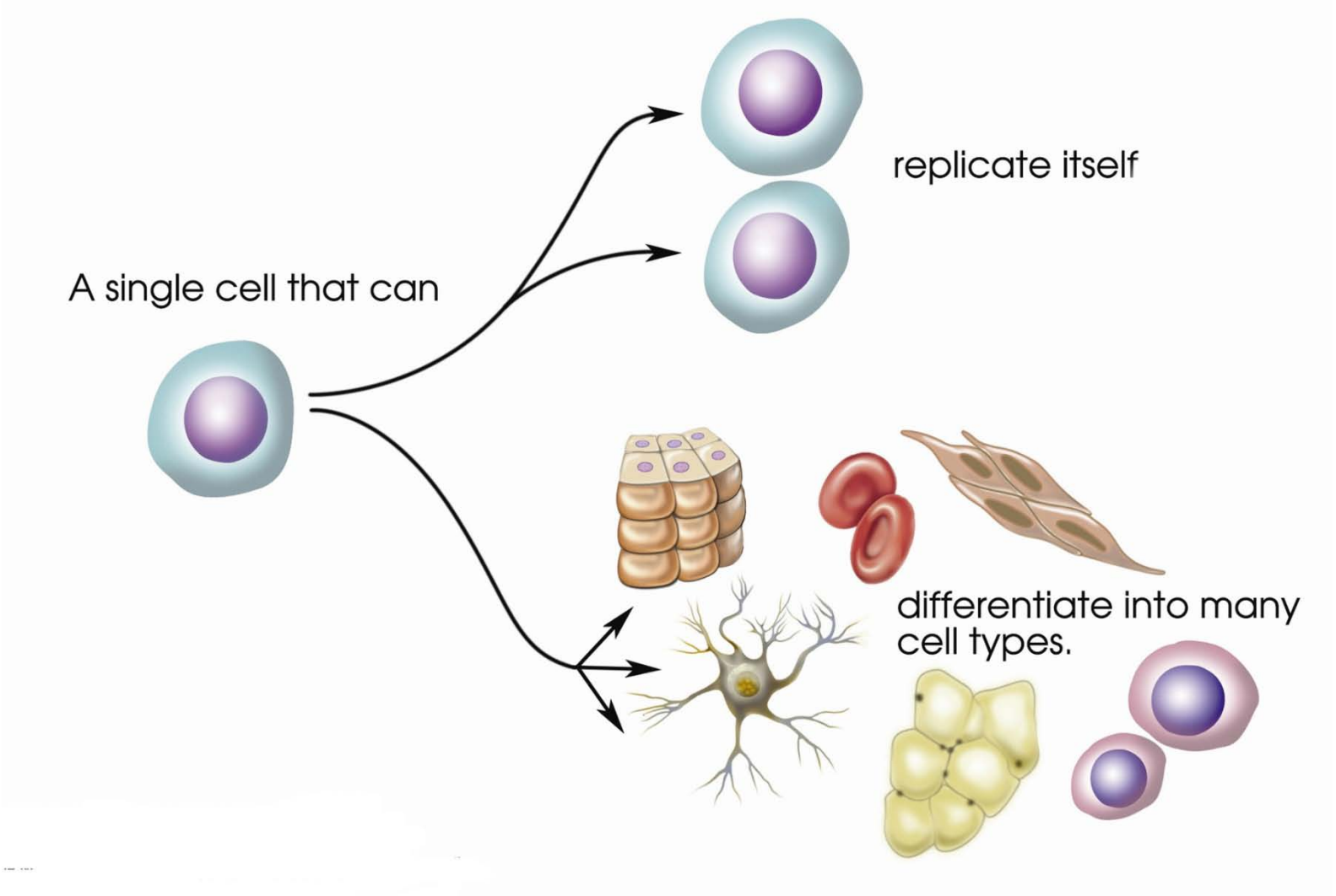
Stem cells & gene therapy

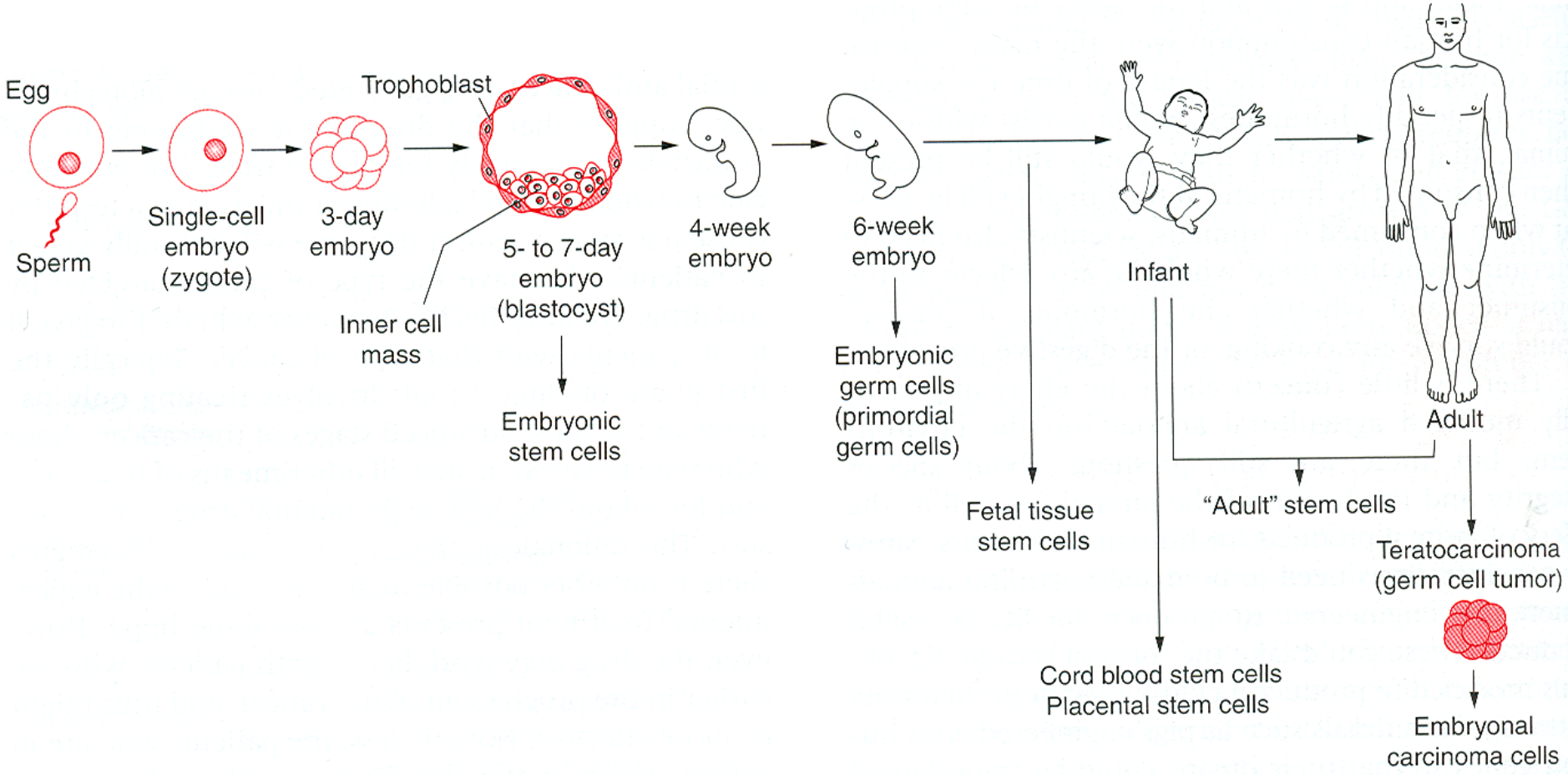
Lecture 14

23th January 2012

What is a stem cell?



Sources of stem cells



Embryonal

Adult

Classification of SCs

1. Based on the tissue commitment/ differentation capacity

- Totipotent SCs - zygote
- Pluripotent SCs
- Multipotent SCs
- Unipotent SCs (Tissue progenitors)

2. Based on their origin

- Embryonic SCs (ESCs)
- Fetal SC („adult" SC)
- Umbilical cord blood stem cells („adult")
- Postnatal - Adult SCs
- Reprogrammed SCs (Inducible Pluripotent SCs = iPS cells)

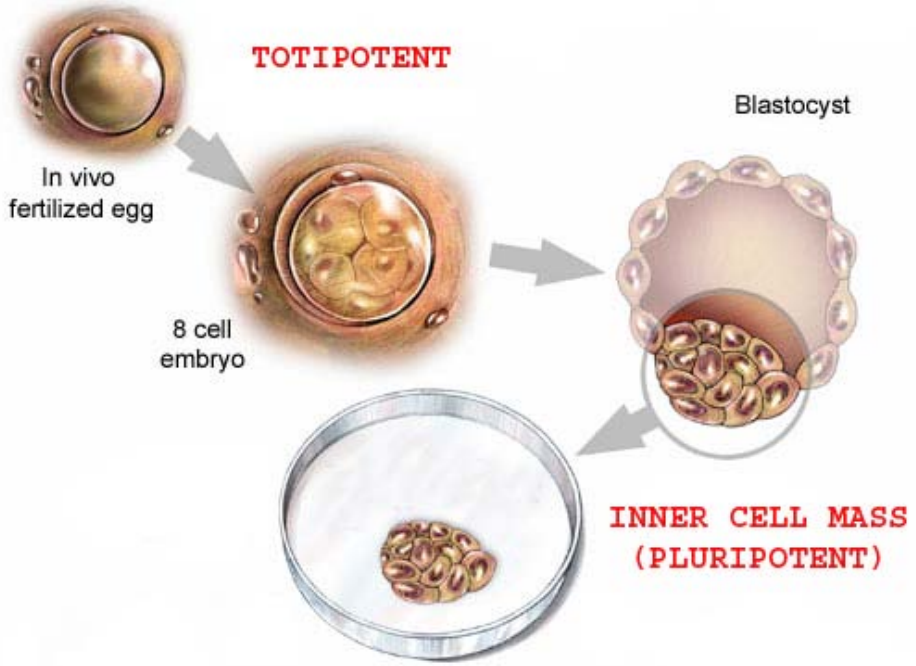
Stem cells

1. Embryonic stem cells (ESC)

2. Somatic („adult") stem cells
    - 2.1. Fetal, tissue specific stem cells
    - 2.2. Umbilical cord bloods stem cells
    - 2.3. bone marrow
        - 2.3.1. hematopoietic
        - 2.3.2. mesenchymal
        - 2.3.3. proangiogenic (endothelial) progenitor cells
    - 2.4. skin
    - 2.5. nervous (brain)
    - 2.6. intestine
    - 2.7. other adult, organ specific (heart, fat tissue)
    - 2.8. *embryonal carcinoma cells*

3. Tumor stem cells

What are embryonic stem cells?

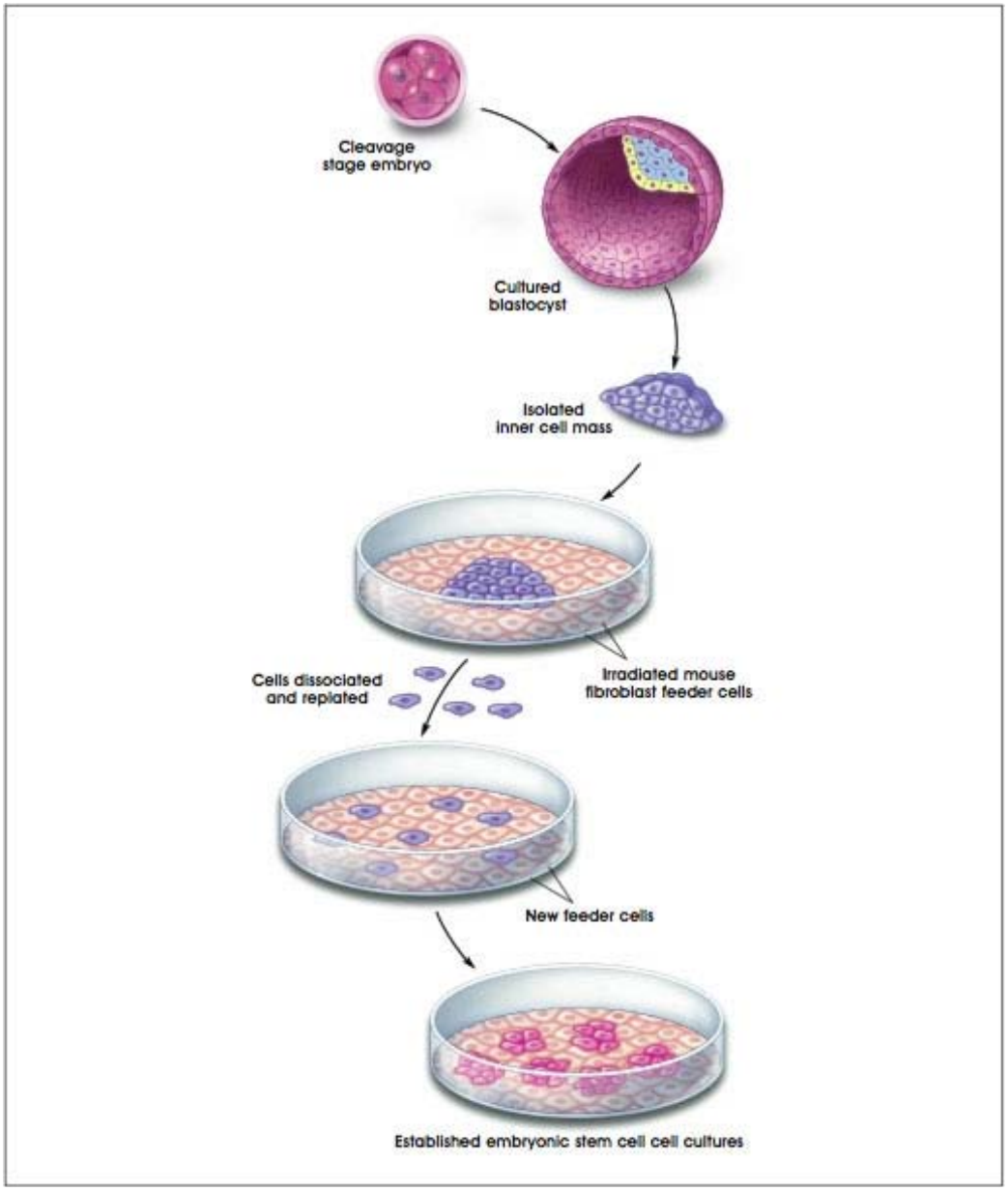


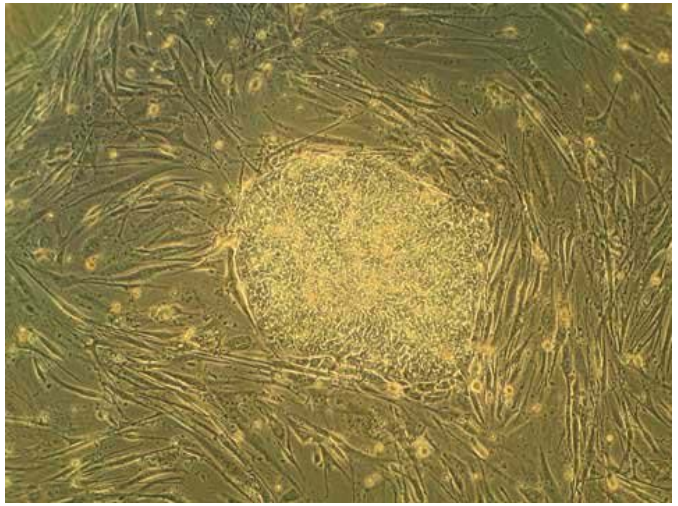
- develop from eggs fertilized in vitro

- derived from 4-5 days old embryos

- isolated from ~ 8 cell embryo or inner cell mass

Human embryonic stem cells



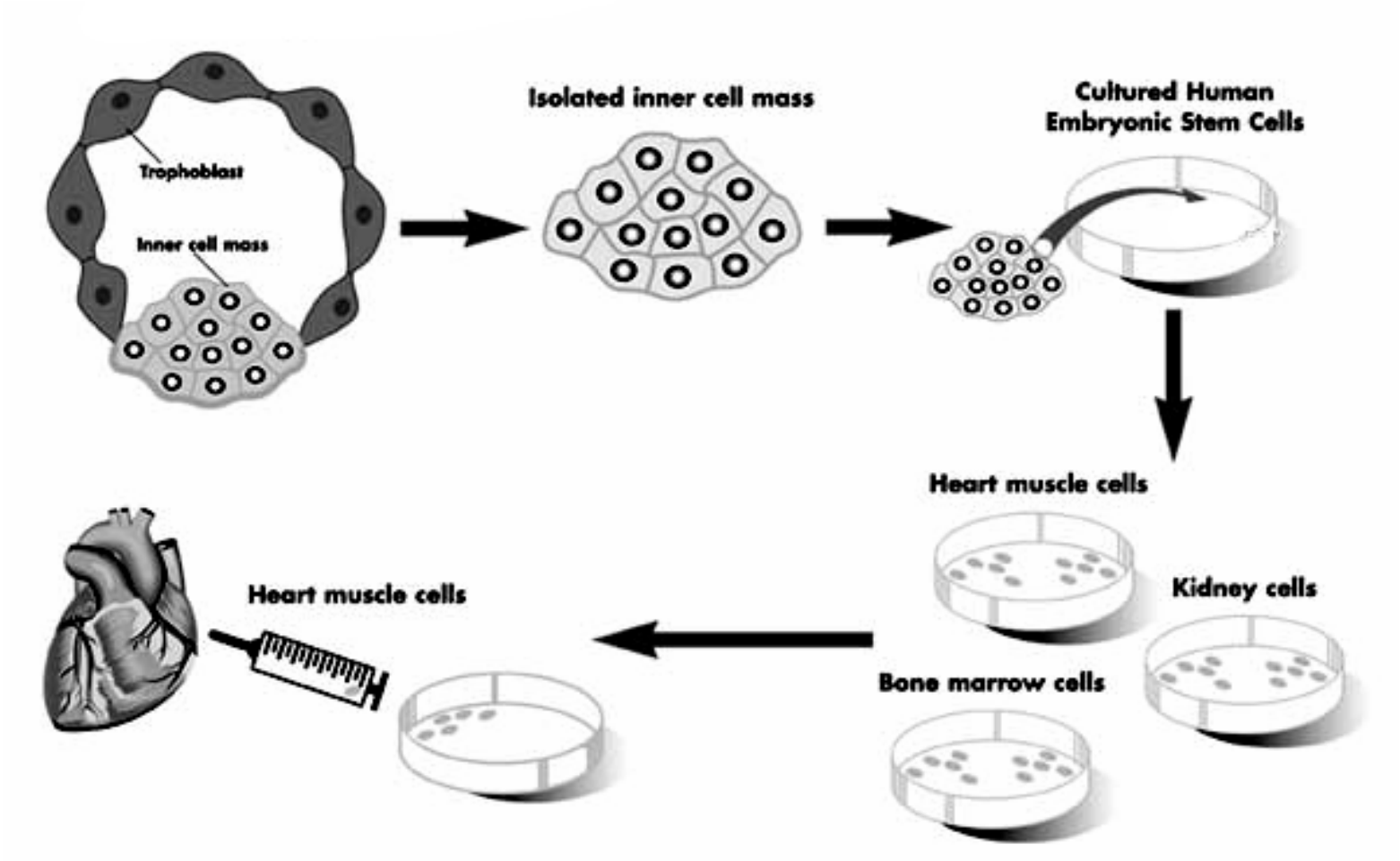


Obtained in 1998
by J. Thompson

Stem Cell Information

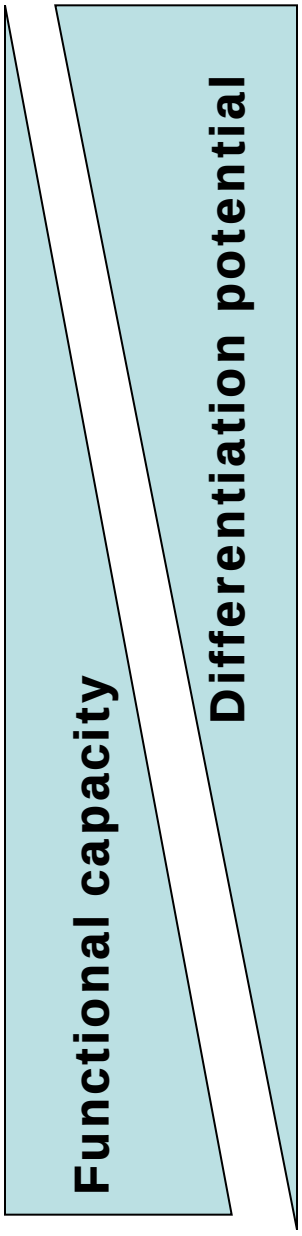
The National Institutes of Health
resource for stem cell research

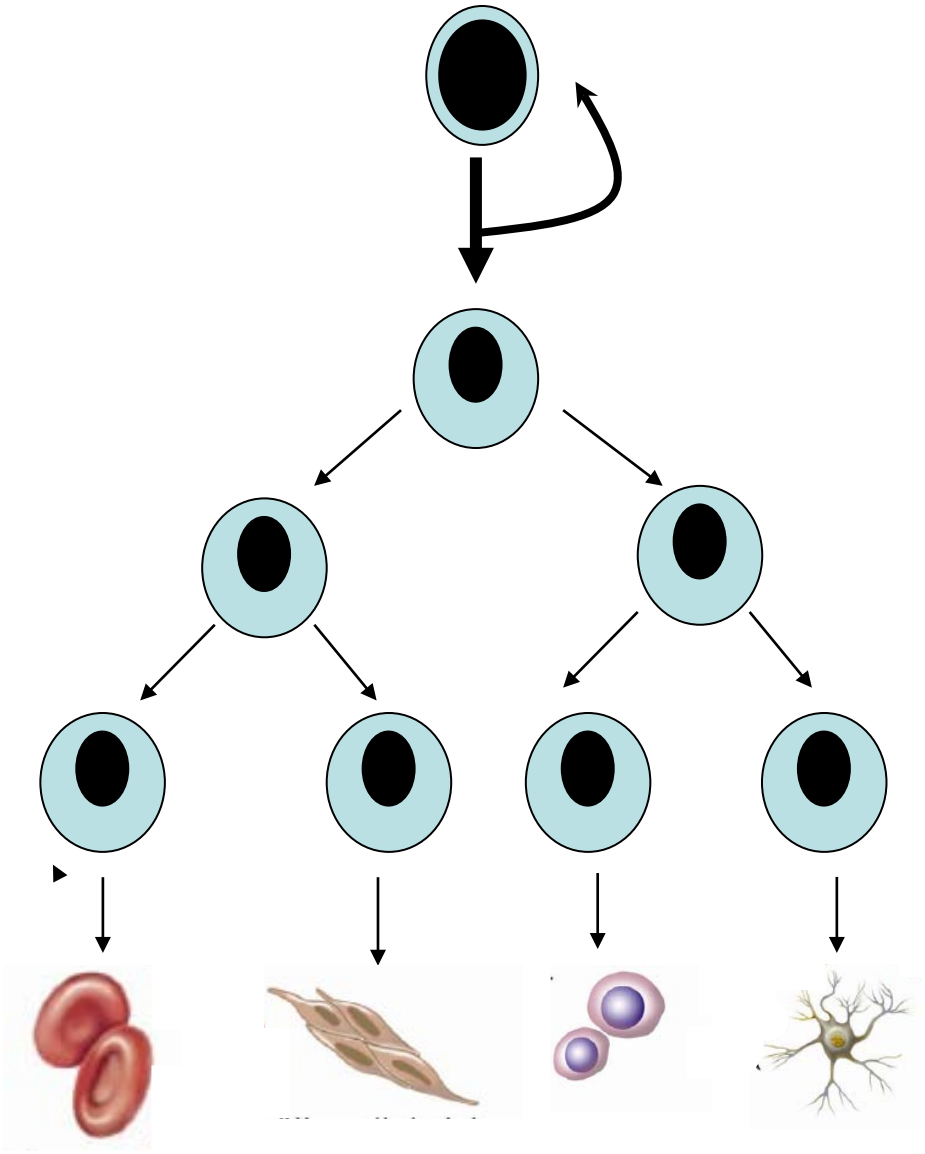
Embryonic stem cells are pluripotent



Human ESC, after being differentiated to a specific cell type, can be potentially used for the therapy

The hierarchical structure of differentiation





stem cells

progenitor cells

terminally differentiated cells

Methods for assessing the pluripotency of stem cells

	Experimental approach
In vitro differentiation to all cell lineages	Differentiation induced in cultured cells and cells are assayed for the expression of cell-type specific markers
Teratoma formation	Induction of tumors demonstrating the potential to generate differentiated cell types of various lineages
Chimera formation	Contribution of cells to normal development following injection into host blastocyst
Germline contribution	Ability of test cells to generate functional germ cells
Tetraploid complementation of the blastocyst	Injection of test cells into 4n host blastocyst. Because 4n host cells cannot contribute to somatic lineages embryo is exclusively composed of test cells

Note:

not every tests of pluripotency can be applied to human embryonic/pluripotent cells due to ethical reasons

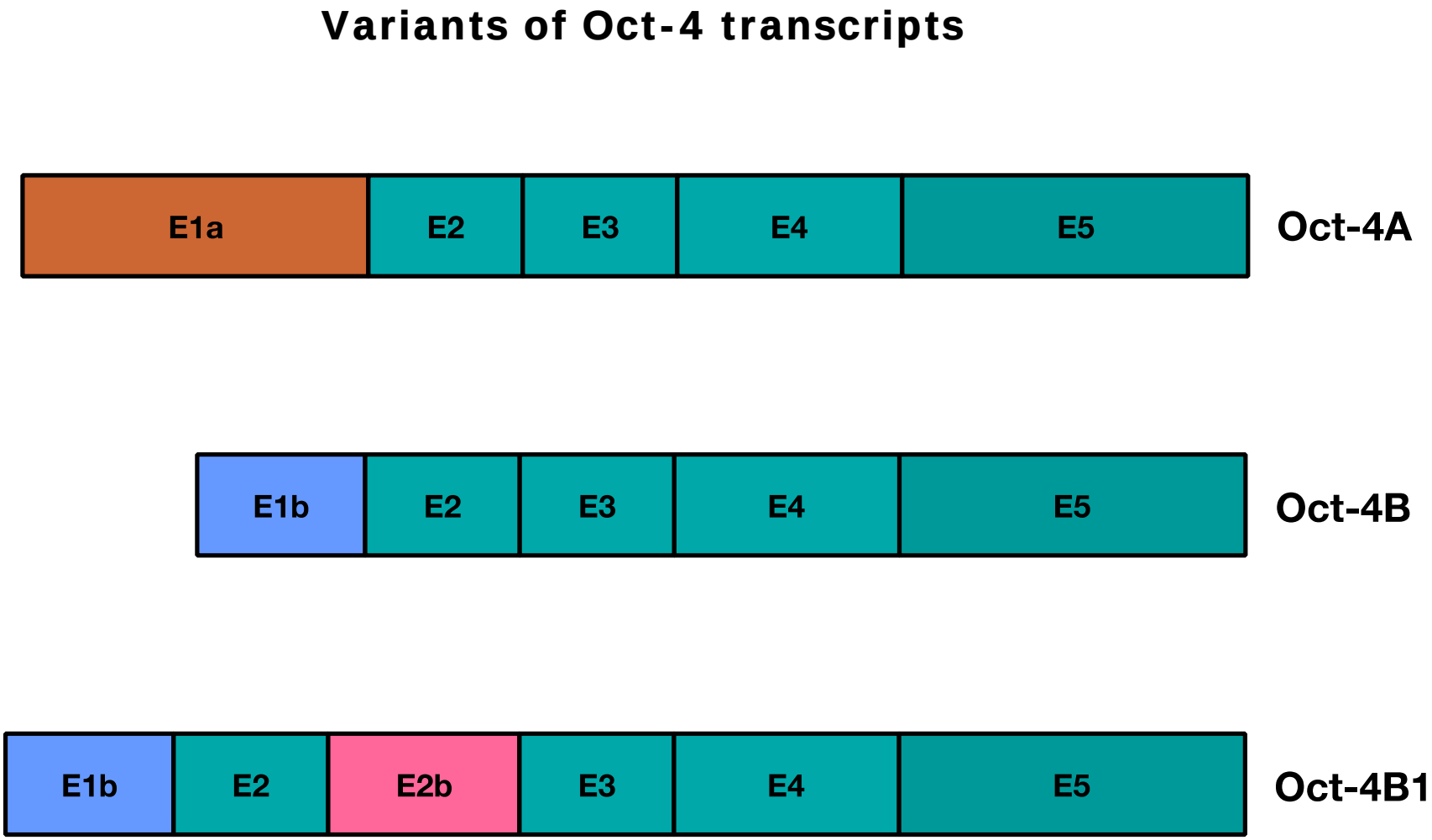
Methods for assessing the pluripotency of stem cells

Expression of genes considered as markers of pluripotency: ***Oct4* gene**

The *octamer-binding transcription factor 4* gene encodes a nuclear protein (Oct4, also known as Pou5F1 and Oct3/4) that belongs to a family of transcription factors containing the POU DNA-binding domain. Expression can be detected in embryonic stem cells as well as in adult stem cells, such as bone marrow-derived mesenchymal stem cells. Expression of *Oct4* is downregulated coincident with stem cell differentiation and loss of expression leading to differentiation. A role for maintaining pluripotency and self-renewal of embryonic stem cells is ascribed to Oct4 as a pluripotency marker. Results describing Oct4 expression in differentiated cells, including peripheral blood mononuclear cells (PBMCs), neonatal and adult stem cells, as well as cancer cells, must be interpreted with caution. In several publications, Oct4 has been ascribed a function in maintaining self-renewal of adult stem cells. In contrast, other publications reported Oct4 expression in human tumor cells. Here, we summarize

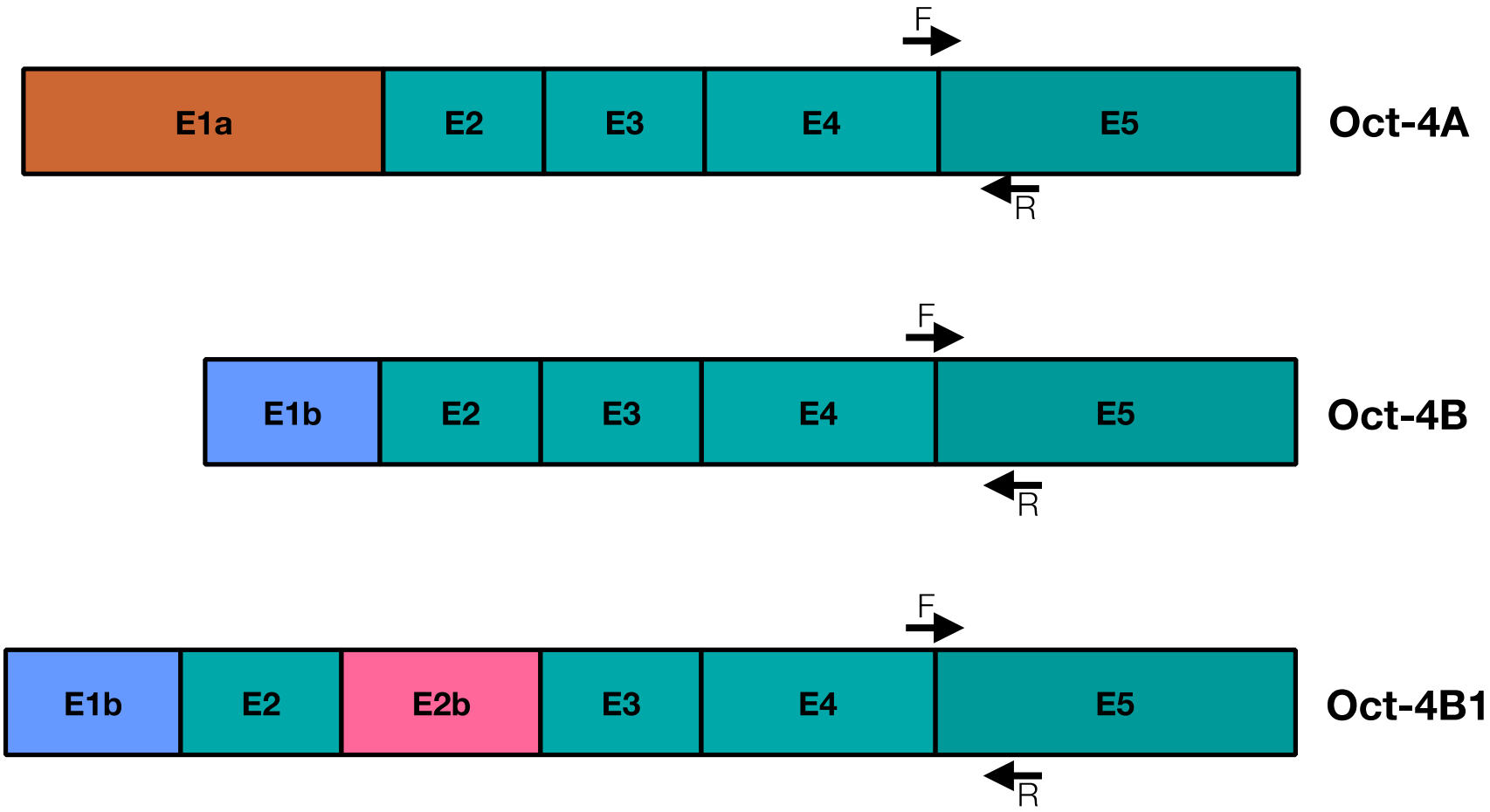
Liedtke et al., Biol Chem 2008

Pitfalls with using Oct4 as the marker of pluripotency



Based on: *OCT4 spliced variants are differentially expressed in human pluripotent and nonpluripotent cells,* Atlasi *et al.*, *Stem Cells,* 2008

Pitfalls with using Oct4 as the marker of pluripotency



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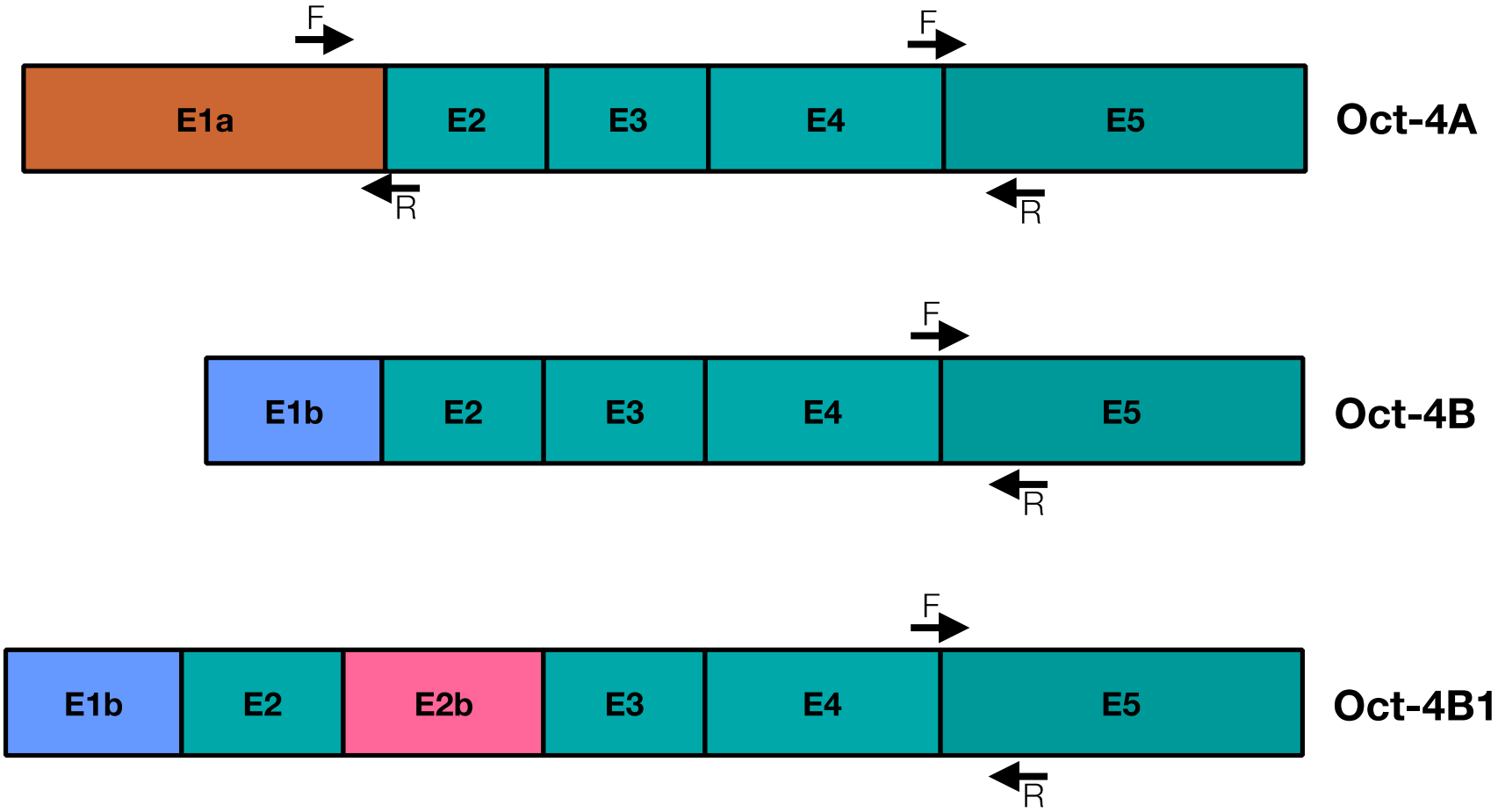
Pitfalls with using Oct4 as the marker of pluripotency

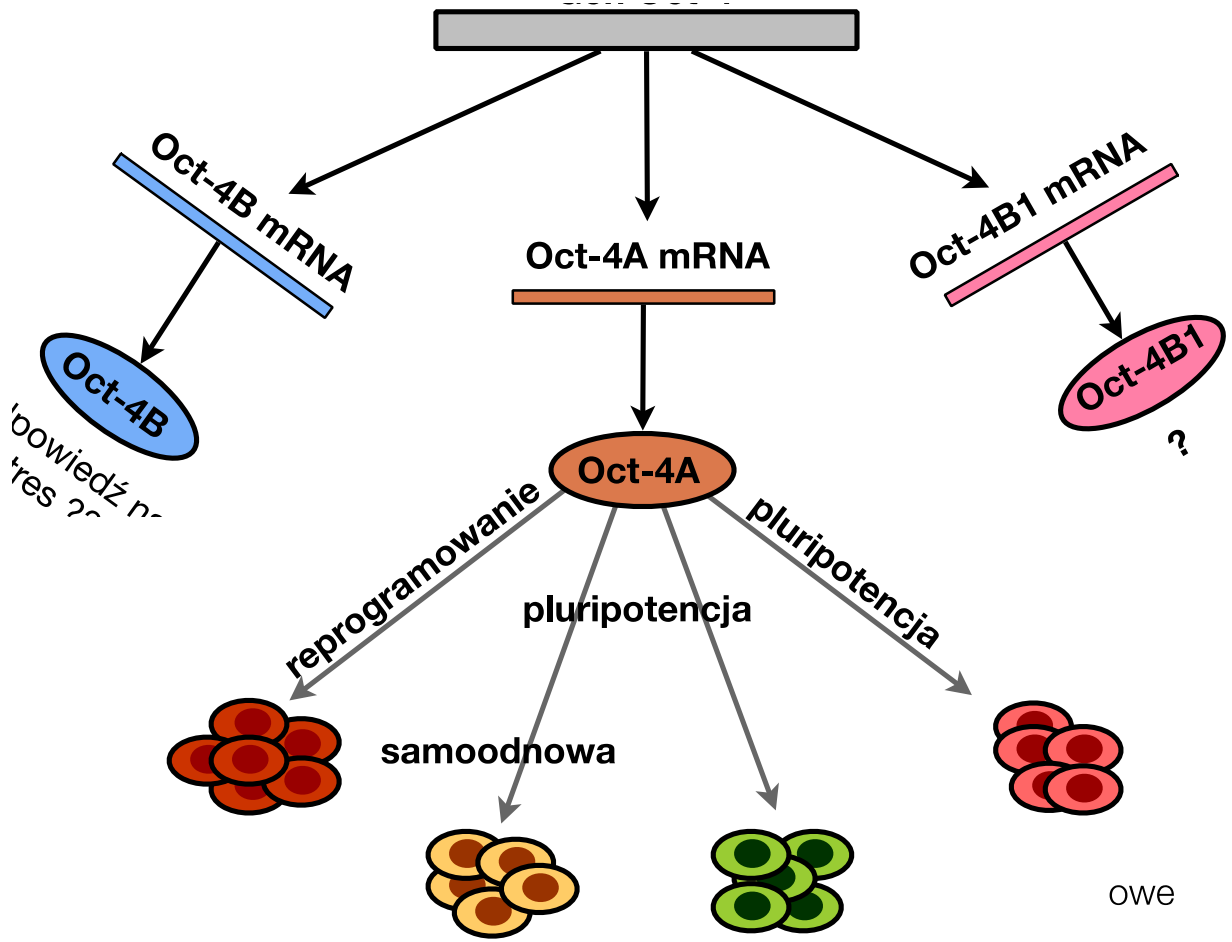


Additional danger: Oct-4A pseudogenes !!!

Based on: *OCT4 spliced variants are differentially expressed in human pluripotent and nonpluripotent cells,* Atlasi *et al.*, *Stem Cells,* 2008

Methods for assessing the pluripotency of stem cells

Expression of genes considered as markers of pluripotency: Oct4 gene



Adult stem cells

bone marrow

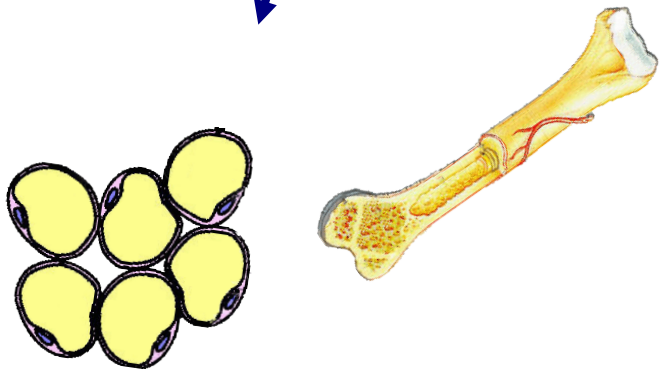
hematopoietic stem cells

Adult stem cells

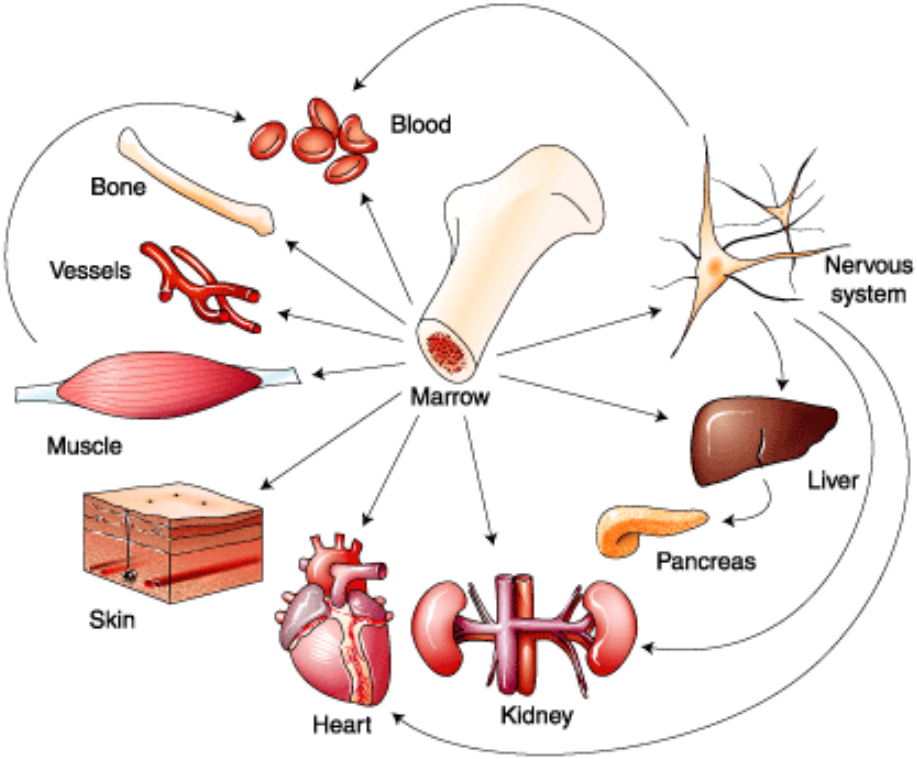
bone marrow

hematopoietic stem cells

mesenchymal stem cells



Plasticity of adult stem cells?

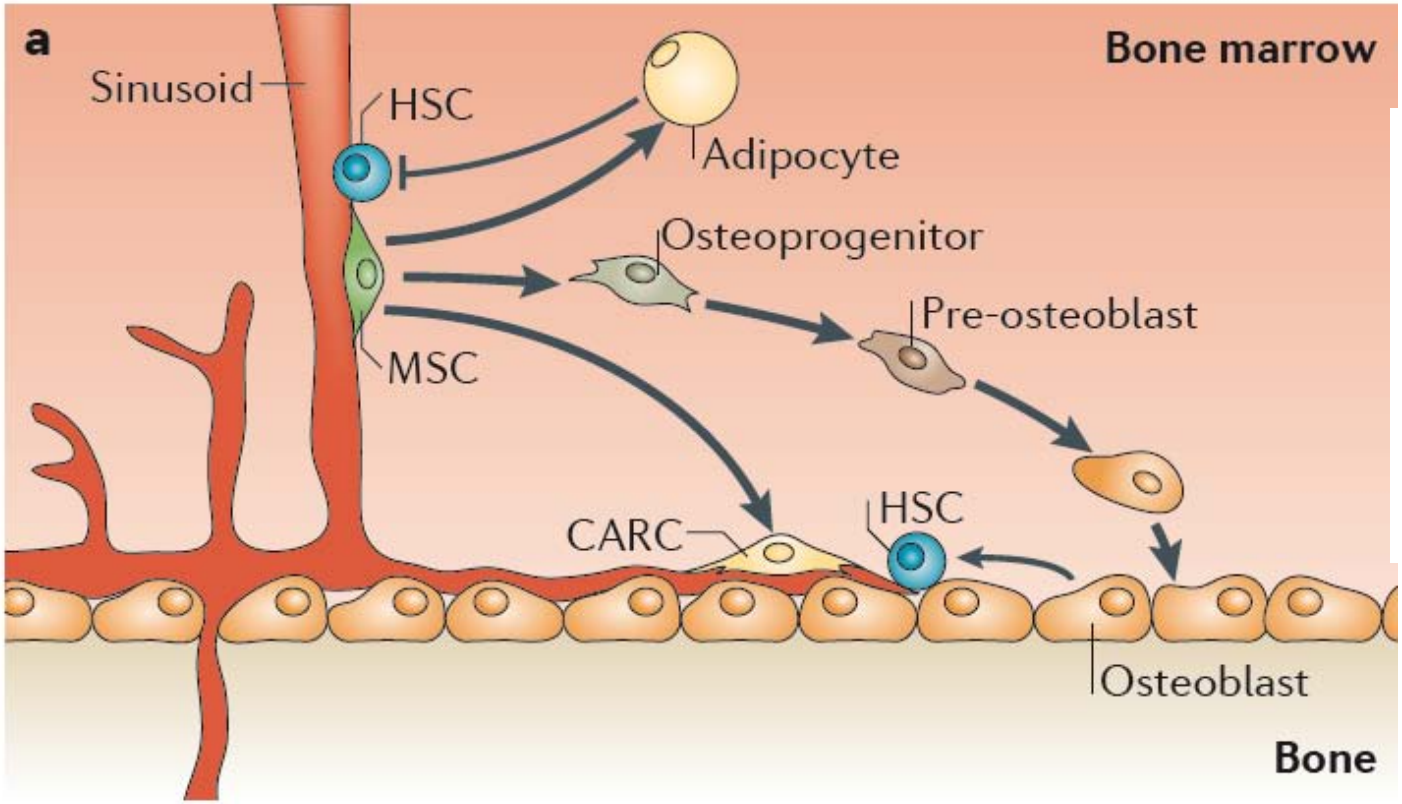


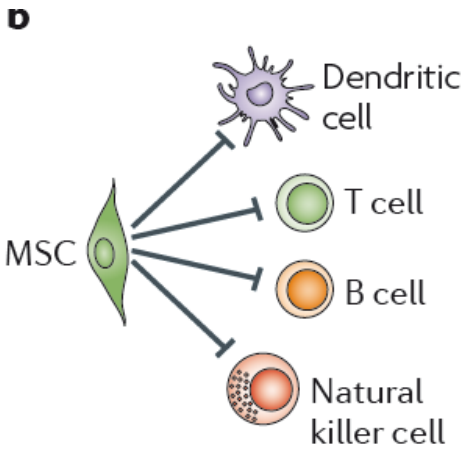
the ability to form specialized cell types of other tissues

(also called transdifferentiation)

It is disputable whether adult stem cells can have the pluripotent potential: there are reports which claim such properties, but there are doubts that in adult organism there are real pluripotent cells, equivalent to ESC

Mesenchymal stem cells





Nombela-Arrieta C et al., Nature Rev Mol Cell Biol February 2011

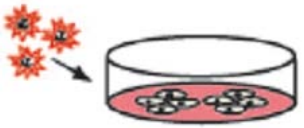
Properties of mesenchymal stem cells

1. Can be easily isolated and propagated
2. Mutlipotent – can be differentiated in several cells types
3. They are characterized by low immunogenecity
4. May be genetically modified (their properties can be improved)
5. May be isolated from different sources (bone marrow, fat)

Genetic modification of pig bone marrow MSC for therapy of myocardial infarction

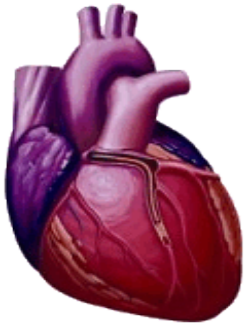
Separation of BM mononuclear cells

differentiation and expansion of cells



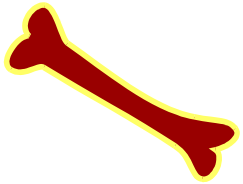
GFP and HO-1 adenoviral transfer

Injection into ischemic myocardium

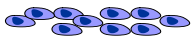


Wojakowski , Szade et al., in preparation

Bone marrow-derived proangiogenic progenitor cells (PPCs)



bone marrow



mononuclear cells

fibronectin /gelatin coated dish

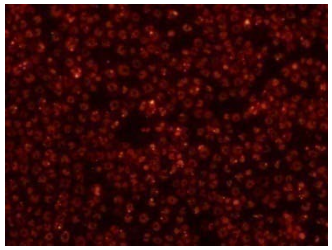
adherent cells

EPCs

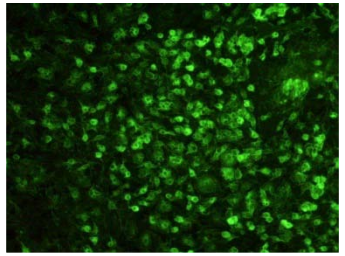
Characteristics:

CD31+/ CD34+/CD133 +/VEGFR-2+/CXCR4+/CD45-

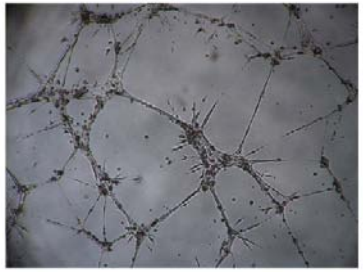
Uptake of AcLDL



Binding of lectins

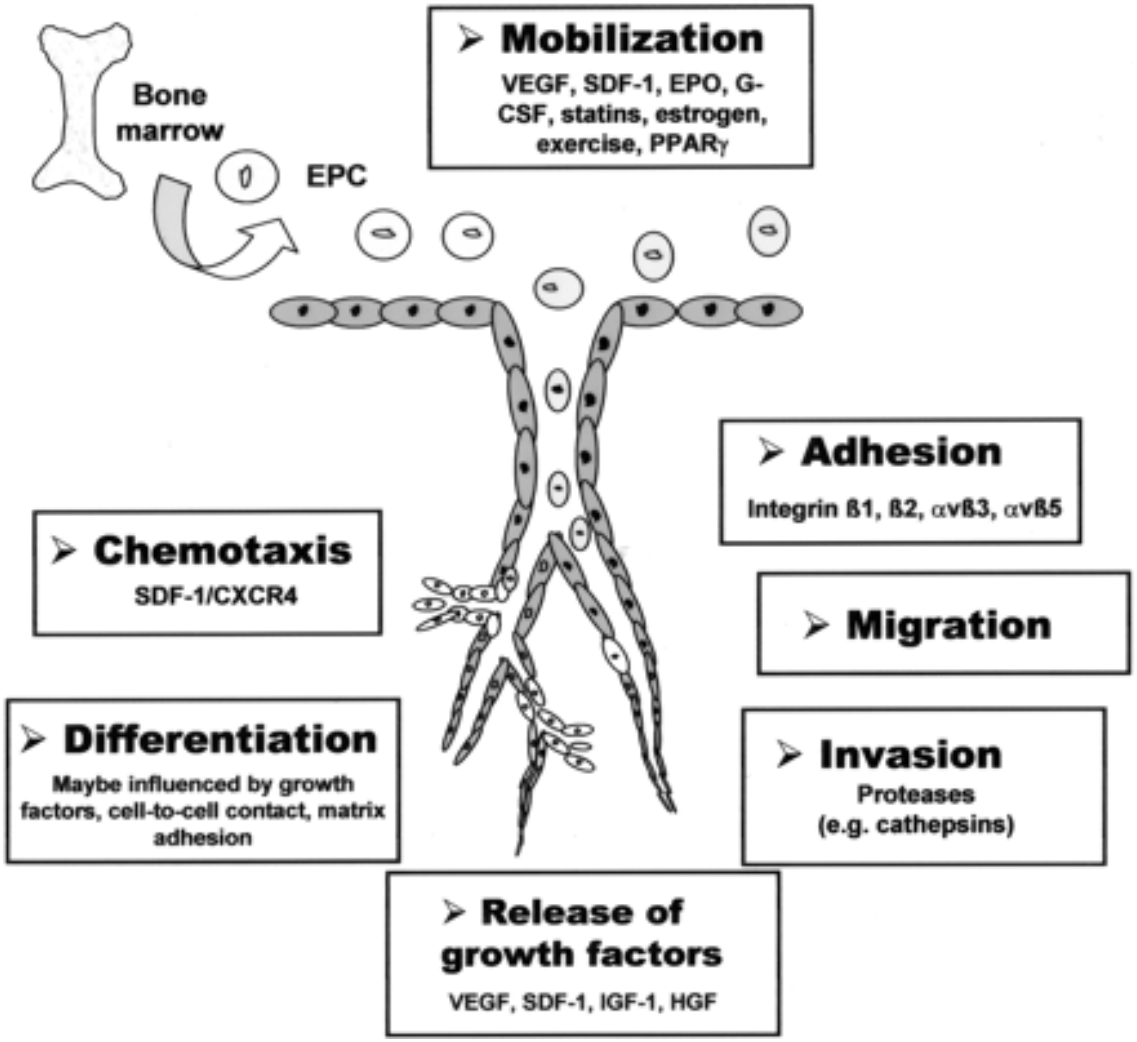


Tube formation on matrigel



Named also: endothelial progenitor cells (EPC)

Post-natal vasculogenesis



EPCs are claimed to contribute to postnatal vasculogenesis

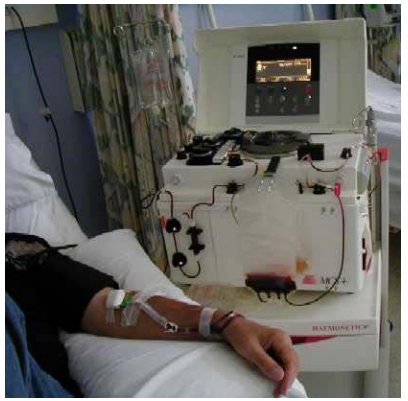
Endothelial progenitor cells (EPCs)

1. Circulating cells
2. display the ability to display cell surface antigens similar to endothelial cells in vitro
3. Circulate and are able to lodge in areas of ischemia or vascular injury
4. Facilitate repair of damaged blood vessels
5. Augment development of new vessels by differentiation into endothelial cells

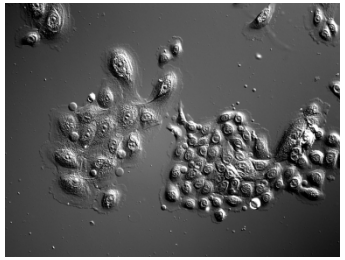
M. Yoder, J Cell Mol Cardiol, Feb 2011

Stem cells in therapy

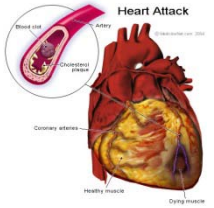
1. Hematopoietic stem cells (bone-marrow, cord blood (leukemias, immunodeficiencies , anemias but also other, like Krabbe's diseases, adrenoleukodytrophy)



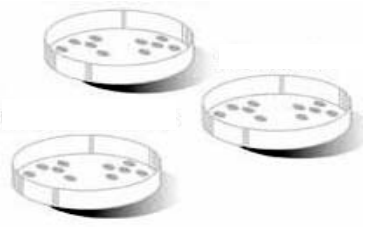
2. Skin stem cells (burns, ulcers)

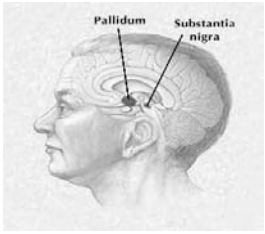


3. Endothelial progenitor cells and others – therapy of myocardial infarctions



4. Neural stem cells – Parkinson disease, Alzheimer disease



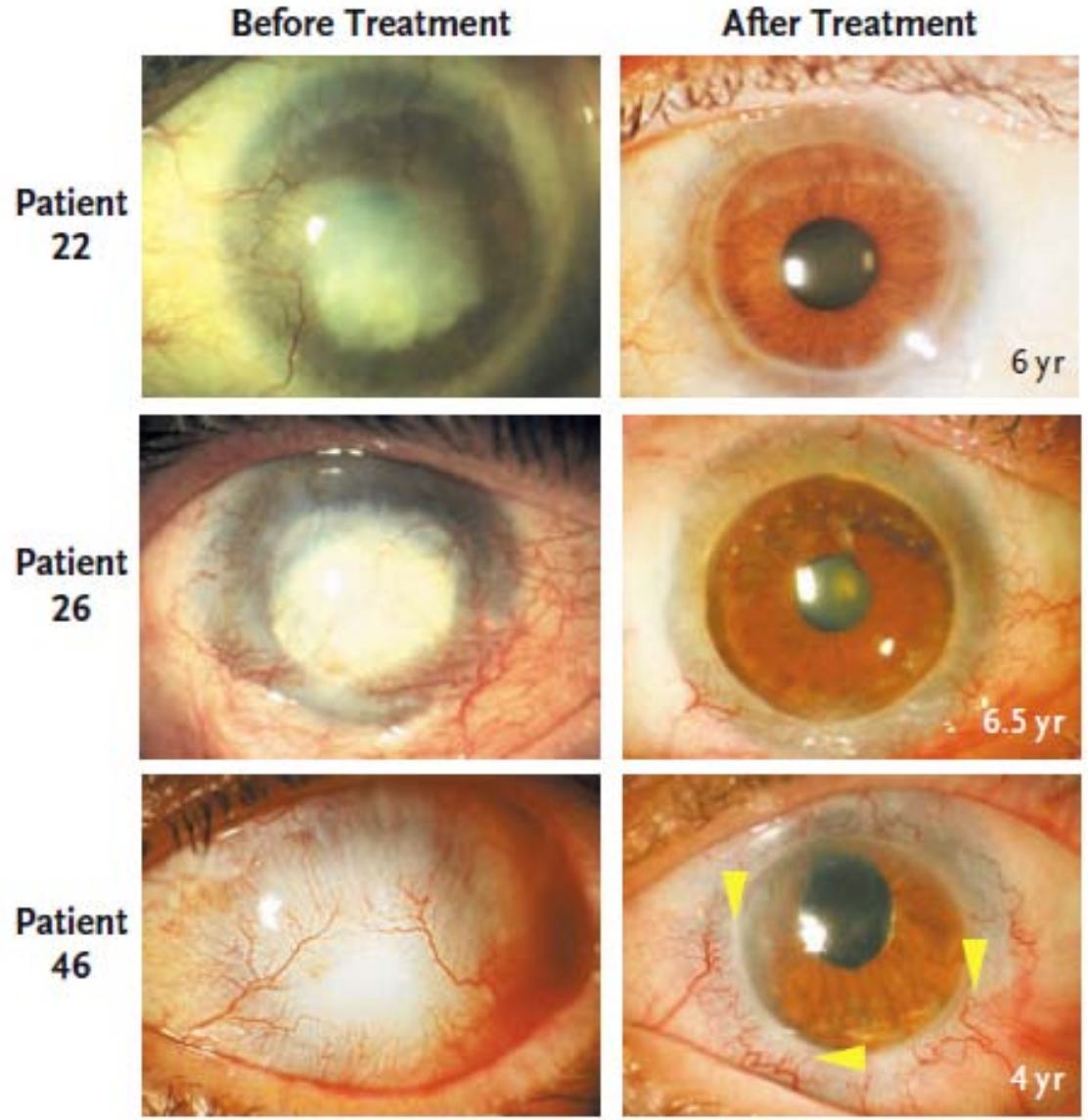


5. Bone marrow cells for treatment of diabetes type I

Limbal stem cells in treatment of blindess caused by damage (mostly burn-caused)

The autologous limbal cells were used for the transplantation

Permanent restoration of a transparent, renewing corneal epithelium was attained in 76.6% of eyes. The failures occurred within the first year. Restored eyes remained stable over time, with up to 10 years of follow-up (mean, 2.91±1.99; median, 1.93).

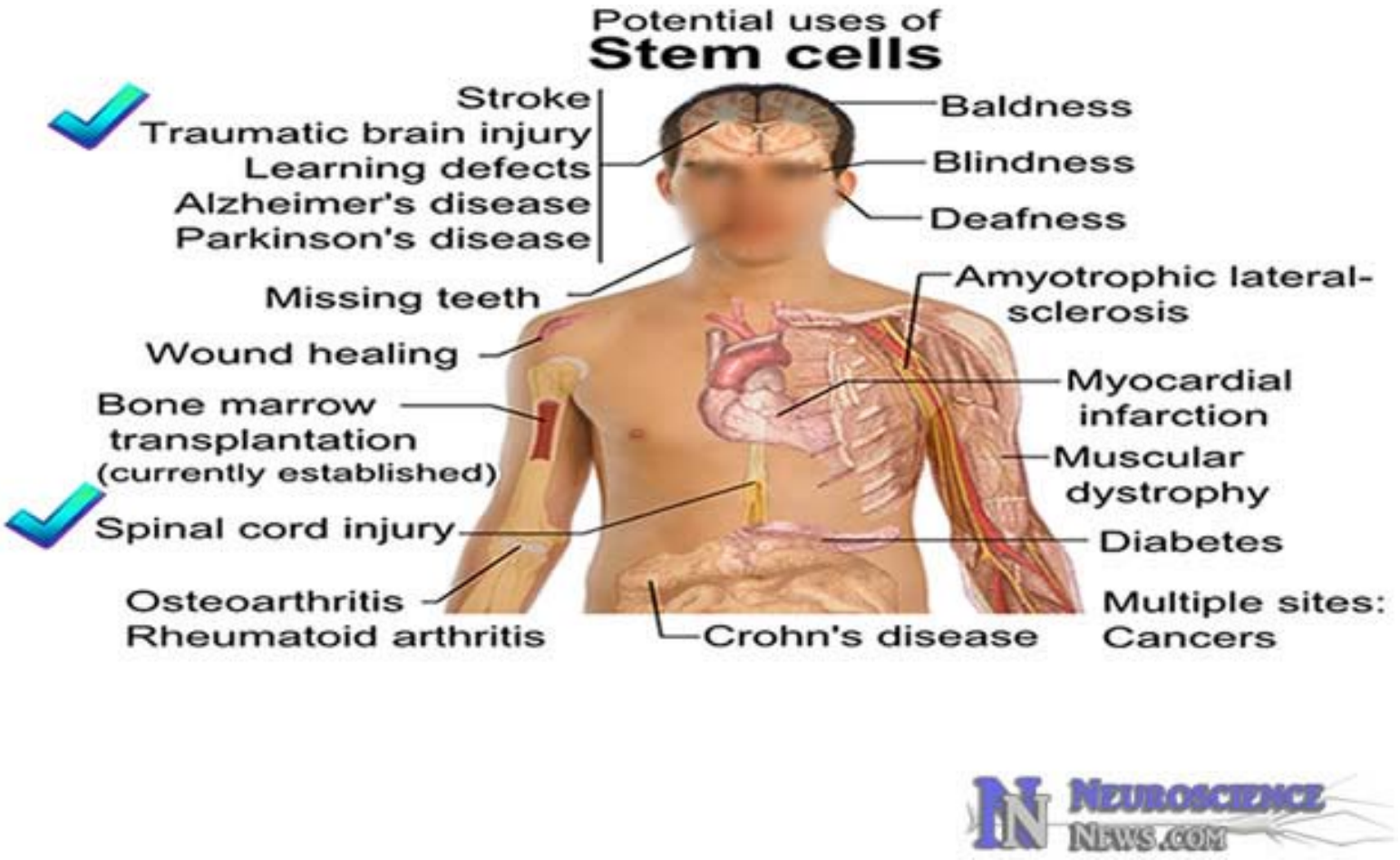


P. Rama (G. Pellegrini) et al., NEJM 2010

Embryonic vs adult in terms of cell therapy

	embryonic SC	**adult S.C. / progenitor cells**
potency	pluripotent	unipotent multipotent
telomerase expression	yes	no
culturing	easily grown	hard to obtain large numbers of cells
stem cell therapy	rejection problem (but no in case of autologous ESc)	no rejection Problem if autologous

Embryonic stem cells in therapy of human diseases



First clinical trial based oh human embryonic stem cells – **Geron corp - ESC differentiated to astrocytes – for treatment of spinal cord damage -** halted recently

Important!

In therapy no one will use un-differentiated embryonic stem cells!

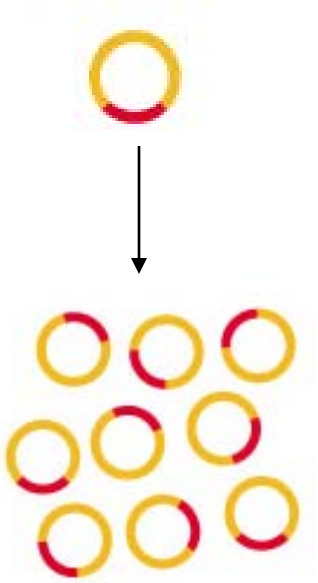
The ESC before application to human are differentiated to the specific cell type

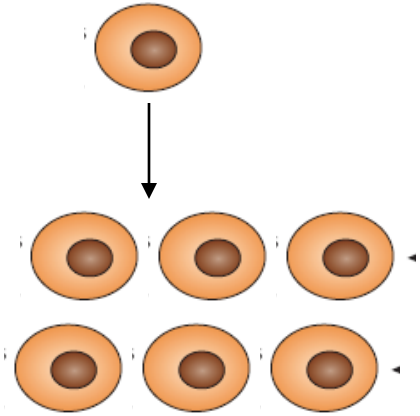
However, the risk of contamination with un-diiferentiated (not fully differentiated) ESC exists

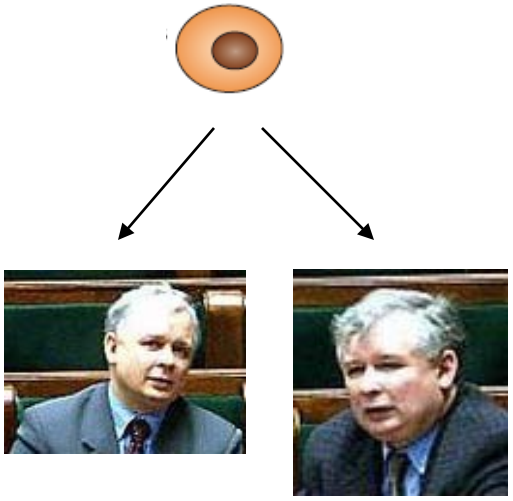
There is always a risk of rejection of transplanted cells due to genetic differences with the host

Cloning

A term that is applied to genes, cells or organisms that are totally derived from, and therefore identical to, a single common ancestor gene, cell, or organism, respectively





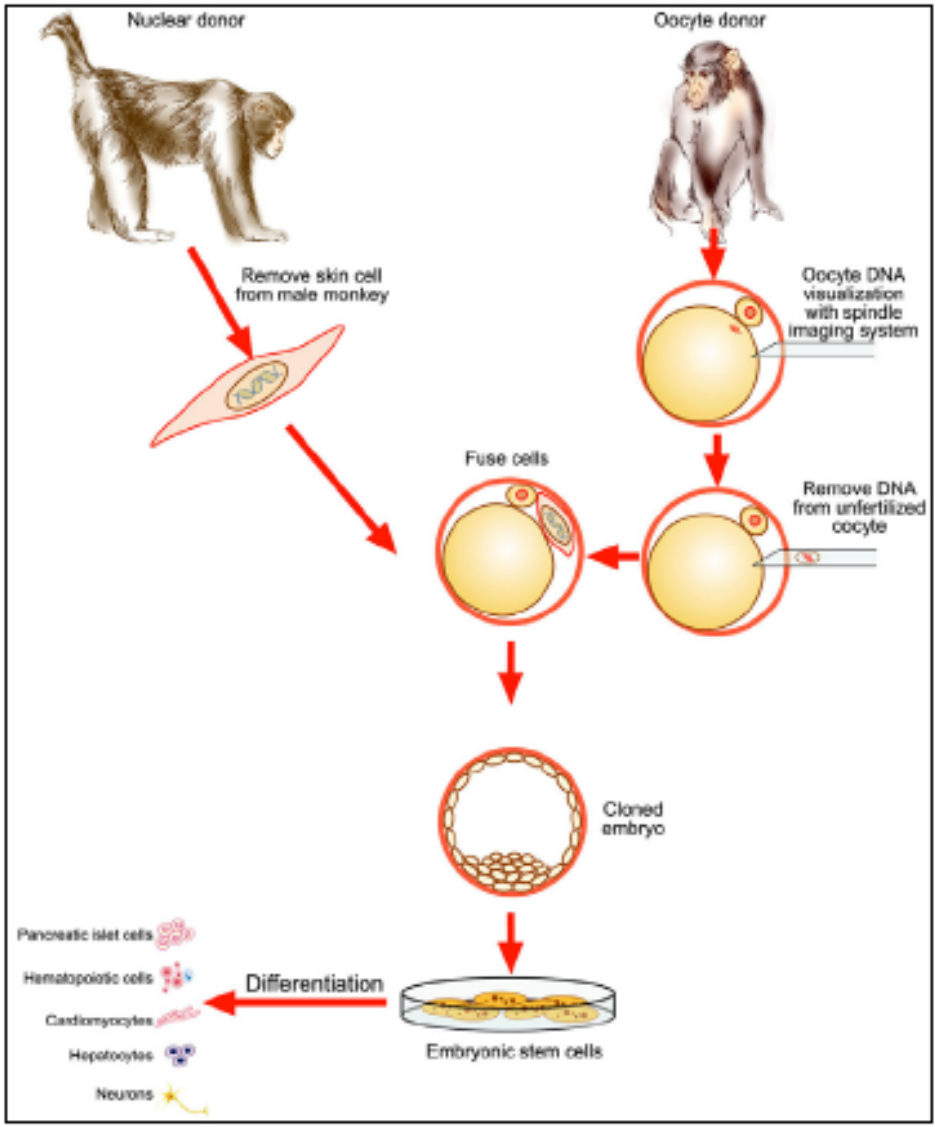


Cloning

reproductive

Therapeutic (SCNT – Somatic cell nuclear transfer)

Producing primate embryonic stem cells by somatic cell nuclear transfer



Byrne JA et al. (Mitalipov), Nature 22 November 2007

Primate cloned stem cells

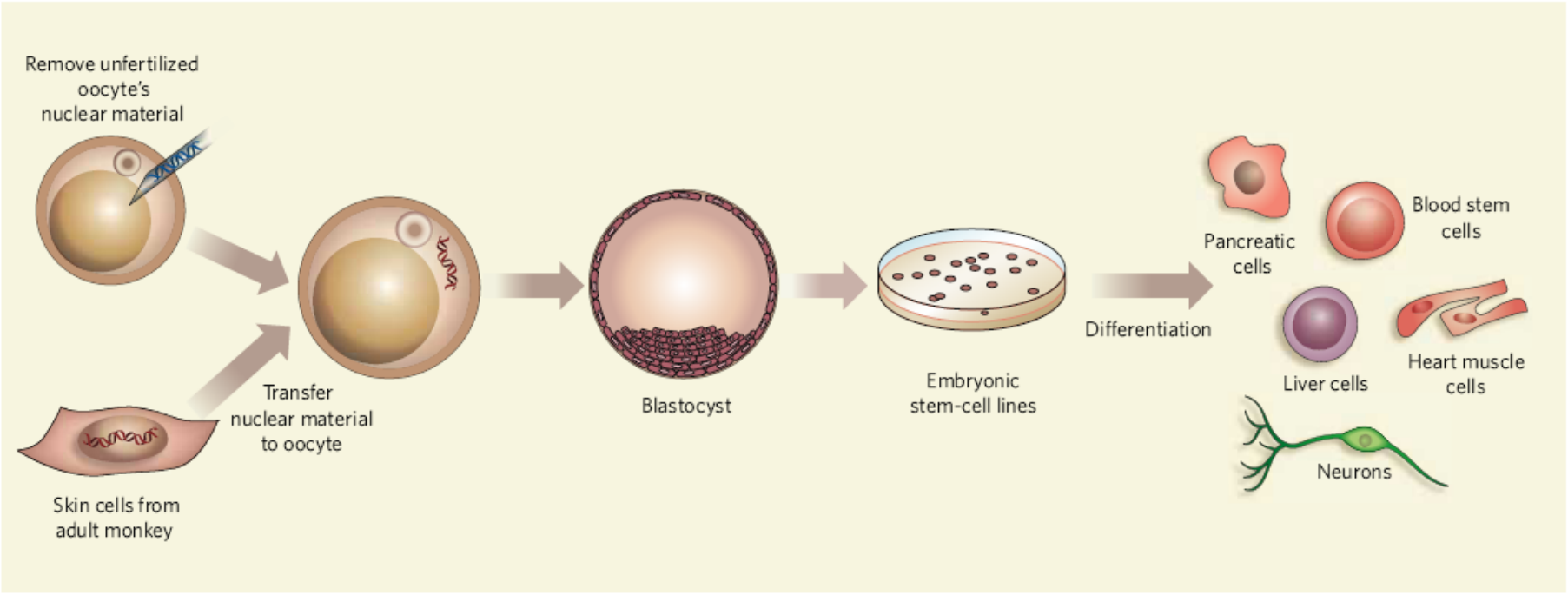
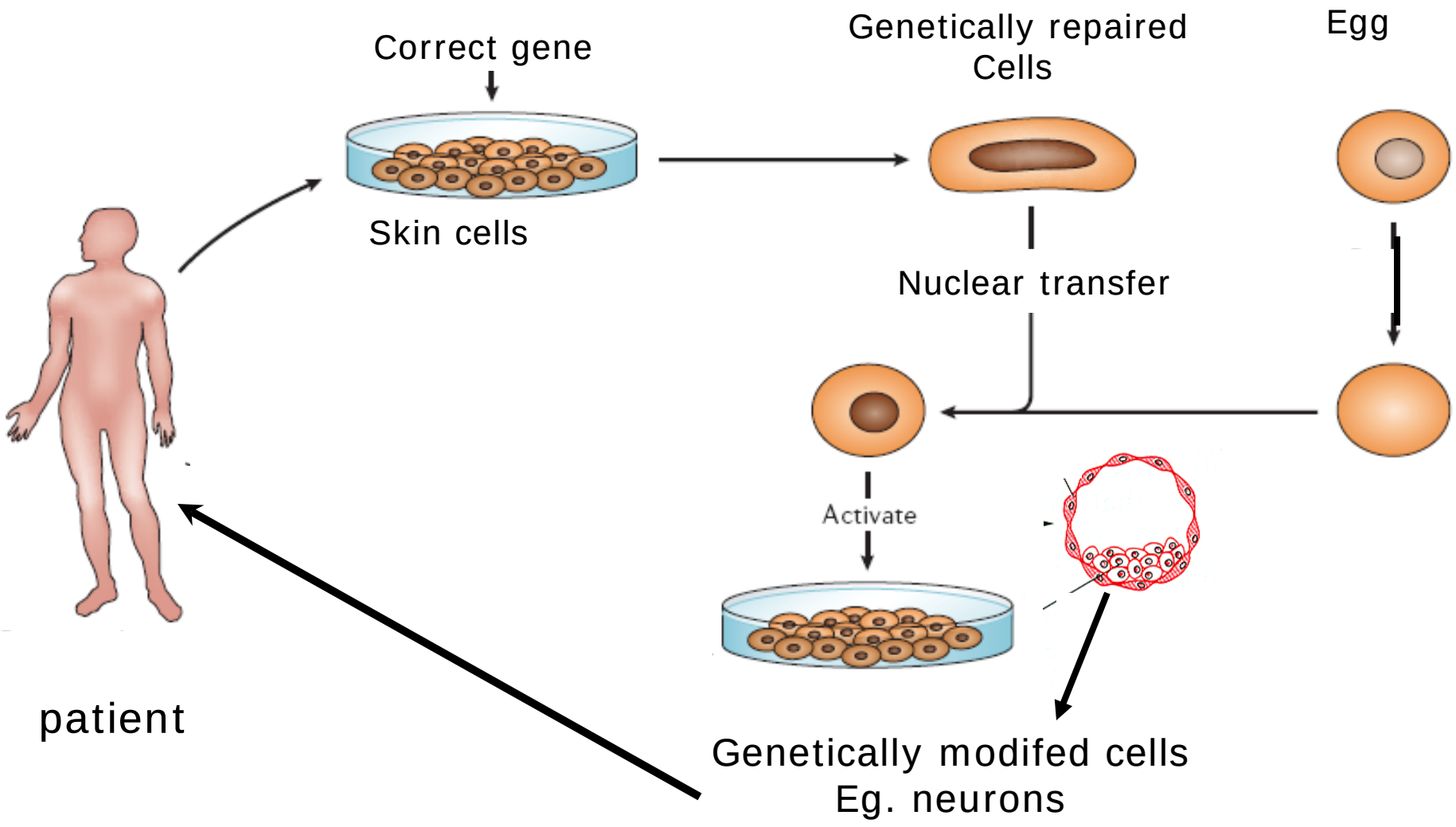


Figure 1 | The technique of somatic-cell nuclear transfer (SCNT). In much the same way as women undergoing *in vitro* fertilization procedures are treated to make them super-ovulate, Byrne *et al.*[2] treated female rhesus monkeys with hormones to induce the shedding of extra eggs. After recovering these cells, the authors removed the cells' nuclear genetic material. Meanwhile, they obtained skin cells from an adult male monkey, allowed these to multiply in culture, and then treated them to halt their progress through the cell cycle once they had entered the resting phase known as G0. Next, the authors extracted the nuclear genetic material from the skin cells and introduced it by electric pulses into the nucleus-free eggs. The fused cells were allowed to reach the blastocyst stage of embryonic development before embryonic stem cells were derived from them. Such cells have the potential to differentiate into different cell types.

Wilmut & Taylor, Nature, 22 Nov 2007

Therapeutic cloning & gene therapy – effective in future?



Eg. Potentially for treatment of Lesh-Nyhan syndrome

Difficulties in generation of human cloned embryonic stem cells

South Koreans clone human embryo

In a scientific first, researchers in South Korea successfully cloned a human embyro. Stem cells, the human body's building blocks, were culled from it – an important step in eventually growing patients' own replacement tissue.

Just the first step

It will be years before the technique is perfected and used in people.

From ...	they cloned ...	to harvest ...
242 donor eggs	30 blastocysts	1 stem cell line

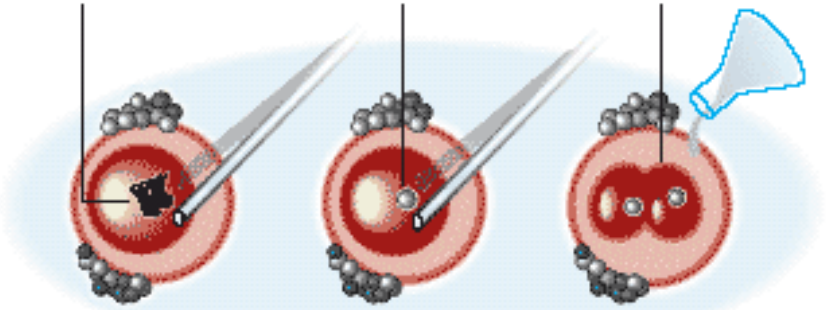
Cell swap

The method used by the researchers – nuclear transfer – has been successful in cloning sheep and other animals.

A needle is used to puncture the wall of a mature egg and suction out its genetic material.

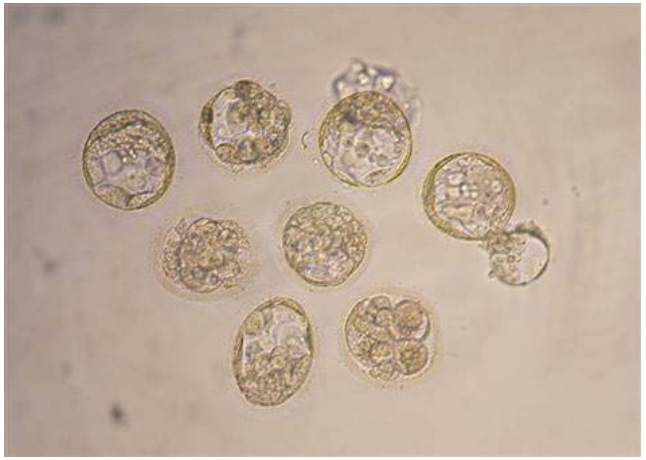
A cumulus cell, a remnant from the ovary, is inserted into the emptied egg. This cell is meant to provide genetic material for the developing egg – and the resulting stem cells.

Added chemicals and other growth factors fool the egg into dividing, as if it had been fertilized by a sperm.



Cell division results in a blastocyst, a hollow ball of about 100 cells containing stem cells.

SOURCES: Scientific American; Associated Press AP

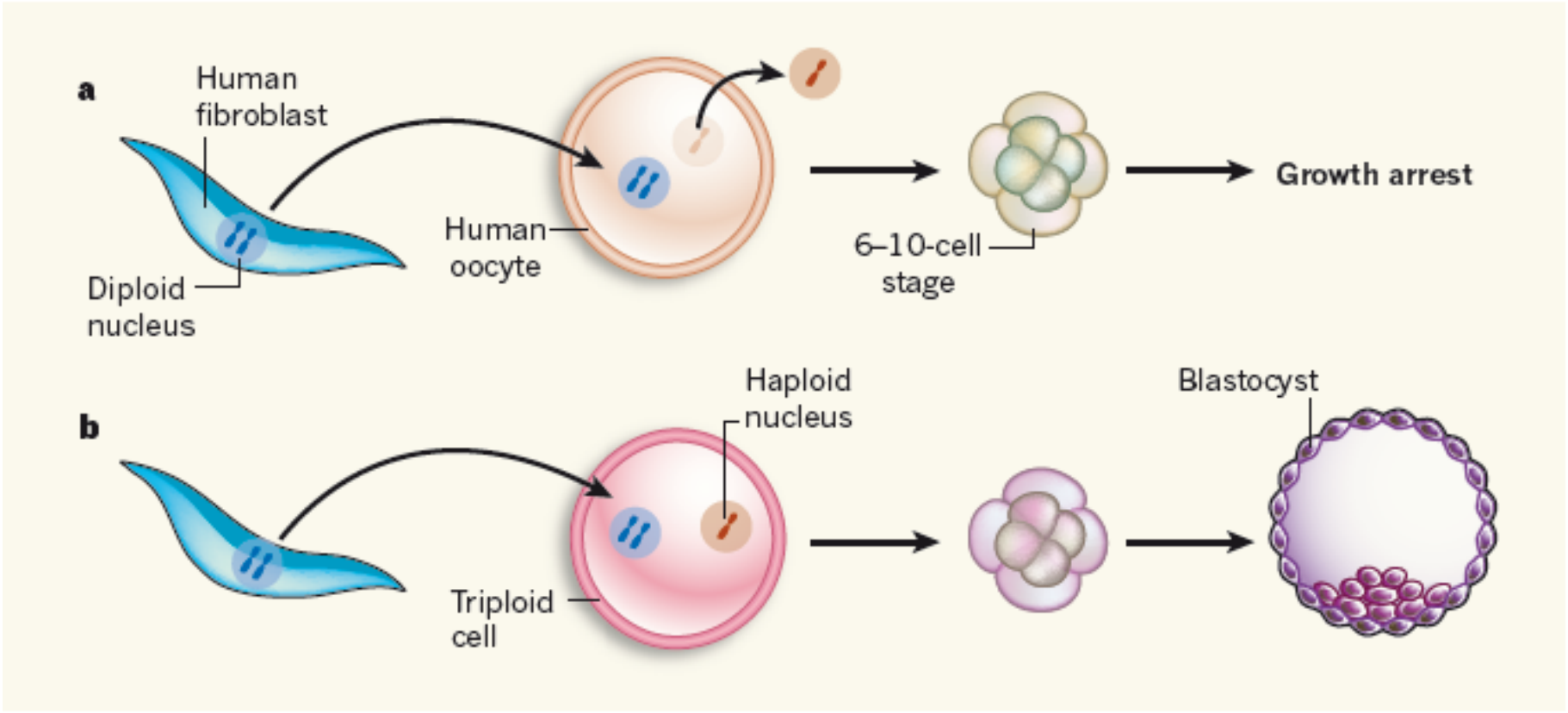


Scientific fraud...

Woo Suk Hwang,

The announcement finally confirms the gravest suspicions of Hwang's work with humans. There are two papers in which Hwang's group claimed to clone human cells - a 2004 article that describes the first cloned embryo and derivation of a stem-cell line from it (W. S. Hwang et al. **Science 303, 1669-1674; 2004**), and a 2005 article that claims the establishment of eleven 'patient-specific' stem-cell lines (W. S. Hwang et al. **Science 308, 1777-1783; 2005**). Both have turned out to be **complete and deliberate fakes**.

Recently human ESC by SCNT have been obtained



G.O. Daley, Nature, 6th October 2011

Triploid human ESCs have been recently obtained by S. Noggle et al. (D. Egli) – Nature, 6th October 2011

Human ESC – ethical and practical problems

1. Classic ESC are geneticall different from the host

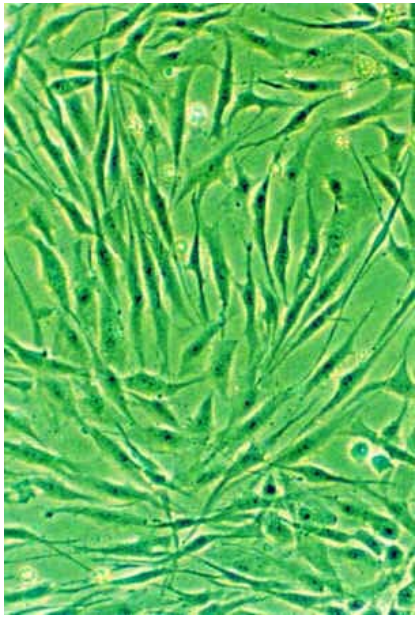
2. Side effects – teratocarcinoma formation

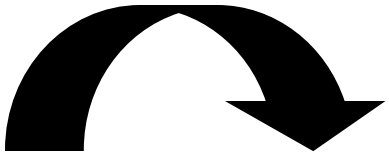
3. ESC are obtained from the surpluss embryos generated by in vitro fertilisation (for reproductive purposes)

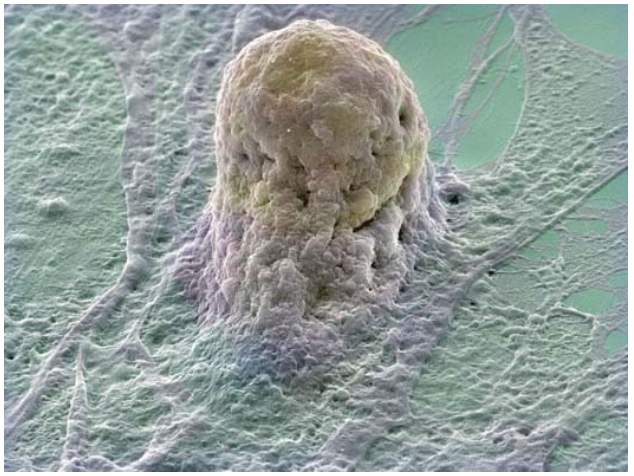
(in vitro fertiliation for research pursposes only is forbidden in most countries)

4. Ethical problems for belivers that human entity starts from the conception

Is the other way possible???



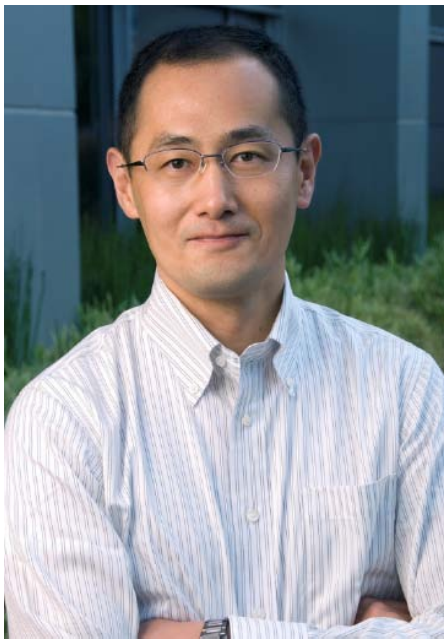




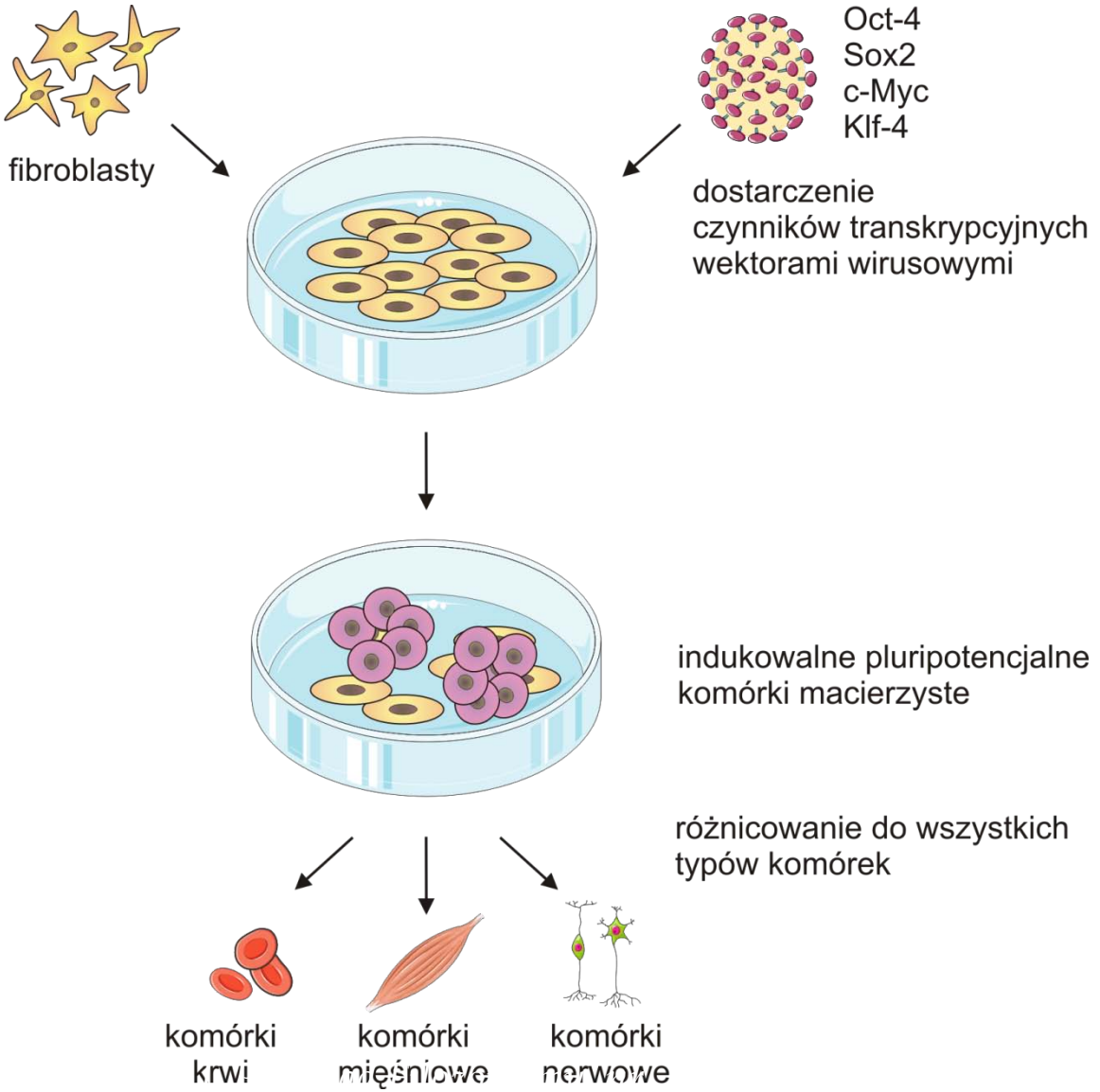
Human Dermal Fibroblasts

Stem Cell

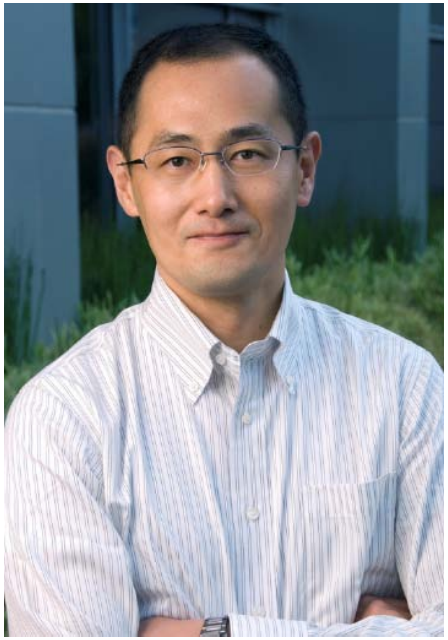
Induced pluripotent stem cells
indukowane pluripotencjalne komórki macierzyste (iPS)



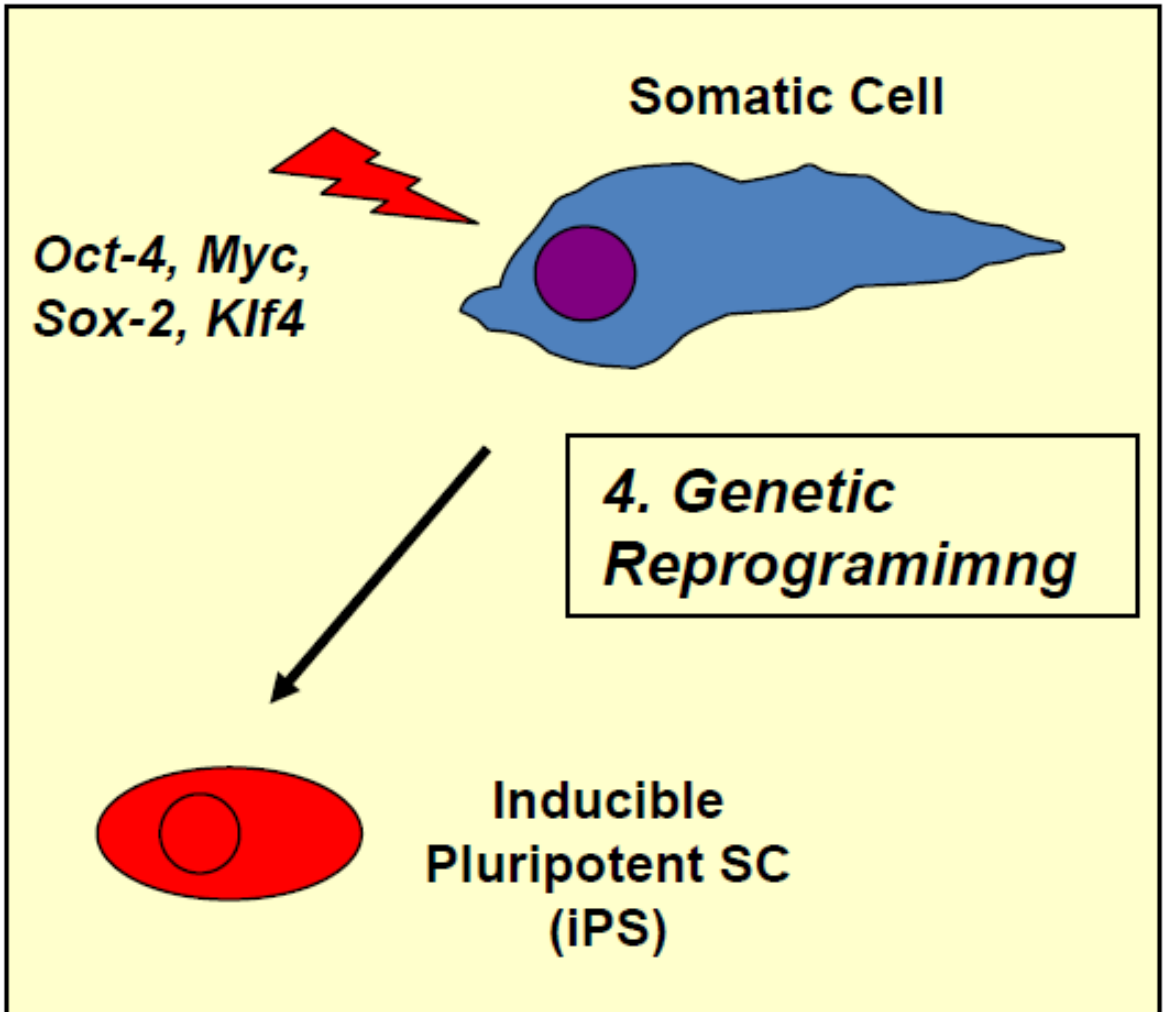
Shinya Yamanaka
2006



Induced pluripotent stem cells

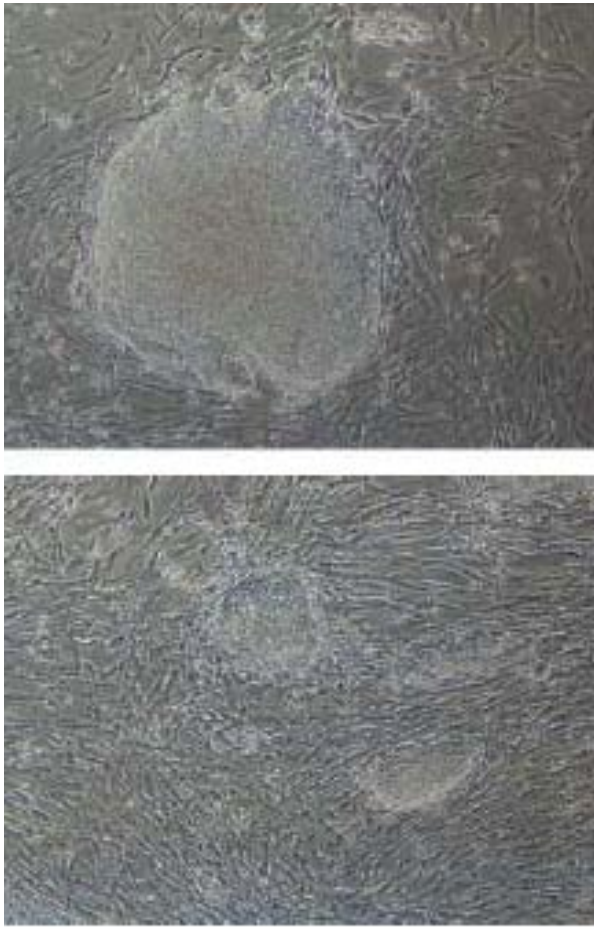


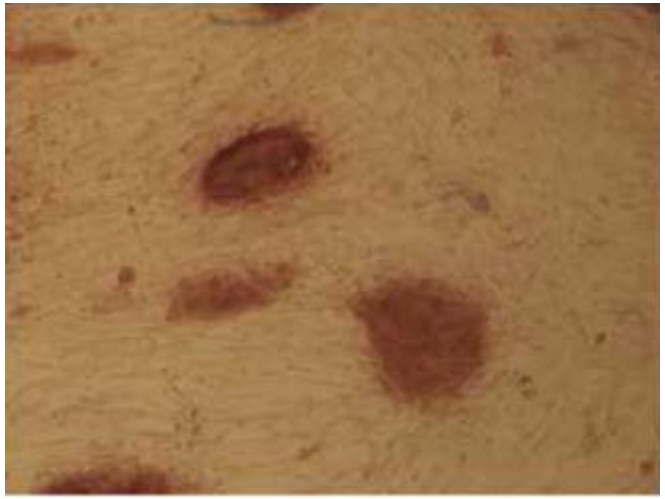
Shinya Yamanaka
2006



Mouse fibroblasts reprogrammed to iPSCs

Mouse iPS obtained
after OSKM gene transfer to fibroblasts



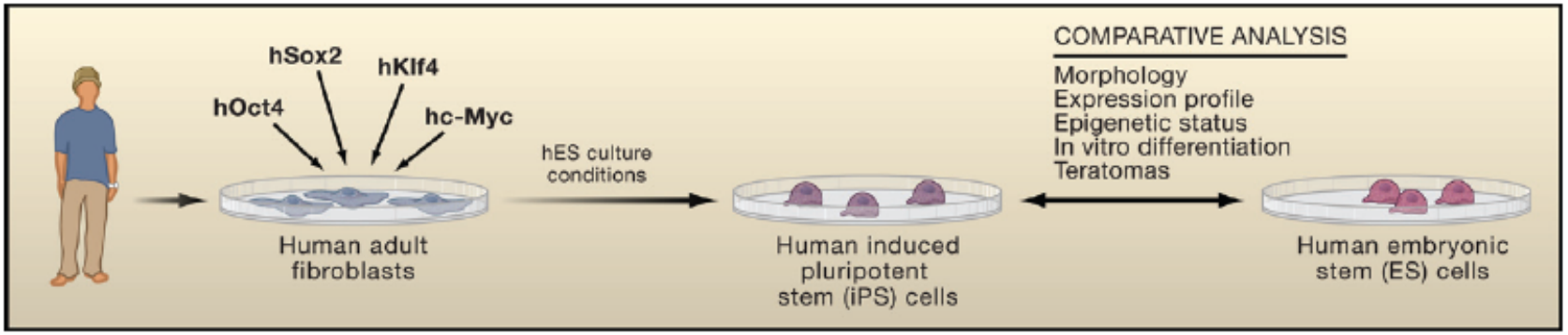


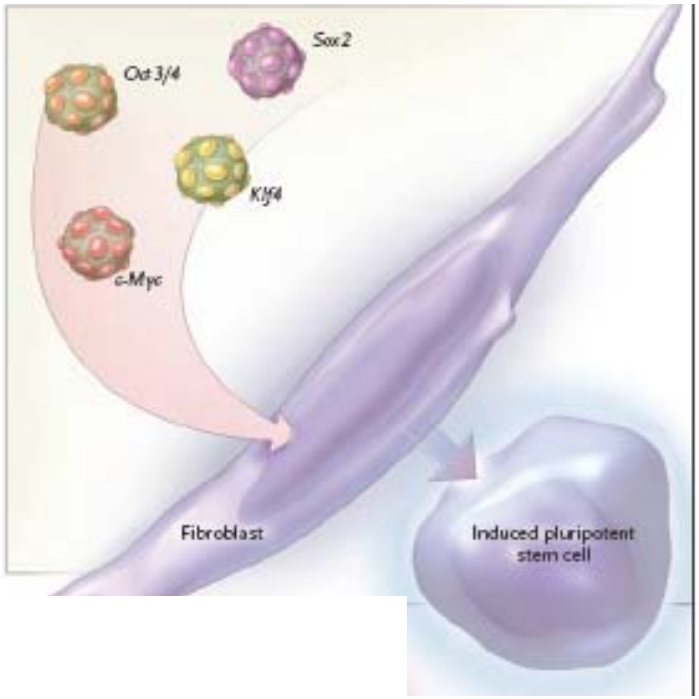
Positive for alkaline phosphatase

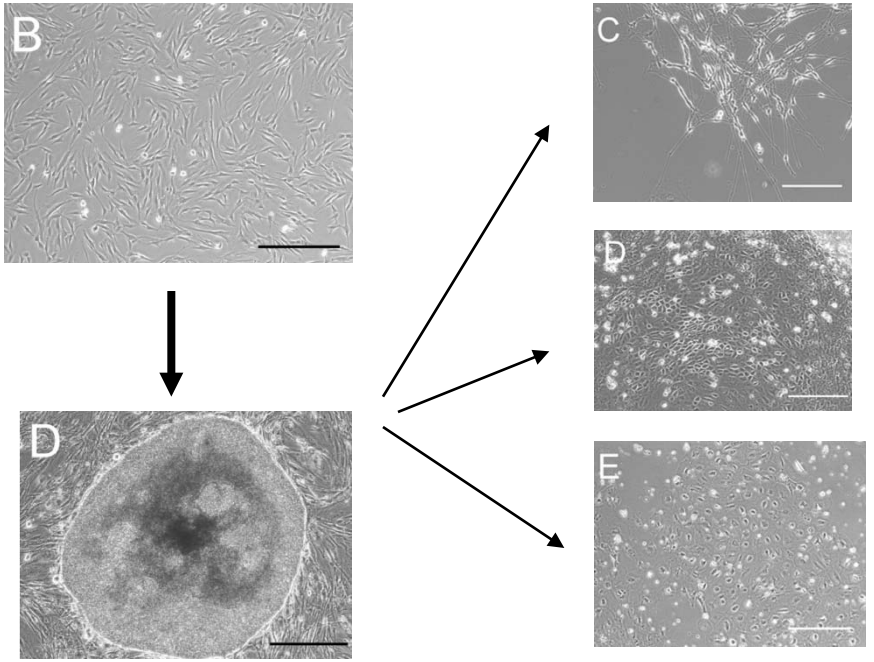
Transcription-factor induced pluripotency

Induced pluripotent stem cells (iPS)

Yamanaka et al. 2006



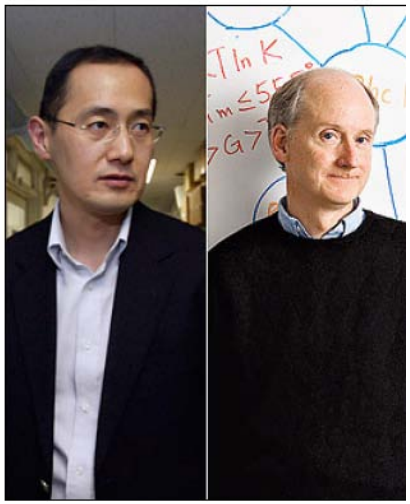




Zaehres & Scholler, Cell 2008

Differentiation into ecto, endo and mesoderm

Different groups demonstrated the possibility of reprogramming human somatic cells



1. Takahasi et al. (S. Yamanaka) - Cell, Nov 20, 2007
   Four factors: Oct3/4, Sox2, Klf4, c-Myc

2. Yu et al., (JA Thomson) Science, Dec 21, 2007
   four factors: Oct4, Sox2, Nanog, Lin28

3. Park H-I et al. (GQ Daley), Nature Dec, 2007
   four factors: Oct4. Sox2, Klf4, c-Myc
   three factors sufficient: Oct4, Sox 2 and either Myc or Klf4
   (the latter two enhance the efficiency of colony formation)

4. Nakagawa M et al. (S. Yamanaka) – Nature Biotechnology, Dec 2007
   three factors sufficient; Oct3/4, Sox2, Klf4

Incidence of tumor-associated deaths in chimeras derived from iPS cells was significantly reduced

iPS cells are really pluripotent

1. Fullfill the test of tetraploid blastocyste complementation – make chimeras and contribute to the germline formation (of course, this was not tested for human iPSCs)

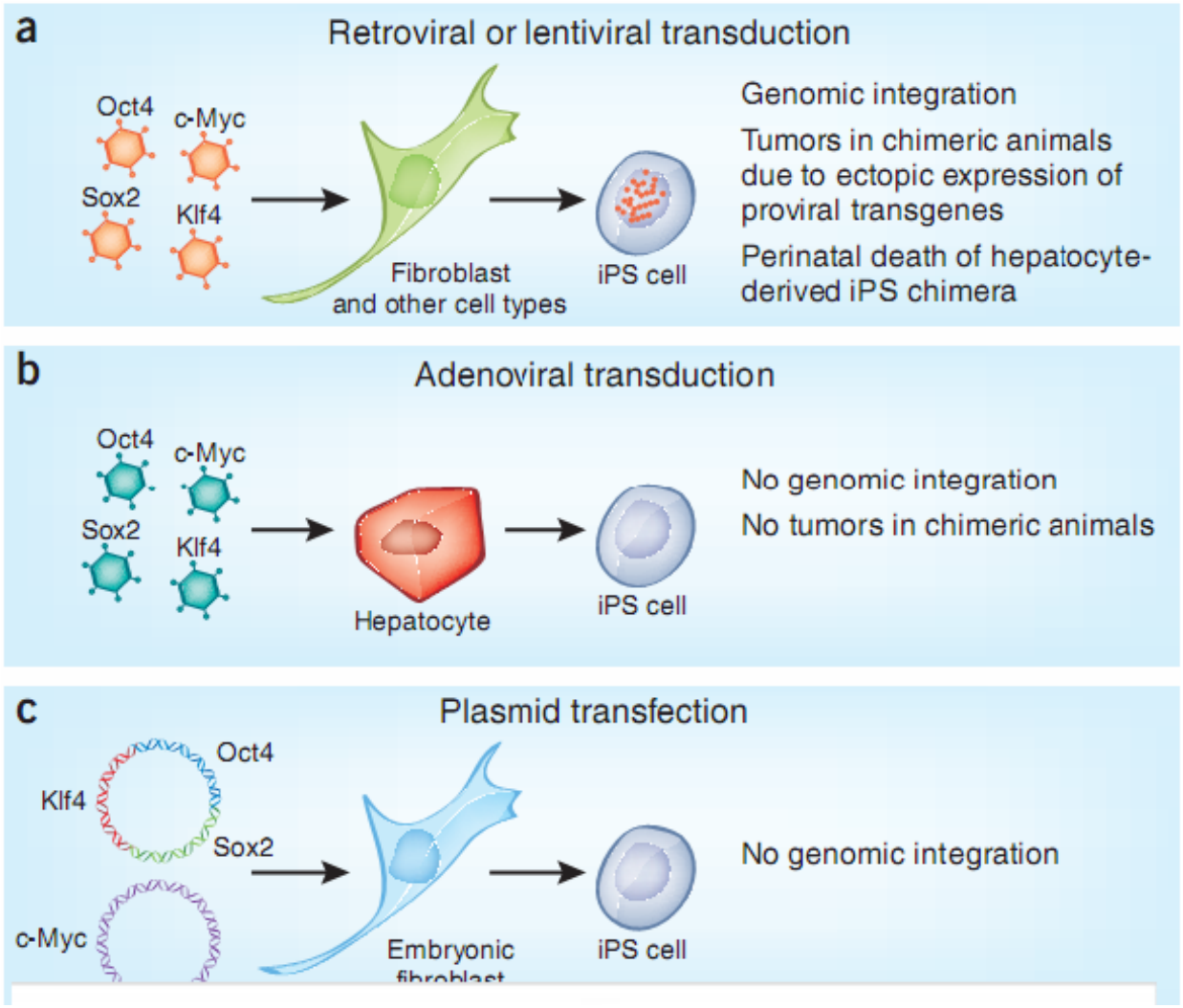
2. Form teratocarcionams when injected undifferentiated into the immunodeficient animals

3. Differentiate into the endoderm, ectoderm and mesoderm

Problems with application of iPS cells in human transplantation

- Use of viral vectors (ectopic transgene expression)
- Integration of vectors with genome (mutagenesis)
- Teratoma formation (unlimited differentiation)

Other reprogramming methods – other vectors



Also: Sendai virus, delivery of RNA, microRNAs

Table 1 | Methods for reprogramming somatic cells to iPS cells

Vector type		Cell types	Factors*	Efficiency (%)	Advantages	Disadvantages
Integrating	Retroviral[1,14,82,83]	Fibroblasts, neural stem cells, stomach cells, liver cells, keratinocytes, amniotic cells, blood cells and adipose cells	OSKM, OSK, OSK + VPA, or OS + VPA	~0.001–1	Reasonably efficient	Genomic integration, incomplete proviral silencing and slow kinetics
	Lentiviral[15,16,84,85]	Fibroblasts and keratinocytes	OSKM or *miR302/367* cluster + VPA	~0.1–1.1	Reasonably efficient and transduces dividing and non-dividing cells	Genomic integration and incomplete proviral silencing
	Inducible lentiviral[23,28]	Fibroblasts, β cells, keratinocytes, blood cells and melanocytes	OSKM or OSKMN	~0.1–2	Reasonably efficient and allows controlled expression of factors	Genomic integration and requirement for transactivator expression
Excisable	Transposon[86]	Fibroblasts	OSKM	~0.1	Reasonably efficient and no genomic integration	Labour-intensive screening of excised lines
	loxP-flanked lentiviral[87]	Fibroblasts	OSK	~0.1–1	Reasonably efficient and no genomic integration	Labour-intensive screening of excised lines, and *loxP* sites retained in the genome
Non-integrating	Adenoviral[88,89]	Fibroblasts and liver cells	OSKM	~0.001	No genomic integration	Low efficiency
	Plasmid[90,91]	Fibroblasts	OSNL	~0.001	Only occasional genomic integration	Low efficiency and occasional vector genomic integration
DNA free	Sendai virus[92]	Fibroblasts	OSKM	~1	No genomic integration	Sequence-sensitive RNA replicase, and difficulty in purging cells of replicating virus
	Protein[93,94]	Fibroblasts	OS	~0.001	No genomic integration, direct delivery of transcription factors and no DNA-related complications	Low efficiency, short half-life, and requirement for large quantities of pure proteins and multiple applications of protein
	Modified mRNA[95]	Fibroblasts	OSKM or OSKML + VPA	~1–4.4	No genomic integration, bypasses innate antiviral response, faster reprogramming kinetics, controllable and high efficiency	Requirement for multiple rounds of transfection
	MicroRNA[96]	Adipose stromal cells and dermal fibroblasts	miR-200c, miR-302s or miR-369s	~0.1	Efficient, faster reprogramming kinetics than commonly used lentiviral or retroviral vectors, no exogenous transcription factors and no risk of integration	Lower efficiency than other commonly used methods

*OSKM and similar factor names represent combinations of reprogramming factors: K, KLF4; L, LIN28; M, c-MYC; N, NANOG; O, OCT4; S, SOX2; and VPA, valproic acid.

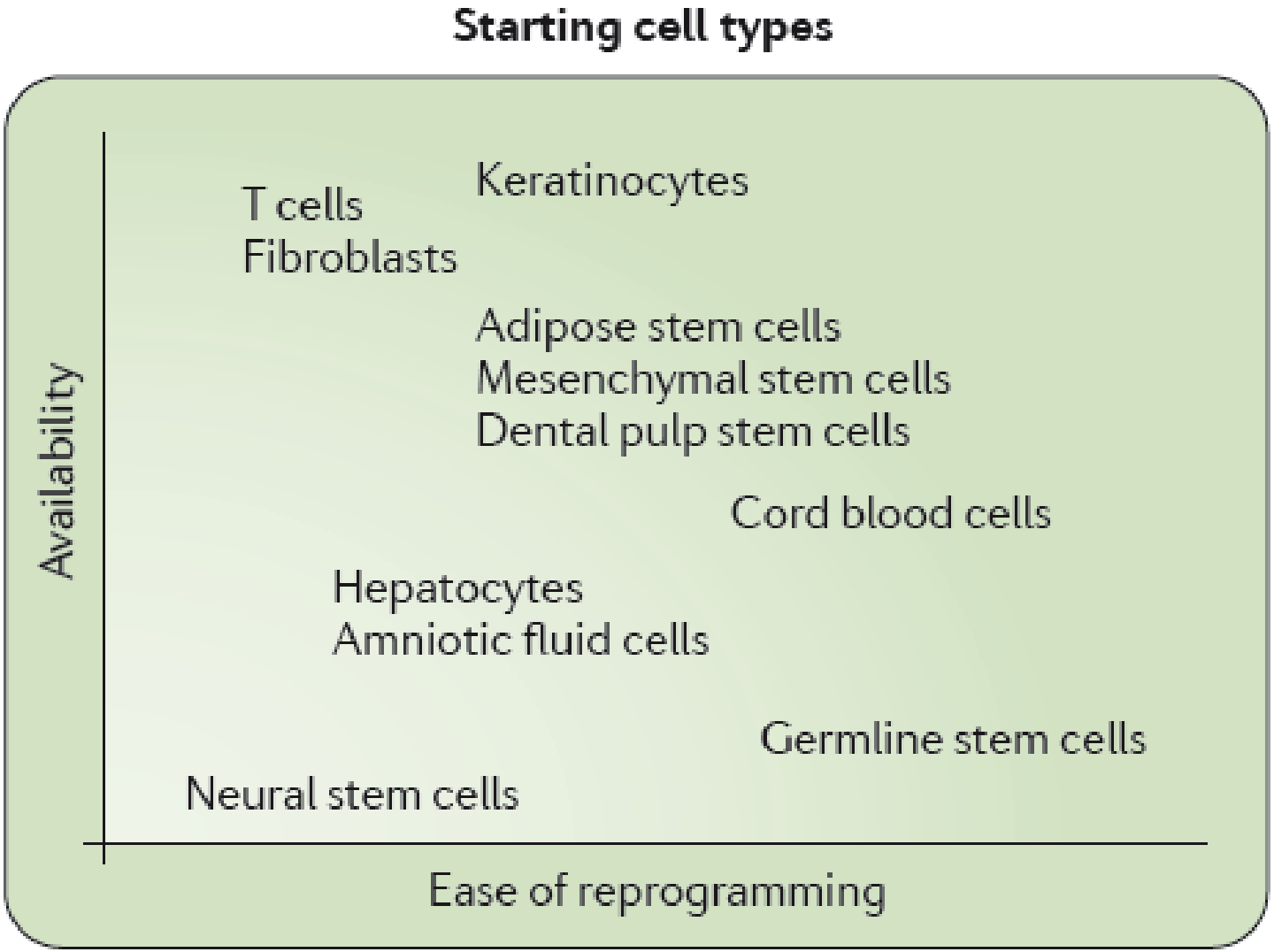
Robinton & Daley , Nature 19th January 2012

Table 1. iPS induction methods in human fibroblasts.

type of vector	method	genomic integration	factors[d]	reprogramming efficiency in human fibroblasts [e]	reference
virus	retrovirus	+	OSKM	++++	[13]
	lentivirus	+	OSNL	+++	[14]
	adenovirus	−[a]	OSKM	+	[19]
	Sendai virus	−[b]	OSKM	++++	[20]
DNA	episomal plasmid	−[a]	OSKMNLT	+	[24]
	transposon	−[a,c]	OSKM	++	[21,22]
	minicircle	−[a]	OSNL	+	[23]
RNA	RNA	−	OSKM	+++	[25]
protein	cell transparent protein	−	OSKM	+	[26]

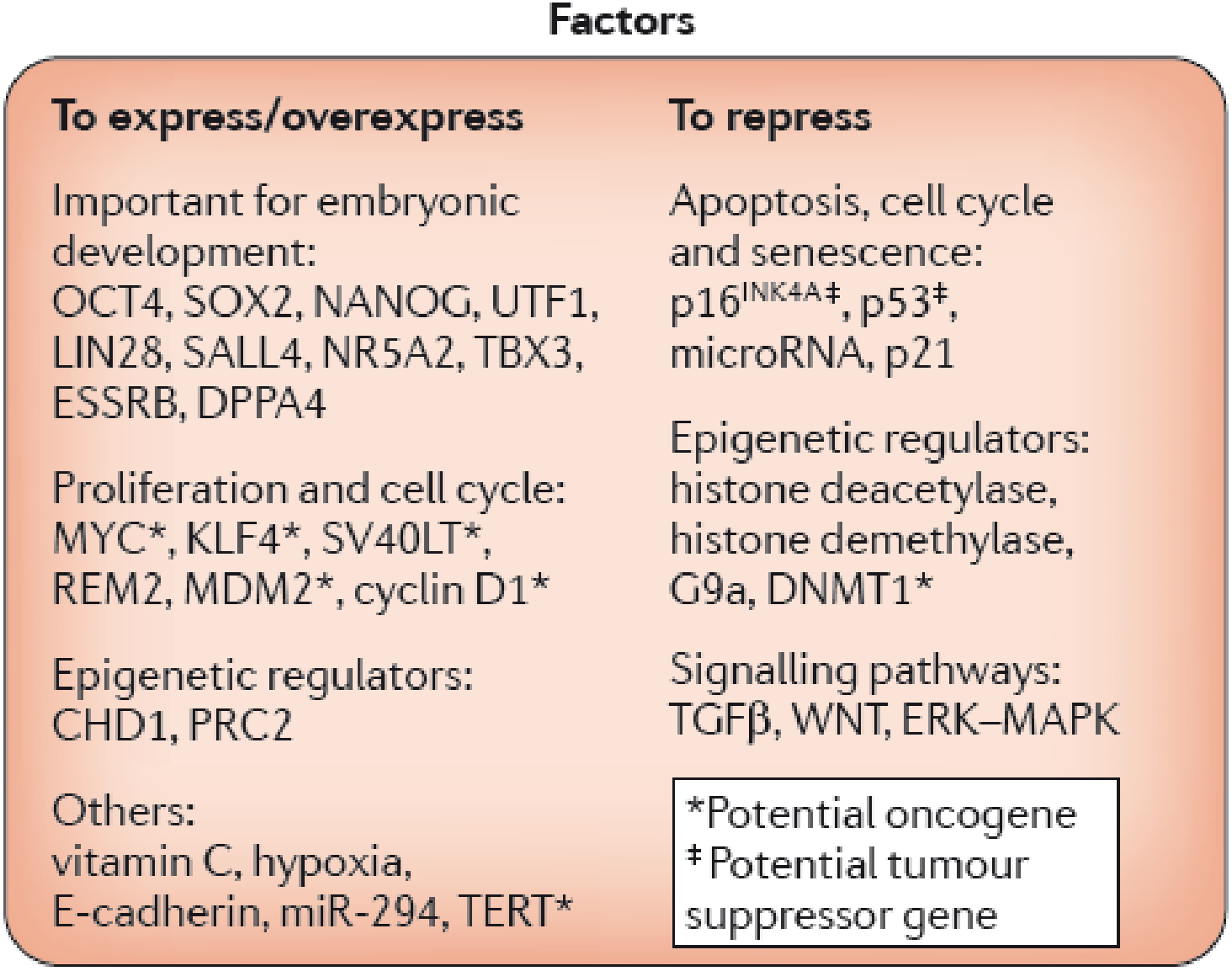
[a]Absence of genomic integration should be experimentally examined.
[b]Absence of virus RNA genome should be experimentally examined.
[c]Transposon vector is integrated into genome, but it can be removed.
[d]O, OCT3/4; S, SOX2; K, KLF4; M, C-MYC; N, NANOG; L, LIN28; T, SV40-large T antigen.
[e]+, <0.001%; ++, <0.01%; +++, <0.1%; ++++, >0.1%.

Different cells types can be used for reprogramming



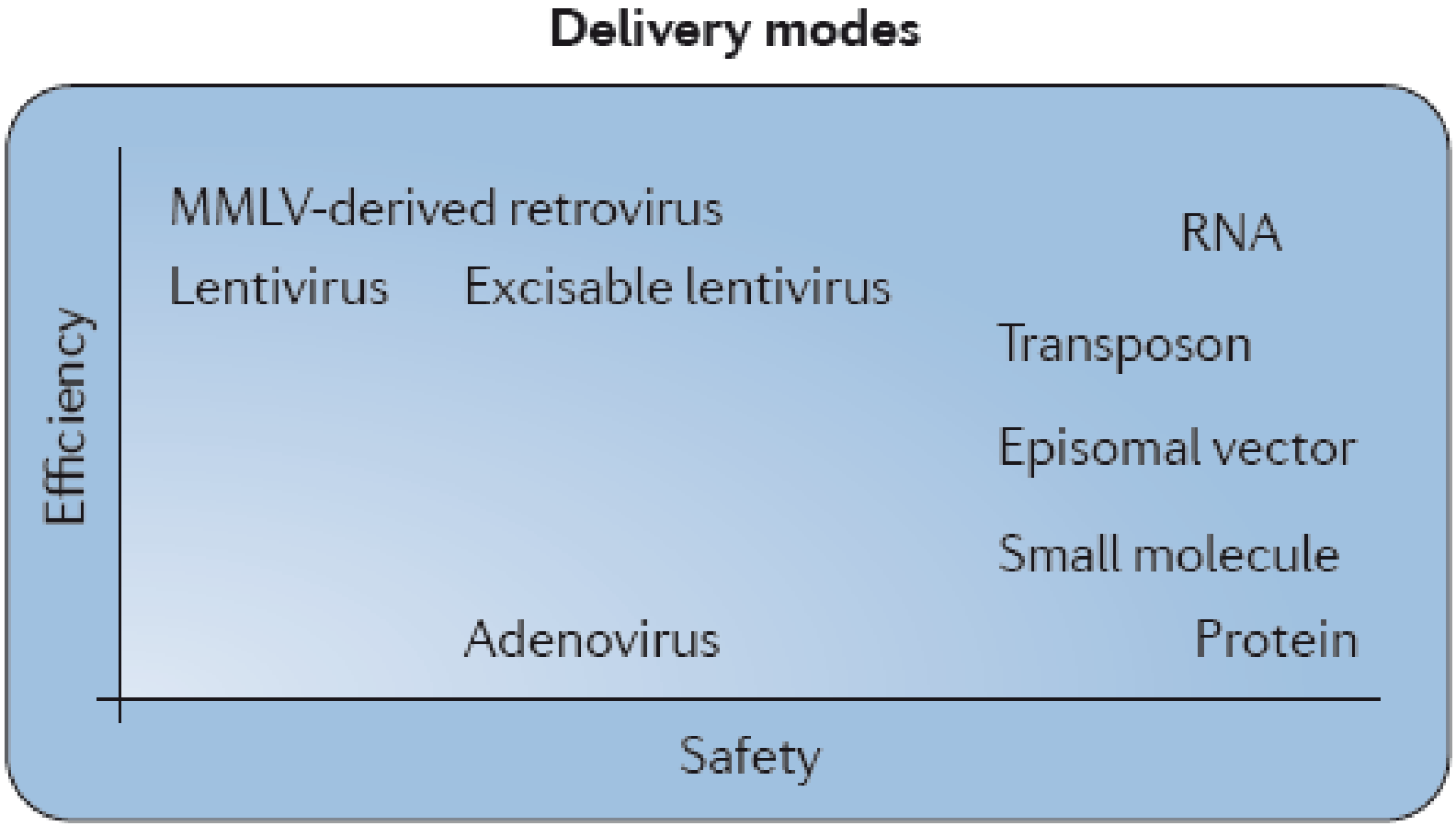
Gonzalez et al., Nature Reviws Genetics 20011

Pathways affected by reprogramming



Gonzalez et al., Nature Reviws Genetics 20011

Methods of reprogramming



Gonzalez et al., Nature Reviws Genetics 20011

Reprogramming with small chemicals

-Valproic acid (VPA) – histone deacetylase inhibitor
-5-azacytidine - DNA methyltransferase inhibtor
-BIX-01294 (BIX) – G9a histone methylase inhibitor
-BayK8644 (BayK) – L-channel calcium agonist

Those compounds are used together with transfer of some genes (Oct4, Klf4 are usually necessary)

iPS – long term application and challenges

Regenerative medicine

1. Overcoming two important obstacles:
   a) immune rejection after transplantation
   b) ethical concerns regarding the use of human embryos

2. New obstacles with iPS
   a) teratoma formation
   b) aberrant reprogramming
   c) impaired differentiation of iPS into the required cell type
   d) presence of transgene in iPS

Applications of iPS

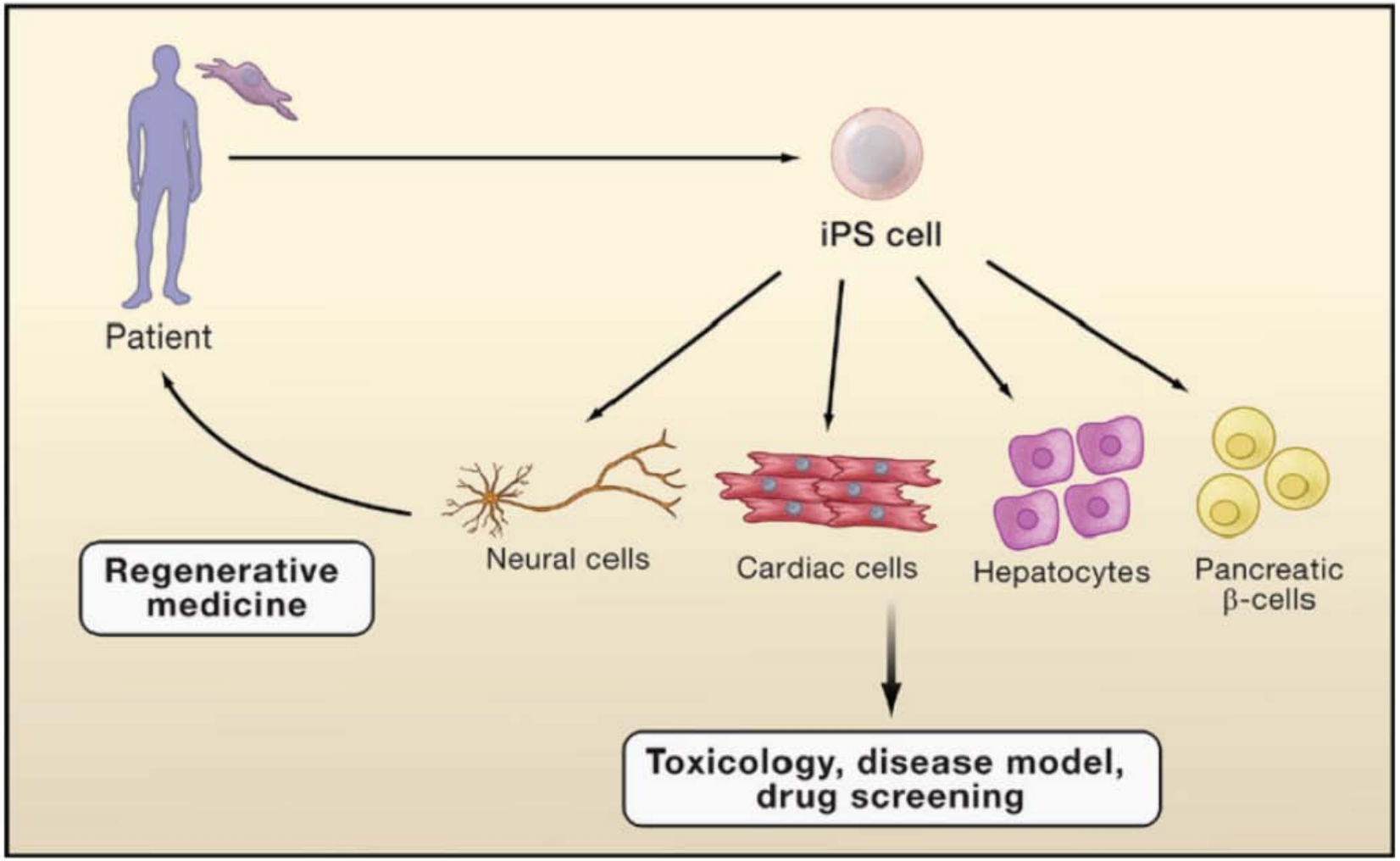
1. Regenerative medicine – iPS as ***medicines***
   problems to solve: tumors risk – due to transgene integration
   - due to persistence of undifferentiated cells

2. In vitro applications – ***testing of*** medicines

- development of disease models
- Drug screening
- Toxicology

The second applications are around the corner…

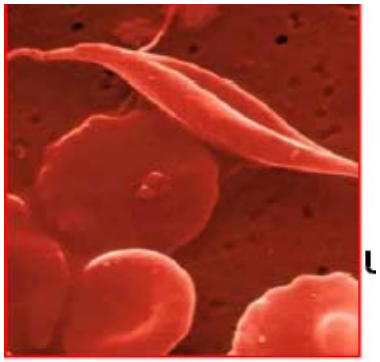
Potential Applications of iPS cells



Shinya Yamanaka Cell *137*, April 3, 2009

iPS-based gene therapy

Sickle cell anemia



- Caused by a point mutation in the β-globin chain of hemoglobin - hydrophilic glutamic acid is replaced with the hydrophobic valine at the sixth position.

- Under low-oxygen conditions the absence of a polar amino acid at position six of the β-globin chain promotes the non-covalent polymerisation (aggregation) of haemoglobin, which distorts red blood cells into a sickle shape and decreases their elasticity

Mice models of sickle cell anemia

A humanized knock-in-mice: mouse a-globin genes replaced with human a-globin

mouse B-globin genes replaced with human $A\gamma$ and B^S (sickle) globin genes

-Remain viable for up to 18 months but develop typical disease symptoms:

- severe anemia
- splenic infarcts

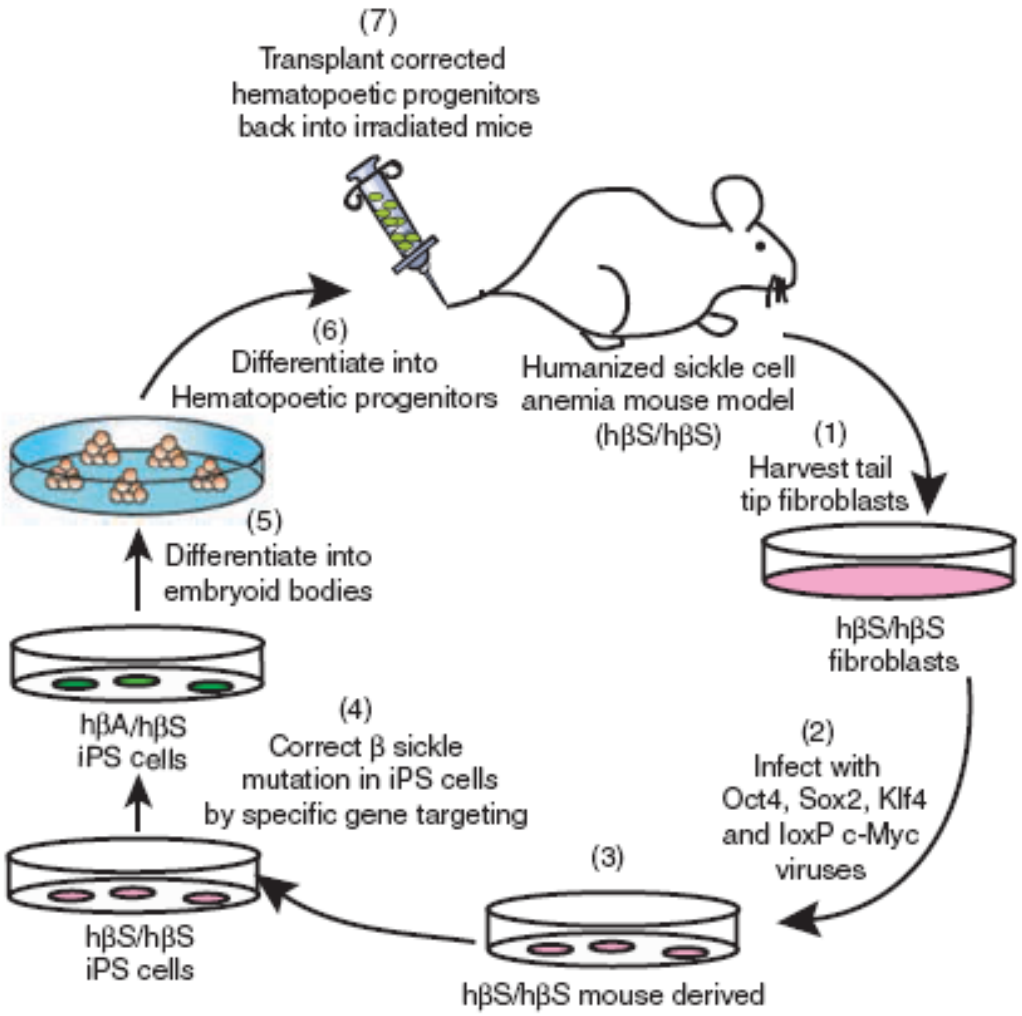
urine concentration defects

- overall poor health

iPS cells were electroporated with a targeting construct containing the human β^A wild type globin gene

- About 70% of the peripheral blood in the treated hb^S/hb^S mice were derived from the iPS cells – thus more than was observed in heterozygous hb^A/hb^S

iPS cells-based gene therapy



1. Reprogramming of mutant donor fibroblasts into iPS cells
2. Repair of the genetic defect through homologous recombination
3. In vitro differentiation of the repaired iPS cells into HPs
4. Transplanting these cells into affected donor mice after irradiation

Hanna et al. (Jaenisch) Science, 21 Dec, 2007

Future therapeutic applications of iPS cells in humans

Necessity to overcome several obstacles:

1. Bypassing the use of harmful oncogenes as part of the reprogramming factor

2. Avoiding the use for gene delivery of retroviral vectors that carry the risk of insertional mutagenesis

3. Developing robust and reliable differentiation protocols for human iPS cells

Challenges with adult progenitor cell therapy (may also hinder the effectiveness of iPS-based treatment)

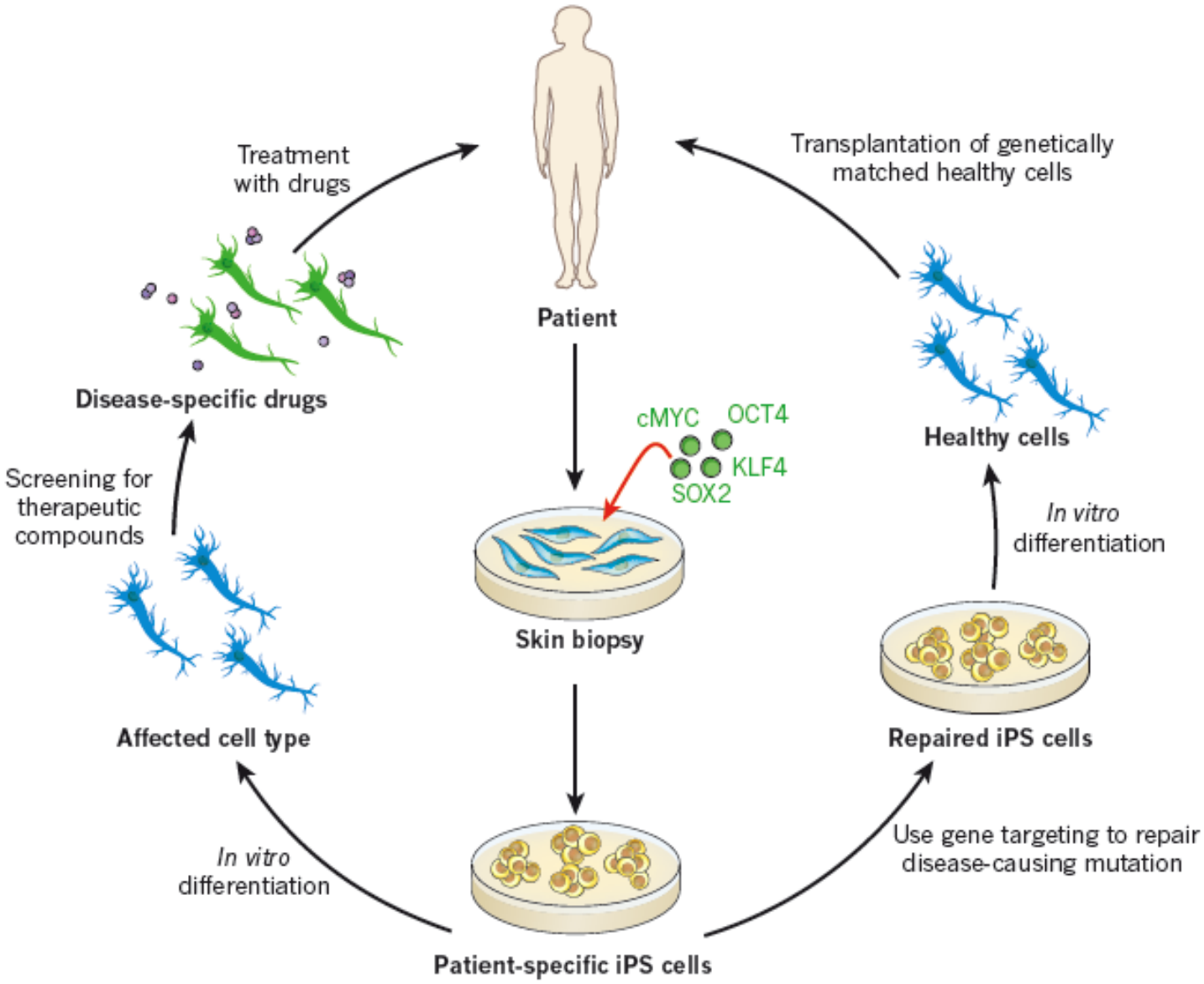
1. Age

2. Underlying diseases: diabetes, hypertension.

3. Smoking

4. Genetic background: polymorphism of some genes may influence the effectiveness of application of cell therapy

Medical applications of iPS cells



Robinton & Daley , Nature 19th January 2012

Induced pluripotents stem cells (iPS)

Ethical issues

1. Reprogrammable cells can form viable chimeras and contribute to the germline when injected into blastocysts

Humans might be able to pass on their genes (or genetically modified genes) to future generations from just a few cells

The magic act of nuclear reprogramming

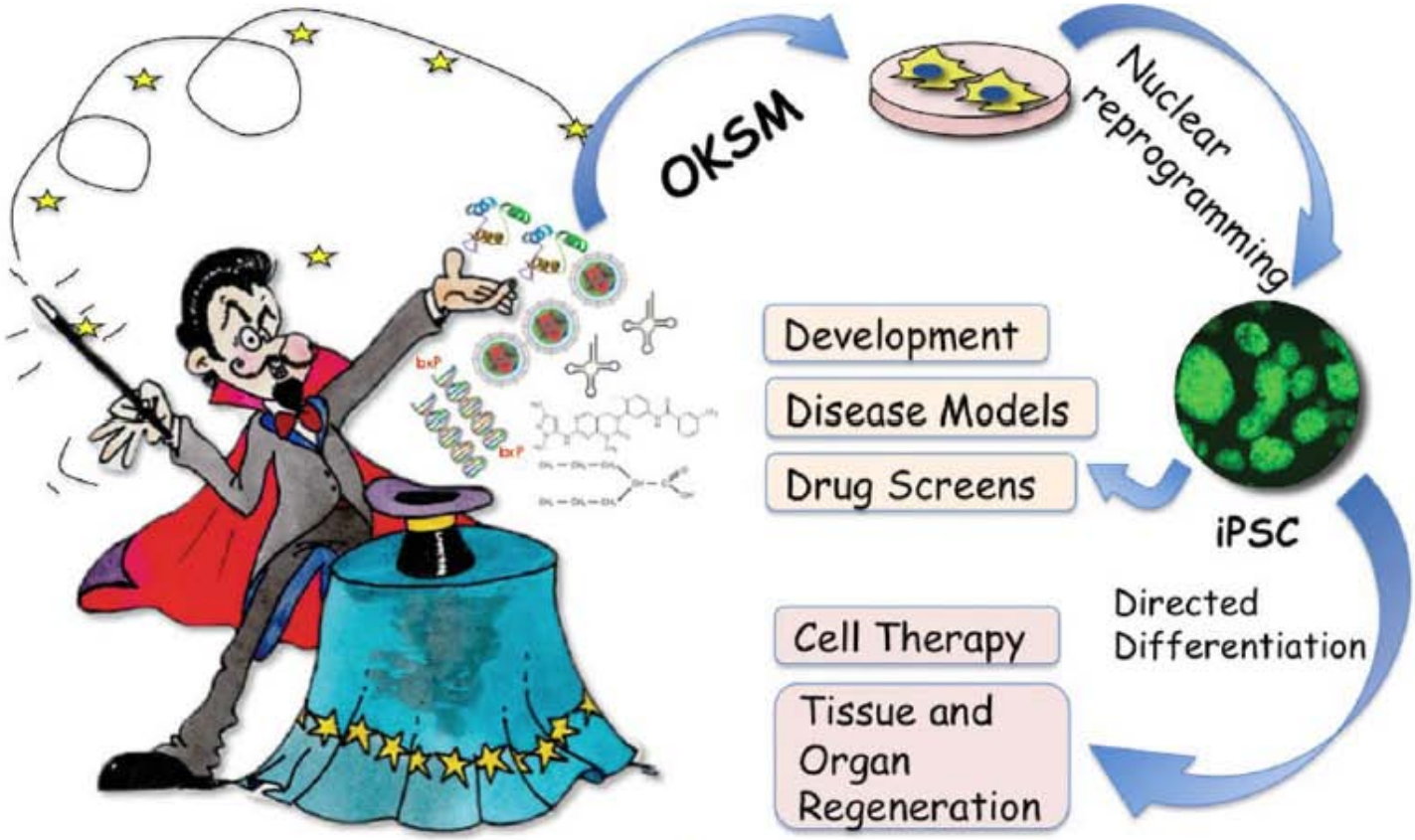


Figure 1. The "magic act" of nuclear reprogramming. A toolbox full of tricks is now available for scientists to achieve reprogramming of somatic cells to generate normal and disease-specific iPSC, which will open new avenues of research in human disease modeling, drug discovery and therapy. Abbreviations: iPSC, induced pluripotent stem cell; OKSM, Oct3/4, Klf4, Sox2, and cMyc.

Mostoslavsky G, Stem Cells 2012

Summary – gene transfer in stem cells for therapeutic purposes

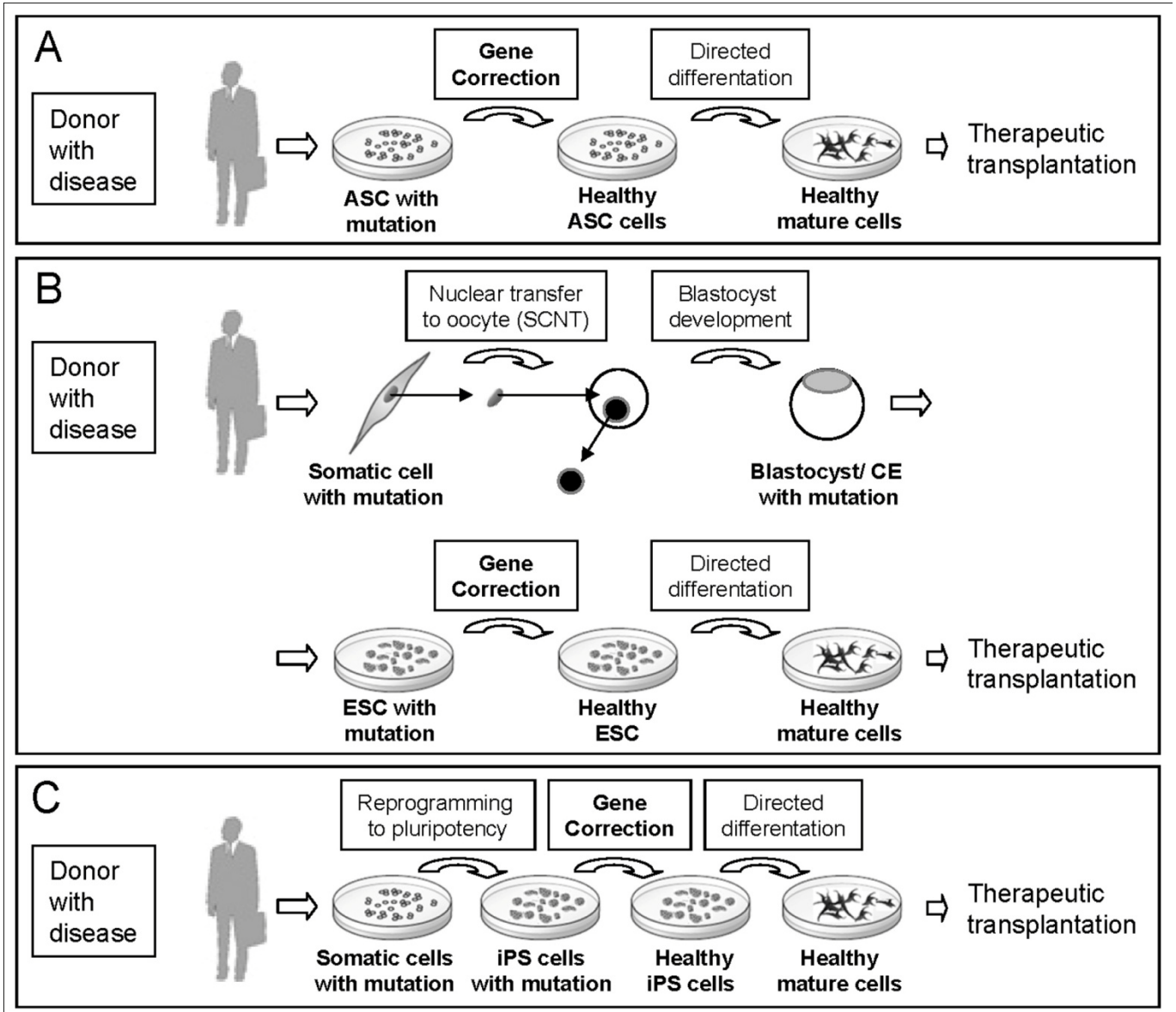


Figure 2

Zuba-Surma, Jozkowicz, Dulak – Current Pharmaceutical Biotechnology 2011

Summary – gene transfer in stem cells for drug research purposes

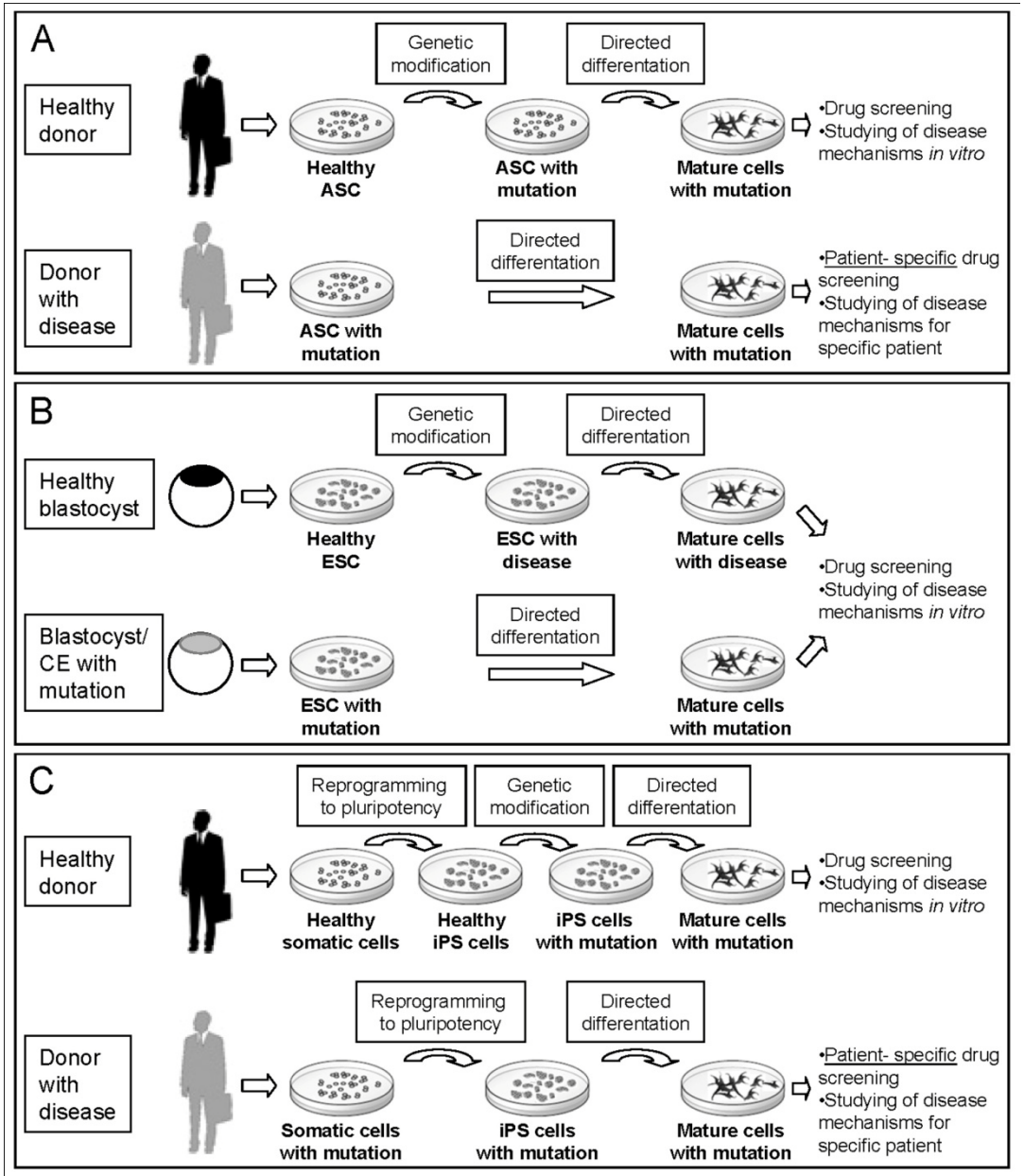


Figure 1

Zuba-Surma, Jozkowicz, Dulak – Current Pharmaceutical Biotechnology 2011

Stem cells therapies

1. Approved and effective applications of autologous and allogeneic bone marrow stem cells in treatment of leukemias, immunodeficiency diseases and some metabolic diseases (eg. adrenoleukodystrophy)

2. Approved applications of skin stem/progenitor cells for treatment of burns and other unhealing wounds

3. Clinical trials demonstrated the feasibility of stem cells applications (bone marrow-derived) for treatment of myocardial infarction (eg. *Tendera et al., Eur Heart J. 2009; 30:1313-21*
- REGENT Trial), but the clinical effects are so far minor and temporary.

4. Pre-clinical studies suggest the possibility of beneficial effects in treatment of some other diseases, eg. the spinal cord injury with neurons obtained from embryonic stem cells. On such a basis Geron Corp. has obtained an FDA agreement to start first clinial trial in human with embryonic stem cells-derived neurons

Are we ready for (commercial) application of adult stem cell therapies ?

Hopes and hypes of regenerative medicine

Stem cell bussiness – Stem cells tourism

China cracks down on stem cell tourism
00:01 04 September 2009 by **Andy Coghlan**

But not only China….

Not only in „exotic” countries…

Warnings are being issued by experts of the dangers of medical tourism saying that unproven stem cell therapy overseas could leave patients worse off.

Facts and threats of commercialisation of stem cell therapies

1. Treatments offered on stem cells website are generally unsupported by the clinical evidence

2. Numerous scientific questions remain unanswered and scientists generally do not recommend these therapies for general access

3. Hypocrysy in discussions –
   a) embryonic stem cells are bad (by defintion – becuase unethical…), adult stem cells are good…
   b) research on embryonic stem cells is unethical, but offering the unproved treatment based on adult stem cells is good…

4. Creation the atmosphere suggesting the possibility of immediate applications of stem cells therapy for treatment of chronic diseases, such as neurological diseases, diabetes…

Hopes and hypes of regenerative medicine

Clinicians and patients have the right to undertake the risk of experimental therapy but this can be only when the benefit of patients, not economical profits are considered !

Therefore, in current stage of knowledge and development of therapy there is **no justification for the private enetrprises** offering commercialy the stem cells treatment.

Using adult stem cells does not make such a company ethical… !

There is no justification for wide use and offering the stem cell therapy for treatment of diseases outside specialised clinics and beyond controlled clinical trials

Stem cell therapy is not teeth repair!

Hope, hypes and cheating

Selected Companies and Clinics Offering Stem Cell Therapies

Company	Location	Conditions	Patients treated	Cost ($)	Remarks
PATIENTS' OWN CELLS					
Cells4Health	Leuvenheim, the Netherlands	Myocardial infarction, vascular disease, spinal cord injury, stroke	NA	+25,000	Treatment takes place at clinics in Turkey and Azerbaijan
NeuraVita	Moscow, Russia	Neurological diseases and injuries	NA	~20,000	
FETAL CELLS					
EmCell	Kiev, Ukraine	More than 50, including neurological disorders, aging, impotence, diabetes, cancer, HIV	Almost 2000 in 13 years	+15,000	
Medra	Malibu, U.S.A.	More than 20, including neurological disorders, depression, autism, sickle cell anemia	More than 1000	NA	Procedures performed in Dominican Republic
Beijing Xishan Institute for Neuroregeneration and Functional Recovery	Beijing, China	Spinal cord injury, ALS, and other neurological conditions	More than 1000 since 2001	20,000	Thousands more on waiting list
Institute for Regenerative Medicine	St. John, Barbados	More than 40	More than 50 since 2004	25,000	Treatment based on research in the former Soviet Union
UMBILICAL CORD BLOOD CELLS					
Biomark	Atlanta, U.S.A.	ALS, Parkinson's, muscular dystrophy, and others	At least 23 in 2003	10,000 to 32,000	No longer operative; founders wanted by FBI
Advanced Cell Therapeutics	Zurich, Switzerland	More than 80	More than 600 in 4 years	25,000	Treatments performed at 12 collaborating clinics worldwide
Preventive Medicine Center	Rotterdam, the Netherlands	More than 50, including neurological, digestive, and psychological disorders and aging	More than 200 in 2 years	23,000	Also treats patients referred by Advanced Cell Therapeutics

SOURCE: COMPANY AND CLINIC WEB SITES, INFORMATION PACKAGES, INTERVIEWS, ALSTDF, BIOMARK CRIMINAL INDICTMENT. NA=INFORMATION NOT AVAILABLE.

Be aware of dishonest people!

Future of stem cell therapy

1. The highest differentiation potential have embryonic stem cells

2. Nuclear transfer may allow to generate patient-specific embryonic stem cells

3. Therapeutic applications of ESCs is at the moment limited by risk of side effects (teratoma formation) and ethical consideration

4. Patient-specific, induced pluripotent stem cells can be obtained by reprogramming of adult somatic cells by transfer of 3-4 key genes. In future, reprogramming could be achieved by culture conditions

5. Therapeutic potential of iPS – in combination with gene therapy – has been demonstrated in mice model of heamophilia; as well as some other disease

6. Adult progenitor cells (eg. bone marrow derived) remain the major target of therapeutic approaches

7. Effective applications of adult progenitor cells may require overexpression of certain crucial genes, eg. involved in anti-oxidant defence and angiogenesis

Our interests

Bone marrow derived stem cells

1. **Hematopoietic stem cells**

2. **Mesenchymal stem cells**

3. **Progenitor cells – eg. endothelial progenitor cells**

4. **Very small embryonic-like stem cells (VSEL) –**

Tissue stem / progenitor cells

1. Skin stem cells/skin progenitor cells

2. **Satellite cells**

Induced pluripotent stem cells

Exam – 30th January (Monday) –1 pm – room D107

Multiple choice test

Please fill the course assessment at the USOS website ….