



Emerging Issues in Human Embryonic Stem Cell Research

The National Academy of Science, November 7-8, 2006

**Alternative methods for deriving
"Embryonic stem cells"**

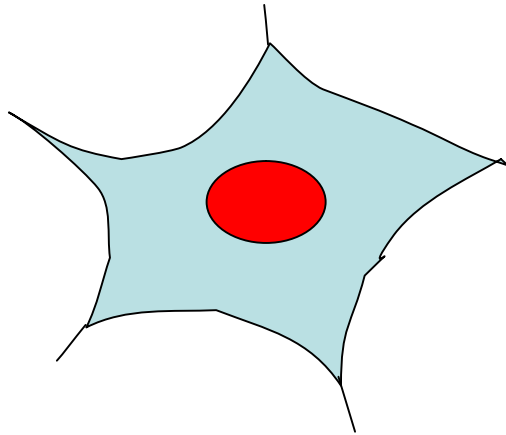
**Induction of pluripotency
in somatic cells**

Kyoto University, Japan

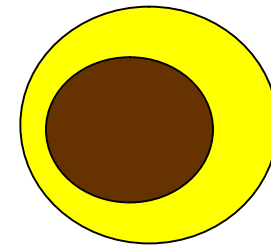
Shinya Yamanaka

Induction of Pluripotent Stem Cells

Patient's somatic cells



**ES-like
Pluripotent stem cells**

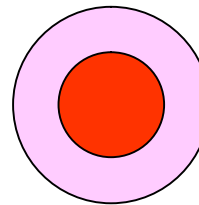
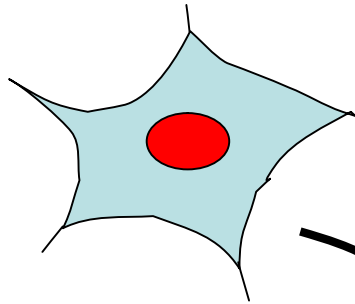


**Pluripotency-inducing factors
(PIF)**

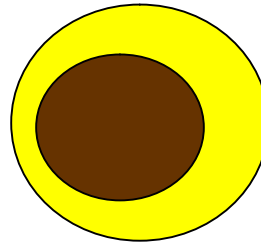
ES Cells Have PIF

Somatic cells

ES cells



fusion



ES-like cells

Our Hypothesis

PIF in ES cells

||.

**Factors that maintain pluripotency
and proliferation in ES cells**

Candidates of PIF

Group 1

Oct3/4, Sox2, Nanog

ES cell-specific transcription factors

Essential for pluripotency
in ES cells and early embryos

Candidates of PIF

Group 2

Tcl1, Stat3, c-Myc, ERas....

(proto)oncogenes

Important for proliferation of ES cells,
but not in early embryos

Candidates of PIF

Group 3

ECAT1, Esg1, Fbx15, Klf4.....

less famous

Specifically expressed in ES cells
and/or

Important roles in ES cells

Candidates of PIF

24 factors

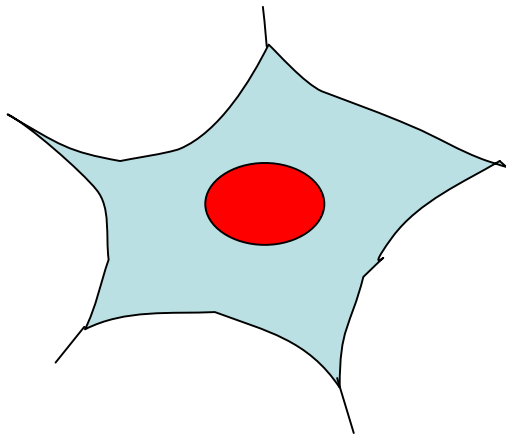
Group 1: Oct4, Sox2, Nanog

Group 2: Tcl1, Stat3, c-Myc, ERas....

Group 3: ECAT1, ESG1, Fbx15, Klf4....

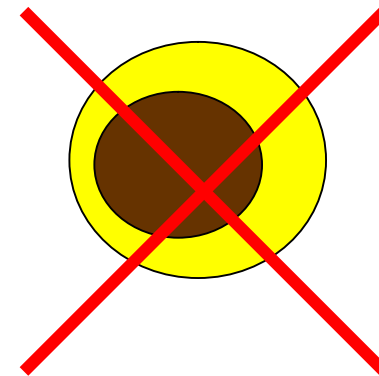
Can induce pluripotency?

Evaluation of PIF Candidates



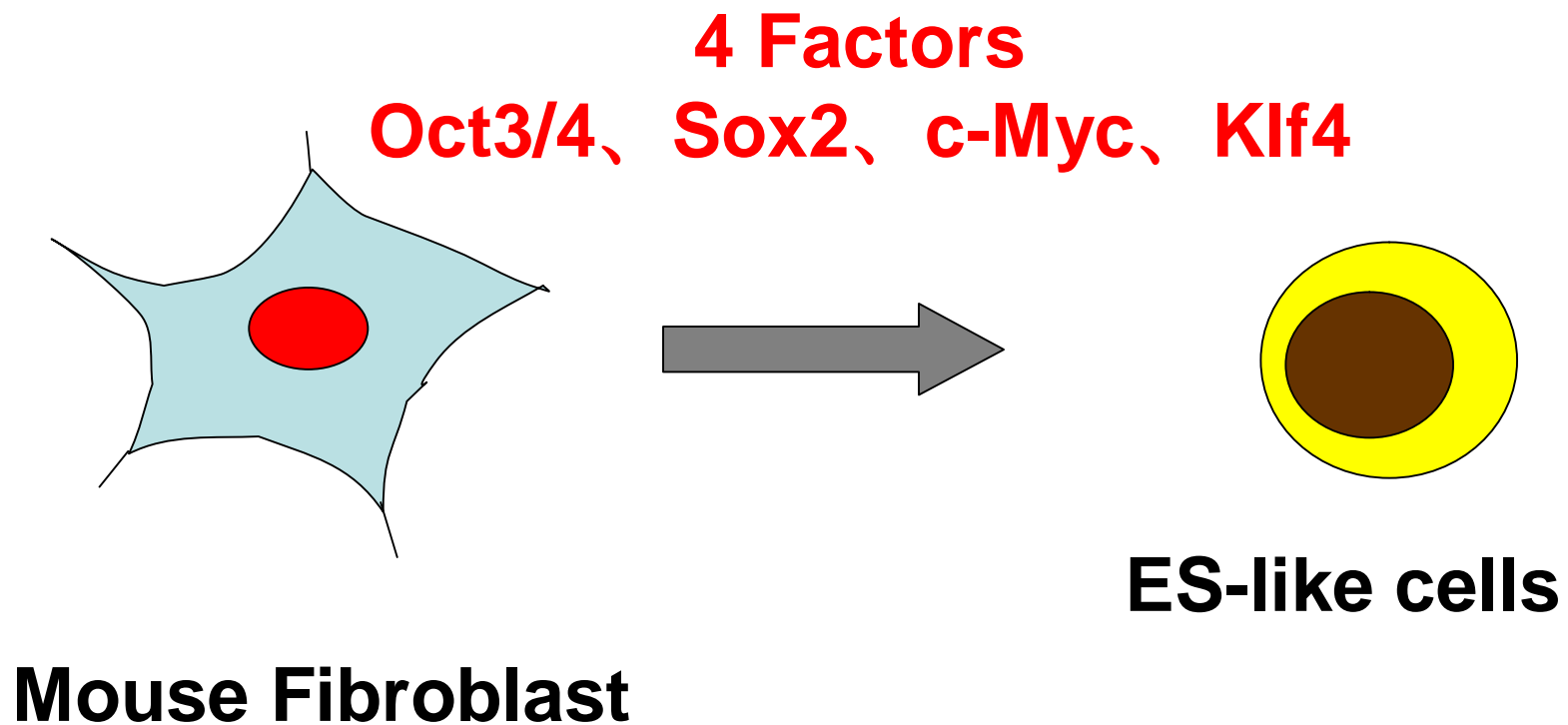
Mouse Fibroblast

**Single
factor**



ES-like cells

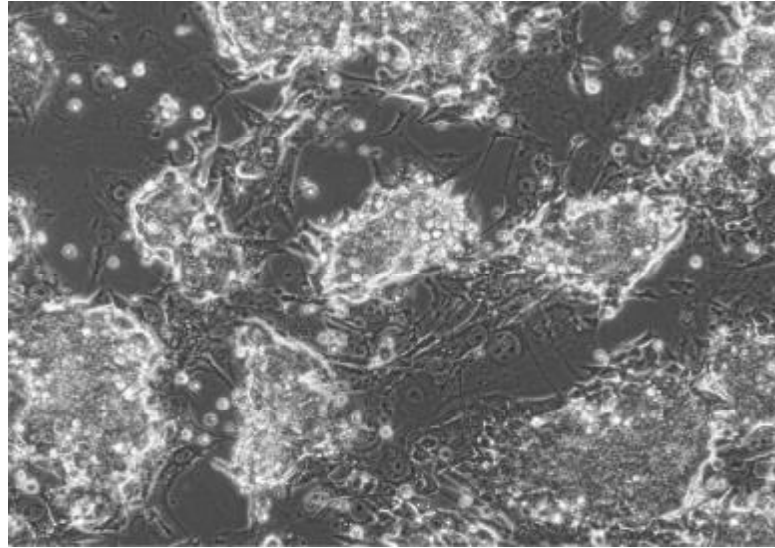
Evaluation of PIF Candidates



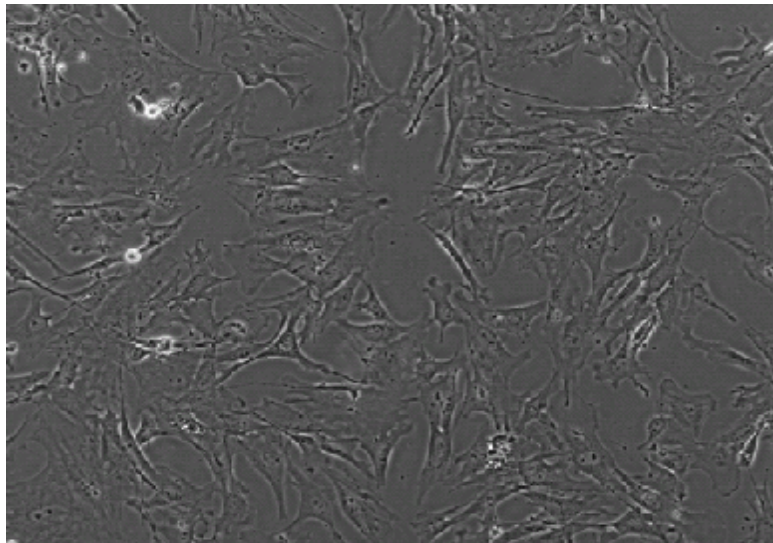
iPS cells
(Induced pluripotent stem cell)

iPS Cells: ES-like Morphology

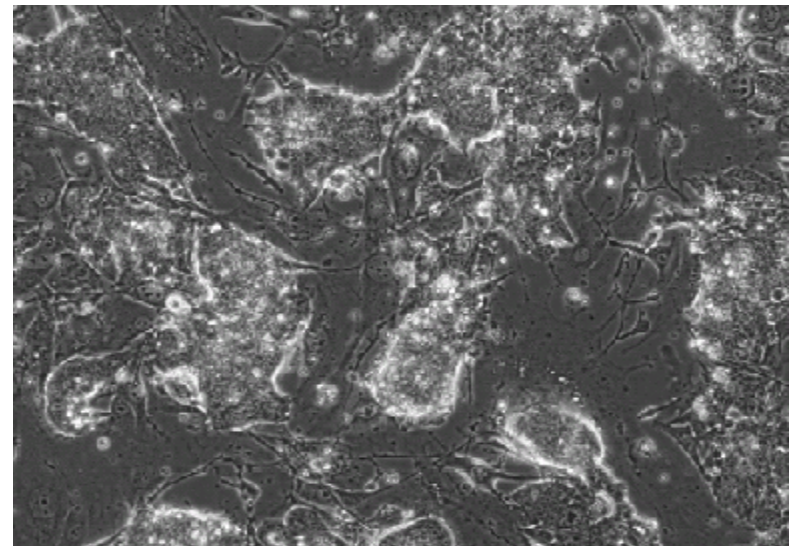
iPS



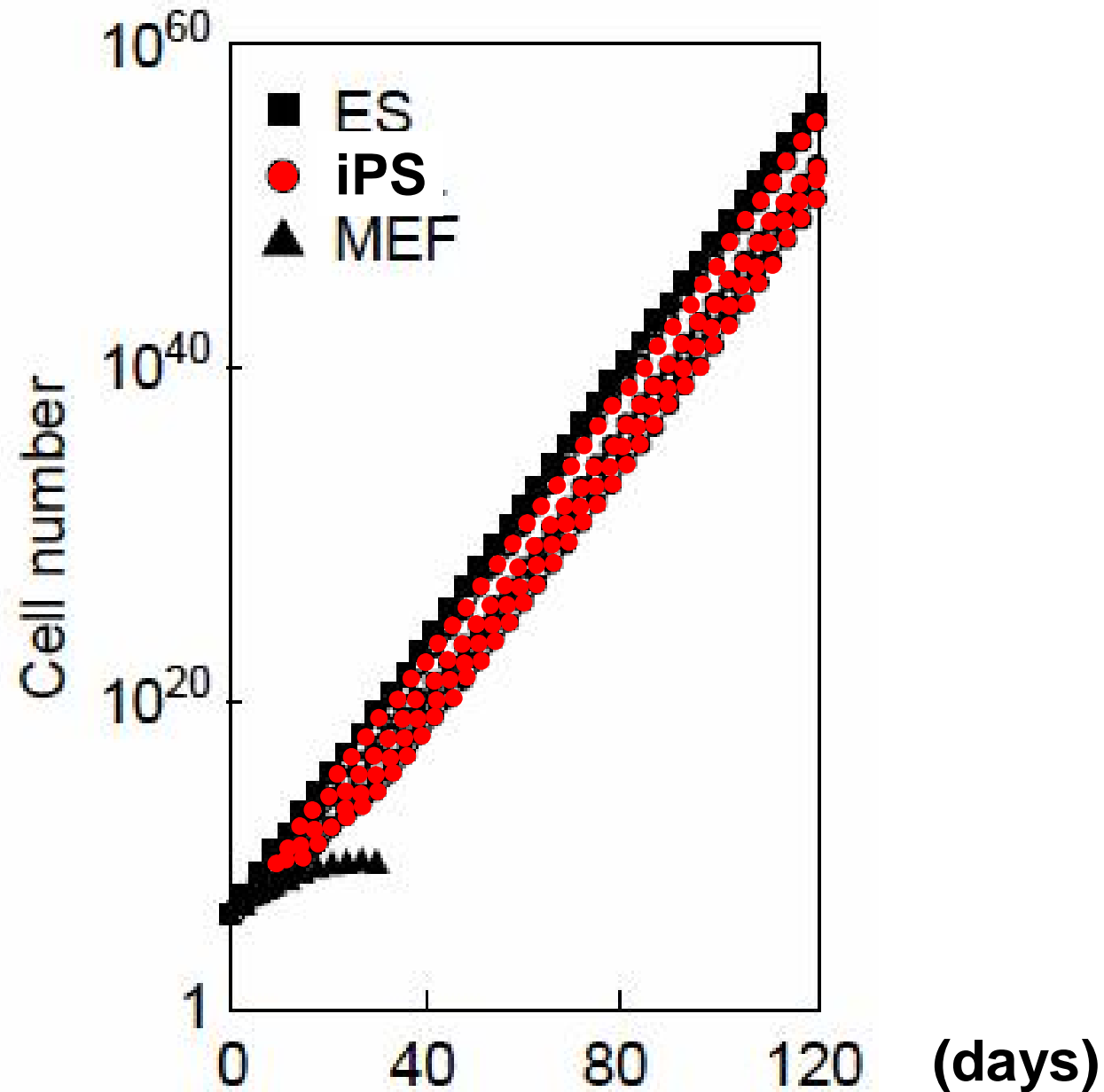
MEF



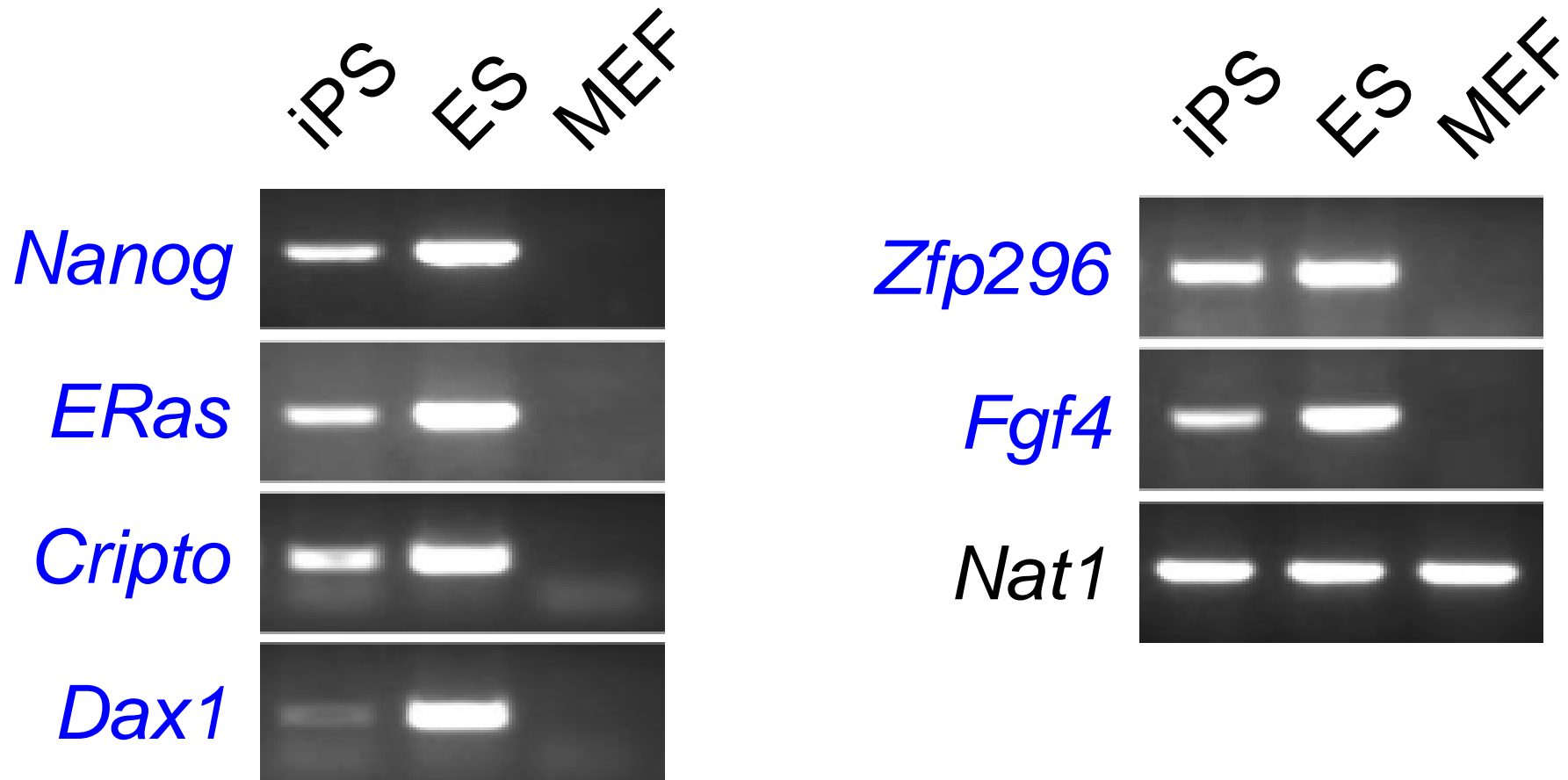
ES



iPS Cells: ES-like Proliferation



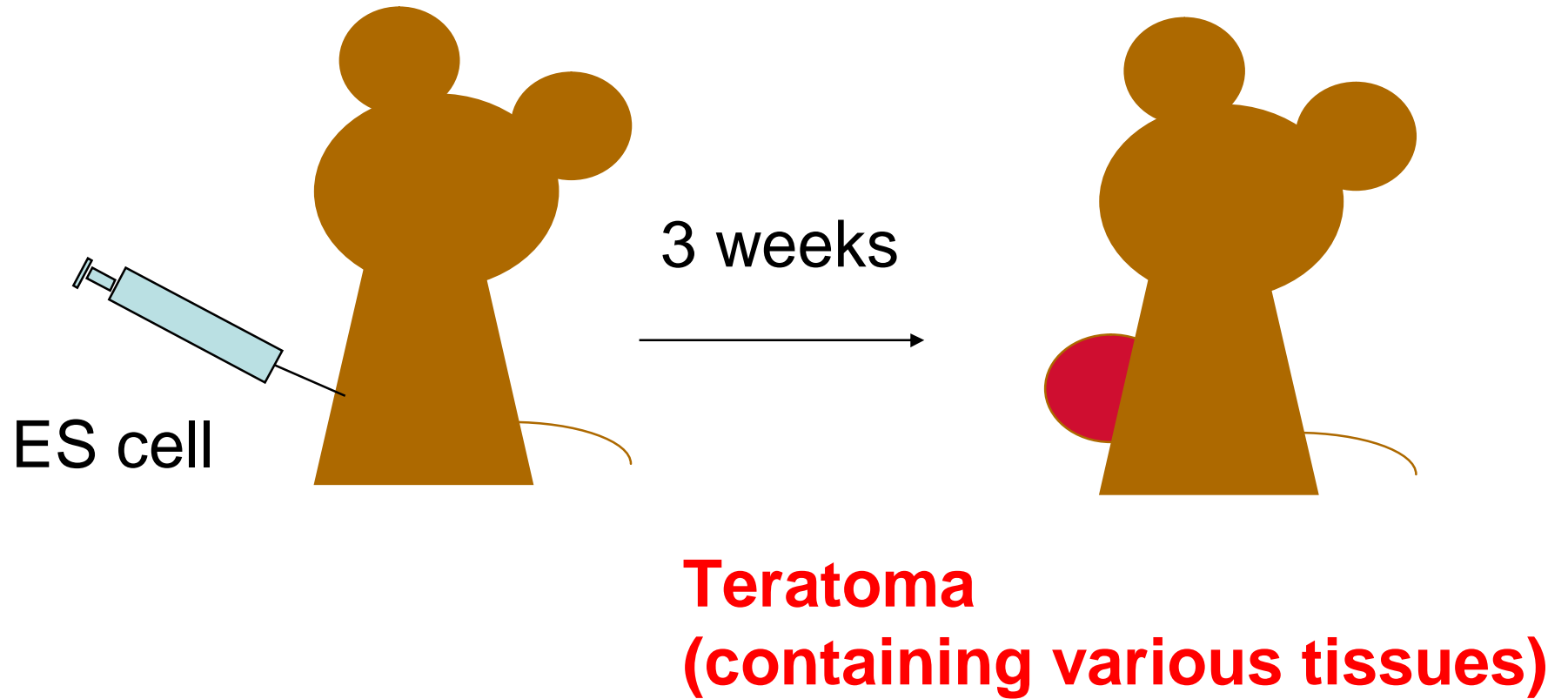
iPS Cells: ES-like Gene Expression



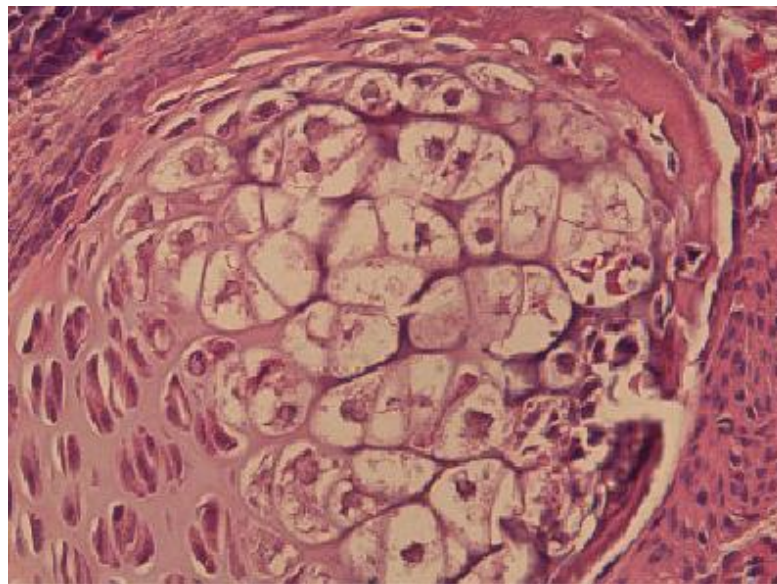
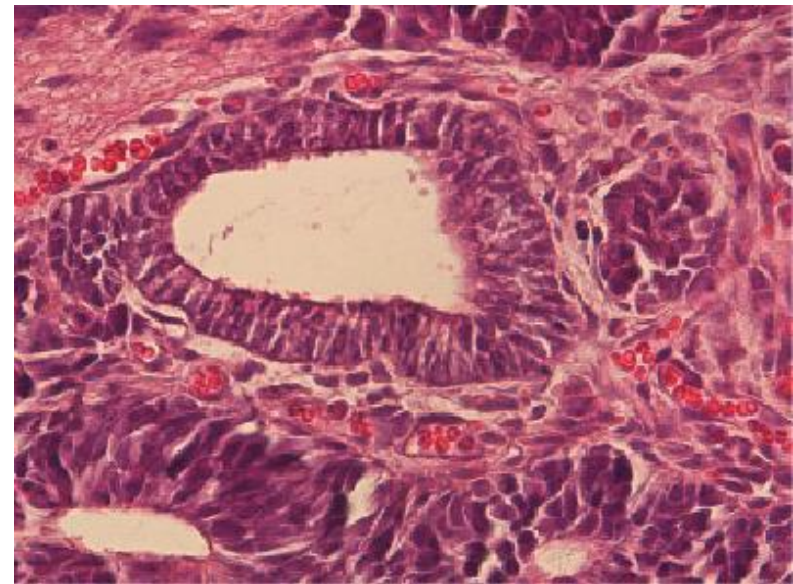
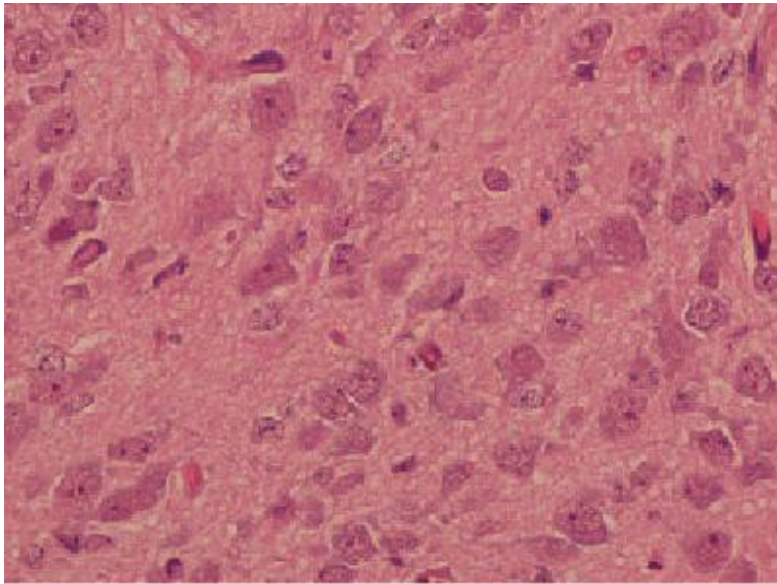
Pluripotency?

Teratoma

Immuno-deficient mice



iPS cells: ES-like pluripotency



Neural
tissue

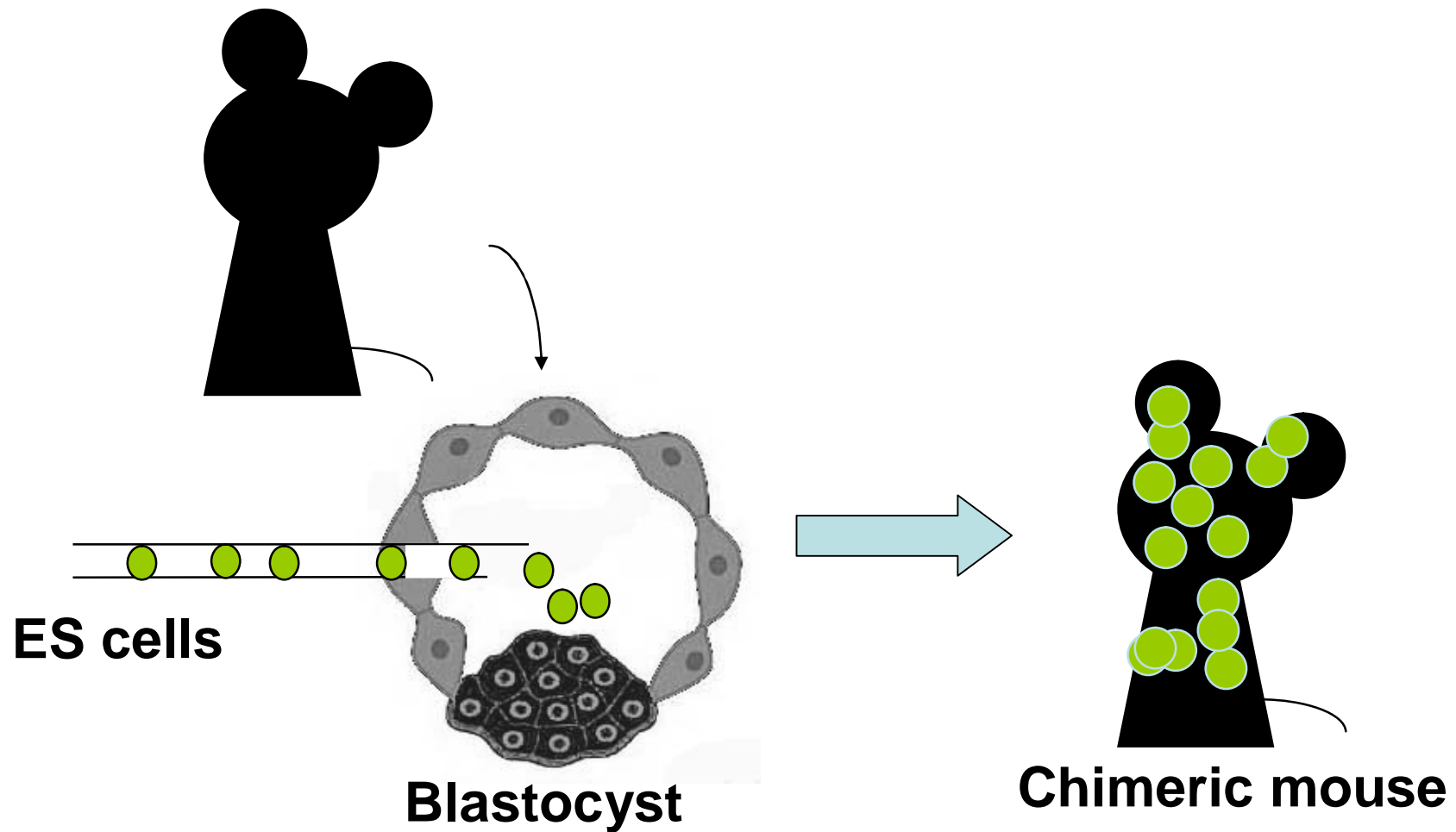
Gut-like
tissue

Cartilage

Teratoma

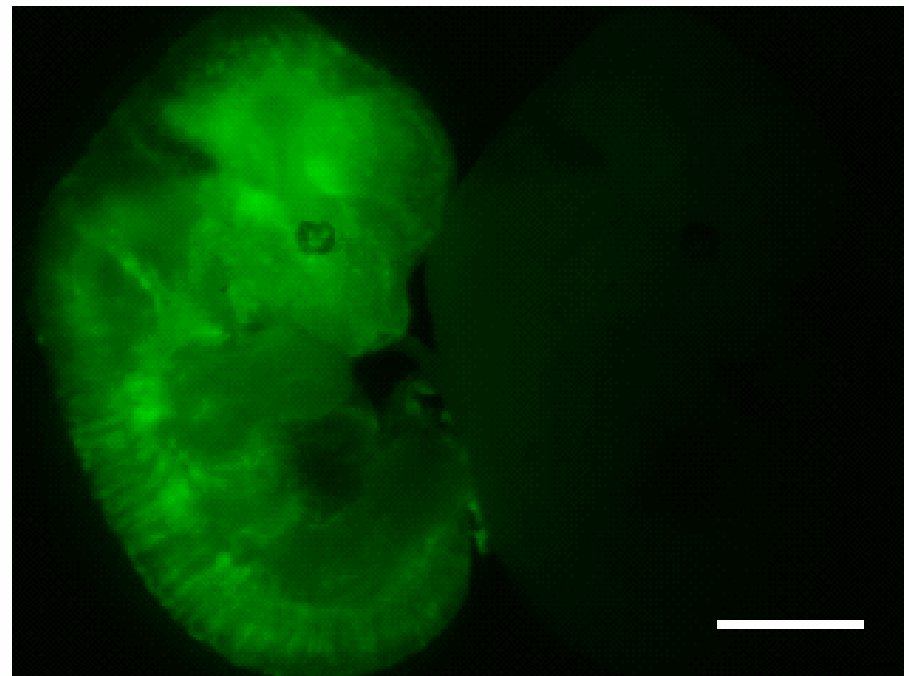
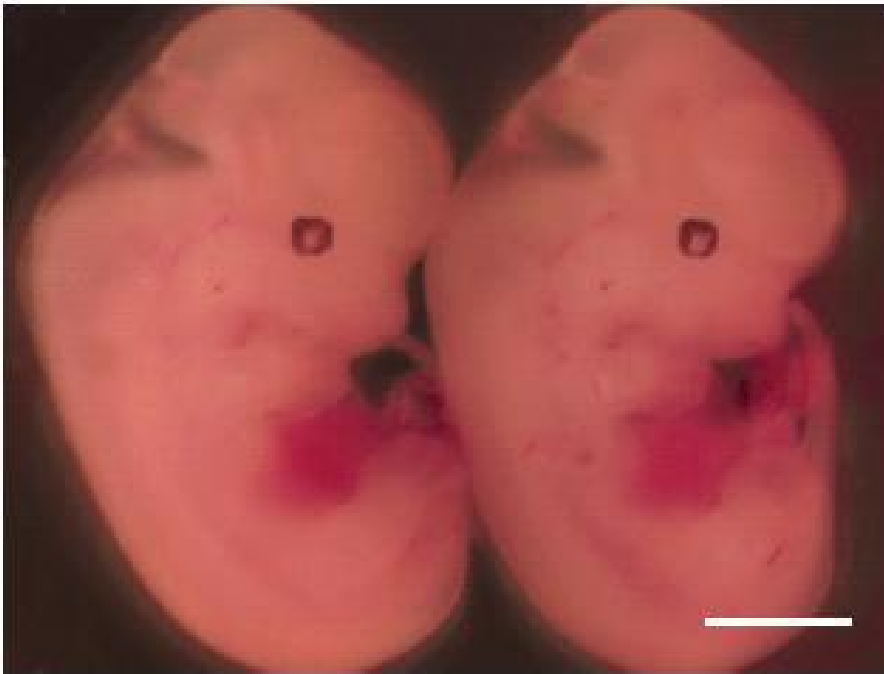
Pluripotency?

Chimeric mice

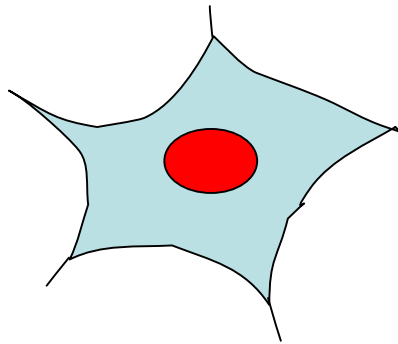


iPS cells: ES-like pluripotency

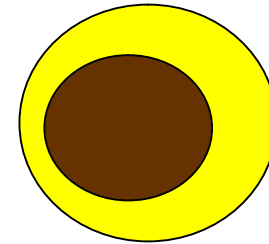
Chimeric Embryos



Summary



4 factors



Mouse fibroblast cultures

iPS cells

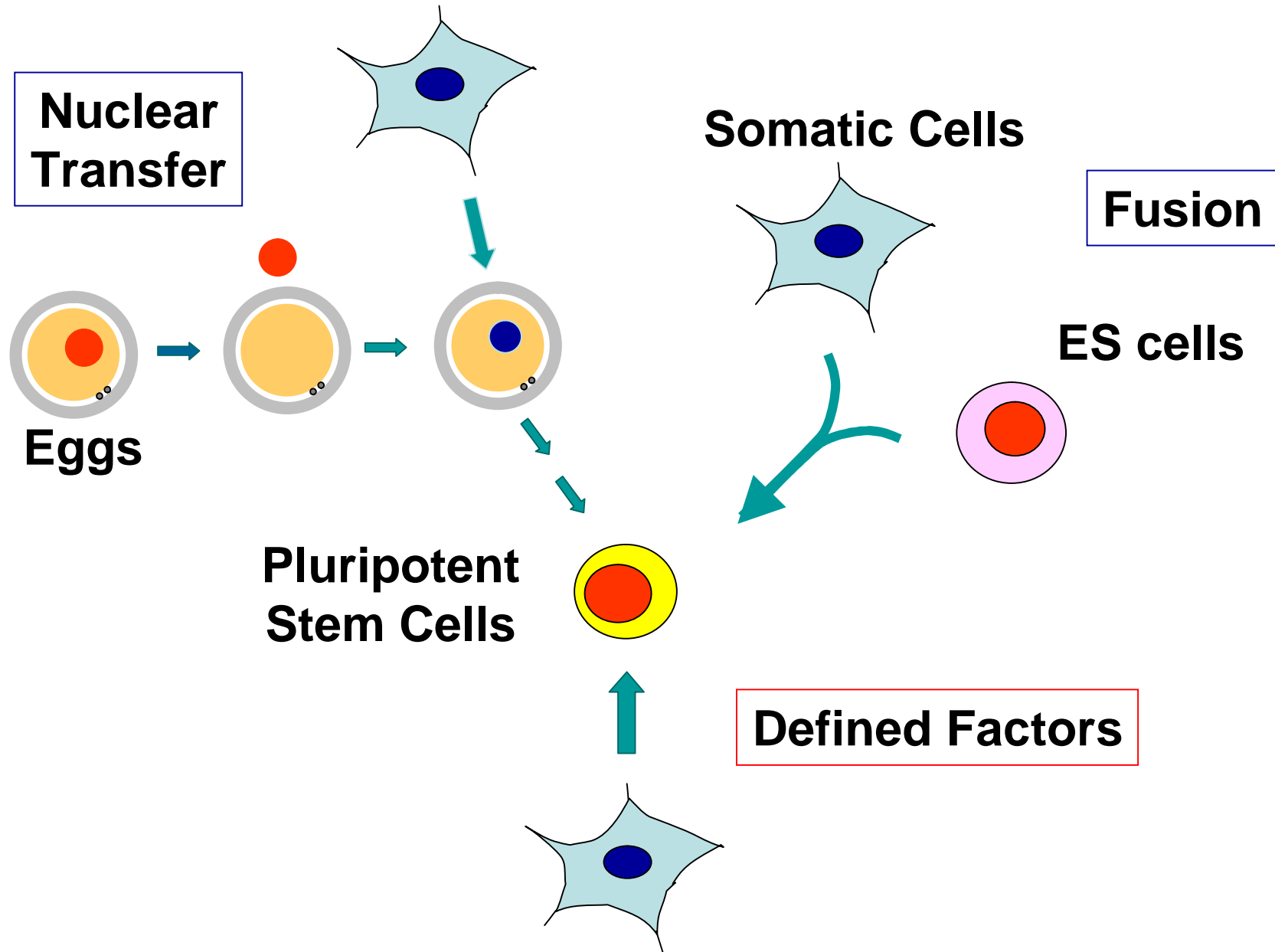
Low efficiency (<0.1%)

Tissue stem cells?

Insertion of retroviruses?

Appropriate expression levels?

The Third Methods



Comparison to Other Methods

	Eggs or Embryos	Human	Tumor	
Nuclear Transfer	+	?	+	Human cloning
Fusion	+	+	++	tetraploid
iPS Cells	-	?	++	retrovirus c-Myc

Blue: Pros **Red: Cons**

Acknowledgement

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