2011 China-America Frontiers of Engineering Symposium

Current Progress in Stem Cell Technology:

Realistic Opportunity for a New Frontier in Personalized Medicine?

Fanyi Zeng, M.D., Ph.D.

Shanghai Jiao Tong University

San Diego, CA, U.S.A.

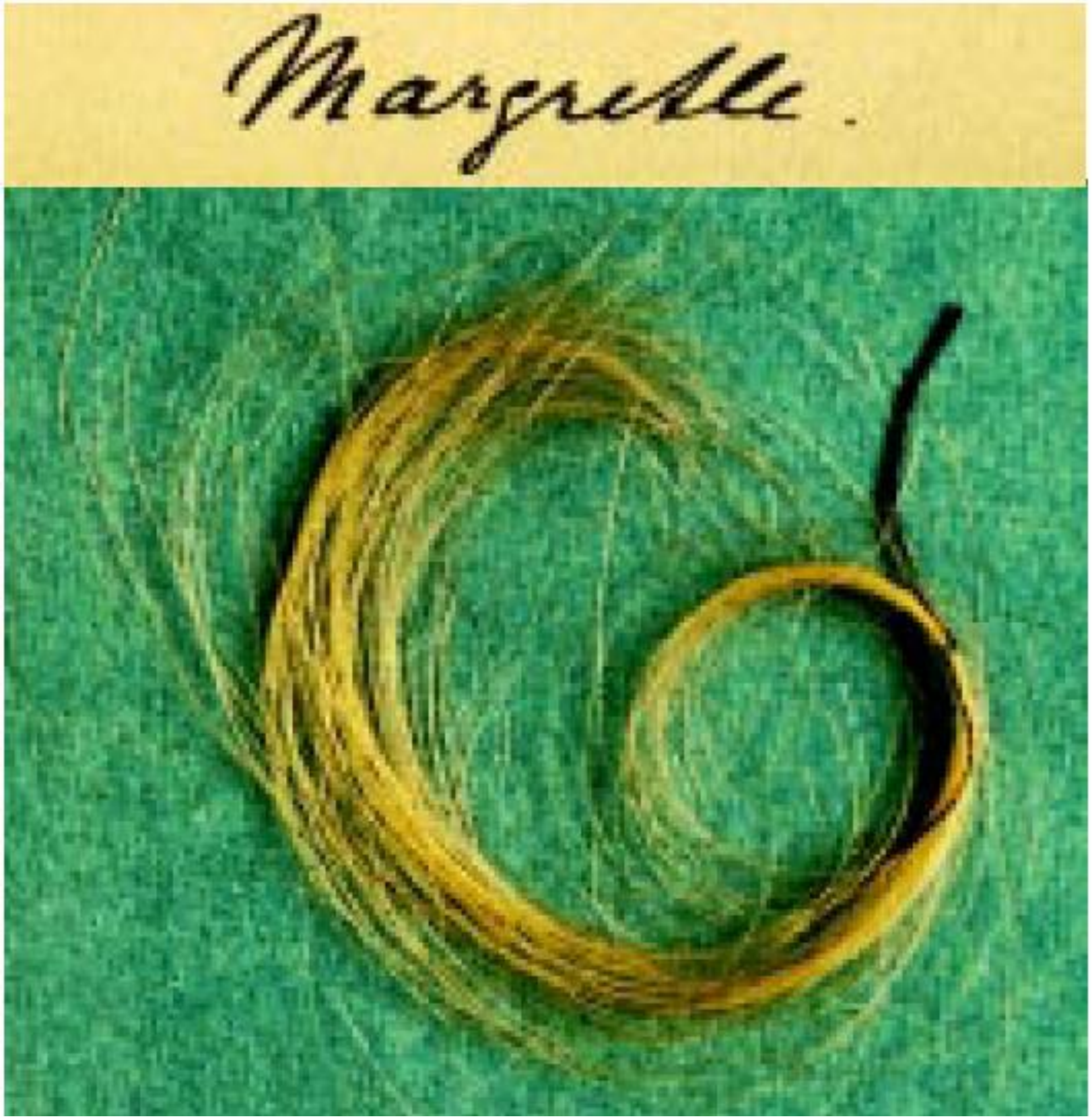
March 29, 2011

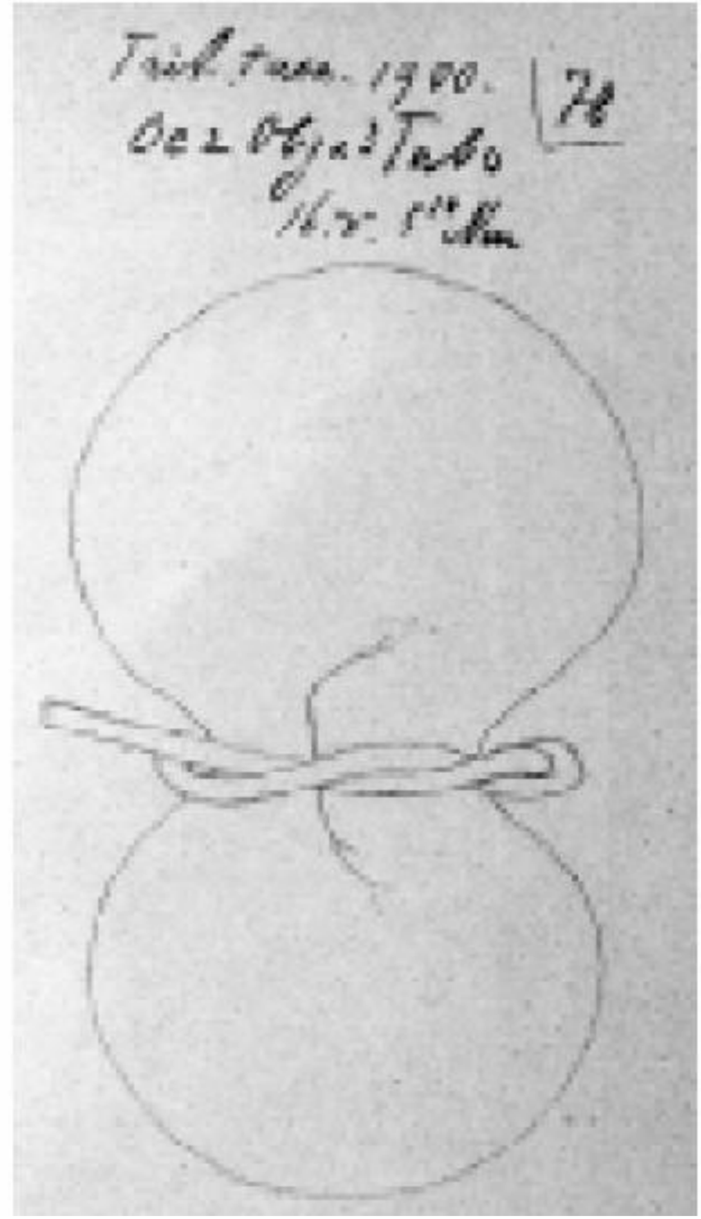
Stem Cells:

What are they?

Where and how did we start?

What types do we have now?



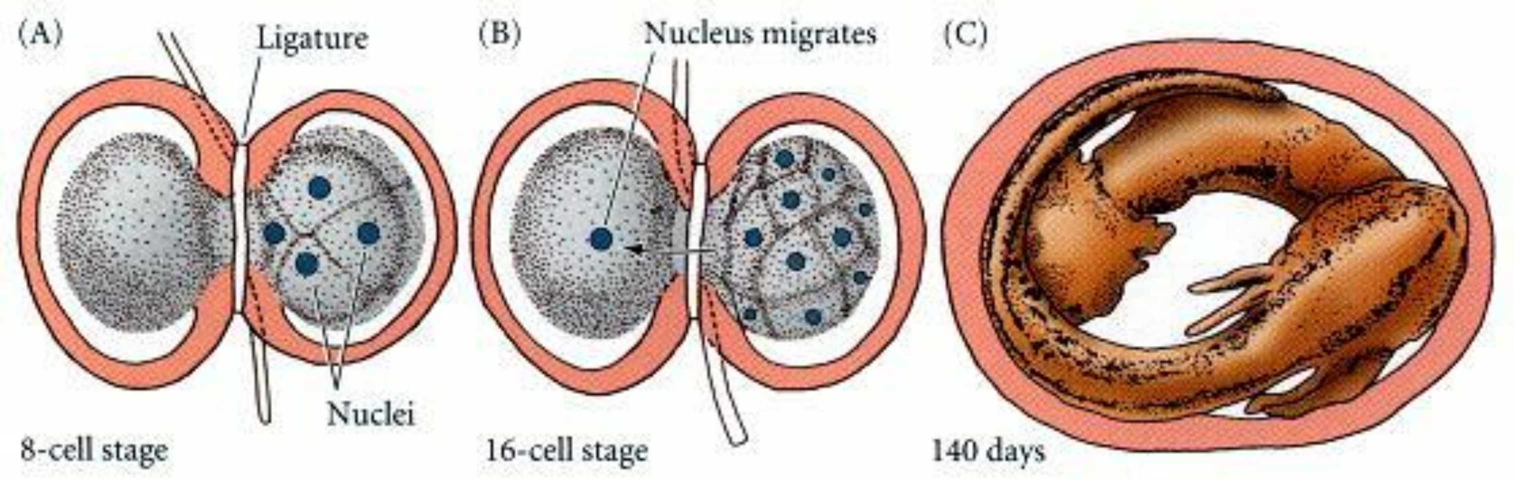


Hans Spemann
(1869-1941)

➢How form and pattern emerge from the simple beginnings of a fertilized egg.

➢How and when do individual cells and tissues decide which developmental route to take?

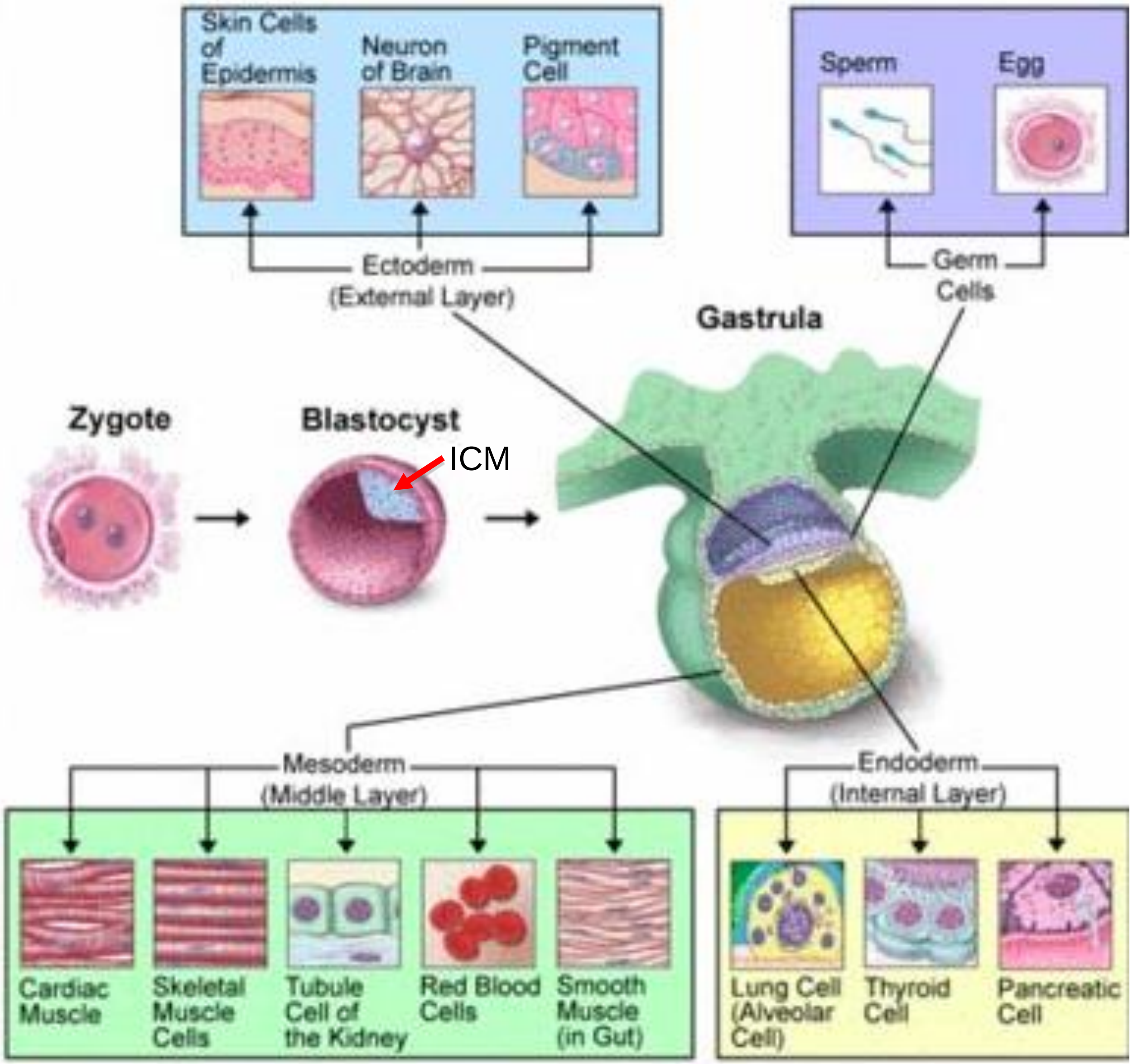
➢Are cell fates somehow predetermined or do cells and tissues interact with one another to orchestrate developmental processes?



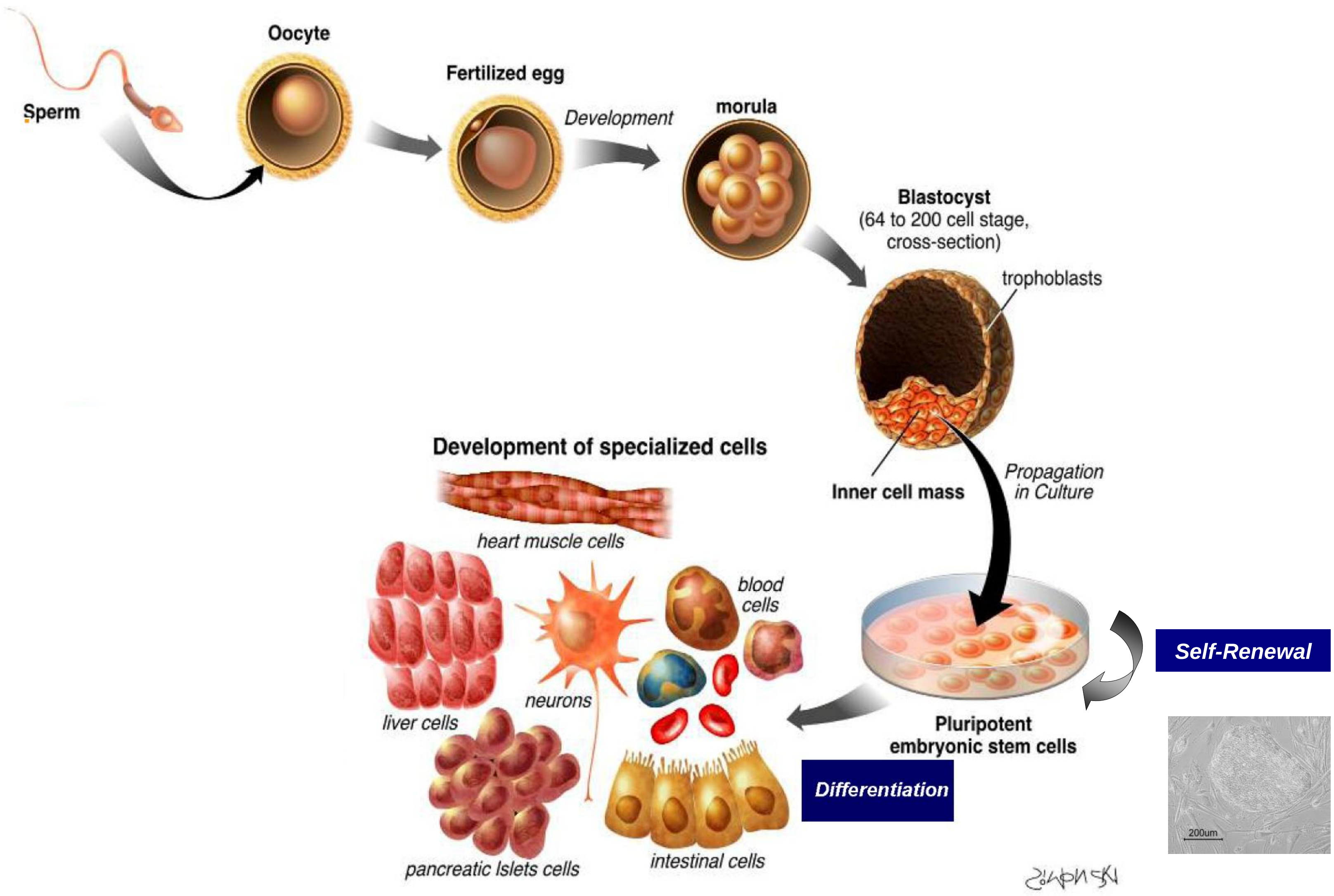
Nobel Prize in Physiology or Medicine in 1953

Embryonic induction and the organiser

Embryonic induction and the organiser



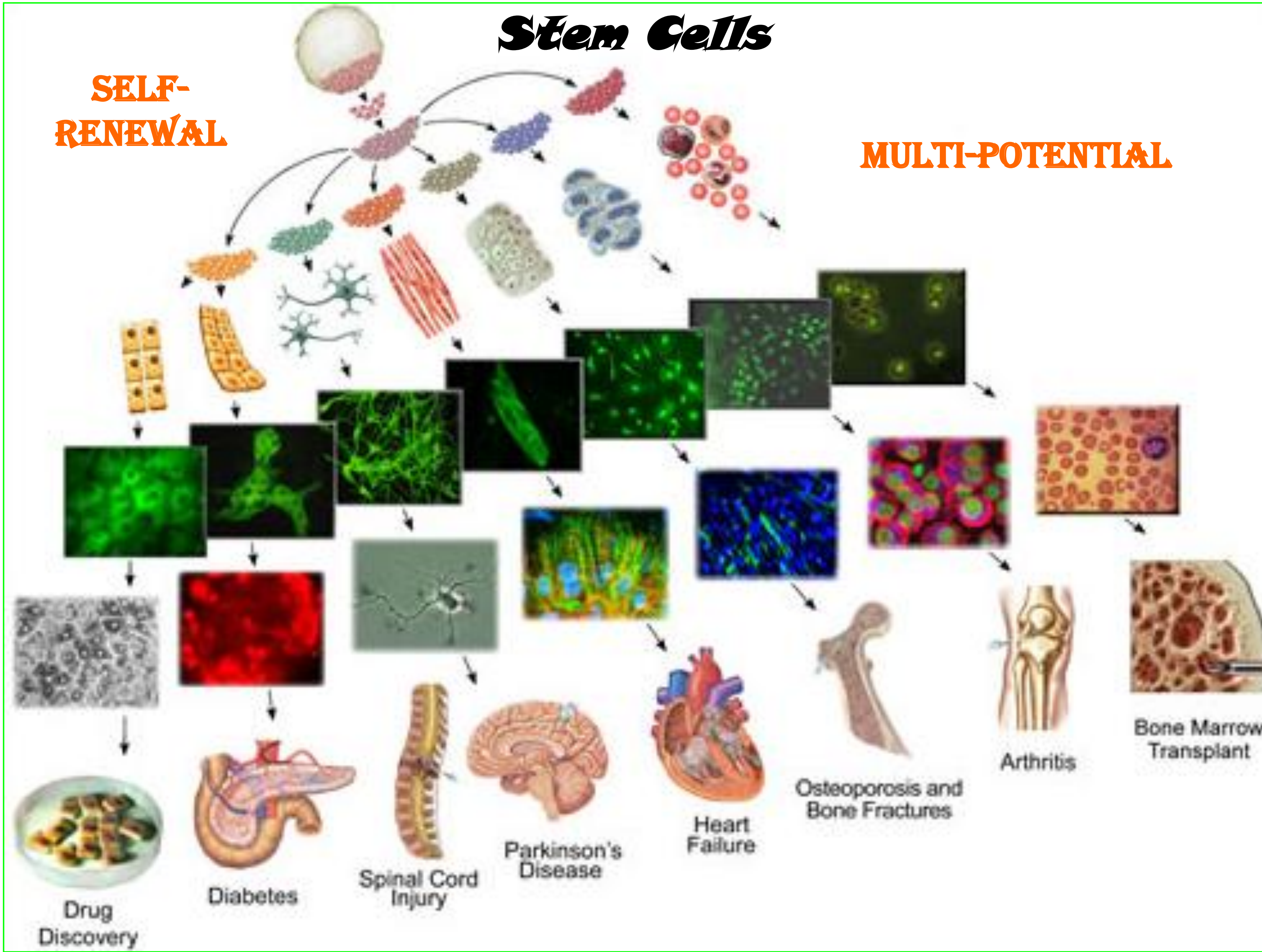
Discovery of Stem Cells



Stem Cells

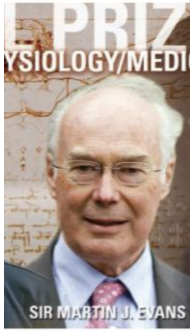
SELF-RENEWAL

MULTI-POTENTIAL

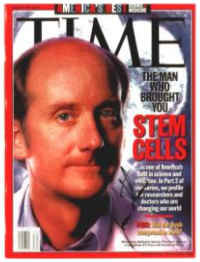


Milestones in stem cell and cloning technology development

First murine ES cell line derived by
Sir. Martin J. Evans



First human ES cell line
James A. Thomson



1981

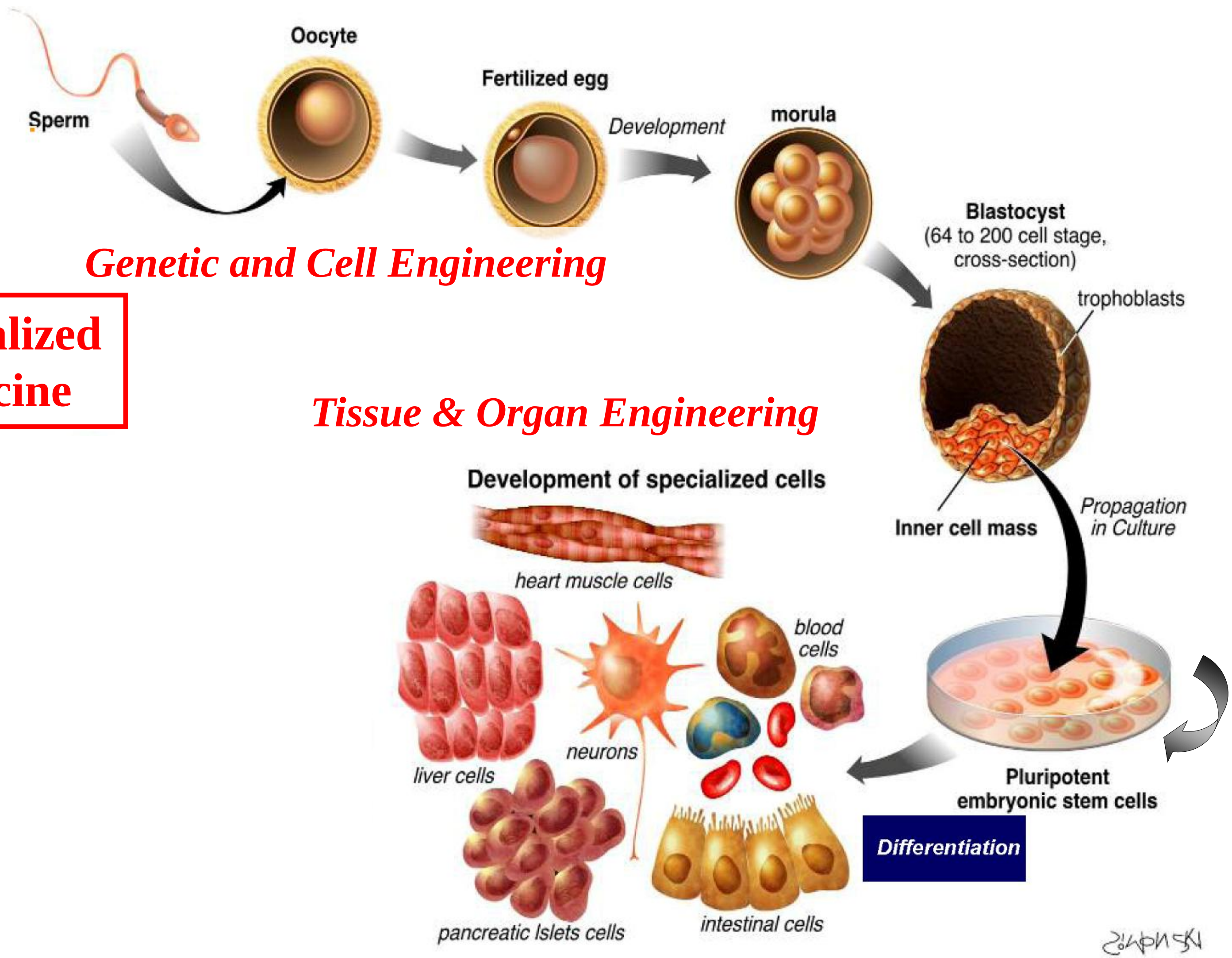
1998

Modern Disease Therapy

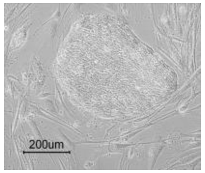
Personalized Medicine

Genetic and Cell Engineering

Tissue & Organ Engineering



Self-Renewal



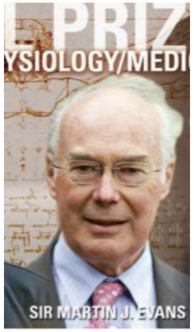
Major Challenge for hESCs research

Immune rejection

The present hES cell lines are not suitable for transplantation into patients.

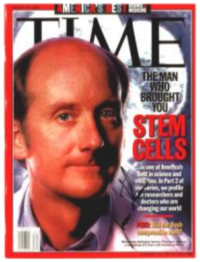
Milestones in stem cell and cloning technology development

First murine ES cell line derived by
Sir. Martin J. Evans



First human ES cell line
James A. Thomson

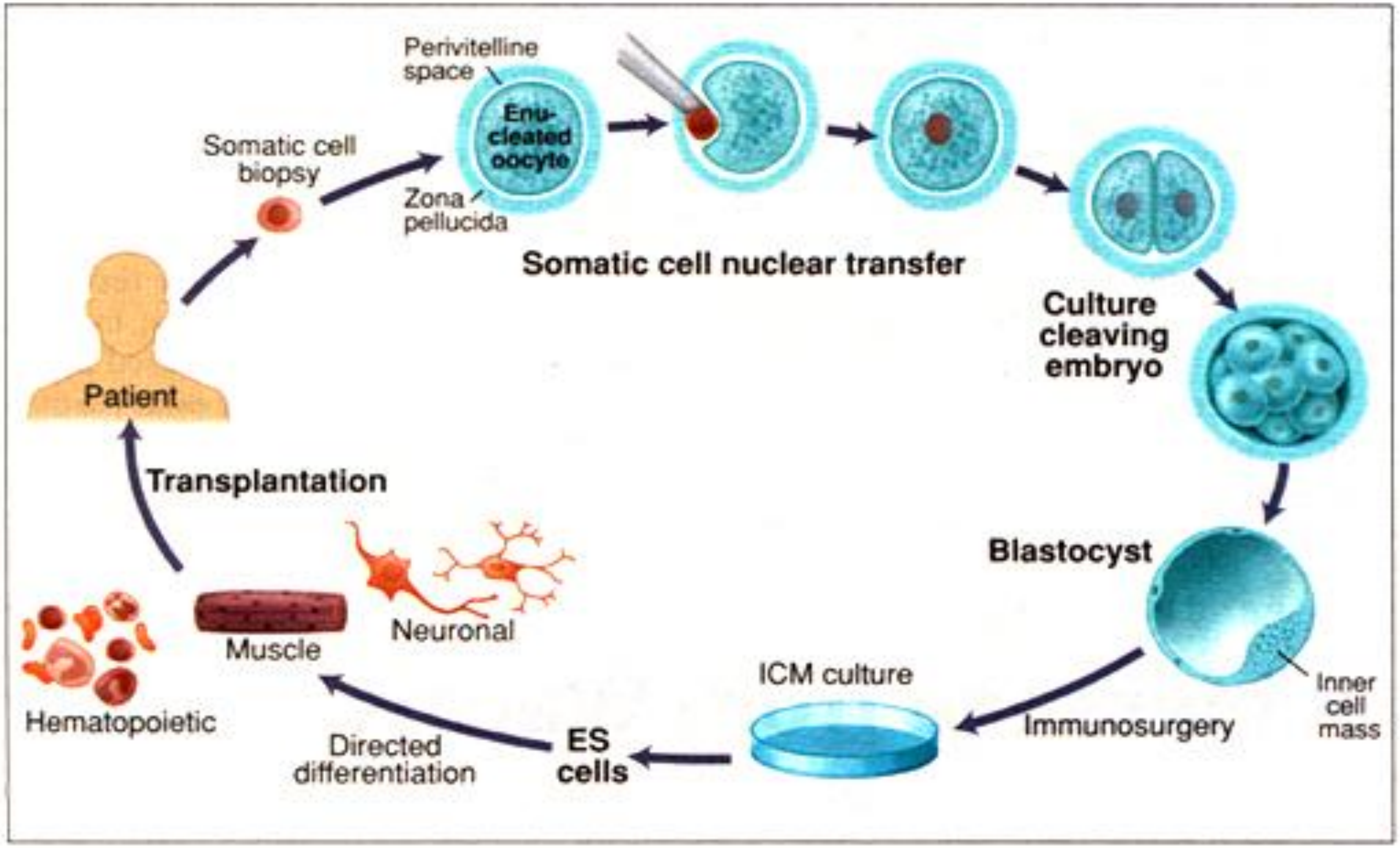
First cloned sheep
Sir. Ian Wilmut



1981 1997 1998

"Therapeutic" cloning:

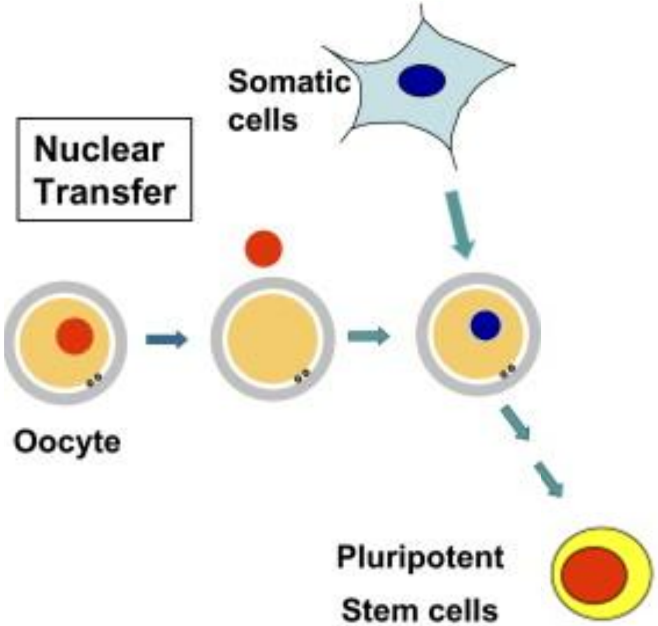
Derivation of embryonic stem cells from the patient



Solter and Gearhart, *Science* 1999

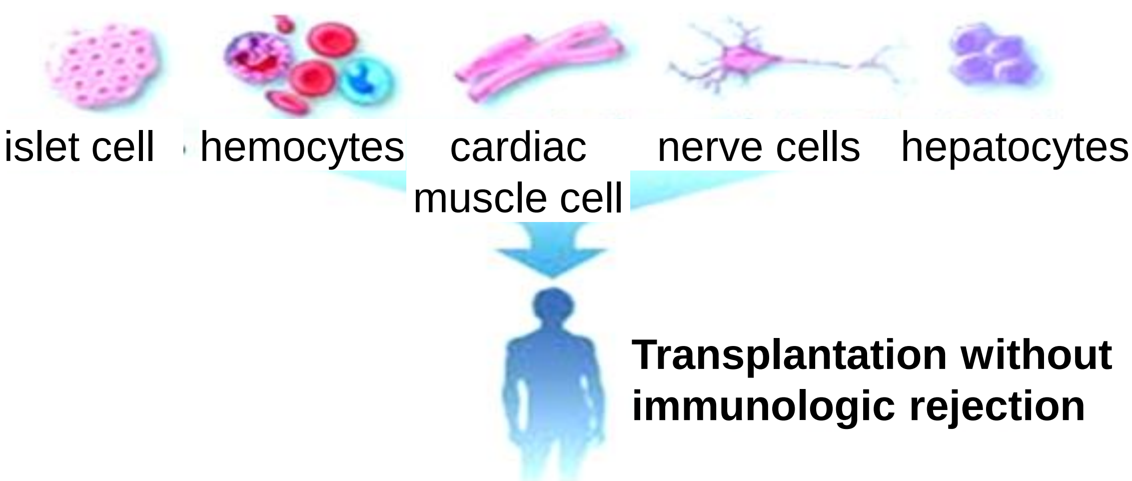
"Therapeutic" cloning:

Derivation of embryonic stem cells from the patient



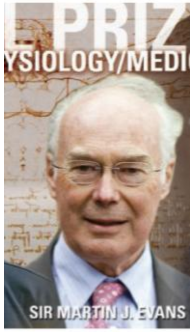
Limitations

- Inefficient process
- Long term culture defects
- Ethics concerns



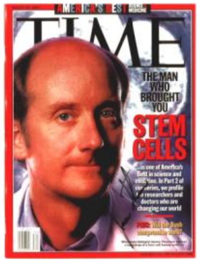
Milestones in stem cell and cloning technology development

First murine ES cell line derived by
Sir. Martin J. Evans



First cloned sheep
Sir. Ian Wilmut

First human ES cell line
James A. Thomson

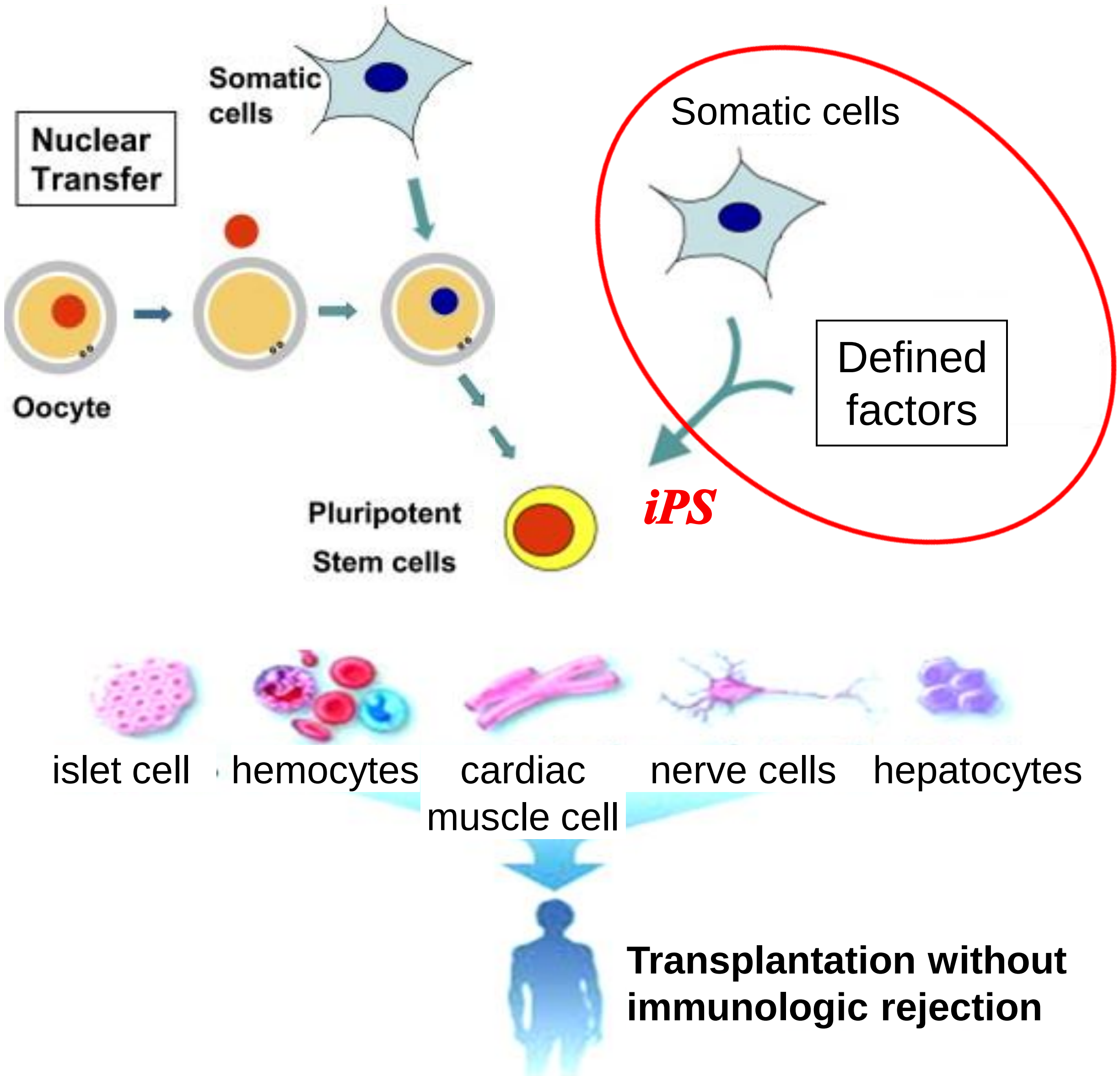


First iPS cell
Shinya Yamanaka

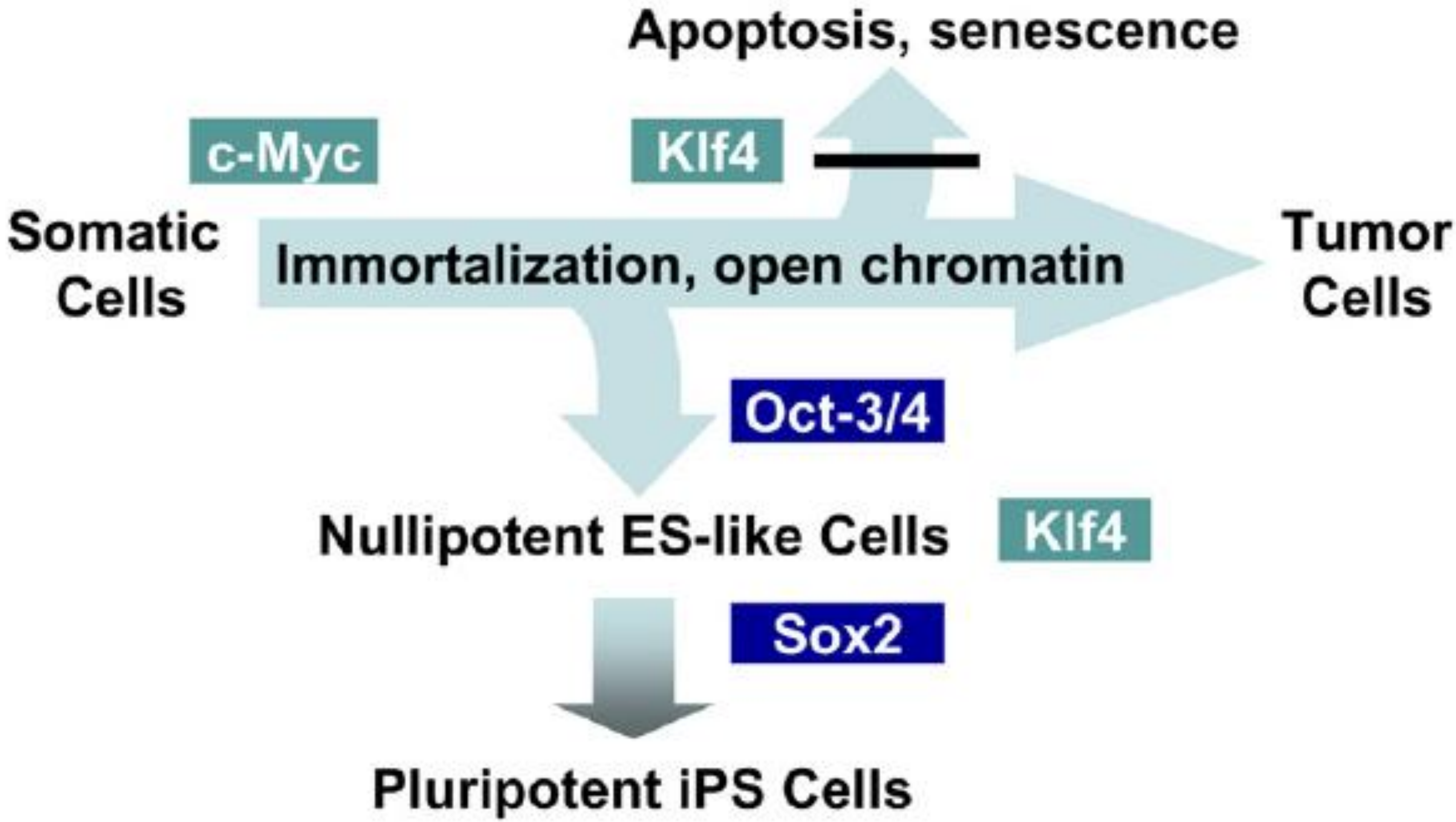
1981 — 1997 — 1998 — 2006

Induced Pluripotent Stem Cells (iPS Cells)

From somatic cells to pluripotent cells



Background of iPS cells



Key Question:

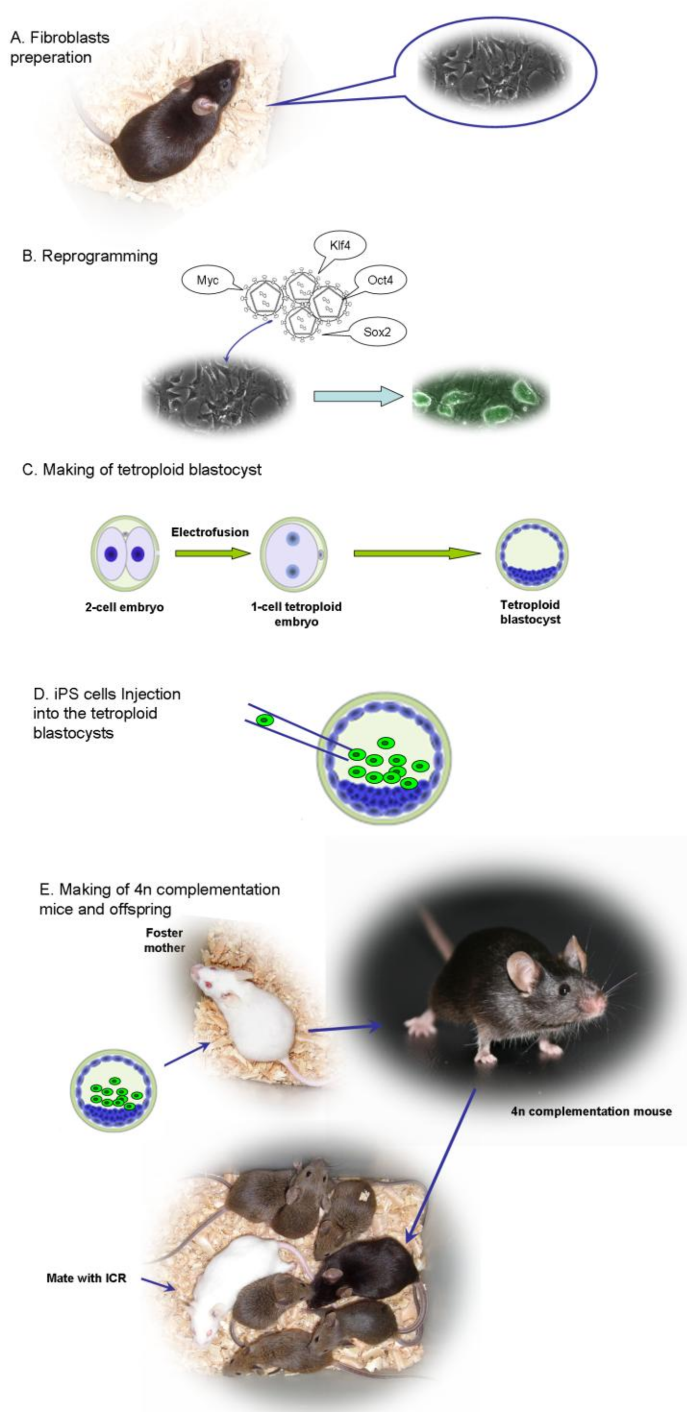
Do iPS cells have true pluripotency ?

(i.e. can they become any type of cell in the body?)

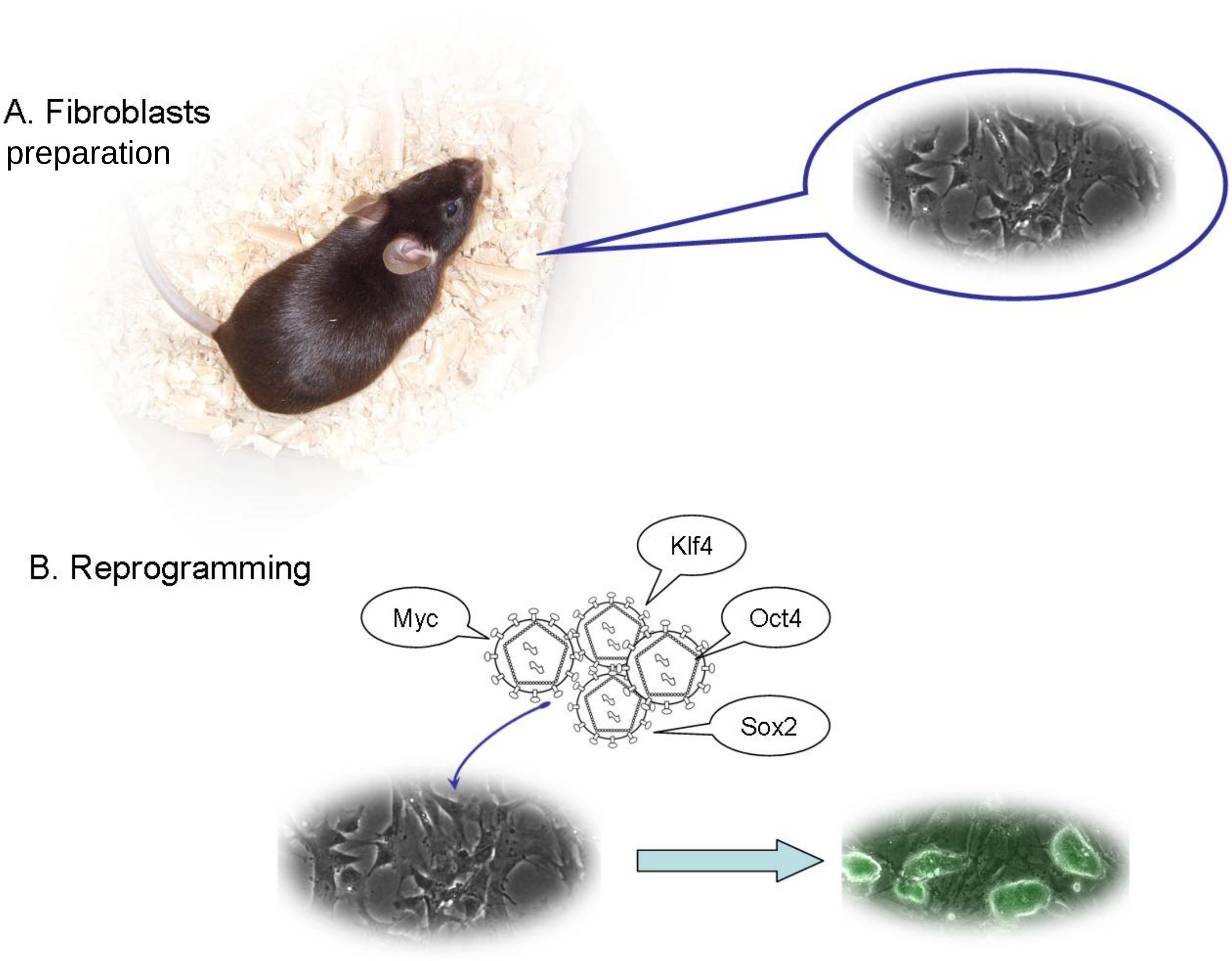
Tetraploid Complementation Assay:

the gold standard for pluripotency

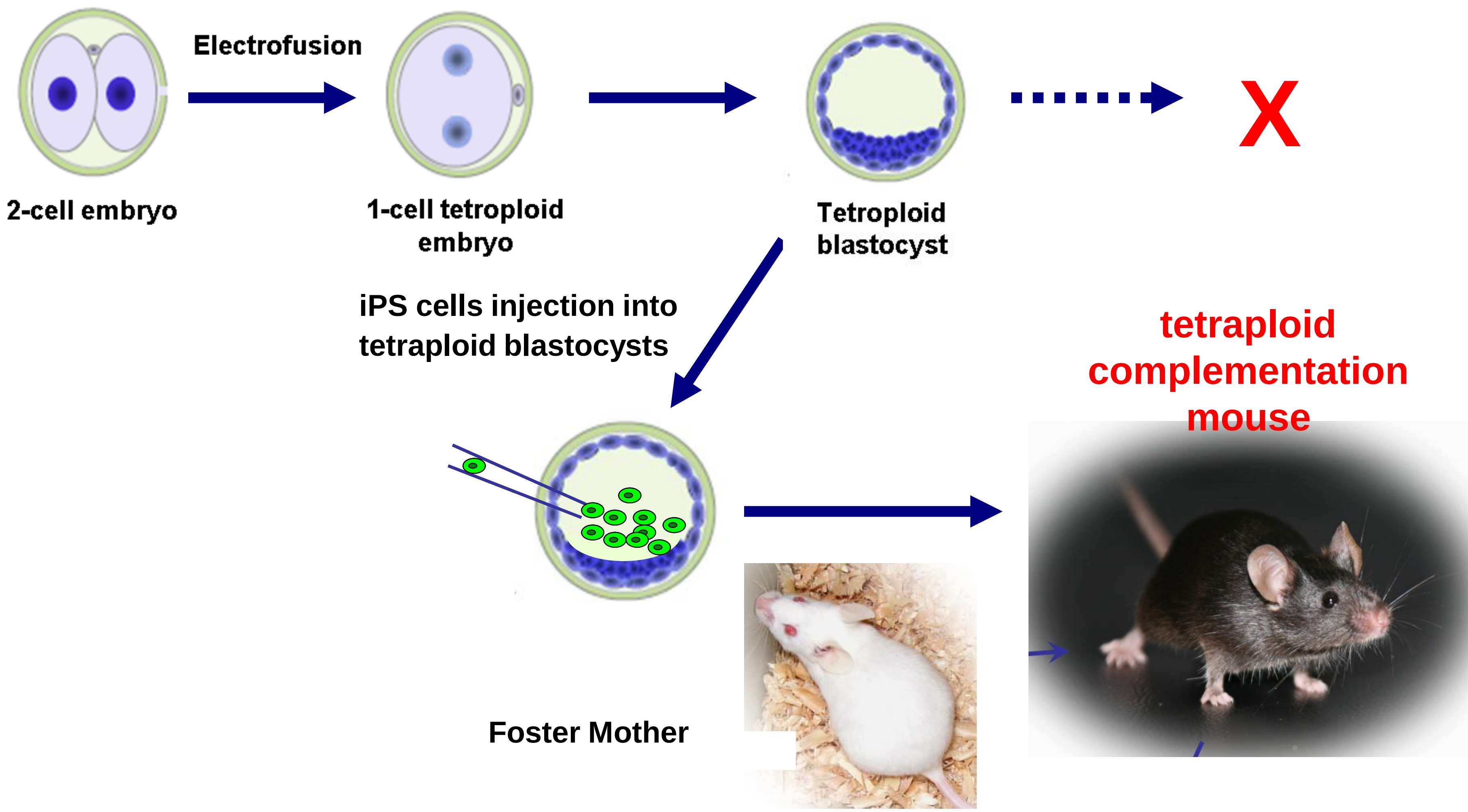
From Somatic Cells to iPS Cells, & to Live Animal?


A. Fibroblasts preperation
B. Reprogramming
Klf4
Myc
Oct4
Sox2
C. Making of tetroploid blastocyst
Electrofusion
2-cell embryo
1-cell tetroploid embryo
Tetroploid blastocyst
D. iPS cells Injection into the tetroploid blastocysts
E. Making of 4n complementation mice and offspring
Foster mother
4n complementation mouse
Mate with ICR

Generation of iPS cell lines



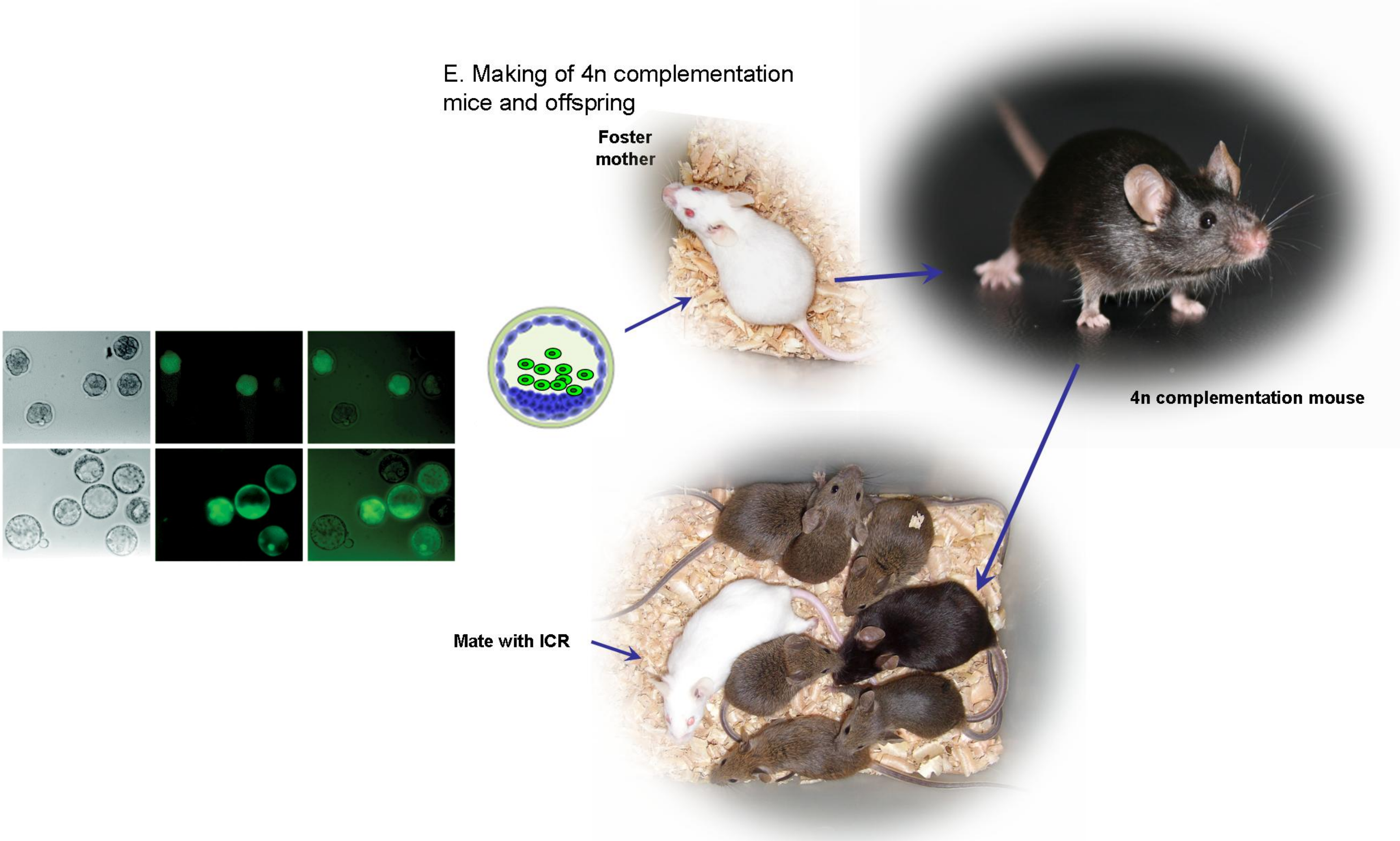
Generation of live-born iPS mice through tetraploid complementation



“Tiny”

born October, 2008

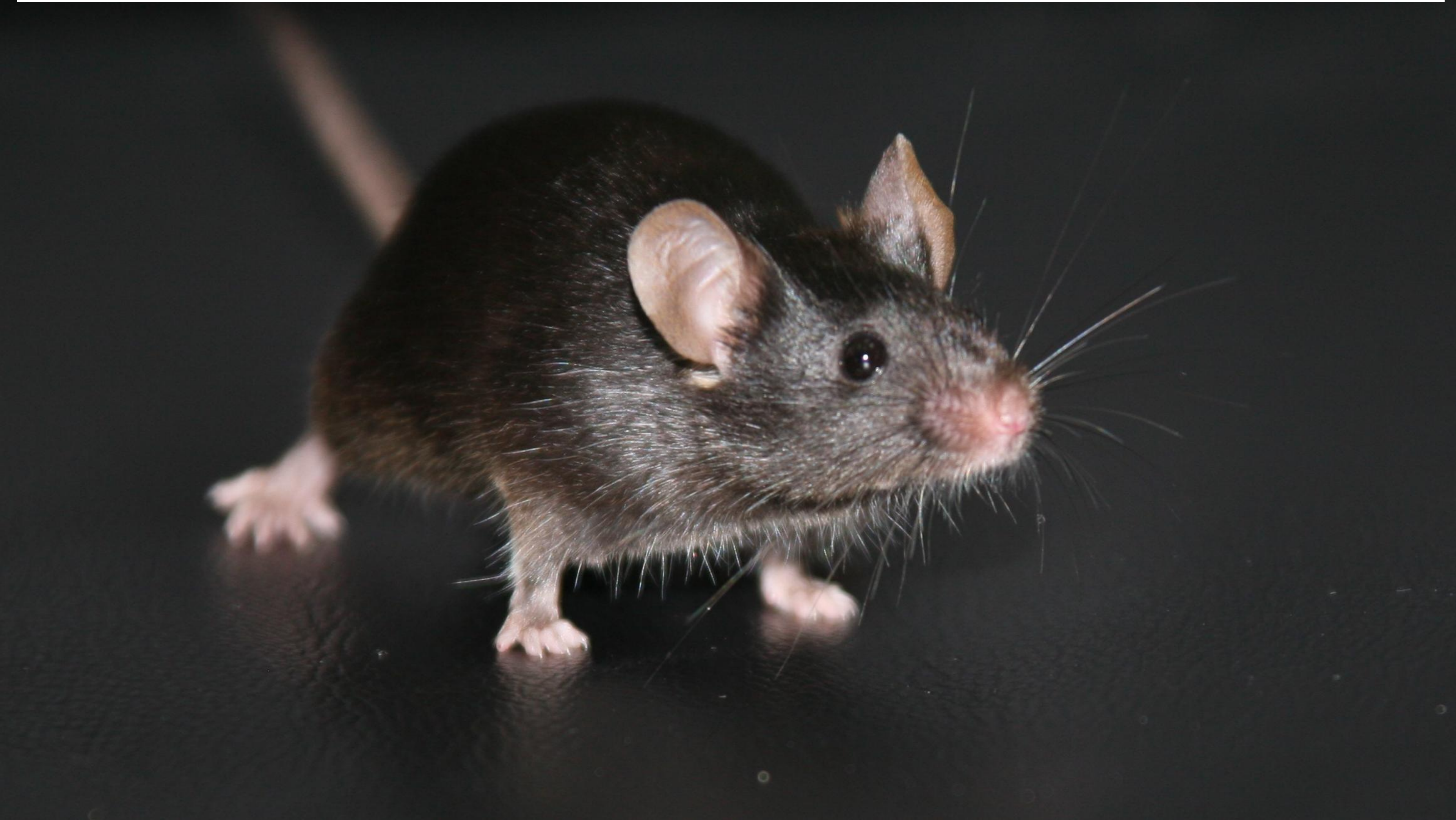
E. Making of 4n complementation mice and offspring



“Tiny”

(a.k.a. “Xiao-xiao” or “小小”)

The first live iPS mouse after tetraploid complementation



TIME
IN PARTNERSHIP WITH CNN

Top 10 Medical Breakthroughs of 2009

TIME charts the highs and lows of the past year in 50 wide-ranging lists

Select a Section | Story | All Best and Worst Lists

Top 10 Medical Breakthroughs

BACK
NEXT
235 of 500 | View All

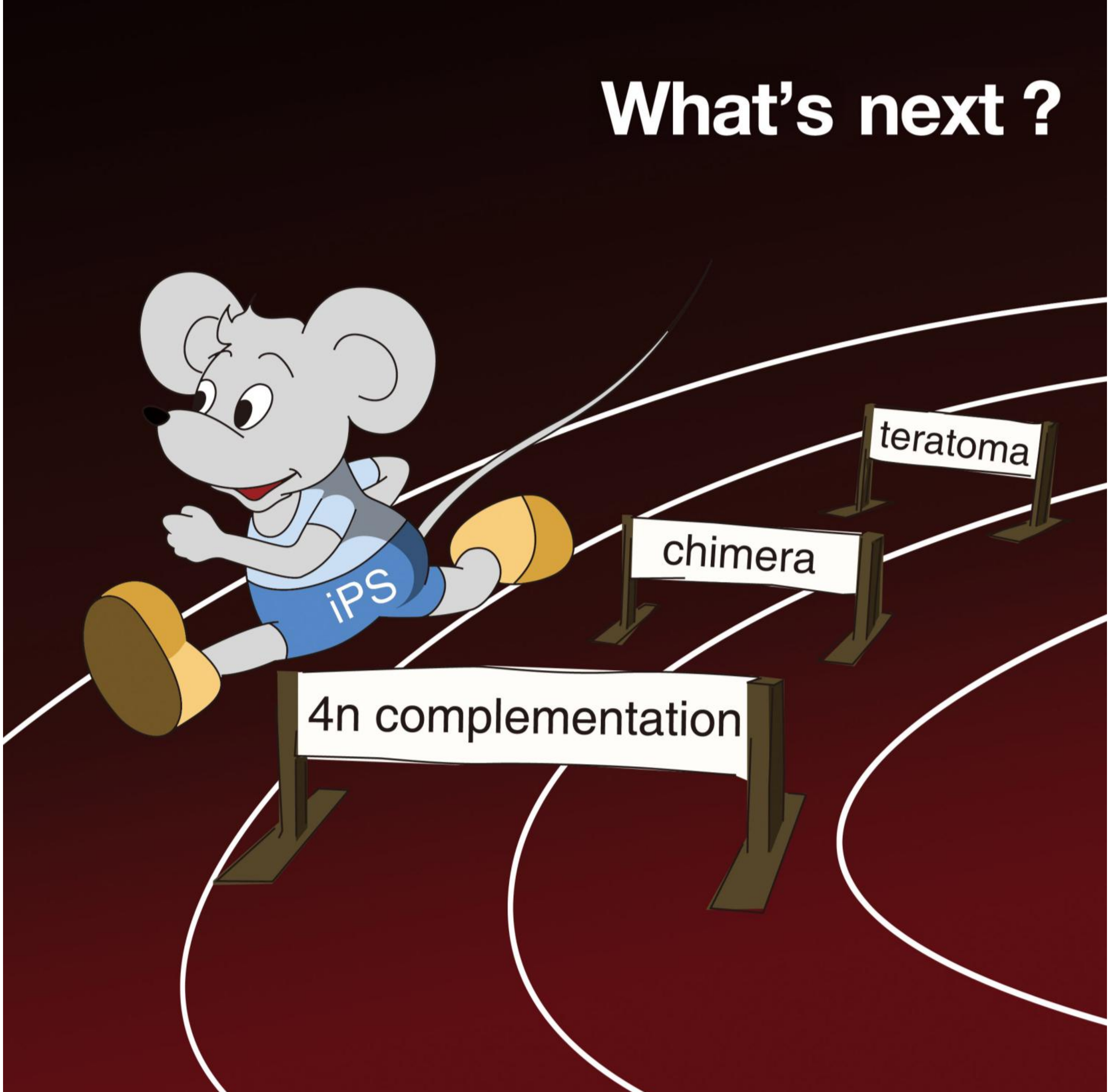
5. Stem-Cell-Created Mice

By **ALICE PARK** Tuesday, Dec. 08, 2009

ZHOU QI / XINHUA PRESS / CORBIS

PRINT EMAIL MORE

The birth of yet another laboratory mouse is hardly worth noting — unless the furry creature is the first to be developed from stem cells that do not involve embryonic cells. That deserves to be called a breakthrough. The new pups, whose creation in two separate labs in China was announced in July, were the first to be bred from induced pluripotent stem (iPS) cells. These are adult cells (usually skin cells) that scientists reprogram back to their embryonic state by introducing four genes. The reprogrammed stem cells are then programmed again to develop into mice, a feat that has been accomplished before only using embryonic stem cells. Breeding an entire mouse that is itself capable of reproducing — as the mice did in one of the Chinese labs — is a strong sign that iPS cells may be as useful as embryonic stem cells for a potential source of treatments for disease, scientists said.


What's next ?
teratoma
chimera
iPS
4n complementation

Stem Cell Research: Moving toward the clinic

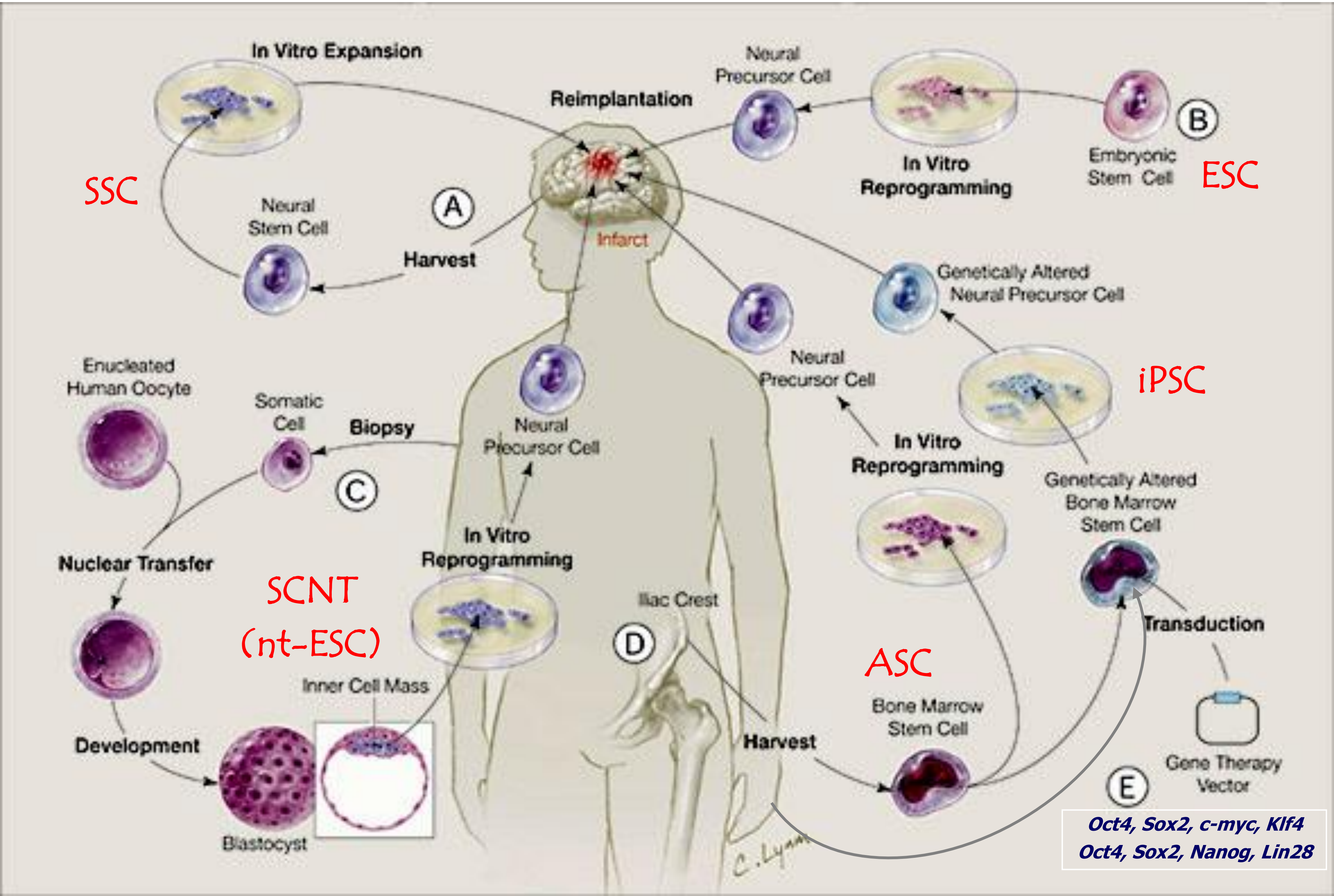
- Regenerative medicine
- Patient-specific studies of disease mechanism and treatment

Persons in the US affected by diseases that may be helped by HPSC research.

Condition	Number of persons affected
Cardiovascular diseases	58 million
Autoimmune diseases	30 million
Diabetes	16 million
Osteoporosis	10 million
Cancer	8.2 million
Alzheimer’s disease	4 million
Parkinson’s disease	1.5 million
Burns (severe)	0.3 million
Spinal cord injuries	0.25 million
Birth defects	150,000 (per year)
Total	128.4 million

Data are from the Patients’ Coalition for Urgent Research, Washington, DC.

Stem Cell Therapy



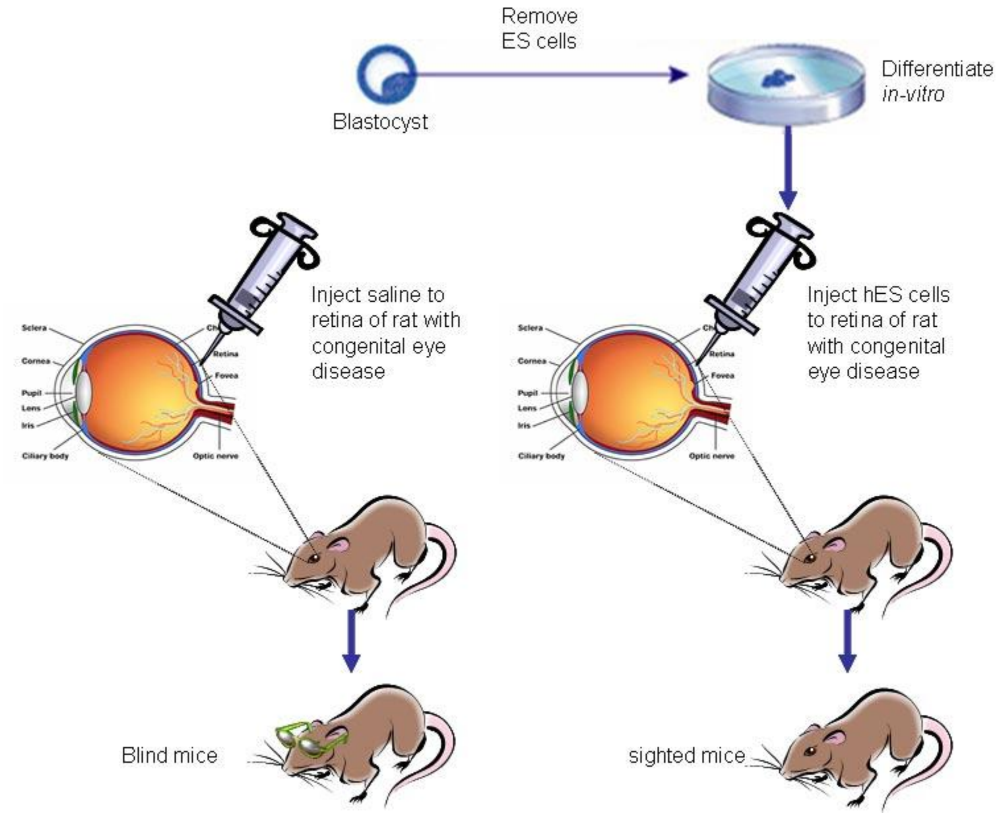
Stem cells and retina disease

Dr. Robert Lanza, Vice-President of research and scientific development at Advanced Cell Technology, Inc., and coworkers:

Culture stem cells ➔ Differentiate into RPE ➔ Isolate cells ➔ Replicate cells ➔ Replace damaged retinal cells of rodents with macular degeneration

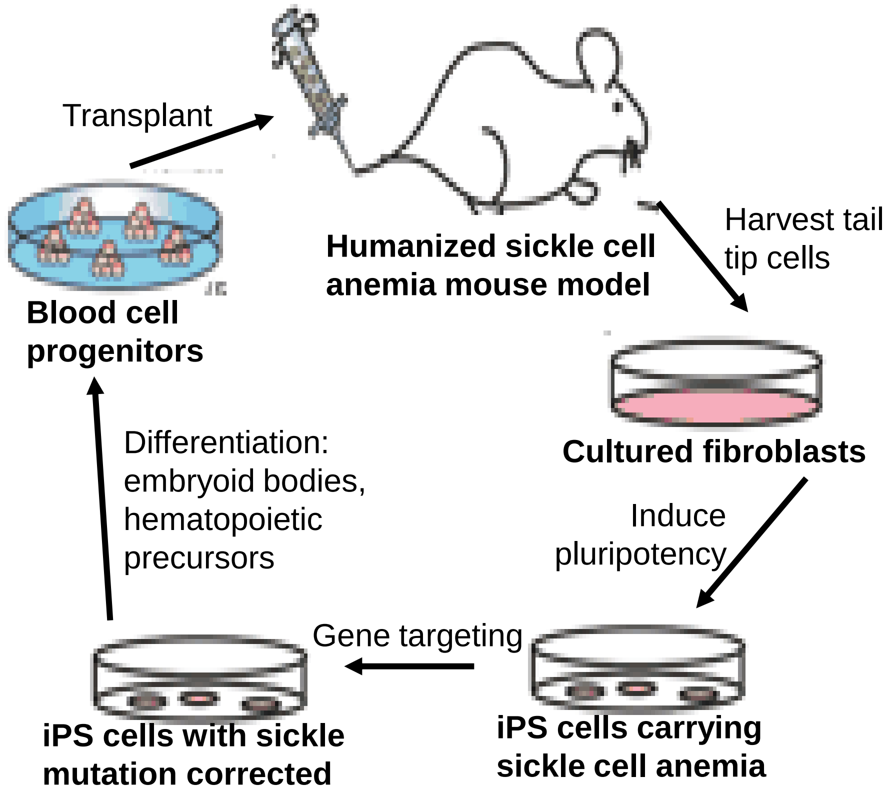
Human embryonic stem cell-derived cells rescue visual function in dystrophic RCS rats.（Cloning Stem Cells 2006）

Lund RD, Wang S, Klimanskaya I, Holmes T, Ramos-Kelsey R, Lu B, Girman S, Bischoff N, Sauvé Y, Lanza R.



Rats treated with hES cells are saved from blindness.

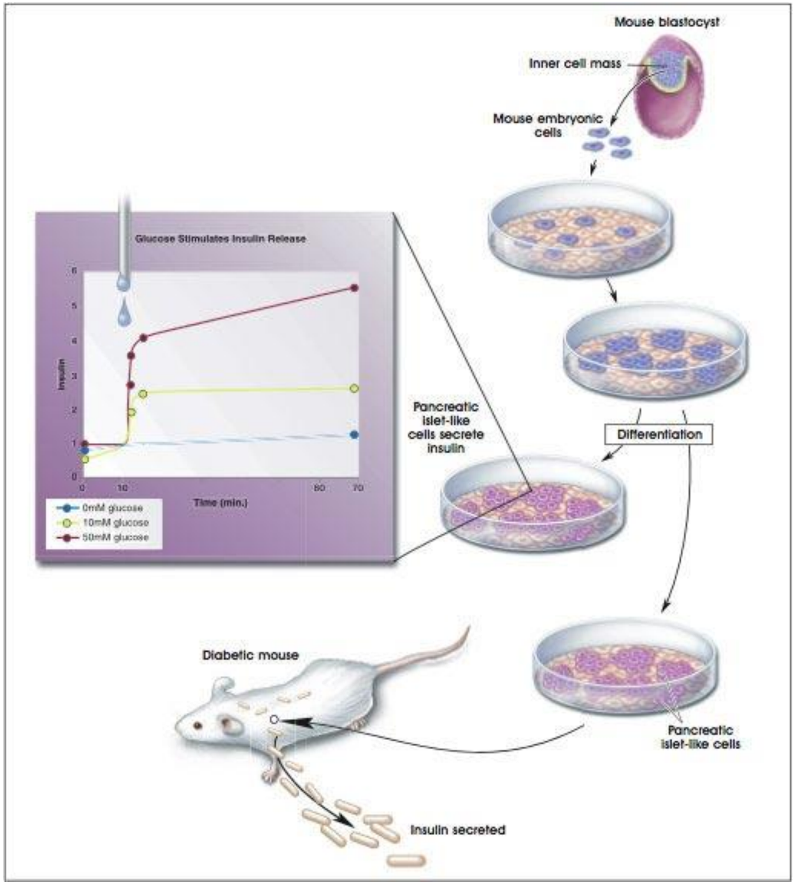
iPS cell therapy in a blood disease model



ES cells and diabetes

In mice with diabetes, adult stem cells from the bone marrow have been shown to be able to navigate to the pancreas and effectively restore function of damaged pancreatic cells that were damaged;

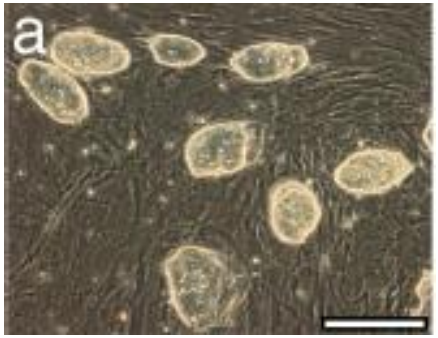
and in humans, a risky trial of 15 patients was undertaken, in which hematopoietic stem cells were removed, treated in the laboratory and infused into patients.



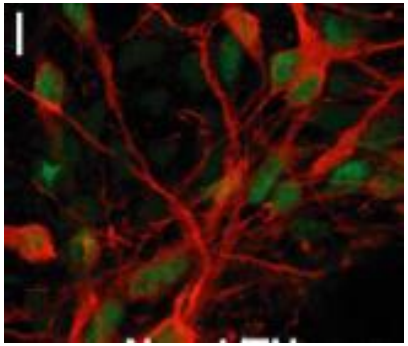
Shedding Light on Blindness-2007 - Gadi Howard

ES cells differentiated in culture and injected into mice can cure diabetes (Credit: NIH)

Therapy of Parkinson's disease in rat model



differentiation



integration

iPS cell

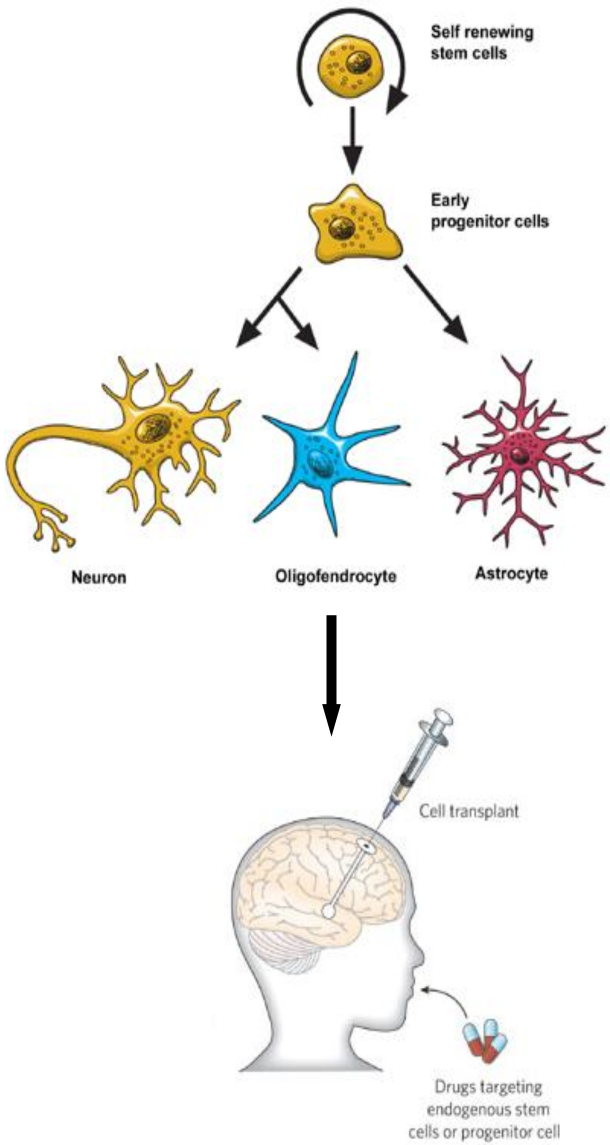
7 days of neuronal differentiation

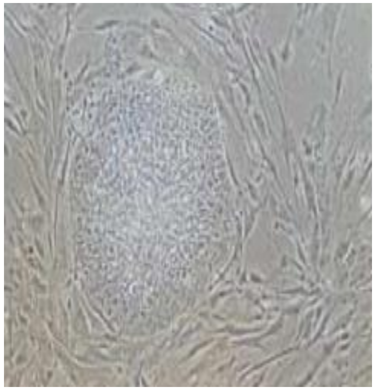
Integration into brain

Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease

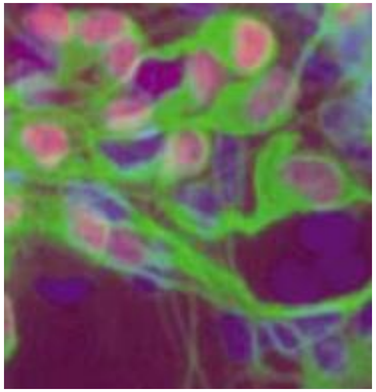
Marius Wernig and Rudolf Jaenisch et al. PNAS(2008)

iPS cells and regenerative medicine: ALS





differentiation



Induced Pluripotent Stem Cells Generated from Patients with ALS Can Be Differentiated into Motor Neurons

John T. Dimos and Kevin Eggan

SCIENCE(2008)

Patient-Specific Stem Cells

Amyotrophic lateral sclerosis (Lou Gehrig's disease)
ADA-SCID
Gaucher disease type III
Duchenne muscular dystrophy
Becker muscular dystrophy
Down syndrome
Parkinson's disease
Juvenile diabetes mellitus
Shwachman-Bodian-Dianmond syndrome
Huntington disease
Lesch-Nyhan syndrome (carrier)
Spinal muscular atrophy

Stem Cell Research:

How much do we know?

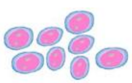
- A lesson learned from experiments on Stem Cell In Utero Transplantation

An In vivo Model to Study Stem Cell Biology

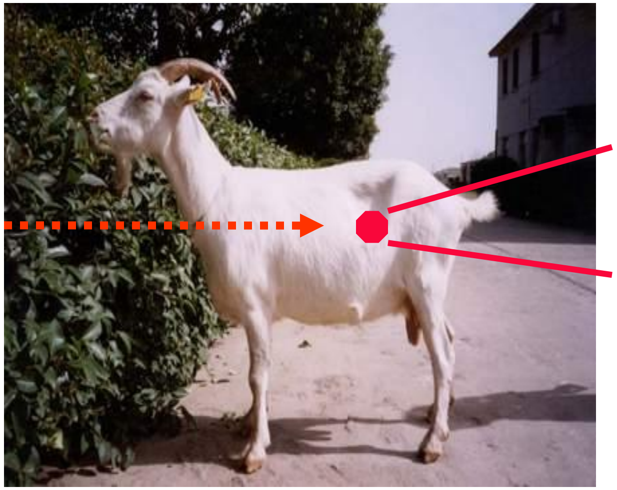
How do the stem cells function in the body?

? Engraftment
? Survival
? Phenotype stability

Transgenic Human Stem Cells



- Donor Cell Preparation



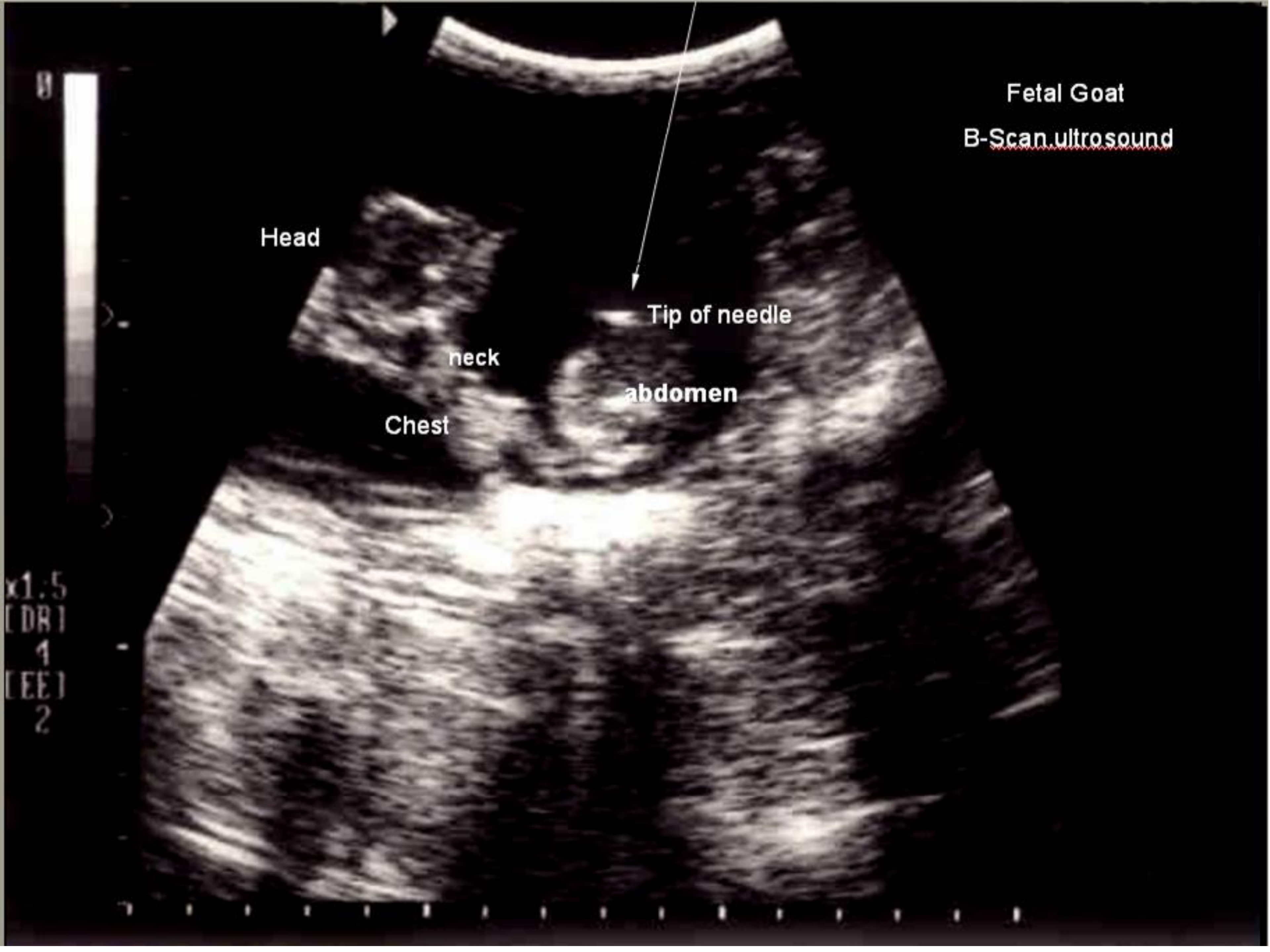
- Recipient Preparation
- hHSC in utero Transplantation

Fetus

In utero

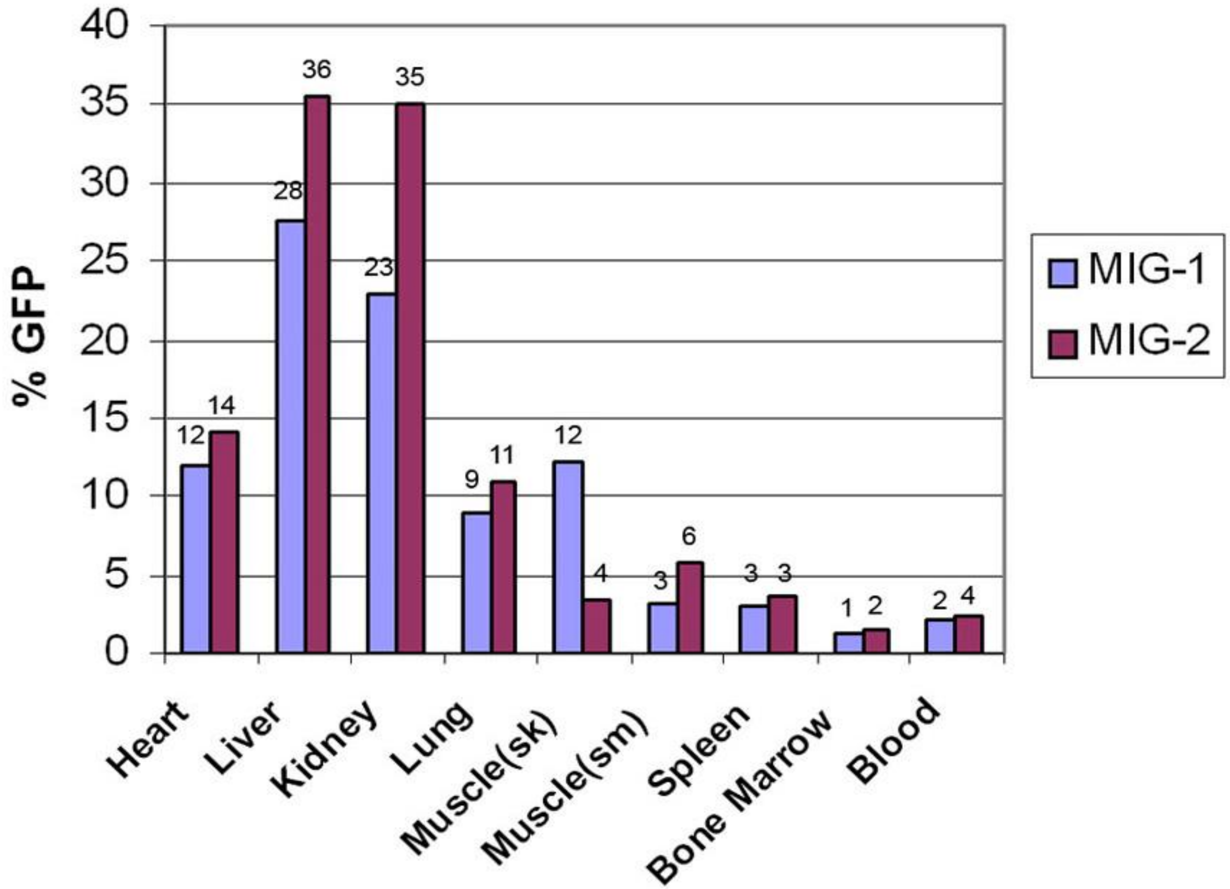
? Multilineage differentiation

? Function
? Plasticity



Fetal Goat
B-Scan ultrosound
Head
Tip of needle
neck
abdomen
Chest
x1.5
[DR]
4
[EE]
2

FACS analysis of GFP+ human cells in various hematopoietic (blood related) and non-hematopoietic organs of chimeric goats

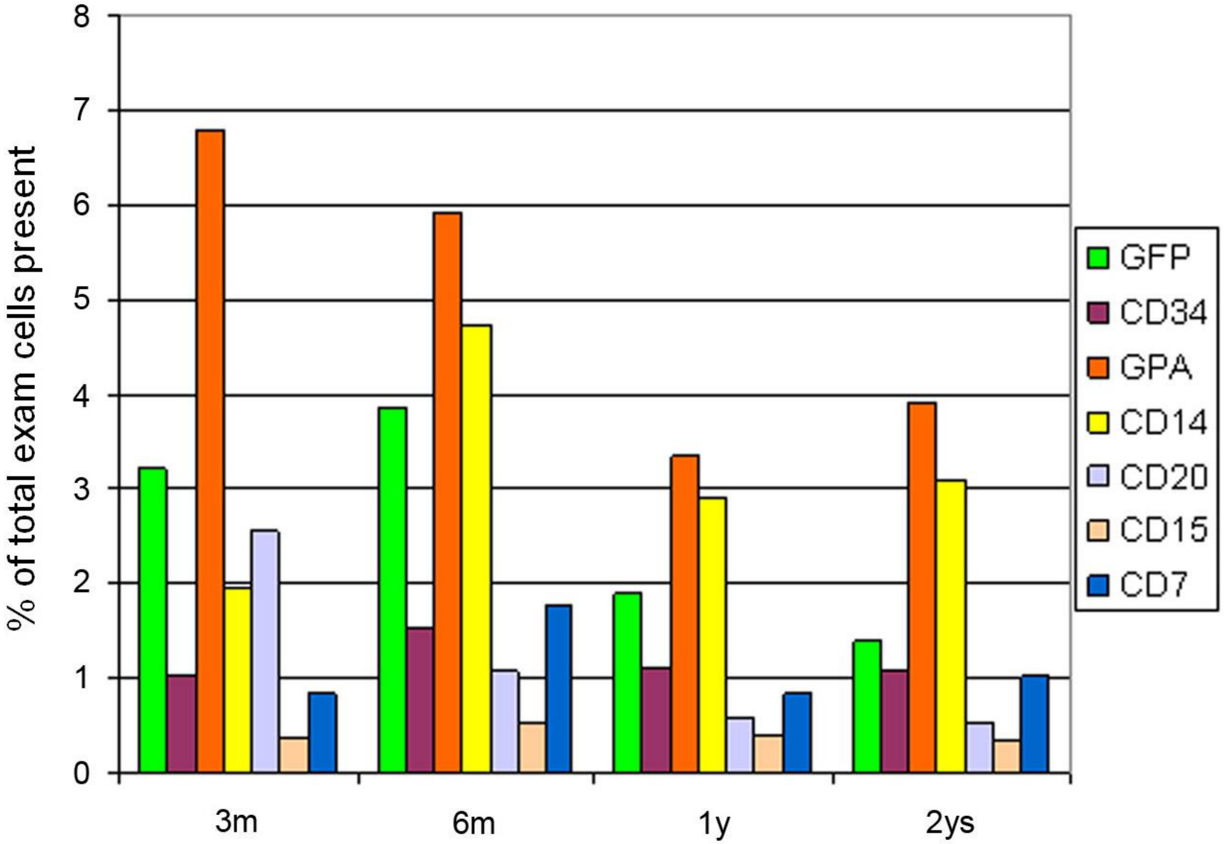


GFP+ human cells were detected in hematopoietic and non-hematopoietic organs including :

Blood, bone marrow, spleen, liver, kidney, muscle,
lung and heart of the recipient goats
(1.2-36% of total examined cells).

FACS analysis of blood cells in MIG-goats

(Transduction of human CD34$^+$lin$^-$ cells with MSCV-IRES-GFP vector)



Human cell surface antigens as well as GFP expression were detected through 24 months after birth

(currently up to 5 years)

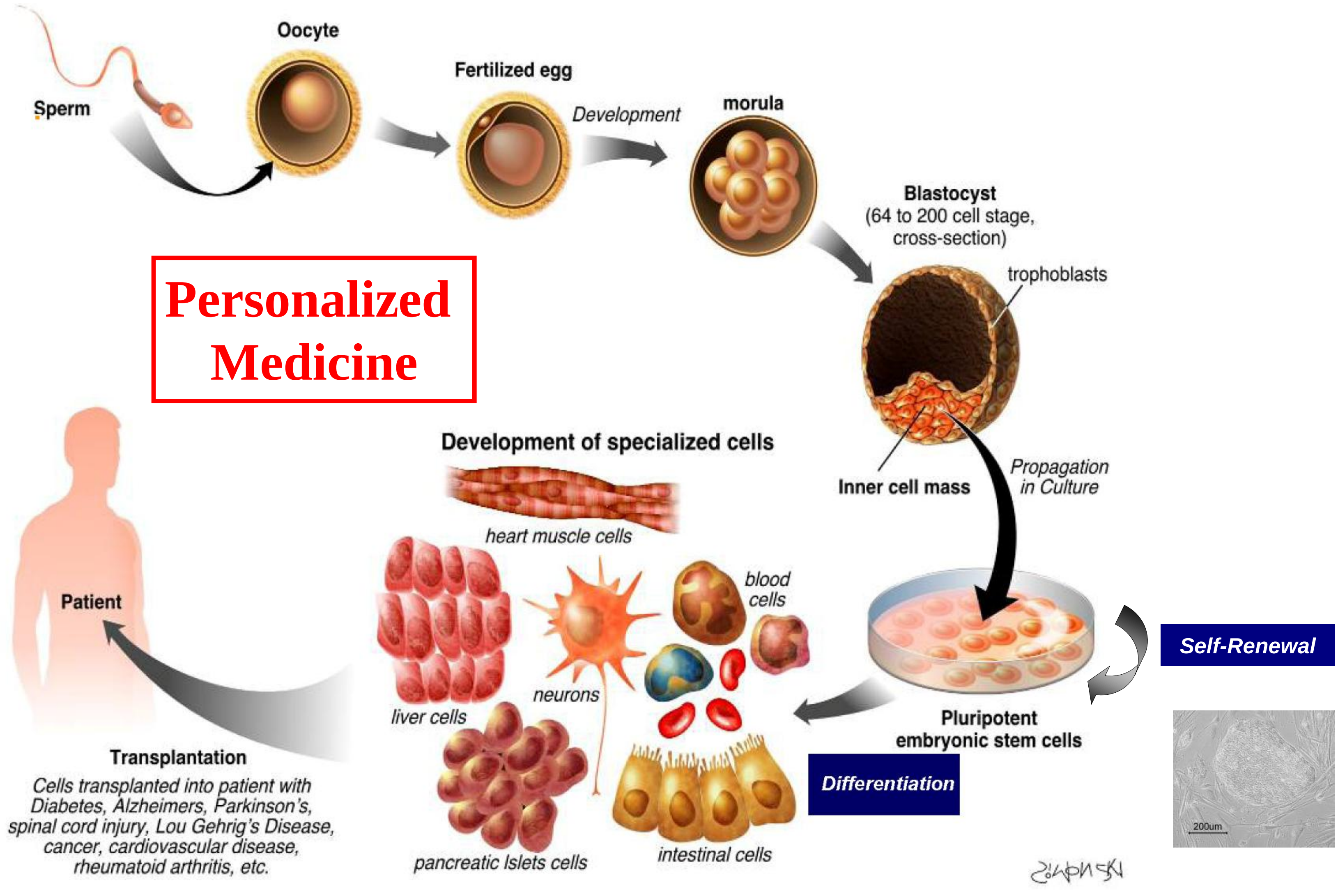
Current Progress in Stem Cell Technology

Summary:

- **We have come a long way in the past 30 years…**
- **There are still much to be learned, but hope is here**
- **We should continue all kinds of stem cell and pluripotent cell research**
- **Ethics, legislation and regulation**

Goal of Modern Disease Therapy:

Personalized Medicine



Acknowledgements

Professor Qi Zhou

Institute of Zoology
Chinese Academy of Sciences

Xiao-yang Zhao
Wei Li
Zhuo Lv
Lei Liu, Ph.D.
Man Tong
Tang Hai
Jie Hao
Chang-long Guo
Liu Wang, Ph.D.

Professor Fanyi Zeng

Shanghai Jiao Tong University
Shanghai Institute of Medical Genetics

Qingwen Ma, Ph.D.
Xiang Wang
Yi-ye Zhou
Chuanliang Guo
Qing Cai
Meijue Chen, M.D.
Zhong-hai Yan

##*Professor Shu-zhen Huang*##

Mei-jue Chen
Zhi-juan Gong
Jing-bin Yan
Hui Qian
Juan Wang
Zhao-rui Ren
Deming Sun