HLA typing

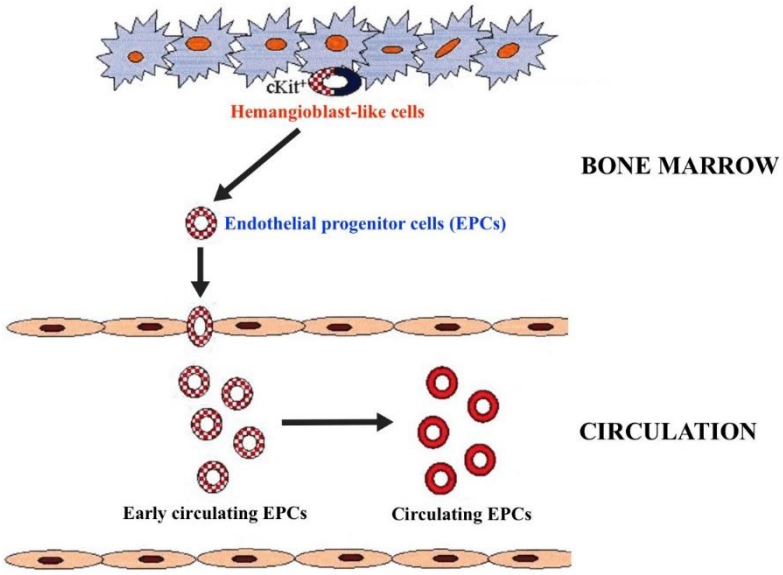
We are going to make the clinical GMP-grade hESCs.

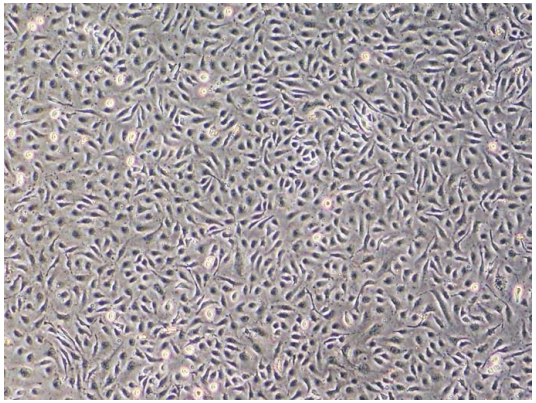
What do we have now

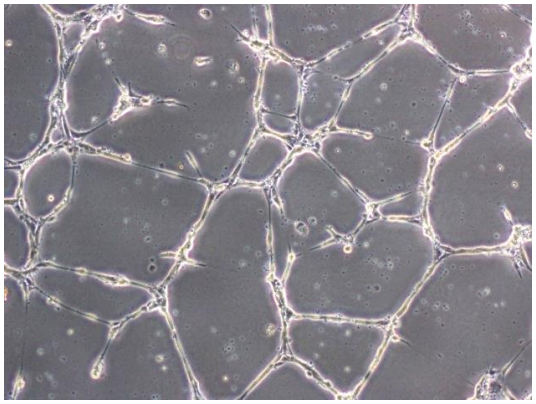
1. Clean room (Class 100) for human embryos culture and generation of hESC lines.
2. High efficiency for hESCs derivation (70%)
3. GMP grade hESCs culture media (Nutristem) and extracellular matric (CellStart/rLaminin).

# Endothelial Progenitor Cell Dysfunction in Diabetes Mellitus

# ENDOTHELIAL PROGENITOR CELLS (EPCS)

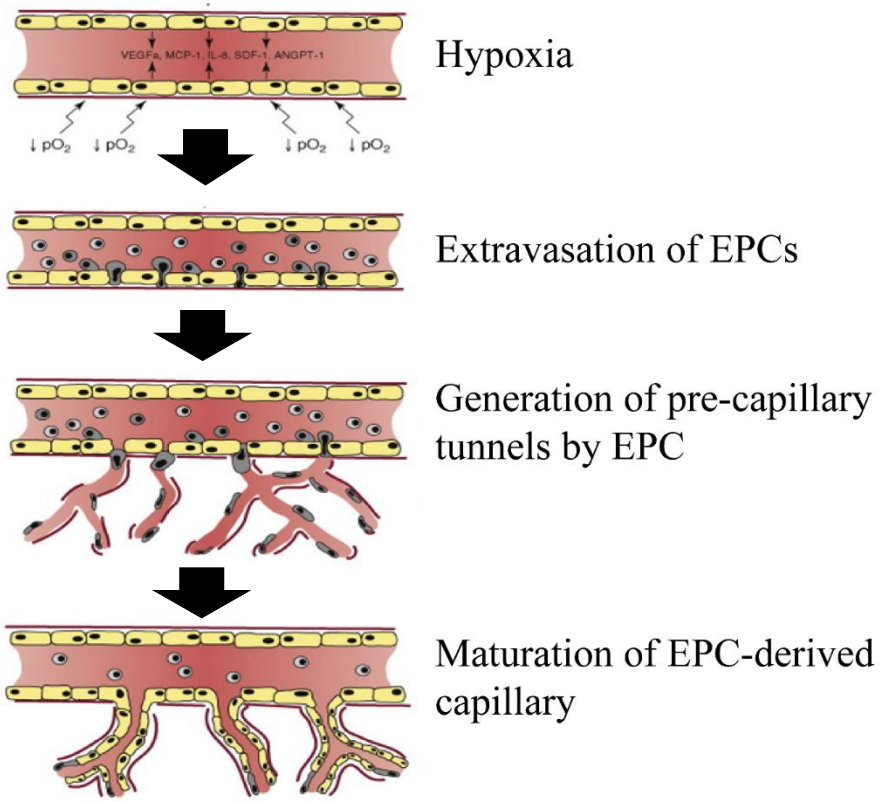




From: *Mihail Hristov et al. Arterioscler Thromb Vasc Biol. 2003;23:1185-1189*

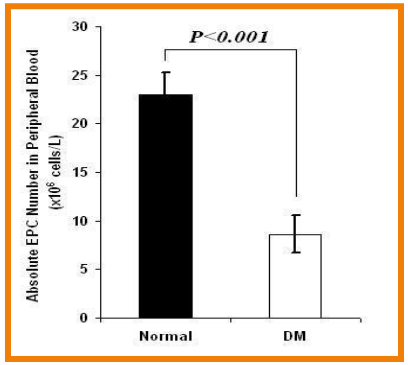
# *IN VIVO* NEOVASCULARIZATION BY EPCS

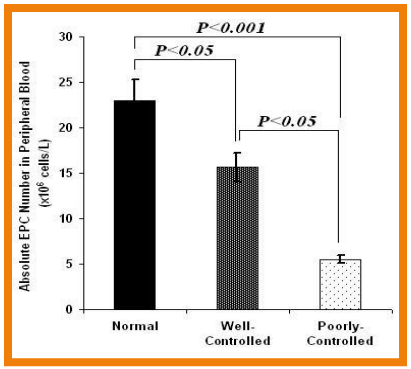



From: *Krenning et al. Trend in molecular Medicine, Vol. 15 (4), 2009, 180–189*

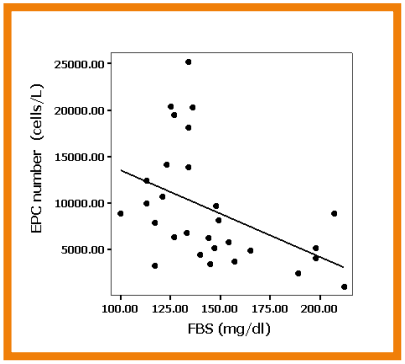
# EPC Number in Normal and Diabetic Subjects

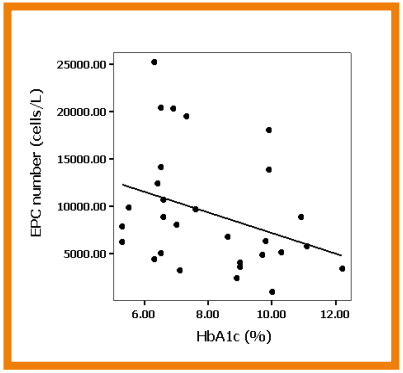
Number



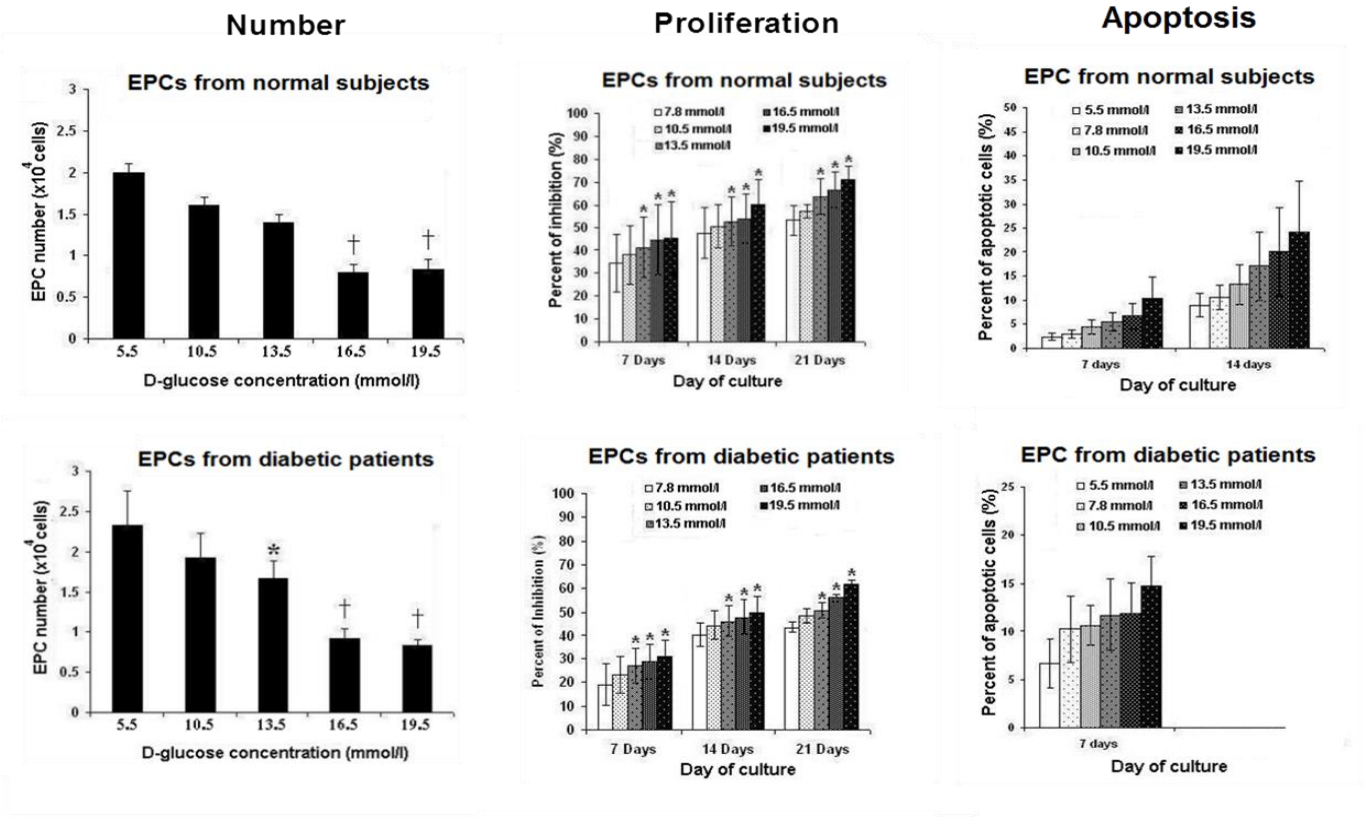

Correlation with FBS and HbA1C



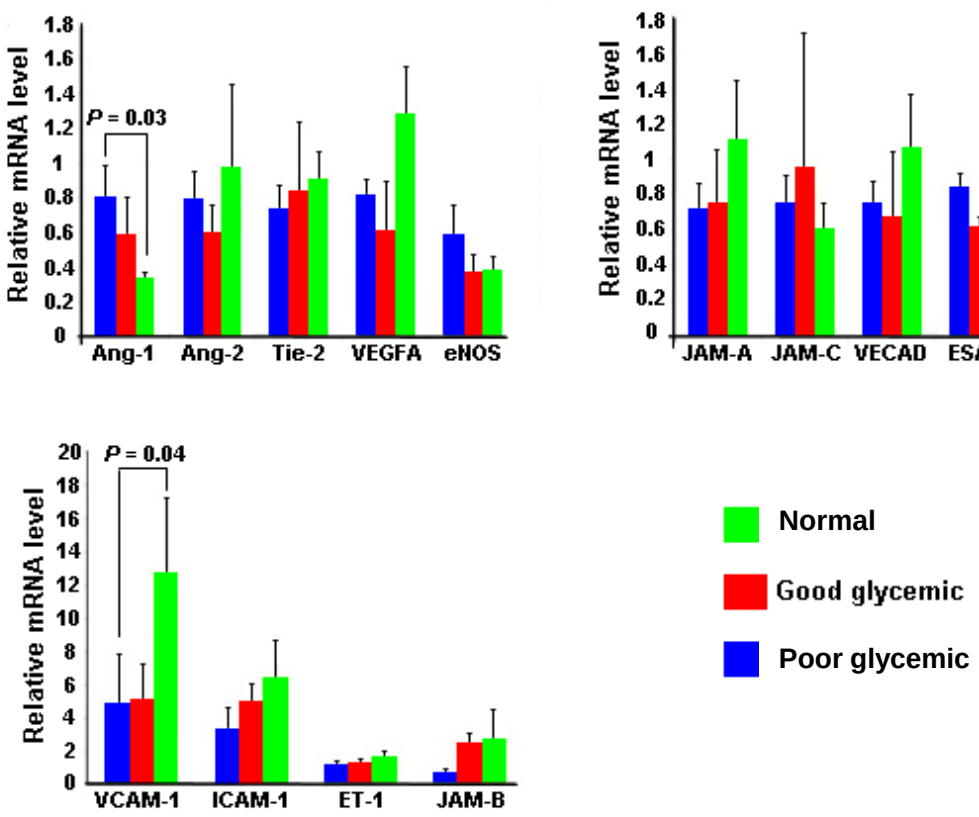

From: Churdchomjan *et.al.*, BMC Endocr Disord. 2010 Apr 7;10:5.

# Viability, Proliferative Capacity and Apoptotic Rate of EPCs in Hyperglycemic Conditions



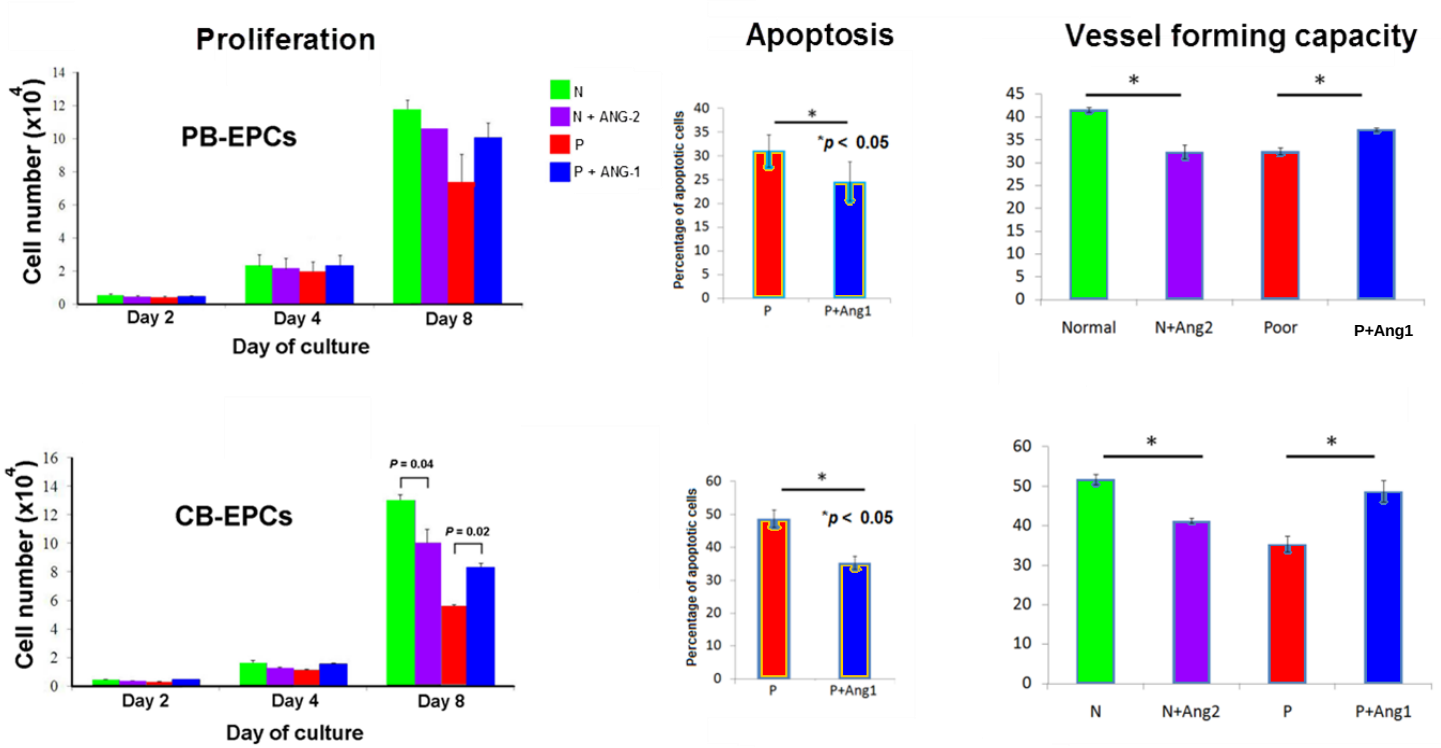

From: Churdchomjan *et.al.*, BMC Endocr Disord. 2010 Apr 7;10:5.

# Gene Expression Profile of EPCs In Hyperglycemic Conditions



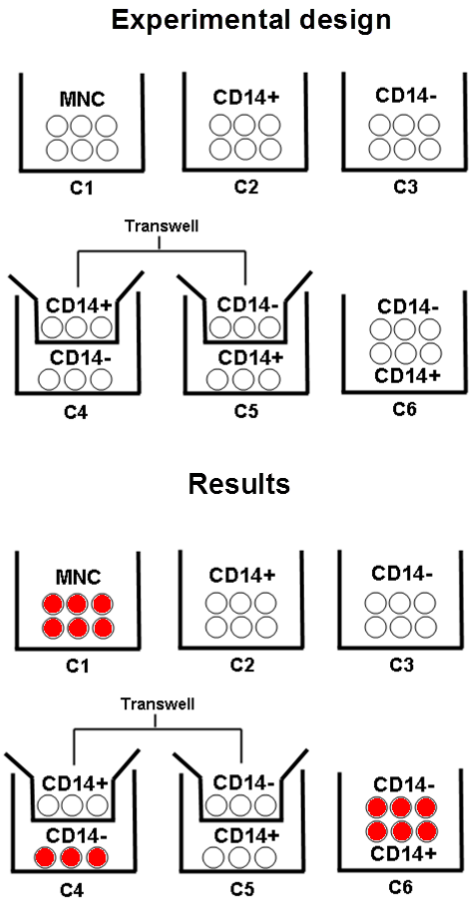

From: Jiraritthamrong *et.al*., Ann Hematol. 2012 Mar;91(3):311-20.

# Proliferative Capacity, Apoptotic Rate and Vessel Forming Capacity of EPCs In The Presence of Ang-1 And Ang-2




From: Jiraritthamrong *et.al.*, Ann Hematol. 2012 Mar;91(3):311-20.

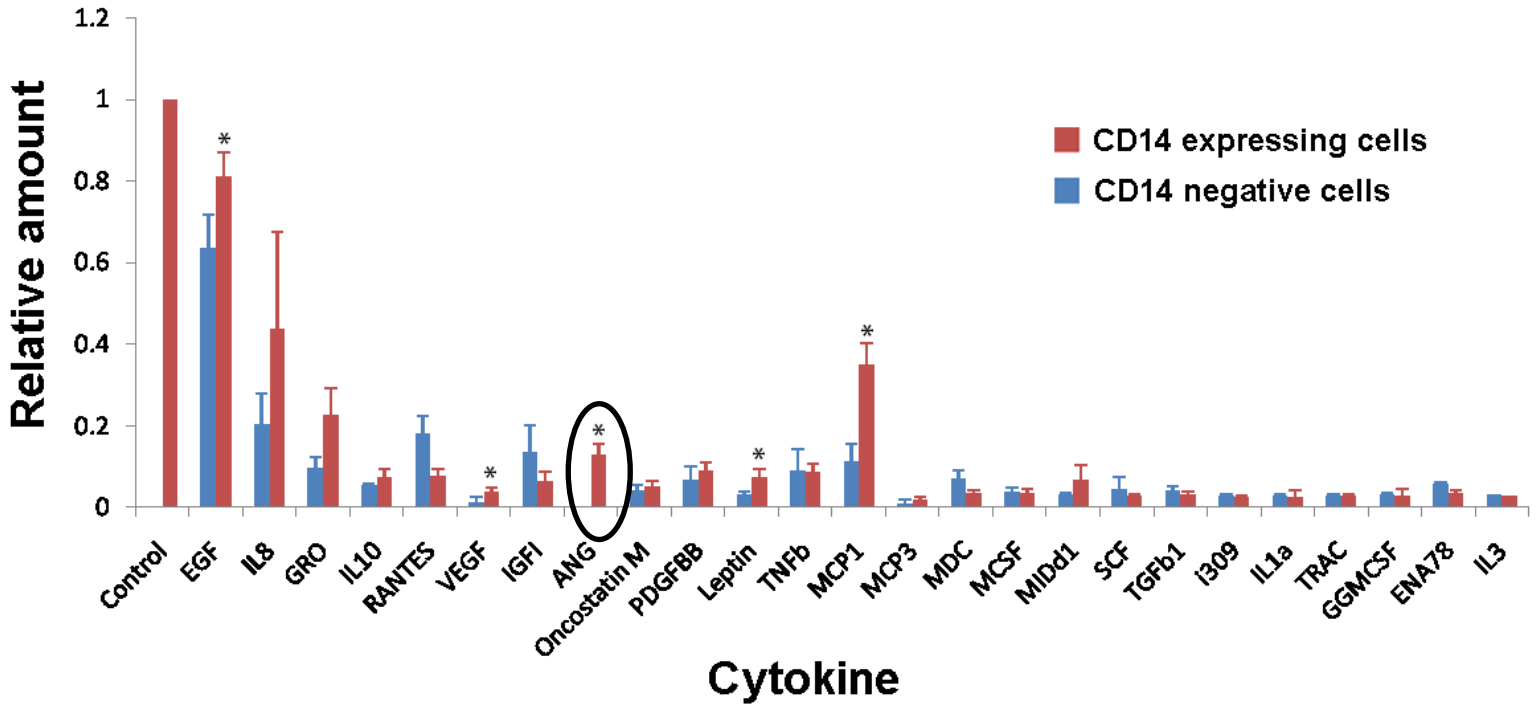
# The Founding Population and Factors Required for The Establishment of EPC Colonies




From: Sudchada *et.al.*, Ann Hematol. 2012 Mar;91(3):321-9.

CD14-CD34+

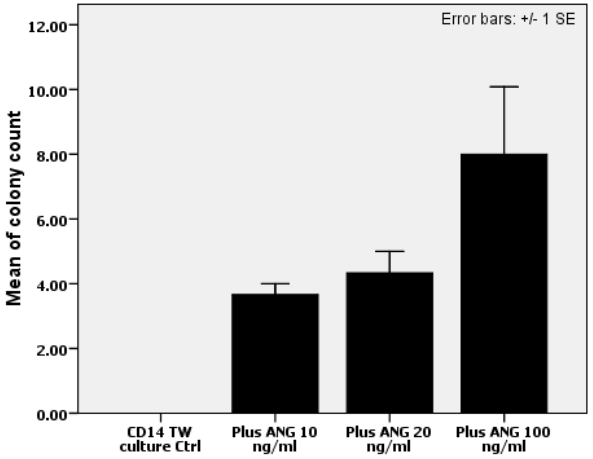
# CYTOKINE ARRAY



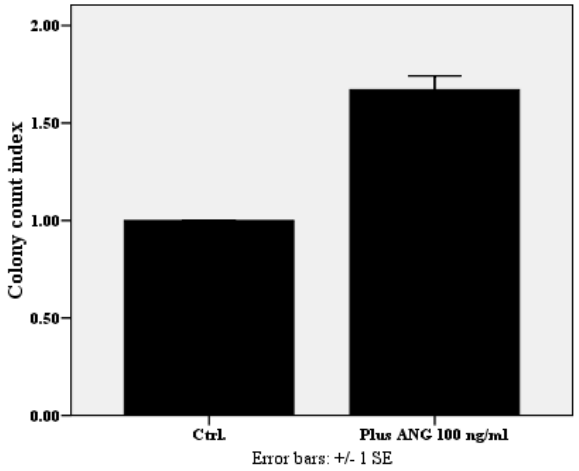

From: Sudchada *et.al.*, Ann Hematol. 2012 Mar;91(3):321-9.

# EFFECT OF ANGIOGENIN ON EPC DERIVATION

CD14$^{-}$




CD14$^{-}$/CD34$^{+}$




From: Sudchada *et.al.*, Ann Hematol. 2012 Mar;91(3):321-9.

# CONCLUSION

- There was EPC dysfunction in type2 DM which might be improved by strict glycemic control.
- However, the circulating EPC number and proliferative function in patients with good glycemic control did not reach the level in healthy controls
- The in vitro  vessel-forming capacity of EPCs cultured in high glucose concentration id impaired due to low levels of angiopoietin 1.
- The UCB-derived EPCs are confined to CD14-/CD34+ subpopulation and angiogenin 1 released from CD14+ supopulation may be an important factor promoting the EPC colony formation

# Future of Stem Cells

# SUMMARY

- Stem cell research holds great promise for regenerative medicine
- Ethical and moral issues should be very much concerned
- A clear legal and regulatory framework that will allow and support stem cell research under the appropriate ethical guideline is required
- Stem cell therapy is mostly experimental except for hematopoietic stem cell transplantation and skin stem cell graft to treat severe burns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สวนเฉลิมพระเกียรติ