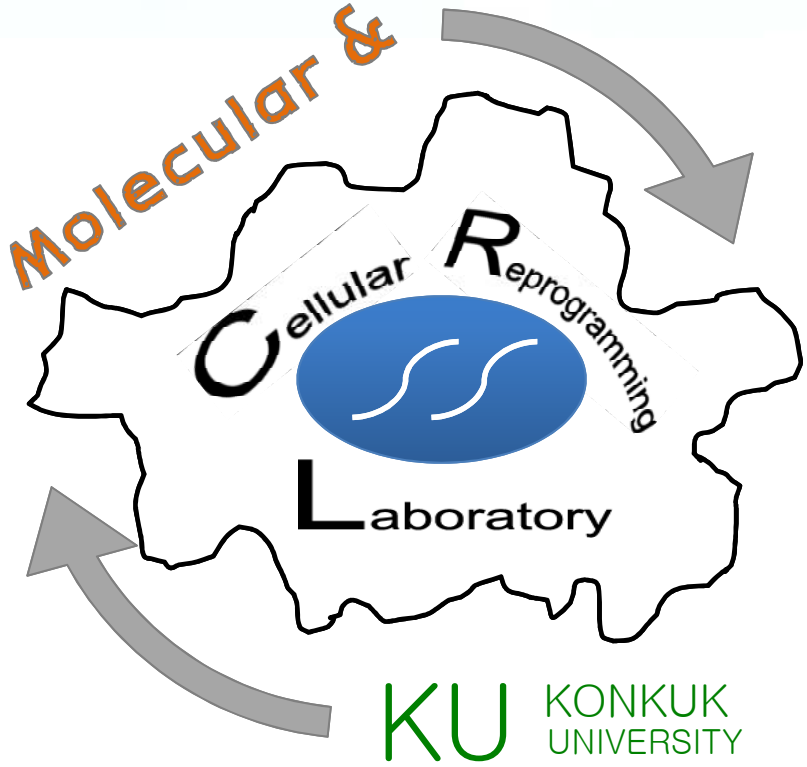
KU-IDASI

Incurable Disease Animal model & Stem cell Institute

KU 건국대학교 KONKUK UNIV.

Differentiation and transplantation of functional pancreatic beta cells generated from iPS cells derived from a type 1 diabetes mouse model

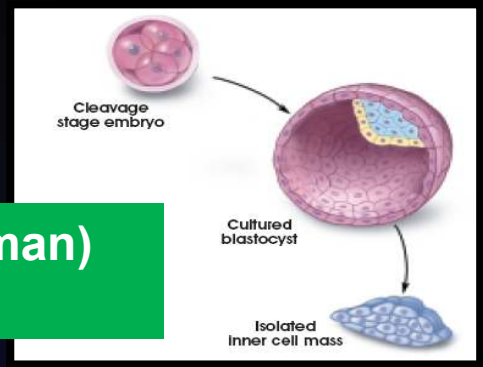


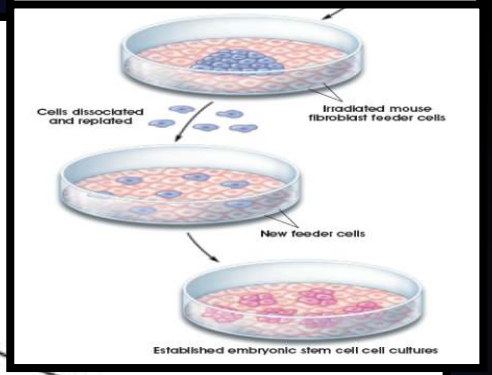
Ssang-Goo Cho

Lab of Molecular Cell Biology and Proteomics,
Molecular & Cellular Reprogramming Center,
Department of Animal Biotechnology,
Incurable Disease Animal model & Stem cell Institute (IDASI)

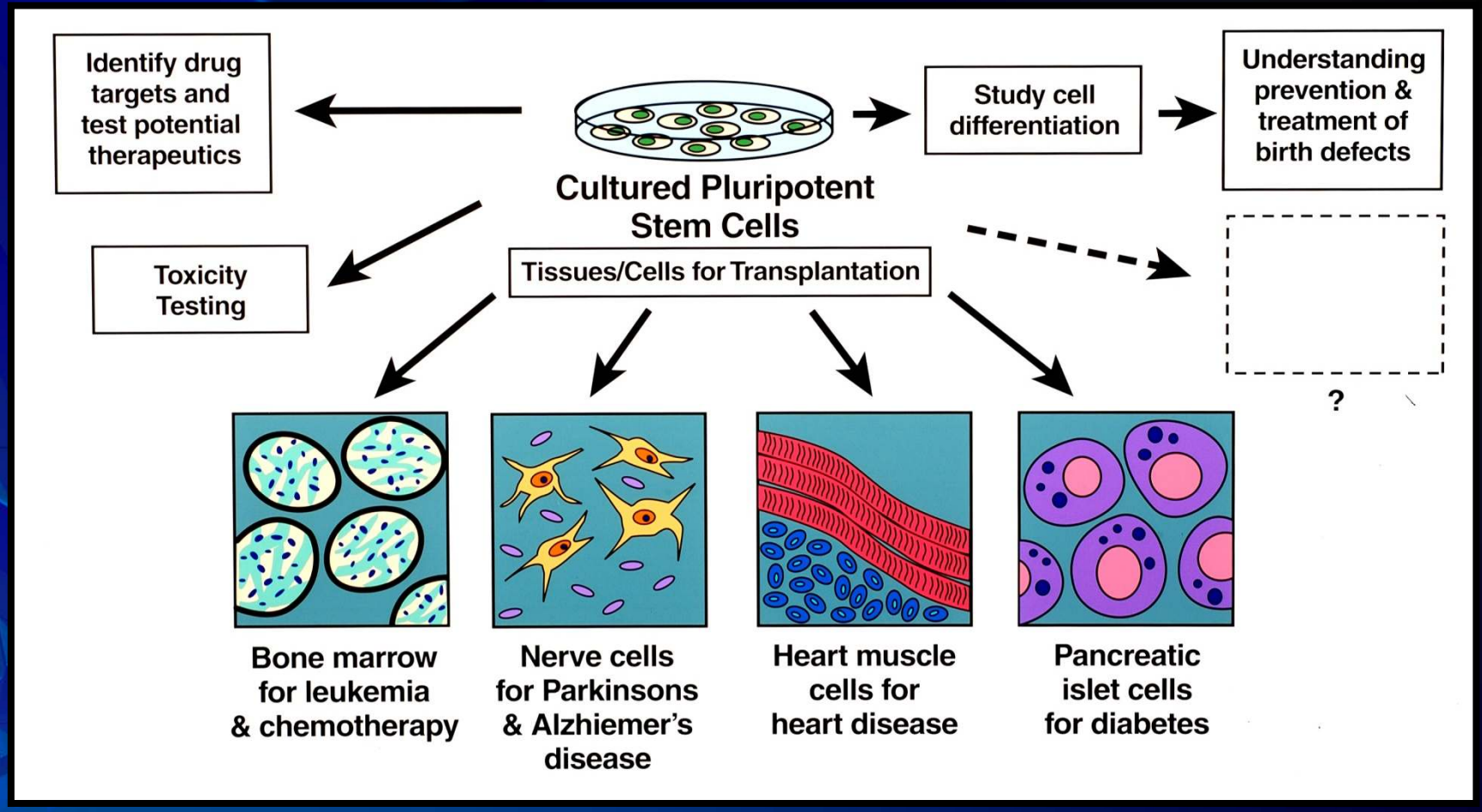
Development & Differentiation

* mESC in 1981 (Martin Evans and Matthew Kaufman)
* hESC in 1998 (James Thomson)



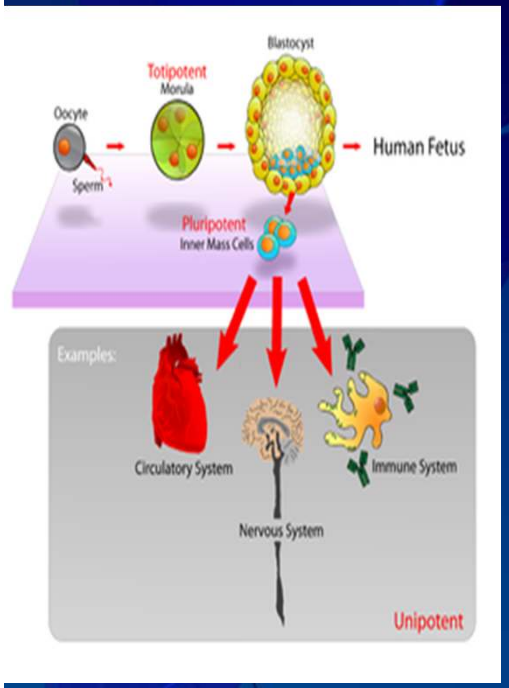


The Promise of Stem Cell Research



Hierarchy of stem cells during differentiation

at each stage, differentiation potential decreases
and specialization increases.



Zygote (totipotent)

↓

Embryonic stem cell (pluripotent)

↓

Germ layer stem cell (multipotent)

↓

Lineage stem cell (oligopotent)

↓

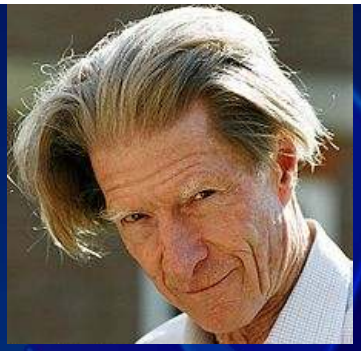
Tissue determined stem cell (tri- or bi-potent)

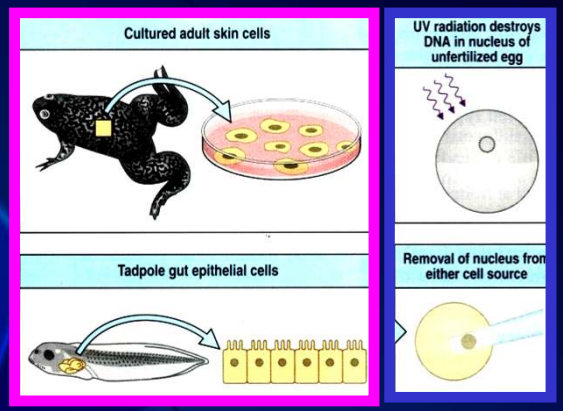
↓

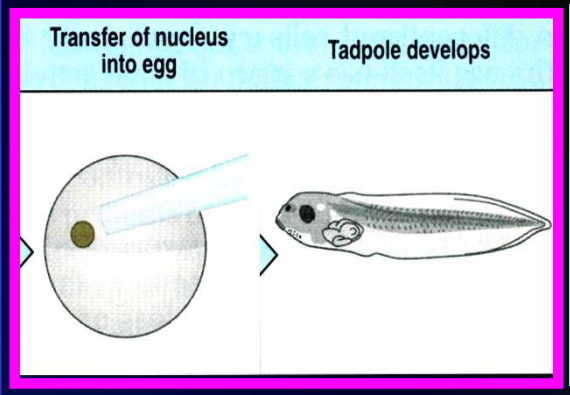
Terminally differentiated cell (nullipotent)

Reversibility of Nucleus of Differentiated Frog Cells: NT(1960s)

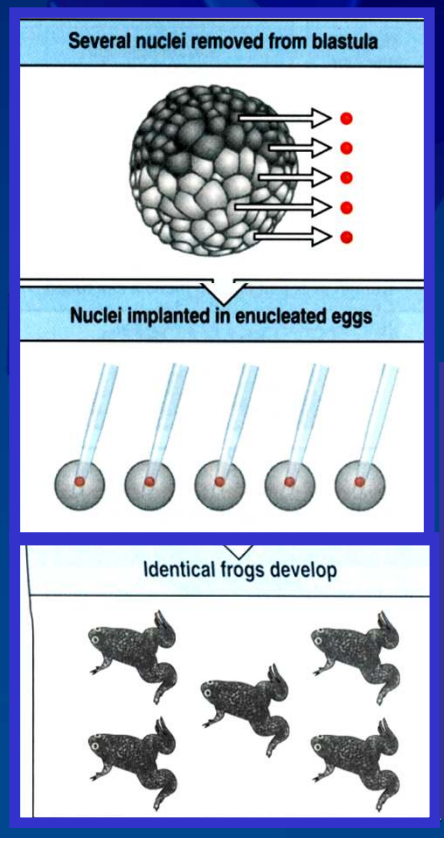
in1962: frog cloning
John Gurdon







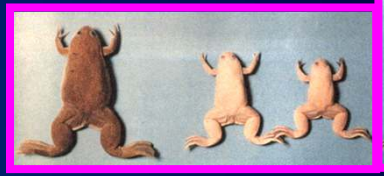
Differentiated nuclei is completely reversible in the aspect of developmental potential–becomes multipotent.



Reversibility of Nucleus is Much Higher with Earlier Embryonic Nuclei: Cloning by Nuclear Transfer

–Differentiated nuclei is completely reversible in the aspect of developmental potential–become totipotent.

–Note that genetic markers between egg donor (wild type–black eye) & nucleus donor(mutant–albino eye)



Albert Lasker Award for Basic Medical Research

The Albert Lasker Award for Basic Medical Research is one of the prizes awarded by the Lasker Foundation for the understanding, diagnosis, prevention, treatment, and cure of disease. The award frequently precedes a Nobel Prize in Medicine: almost 50% of the winners have gone on to win one.

1946 Carl Ferdinand Cori
1947 Oswald T. Avery, Thomas Francis, Jr., Homer Smith
1948 Vincent du Vigneaud, Selman Waksman, René J. Dubos
.....
1960 M.H.F. Wilkins, F.H.C. Crick, James D. Watson, James V. Neel, L.S. Penrose, Ernst Ruska, James Hillier (1962) Nobel
.....
1991 Edward B. Lewis, Christiane Nüsslein-Volhard Drosophila (1995) Nobel
1993 Günter Blobel protein targeting (1999) Nobel
1994 Stanley B. Prusiner prion (1997) Nobel
1995 Peter C. Doherty, Jack L. Strominger, Emil R. Unanue, Don C. Wiley, Rolf M. Zinkernagel MHC immune sys(1996) Nobel
1996 Robert F. Furchgott, Ferid Murad Nitric Oxide (1998) Nobel
1997 Mark S. Ptashne lambda phage
1998 Leland H. Hartwell, Yoshio Masui, Paul Nurse cell cycle (2001) Nobel
1999 Clay Armstrong, Bertil Hille, Roderick MacKinnon ion channel (2003)
2000 Aaron Ciechanover, Avram Hershko, Alexander Varshavsky ubiquitin (2004) Nobel
2001 Mario Capecchi, Martin Evans, Oliver Smithies : ES and knockout mouse (2007) Nobel
2002 James E. Rothman, Randy W. Schekman cellular trafficking
2003 Robert G. Roeder eukryotic transcription
2004 Pierre Chambon, Ronald M. Evans, Elwood V. Jensen estrogen receptor
2005 Ernest McCulloch, James Till stem cell (bone marrow)
2006 Elizabeth Blackburn, Carol W. Greider, Jack Szostak telomere & telomerase (2009) Nobel
2007 Ralph M. Steinman dendritic cell immunology
2008 Victor R. Ambros, David C. Baulcombe, Gary B. Ruvkun microRNA

2009 John Gurdon, Shinya Yamanaka nuclear cloning, iPSc

2010 Douglas L. Coleman, Jeffrey M. Friedman leptin

KU KONKUK UNIVERSITY

The Nobel Prize in Physiology or Medicine 2012
Sir John B. Gurdon, Shinya Yamanaka

The Nobel Prize in Physiology or Medicine 2012

Sir John B. Gurdon

Shinya Yamanaka

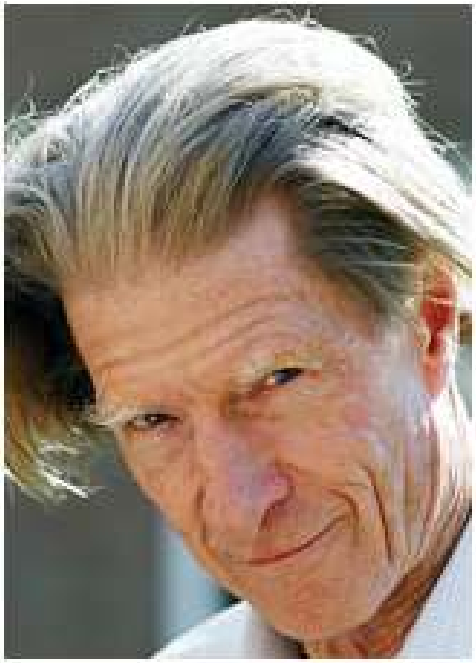


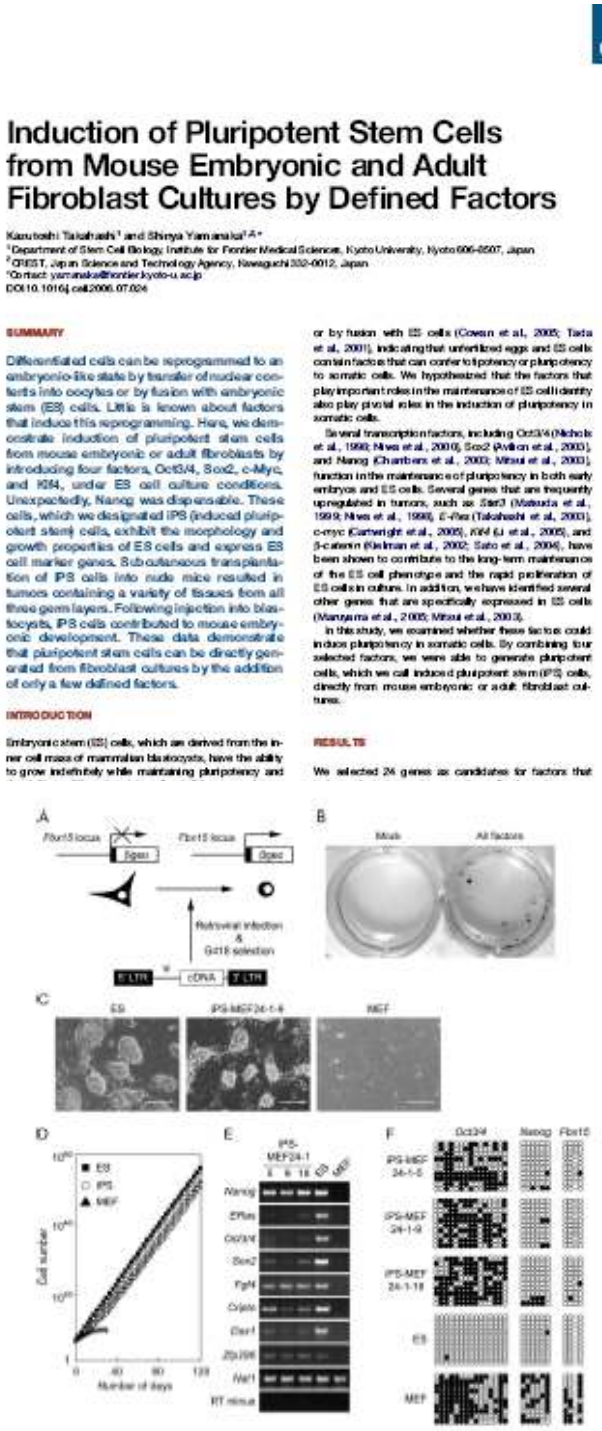
Photo: Creative Commons Attr. 2.0 Generic license

Sir John B. Gurdon

Photo: Creative Commons Attr. 2.0 Generic license

Shinya Yamanaka

The Nobel Prize in Physiology or Medicine 2012 was awarded jointly to Sir John B. Gurdon and Shinya Yamanaka *"for the discovery that mature cells can be reprogrammed to become pluripotent"*



Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi[1] and Shinya Yamanaka[1,2,*]

[1]Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan

[2]CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan

*Contact: yamanaka@frontier.kyoto-u.ac.jp

DOI 10.1016/j.cell.2006.07.024

SUMMARY

Differentiated cells can be reprogrammed to an embryonic-like state by transfer of nuclear contents into oocytes or by fusion with embryonic stem (ES) cells. Little is known about factors that induce this reprogramming. Here, we demonstrate induction of pluripotent stem cells from mouse embryonic or adult fibroblasts by introducing four factors, Oct3/4, Sox2, c-Myc, and Klf4, under ES cell culture conditions. Unexpectedly, Nanog was dispensable. These cells, which we designated iPS (induced pluripotent stem) cells, exhibit the morphology and growth properties of ES cells and express ES cell marker genes. Subcutaneous transplantation of iPS cells into nude mice resulted in tumors containing a variety of tissues from all three germ layers. Following injection into blastocysts, iPS cells contributed to mouse embryonic development. These data demonstrate that pluripotent stem cells can be directly generated from fibroblast cultures by the addition of only a few defined factors.

INTRODUCTION

Embryonic stem (ES) cells, which are derived from the inner cell mass of mammalian blastocysts, have the ability to grow indefinitely while maintaining pluripotency and

or by fusion with ES cells (Cowan et al., 2005; Tada et al., 2001), indicating that unfertilized eggs and ES cells contain factors that can confer totipotency or pluripotency to somatic cells. We hypothesized that the factors that play important roles in the maintenance of ES cell identity also play pivotal roles in the induction of pluripotency in somatic cells.

Several transcription factors, including Oct3/4 (Nichols et al., 1998; Niwa et al., 2000), Sox2 (Avilion et al., 2003), and Nanog (Chambers et al., 2003; Mitsui et al., 2003), function in the maintenance of pluripotency in both early embryos and ES cells. Several genes that are frequently upregulated in tumors, such as Stat3 (Matsuda et al., 1999; Niwa et al., 1998), *E-Ras* (Takahashi et al., 2003), c-myc (Cartwright et al., 2005), *Klf4* (Li et al., 2005), and β-catenin (Kielman et al., 2002; Sato et al., 2004), have been shown to contribute to the long-term maintenance of the ES cell phenotype and the rapid proliferation of ES cells in culture. In addition, we have identified several other genes that are specifically expressed in ES cells (Maruyama et al., 2005; Mitsui et al., 2003).

In this study, we examined whether these factors could induce pluripotency in somatic cells. By combining four selected factors, we were able to generate pluripotent cells, which we call induced pluripotent stem (iPS) cells, directly from mouse embryonic or adult fibroblast cultures.

RESULTS

We selected 24 genes as candidates for factors that

iPS Cells

"Mouse iPS cells" (Shinya Yamanaka. 2006)

Induction of Pluripotent Stem Cellsfrom Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

- Cell line : MEF
- virus : Retroviral Infection

-gene : Oct3/4 (Nichols et al., 1998; Niwa et al., 2000), Sox2 (Avilion et al., 2003), c-Myc(Cartwright et al., 2005), Klf4 (Li et al., 2005)

- feeder : STO
- gene expression (RT-PCR)
  - * IPS genes : Oct3/4, Sox2
  - * other genes : Ecat1, Esg1, Nanog, ERas, Gdf3, Fgf4, Cripto, Dax1, Zfp296, Slc2a3, Nat1

- IPS gene silencing (deletion) : No
- Teratoma / 3 layer : Yes
- Differentiation : all three germ layers

Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors
K Takahashi, S **Yamanaka** - cell, 2006 - Elsevier
Differentiated cells can be reprogrammed to an embryonic-like state by transfer of nuclear contents into oocytes or by fusion with embryonic stem (ES) cells. Little is known about factors that induce this reprogramming. Here, we demonstrate induction of pluripotent ...
6232회 인용 관련 학술자료 전체 105개의 버전

Induction of pluripotent stem cells from adult human fibroblasts by defined factors
..., M Narita, T Ichisaka, K Tomoda, S **Yamanaka** - cell, 2007 - repository.kulib.kyoto-u.ac.jp
抄録: Successful reprogramming of differentiated human somatic cells into a pluripotent state would allow creation of patient-and disease-specific stem cells. We previously reported generation of induced pluripotent stem (iPS) cells, capable of germline transmission, from ...
5049회 인용 관련 학술자료 전체 131개의 버전

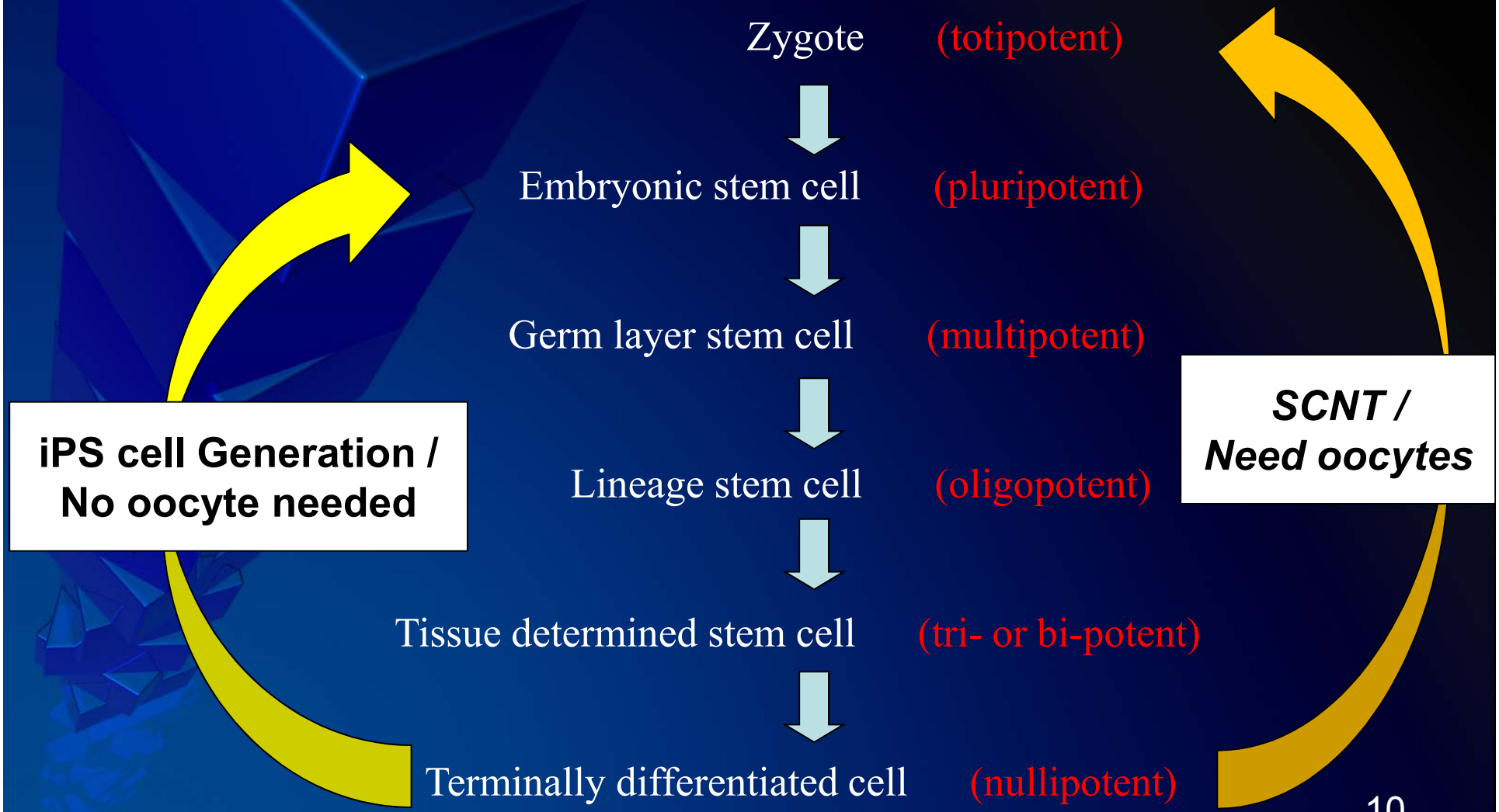
Generation of germline-competent induced pluripotent stem cells
K Okita, T Ichisaka, S **Yamanaka** - Nature, 2007 - nature.com
Abstract We have previously shown that pluripotent stem cells can be induced from mouse fibroblasts by retroviral introduction of Oct3/4 (also called Pou5f1), Sox2, c-Myc and Klf4, and subsequent selection for Fbx15 (also called Fbxo15) expression. These induced ...
2167회 인용 관련 학술자료 전체 49개의 버전

[PDF] The homeoprotein Nanog is required for maintenance of pluripotency in mouse epiblast and ES cells
..., K Takahashi, M Maruyama, M Maeda, S **Yamanaka** - cell, 2003 - ccsu.edu
... underlying pluripotency. Mitsuyo Maeda,2 and **Shinya** Yamanaka1,* Leukemia inhibitory factor (LIF) has been utilized to ... The second cell fate determination subsequently scribed (**Yamanaka** et al., 2000, 1998). For RT-PCR, first strand cDNA ...
1779회 인용 관련 학술자료 전체 31개의 버전 더보기

Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts
..., K Okita, Y Mochiduki, N Takizawa, S **Yamanaka** - Nature ..., 2007 - nature.com
Abstract Direct reprogramming of somatic cells provides an opportunity to generate patient- or disease-specific pluripotent stem cells. Such induced pluripotent stem (iPS) cells were generated from mouse fibroblasts by retroviral transduction of four transcription factors: ...
1350회 인용 관련 학술자료 전체 18개의 버전

Hierarchy of stem cells during differentiation

at each stage, differential potential decreases
and specialization increases.



1. Factors used for iPSc production

No.	Symbol
1	Ecat1
2	Dppa5(Esg1)
3	Fbox15
4	Nanog
5	Eras
6	Dnmt31
7	Ecat8
8	Gdf3
9	Sox15
10	Dppa4
11	Dppa2
12	Fthl17
13	Sall4
14	Oct3/4
15	Sox2
16	Rex1
17	Utf1
18	Tcl1
19	Dppa3
20	Klf4

Takahashi and Yamanaka,
August 25 2006, Cell
24 candidate factors

Oct4 (POU-domain containing transcription factor)

• Oocytes, fertilized embryo, ICM, epiblast, ES cells, and germ cells.

• Crucial for the maintenance of pluripotency

Sox2 (SRY-related HMG-box DNA-binding protein)

• Oocytes, ICM, epiblast, germ cells, multipotent cells of extra-embryonic ectoderm, cells of neural lineage, brachial arches, and gut endoderm.

• Regulates the pluripotent state;

KIF4 (Member of the Kruppel-like factor family of transcription)

• Gut, skin, and ES cells; also expressed in cells of the blood

• Tumor suppressor or oncogene that functions in regulating cell differentiation,cell growth, and cell cycle

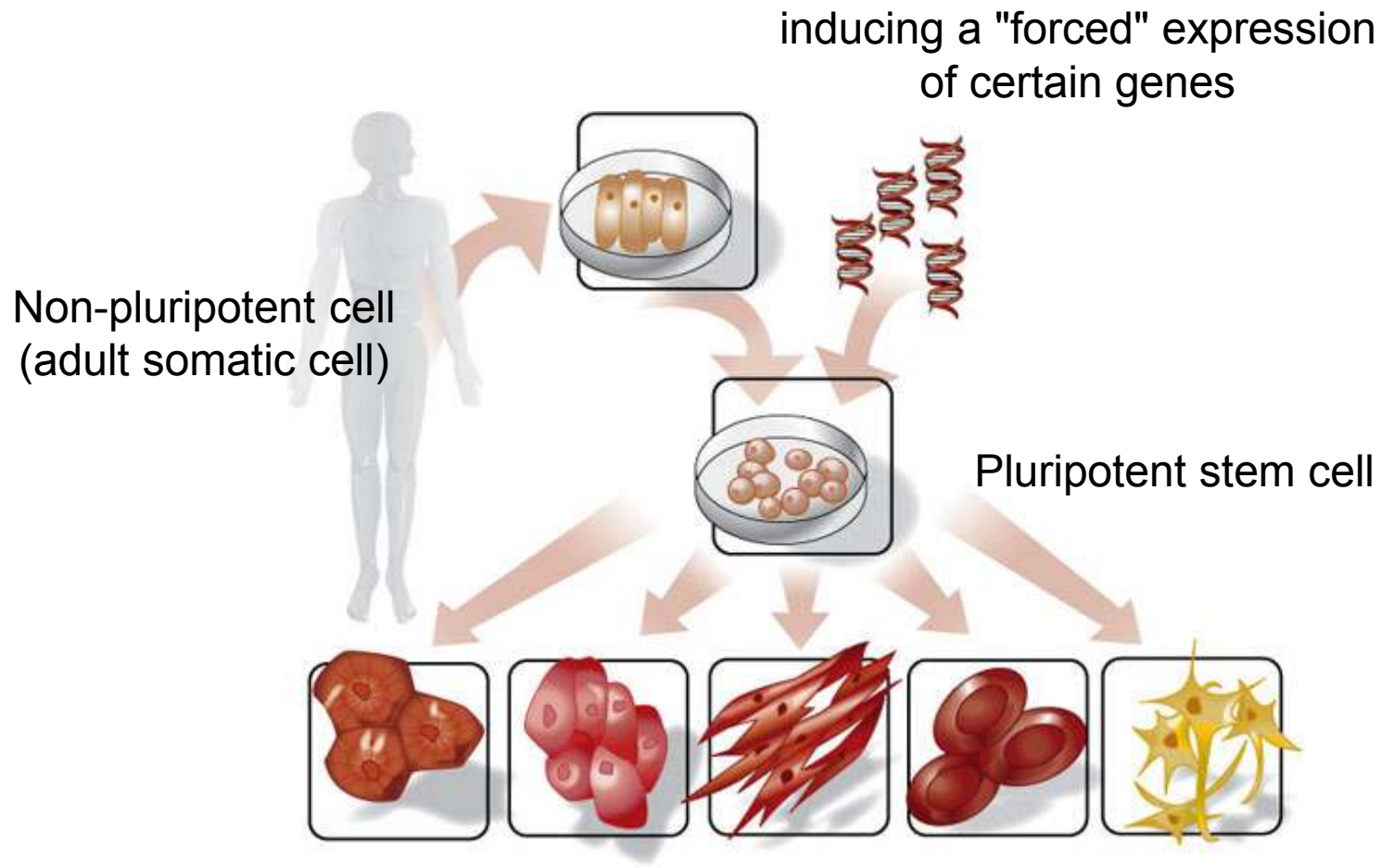
C-Myc (Basic helix-loop-helix transcription factor)

• Multiple tissues including the heart, liver, intestine, spleen, kidney, lung, and mammary gland

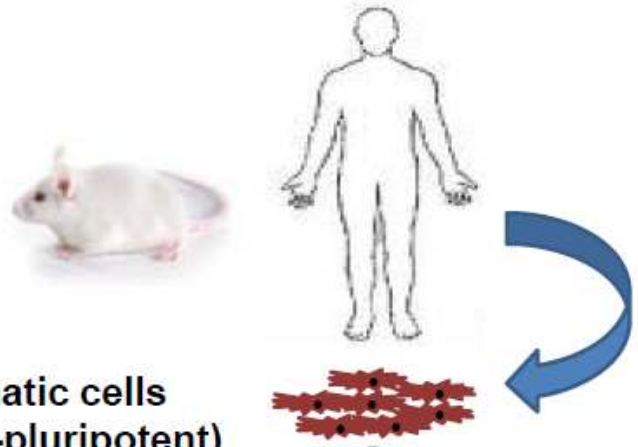
• Involved in cell cycle progression, apoptosis, and cellular transformation

Current Opinion in Genetics & Development 2008, 18:123–129

What is iPSc (induced Pluripotent Stem cells) ?



B



Somatic cells
(Non-pluripotent)

Reprogramming
(with OCT4, SOX2, KLF4, c-MYC)

Retrovirus / Lentivirus
Adenovirus / Sendai virus etc
Episomal vectors
PiggyBac transposon
Transient transfection
Magnet-based Nanofection

Synthetic mRNA / micRNA

Proteins

Small molecules

iPS cells

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DOI

Archives of Pharmacal Research
www.springer.com/12272

REVIEW

Induced Pluripotent Stem Cell Research: A Revolutionary Approach to Face the Challenges in Drug Screening

Minjung Song*, Saswati Paul*, Hyejin Lim, Ahmed Abdal Dayem, and Ssang-Goo Cho
Department of Animal Biotechnology, Animal Resources Research Center, and SMART-IABS, Konkuk University, Seoul 143-701, Korea

(Received October 12, 2011/Revised November 8, 2011/Accepted November 10, 2011)

Biomaterials 32 (2011) 6683–6691

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

The generation of iPS cells using non-viral magnetic nanoparticle based transfection

Chang Hyun Lee [a,b,1], Jung-Hyun Kim [a,1], Hyun Joo Lee [a], Kilsoo Jeon [a], HyeJin Lim [a], Hye yeon Choi [a], Eung-Ryoung Lee [a], Seung Hwa Park [c], Jae-Yong Park [d], Sunghoi Hong [e], Soonhag Kim [b,*], Ssang-Goo Cho [a,**]

Generation of iPSc using magnet-based nanofection (*Biomaterials (IP: 7.9)*)

ENGINEERING, BIOMEDICAL분야 상위 5%이내의 저널

ENGINEERING, BIOMEDICAL	ANNU REV BIOMED ENG	1523-9829	11
	BIOMATERIALS	0142-9612	7.882

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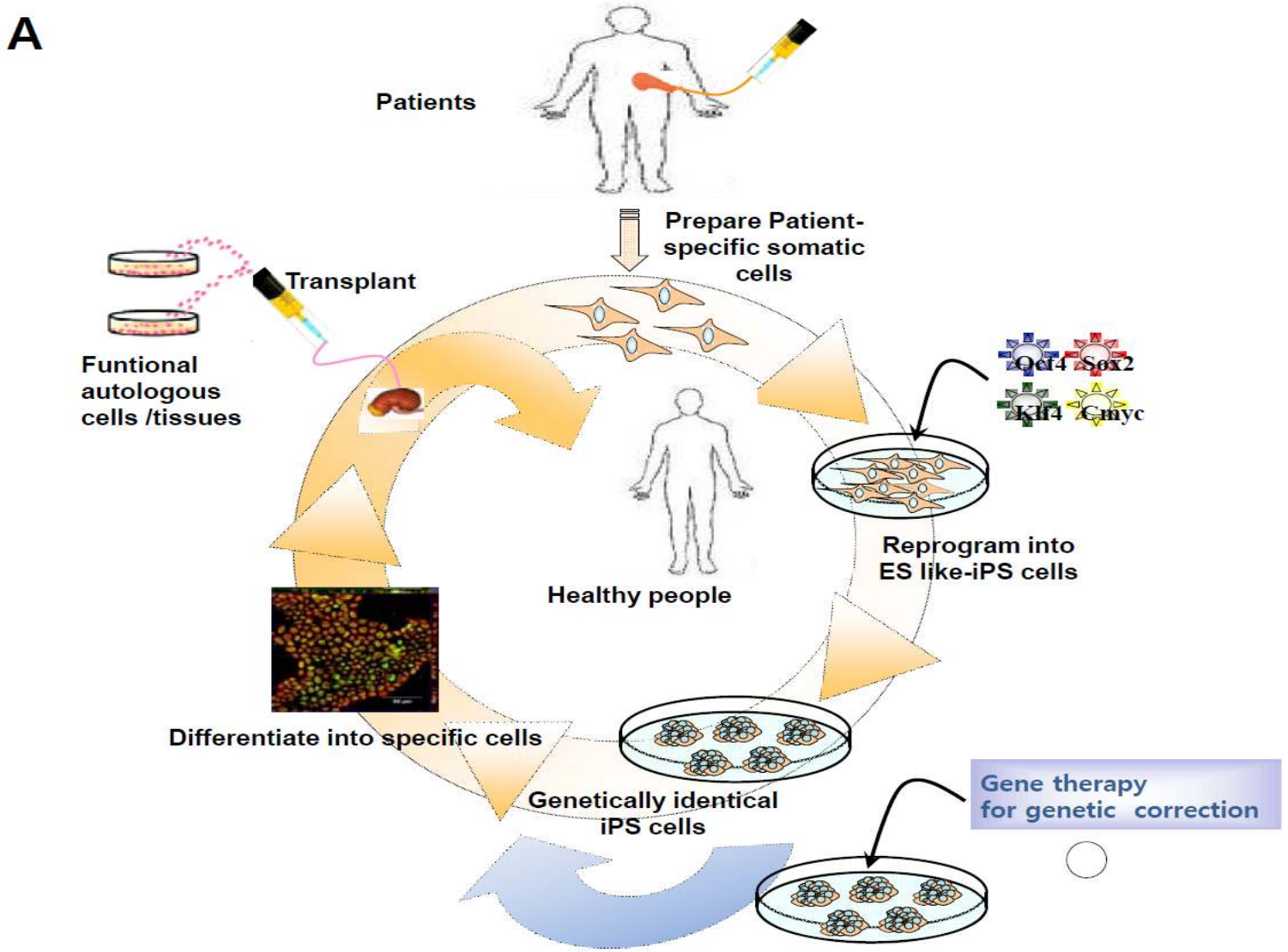
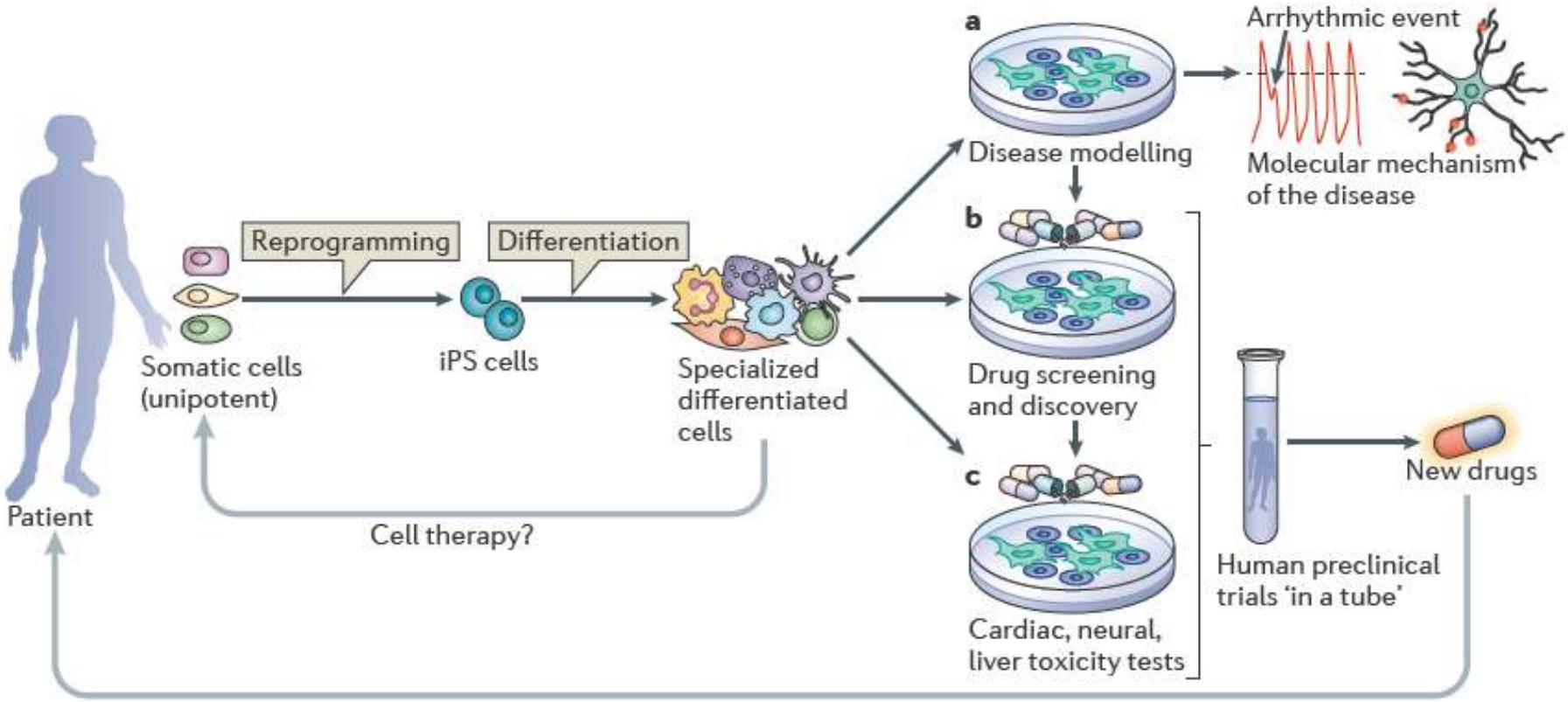
[a] *Department of Animal Biotechnology and Animal Resources Research Center, Konkuk University, Seoul, 143-701, Republic of Korea*
[b] *Department of Applied Bioscience, CHA Stem Cell institute, CHA University, 605-21 Yoeksam 1-dong Gangnam-gu, Seoul 135-081, Republic of Korea*
[c] *Department of Anatomy, College of Medicine, Konkuk Universitry, Seoul 143-701, Republic of Korea*
[d] *Department of Physiology, Institute of Health Science, and Medical Research Center for Neural Dysfunction, Gyeongsang National University School of Medicine, Jinju 660-751, Republic of Korea*
[e] *Department of Biomedical Science, Korea University, Seoul 136-703, Republic of Korea*

The potential application of patient-derived iPSCs in autologous cell transplantation in the treatment of various diseases.

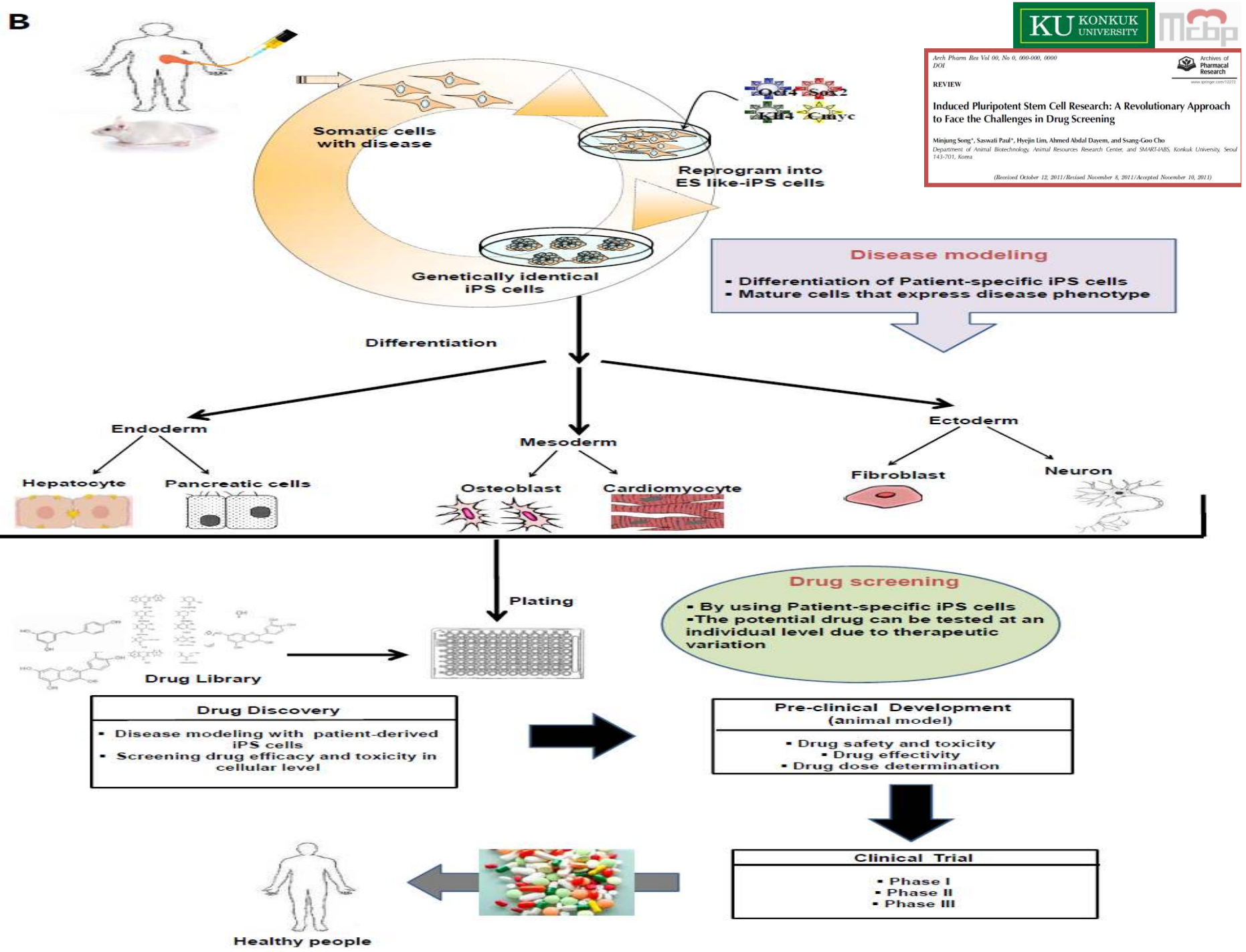


Human iPS cell derivation, differentiation and applications



Bellin et al, 2012 Nature Reviews

Adult somatic cells (unipotent) from any patient can be reprogrammed into induced pluripotent stem (iPS) cells. After inducing differentiation *in vitro,* human iPS cells form specialized cells that have several applications.



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REVIEW

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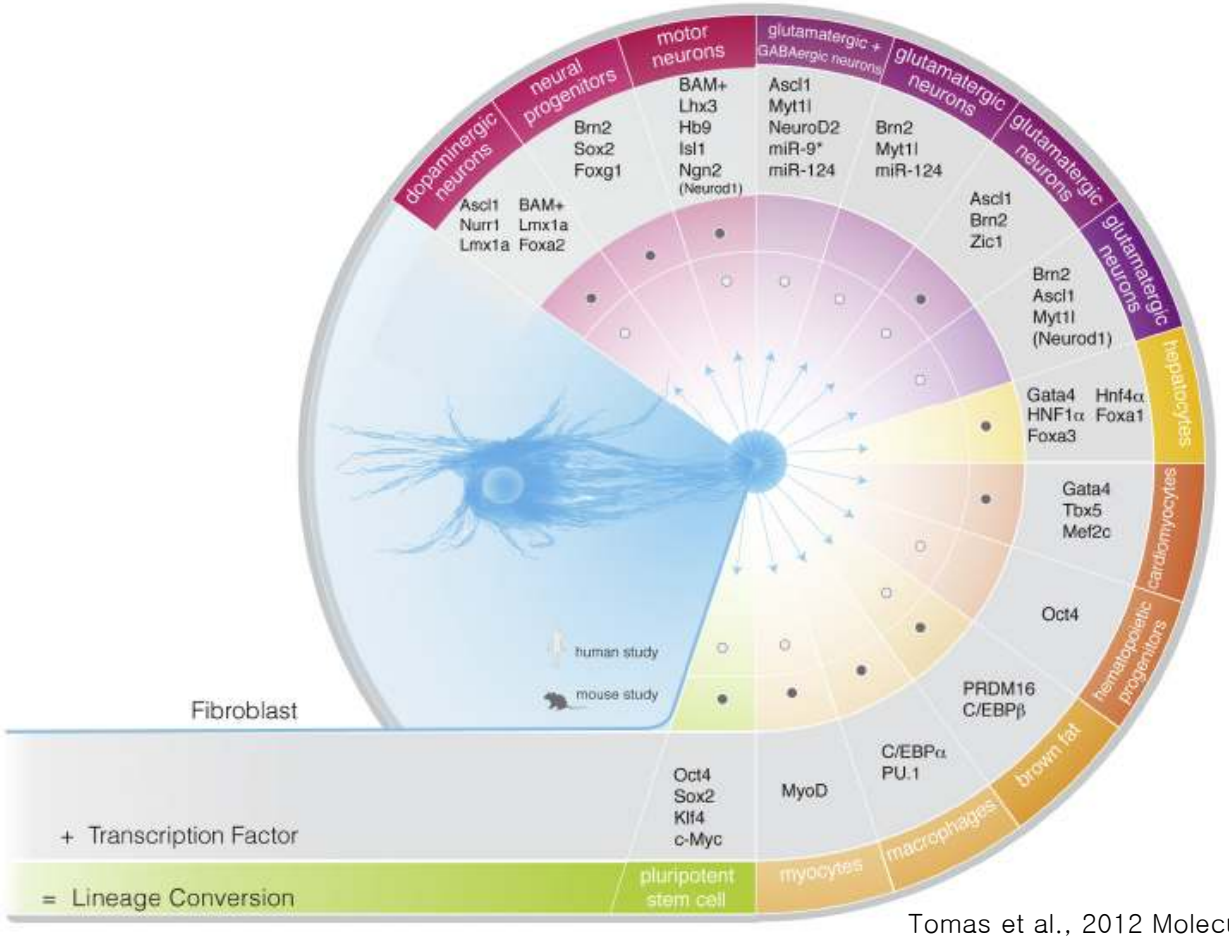
Transcription Factor-Mediated Conversion of Fibroblasts into Diverse Cellular Lineages



Tomas et al., 2012 Molecular cell

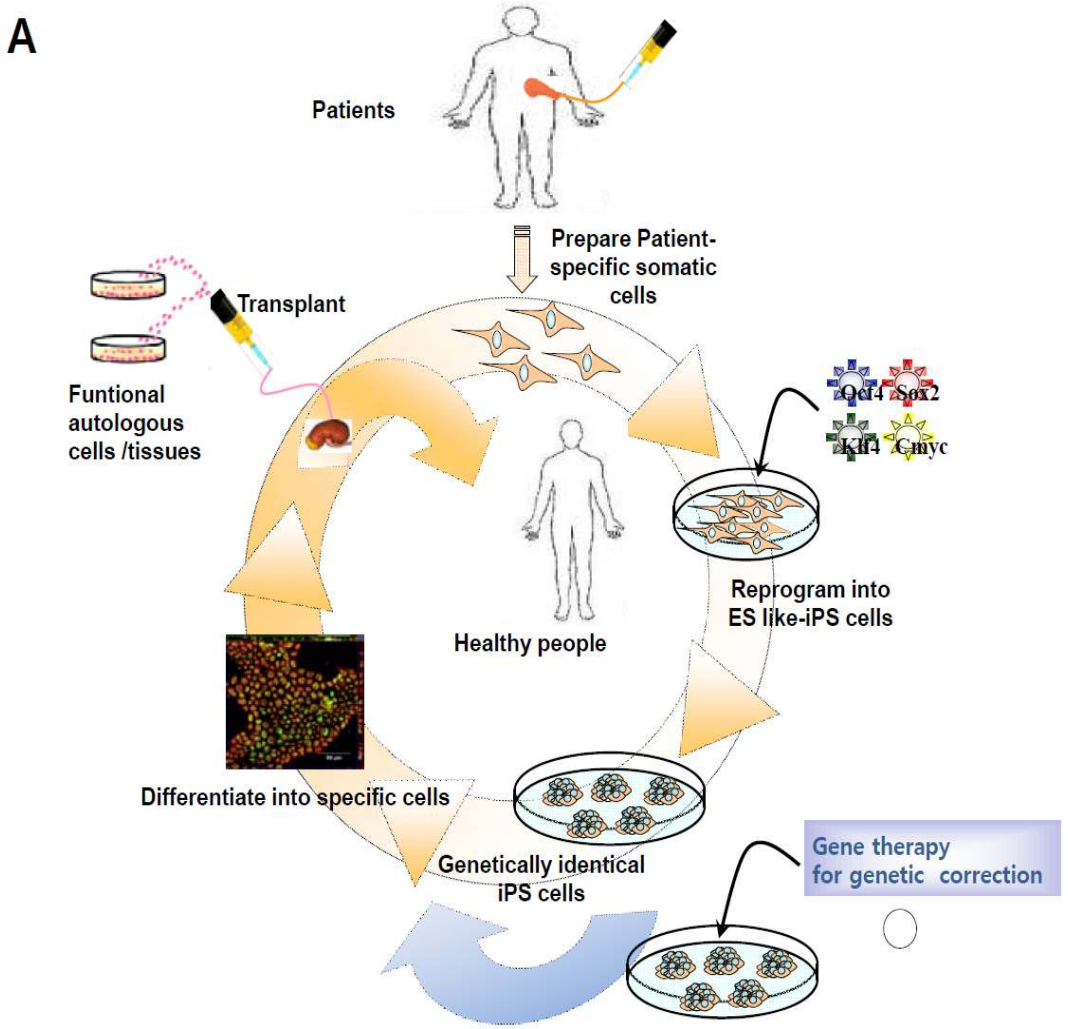
Summary of the diverse cell types generated directly from mouse and human fibroblasts by lineage reprogramming. Factors listed in parentheses are required for reprogramming human cells but not for mouse cells. References (starting from the bottom left of the figure and going counterclockwise): Ambasudhan et al., 2011; Caiazzo et al., 2011; Davis et al., 1987; Feng et al., 2008; Huang et al., 2011; Ieda et al., 2010; Kajimura et al., 2009; Lujan et al., 2012; Pang et al., 2011; Pfisterer et al., 2011; Qiang et al., 2011; Sekiya and Suzuki, 2011; Son et al., 2011; Szabo et al., 2010; Takahashi and Yamanaka, 2006; Yoo et al., 2011.

From 2008

Differentiation and transplantation of

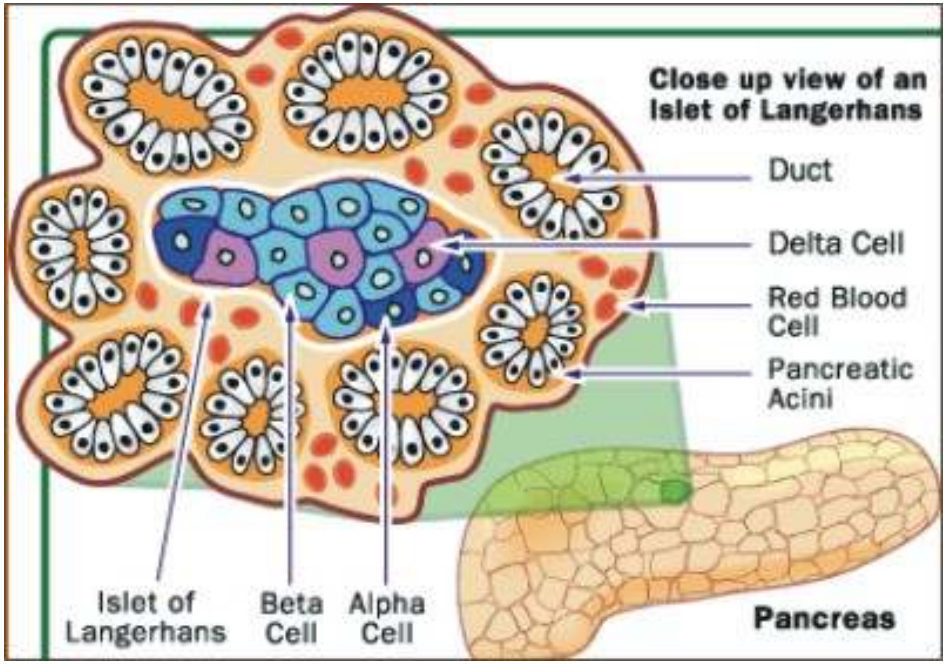
functional pancreatic beta cells generated from

Type 1 diabetes model – iPS cells



Therapeutic application of iPS cells (Diabetes)

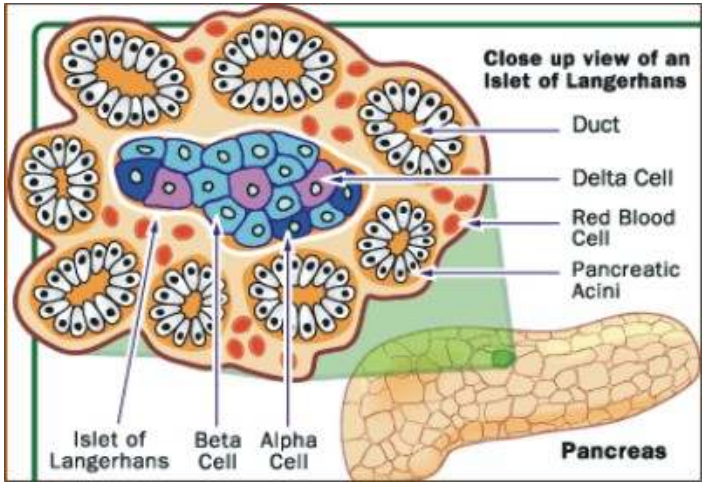
Type 1 diabetes is an immune-mediated disease in which pancreatic insulin-producing beta cells are damaged and destroyed. (Insulitis)



- **Alpha cells** :
  producing glucagon (15-20%)
- **Beta cells** :
  producing insulin and amylin (65-80%)
- **Delta cells** :
  producing somatostatin (3-10%)
- **PP cells** :
  producing pancreatic polypeptide (3-5%)
- **Epsilon cells** :
  producing ghrelin (<1%)

What is Type 1 Diabetes?

- ✓ **Diabetes mellitus type 1** (Type 1 **diabetes**, T1D, T1DM, IDDM, juvenile diabetes) is a form of diabetes mellitus.
- ✓ **Type 1 diabetes** is an **autoimmune disease** that results in destruction of **insulin**-producing beta cells of the **pancreas**.
- ✓ **Type 1 diabetes** is fatal unless treated with **exogenous insulin**.
- ✓ **Islet cell transplant** is also being investigated and has been achieved in mice and rats, and in experimental trials in humans as well.
- ✓ **Use of stem cells** to produce a new population of functioning beta cells seems to be a future possibility, but has yet to be demonstrated even in laboratories.



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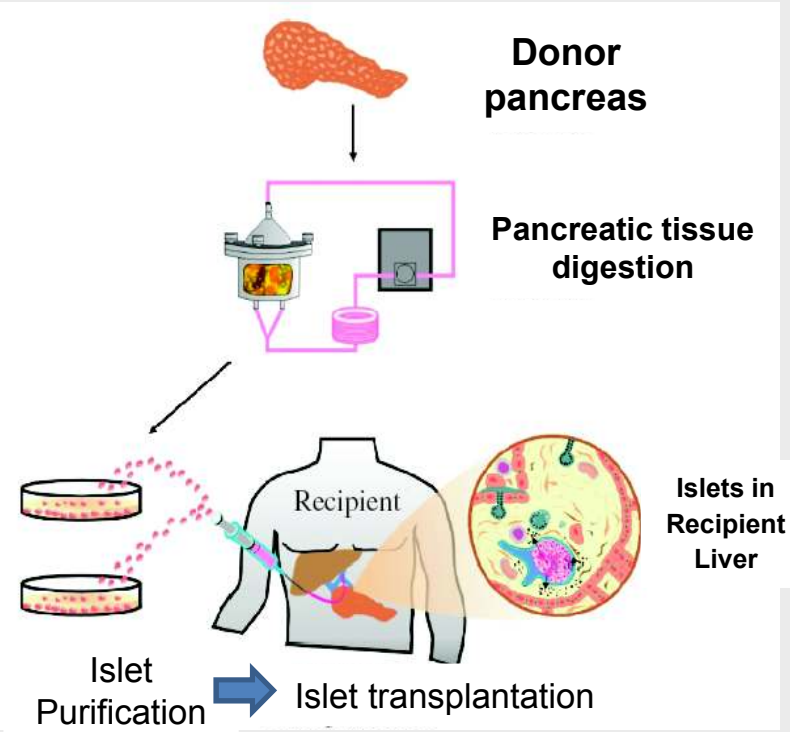
- **PP cells** :
  producing pancreatic polypeptide (3-5%)
- **Epsilon cells** :
  producing ghrelin (<1%)

New treatment methods and challenges of diabetes

The advantage of islet transplantation

- The treatment without the risk of hypoglycemia
- The possibility of repeating the procedure
- No complications of pancreatic exocrine enzymes



Limitations of current islet transplantation

- Requires multiple pancreas donors
- Lack of donors- Lack of islets transplantation

Solution

Differentiation of insulin-secreting cells from embryonic stem cells

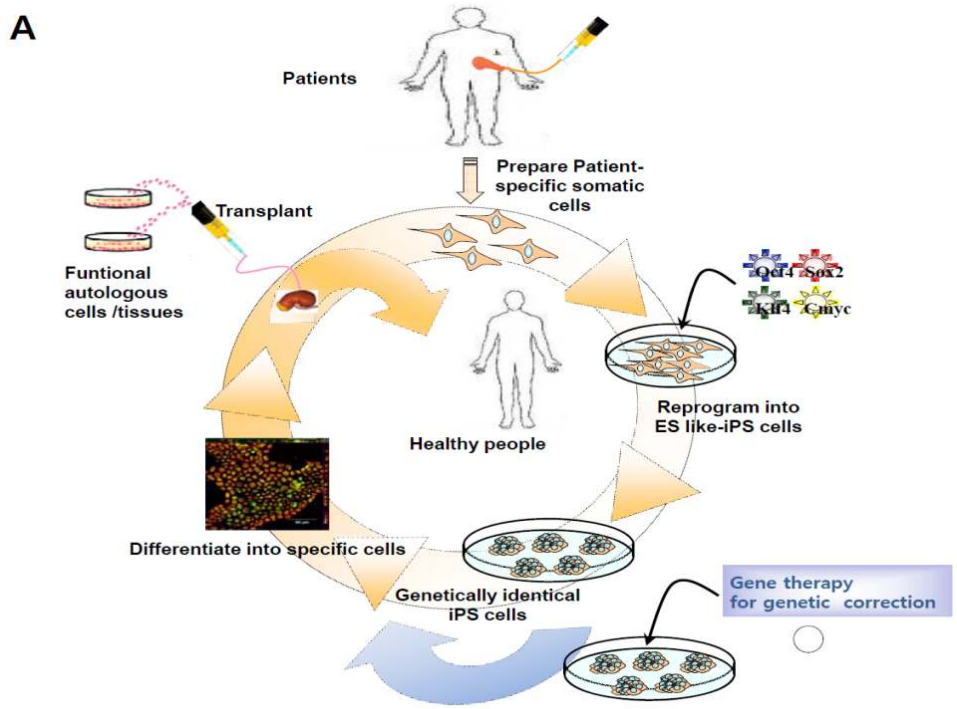
Limitations (ES)

- Ethical problems of using embryo
- Require patient-specific embryonic stem cells
- the concern of immune rejection
- The risk of teratoma tumor formation

Possibility (iPS)

- By removing the bioethical issues
- eliminate the concern of immune rejection
- iPS cells generated from subjects with a genetic disease
- Genetically matched cell lines
- Easier to create
- Highly efficient differentiation into insulin-producing cells

Potential application of patient-derived iPSCs in autologous beta-cell transplantation in the treatment of diabetes.

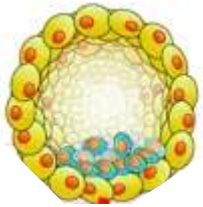


- We hypothesized that a combination of the cell reprogramming and differentiation techniques could be used for generation of patient-specific iPSCs and differentiation into pancreatic beta-like cells.

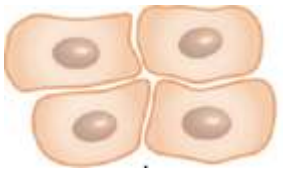
- Such cells could provide a promising resource for cell therapy to treat diabetes.

Limited source resolved through the production of insulin-secreting cells

Embryo

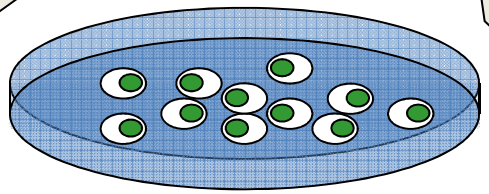


Cultured blastocyst



Patient cells

iPS

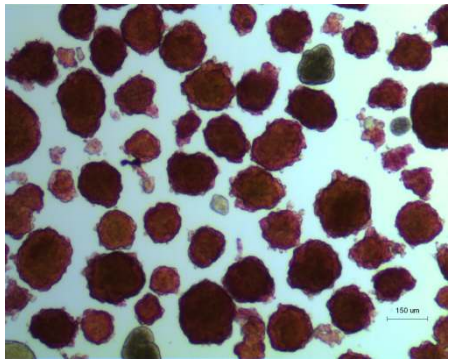


Cultured Stem cells

In vitro Differentiation

- Definitive Endoderm
- Pancreatic Progenitor
- Progenitor Expansion
- Insulin-Producing Cells

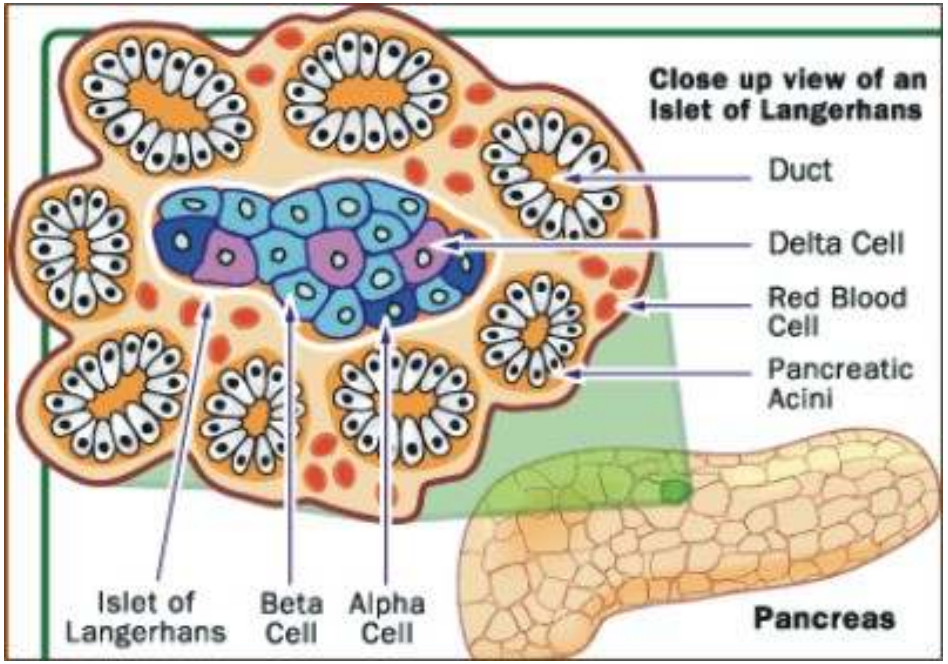
Solves lack of islet transplantation



Islet like cells

Therapeutic application of iPS cells (Diabetes)

Type 1 diabetes is an immune-mediated disease in which pancreatic insulin-producing beta cells are damaged and destroyed. (Insulitis)



- **Alpha cells** :
  producing glucagon (15-20%)
- **Beta cells** :
  producing insulin and amylin (65-80%)
- **Delta cells** :
  producing somatostatin (3-10%)
- **PP cells** :
  producing pancreatic polypeptide (3-5%)
- **Epsilon cells** :
  producing ghrelin (<1%)

Animal models have served a prominent function in the development of the present ideas of pathogenesis and approaches to therapy. This commentary addresses the utility and limitations of these models for facilitating the 'translation' of immunology research into clinical applications.

Differences of gene expression between normal mice & NOD mice?

Type 1 diabetes is a polygenic disease, meaning many different genes contribute to its expression. Depending on locus or combination of loci, it can be dominant, recessive, or somewhere in between.

Locus	Chromosome	Marker
IDDM1	6p21.31	HLA
IDDM2	11p15.5	5' insulin VNTR
IDDM3	15q26	D15S107
IDDM4	11q13	Fibroblast growth factor-3 (FGF3)
IDDM5	6q24-27	D65476-D65448
IDDM6	18q21	D18S64
IDDM7	2q31-33	D2S152
IDDM8	6q27	D6S1590
IDDM9	3q21-q25	D3S1303
IDDM10	10p11-q11	D10S193
IDDM11	14q24.3-14q31	DD14567
IDDM12	2q33	CTLA-4
IDDM13	2q34	D2S164
IDDM15	6q21	D65283
IDDM17	10q25.1	D10S1681
No "IDDM"	16q	D1653098
No "IDDM"	1q	D15617

The strongest gene, IDDM1, is located in the MHC Class II region on chromosome 6, at staining region 6p21.

This is believed to be responsible for the histocompatibility disorder characteristic of type 1: Insulin-producing pancreas cells (beta cells) display improper antigens to T cells.

-The non-obese diabetic (NOD) mouse is a classical animal model for autoimmune type 1 diabetes (T1D), and exhibit clinical or immunological features that closely mimic those of human T1D patients.

-Thus, the prospect of induced pluripotent stem cells (iPSCs) as a therapeutic modality against established T1D should be verified in NOD mouse model.

Stem cells and a cure for type 1 diabetes?

John A. Todd[1]

Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Cambridge CB2 0XY, United Kingdom

The discovery that adult stem cells can be reprogrammed, backwards, to induced pluripotent stem cells (iPS) was a remarkable and landmark breakthrough in 2006 (1). These iPS then can be differentiated by using specific gene transfections into a wide variety of cell types. Now, at a tremendous pace, many laboratories are improving the efficiency and homogeneity of this process, including the replacement of gene transfection with proteins and small m
Perhaps not surprisingly,
shown that iPS can be m
cells from people with di
3), and in this issue of P
al. (4) illustrate this proc
1 diabetes. Type 1 diabet
most common diseases i
causing significant morbi
tality and enormous heal
nomic costs. Worse still,
children aged under 5 ye
double by 2020 (5). Curr
no idea how to prevent t
crease, which must be ca
creasing permissiveness
ment acting on a genetic
background in many cou
worldwide.

What are the implicat
vance for research and
tion in type 1 diabetes?
al. (4) state, the clinical
are a very long way off.
mount, and cellular ther
quire rigorous clinical e
pecially given the possibility that transplanted cells could conceivably change their phenotype and functions in vivo and have harmful effects. Such alterations in phenotype or effect could depend on a patient's genotype or exposure to environmental factors, such as infection. In type 1 diabetes, the specific challenge is that any transplant of pancreas, purified islets, or engineered insulin-expressing, glucose-responsive cells will be rapidly destroyed by the body's own immune system, in the absence of immunosuppression or (and this is an active, major research activity) in the absence of induced antigen-specific tolerance, which could be safer than any form of general immunosuppression (6). Type 1 diabetes results from an inherited loss of immune tolerance to insulin and its precursors and other pancreatic islet antigens, leading to destruction of the insulin-producing islet β cells by the autoimmune activities of antigen-presenting cells such as B lymphocytes, macrophages, dendritic cells, and CD4 and $CD8^+$ T lymphocytes. The anti-islet memory T cell response, once established, is very strong and long-lasting, akin to the lifelong protection provided by memory T cells against infections.

Therefore, the exciting and nearer-term implications of type 1 diabetes-

compared with the mouse (11, 12). Meanwhile, the spontaneous NOD model remains an invaluable experimental tool and preclinical model, not least because it has genetic alterations in pathways that are directly conserved with human genetic susceptibilities, including the HLA or MHC class II molecules, the IL-2 pathway, and T cell activation pathways (13, 14). This con-

servation is remarkable and the extent
Versus DR3/3 or DR4/4 found in Caucasians.

Clearly, the DR3/4 genotype has been associated with a decreased age at diagnosis and perhaps interacts differently with the unknown, but increasingly permissive, environmental factors (7). These HLA class II genes are the major genetic effect in type 1 diabetes (8), and the frequencies of the various susceptibility alleles and haplotypes correlate with the incidence of type 1 diabetes across several countries. One goal is to make DiPS that are resistant to autoimmune attack. In the widely used spontaneous mouse model of autoimmune type 1 diabetes, the nonobese diabetic (NOD) strain, >10 genes have been tested over the past 10 years in transgenic modification of NOD mice to try to make their β cells resistant to autoimmune destruction in vivo. The most successful example, with the least side effects, was the β cell expression of the decoy receptor 3 gene (DCR3 or TR6) (9).

It may be possible to examine the interactions of DiPS immune cells and β cells in vivo in humanized mice by transfer, for example, into an immune-deficient version of the NOD strain in which the immune genes *scid* and *il2rg* have been knocked out (10). However, this approach may be limited by the extent that the mouse model can be humanized and remain physiologically
vant to the human disease. Fur-
more, we understand relatively
e about the normal and disease-
cted immune systems of humans
pared with the mouse (11, 12).
nwhile, the spontaneous NOD
del remains an invaluable experi-
ital tool and preclinical model, not
t because it has genetic alterations
athways that are directly conserved
human genetic susceptibilities,
uding the HLA or MHC class II
ecules, the IL-2 pathway, and T cell
vation pathways (13, 14). This con-
ation is remarkable and the extent
will likely increase as we continue
nap and identify the genes that af-
the human disease. Nevertheless, it
robably not that surprising if we
sider that many of these rate-
ting functions in the immune sys-
, manifested by the existence of
mon functional polymorphisms in
se, rat, and human populations,
e been under Darwinian selection in mammals in the constant and ancient war against pathogens. Some authors have criticized the NOD model in that it has not led to successful human clinical trials (15), but I suggest the real reasons for the current failures of several prevention trials of type 1 diabetes lie in our remaining state of ignorance (about disease etiology) and consequent inadequate design of the trials (the wrong dose of reagent, wrong timing, wrong delivery, too little, too late, and the necessity of safety first especially in children) (6, 16). No one will accept any risks of altering the immune response of a child in a way

Author contributions: J.A.T. wrote the paper.

The author declares no conflict of interest.

See companion article on page 15768.

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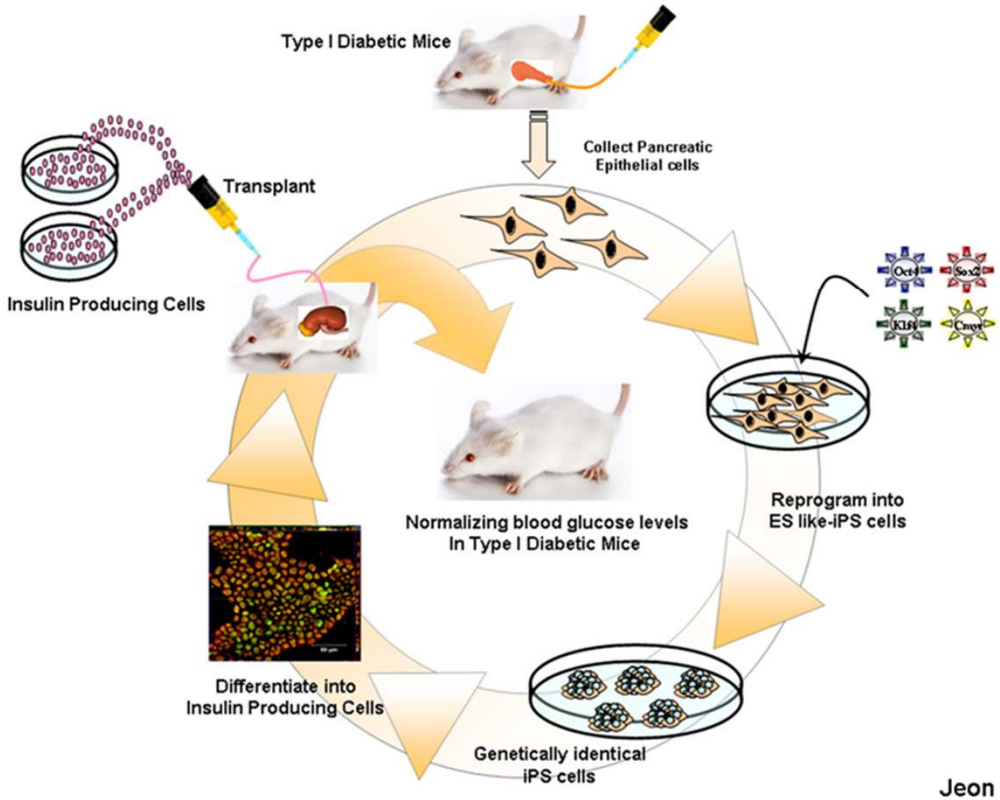
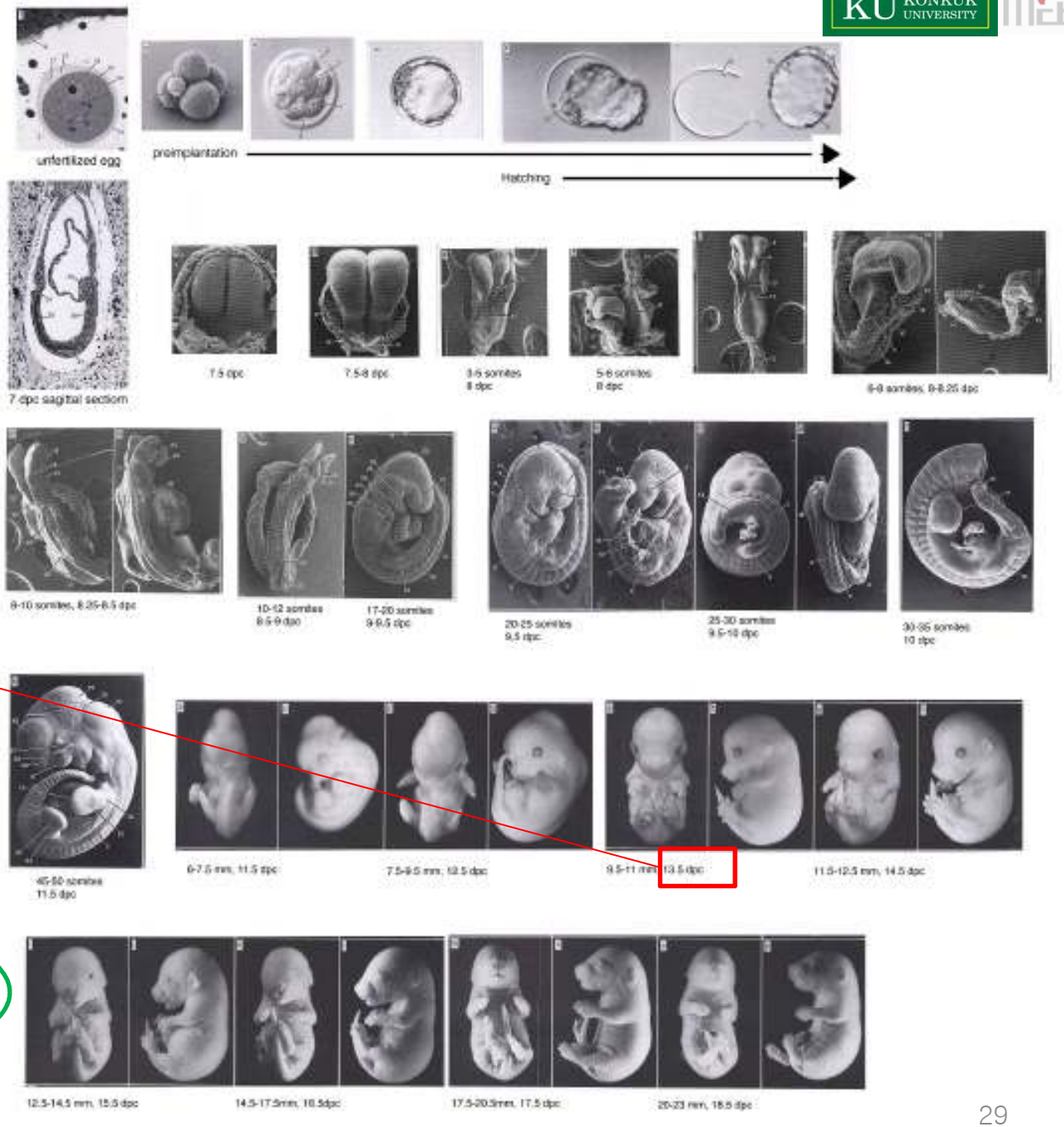


Jeon *et. al*

- We developed an **optimized stepwise differentiation protocol**, based on several different direct differentiation methods [Melton,Deng], that led to the successful differentiation of NOD-iPSCs into **insulin-producing cells**.

Mouse Development



- MEF (13.5 dpc)
(mouse embryonic fibroblast)

- PDE (3 months)
(Pancreas-derived epithelial cells)
: Adult-stage

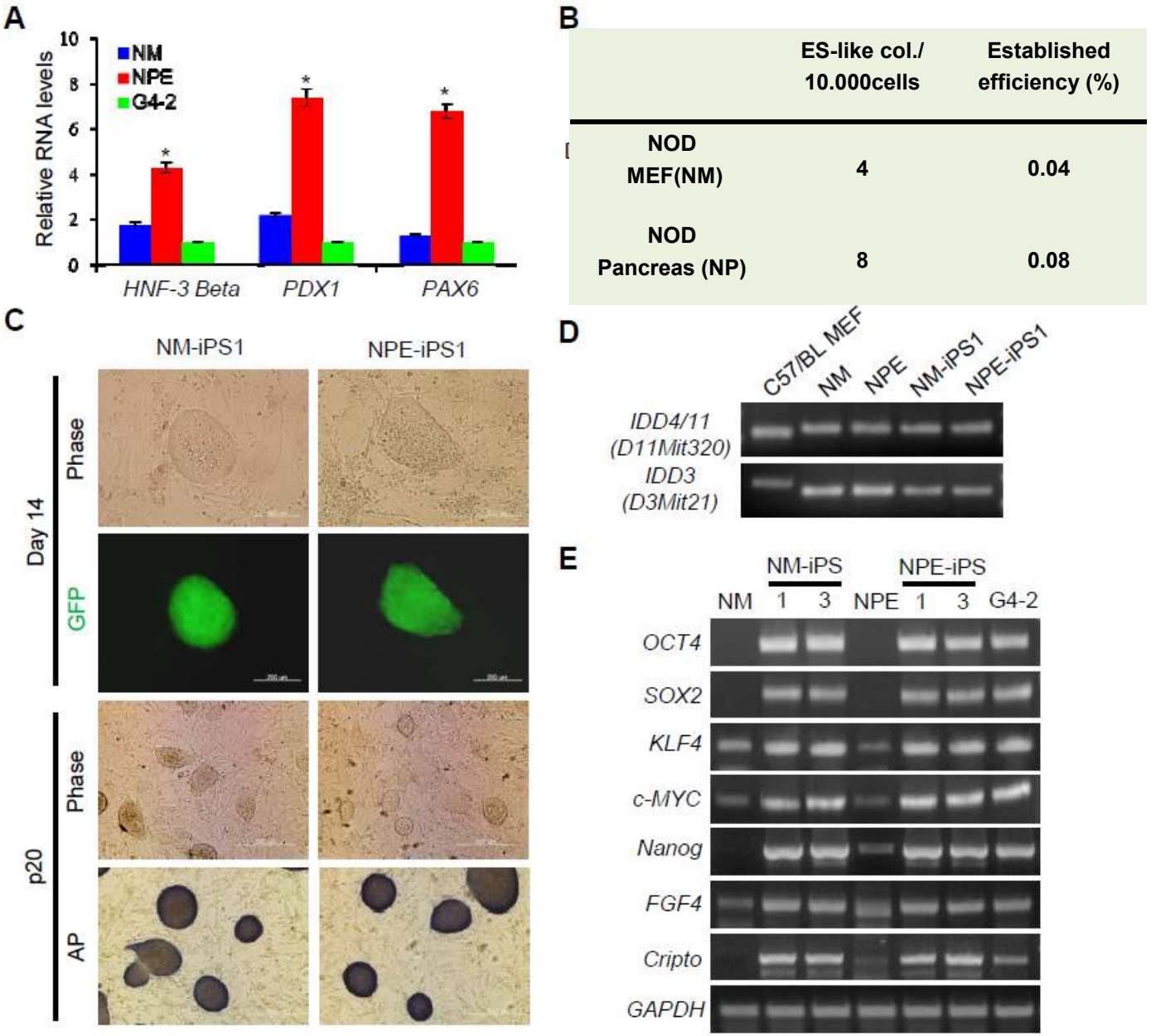


Figure. 1 Generation of NOD-iPSCs from NOD mouse

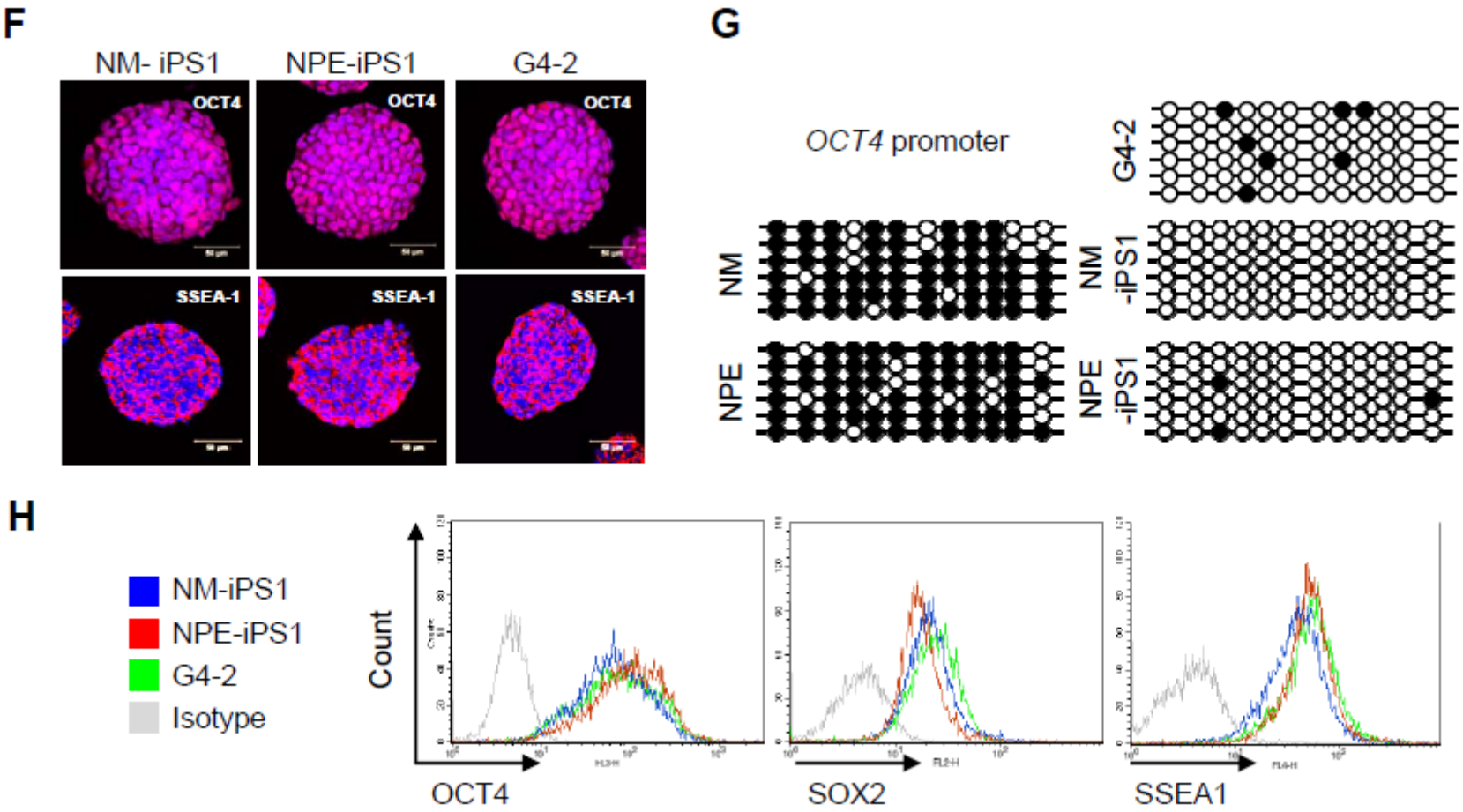
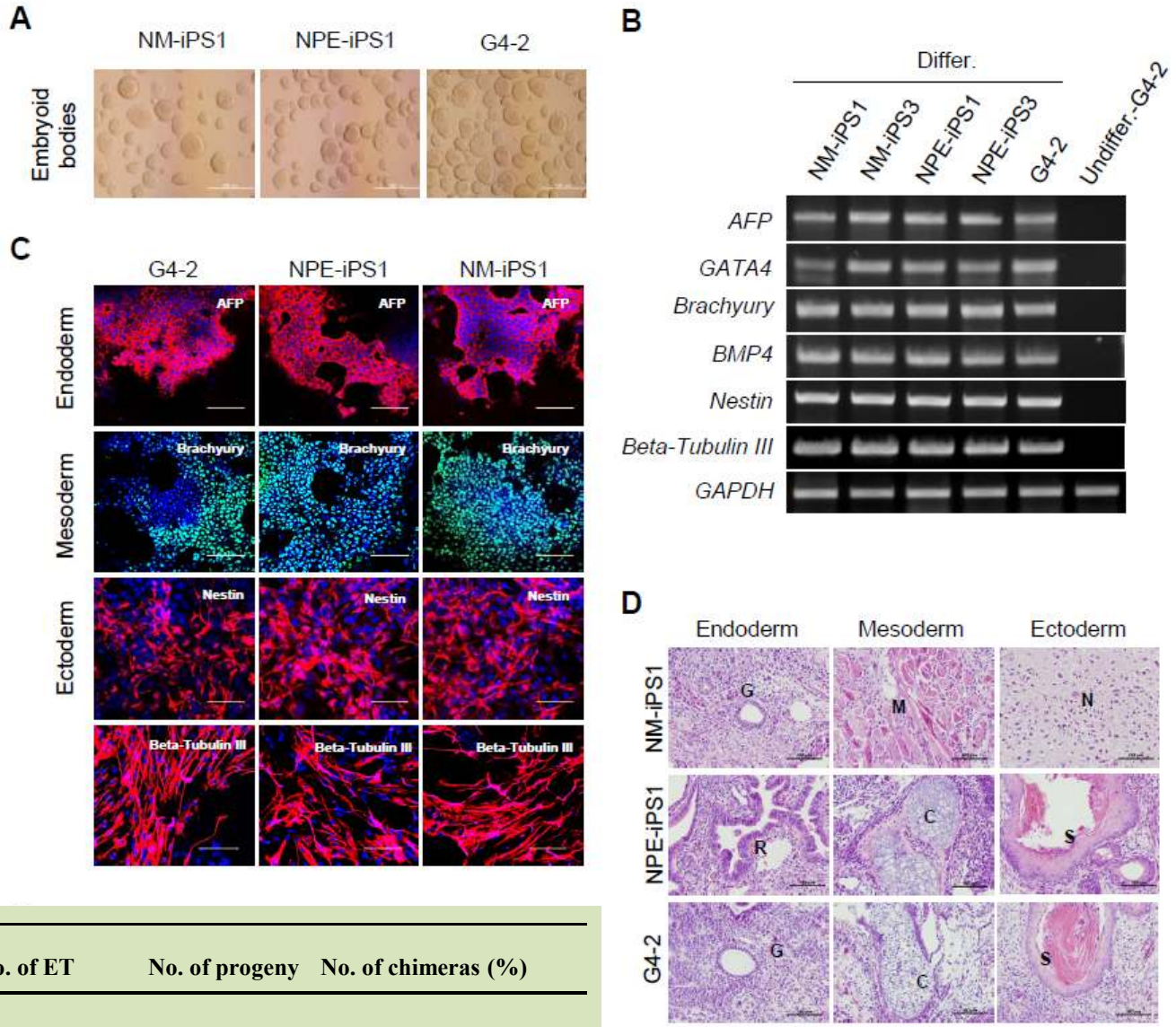


Figure. 1 Generation of NOD-iPSCs from NOD mouse



iPS cell line	No. of ET	No. of progeny	No. of chimeras (%)
NOD-iPS	37	19	3 (8%)
Control	51	24	5 (9%)

Control: 129-ES cells

Figure. 2 *In vitro* and *in vivo* differentiation of NOD-iPSCs into the 3 germ layers

ß- cell differentiation – From 2008

KU 건국대학교 KONKUK UNIV.

Differentiation of mouse nuclear transfer embryonic stem cells into functional pancreatic beta cells

Diabetologia (2008) 51:1671–1679

W. Jiang · Z. Bai · D. Zhang · Y. Shi · J. Yong · S. Chen · M. Ding · H. Deng

Generation of pluripotent stem cells from patients with type 1 diabetes

PNAS

Contributed by Douglas A. Melton, July 8, 2009 (sent for review May 18, 2009)

René Maehr[a], Shuibing Chen[a], Melinda Snitow[a], Thomas Ludwig[b], Lisa Yagasaki[a], Robin Goland[c], Rudolph L. Leibel[c], and Douglas A. Melton[a,1]

Metastable Pluripotent States in NOD Mouse Derived ES Cells

Cell Stem Cell. 2009 June 5; 4(6): 513–524.

Jacob Hanna[1,*], Styliani Markoulaki[1,*], Maisam Mitalipova[1], Albert W. Cheng[1,2], John P. Cassady[1,3], Judith Staerk[1], Bryce W. Carey[1,3], Christopher J. Lengner[1], Ruth Foreman[1,3], Jennifer Love[1], Qing Gao[1], Jongpil Kim[1], and Rudolf Jaenisch[1,3]

Stem cells and a cure for type 1 diabetes?

PNAS | September 15, 2009 | vol. 106 | no. 37 | 15523–15524

John A. Todd[1]

Highly efficient differentiation of human ES cells and iPS cells into mature pancreatic insulin-producing cells

Cell Research (2009) 19:429–438.

Donghui Zhang[1, 2, *], Wei Jiang[1, *], Meng Liu[1, 2], Xin Sui[1, 2], Xiaolei Yin[1, 2], Song Chen[1], Yan Shi[2], Hongkui Deng[1, 2]

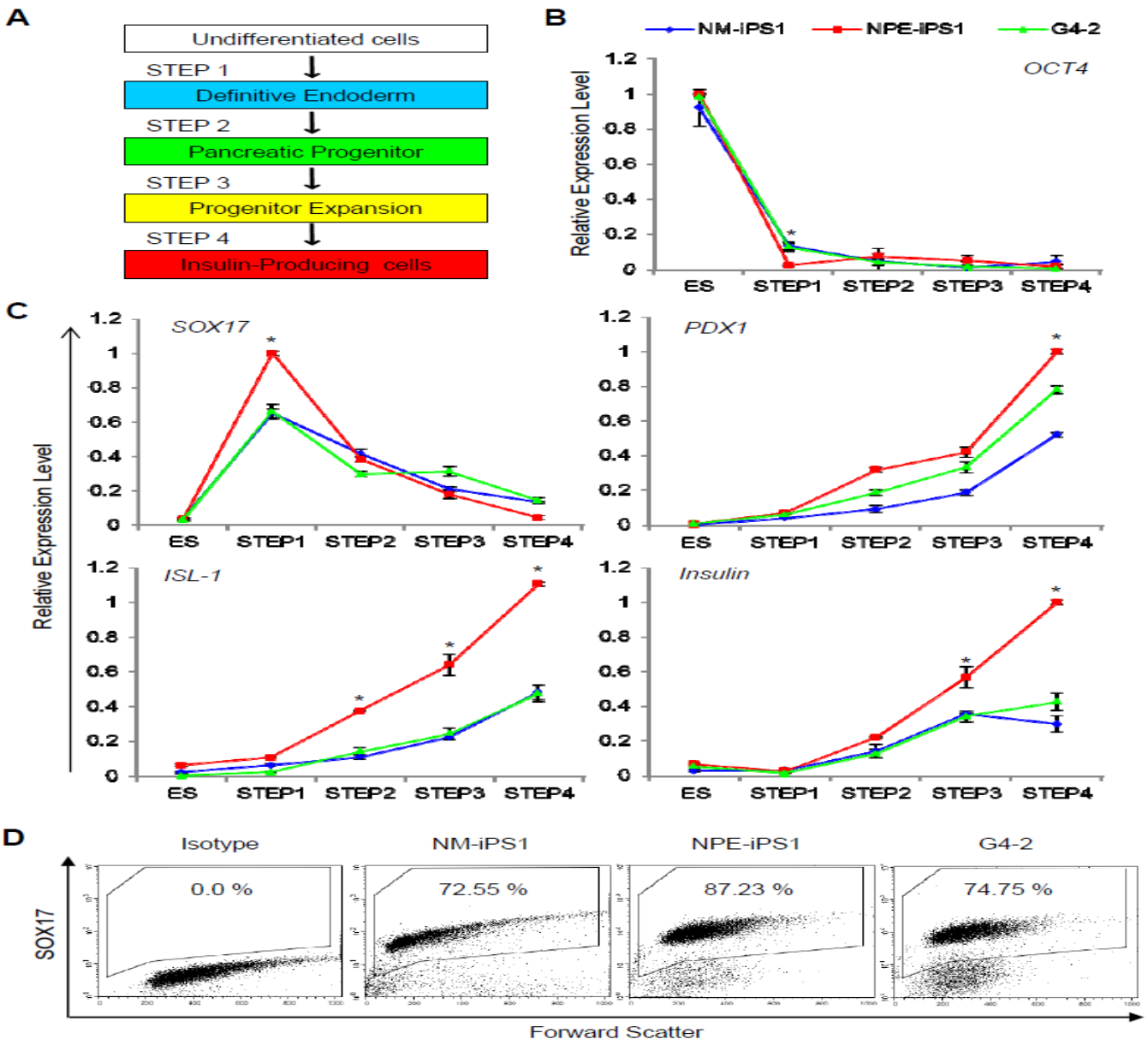


Figure. 3 Dynamic expression patterns of pancreatic lineage genes during direct pancreatic differentiation from NOD-iPSCs

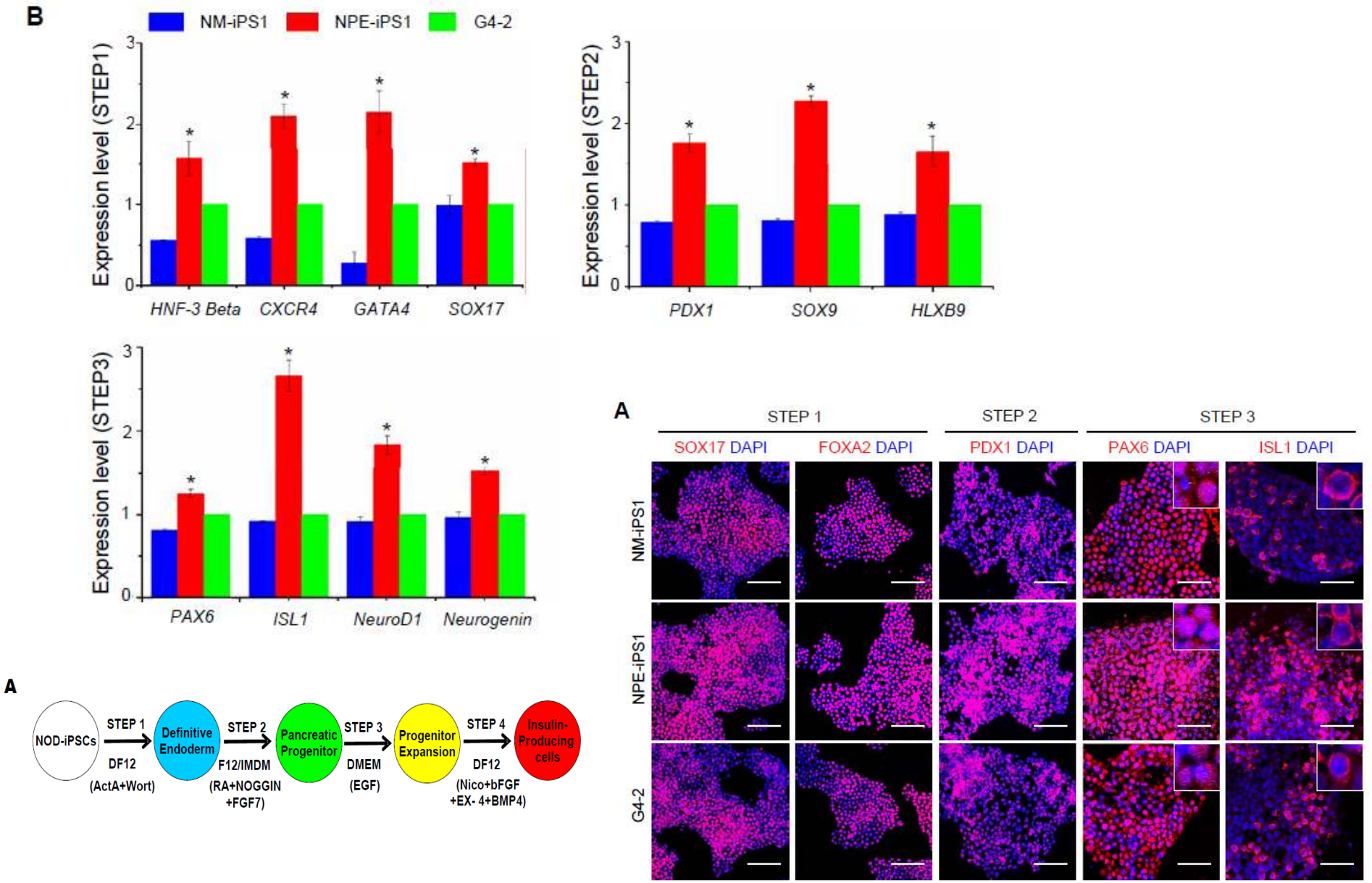
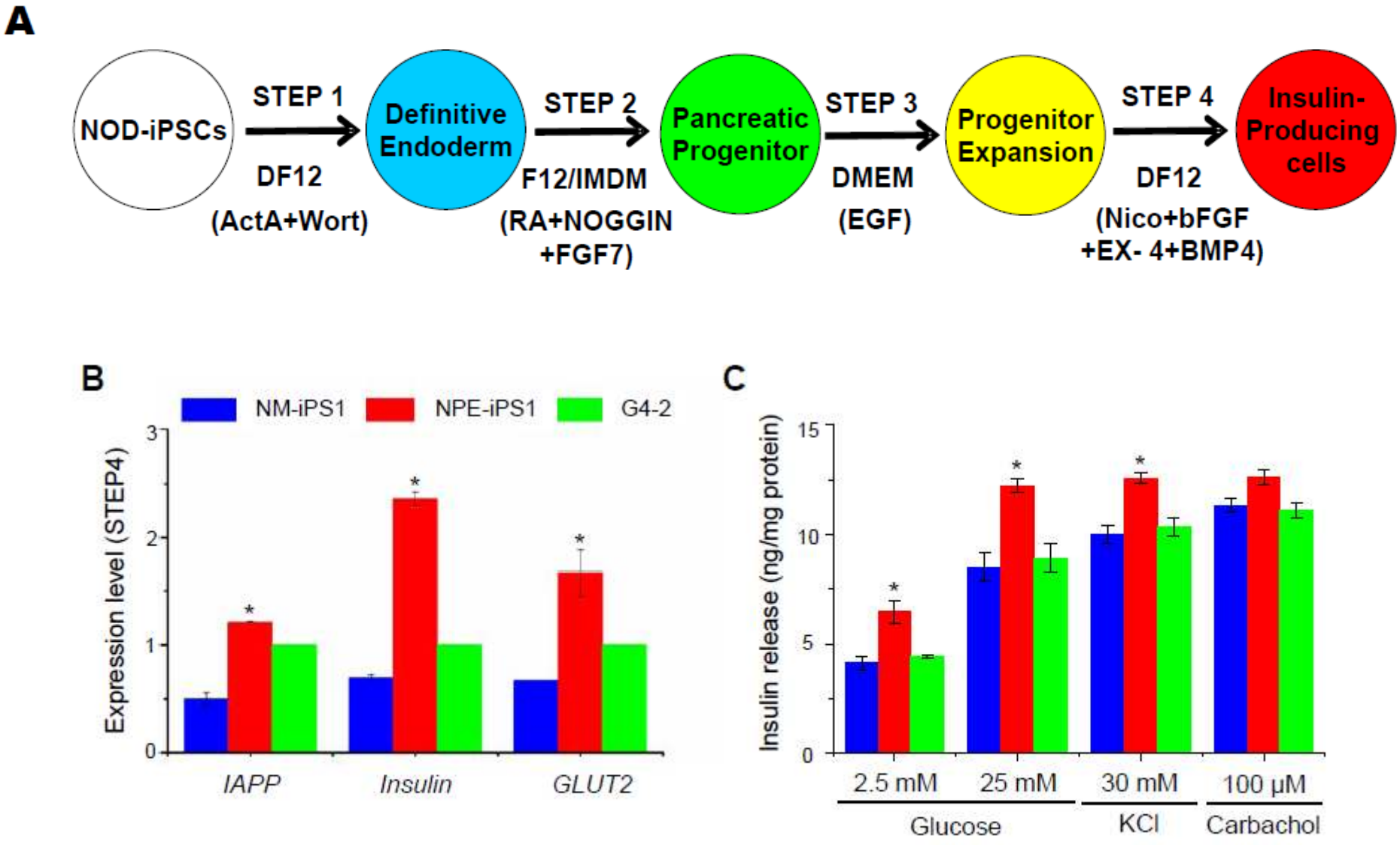


Figure. 4 Differentiation of NOD-iPSCs into insulin-producing cells by a stepwise direct differentiation protocol



Expression of pancreatic beta cell–specific genes, including IAPP, insulin, and Glut2, in differentiated cells

Insulin secretion from these cells is responsive to glucose and other physiological (KCl) stimulation

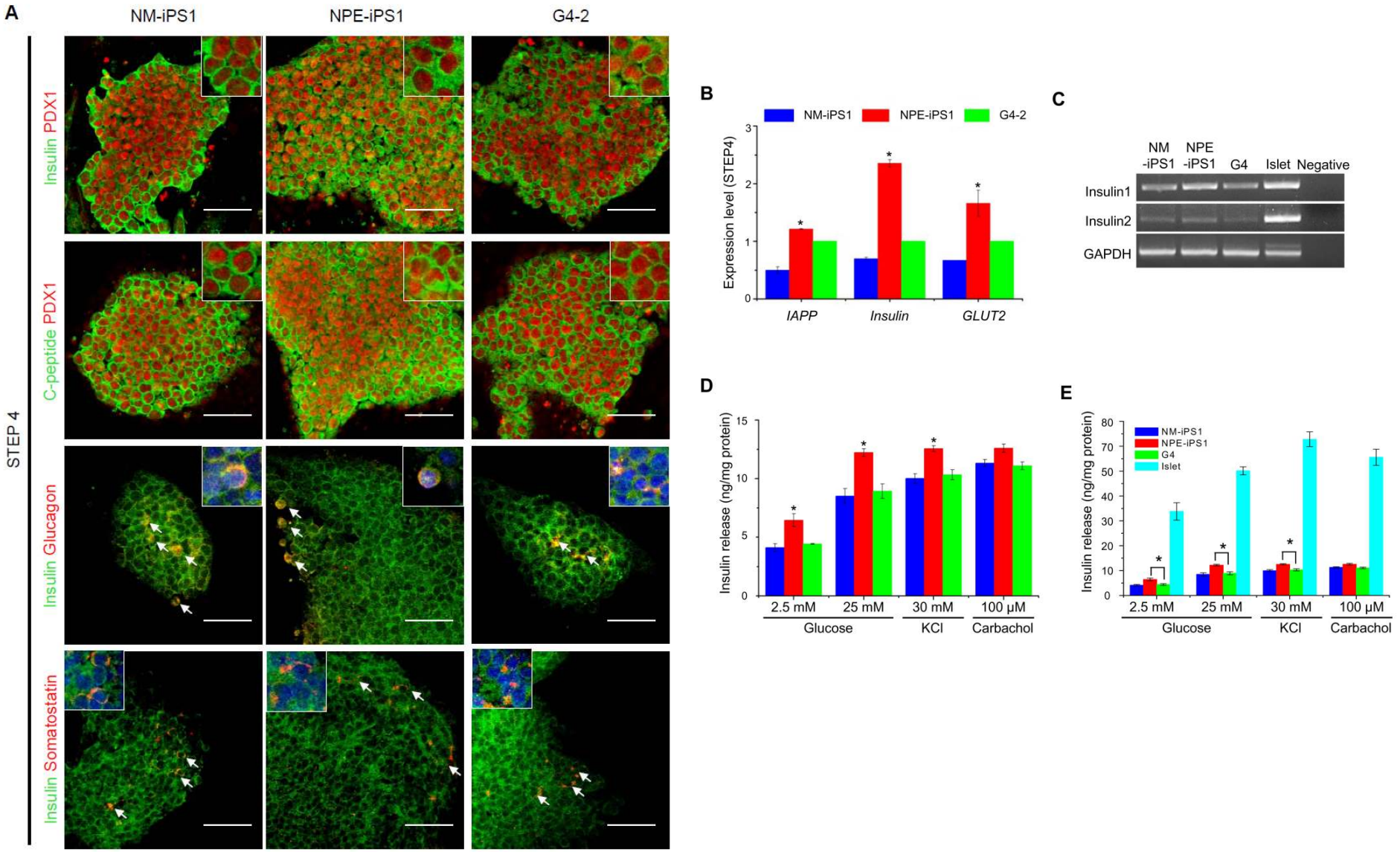


Figure. 5 Differentiation of NOD-iPSCs into pancreatic insulin-producing cells.

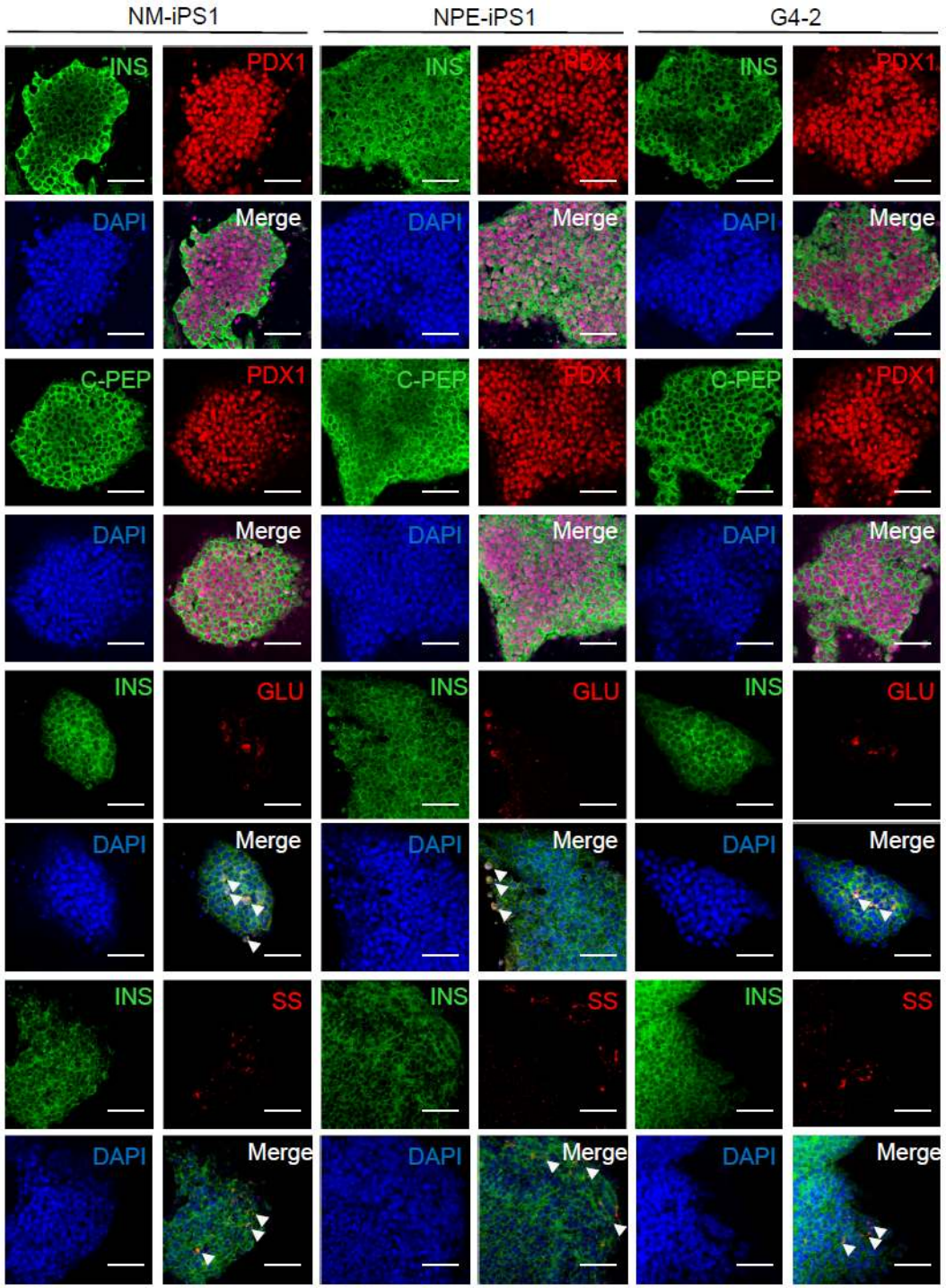


Fig. S7. Differentiation of NOD-iPSCs into pancreatic insulin-producing cells.

Note that immunocytochemical staining revealed that 2 NOD-iPSC lines (NM-iPS1 and NPE-iPS1) and control ESCs (G4-2) differentiated into pancreatic beta-like cells, which expressed

Pdx-1, insulin (INS), C-peptide (C-PEP), glucagon (GLU), and somatostatin (SS)

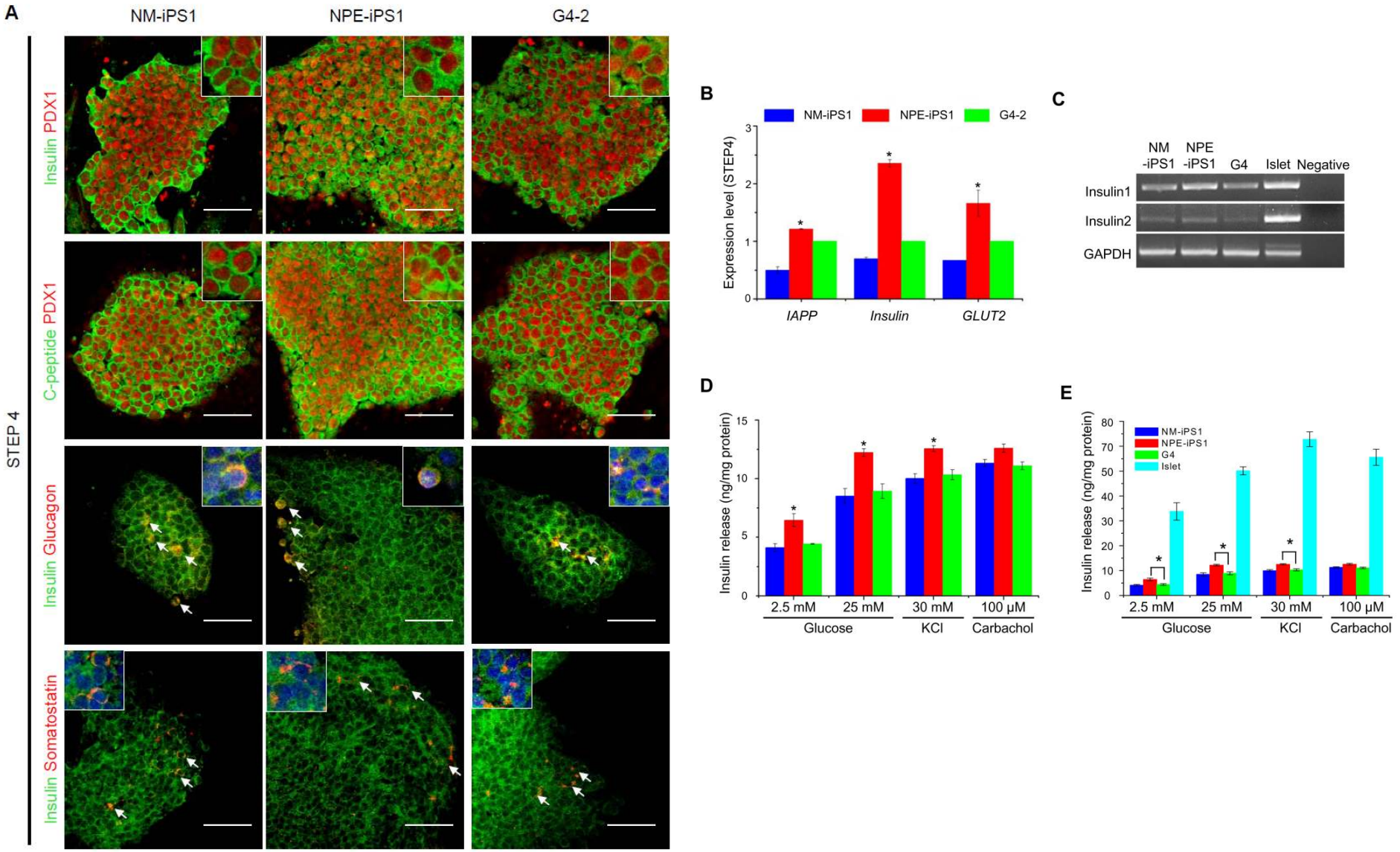


Figure. 5 Differentiation of NOD-iPSCs into pancreatic insulin-producing cells.

Epigenetic memory and preferential lineage-specific differentiation

Hepatology

Generation of endoderm-derived human induced pluripotent stem cells from primary hepatocytes†

Hua Liu, Zhaohui Ye, Yonghak Kim, Saul Sharkis, Yoon-Young Jang*

Article first published online: 1 MAR 2010

DOI: 10.1002/hep.23626

Prospects for Pluripotent Stem Cell-Derived Cardiomyocytes in Cardiac Cell Therapy and as Disease Models

Christian Freund and Christine L. Mummery*

Department of Anatomy & Embryology, Leiden University Medical Center, Postal Zone: S-1-P, P.O. Box 9600, 2300 RC Leiden, The Netherlands

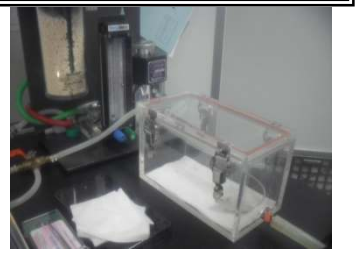
Protective Effects of Human iPS-Derived Retinal Pigment Epithelium Cell Transplantation in the Retinal Dystrophic Rat

Amanda-Jayne Carr[1,3]*, Anthony A. Vugler[1,3], Sherry T. Hikita[2,3], Jean M. Lawrence[1,3], Carlos Gias[1], Li Li Chen[1], David E. Buchholz[2], Ahmad Ahmado[1], Ma'ayan Semo[1], Matthew J. K. Smart[1], Shazeen Hasan[1], Lyndon da Cruz[4], Lincoln V. Johnson[2,3], Dennis O. Clegg[2,3], Pete J. Coffey[1]

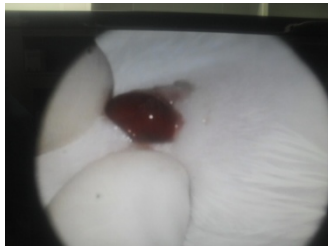
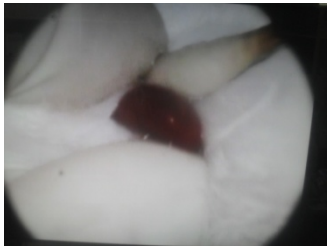
1 Department of Ocular Biology and Therapeutics, Institute of Ophthalmology, University College London, London, United Kingdom, 2 Center for Stem Cell Biology and Engineering, Department of Molecular, Cellular and Developmental Biology, University of California Santa Barbara, Santa Barbara, California, United States of America, 3 Center for the Study of Macular Degeneration, University of California Santa Barbara, Santa Barbara, California, United States of America, 4 Department of Vitreoretinal Surgery, Moorfields Eye Hospital, London, United Kingdom

Beta cell transplantation

1. Preparation of Mouse for Transplant : Anesthetize

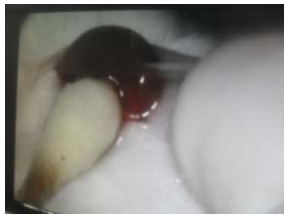
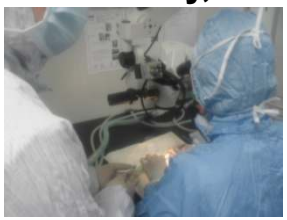
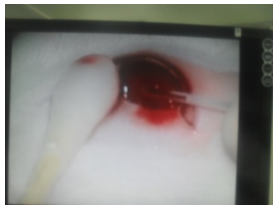
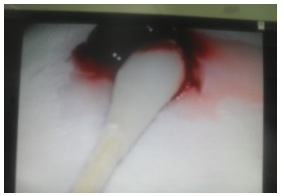
2. Make a small incision in the peritoneum exposing the kidney.

3. Apply a slight pressure to both sides of the incision, raise or pop the kidney out of the mouse.
   Keep the kidney moist by applying normal saline with a cotton tipped swab

4. Using a syringe needle, make a small scratch on the right flank of the kidney,

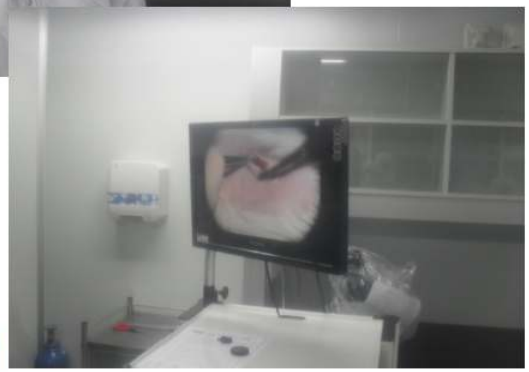
5. Into the nick made in the kidney, carefully slide the PE50 tubing under the capsule.

6. slowly advance beta-cells under the capsule.
   Dry the area with a dry swab and carefully cauterize the nick with low heat.

Kilsoo Jeon

Haejin Lim



Jeong Hyun Kim

the institutional animal care and use committee (IACUC), Konkuk University (KU10069 and KU10070).

Kilsoo Jeon and Haejin Lim:

generation of NOD-iPSCs and performed cell culture and stepwise differentiation of ES/NOD-iPSCs toward insulin producing cells.

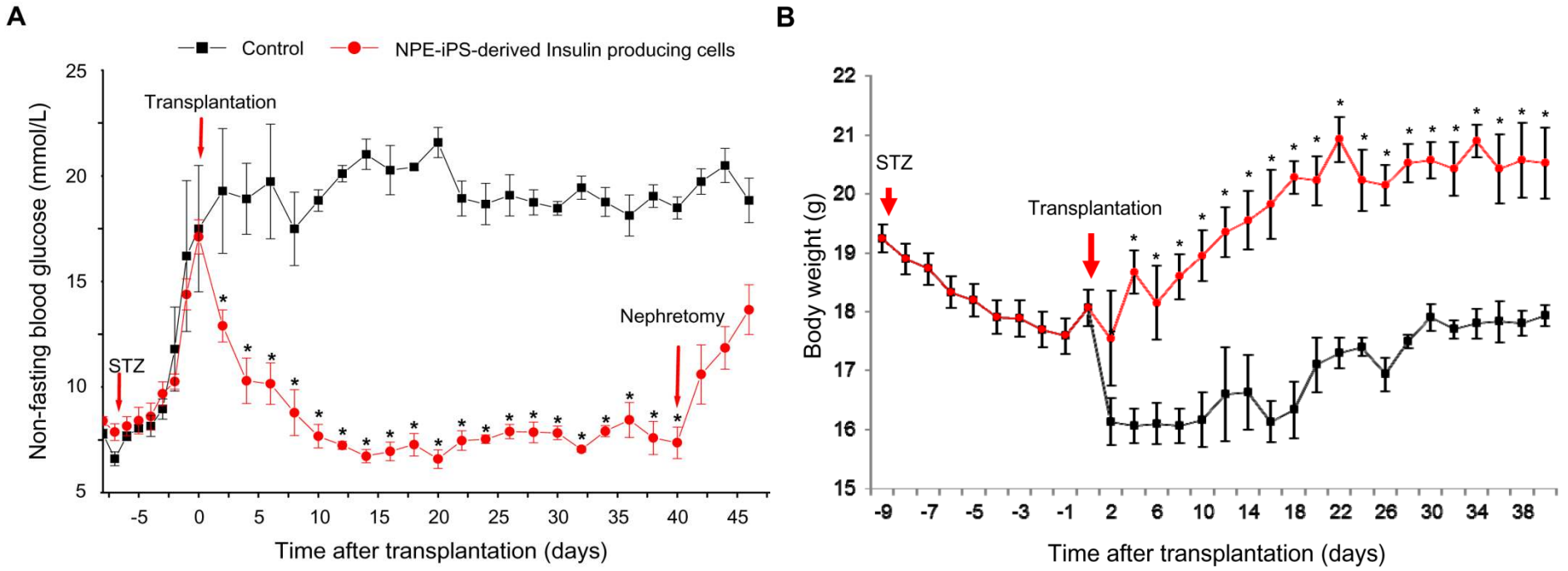
Jeong Hyun Kim and Hae Yeon Choi:

measured insulin release and glucose level in diabetic mice.

Seung Hwa Park (prof. in anatomy) and Jeong Hyun Kim:

performed procedures for paraffin embedding, haematoxylin/eosin, and immunohistochemistry staining.

Before transplantation, streptozotocin was injected intraperitoneally for 3 days at 50 mg/kg into 6- to 8-week old NOD/SCID mice and When non-fasting blood glucose levels were above 13.9 mmol/l on 2 consecutive days, 5 × 10^6 differentiated cells were transplanted into the left subcapsular renal space.



Transplantation of the differentiated NPE-iPSCs into diabetic model mice resulted in kidney engraftment of insulin-producing cells and normalization of blood glucose levels (hyperglycemia).

Figure. 6 Transplantation of NPE-iPSCs-derived insulin-producing cells into STZ-induced diabetic NOD/SCID mice.

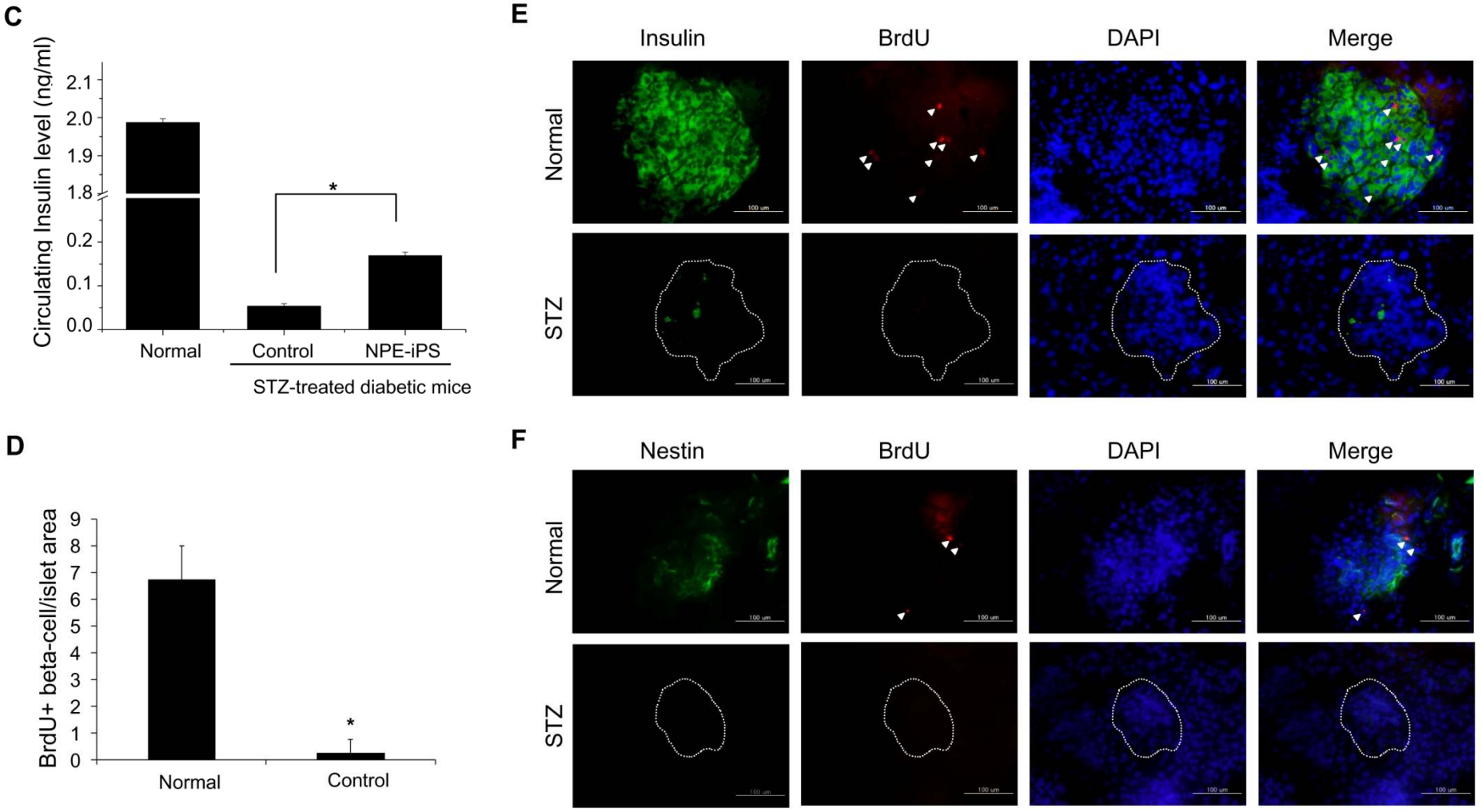
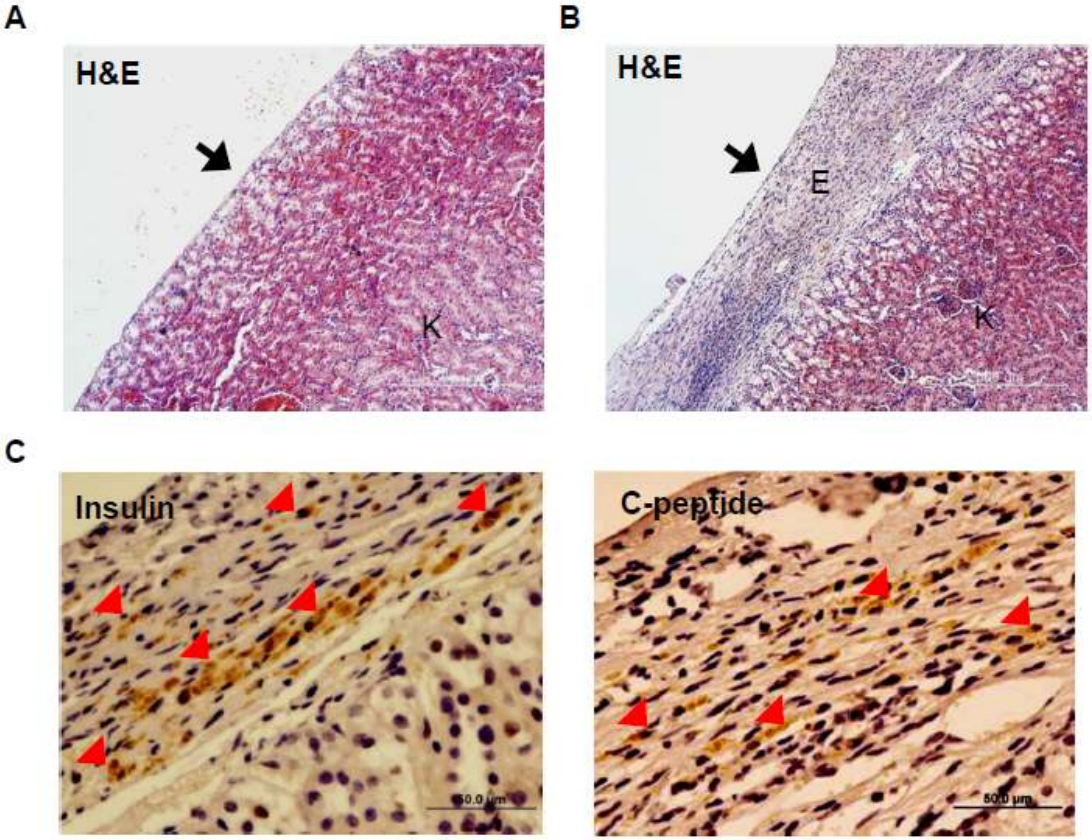


Figure. 6 Transplantation of NPE-iPSCs-derived insulin-producing cells into STZ-induced diabetic NOD/SCID mice.



Analysis of grafted kidney.

(A–B): Hematoxylin/eosin staining of grafted kidney.

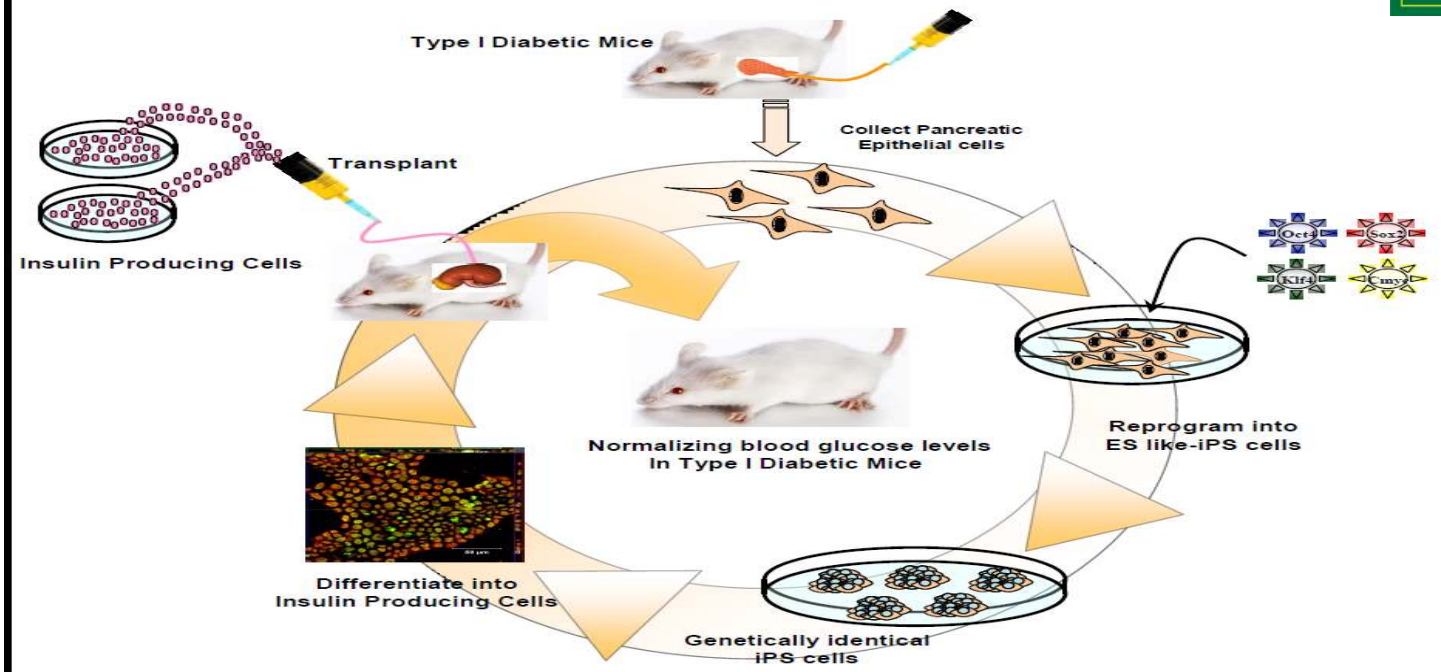
Grafts were removed 5 weeks after transplantation and analyzed by hematoxylin/eosin staining, either on the non-transplanted kidney (A) or the NPE-iPSC group kidney (B).

The black arrows in (A–B) represent the site of kidney capsule injection. K, kidney; E, engrafted cells.

(C): Expression of insulin, and C-peptide in the graft.

Brown DAB staining was positive. Sections were counterstained with hematoxylin (blue).

Grafts were removed
5 weeks after transplantation and
analyzed by H/E staining or
immunohistochemistry (immunofluorescence and DAB–nickel reactions).



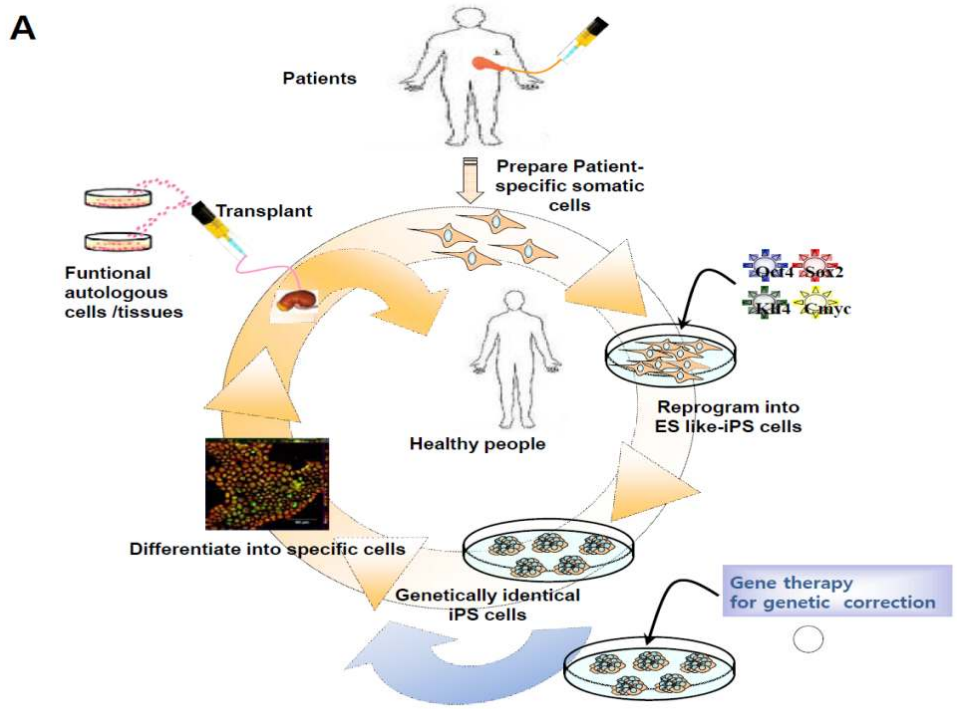
The NOD-iPS cells derived from NOD-MEF and NOD-PDF showed ES cell-like characteristics, including expression of endogenous pluripotency genes, differentiation of three germ layer lineages, and formation of teratomas.

We could differentiate the NOD-iPS cells toward functional pancreatic beta cell-like cells, which may be a promising application tools in biomedical research on type 1 diabetes.

Transplantation of the differentiated NPE-iPSCs into diabetic model mice resulted in kidney engraftment of insulin-producing cells and normalization of blood glucose levels.

We propose that these NOD-iPSCs will provide a useful tool for investigating genetic susceptibility to autoimmune diseases and for generating a cellular interaction model of T1D.

Potential application of patient-derived iPSCs in autologous beta-cell transplantation in the treatment of diabetes.



- a combination of the cell reprogramming and differentiation techniques could be used for generation of patient-specific iPSCs and differentiation into pancreatic beta-like cells.

- Such cells could provide a promising resource for cell therapy to treat diabetes.

From 2008

Our group have started from 2008, but

NOD mouse iPS cell generation – Be scooped by ….

Epigenetic memory and preferential differentiation – Be scooped by ….

Beta-cell differentiation of iPS cells – Be scooped by ….

Transplantation of iPSc-derived beta-like cells – Be scooped by ….

Hope to publish in high-impact factor journal……

NOD mouse iPS cell generation – Be scooped by ….

Cell Stem Cell
Article

Metastable Pluripotent States in NOD-Mouse-Derived ESCs

Jacob Hanna,[1,4,*] Styliani Markoulaki,[1,4] Maisam Mitalipova,[1] Albert W. Cheng,[1,2] John P. Cassady,[1,3] Judith Staerk,[1] Bryce W. Carey,[1,3] Christopher J. Lengner,[1] Ruth Foreman,[1,3] Jennifer Love,[1] Qing Gao,[1] Jongpil Kim,[1] and Rudolf Jaenisch[1,3,*]

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- Although the NOD mouse has been enormously useful, establishing embryonic stem cells (ESCs) from NOD mouse is extremely difficult.

Beta-cell differentiation of iPS cells – Be scooped by ….

SciBX 3(28); doi:10.1038/scibx.2010.879
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Epigenetic memory and preferential differentiation – Be scooped by ….

Cell Stem Cell
Brief Report
Cell Stem Cell 9, 17–23, July 8, 2011 ©2011

Epigenetic Memory and Preferential Lineage-Specific Differentiation in Induced Pluripotent Stem Cells Derived from Human Pancreatic Islet Beta Cells

Ori Bar-Nur,[1,3] Holger A. Russ,[2,3] Shimon Efrat,[2,*] and Nissim Benvenisty[1,*]
[1]Stem Cell Unit, Department of Genetics, Institute of Life Sciences, The Hebrew University of Jerusalem, 91904, Israel
[2]Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel-Aviv University, 69978, Israel
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DOI 10.1016/j.stem.2011.06.007

Transplantation of iPSc-derived beta-like cells – Be scooped by ….

ß- cell differentiation

PNAS

Reversal of hyperglycemia in diabetic mouse models using induced-pluripotent stem (iPS)-derived pancreatic β-like cells

Zaida Alipio[a,1], Wenbin Liao[b,1], Elizabeth J. Roemer[b], Milton Waner[c], Louis M. Fink[a], David C. Ward[d,2], and Yupo Ma[b,2]

[a]Division of Laboratory Medicine, Nevada Cancer Institute, Las Vegas, NV 89135; [b]Department of Pathology, State University of New York, Stony Brook, NY 11794-8691; [c]Vascular and Birthmark Institute of New York, New York, NY 10023; and [d]Cancer Research Center of Hawaii, University of Hawaii, Honolulu, HI 96813

Contributed by David C. Ward, June 8, 2010 (sent for review March 25, 2010)

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STEM CELLS AND DEVELOPMENT
Volume 21, Number 14, 2012

DOI: 10.1089/scd.2011.0665

Differentiation and Transplantation of Functional Pancreatic Beta Cells Generated from Induced Pluripotent Stem Cells Derived from a Type 1 Diabetes Mouse Model

Kilsoo Jeon,[1,*] Hyejin Lim,[1,*] Jung-Hyun Kim,[1] Nguyen Van Thuan,[1] Seung Hwa Park,[2] Yu-Mi Lim,[3] Hye-Yeon Choi,[1] Eung-Ryoung Lee,[1] Jin-Hoi Kim,[1] Myung-Shik Lee,[3] and Ssang-Goo Cho[1]

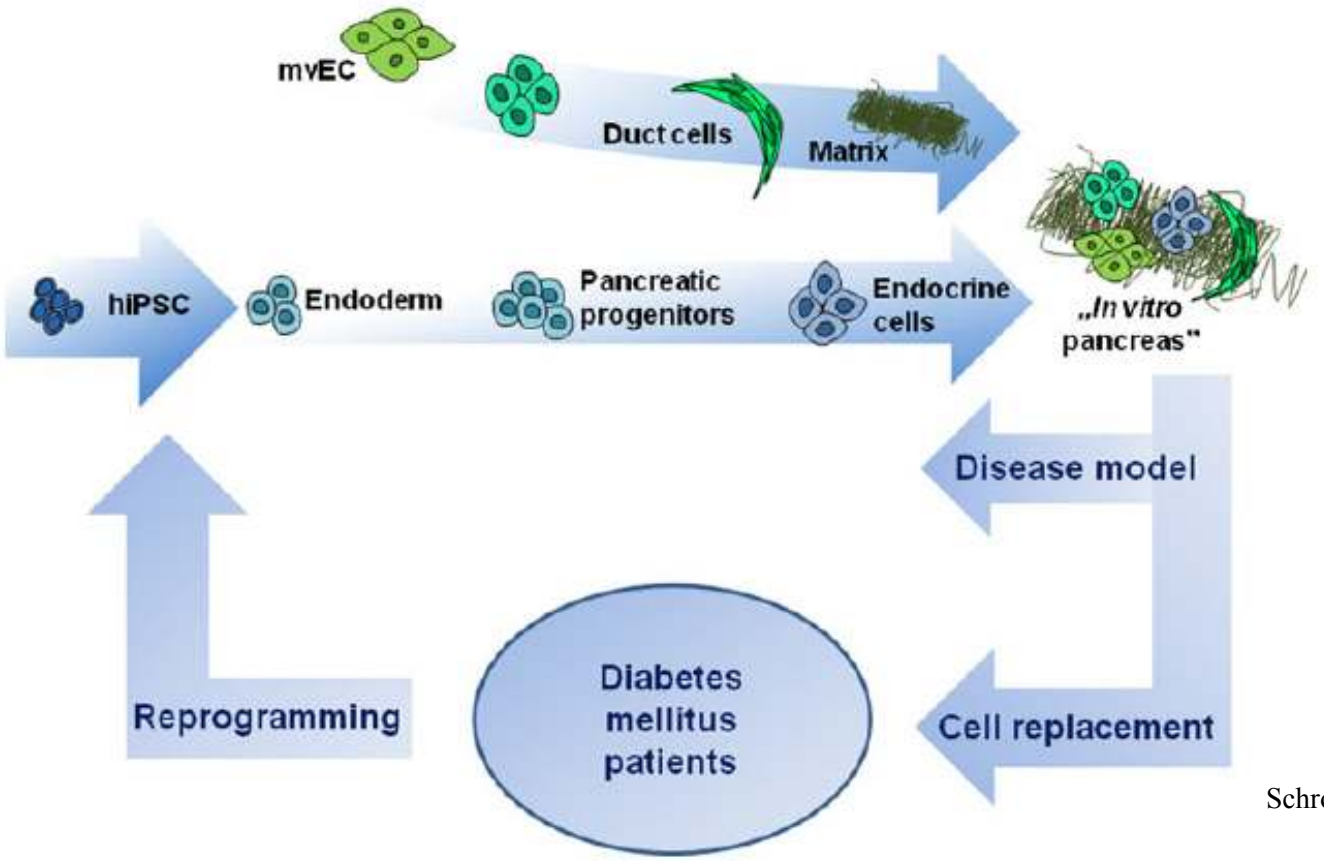
Moving stem cell research into the clinics

Curr Diab Rep (2012) 12:490–498
DOI 10.1007/s11892-012-0292-5

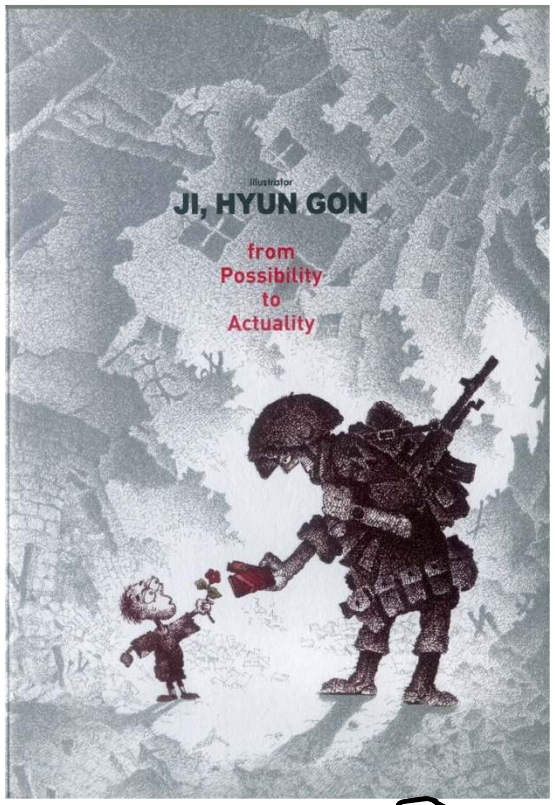
PATHOGENESIS OF TYPE 1 DIABETES (AG ZIEGLER, SECTION EDITOR)

Potential of Pluripotent Stem Cells for Diabetes Therapy

Insa S. Schroeder



Schroeder, 2012 Curr Diab Rep



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Possibility
To
Actuality

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Dr. Eung-Ryong Lee
Dr. Min-Jeong Song
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Rapid Communication

Generation of endoderm-derived human induced pluripotent stem cells from primary hepatocytes†

Hua Liu, Zhaohui Ye, Yonghak Kim, Saul Sharkis, Yoon-Young Jang*

HEPATOLOGY, Vol. 51, No. 5, 2010

Article first published online: 1 MAR 2010

DOI: 10.1002/hep.23626

Journal of Cellular Biochemistry 107:592–599 (2009)

Prospects for Pluripotent Stem Cell–Derived Cardiomyocytes in Cardiac Cell Therapy and as Disease Models

Christian Freund and Christine L. Mummery*

Department of Anatomy & Embryology, Leiden University Medical Center, Postal Zone: S-1-P, P.O. Box 9600, 2300 RC Leiden, The Netherlands

Protective Effects of Human iPS-Derived Retinal Pigment Epithelium Cell Transplantation in the Retinal Dystrophic Rat

Amanda-Jayne Carr[1,3]*, Anthony A. Vugler[1,3], Sherry T. Hikita[2,3], Jean M. Lawrence[1,3], Carlos Gias[1], Li Li Chen[1], David E. Buchholz[2], Ahmad Ahmado[1], Ma'ayan Semo[1], Matthew J. K. Smart[1], Shazeen Hasan[1], Lyndon da Cruz[4], Lincoln V. Johnson[2,3], Dennis O. Clegg[2,3], Pete J. Coffey[1]

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Cell Stem Cell
Article

Cell Stem Cell 4, 513–524, June 5, 2009 ©2009 Elsevier Inc. 513

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ß– cell differentiation

13426–13431 | PNAS | July 27, 2010 | vol. 107 | no. 30

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[a]Division of Laboratory Medicine, Nevada Cancer Institute, Las Vegas, NV 89135; [b]Department of Pathology, State University of New York, Stony Brook, NY 11794-8691; [c]Vascular and Birthmark Institute of New York, New York, NY 10023; and [d]Cancer Research Center of Hawaii, University of Hawaii, Honolulu, HI 96813

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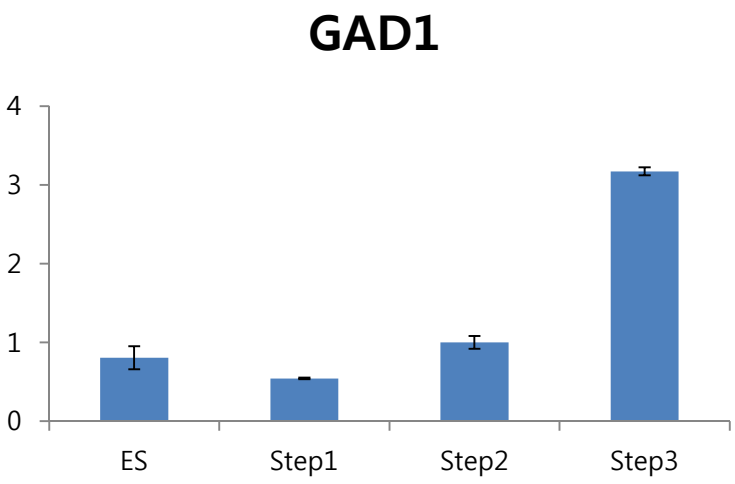
DOI 10.1016/j.stem.2011.06.007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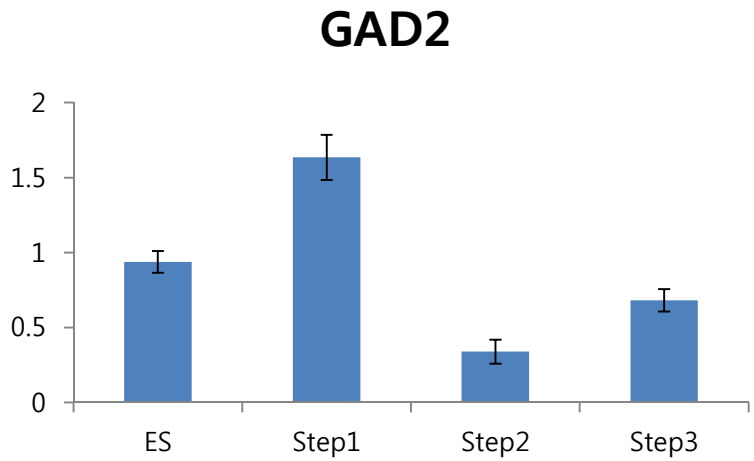
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