Stem and cell gene therapy

Lecture 13

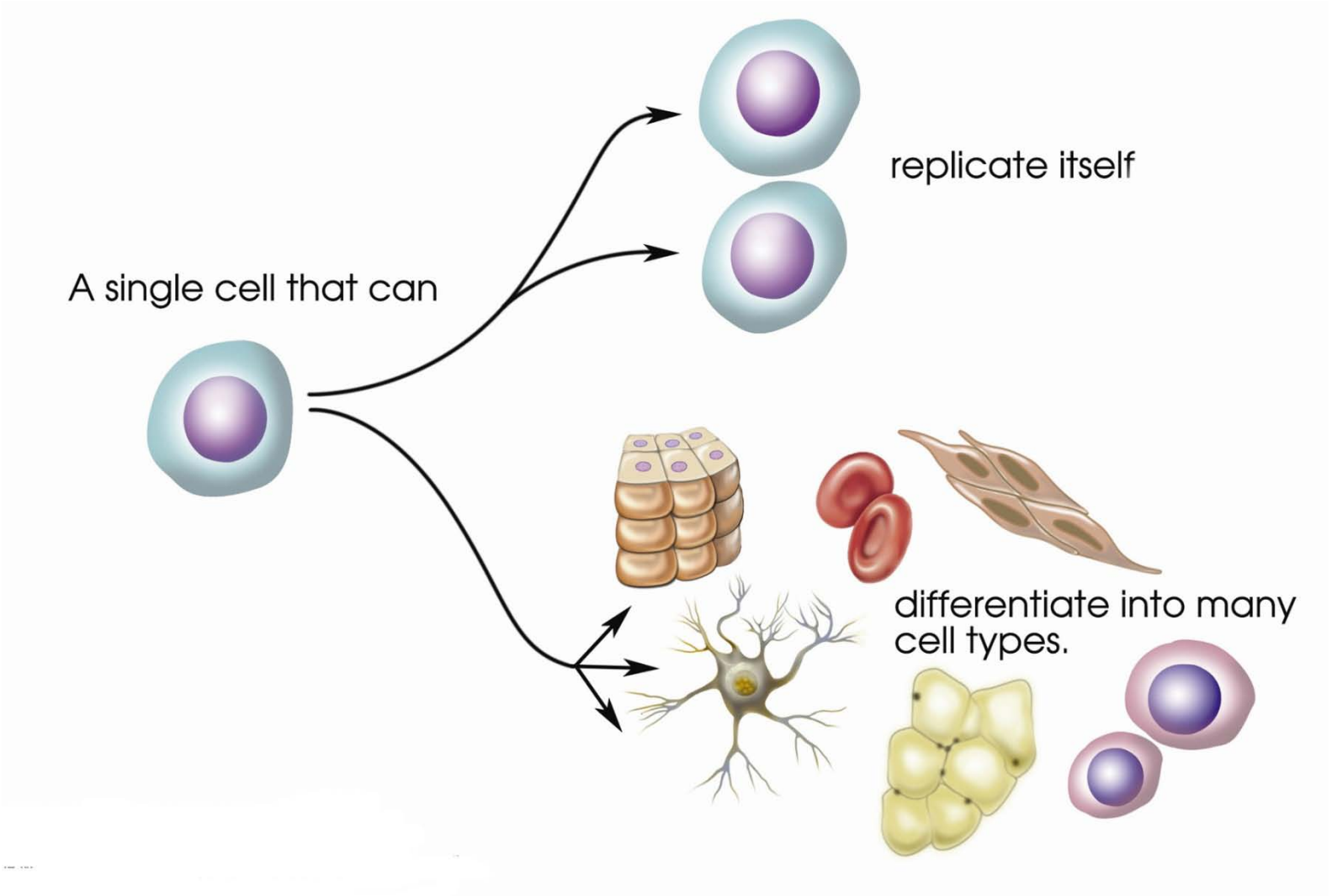
24th January 2011

1. Stem cells – types and potential

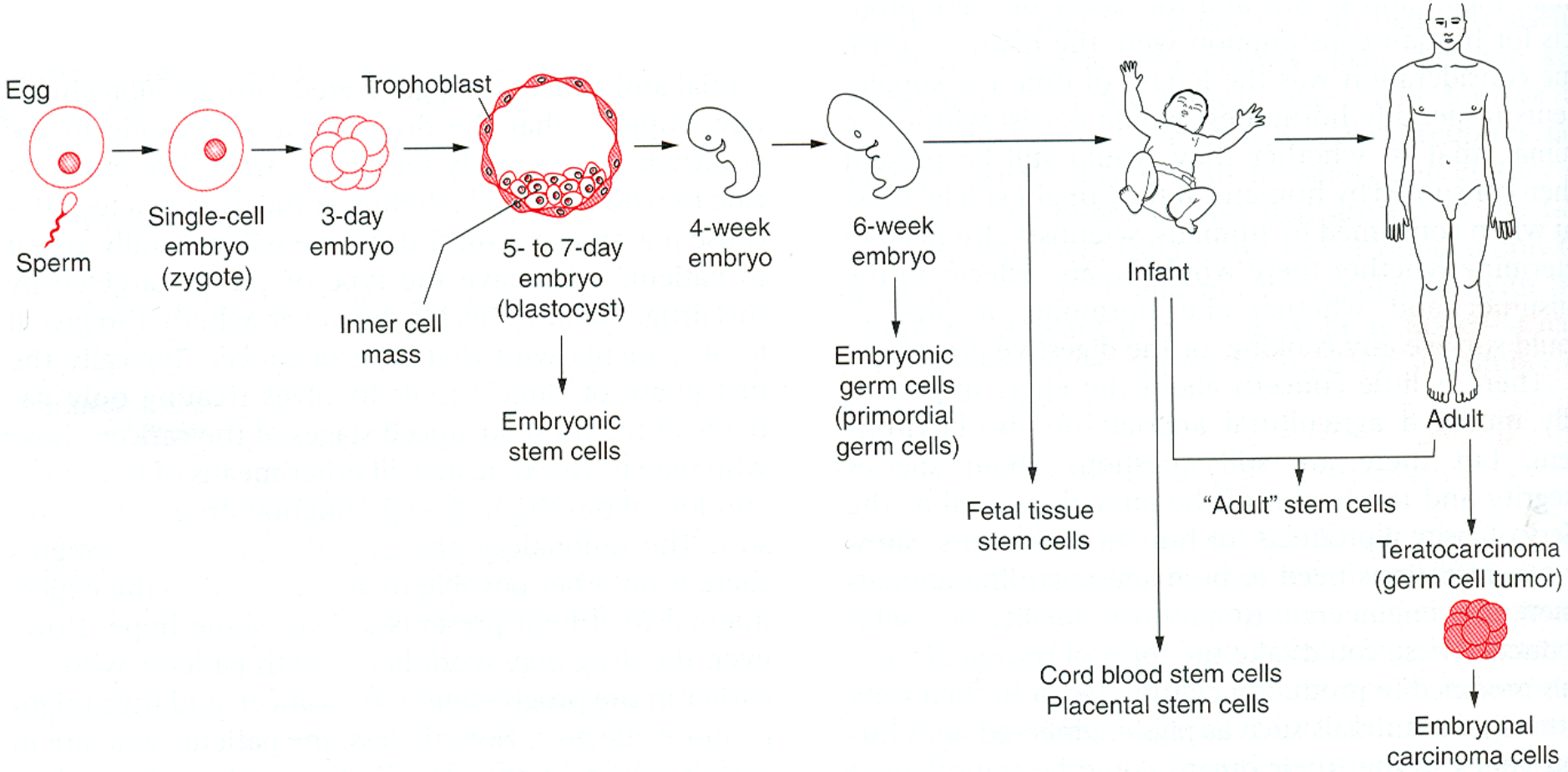
2. (Very) recent achievements in stem cell research

3. Research on stem cells at Department of Medical Biotechnology

What is a stem cell?



Sources of stem cells



Embryonal

somatic

Classification of SCs

1. Based on the tissue commitment/ differentation capacity

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

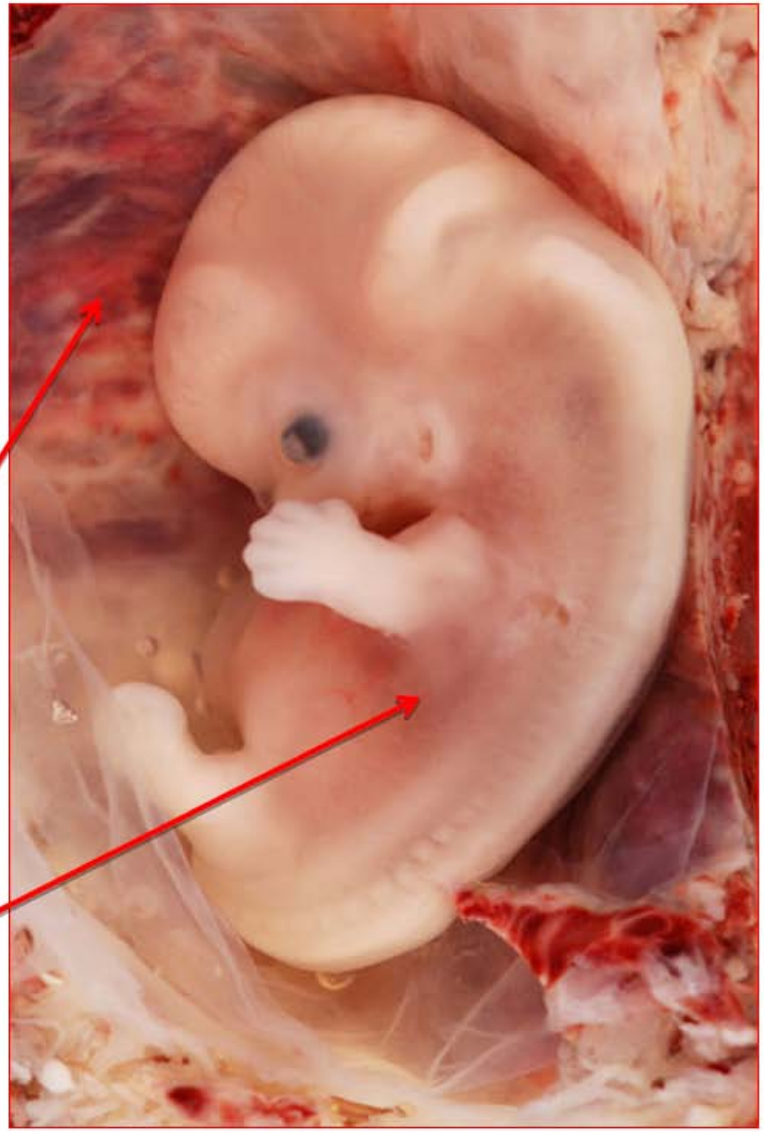
2. Based on their origin

- Embryonic SCs (ESCs)
- Adult SCs
- Reprogrammed SCs (Inducible Pluripotent SCs = iPS cells)

Zygote – the „mother" of all stem cells

ZYGOTE -
Totipotent SC

1. Extraembryonic tissues (Placenta)
2. Embryonic tissues



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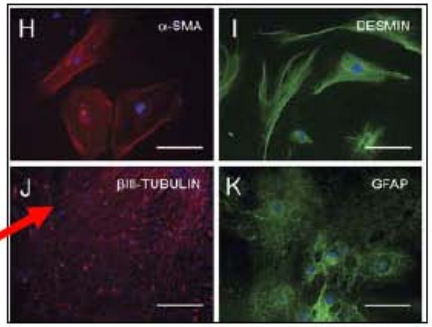
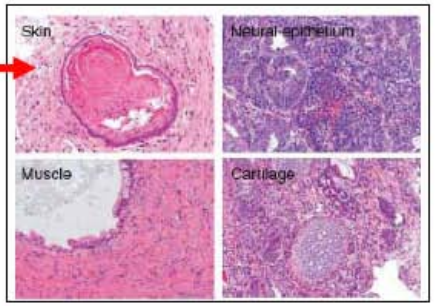
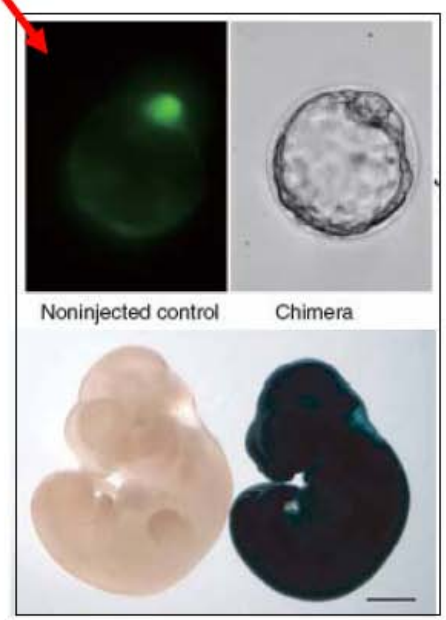
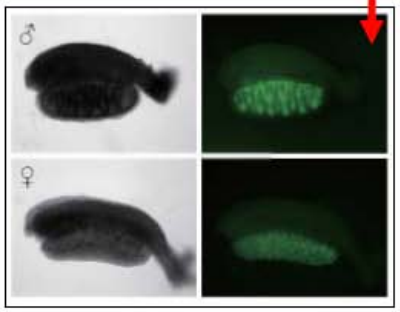
How to asses the pluripotency of SCs?

Assay	Experimental approach
In vitro differentiation	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	Injection of test cells into 4n host blastocyst. Because 4n host cells cannot contribute to somatic lineages embryo is exclusively composed of test cells









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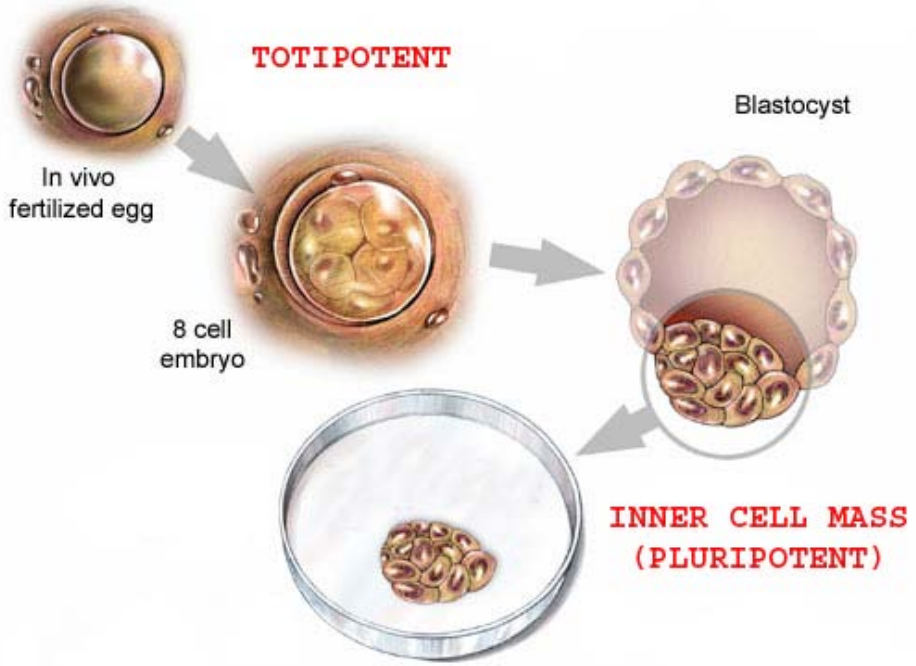
What are embryonic stem cells?

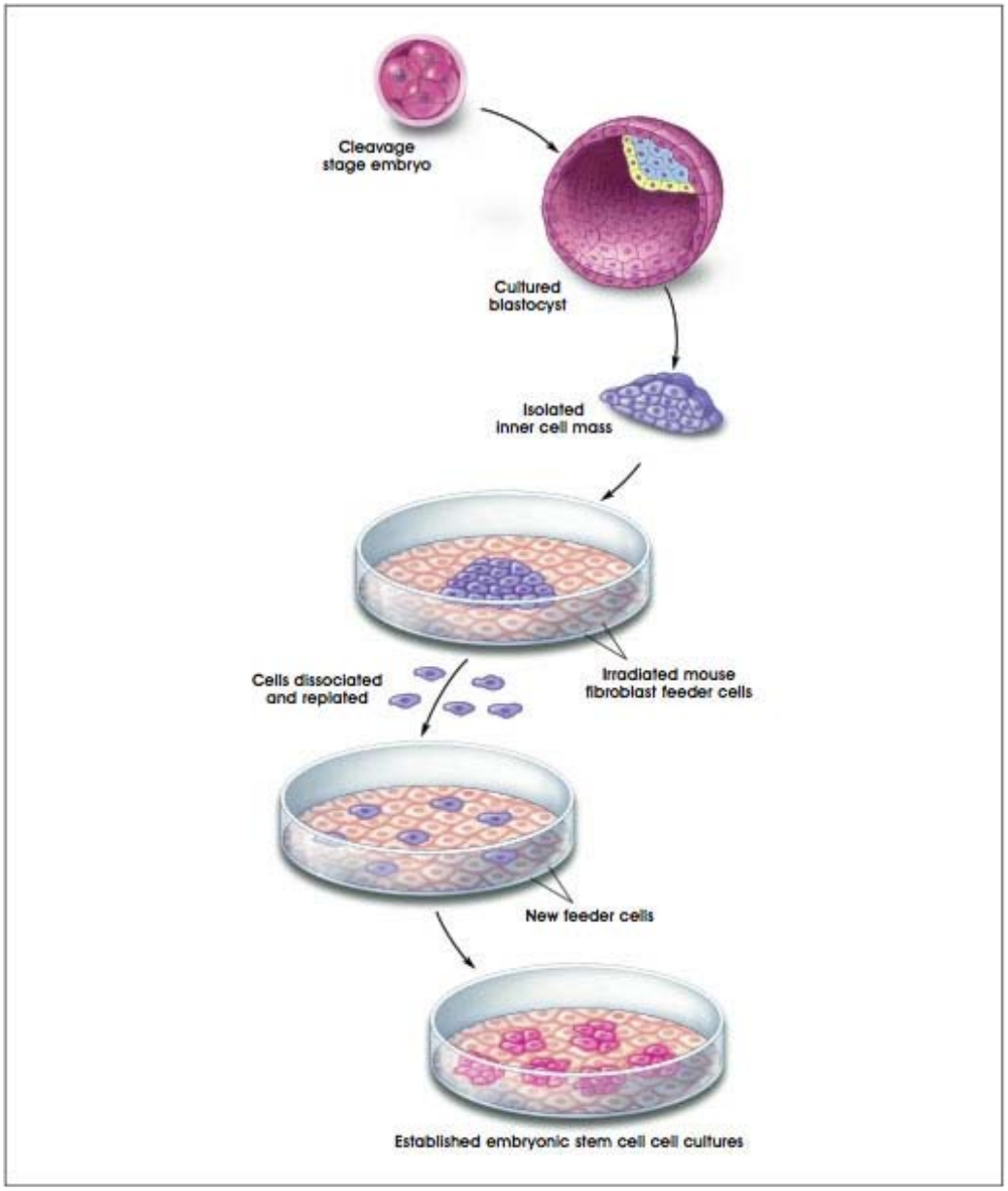


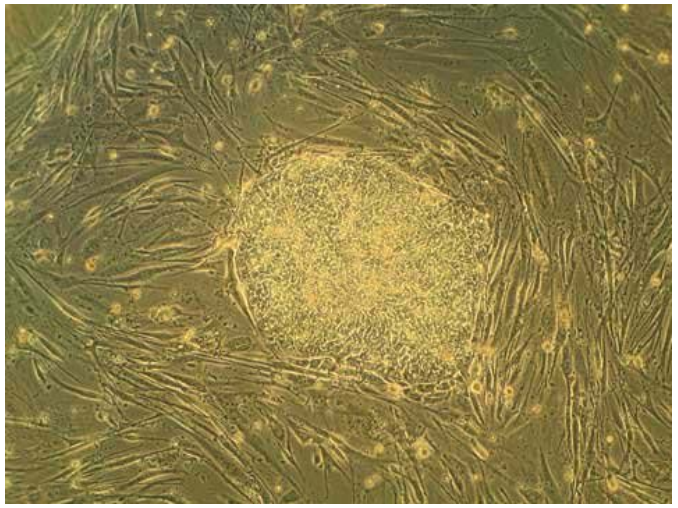
- develop from eggs fertilized in vitro

- derived from 4-5 days old embryos

- isolated from ~ 8 cell embryo or inner cell mass

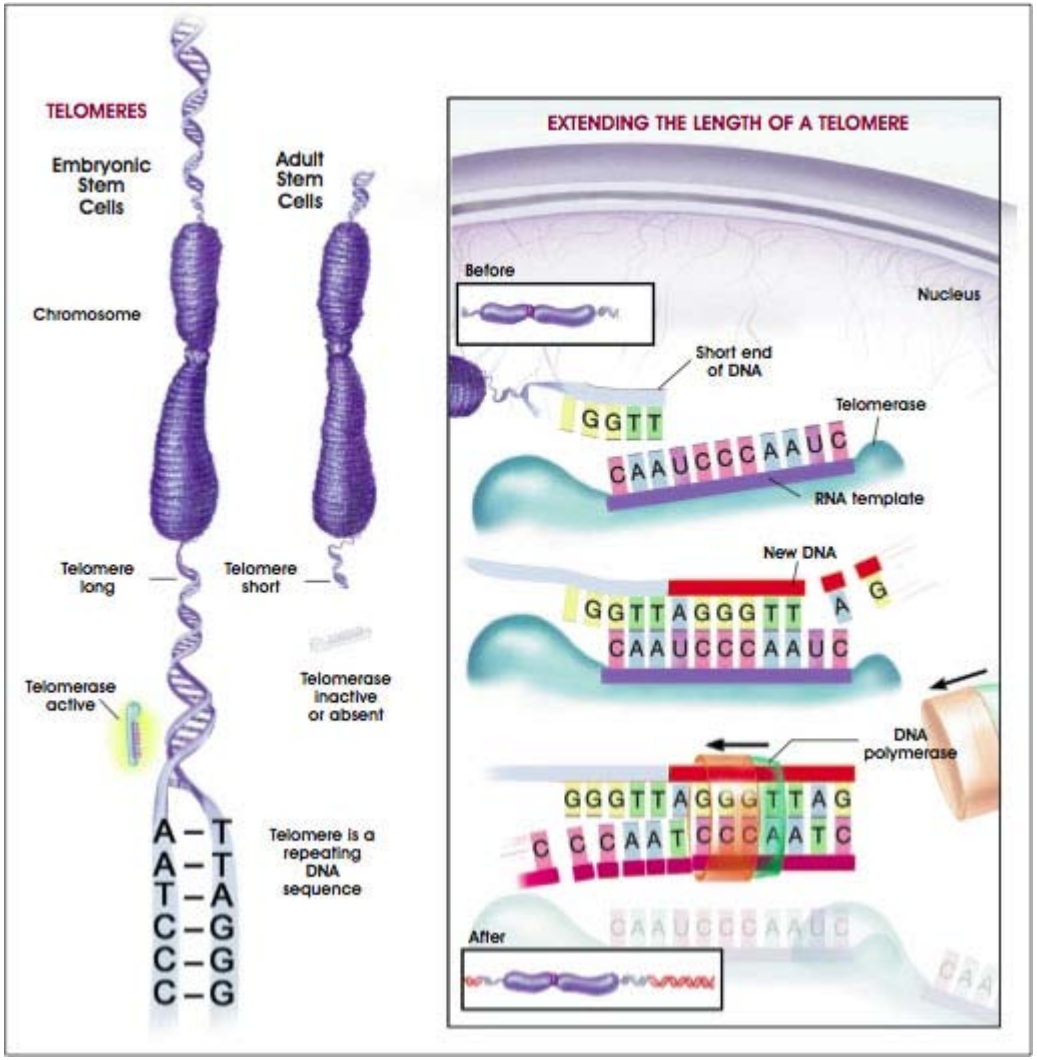
Human embryonic stem cells





Stem Cell Information

The National Institutes of Health resource for stem cell research

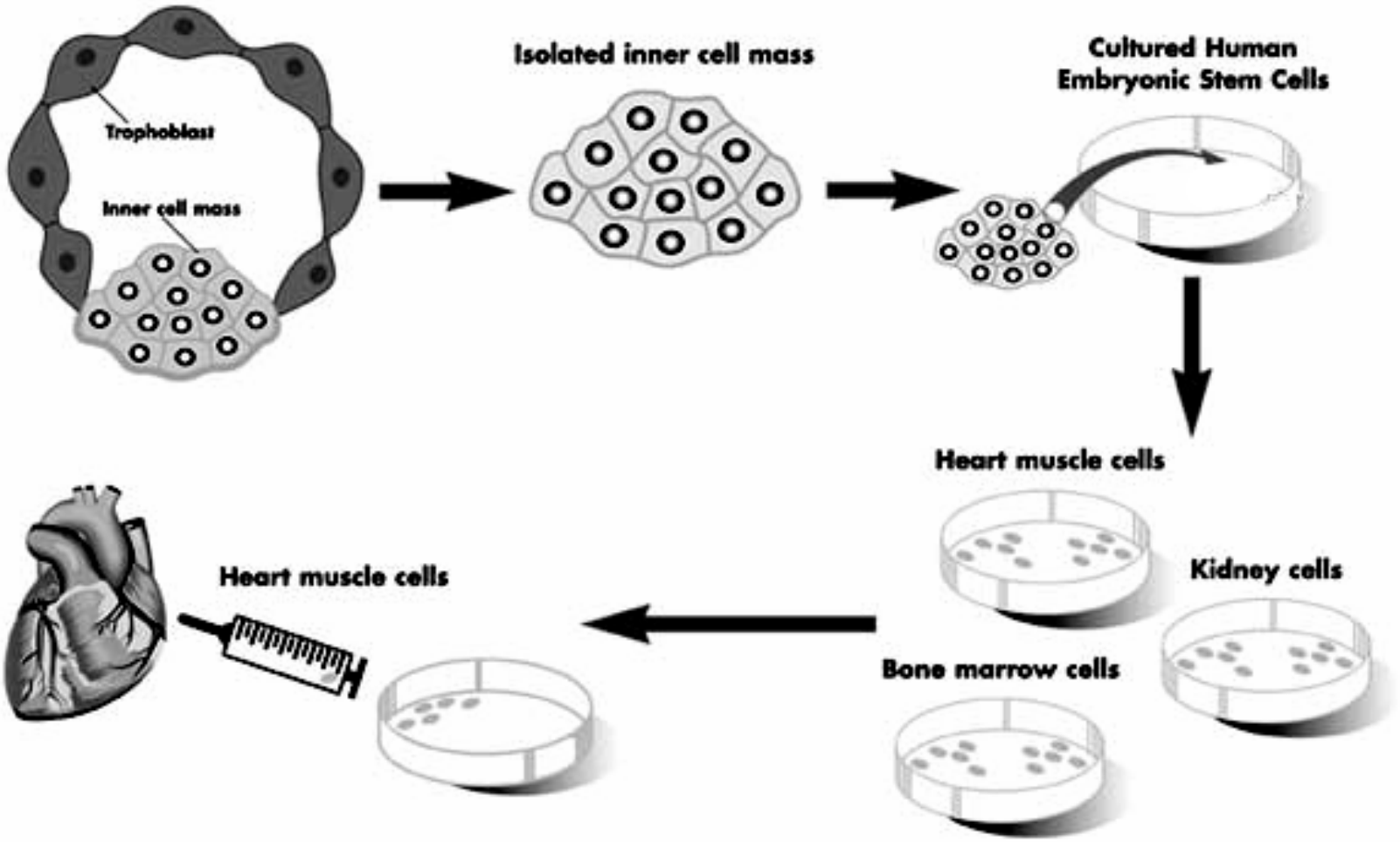


Embryonic stem cells have high telomerase activity

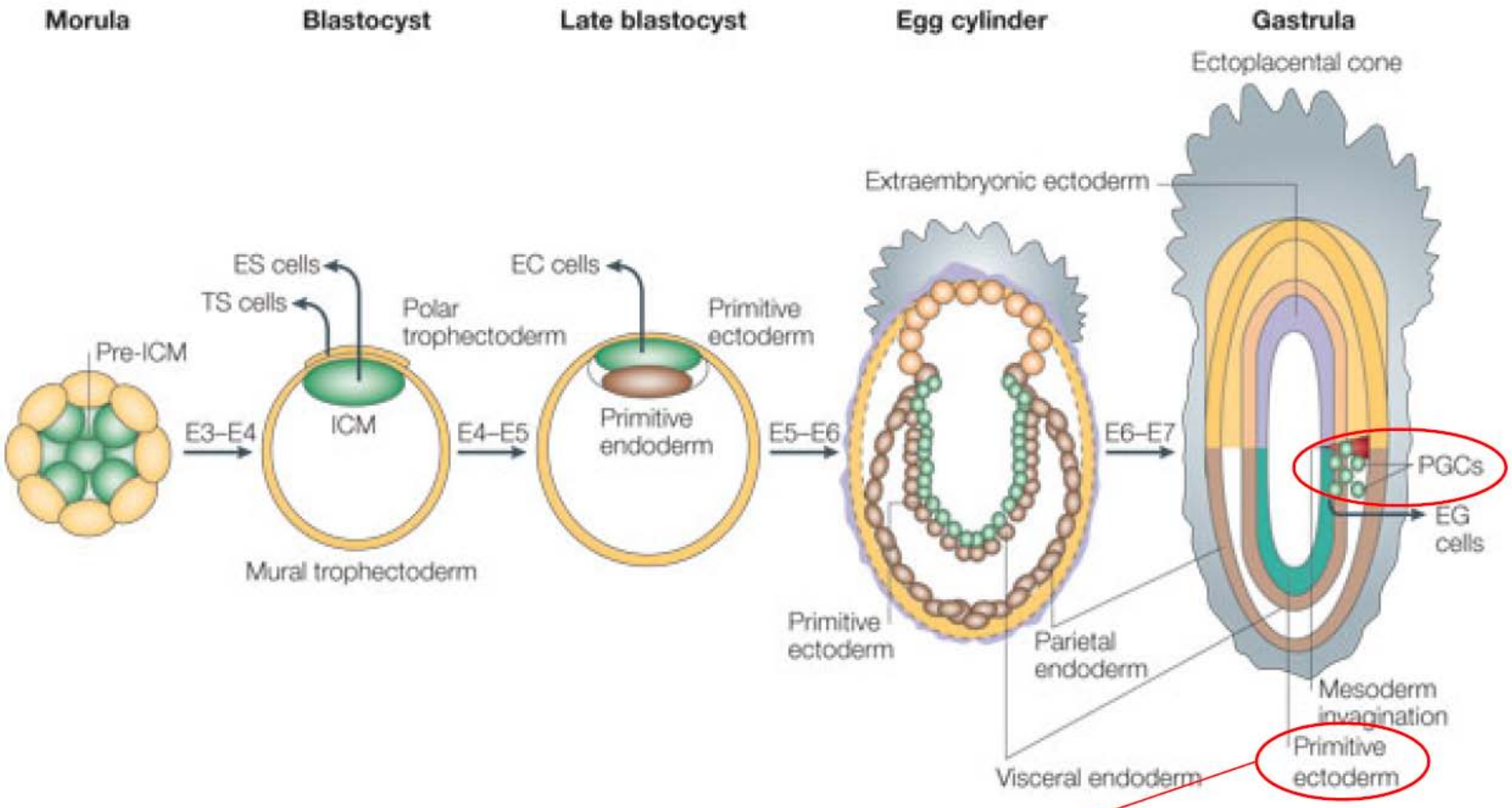
Stem Cell Information

The National Institutes of Health resource for stem cell research

Embryonic stem cells in the lab



Epiblast – other source of pluripotent SC



Epiblast = Primitive Ectoderm

- Primordial Germ Cells (PGCs)→ EG cells
- Very Small Embryonic-Like stem cells (VSELs)

Generation of transgenic mice overexpressing HO-1 in the skin

Malgorzata Gozdecka, Jacek Walczyński, Klaudia Skrzypek, Anna Zagórska, Agnieszka Jaźwa, Claudine Kieda, Alicja Józkowicz, Yann Hérault, Józef Dulak

25.02.2008

Adult stem cells

bone marrow

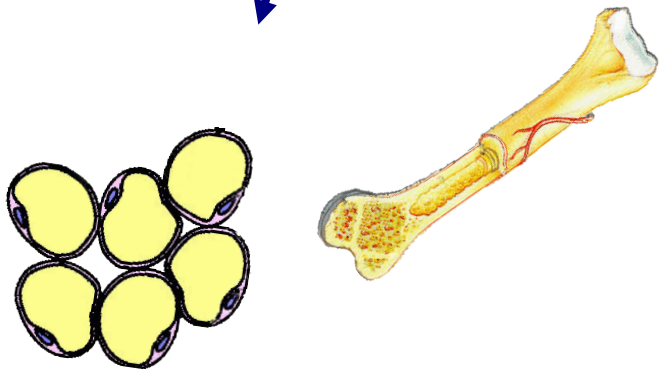
hematopoietic stem cells

Adult stem cells

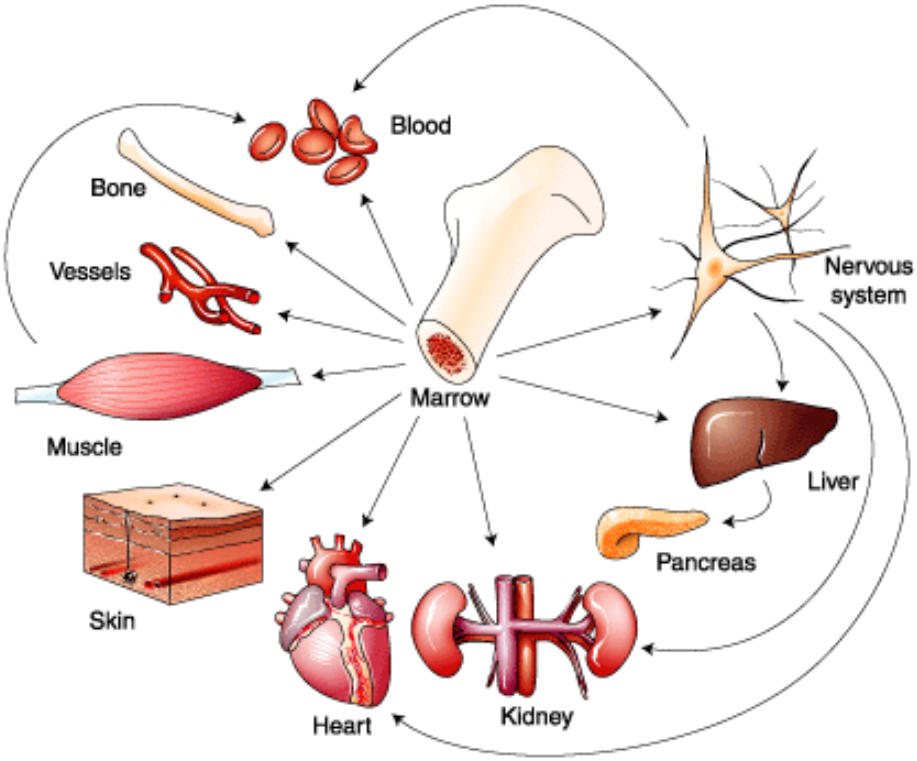
bone marrow

hematopoietic stem cells

mesenchymal stem cells



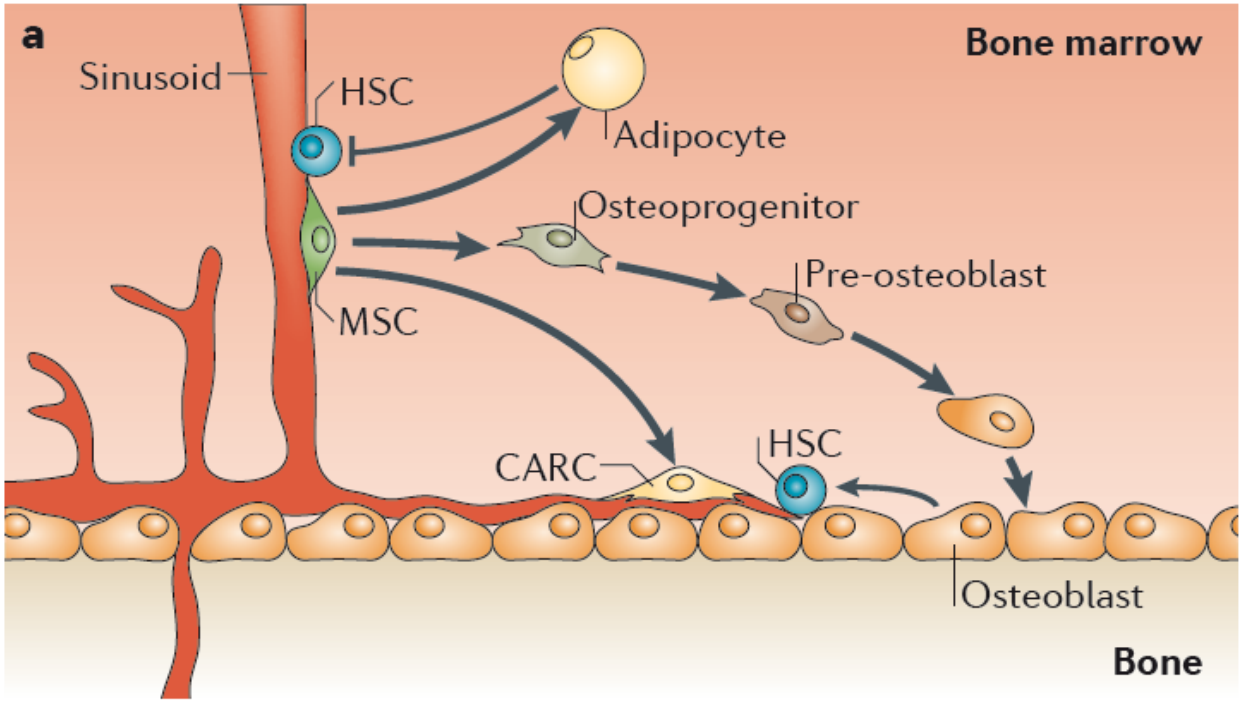
Plasticity of adult stem cells

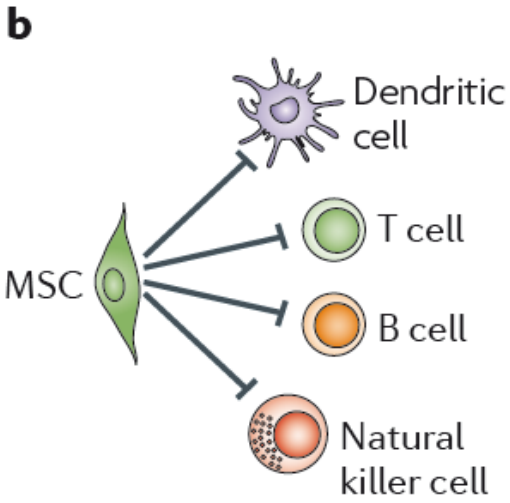


the ability to form specialized cell types of other tissues

(also called transdifferentiation)

Mesenchymal stem cells



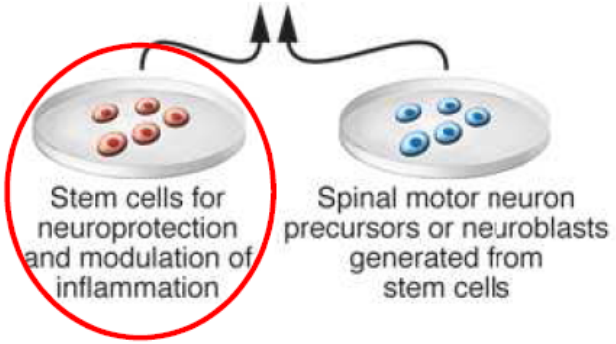


Nombela-Arrieta C et al., Nature Rev Mol Cell Biol February 2011

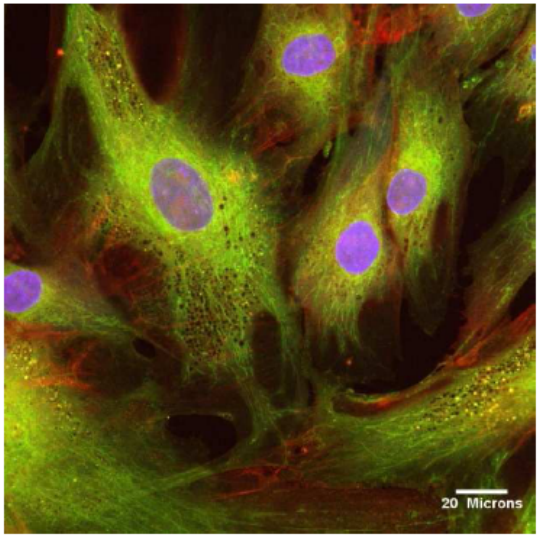
Figure 2 | **Proposed biological functions of BM-resident MSCs *in vivo*. a** | Bone marrow (BM)-derived mesenchymal stem cells (MSCs) differentiate into osteoblasts, adipocytes and reticular cells (indicated by bold arrows), which provide the supportive environment for haematopoietic development and are thought to be responsible for the natural turnover of these mesenchymal cell types in the bone marrow. Osteoblasts are key components of haematopoietic stem cell (HSC) niches and have been proposed to directly interact with, and positively regulate quiescence of, some HSCs in the BM, whereas adipocytes negatively regulate HSC activity. HSCs have also been shown to lie adjacent to CXCL12-abundant reticular cells (CARCs), which are poorly characterized cells with adipogenic and osteogenic potential and may correspond to, or originate from, BM-resident MSCs. In addition to giving rise to a haemosupportive environment, BM-resident MSCs expressing the neural stem cell marker nestin have been shown to physically associate with HSCs in perivascular BM 'dual stem cell niches' and to regulate HSC homeostasis. **b** | BM-resident MSCs are found in perivascular areas of BM microenvironments, where they may associate with cells of the immune system, including dendritic cells, T cells and B cells. Furthermore, mesenchymal stromal cells, which are thought to directly derive from MSCs *in vivo*, are known to regulate the function of lymphocytes (B cells and T cells), dendritic cells and natural killer cells. It is therefore thought that BM-resident MSCs may regulate immune responses occurring in the BM *in vivo*.

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

BM- derived Mesenchymal Stem Cells (MSCs) as modulators for transplantation sites

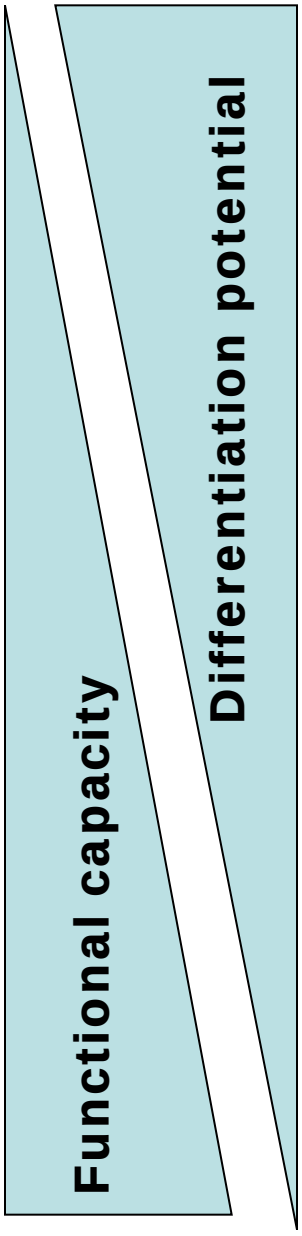


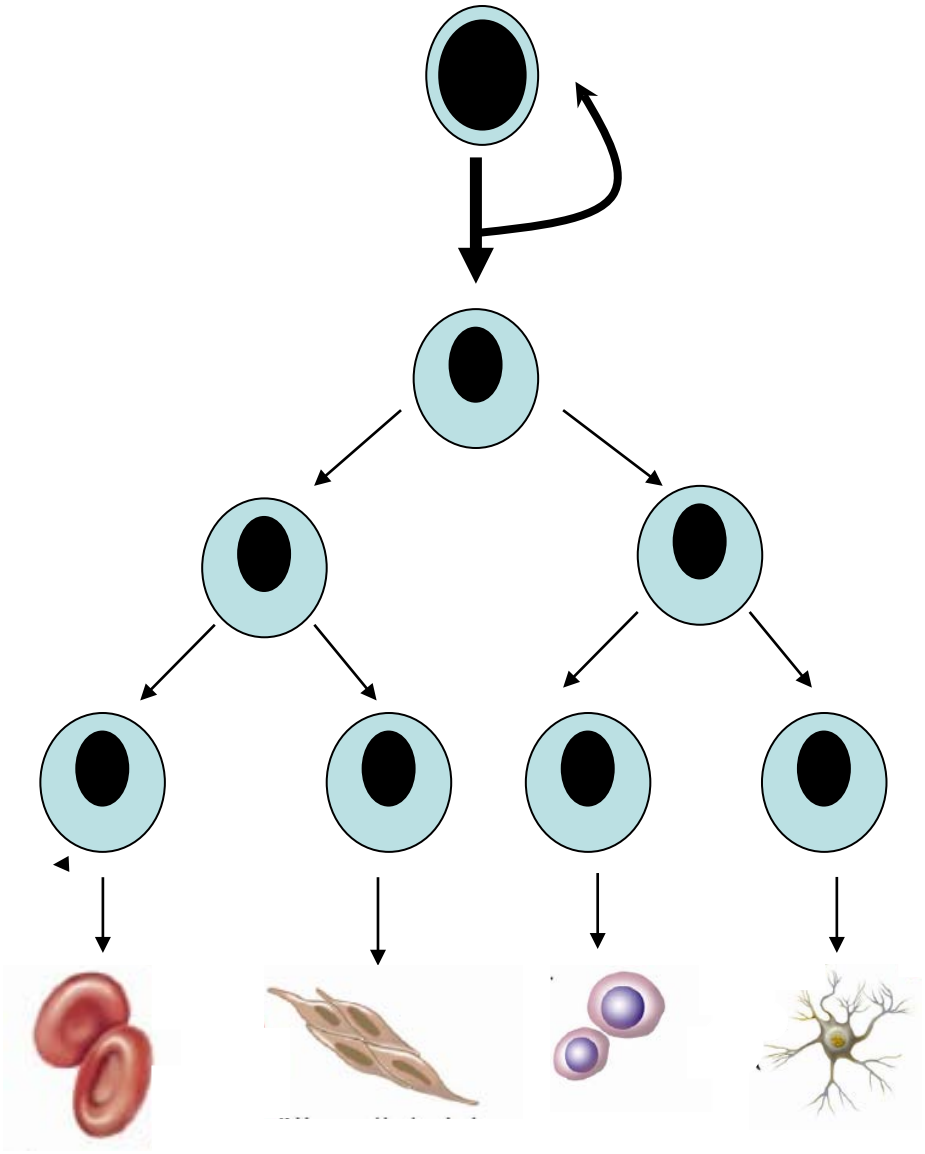
- Adult stem cells
- Easy for isolation and expansion for autotransplantations
- Posses low immunogenity (optimal for allotransplantations)
- Produce immunomodulatory factors
- Posses wide differentiation potential (Multipotent SCs)
- May be genetically modified (gene carriers)



E. Zuba-Surma, lecture 2010

The hierarchical structure of differentiation



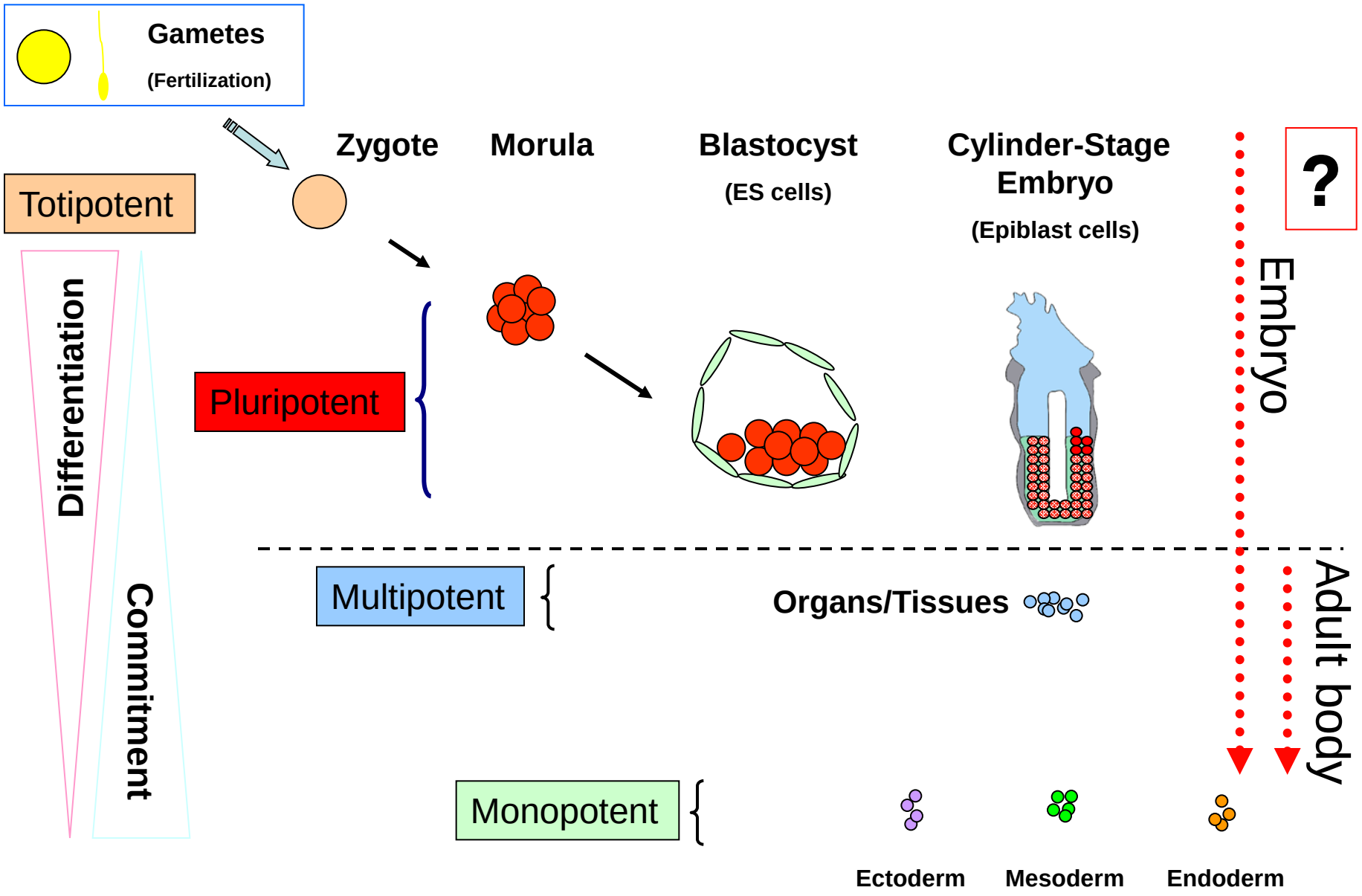


stem cells

progenitor cells

terminally differentiated cells

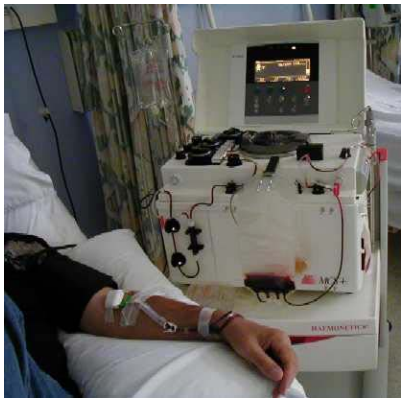
Background Hierarchy of stem cells



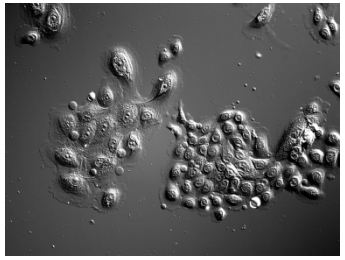
E. Zuba-Surma, lecture 2010

Stem cells in therapy

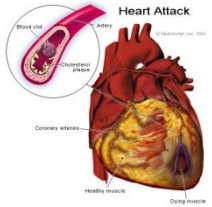
1. Hematopoietic stem cells (bone-marrow, cord blood (leukemias, immunodeficiencies , anemias but also other, like Krabbe's diseases, adrenoleukodytrophy)



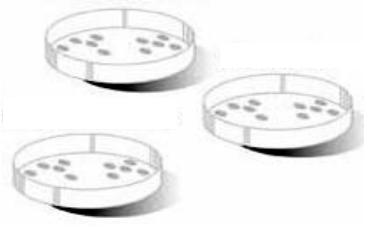
2. Skin stem cells (burns, ulcers)

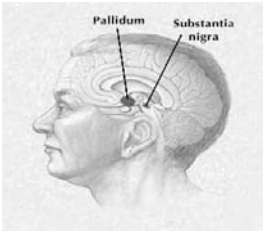


3. Endothelial progenitor cells and others – therapy of myocardial infarctions



4. Neural stem cells – Parkinson disease, Alzheimer disease

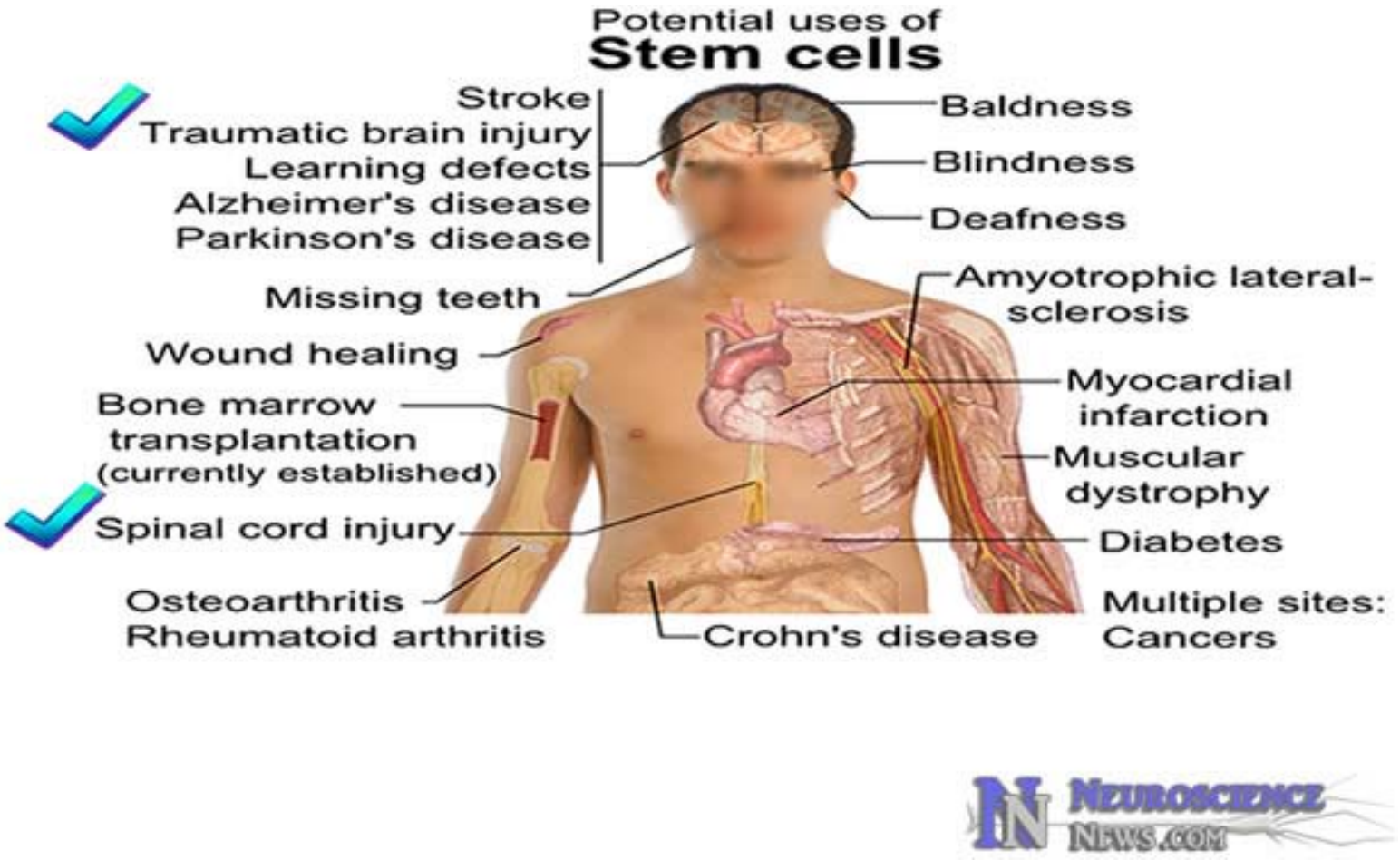




Embryonic vs adult in terms of cell therapy

	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

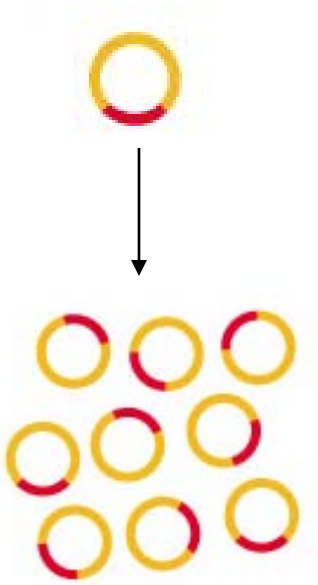
Embryonic stem cells in therapy of human diseases

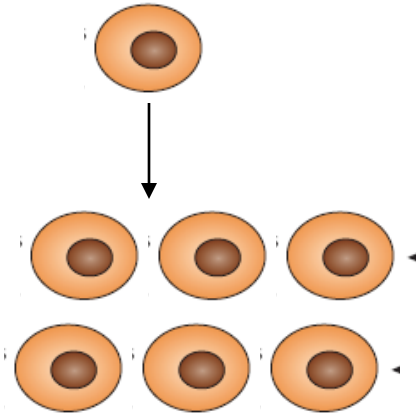


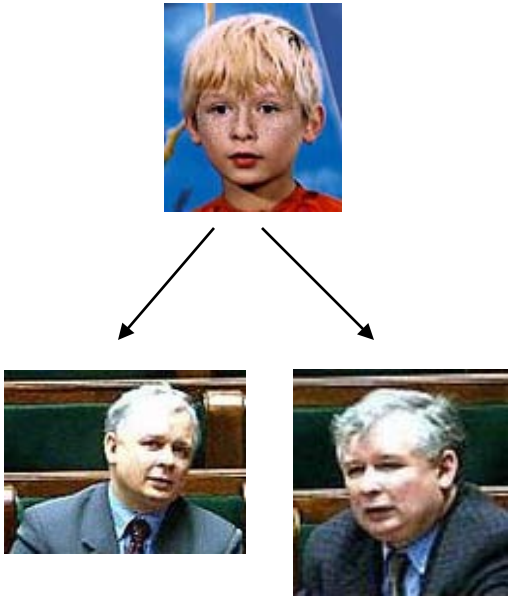
First clinical trial based oh human embryonic stem cells – **Geron corp**

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





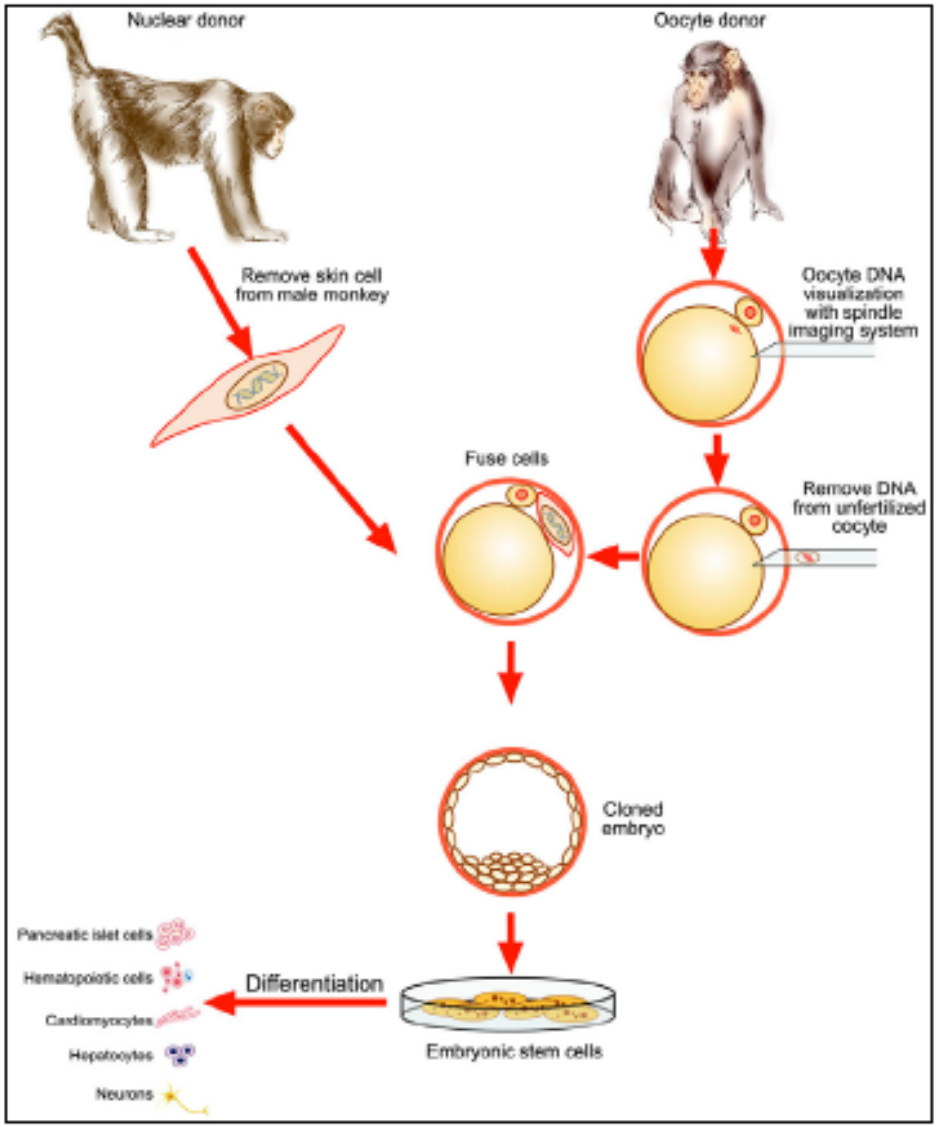


Cloning

reproductive

Therapeutic
(SNCT – somatic
Nuclear cell transfer)

Producing primate embryonic stem cells by somatic cell nuclear transfer



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

Primate cloned stem cells

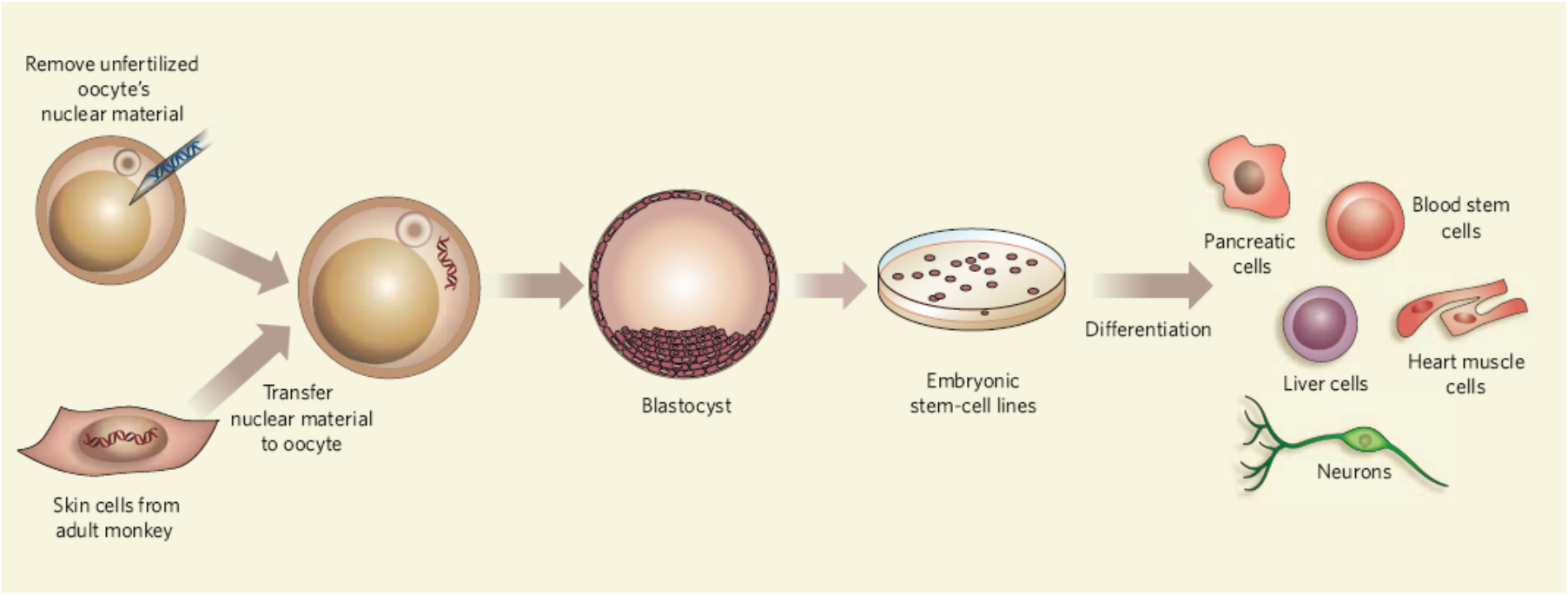
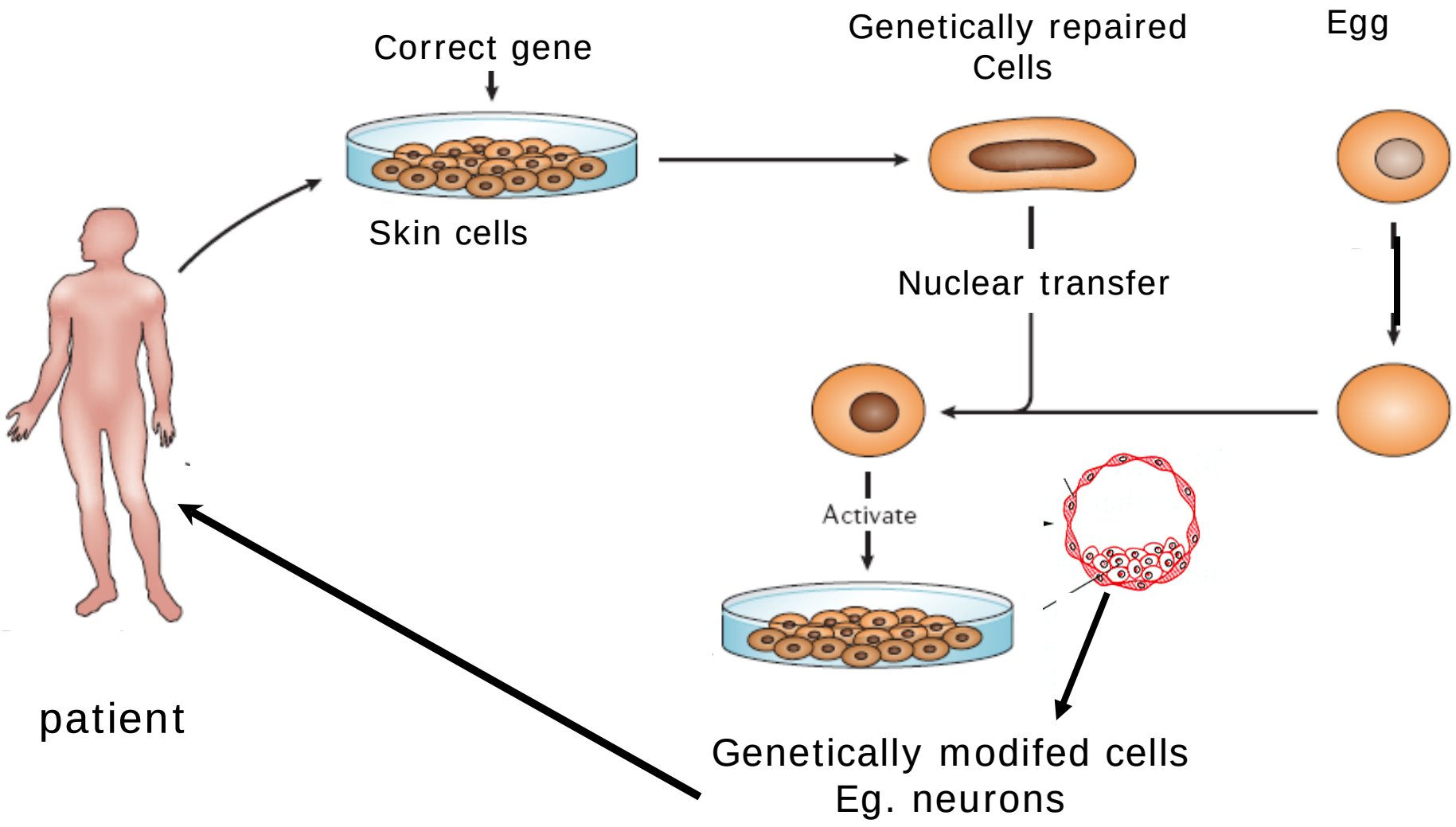


Figure 1 | The technique of somatic-cell nuclear transfer (SCNT). In much the same way as women undergoing *in vitro* fertilization procedures are treated to make them super-ovulate, Byrne *et al.*[2] treated female rhesus monkeys with hormones to induce the shedding of extra eggs. After recovering these 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

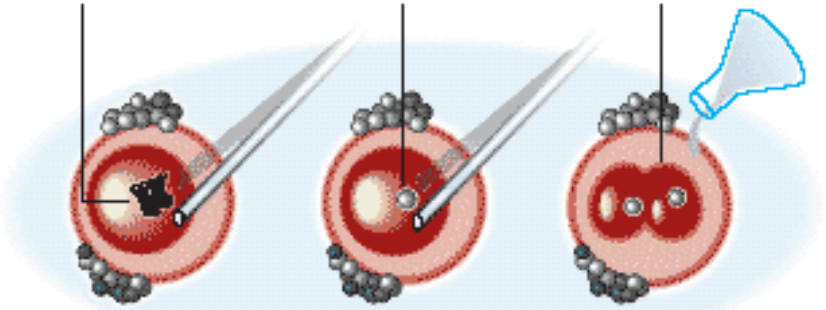
Cell swap

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.

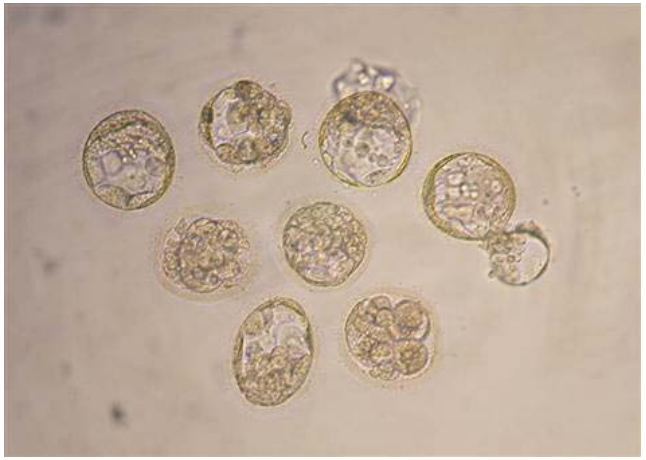
A cumulus cell, a remnant from the ovary, is inserted into the emptied egg. This cell is meant to provide genetic material for the developing egg – and the resulting stem cells.

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

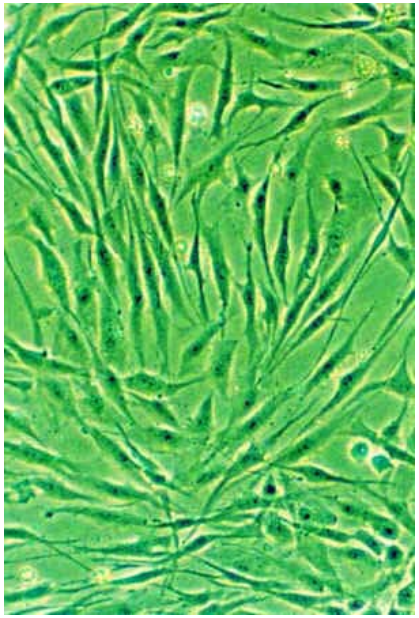


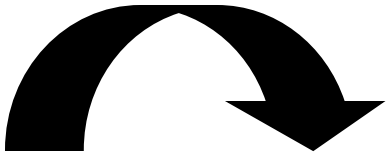
Scientific fraud...

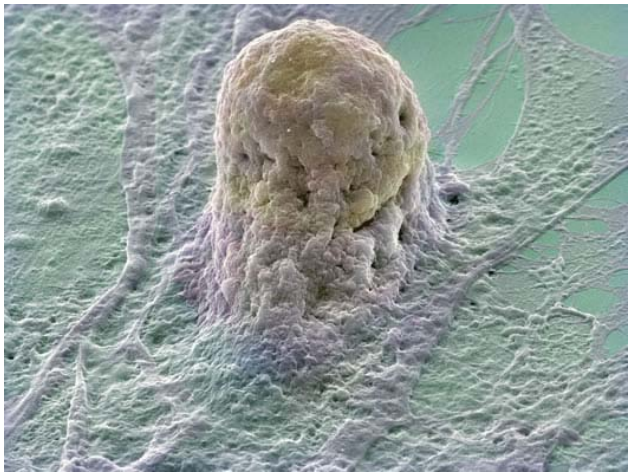
Woo Suk Hwang,

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**.

Is the other way round possible???







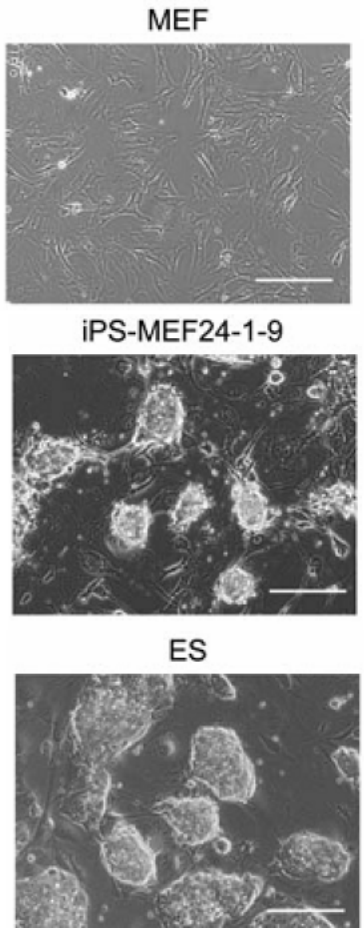
Human Dermal Fibroblasts

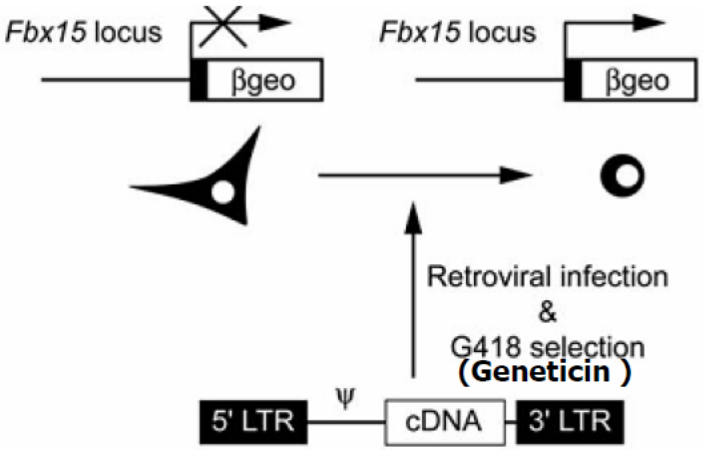
Stem Cell

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

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

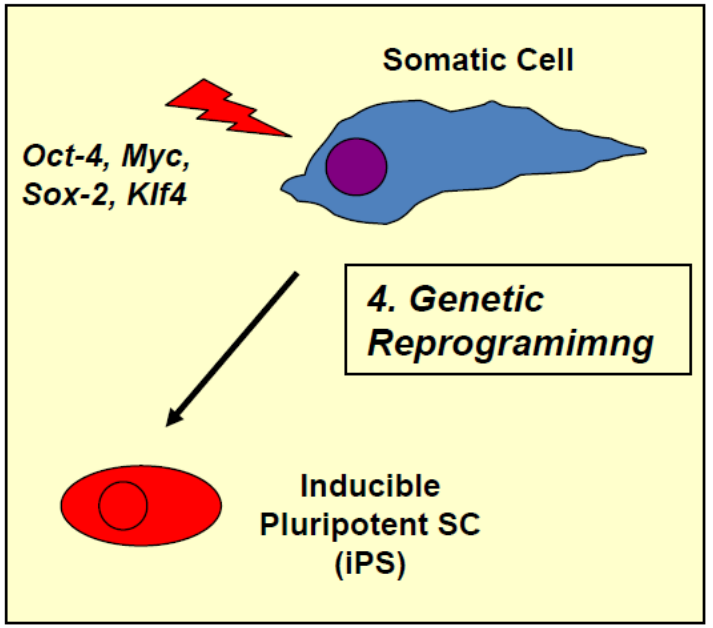
Cell *126*, 663–676, August 25, 2006

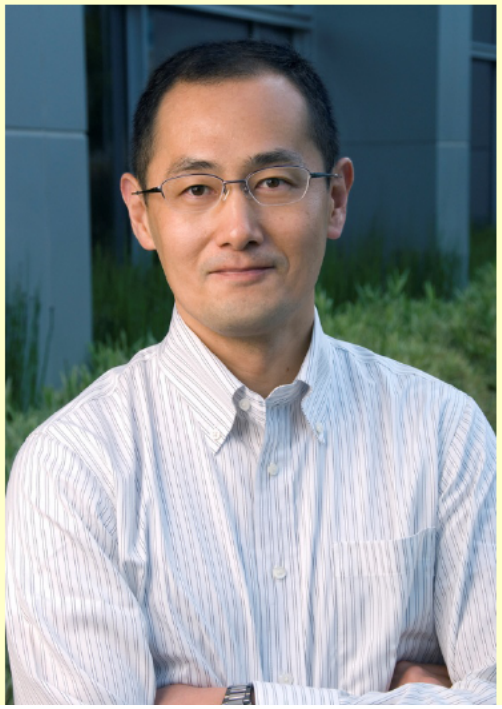




Testing of 24 different reprogramming factors

Oct3/4, Sox2, Klf4, c-Myc



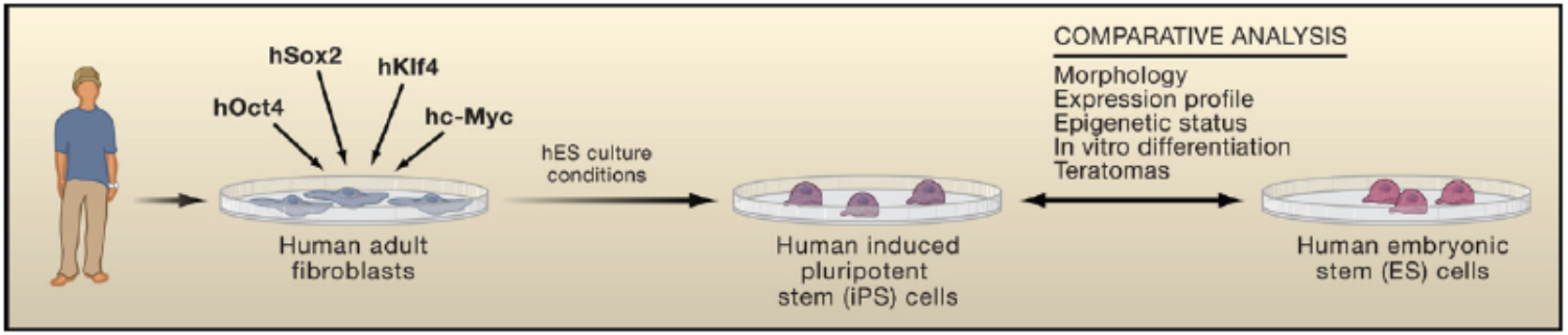


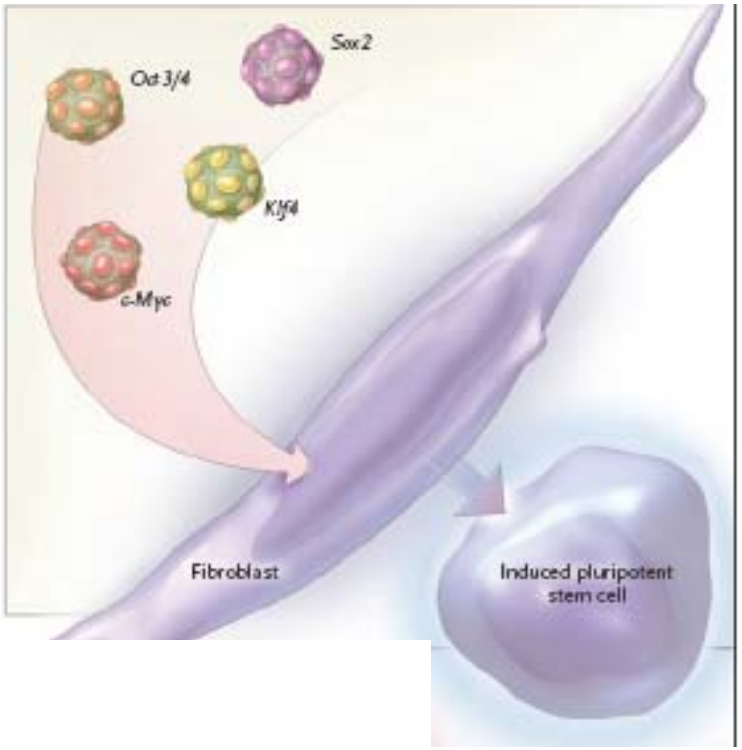
E. Zuba-Surma, lecture 2010

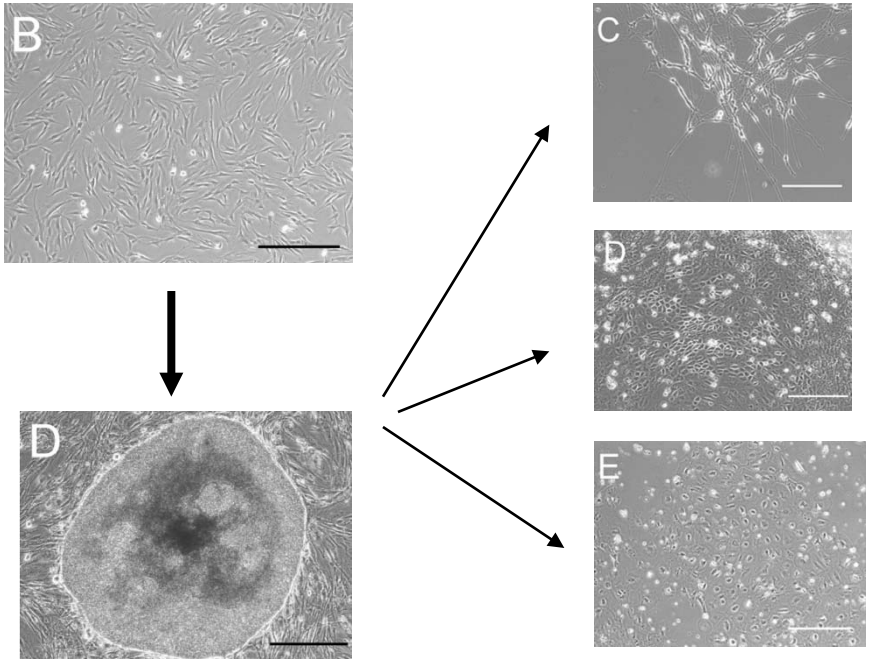
Transcription-factor induced pluripotency

Induced pluripotent stem cells (iPS)

Yamanaka et al. 2006







Zaehres & Scholler, Cell 2008

Three different groups demonstrated the possibility of de-differentiation of human somatic cells

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

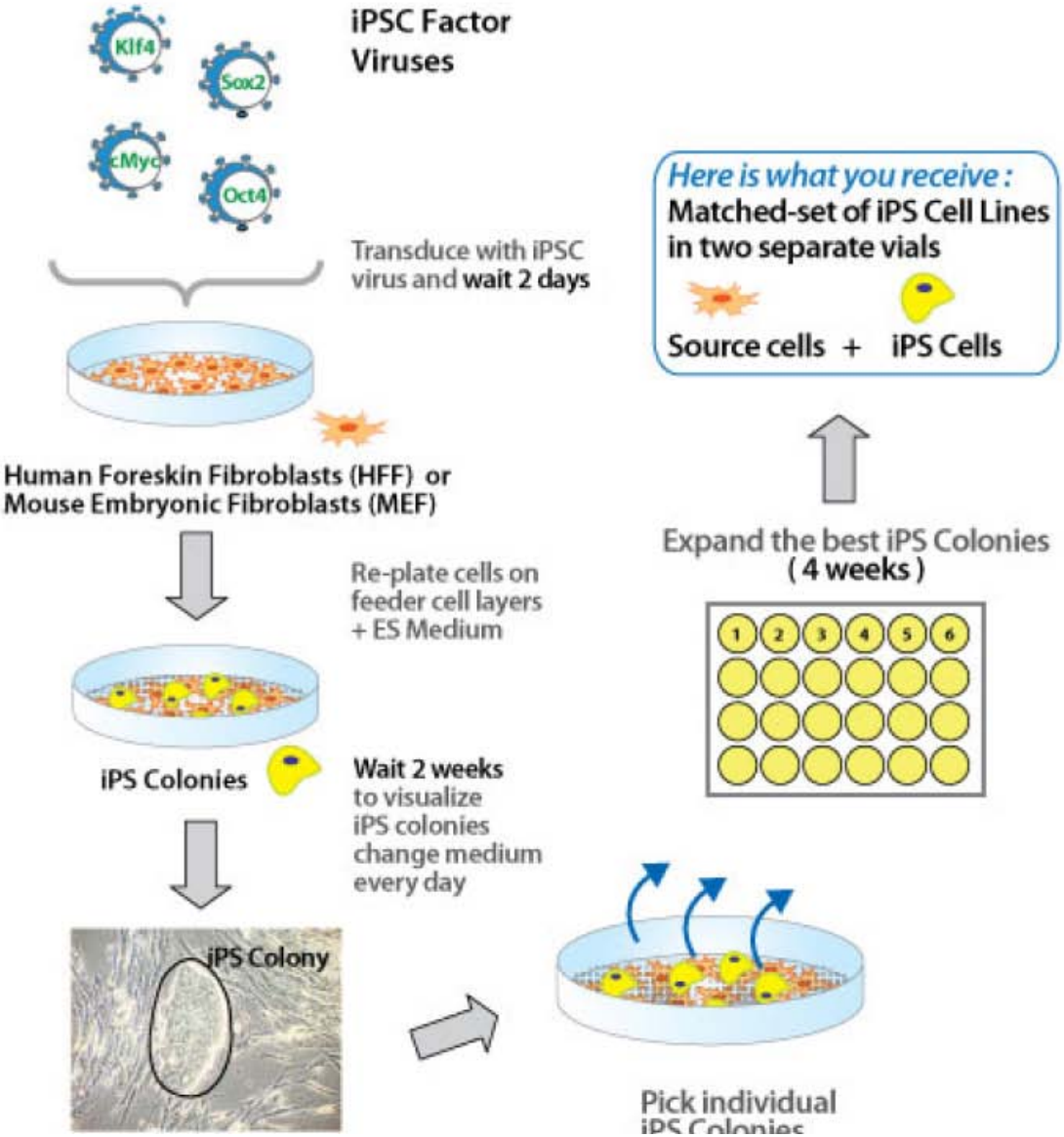
2. Yu et al., (JA Thomson) Science, Dec 21, 2007
   four factors: Oct4, Sox2, Nanog, Lin28

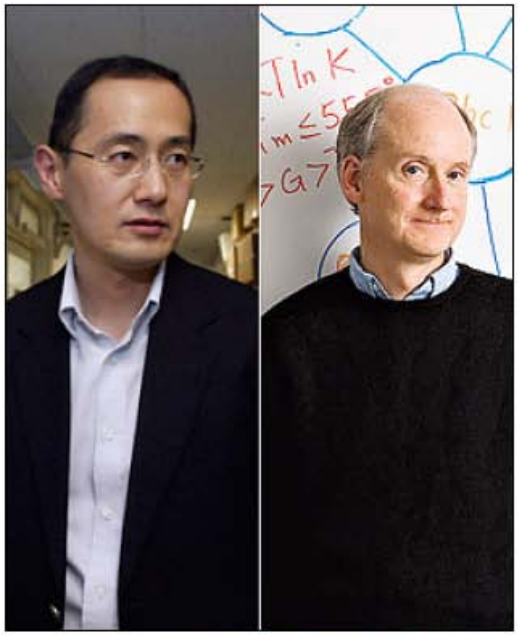
3. Park H-I et al. (GQ Daley), Nature Dec, 2007
   four factors: Oct4. Sox2, Klf4, c-Myc
   three factors sufficient: Oct4, Sox 2 and either Myc or Klf4
   (the latter two enhance the efficiency of colony formation)

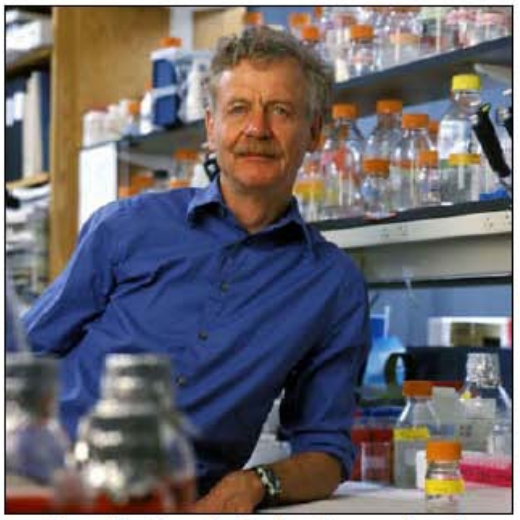
4. Nakagawa M et al. (S. Yamanaka) – Nature Biotechnology, Dec 2007
   three factors sufficient; Oct3/4, Sox2, Klf4

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

iPS Technology – promising approach for tissue regeneration







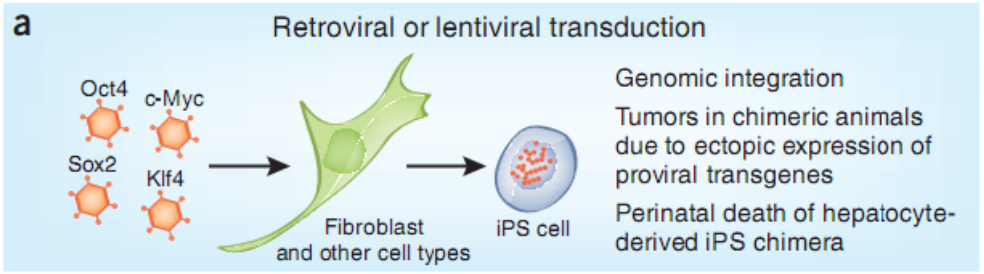
E. Zuba-Surma, lecture 2010

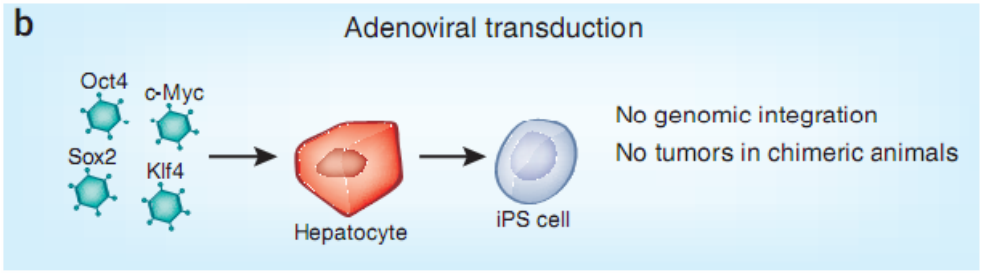
Rudolf Jaenisch

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)

Current Reprogramming Methods and their efficiency





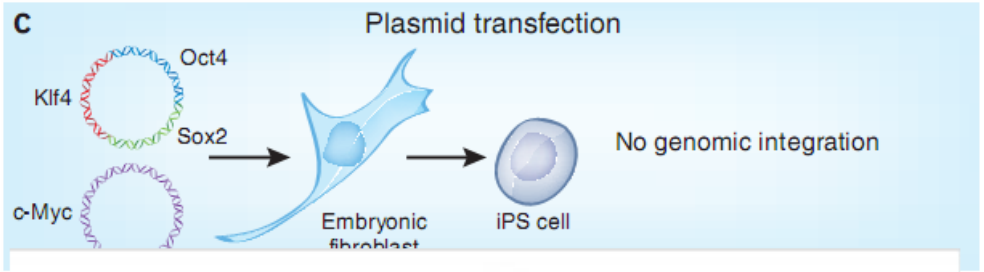
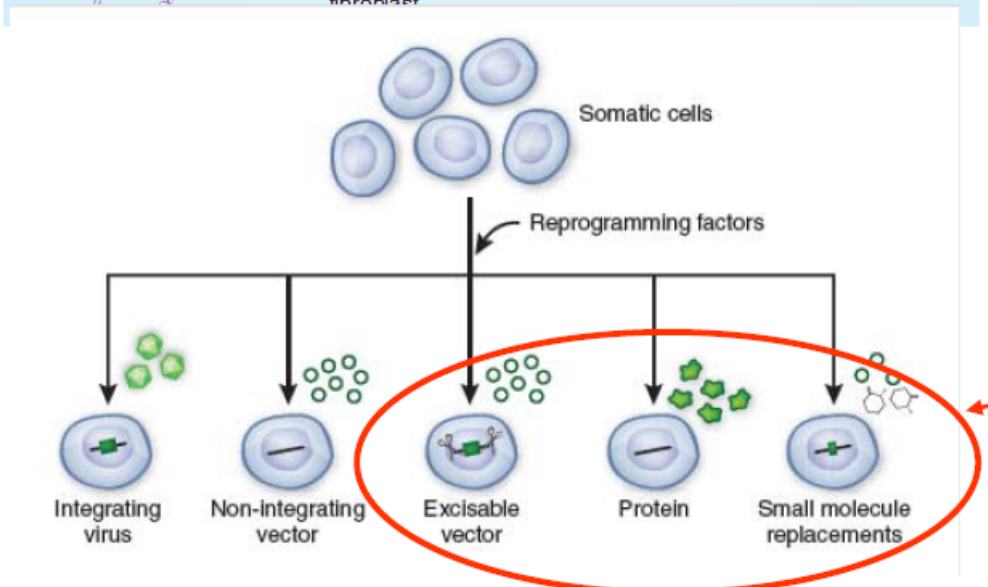


Table 1 Efficiencies of reprogramming methods reported in refs 1–3

Strategy	Cell type	Efficiency[a]
Retroviral transduction		
Four factors (Oct4, Sox2, Klf4, c-Myc)	Mouse embryonic fibroblasts	0.1%
Three factors (Oct4, Sox2, Klf4)	Mouse embryonic fibroblasts	0.01%
Three factors (Oct4, Sox2, Klf4)	Human fibroblasts	0.001%
Three factors (Oct4, Sox2, Klf4) + VPA	Human fibroblasts	1%
Two factors (Oct4, Sox2)	Human fibroblasts	No iPS colonies obtained
Two factors (Oct4, Sox2) + VPA	Human fibroblasts	0.001%
Adenoviral transduction		
Four factors (Oct4, Sox2, Klf4, c-Myc)	Mouse postnatal fibroblasts	No iPS colonies obtained
	Mouse hepatocytes	0.0006%
Plasmid transfection		
One plasmid with Oct4-2A-Klf4-2A-Sox2[b] + one plasmid with c-Myc	Mouse embryonic fibroblasts	0.0015%

NATURE BIOTECHNOLOGY VOLUME 26 NUMBER 11 NOVEMBER 2008
NATURE METHODS | VOL.7 NO.1 | JANUARY 2010



Non-viral reprogramming

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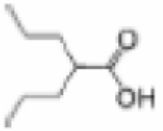
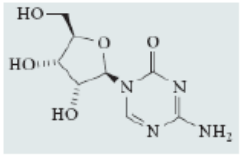
Small molecules – the factors affecting the chromatin structure

Induction of pluripotent stem cells by defined factors is greatly improved by small-molecule compounds

Danwei Huangfu[1], René Maehr[1], Wenjun Guo[2], Astrid Eijkelenboom[1,3], Melinda Snitow[1], Alice E Chen[1] & Douglas A Melton[1]

NATURE BIOTECHNOLOGY VOLUME 26 NUMBER 7 JULY 2008





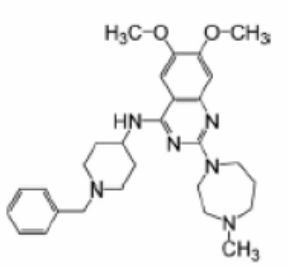
VPA (valproic acid) – histone deacetylase (HDAC) inhibitor
- **5'-azacytidine** – DNA methyltransferase inhibitor

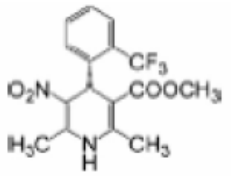
Oct-4, Sox2, Klf4

Induction of Pluripotent Stem Cells from Mouse Embryonic Fibroblasts by Oct4 and Klf4 with Small-Molecule Compounds

Yan Shi,[1,3] Caroline Desponts,[1,3] Jeong Tae Do,[2] Heung Sik Hahm,[1] Hans R. Schöler,[2] and Sheng Ding[1,*]

Cell Stem Cell 3, 568–574,





- **BIX-01294 (BIX)** – G9a histone methyltransferase inhibitor
- **BayK8644 (BayK)** – L-channel calcium agonist

Oct-4, Klf4

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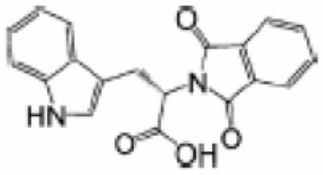
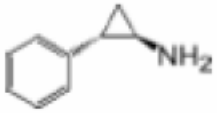
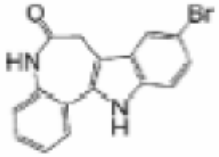
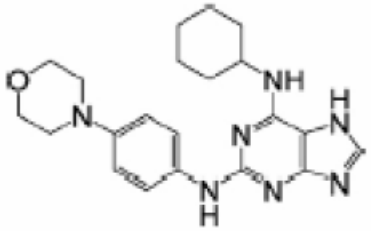
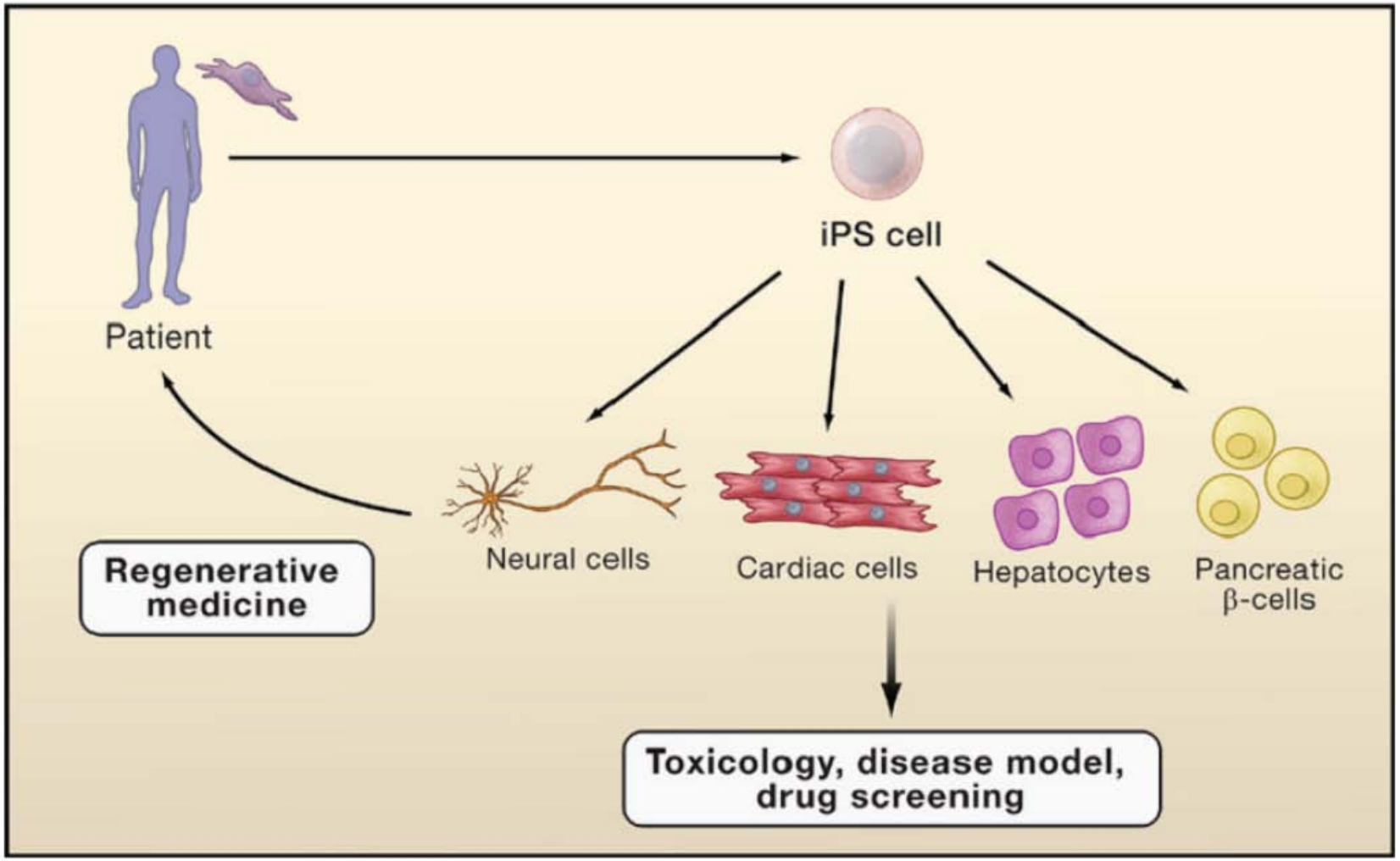
Other small molecules important for cell reprogramming

Molecule	Name	Target(s)	Effects
	RG108	DNA MTase	Promotes MEF reprogramming [71]
	Parnate	lysine-specific demethylase 1	Enable the reprogramming of human keratinocytes transduced by Oct4/Klf4
	Kenpaullone	CDKs and GSK3	Replacse Klf4 to induce MEF reprogramming [76]
	Reversine	nonmuscle myosin II heavy chain and MEK1	Induces dedifferentiation of muscle or fibroblast cells to a more primitive multipotent state [78–81]

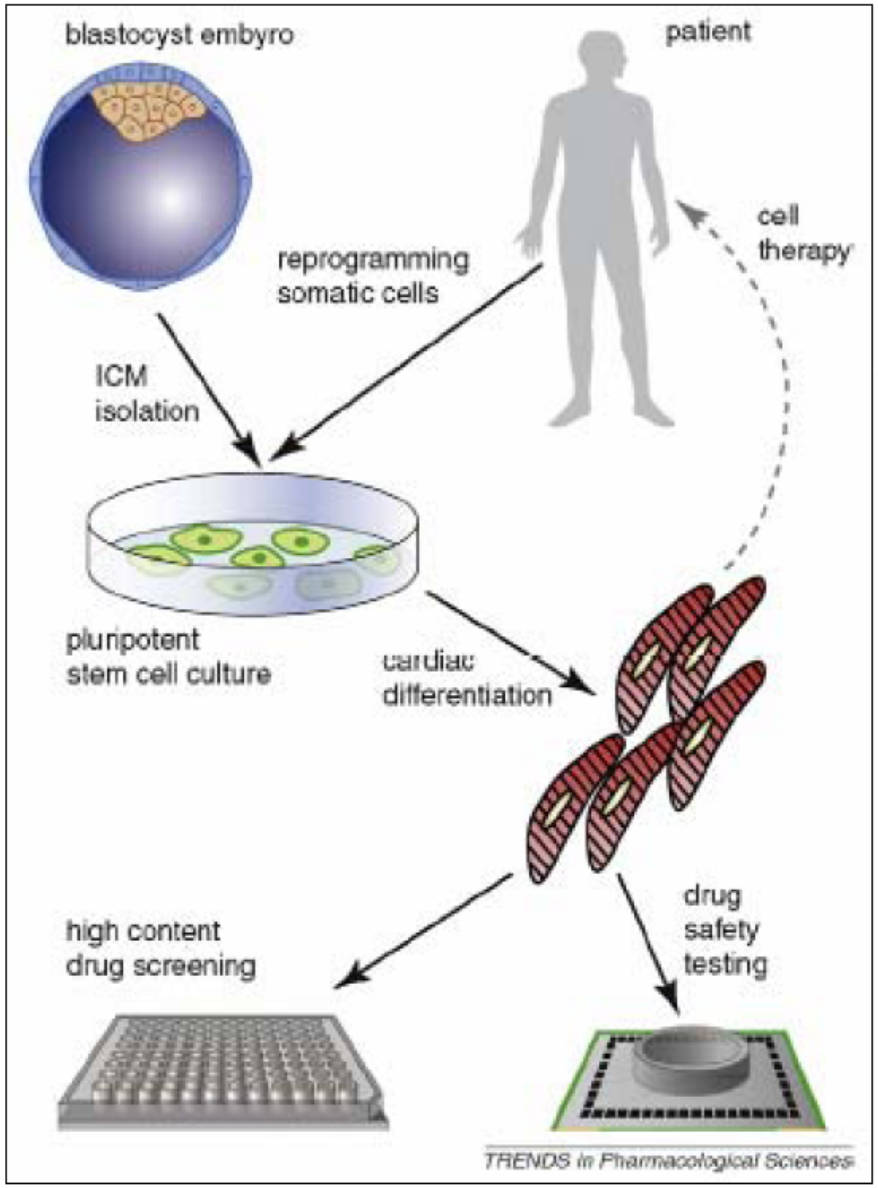
Wenlin Li and Sheng Ding[1] *Trends in Pharmacological Sciences* (in press)

Potential Applications of iPS cells



Shinya Yamanaka Cell *137*, April 3, 2009

iPS cells– toxicology, drug screening



Individual drug screening for each patient –
- Cardiotoxicity

Drug	Indication
Herceptin	Breast cancer
Doxorubicin (and other anthracyclins)	Chemotherapeutic
Sunitinib	RTK inhibitor (anticancer drug)
Rosiglitazone (Avandia)	Antidiabetic
Non-selective NSAIDs	Anti-inflammatory
Mitoxantrone	Antineoplastic agent
Thioridazine	Antipsychotic
Mesoridazine	Antipsychotic
Muromonab	Immunosuppressant
Nilotinib	BCR-ABL inhibitor, anticancer drug
Itraconazole	Antifungal agent
Flecainide,	Class Ic anti-arrhythmic agent
Cetuximab	EGFR inhibitor, metatatic colon cancer
Clozapine	Anti-psychotic
Alglucosidase alfa	Enzyme replacement therapy, Pompe disease
Amiodarone	Class-III anti-arrhythmic
Arsenic trioxide	Chemotherapeutic
Tocaininde	Class Ib anti-arrhythmic agent
Imatinib	BCR/ABL inhibitor, anticancer drug

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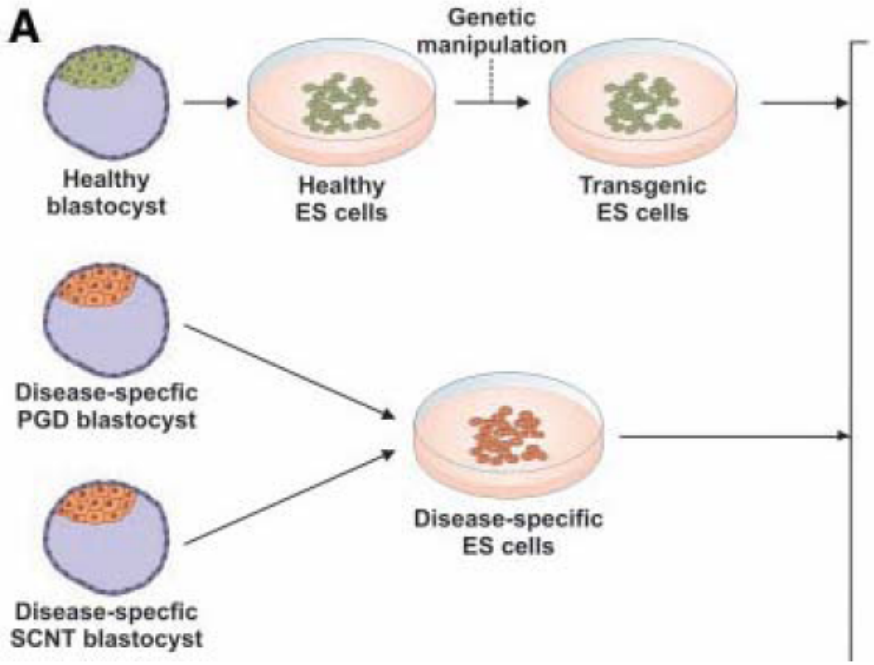
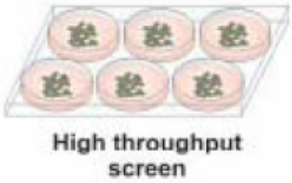
iPS cells – disease modeling and drug discovery

ESC disease models





1. Target gene disruption of cell from healthy blastocyst

2. Cell line isolation from congenitally defective embryos (PGD)

3. Cell line isolation from blastocyst produced by SCNT

PGD – preimplantation genetic diagnosis
SCNT – somatic cell nuclear transfer

Journal of Cellular Biochemistry 105:1361–1366 (2008)

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iPS-based gene therapy

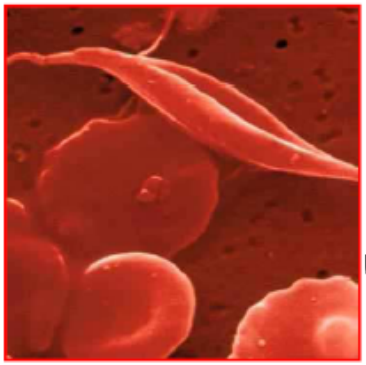
Treatment of Sickle Cell Anemia Mouse Model with iPS Cells Generated from Autologous Skin

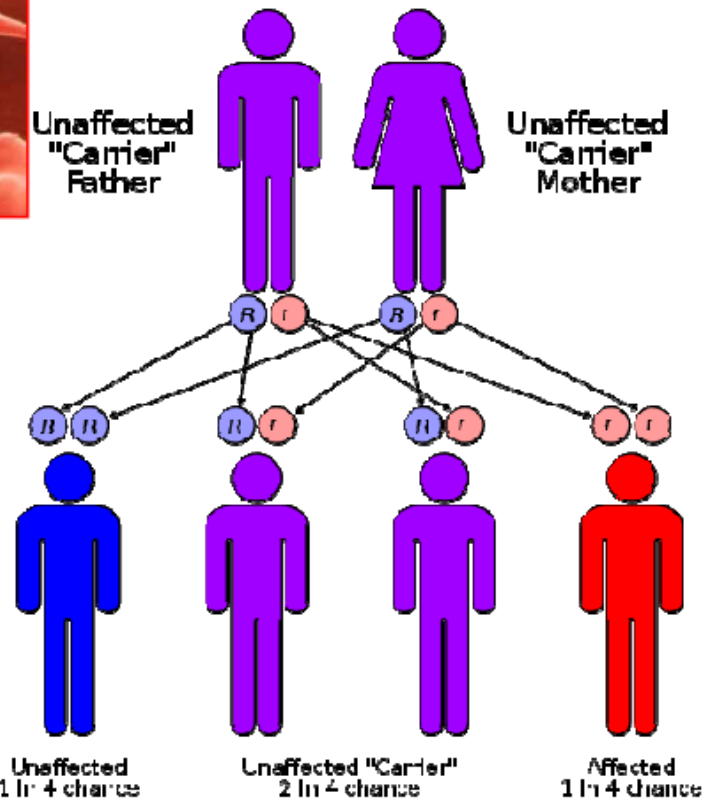
Jacob Hanna,[1] Marius Wernig,[1] Styliani Markoulaki,[1] Chiao-Wang Sun,[2] Alexander Meissner,[1] John P. Cassady,[1,3] Caroline Beard,[1] Tobias Brambrink,[1] Li-Chen Wu,[2] Tim M. Townes,[2]* Rudolf Jaenisch[1,3]*

Science **318**, 1920 (2007);

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.
- The association of 2 wild-type α-globin subunits with 2 mutant β-globin subunits forms haemoglobin S (HbS)
- 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





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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

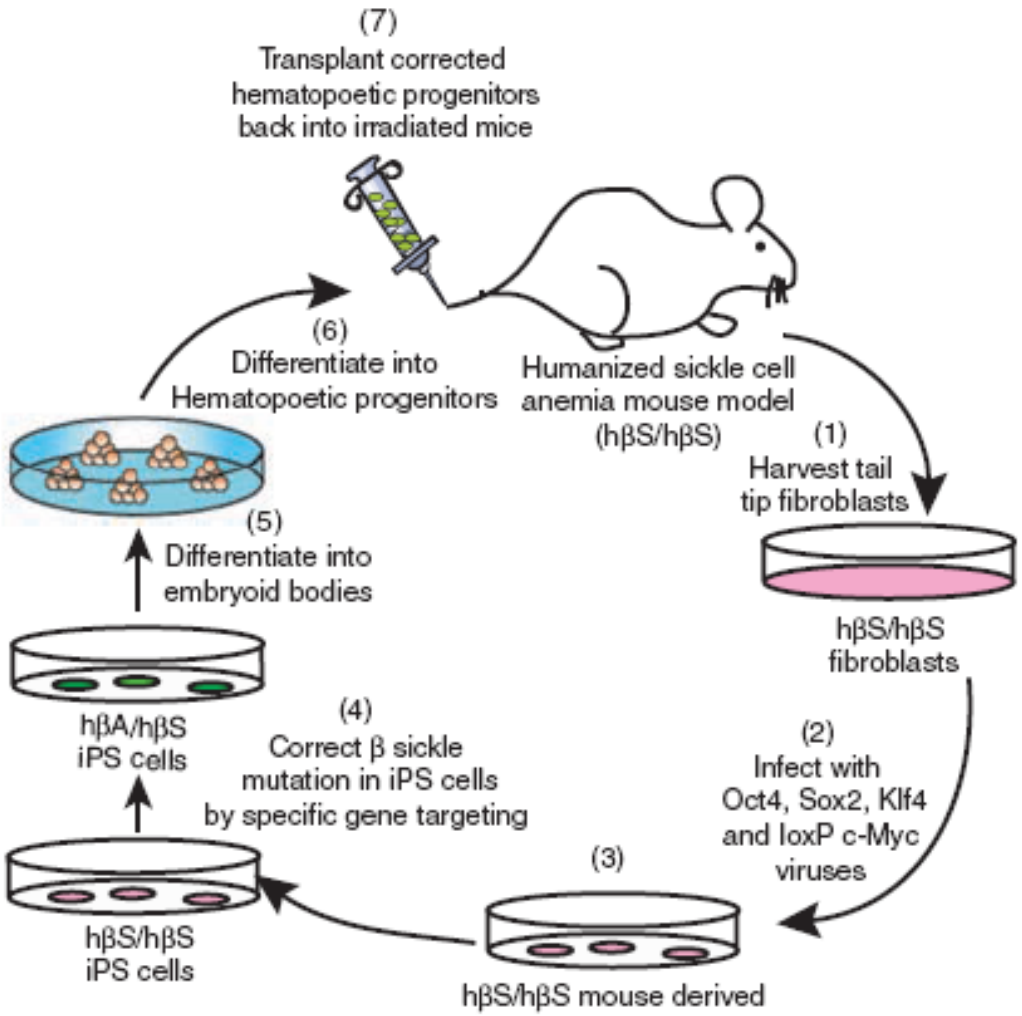
urine concentration defects

- 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

Ian Wilmut sauid that the therapeutic potential of iPS is so enormous that he is stopping his research on human embryonic stem 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

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

Fusing ES with differentiated cells could reprogram the nucleus, producing ES-like cels but with twice the normal number of chromosomes

Summary – gene transfer in stem cells for therapeutic purposes

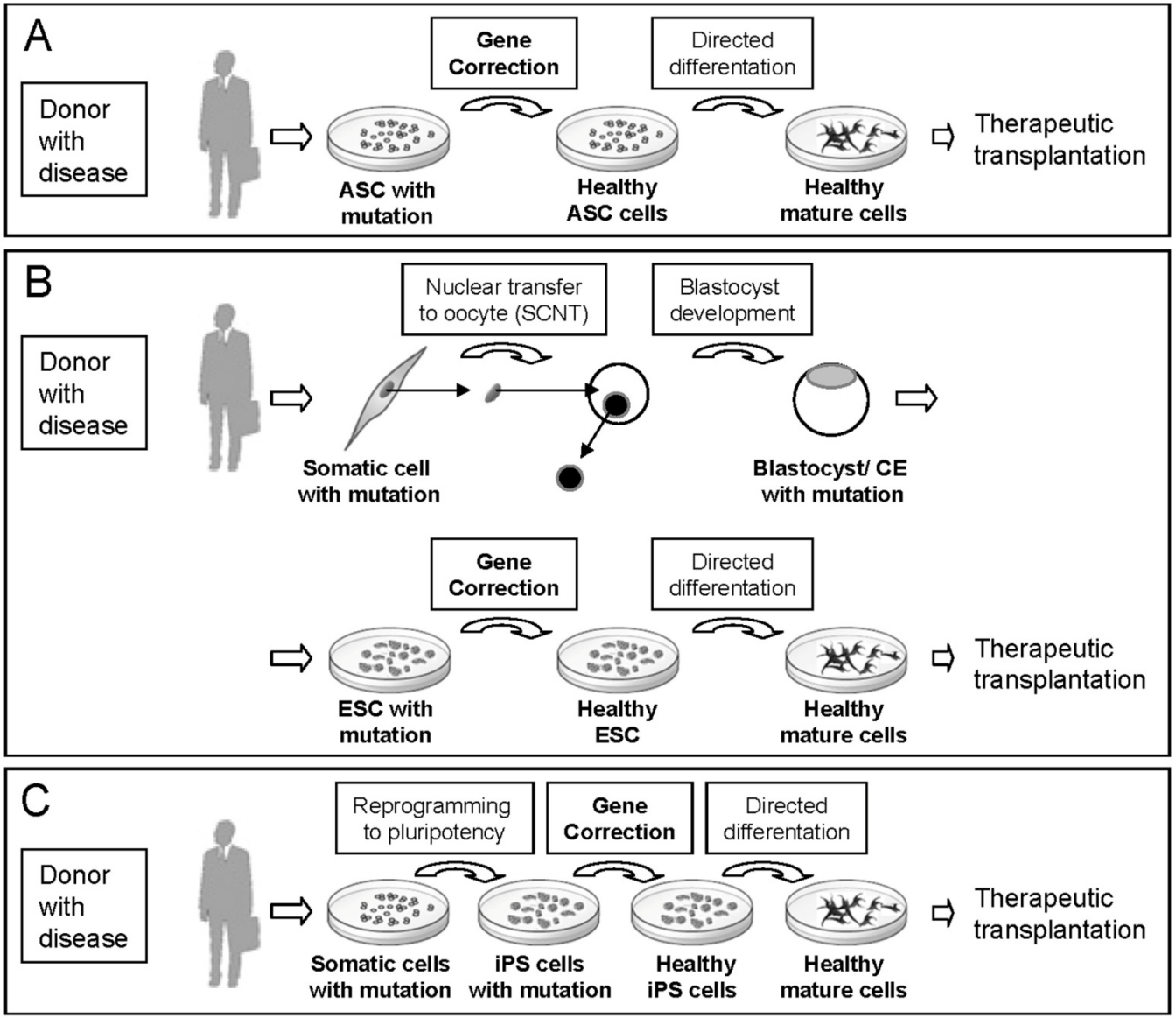


Figure 2

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

Summary – gene transfer in stem cells for therapeutic purposes

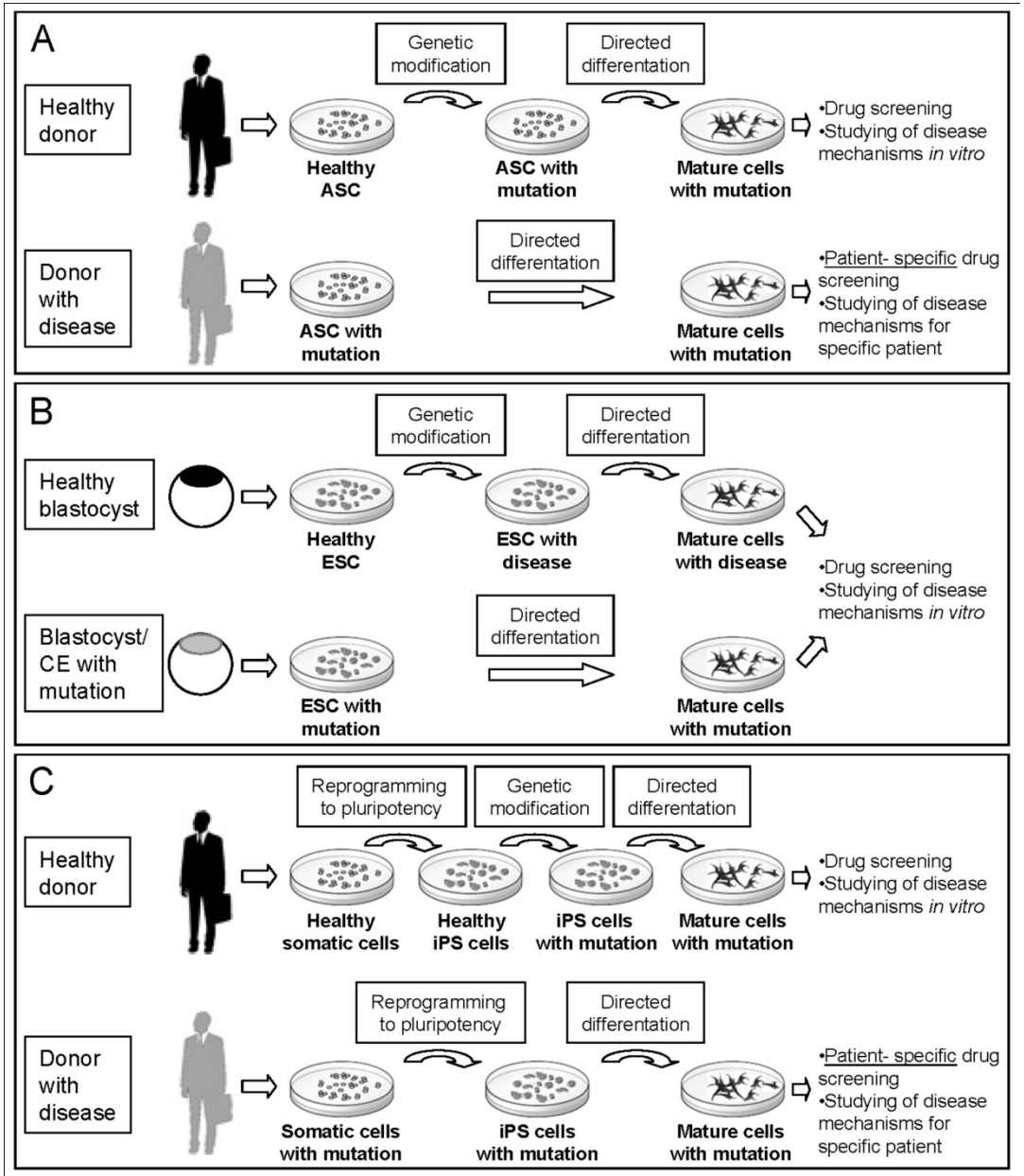


Figure 1

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

Therapeutical Aplications of SCs

Current applications

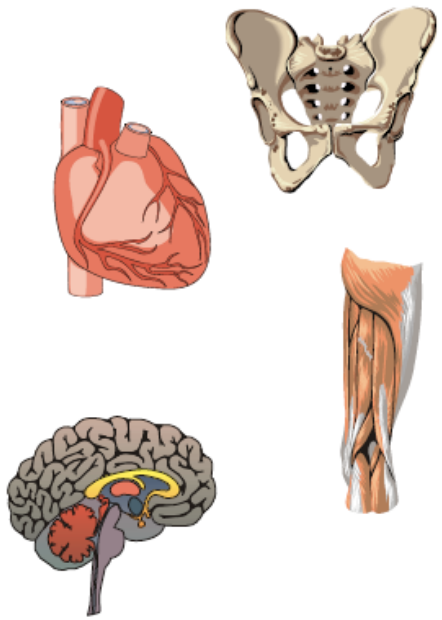
- Hematopoietic Stem/ Progenitor cells - hematological transplantations
- Epithelial Progenitor cells - burns
- Mesenchymal Stem/ Progenitor cells – bone fractures
- Cardiac- committed Stem/ Progenitor cells (BM- derived or endogenous) – Myocardial Infarction

Potential Applications

- Stroke
- Parkinson's Disease
- Spinal Cord injury
- Diabetes
- Miopathy
- Liver injuries

The most potent SC are the most interesting for regenerative medicine

- future of Pluripotent and Multipotent SCs



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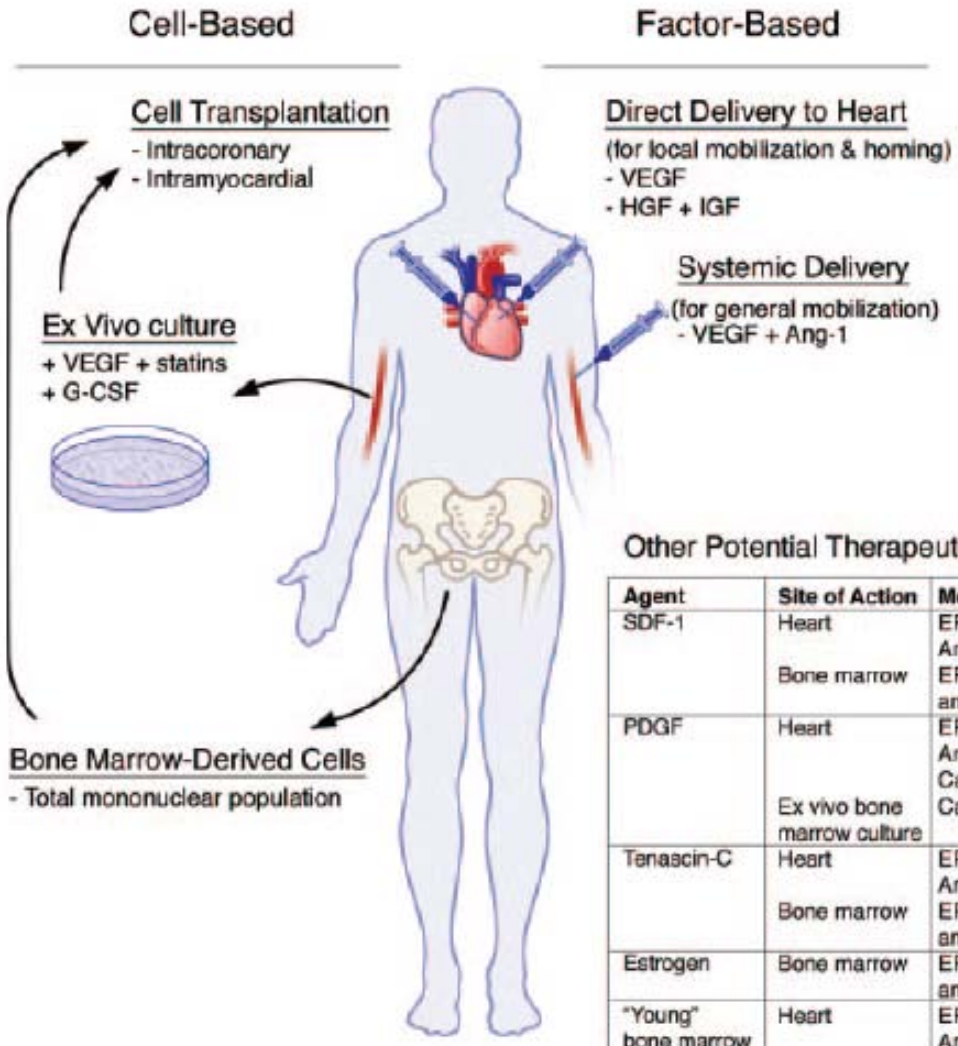
Application of bone marrow cells for regeneration of cardiovascular system

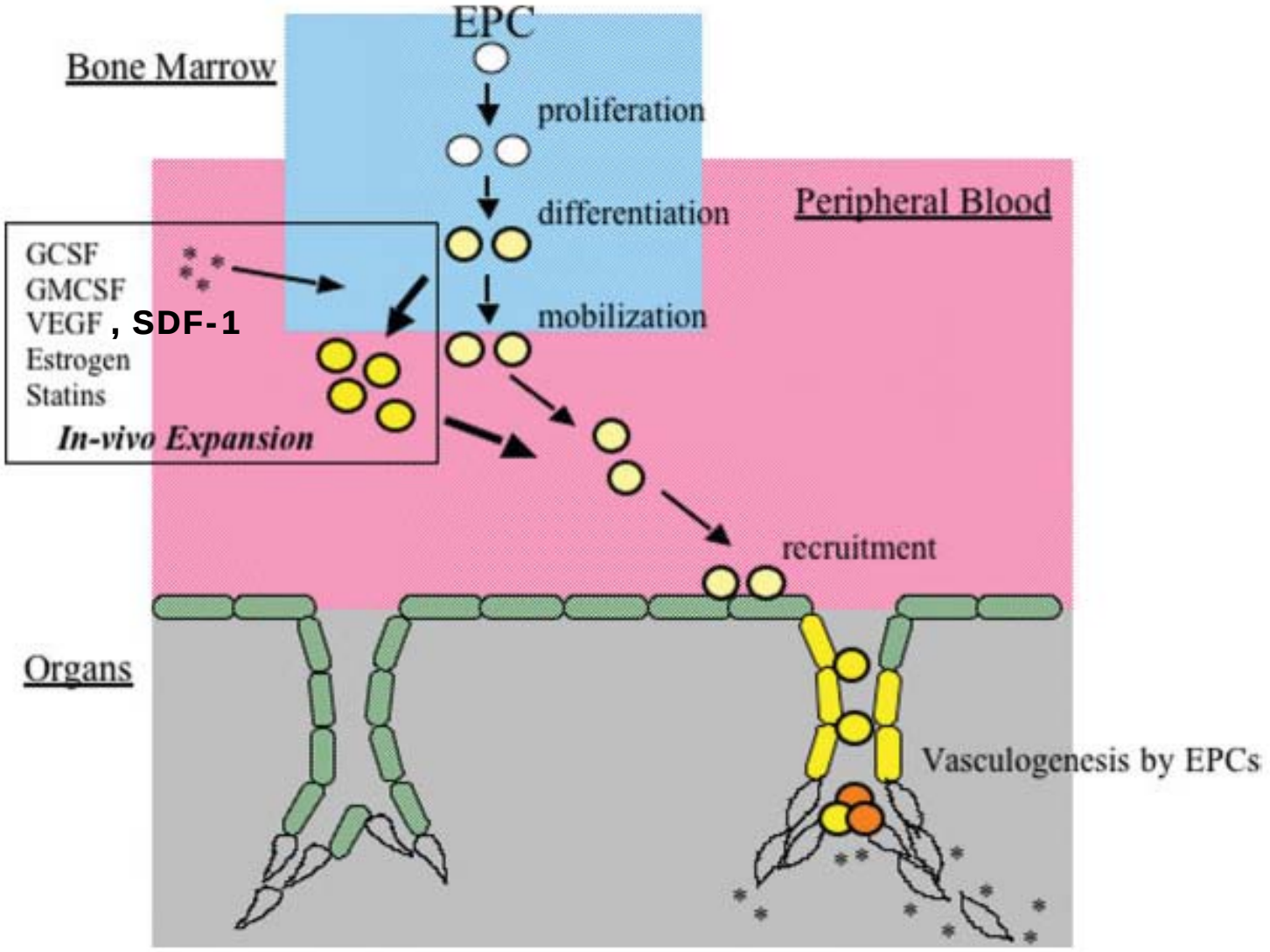


- Myocardial regeneration
- stimulation of neovascularisation
- Prevention of (re)stenosis
- seeding of the artificial blood vessels

Other Potential Therapeutic Agents

Agent	Site of Action	Mode of Action
SDF-1	Heart	EPC homing Angiogenic induction
	Bone marrow	EPC generation and angiogenic function
PDGF	Heart	EPC homing Angiogenic induction Cardiomyogenesis
	Ex vivo bone marrow culture	Cardiomyogenesis
Tenascin-C	Heart	EPC homing Angiogenic induction
	Bone marrow	EPC generation and angiogenic function
Estrogen	Bone marrow	EPC generation, survival and function
"Young" bone marrow	Heart	EPC generation Angiogenic induction Cardiomyogenesis
	Bone marrow	EPC generation
	Ex vivo bone marrow culture	EPC generation Cardiomyogenesis

Bone marrow-derived endothelial progenitor cells in postnatal vascularization



Innovative methods of stem cells applications in medicine

Pomeranian Medical Academy

Coordinator: Prof. Mariusz Ratajczak

Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University

Coordinator: Prof. Jozef Dulak

Silesian Medical University Clinic of Cardiology

Coordinator: Dr Wojciech Wojakowski

Nencki Institute of Experimental Biology Warsaw

Coordinator: Prof. Leszek Kaczmarek

Centre for Postgraduate Medical Treatment Warsaw

Coordinator: Prof. Jerzy Kawiak

2010-2015

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

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

Hopes and hypes of regenerative medicine

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. Nevertheless, further clinical trials are justified

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

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 will 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

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

Exam – 28th January (Friday) – 9 am – room D107

Multiple choice test

Please fill the course assessment at the USOS website ….