Researcher's Perspective on Quality and Non-Clinical Evaluation of Cell/Tissue-based Products

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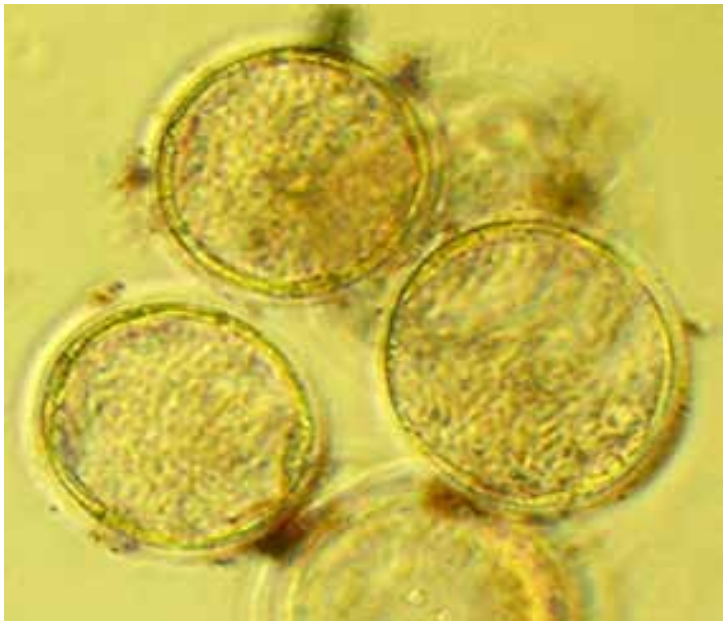
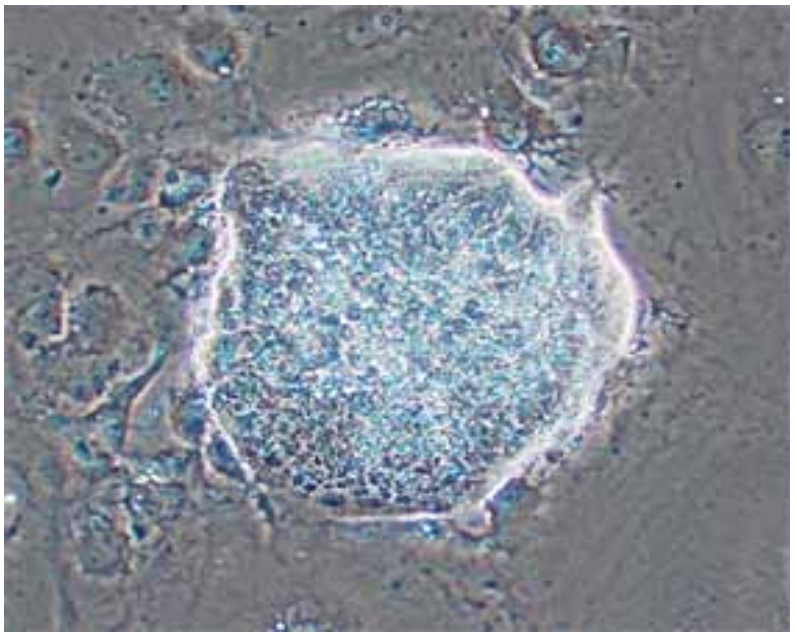
PMDA 5th International Symposium on Biologics
Aug. 26th /2010 Tokyo

Embryonic Stem (ES) Cells

Mouse ES cells; 1981, Sir Martin Evans



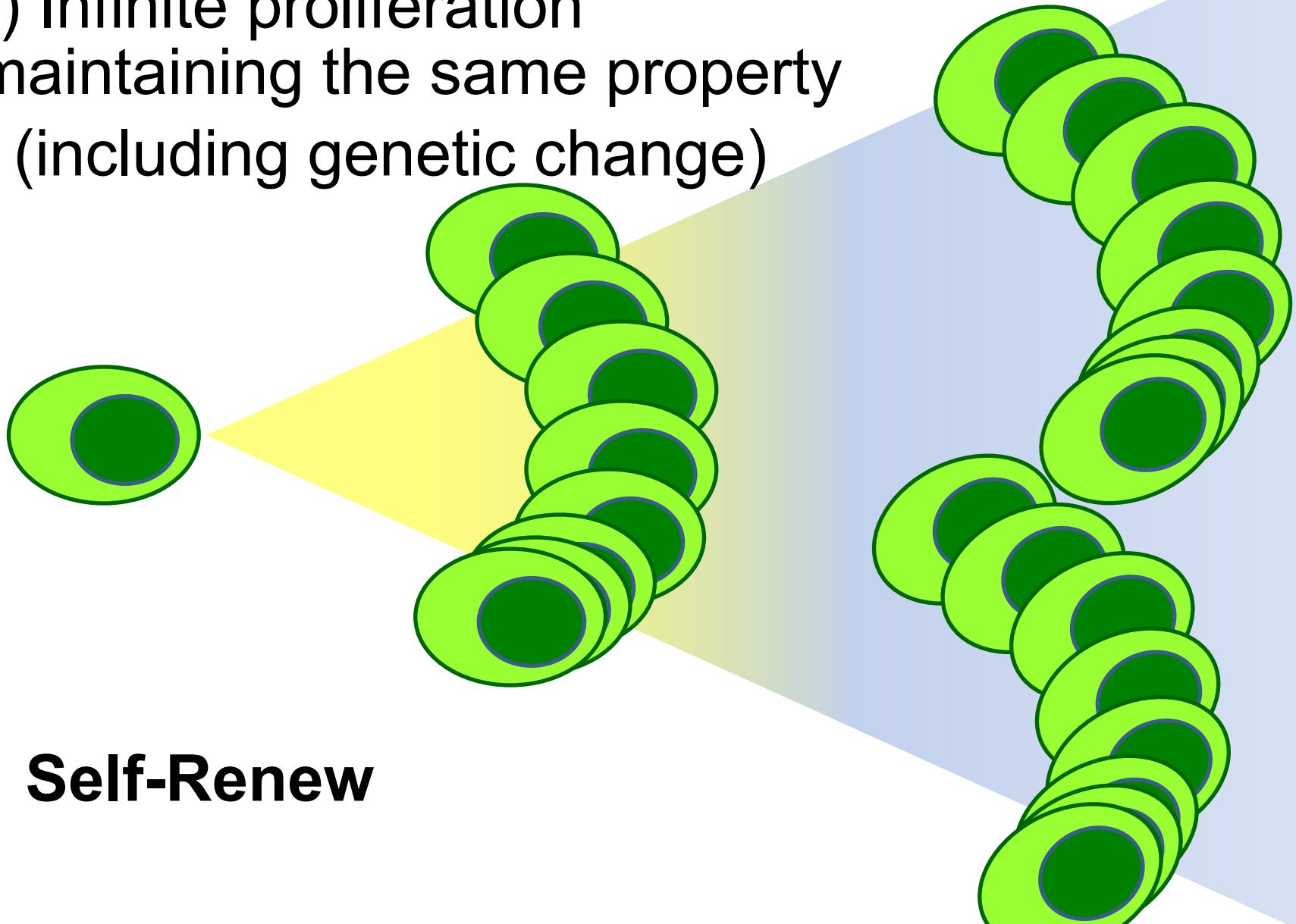


Early embryo
(fertilized egg)

ES cells

Property of ES Cells

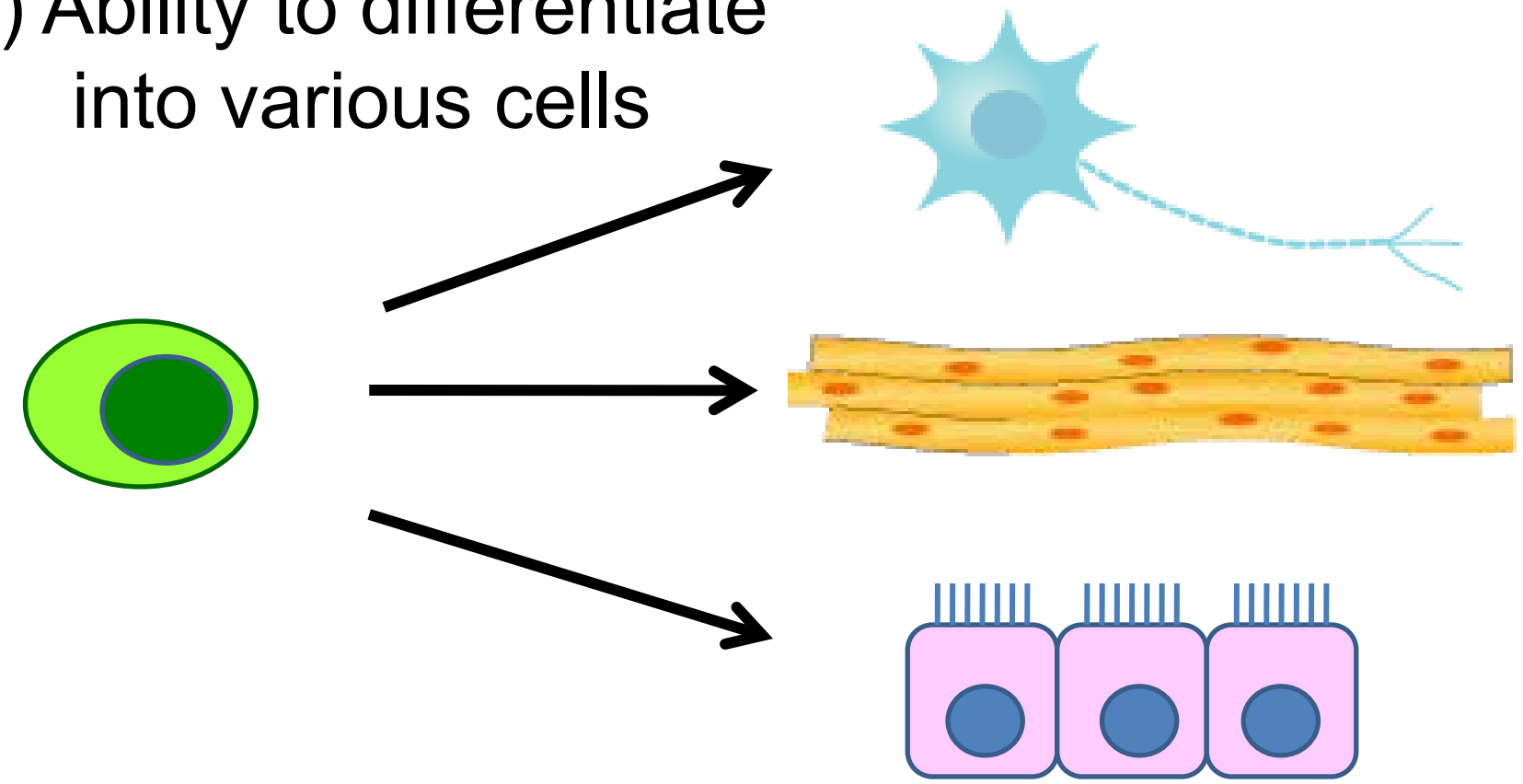
1) Infinite proliferation
maintaining the same property
(including genetic change)



Self-Renew

Property of ES Cells

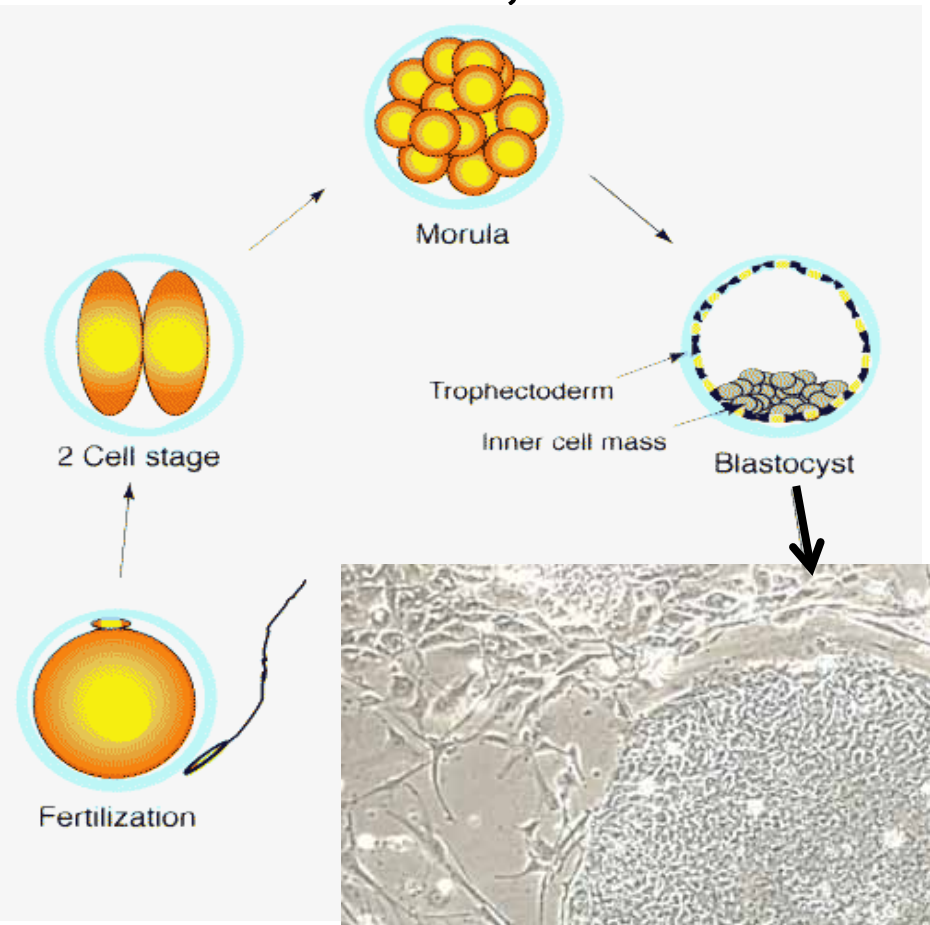
2) Ability to differentiate into various cells

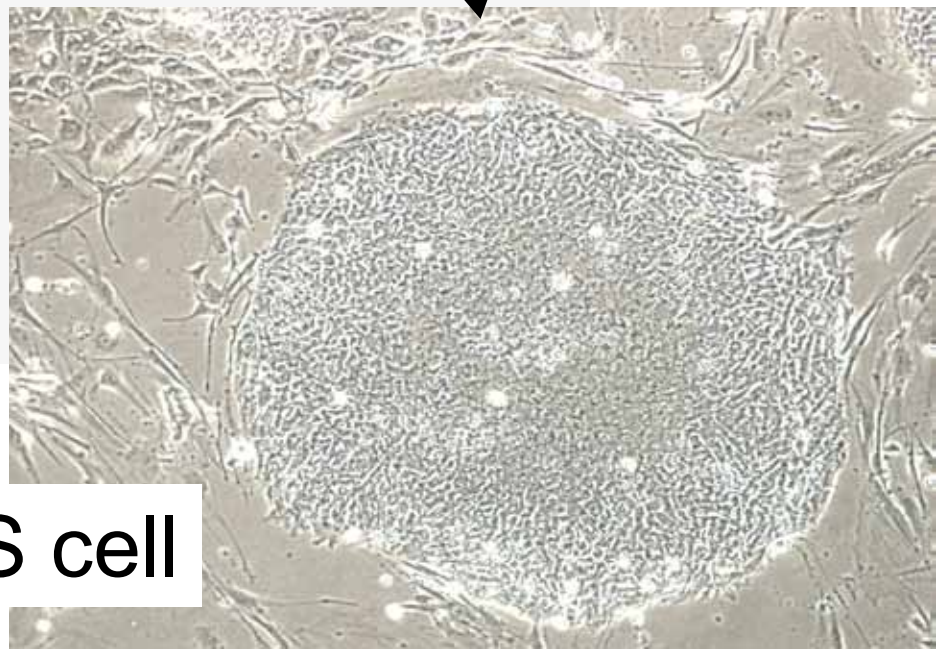


Pluripotency

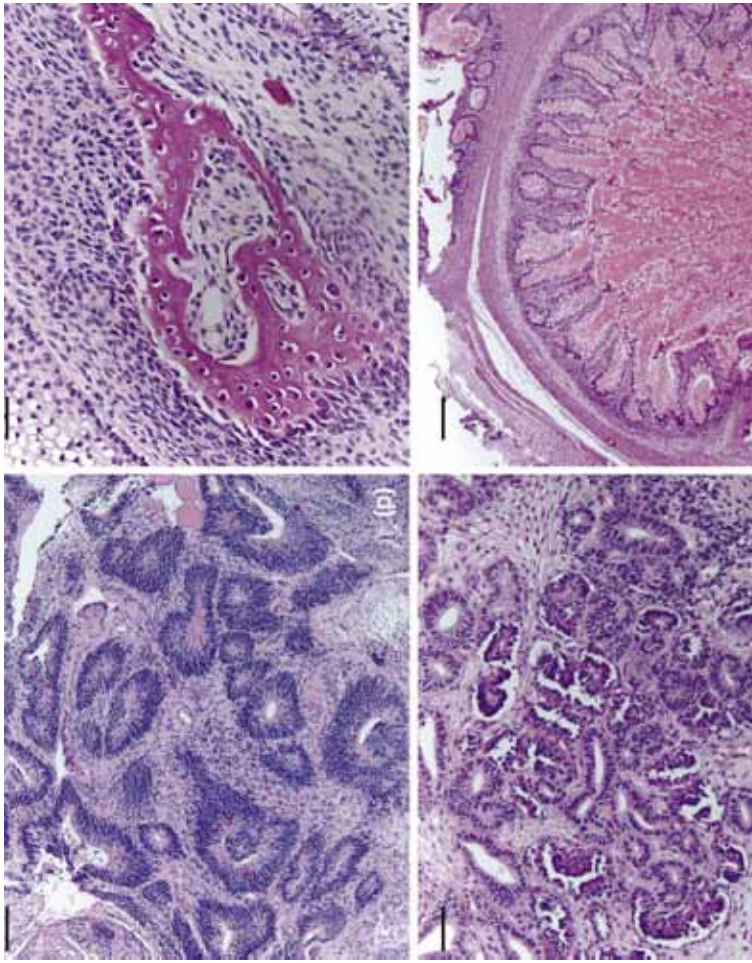
Human ES Cells

1998, James. A.



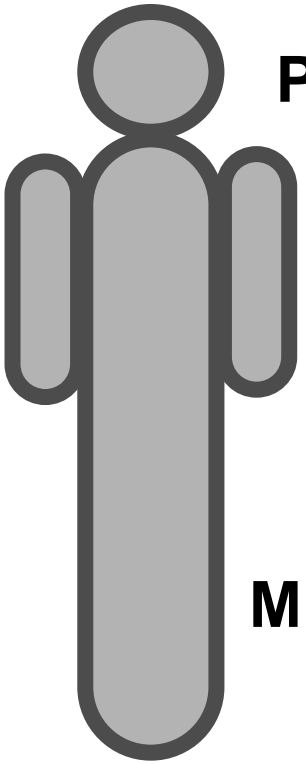


hES cell



teratoma

Regenerative medicine using ES cells



patients

Parkinson disease ← Dopaminergic neuron

Spinal cord injury ← Cholinergic neuron

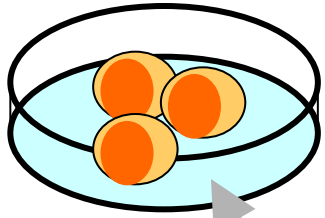
Cardiac failure ← Cardiac muscle

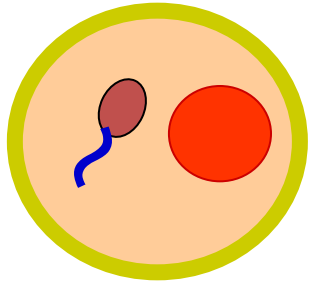
Diabetes ← islet β-cells

Liver dysfunction ← Hepatocyte

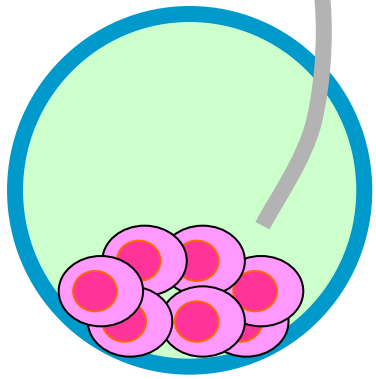
Muscular dystrophy ← Skeletal muscle

ES cells





Fertilized egg



embryo

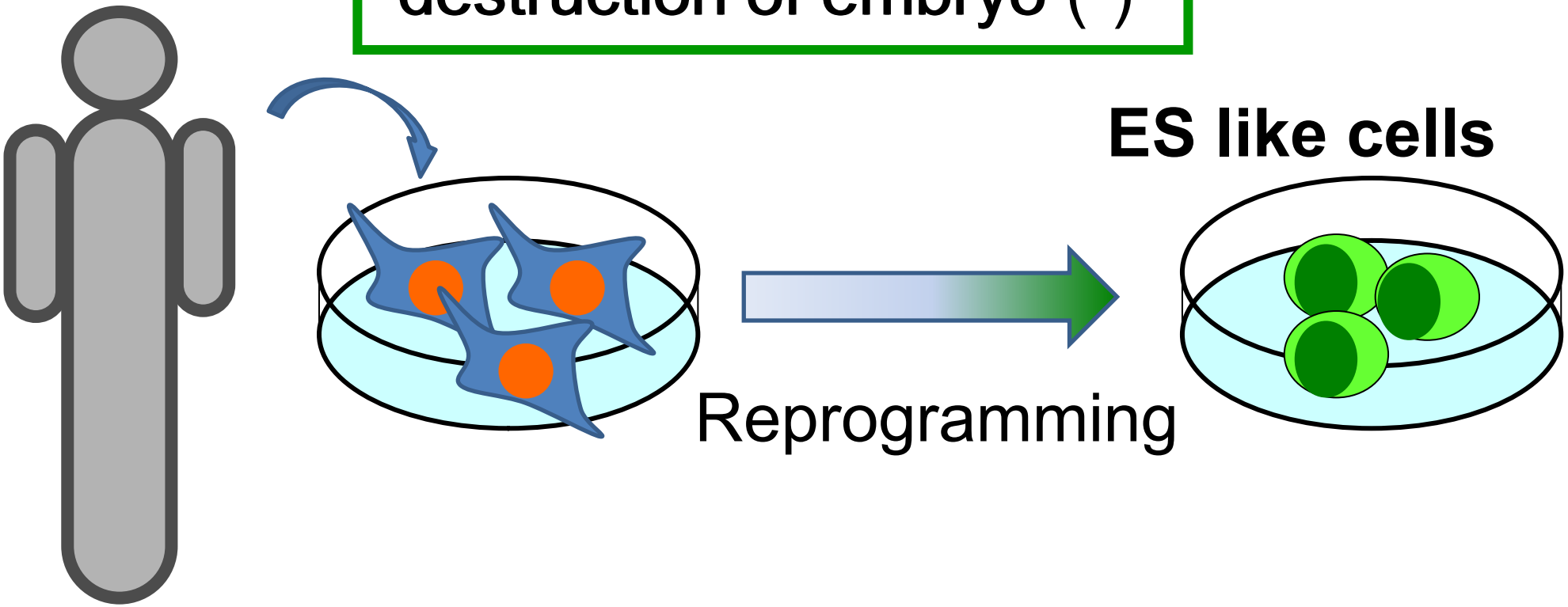
immune rejection (+)

destruction of embryo (+)

To Overcome Issues with ES cells

immune rejection (-)

destruction of embryo (-)

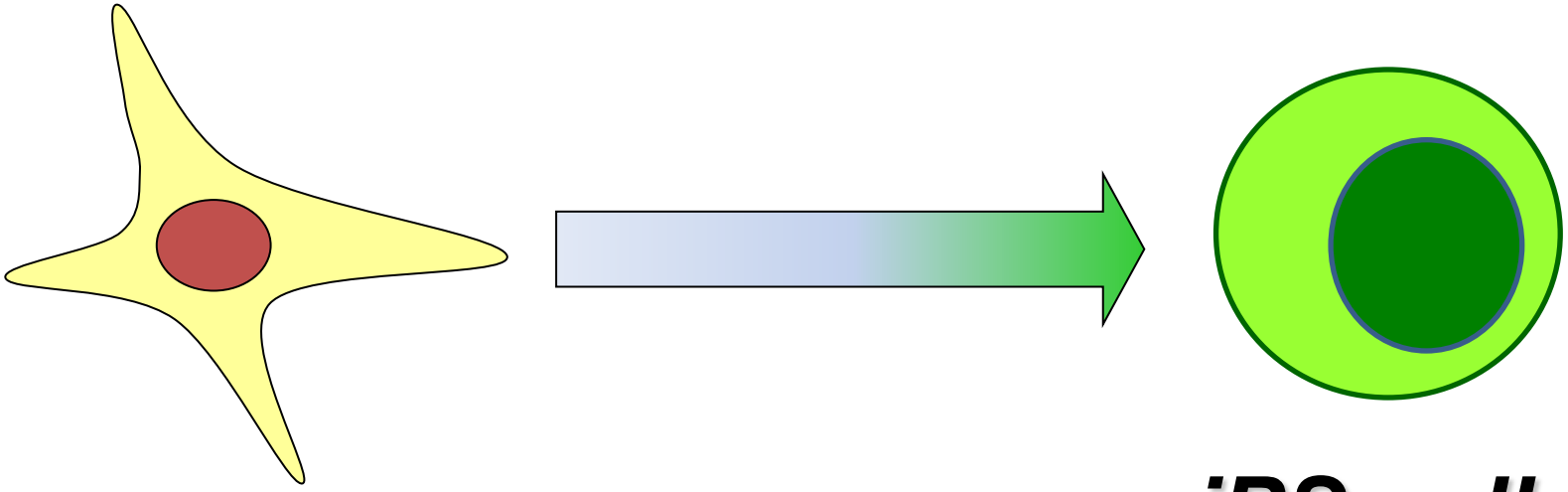


patients
or
HLA-match donor

iPS cell

Mouse: 2006～

Human: 2007～



Somatic cells

iPS cell

induced Pluripotent Stem cell

iPS cells from characterized persons

iPS cell

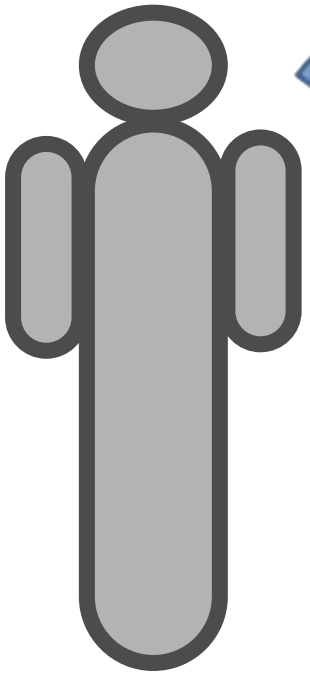
iPS cell

ES cell

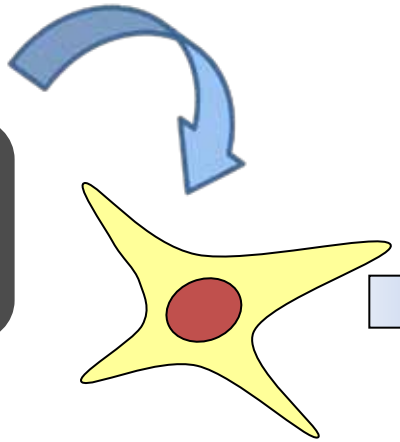
Baseball player？

Beautiful newsreader？

What can iPS cells?

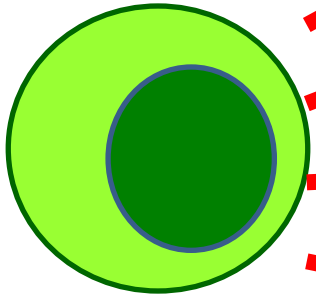


from various persons



Somatic cell

iPS cell



Self-renew

Pluripotency

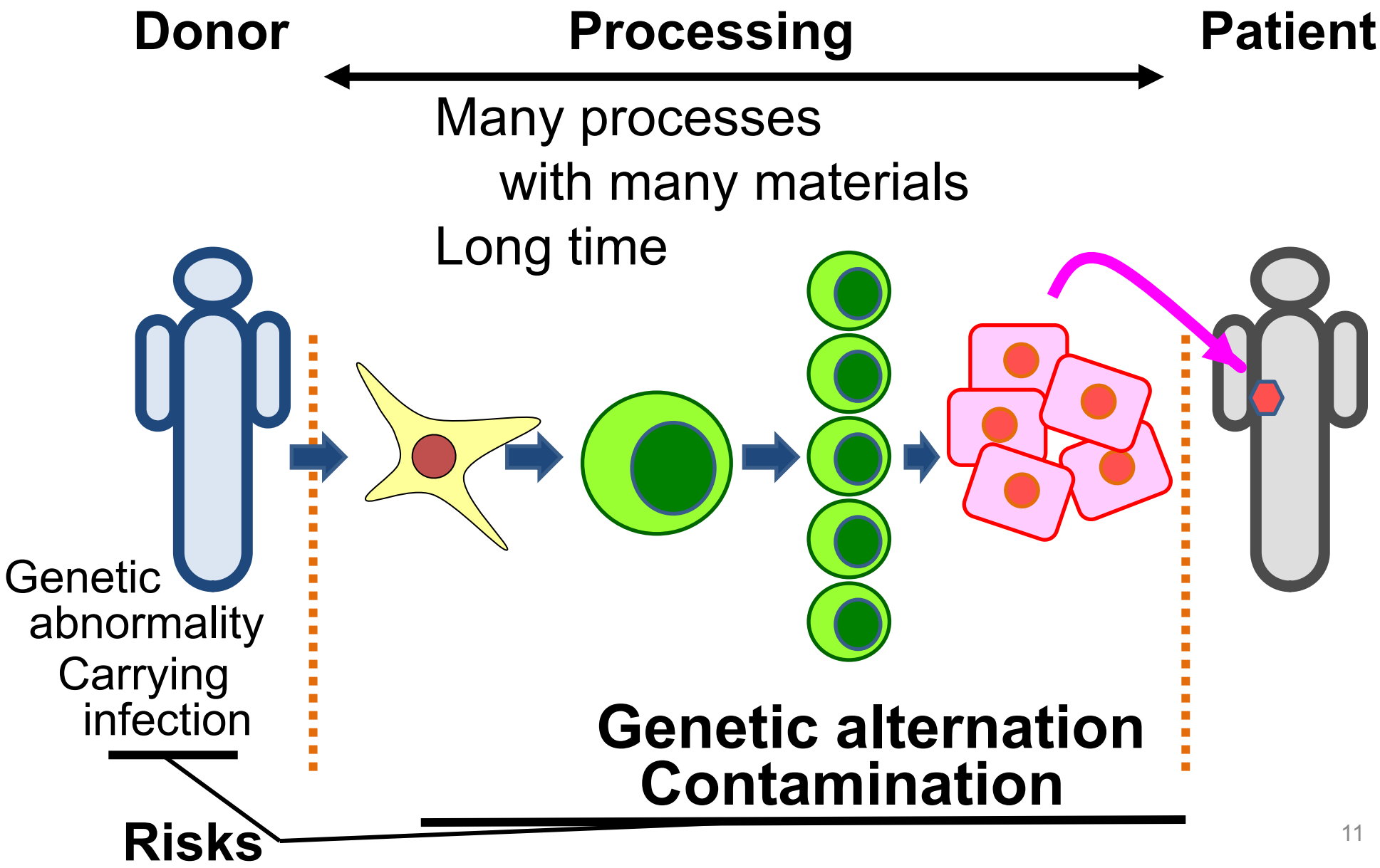
Drug discovery

Study of disease mechanism

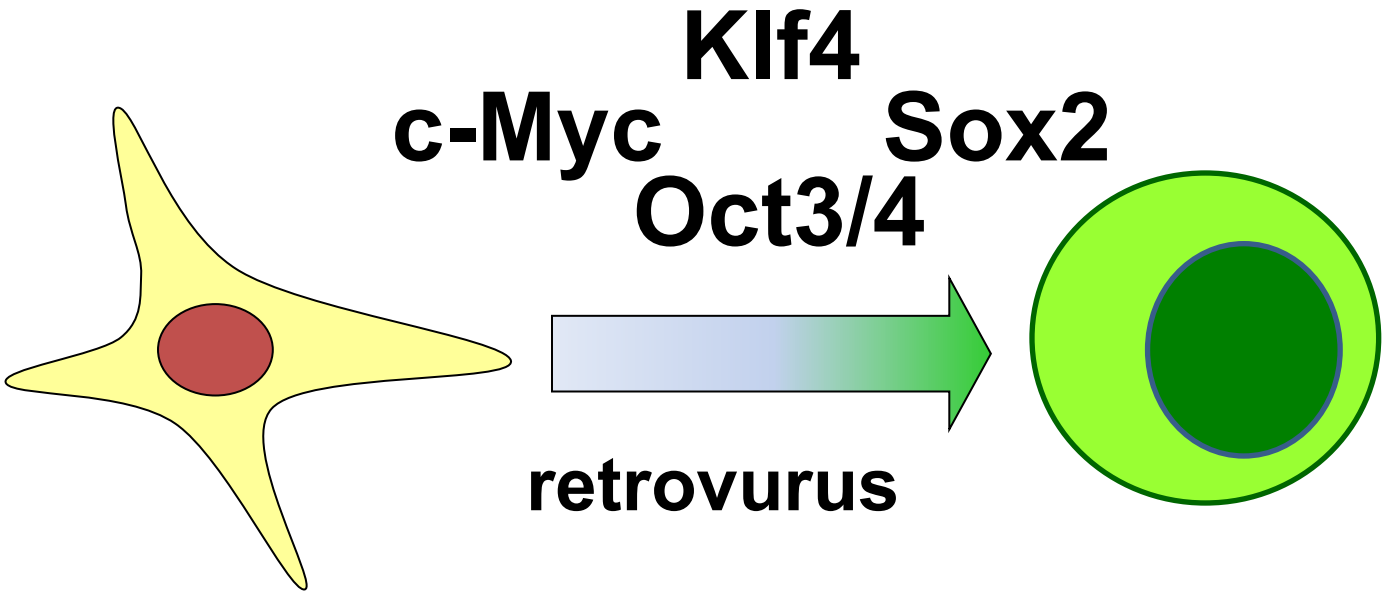
Usage of Embryo(—)

Transplantation

Cell Therapy using iPS cells



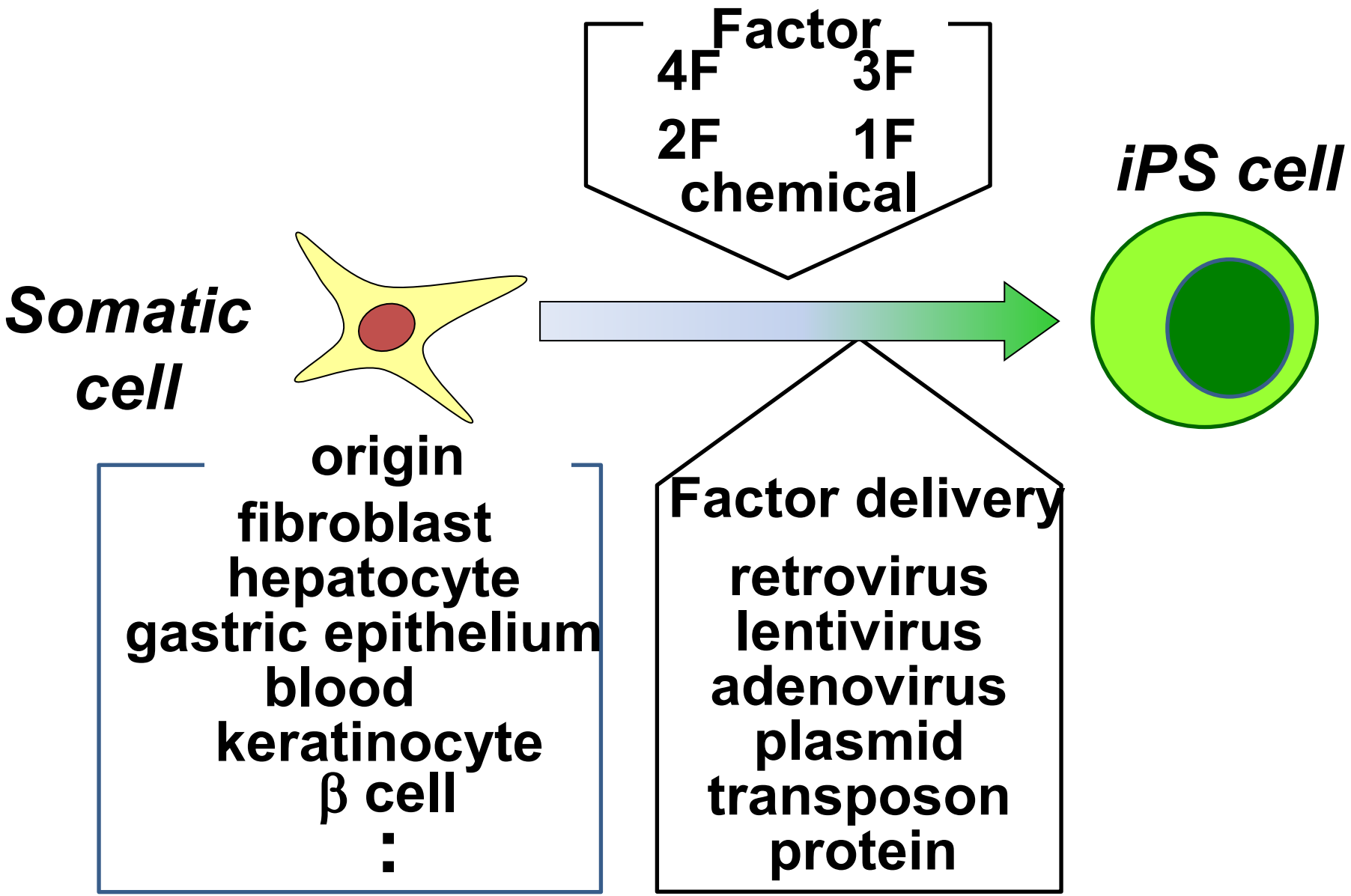
Mouse iPS cell 2006



fibroblast

iPS cell

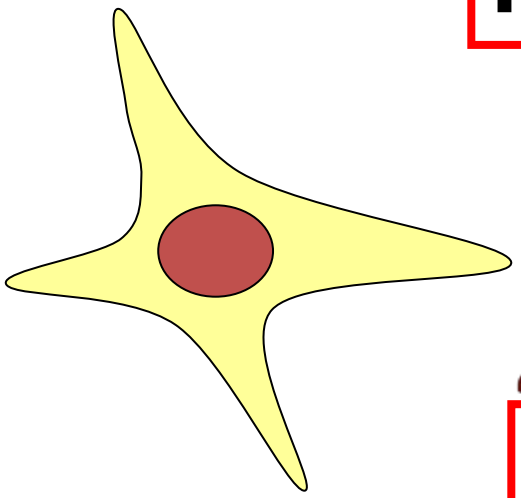
Human/ mouse iPS cell ～2010

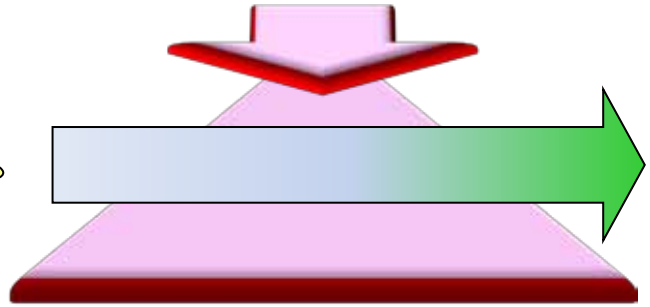


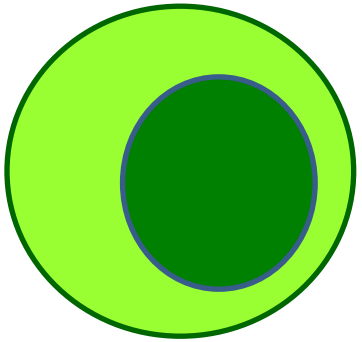
Variation in Generation of iPS cells

Origin

Reprog.Factors







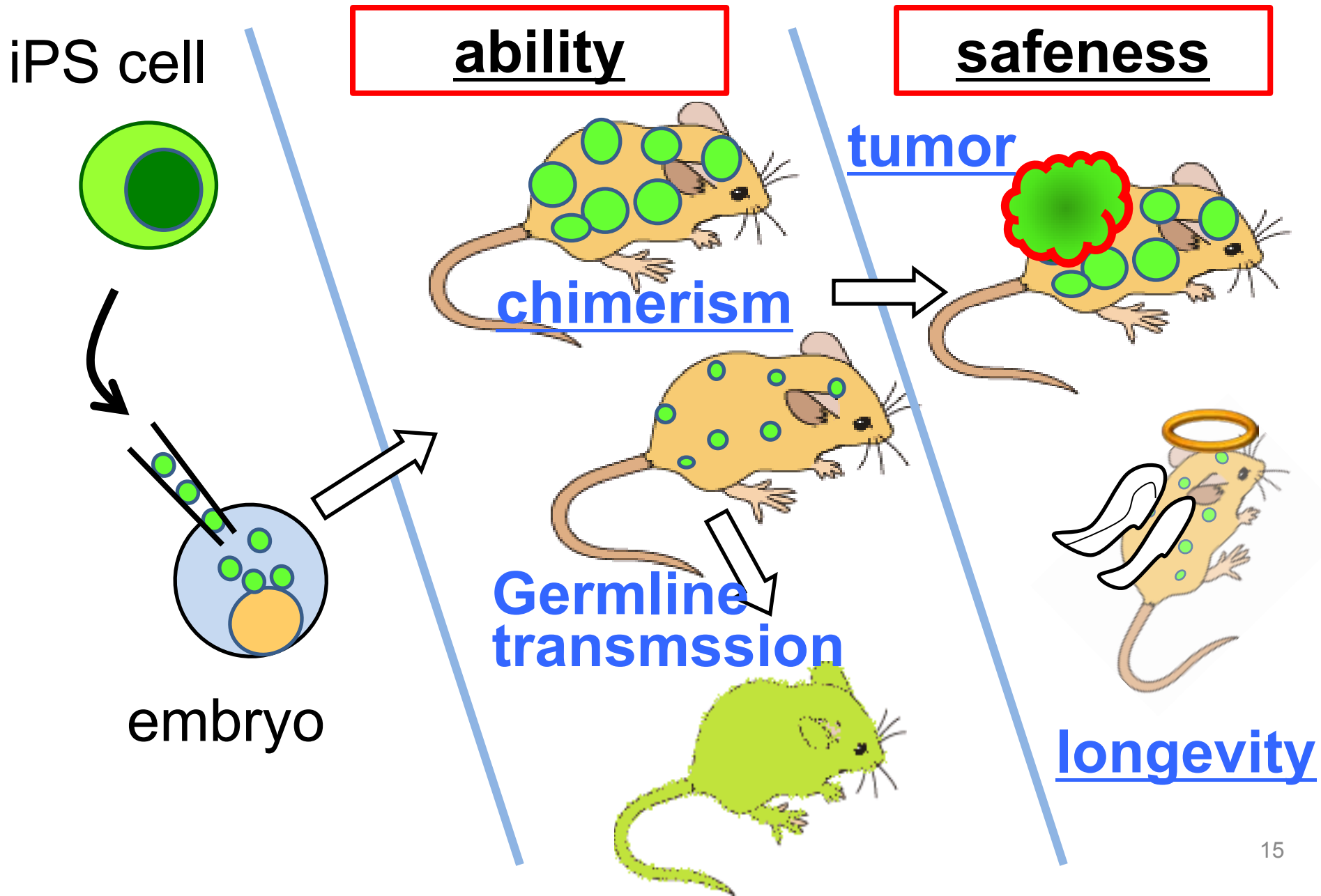
Somatic cells

Transduction method

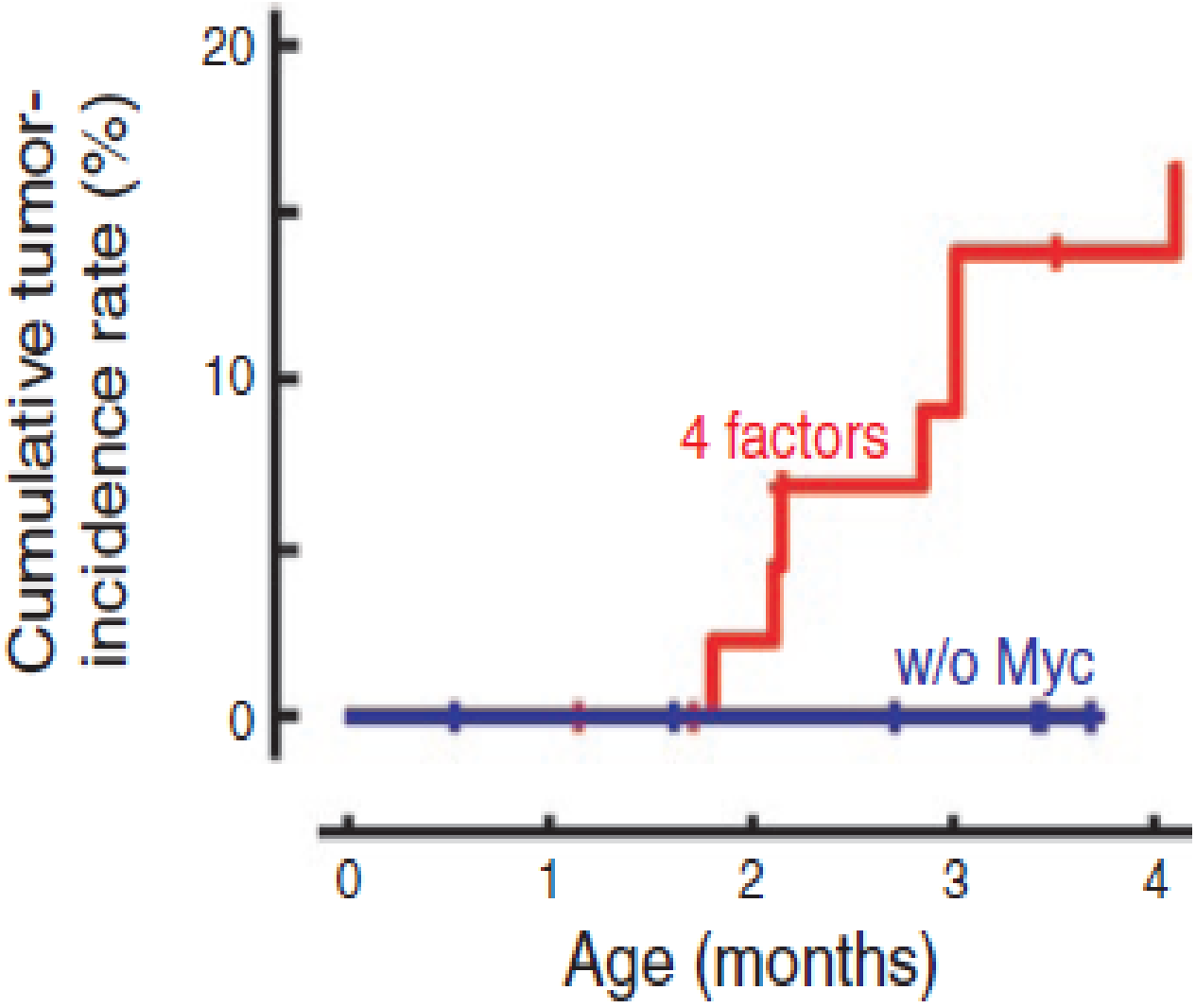
iPS cell

Different methods → different quality?

Chimera formation



c-Myc transgene → tumorigeensity



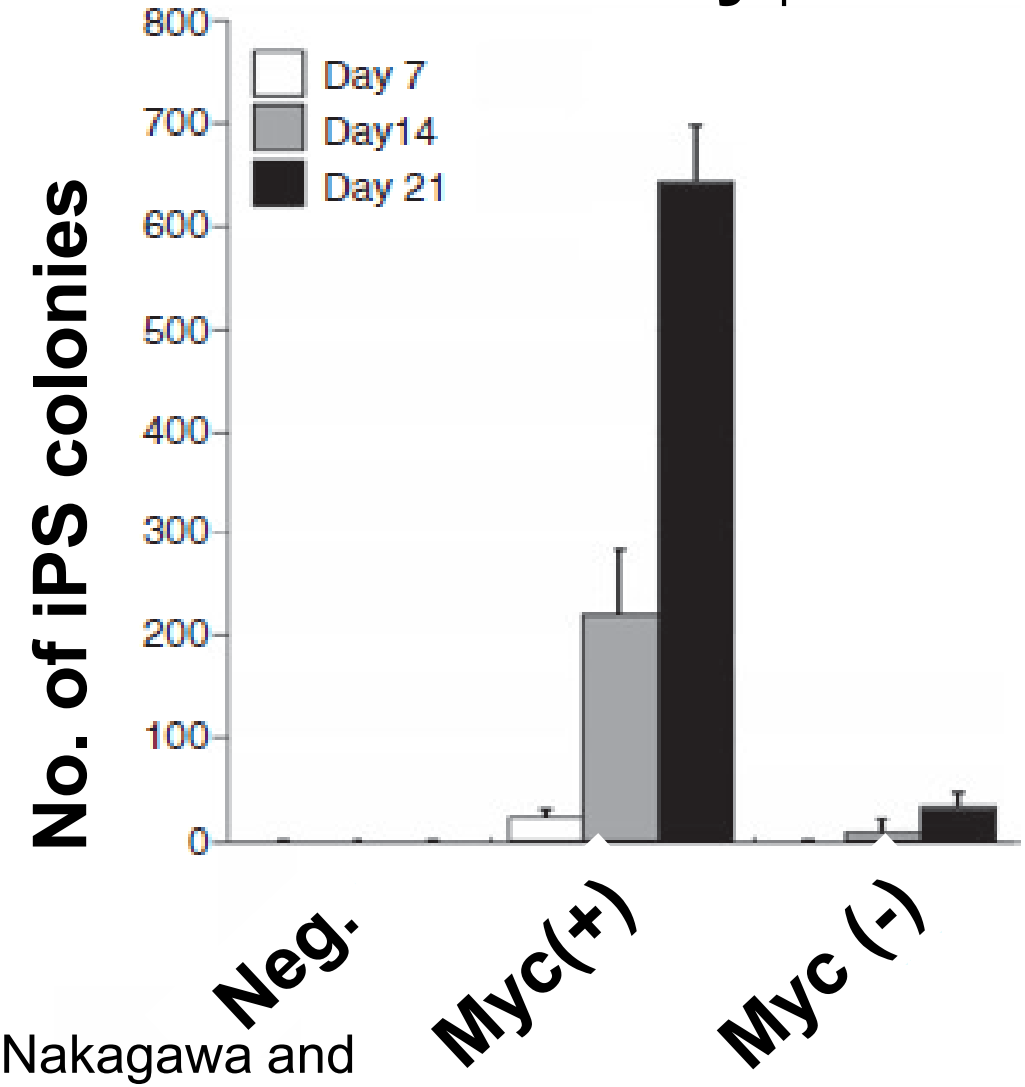
Okita et al. Nature 2007

Reactivation of c-Myc-Tg

Nakagawa and Koyanagi et al. et al
Nature biotech 2007

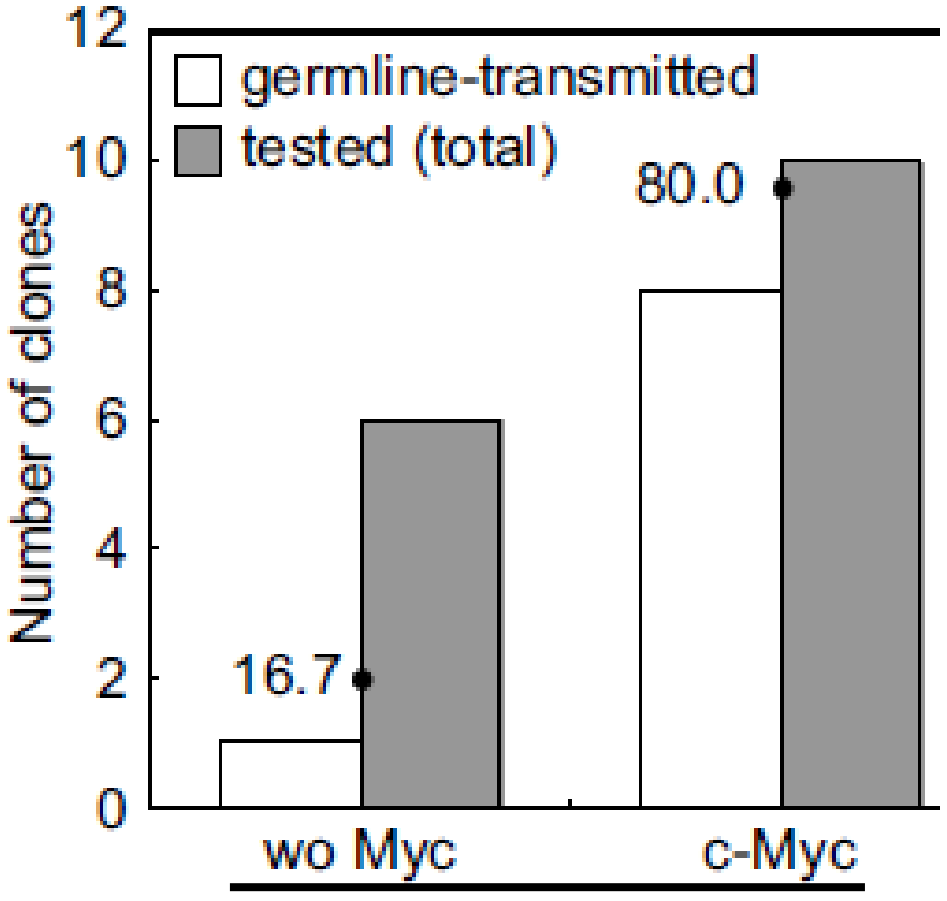
Positive effects of cMyc

Efficiency↑



Nakagawa and Koyanagi et al. et al., Nat. biotech 2007

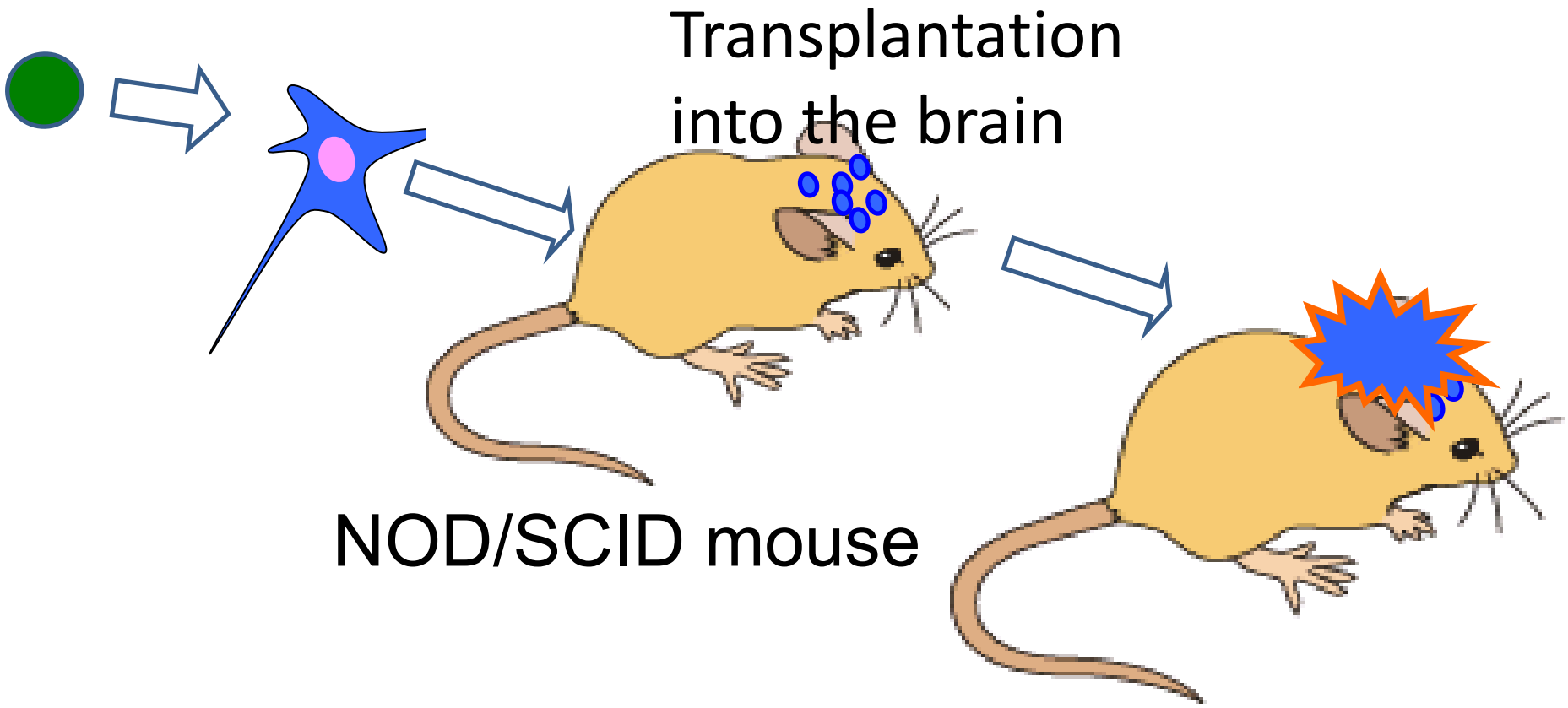
Germline competency↑



Nakagawa et al. et al., PNAS 2010

Mouse iPS cell→neurosphare→transplant

In vitro diff. to neuron



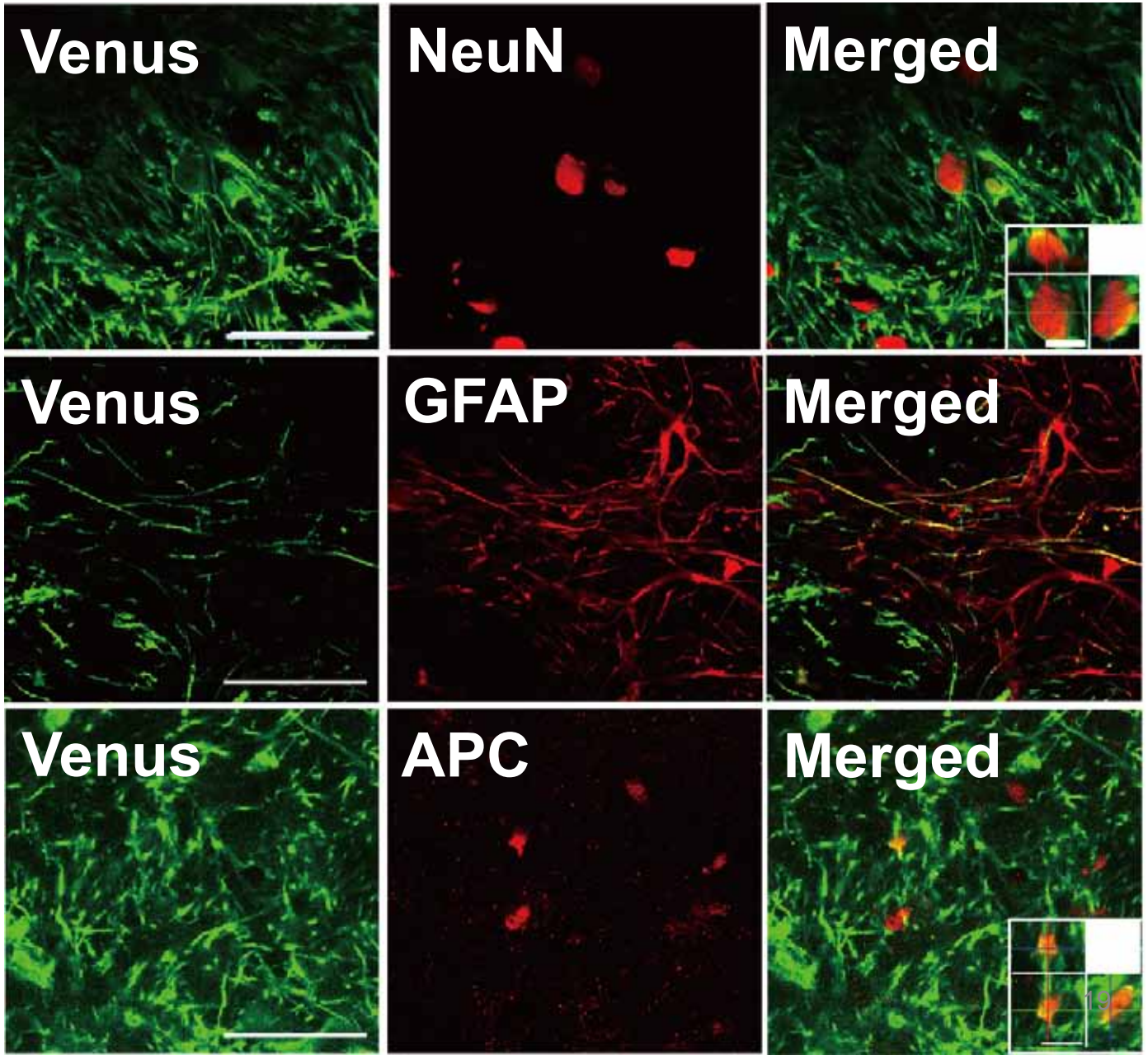
K. Miura Nat.biotech

iPS cells contributes to the CNS

Mature Neuron

Astrocyte

Oligo-dendrocyte



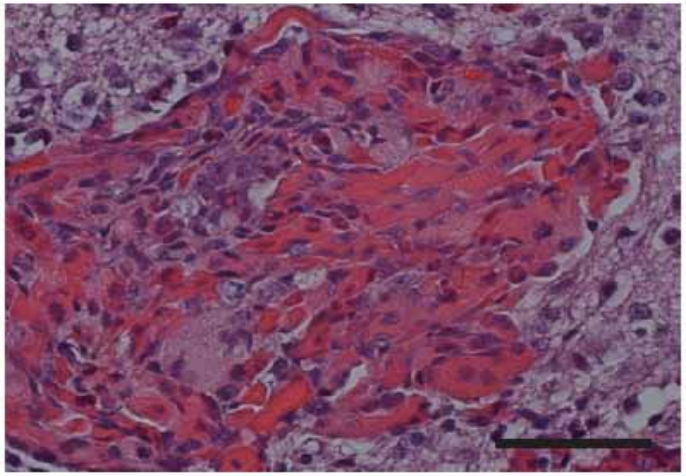
Tumor in recipient mice

After 4 weeks

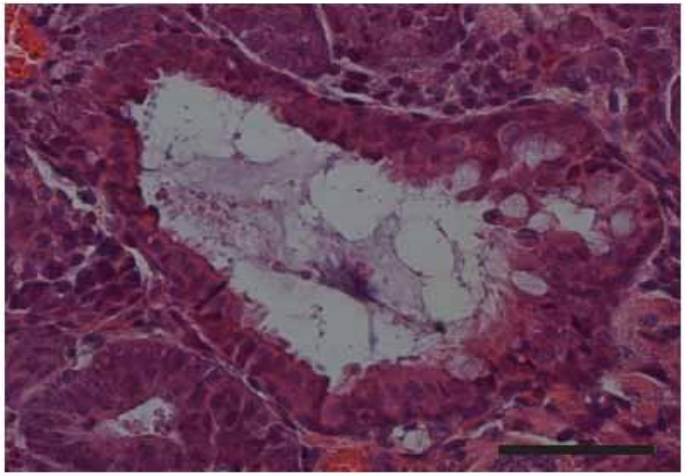
K. Miura Nat.biotech

Tumor = teratoma

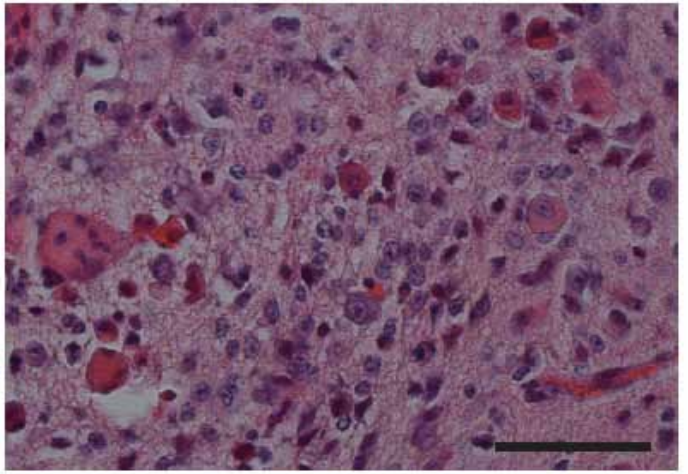
Muscle

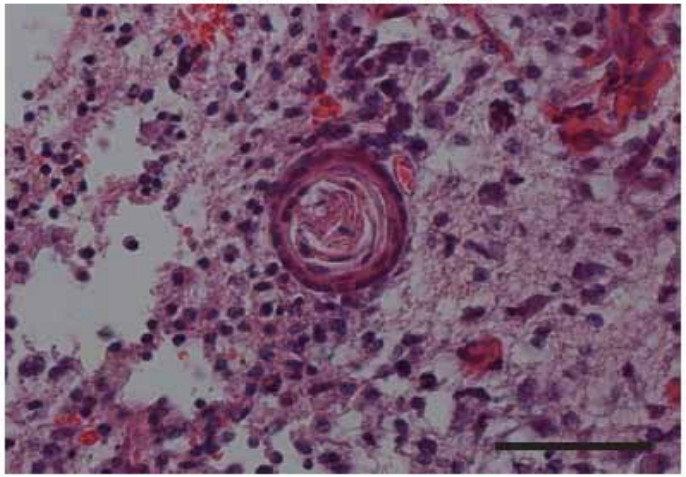


Duct

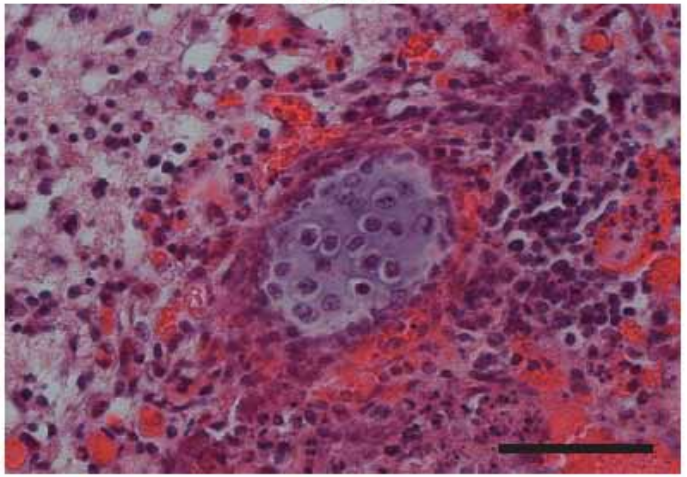


Neural cells

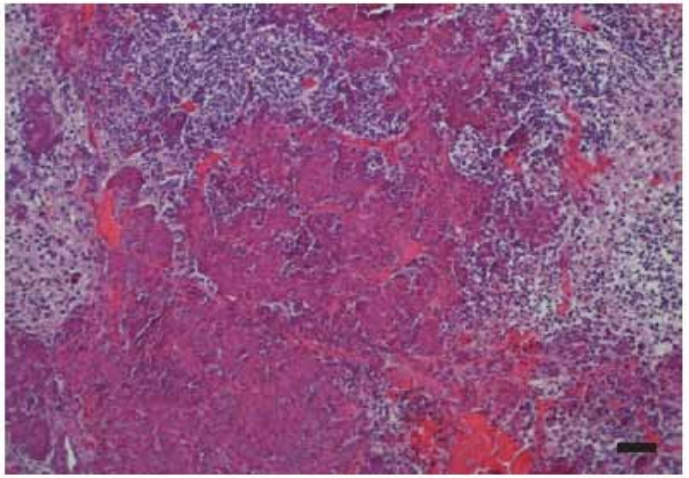




Keratinized epithelium

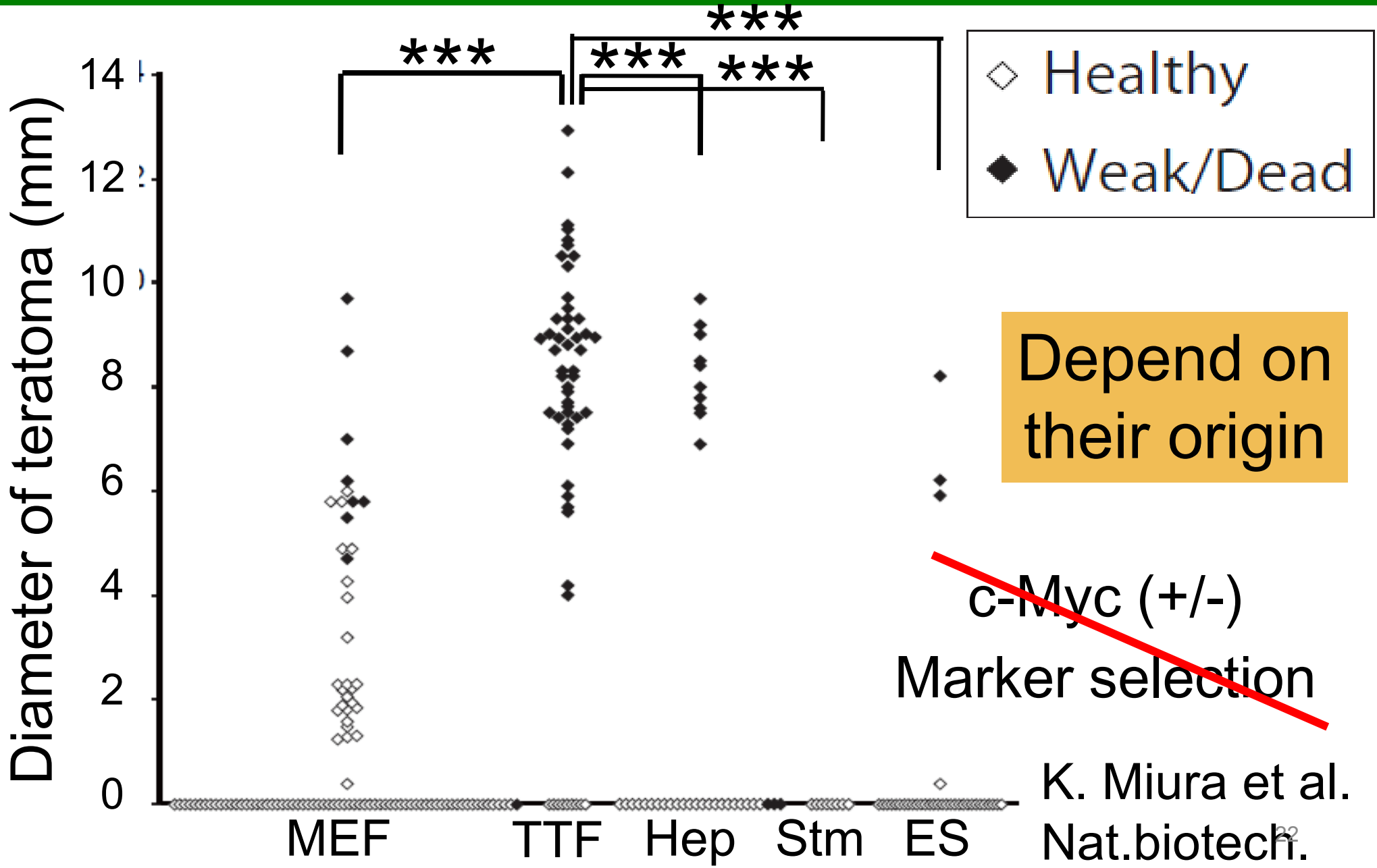


Cartilage



Undifferentiated cells

Diameter of teratoma



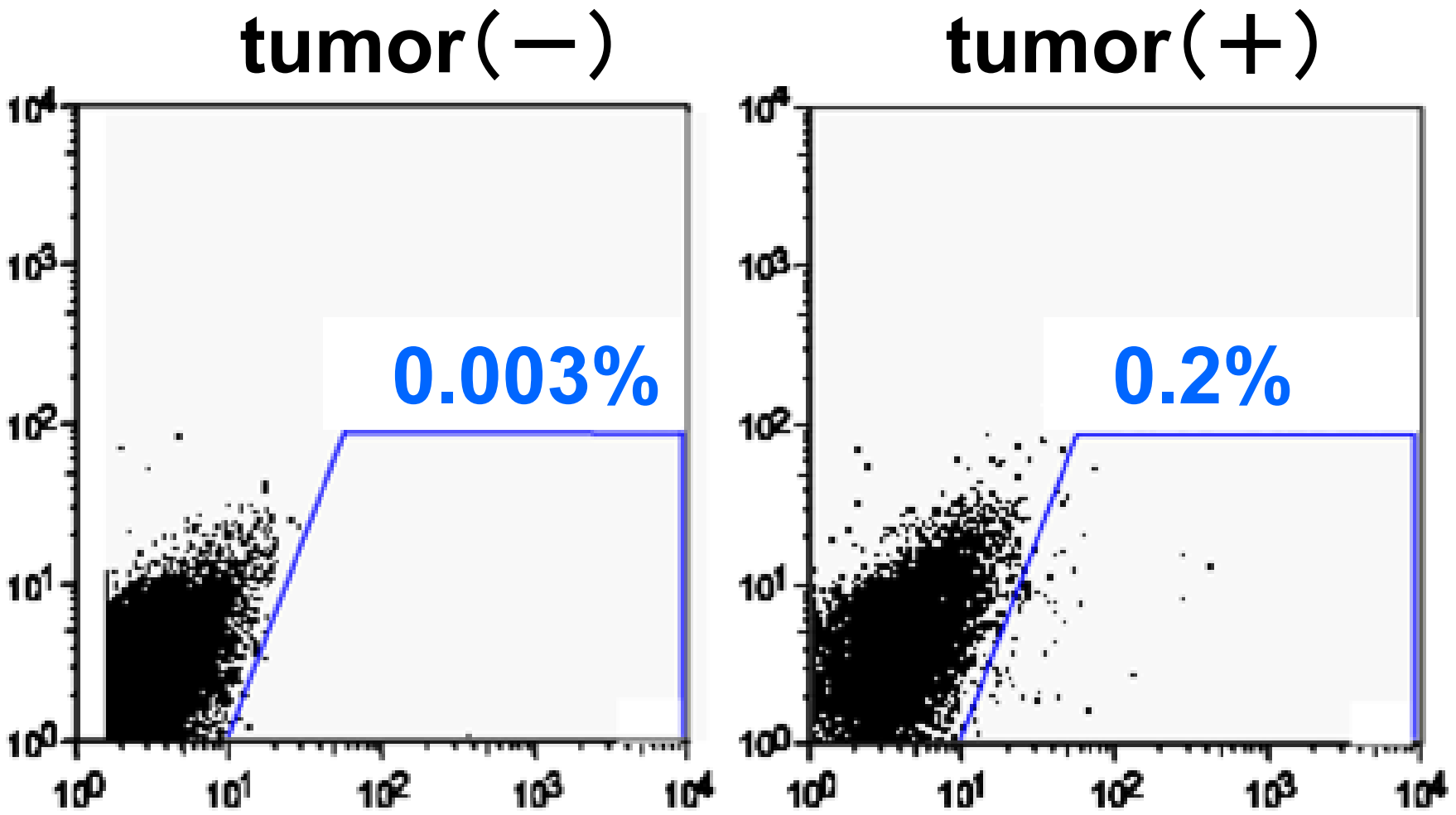
Depend on their origin

~~c-Myc (+/-)~~

Marker selection

K. Miura et al. Nat.biotech.

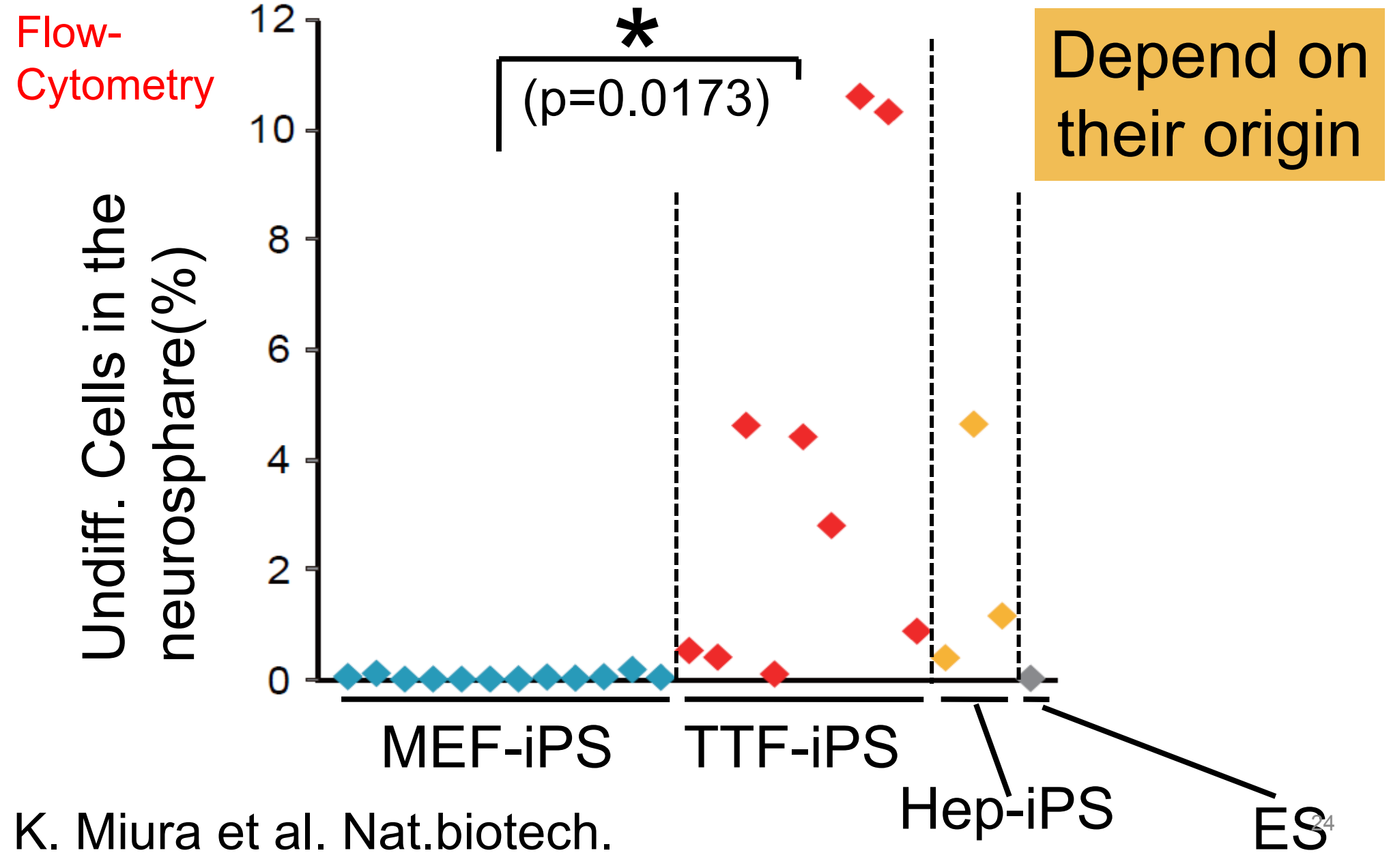
Tumorigenecity depend on undiff. cells in neuroshare



Nanog-EGFP (undiff. cell) →

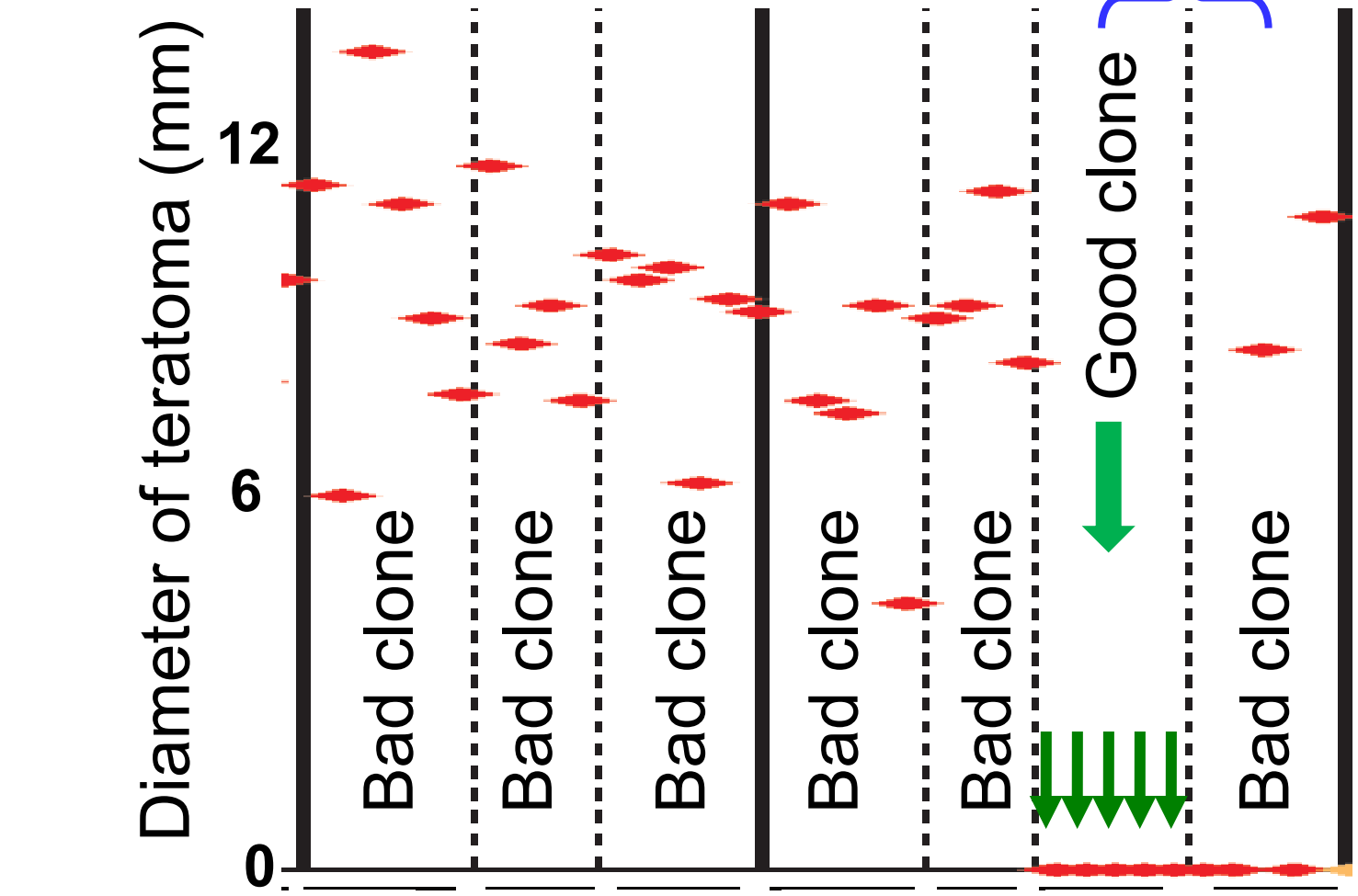
K. Miura et al. Nat.biotech.

Proportion of Undiff. Cells depend on origin of iPS



K. Miura et al. Nat.biotech.

Generated from the same dish



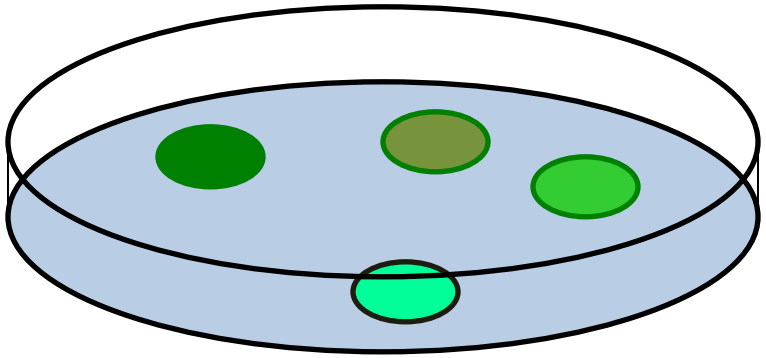
Generated with the same methods

K. Miura et al.
Nat.biotech.

Variation of iPS cells of a single donor.

Different method ⟹ Different propensity

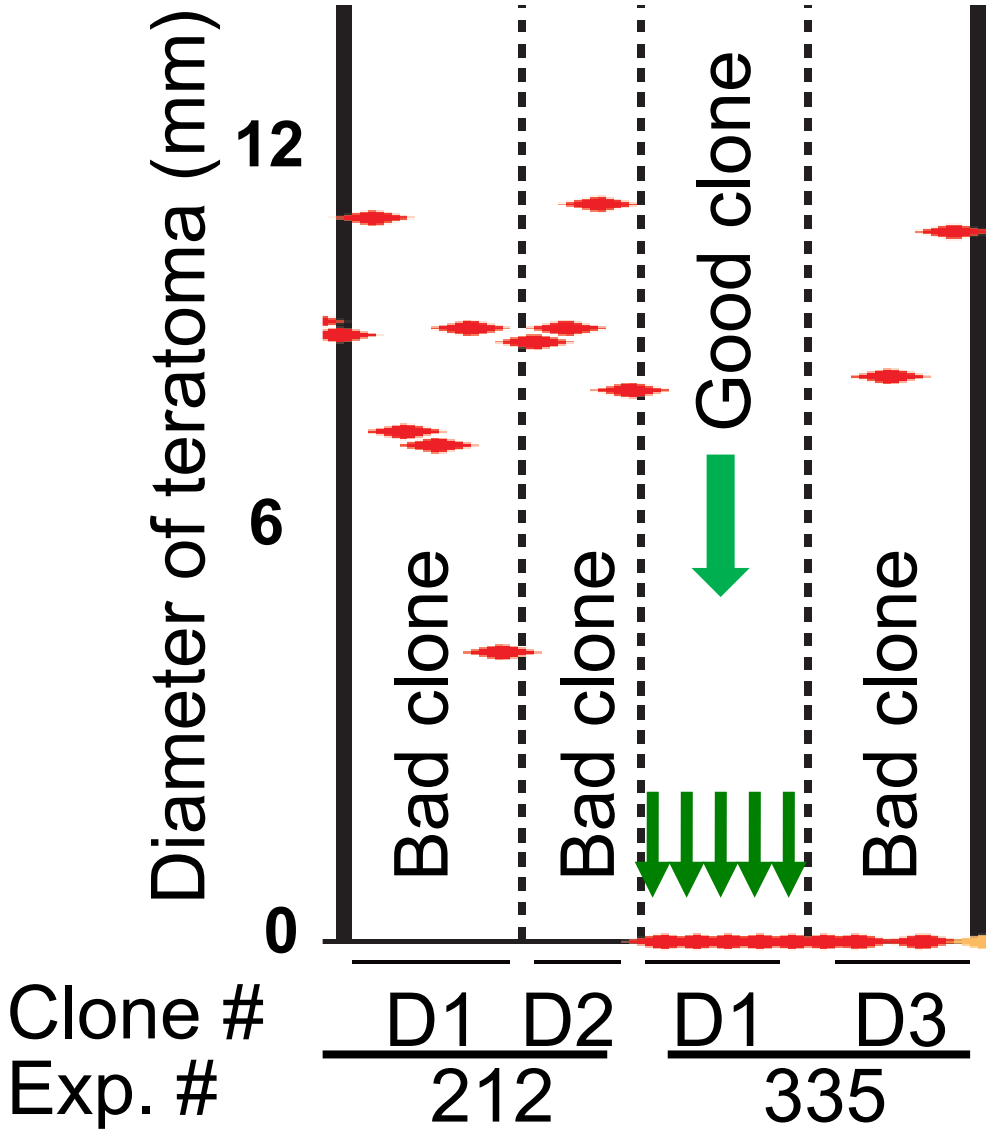
Same method
From a single dish ⟹ Different propensity among clones



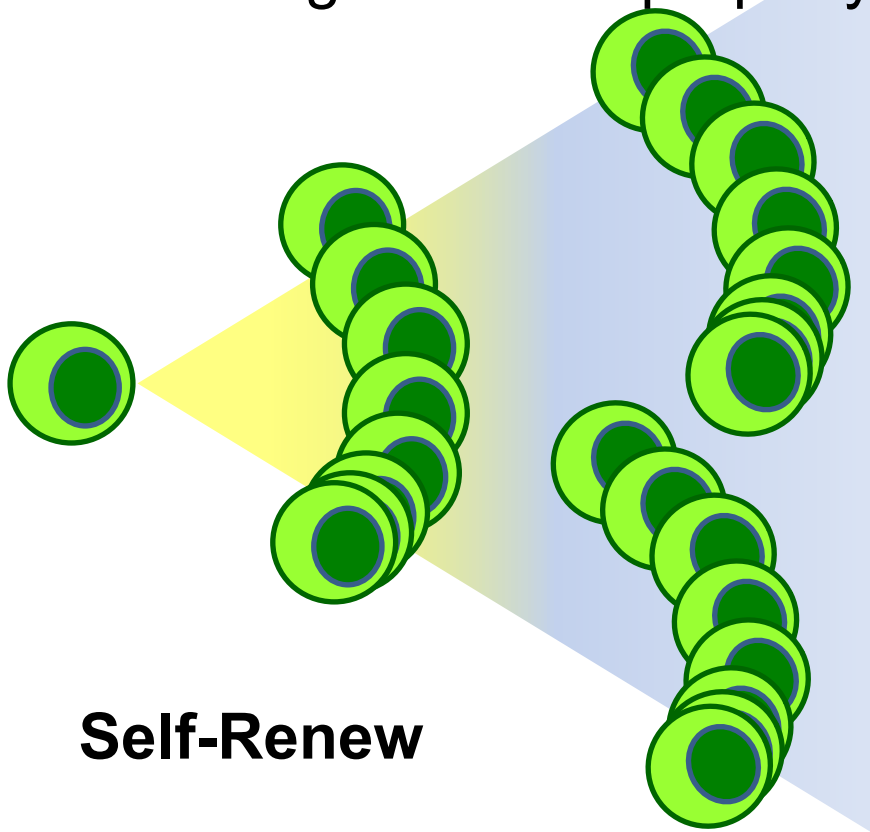
Strategy to select good clones is important!

Once we obtain a “good” clone,
we can obtain “good” iPS cells in large lot

⇨ ***iPS Bank***



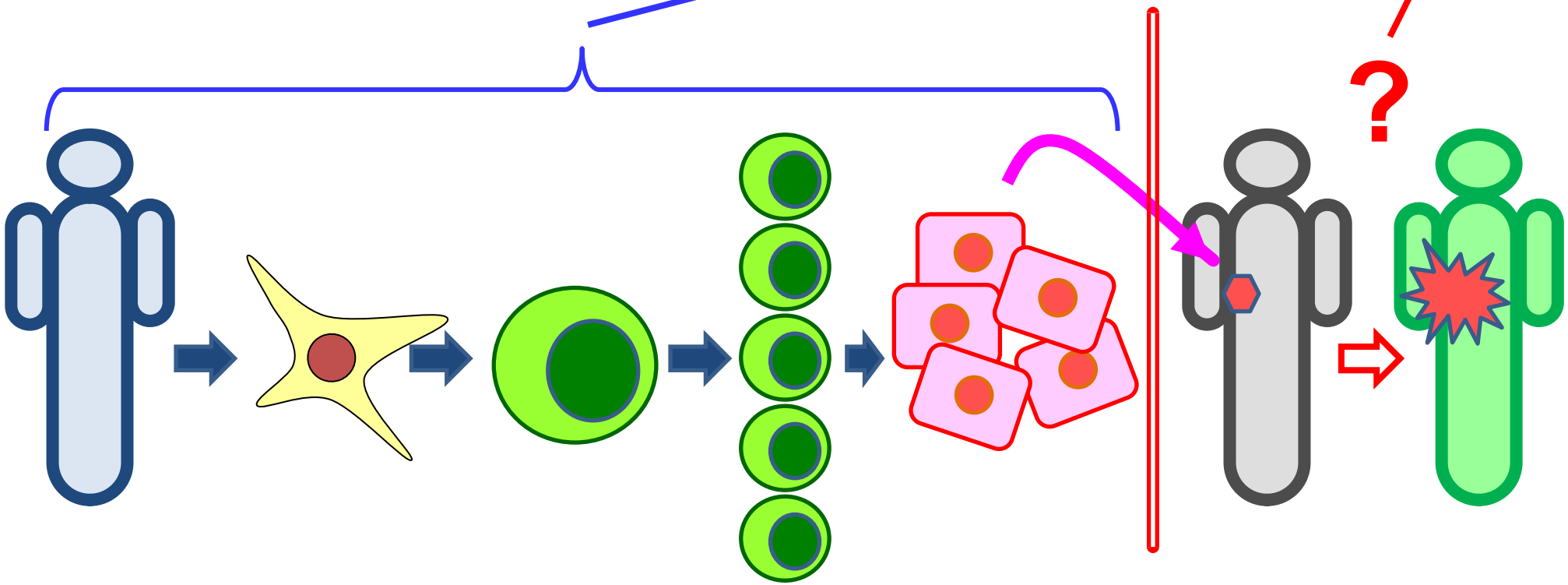
Infinite proliferation
maintaining the same property



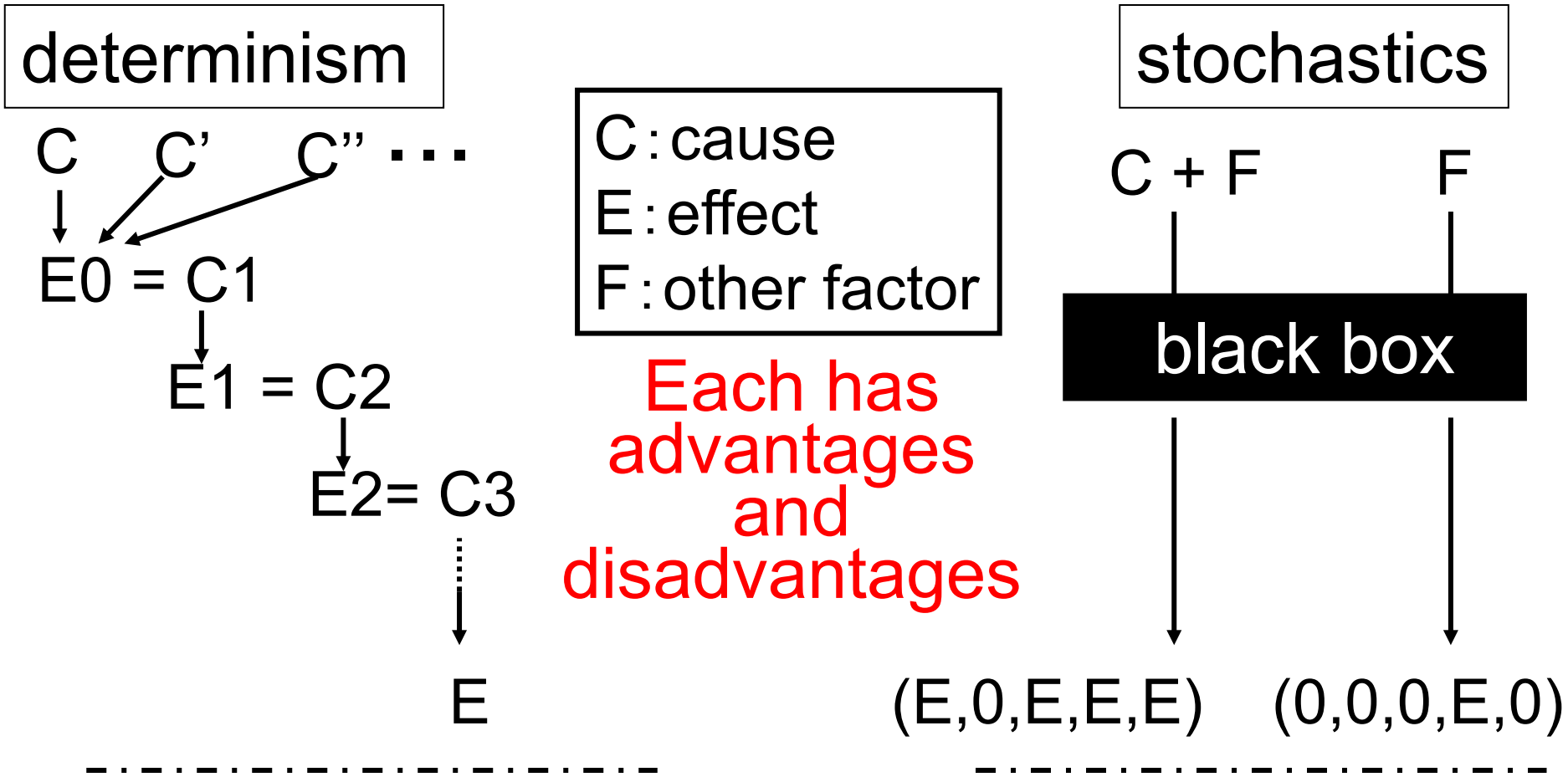
K. Miura et al.
Nat.biotech.

What is “Good” iPS cell in cell therapy?

How to Judge in Non-clinical evaluation?



Two Paradigms to judge “good iPS”



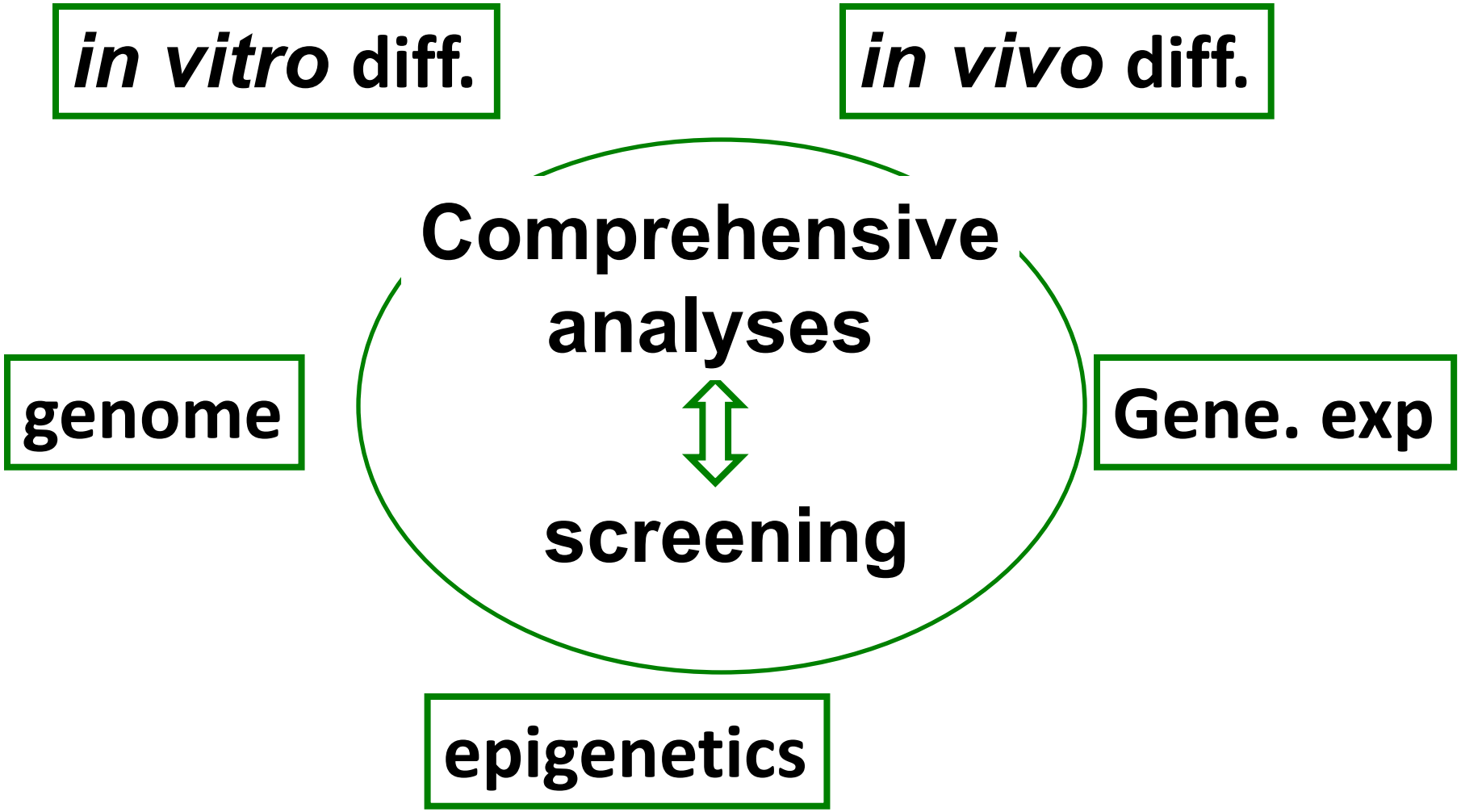
Genomics **Epigenetics**

Gene expression

chimera

transplantation

Evaluation of iPS cells and their derivatives



Summary

- **iPS cell therapy consists of many processes and spends long time.**
- **Methods to generate iPS cells affect their quality (e.g., two-sided effect of c-Myc, impact of origin)**

  ⇒ ***Optimization of generation methods***
- **Even iPS clones with the same genetic background and generated with the same methods vary in quality**

  ⇒ ***Optimization of selection methods***
- **Selected iPS cells can be manufactured in large scale.**
- **Well-managed comprehensive evaluations should be required to select "good" iPS cells**

Aknowlegement

CiRA

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