8. Využití vývojových procesů v regenerační medicíně[1]

Cell replacement therapy[2]

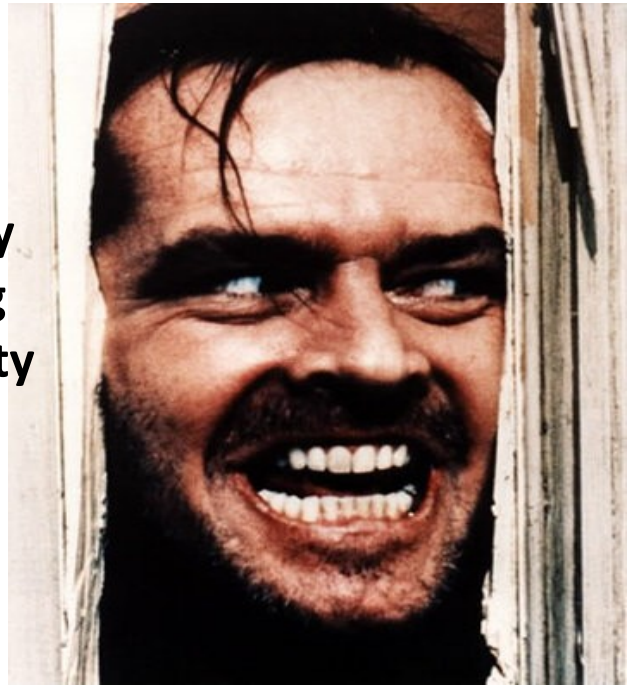
Vendula Pospichalova
(2015/05/28 - Bi9906)

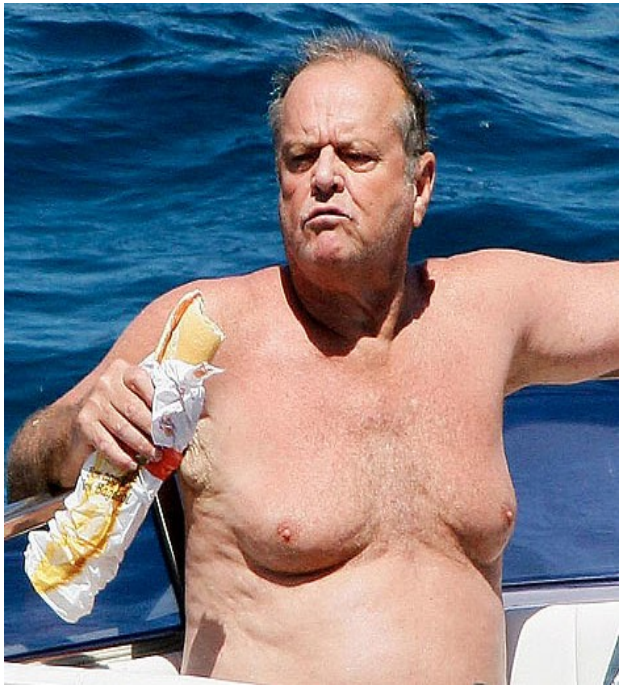
[1] Therapy that enables the body to repair, replace, restore and regenerate damaged or diseased cells, tissues and organs.

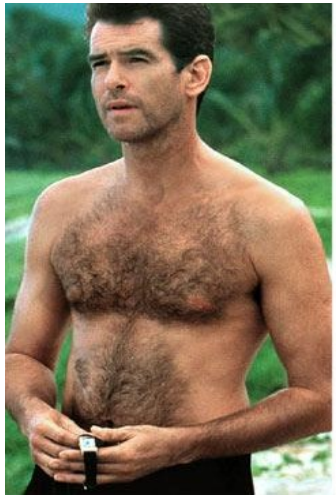
[2] The prevention, treatment, cure or mitigation of disease or injuries in humans by the administration of autologous, allogeneic or xenogeneic cells that have been manipulated or altered *ex vivo*.

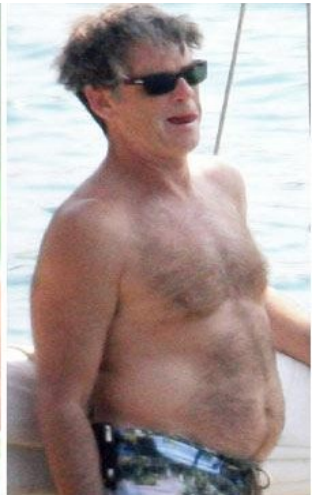
Why are we interested in it?

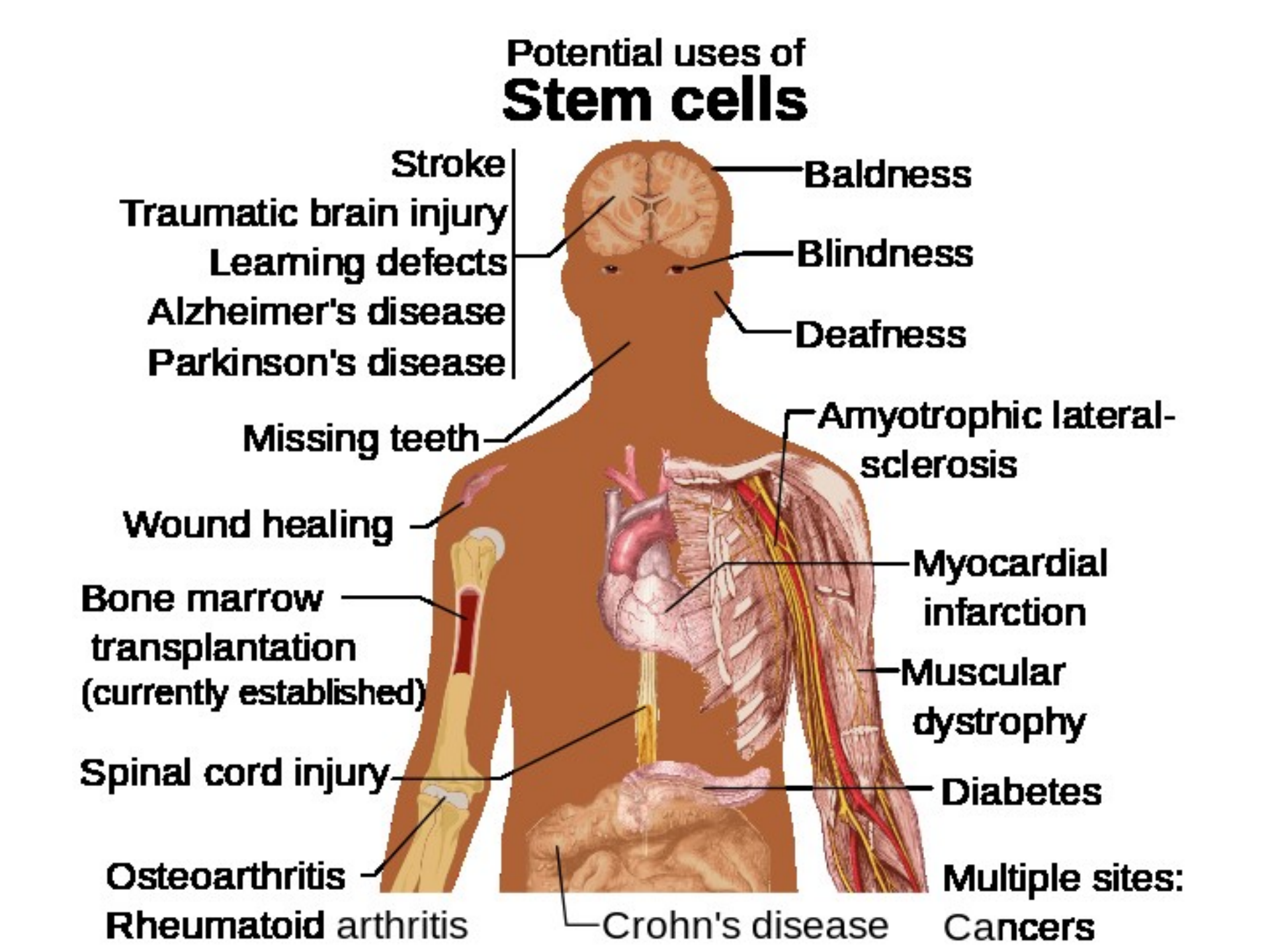
Injury
Aging
Obesity
…










Potential uses of
Stem cells
Stroke
Traumatic brain injury
Learning defects
Alzheimer's disease
Parkinson's disease
Baldness
Blindness
Deafness
Missing teeth
Amyotrophic lateral-sclerosis
Wound healing
Myocardial infarction
Bone marrow transplantation (currently established)
Muscular dystrophy
Spinal cord injury
Diabetes
Osteoarthritis
Rheumatoid arthritis
Crohn's disease
Multiple sites: Cancers

Stem cell researchers are making great advances in understanding normal development, figuring out what goes wrong in disease and developing and testing potential treatments to help patients. They still have much to learn, however, about how stem cells work in the body and their capacity for healing.

Safe and effective treatments for most diseases, conditions and injuries are in the future.

Prerequisites:

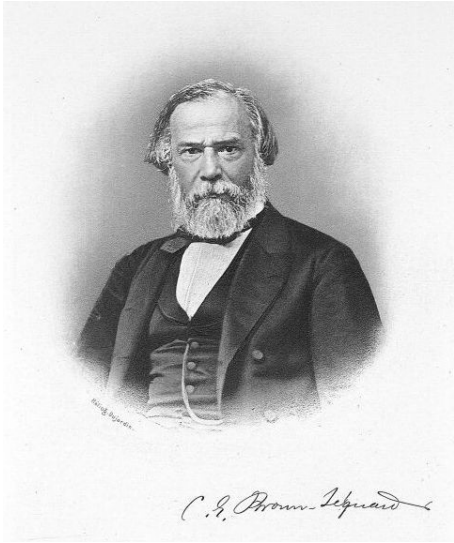
1) Derive

2) Conquer

http://www.closerlookatstemcells.org/stem-cells-and-medicine/nine-things-to-know-about-stem-cell-treatments

History of cell replacement therapy

- 19th century - **Charles-Édouard Brown-Séquard** (1817–1894) injected animal testicle extracts in an attempt to stop the effects of aging



- 1931 - **Paul Niehans** (1882–1971) – **inventor of cell therapy** – attempted to cure a patient by injecting material from calf embryos
  - Niehans claimed to have treated many people for cancer using this technique, though his claims have never been validated by research

- 1953 - laboratory animals could be helped not to reject organ transplants by pre-inoculating them with cells from donor animals

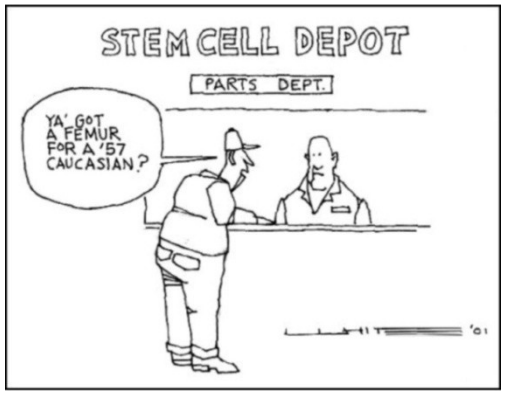
- **1968** - in Minnesota - **first successful human bone marrow transplantation**
  -Till today, the cell replacement therapy is most advanced with

- **1998** – **first isolated human embryonic stem cells** – great leap in research

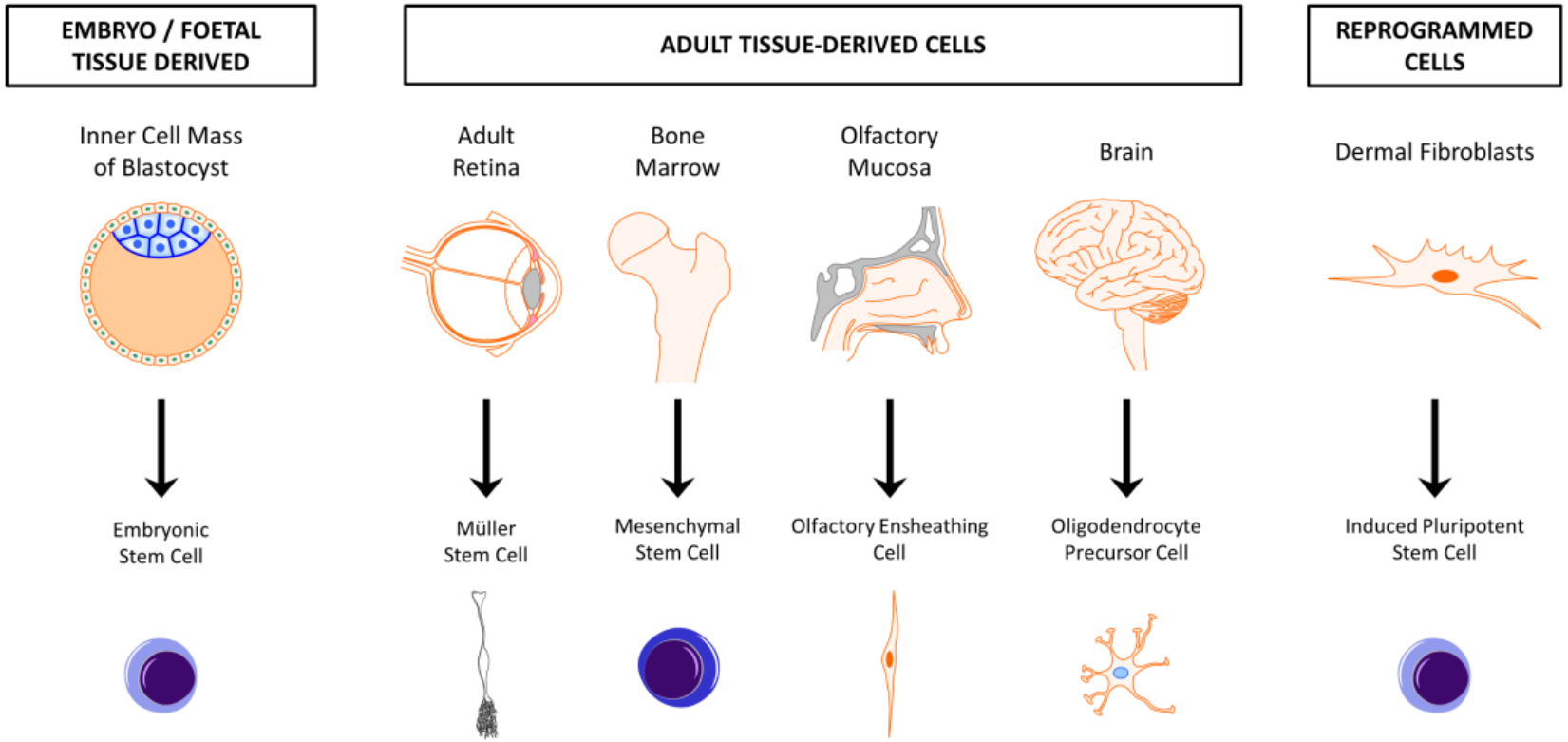
- **2006** – **first Induced Pluripotent Cells** - revolution to the field

Prerequisites for cell replacement therapy

- **1) Unlimited supply of tissue and organ-specific cells, which are capable of circumventing immunogenic rejection** (similar to organ transplantation)



- **<u>Available sources:</u>**



+ Stem cells from placenta and umbilical cord blood and xenogenic cells

The source#1: EMBRYONIC STEM CELLS

REPORTS

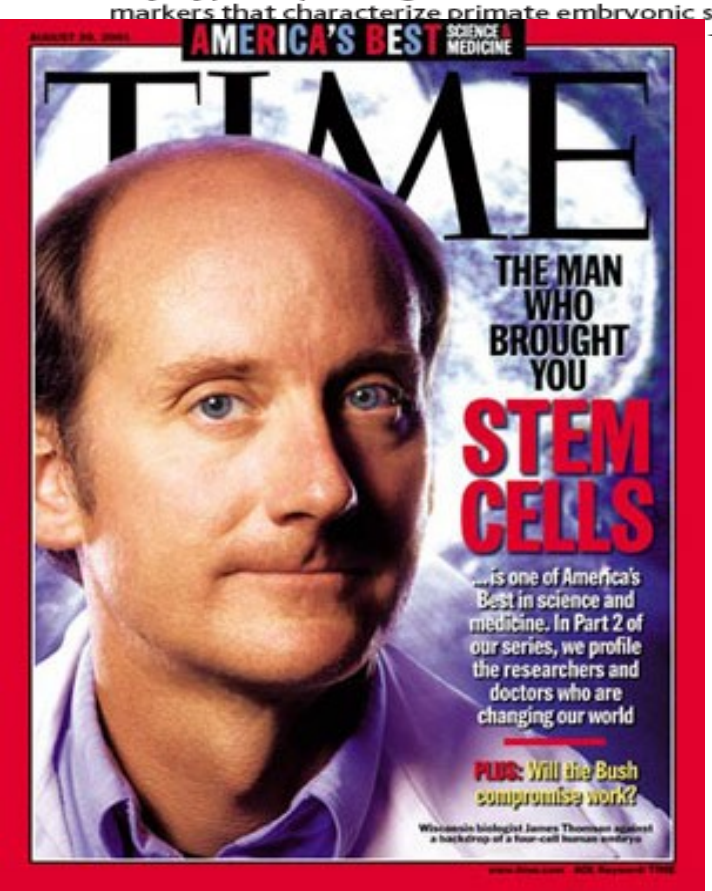
Embryonic Stem Cell Lines Derived from Human Blastocysts

James A. Thomson,* Joseph Itskovitz-Eldor, Sander S. Shapiro, Michelle A. Waknitz, Jennifer J. Swiergiel, Vivienne S. Marshall, Jeffrey M. Jones

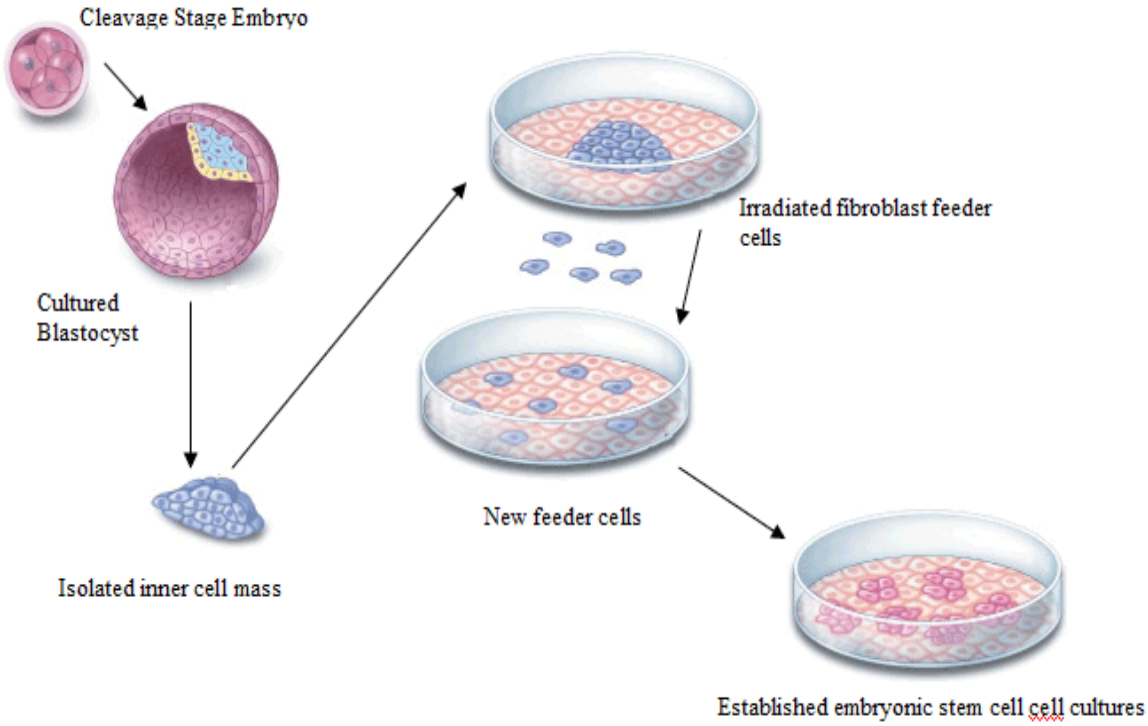
Human blastocyst-derived, pluripotent cell lines are described that have normal karyotypes, express high levels of telomerase activity, and express cell surface markers that characterize primate embryonic stem cells but do not characterize

XX karyotype after 6 months of culture and has now been passaged continuously for more than 8 months (32 passages). A period of replicative crisis was not observed for any of the cell lines.

The human ES cell lines expressed high levels of telomerase activity (Fig. 2). Telomerase is a ribonucleoprotein that adds telomere repeats to chromosome ends and is involved in maintaining telomere length, which plays an important role in replicative life-span (*7*, *8*). Telomerase expression is highly correlated with immortality in human cell lines, and reintroduction of telomerase activity into some diploid human somatic cell



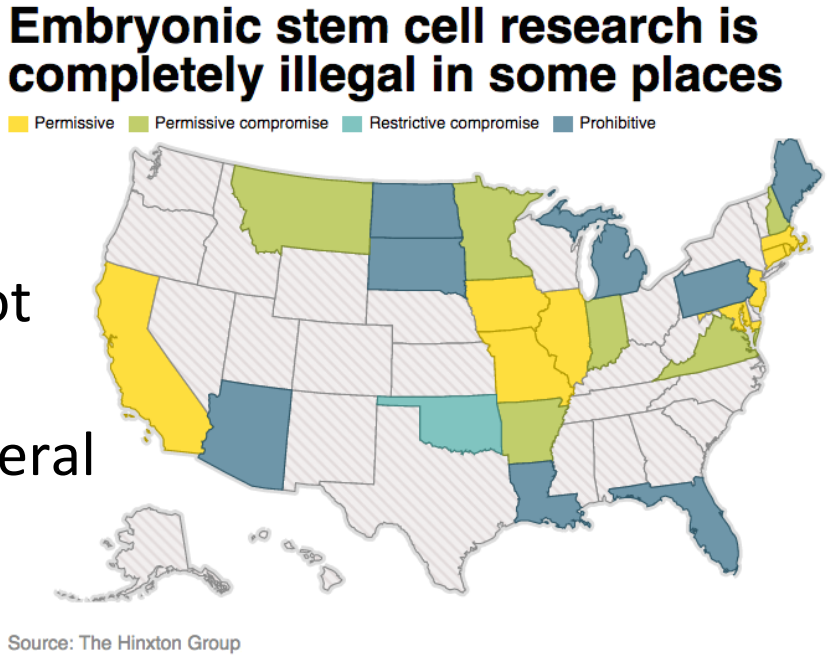
Science. 1998 Nov 6;282(5391):1145-7



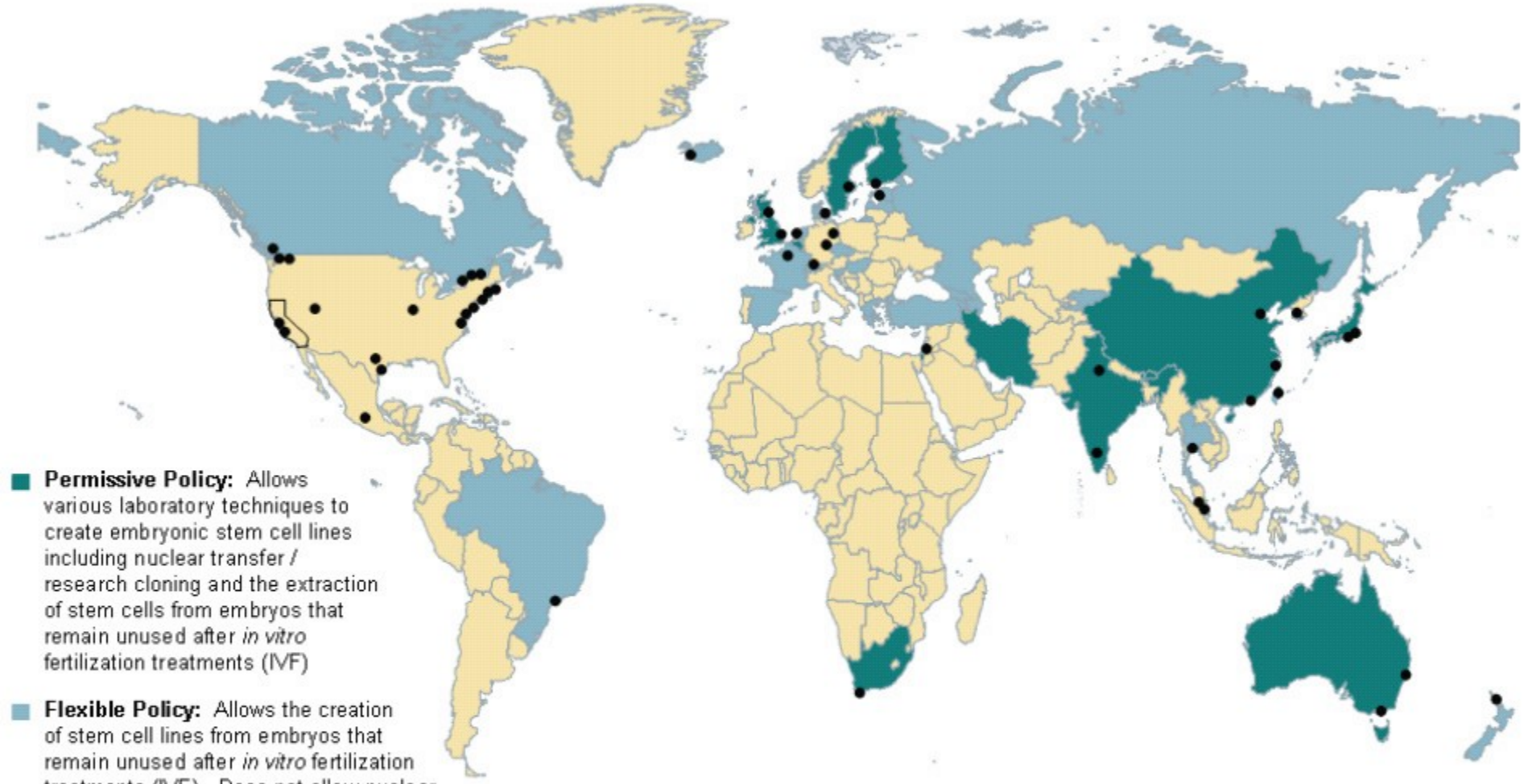
Use of human ESCs for regenerative medicine

- **Pros:** pluripotent, stable in culture, easy to obtain, best source for some tissues
- **Cons:** ethical issues - blastocyst is destroyed

- The actual number of human ES cell lines is a matter of some debate.
- To date, **more than 100** human ES cell lines have been derived worldwide.
- However, most of those lines are not adequately characterized yet.
- Only 22 cell lines are eligible for federal funding in the USA.
- Highly different policy worldwide



World Stem Cell Policy



Permissive Policy: Allows various laboratory techniques to create embryonic stem cell lines including nuclear transfer / research cloning and the extraction of stem cells from embryos that remain unused after *in vitro* fertilization treatments (IVF)

Flexible Policy: Allows the creation of stem cell lines from embryos that remain unused after *in vitro* fertilization treatments (IVF). Does not allow nuclear transfer / research cloning

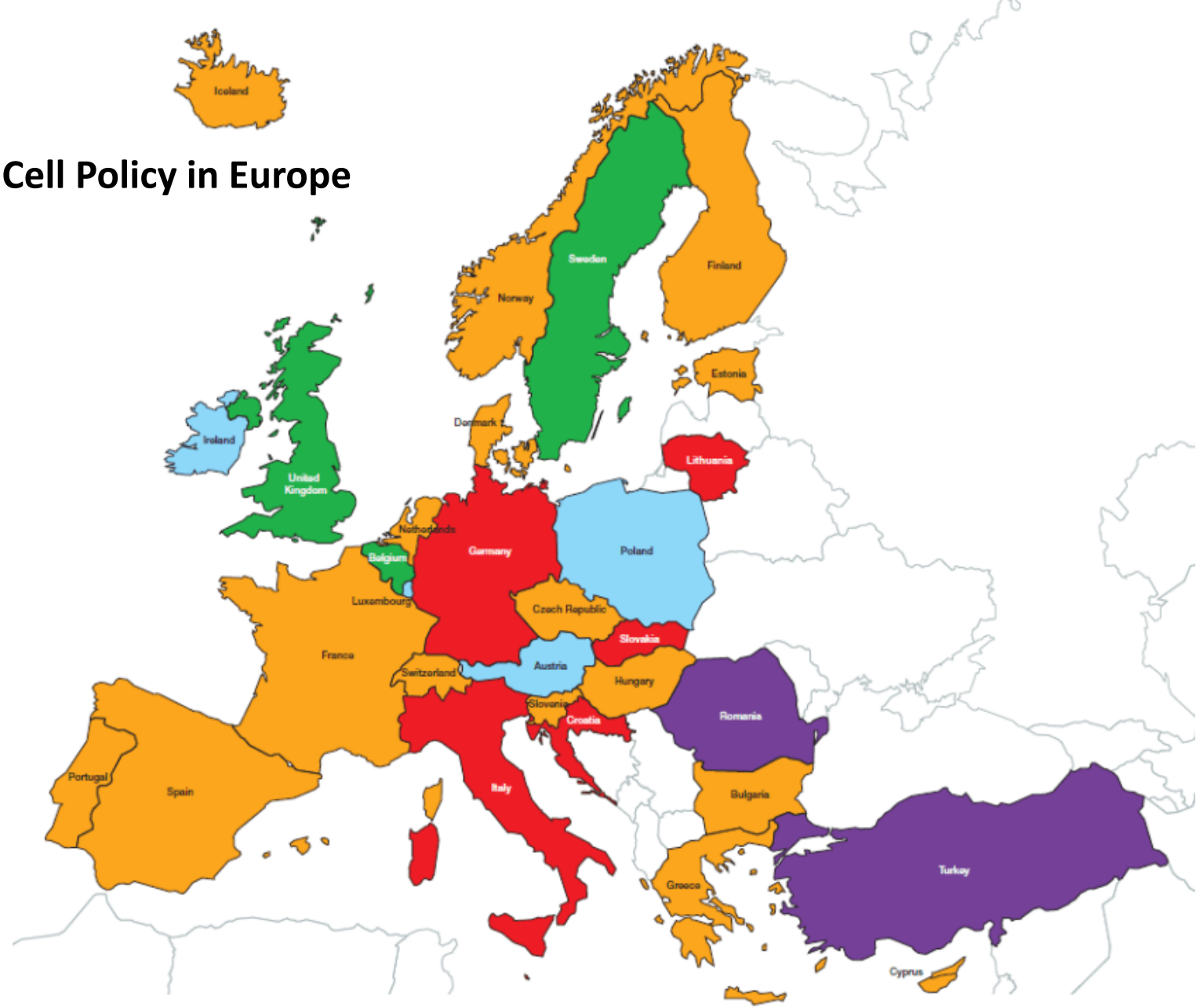
Restrictive Policy or No Established Policy

- Genome Sequencing Research Centers.

California supports embryonic stem cell research through Proposition 71

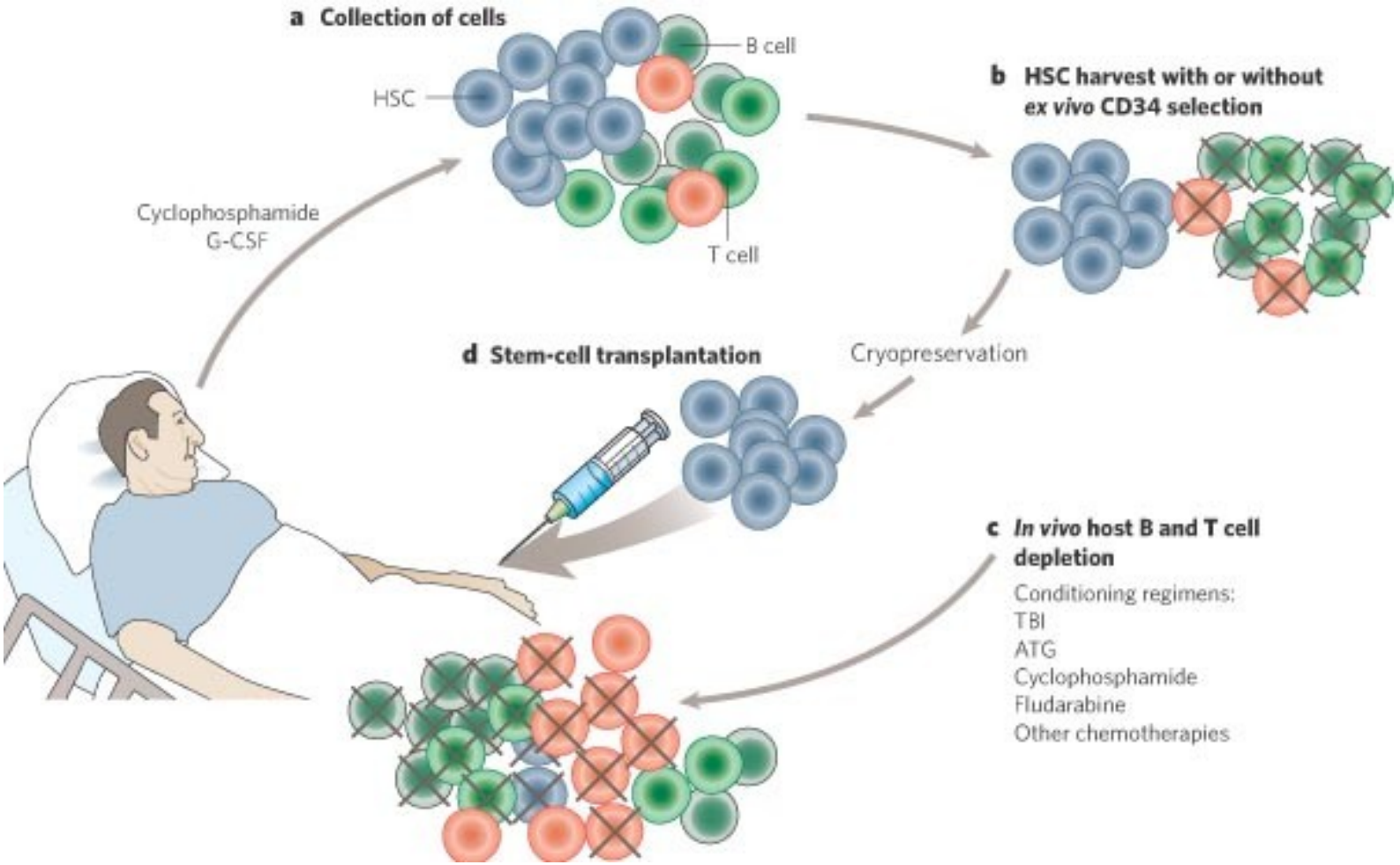
Source: William Hoffman, MBBNet, University of Minnesota. For more detail, see: http://www.mbbnet.umn.edu/scmap.html
Published by the Monitor Company Group, Cambridge, Massachusetts, USA

Stem Cell Policy in Europe



Very permissive (hESC often can derive from different sources, including surplus IVF embryos and embryos created for research).
Permissive with restrictions (hESC research only on surplus IVF embryos).
Restrictive by default. Legislation implicitly prohibits hESC research.
Very restrictive. Legislation clearly prohibits hESC research.
Unlegislated. There is no specific legislation concerning hESC research.

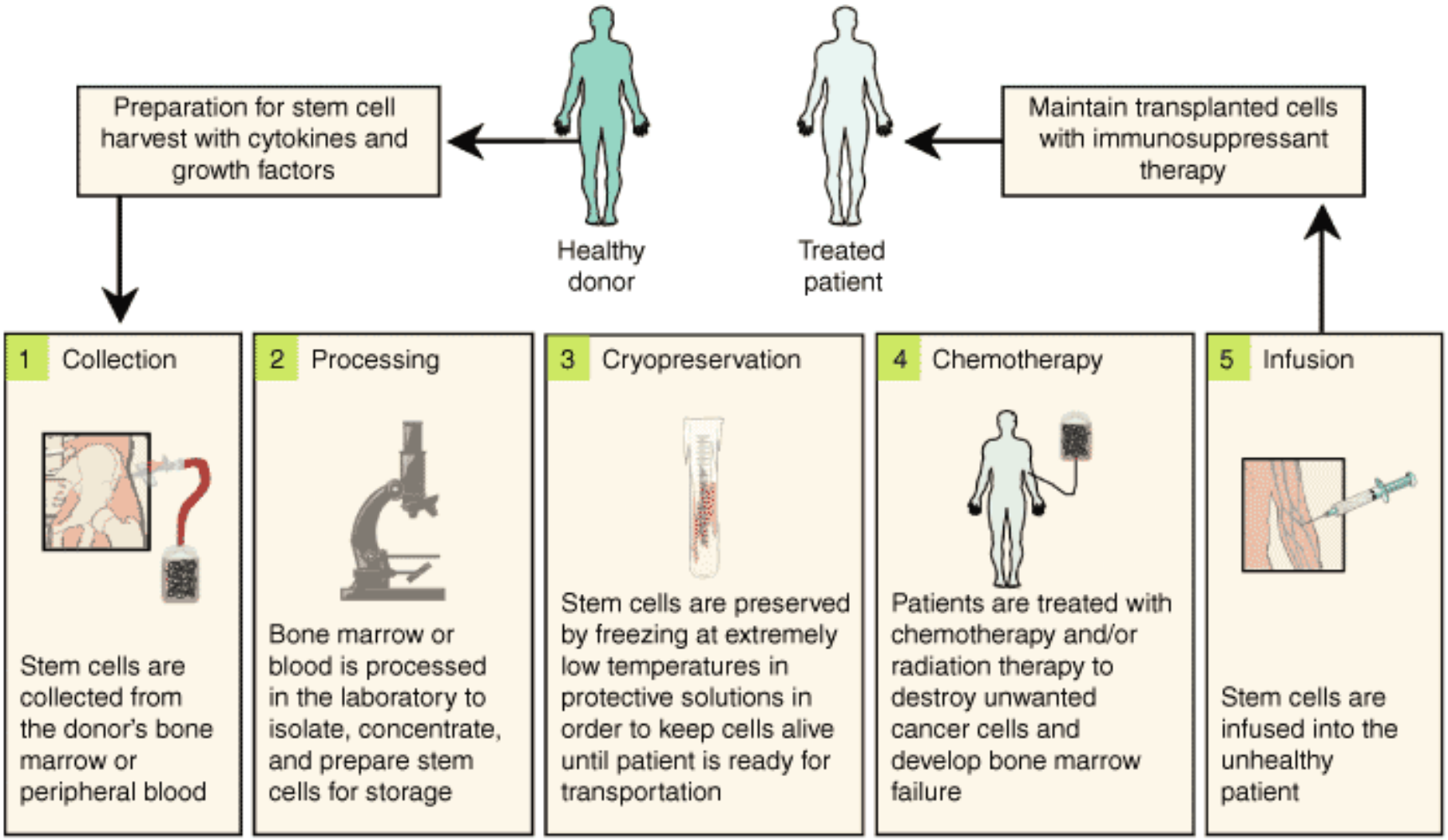
Autologous Stem Cells



Sources of the patient's own stem cells (autologous) are either the cells from patient's own body or his or her cord blood. For autologous transplants physicians now usually collect stem cells from the peripheral blood rather than the marrow

This procedure is easier, unlike a bone marrow harvest, it can take place outside of an operating room and the patient does not have to be under general anaesthesia.

Allogeneic Stem Cells



- Sources of stem cells from another donor (allogeneic) are primarily relatives (familial-allogeneic) or completely unrelated donors (unrelated-allogeneic).

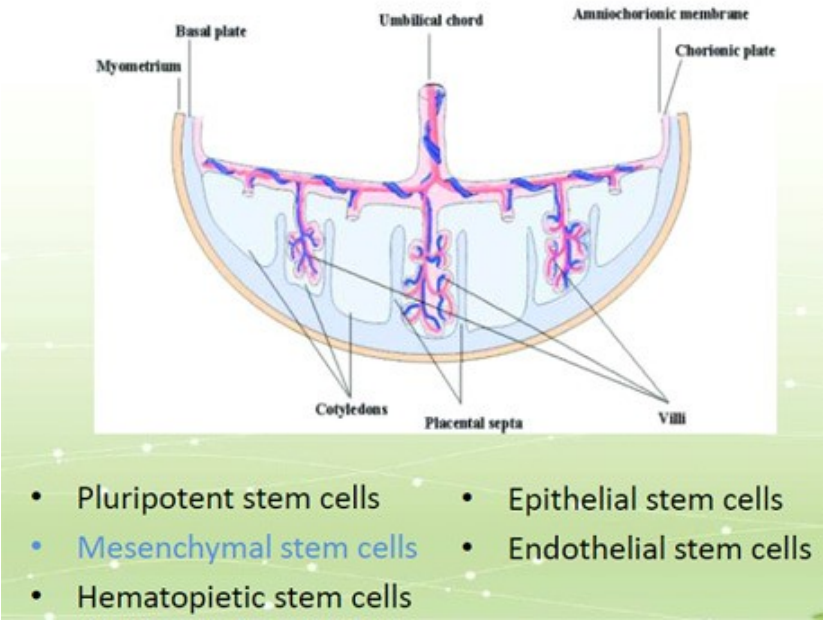
Graft versus host disease (GVHD) may affect the patient. Measures are taken to prevent GVHD.

Xenogeneic Stem Cells

- In this stem cells from different species are transplanted, e.g. striatal porcine fetal ventral mesencephalic (FVM) xenotransplants for Parkinson's disease.
- This has no major ethical concerns and a large amount of tissue is available, however life long immunosupression and risk of rejection are the major limitations.
- Xenocellular transplantation is promising for tissue repair in immunologically privileged sites such as the central nervous system or nonvascularized tissues in which no or moderate immunosuppression is required.
- In vascularized organs, major immune responses are present when cells are transplanted without additional conditioning. Positive results from encapsulation methods that protect cells from the immune system should further stimulate preclinical research. Also, conditioning immunosuppression could be used to circumvent the initial immune response.
- Transgenic pigs cells are probably the best xenogeneic substitute for human application, although basic research on innate and noninnate immunity toward pig cells is still required.
- Suitable for for cardiomyopathy, diabetes, liver failure, neural diseases, and bone regeneration.

The source#3: PLACENTAL/UMBILICAL CORD BLOOD

- world's largest potential source of stem cells, considering the global birth rate of around 135 million per year

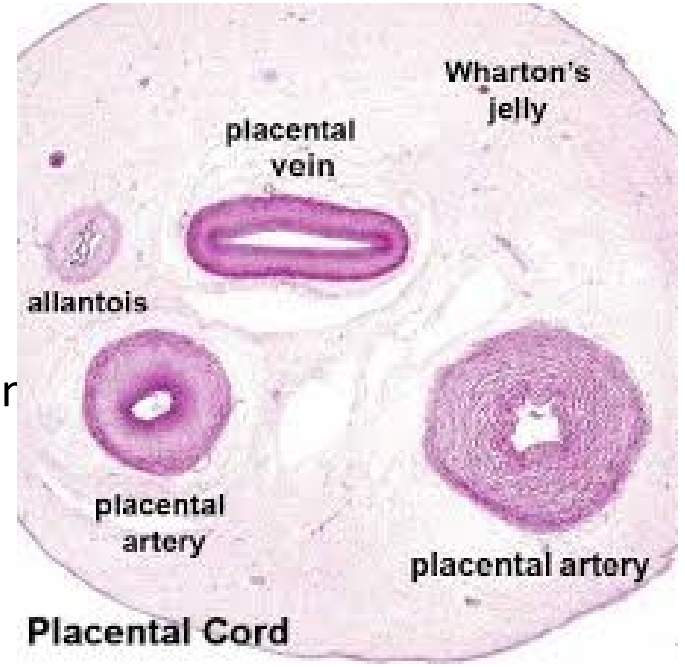


- Placental SCs are those stem cells that are found only in the placenta and are collected after the blood from the umbilical cord is drawn

- The umbilical cord represents a well known source of endothelial progenitor cells, hematopoietic as well as non-hematopoietic stem cells (=CBEs = Cord Blood Embryonic-like stem cells) - have been shown to differentiate into neural, hepatobiliary, pancreatic-like precursors and potentially others

- Placental SCs, like UCB and BM stem cells, can be used to cure chronic blood-related disorders such as sickle cell disease, Thalasemia, and leukaemia – nowadays 80 diseases – complete list at: http://parentsguidecordblood.org/diseases.php

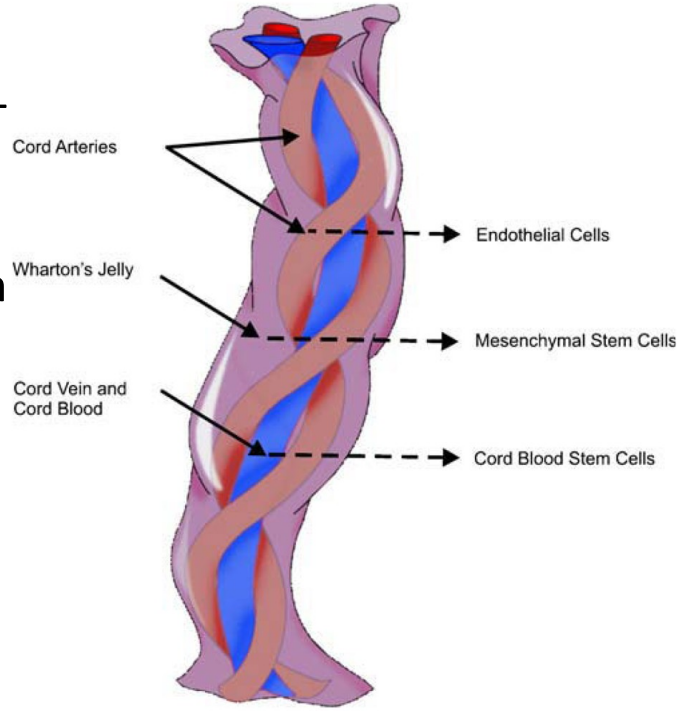
Wharton's jelly gives rise to MSCs



- 5–10 mm^3 of Wharton's jelly has the potential to yield up to 1 billion MSCs in a month

- easy and devoid of side effects associated with collection of MSCs from BM or adipose tissue, high rate of proliferation, immune privileged status, lack of ethical concerns, nontumorigenic properties make them ideal for both autologous and allogeneic use in regenerative medicine applications

- 2008 - first clinical trial, to date 51 clinical trials using WJ-MSC for a very wide range of therapeutic applications - Most of these trials are safety studies (Phase I) and proof of concept (Phase II) with very few in Phase III (comparison of a new treatment to the standard treatment).



- The outer membrane of the UC is an extremely rich source of SCs for burn resurfacing
- The cord lining gives rise to multipotent epithelial stem cells (CL-epithelial stem cells)

Umbilical cord blood in clinics

- **Over the last 25 years, the field of UCB banking and transplantation has grown exponentially**

- **1988 -** The first cord blood transplant – Falconi anemia, donor – HLA-compatible sister (patient now alive and with own kids)

- **1994** – first CB transplant in Czech Republic – Lazy leukocyte syndrome, donor - sibling

- 1996 - The first unrelated UCBTs in children were reported by Joanne Kurtzberg *et al* in 25 children with a variety of malignant and nonmalignant diseases.

- UBC SCs transplants are less prone to rejection than either BM or PB SCs, because the cells have not yet developed the features that can be recognized and attacked by the recipient's immune system

HSCs transplantations from UCB

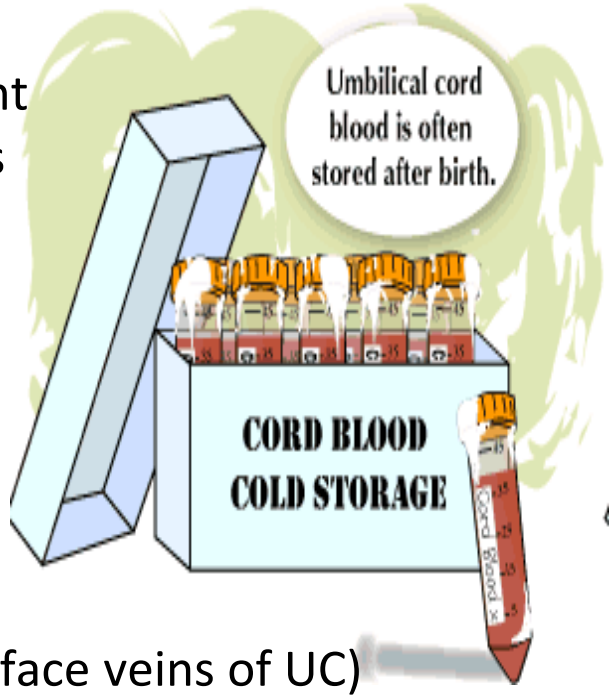
- Over 600 000 UCB units have been stored for transplantation worldwide, and >30 000 UCBTs have been performed
- UCB serves as an alternative stem cell source; only 30% of patients who require an allograft will have a human leukocyte antigen (HLA)-matched sibling donor
- Český registr dárců kostní dřeně (www.kostnidren.cz)
- Despite >20 million adult volunteer donors in the National Marrow Donor Program and affiliated registries,[1] many patients, particularly patients of diverse racial/ethnic backgrounds, will not have a suitably matched, unrelated volunteer donor identified in the required time period
- Pros: ready availability through CB banks,

  - relatively low level of graft vs. host disease (GVHD) elicited after transplantation
  - HLA-A,-B antigen, -DRB1 allele-match can be only 4/6 (in BM – 5/6 in non-related donors, up to 3/6 in related donors)
- Cons: small number of cells in single donor units for adults
  - relatively slower speed to engraftment of neutrophils and platelets
- Current research topics: ex vivo manipulation for earlier and better engraftment etc.

What should I do with the umbilical cord blood of my newborn?

- Free choice of the parent – discard, donate (cord blood bank or research) or commercially freeze down for personal use

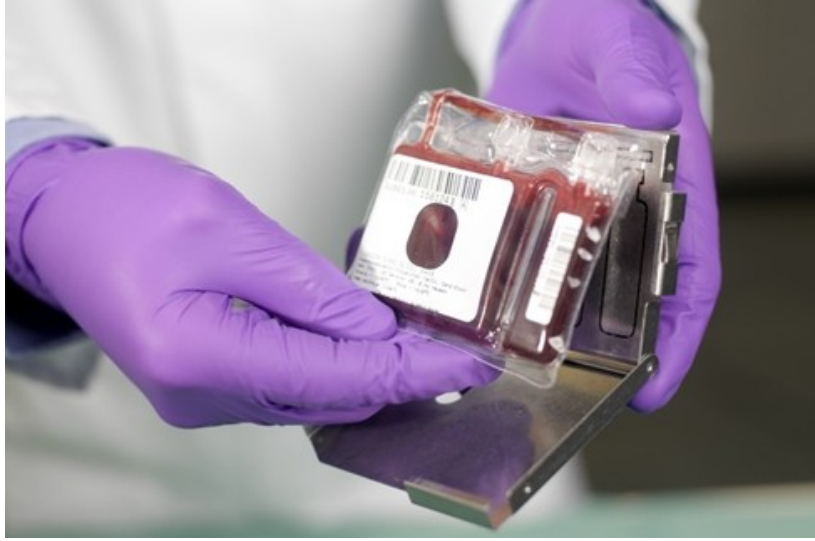
- <u>Cons of commercial freezing for personal use</u> (what is not revealed in ads…)
  - the information provided is given by gynecologists, not stem cells specialists
  - vast majority of the diseases cannot be treated by autologous CB, simply because the SCs in CB may be already afected by the disease (prenatal preleukemic cells, genetic mutations…)
  - autologous CB transplanted so far in limited numbers and experimental settings
    - has never been done in our country
  - autologous cells can be obtained later in development
  - SÚKL has not yet approved the use of any autologous CB transplants for siblings
  - CB is the the second choice method in siblings – BM is preferred choice



+ quite high price (cca 15-20 tis CZK for collection, cca 1 600 CZK /year for archiving

additional costs for collection placental blood (from surface veins of UC)

Donating cord blood



- **How much blood and stem cells does a typical umbilical cord hold?**

The median size of cord blood collections in family banks is 60mL.
- corresponds to 470 million Total Nucleated Cells (TNC) or 1.8 million CD34+ cells

- **How much cord blood is needed for a transplant?**

The crucial thing is not the volume of the cord blood collection, but the number of stem cells it contains. Transplant doctors develop recommendations based on the Total Nucleated Cell count, or TNC, because it is the easiest measure to reproduce between different labs. For treating cancer, the transplant dose should be at least 25 million TNC per kilogram of patient body weight.
The average cord blood collection holds 8.6 million TNC per mL. Thus, the optimal transplant dose requires harvesting:
2.9 mL of cord blood for every kg of patient weight

However, as more transplant centers are adopting the practice of giving adult patients "double cord blood transplants" with two cord blood units, it is less critical for both units to have adequate cell dose.

Banka pupečníkové krve ČR

- **www.bpk.cz**

- **Porodnice, kde můžete darovat pupečníkovou krev:**

Nemocnice Česká Lípa
Fakultní Thomayerova nemocnice s poliklinikou, Praha
Nemocnice Slaný

- **Porodnice, se kterými aktuálně připravujeme spolupráci:**

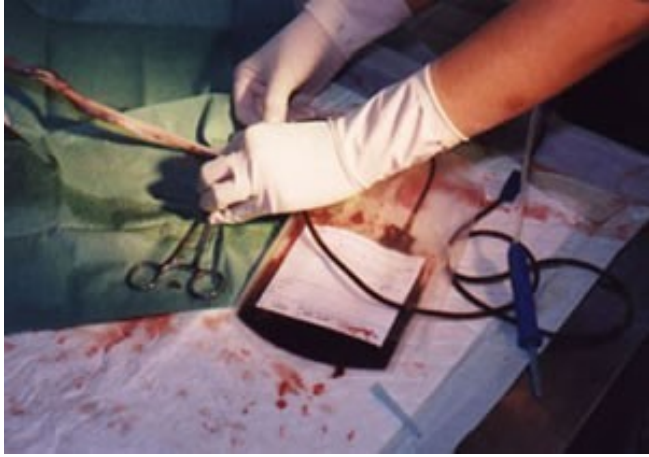
Fakultní nemocnice v Motole, Praha
Všeobecná fakultní nemocnice v Praze
Fakultní nemocnice Královské Vinohrady, Praha

- **Porodnice, které jsou zahrnuty do plánu rozvoje BPK ČR:**

Ústav pro péči o matku a dítě (Praha - Podolí)

V následujících letech plánuje BPK ČR rozšířit svou činnost do porodnic po celé ČR tak, aby měly maminky možnost darovat pupečníkovou krev v každém kraji.

Odběr pupečníkové krve



- **Vlastní odběr pupečníkové krve** :

není žádným způsobem nebezpečný pro dítě či matku

nezasahuje do průběhu porodu

odběr lze kdykoliv odmítnout, i v poslední chvíli před porodem

odběr rodička necítí, protože placenta i pupečník patří ve skutečnosti novorozenci.

Ten je ale po narození již nepotřebuje.

- **Odběr začíná ihned po porodu dítěte**, před porodem placenty, kdy pupečník vybíhá ven porodním kanálem. Porodní asistentka pupečník omyje a opláchne sterilním roztokem, napíchne žílu pupečníku a nechá krev samovolně odtékat do připraveného vaku.
- **Po té, co krev přestane vytékat**, zaškrtí přívodní hadičku. Pokud ještě nějaká krev zbyla v placentě (v případě, že se žíla samovolně uzavřela), může asistentka napíchnutí opakovat druhou jehlou ze setu. Po ukončení odběru čeká porodník na třetí dobu porodní, což je porození placenty. Po jejím prohlédnutí lze ještě zopakovat odběr po zavěšení placenty na speciální stojan. Odebírají se také 2 ml srážlivé krve pro virologickou laboratoř.
- Po porodu je ještě potřeba odebrat krev matce pro provedení infekčních testů. Vak s pupečníkovou krví, zkumavky se sraženou PK a s krví matky a všechny potřebné formuláře k odebranému štěpu se uskladní v ledničce v jednom obalu a pravidelně každý den se odesílají do zpracovávající laboratoře.

Zpracování pupečníkové krve

- **Měření objemu pupečníkové krve** - Malé objemy se nezpracovávají (nedostatečný počet buněk), použijí se k vyzkoušení nových způsobů zpracování a tedy i ke zkvalitnění postupů.

- **Kvalita štěpu -** Ze štěpu se odeberou vzorky, které se mrazí zvlášť a později se používají ke zjišťování kvality štěpu. Dále se odebírají vzorky na zjištění HLA typu buněk v krvi . Sleduje se zpravidla 6 těchto znaků, a je potřeba, aby mezi dárcem a příjemcem byla pokud možno co největší shoda. Ideálně tedy 6 na 6. Pupečníkovou krev lze transplantovat až do neshody 6 na 4 u nepříbuzného dárce (když dárce není z rodiny), ale samozřejmě se stoupajícím rizikem potíží po transplantaci. Další vzorky se posílají na zjištění krevní skupiny, na virologické vyšetření a na bakteriologické vyšetření. Také se spočítá množství bílých krvinek.

- **Kryokonzervace** - Přepuštění z odběrového vaku do kryovaku (vaku dobře snášejícího nízké teploty) a doplní se speciálním roztokem s DMSO (dimethylsulfoxid).

- **Vyšetření vzorků -** Vyšetření vzorků pak probíhá v různých laboratořích. Např. HLA typizace v IKEMu. Část vyšetření se dělá z rozmrazených vzorků, díky kterým se získá lepší představa o tom, jaké budou buněčné hodnoty po rozmrazení celého štěpu při transplantaci. Tímto vyšetřením je třeba kultivace malého vzorku pupečníkové krve v CO2 termostatu po dobu 14 dnů, kdy se zjistí jak jsou buňky ve štěpu schopné se rozmnožovat.

Pokud zjistíme, že nějaký ze zmrazených štěpů nevyhovuje náročným požadavkům, je vyřazen a údaje o něm se do světového registru nedostávají.

The source#2: ADULT STEM CELLS

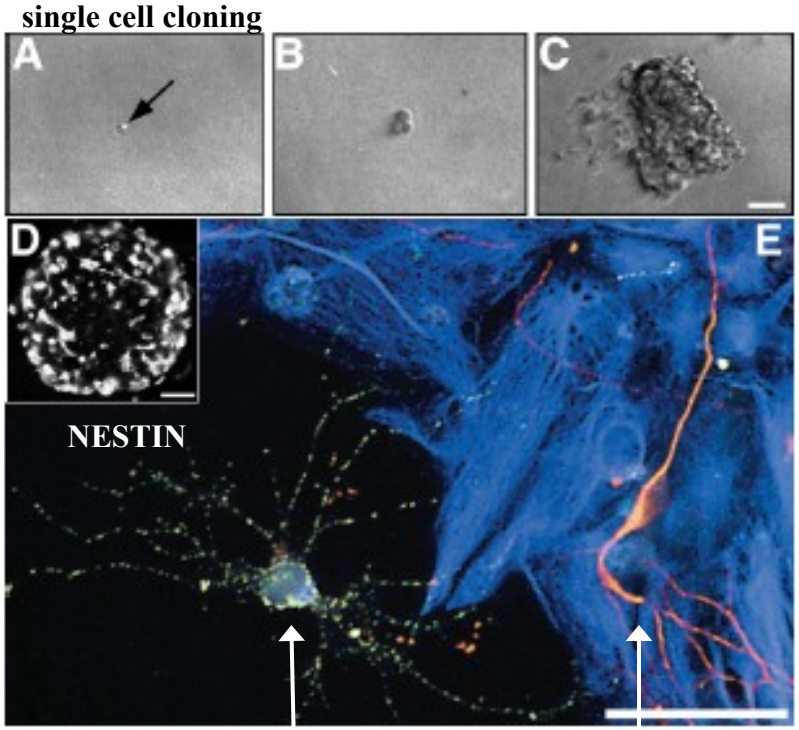
Turning Brain into Blood: A Hematopoietic Fate Adopted by Adult Neural Stem Cells in Vivo

Christopher R. R. Bjornson,*†‡ Rodney L. Rietze,*§
Brent A. Reynolds, M. Cristina Magli, Angelo L. Vescovi‡

Stem cells are found in various organs where they participate in tissue homeostasis by replacing differentiated cells lost to physiological turnover or injury. An investigation was performed to determine whether stem cells are restricted to produce specific cell types, namely, those from the tissue in which they reside. After transplantation into irradiated hosts, genetically labeled neural stem cells were found to produce a variety of blood cell types including myeloid and lymphoid cells as well as early hematopoietic cells. Thus, neural stem cells appear to have a wider differentiation potential than previously thought.

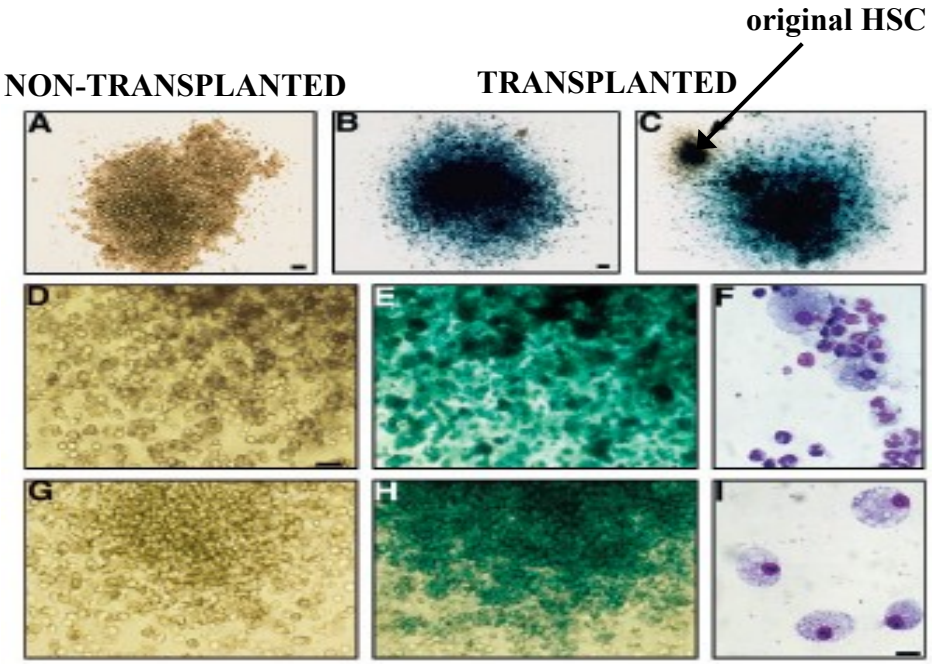
22 JANUARY 1999 VOL 283 SCIENCE www.sciencemag.org

Neural stem cell validation



differentiation

Hematopoietic stem cell validation in irradiated mice trasnplanted with β-gal-labeled NSC (in vitro BM clonogenic assay)

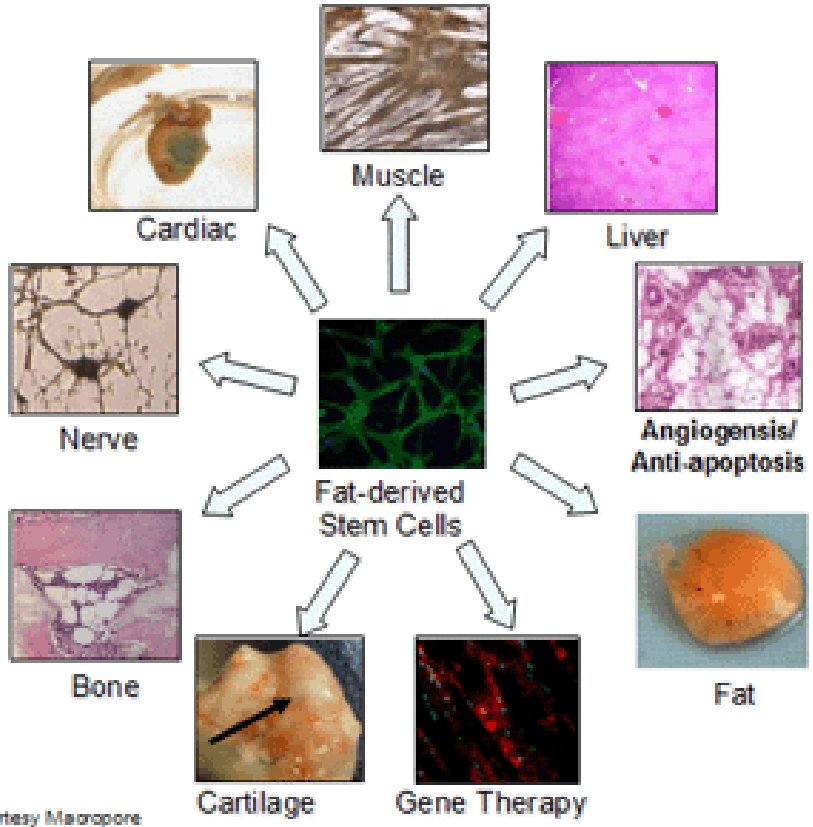


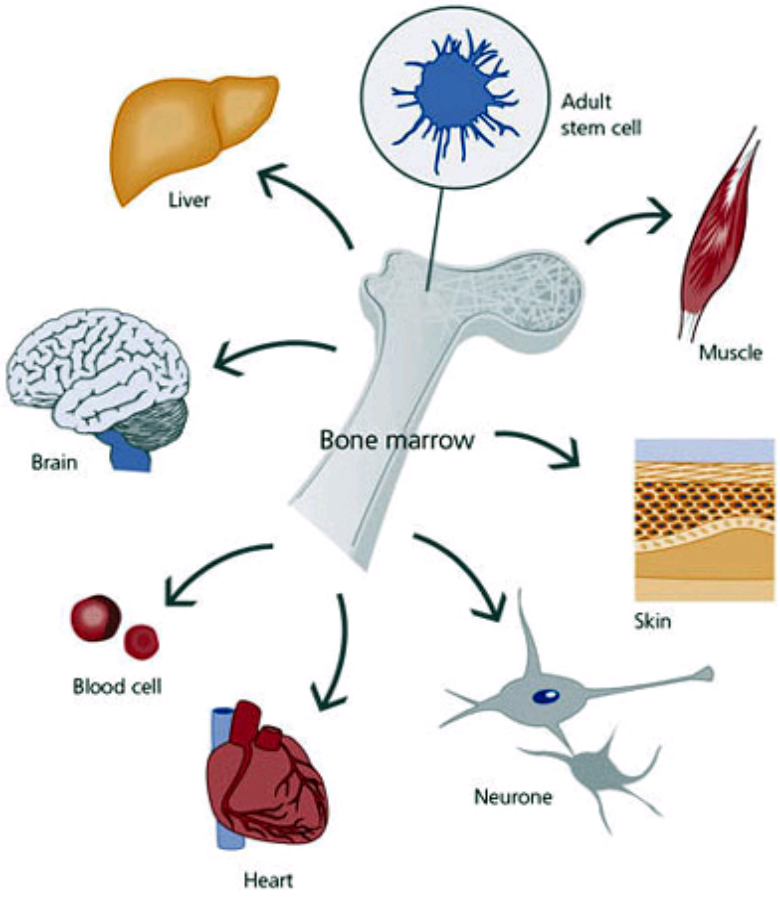
granulocyte/macrophage

macrophage

How stem cell therapy (ideally) works?

When stem cells are transplanted into the body and arrive into the injured part (e.g. Brain) being targeted for tissue regeneration, the stem cells are coming in contact with local (niche) growth signals. These signals program the stem cells to differentiate into the tissue surrounding it.





Adult Mesenchymal Stem Cells

- derived for cell therapy mainly from bone marrow and adipose tissue (high expansion potential and reproducible isolation protocols) and to a lesser extent, placenta, amniotic fluid, umbilical cord, dental pulp, tendon, trabecular bone and synovia.

- hMSCs are characterized by three criteria: (1) plastic-adherent under culture;
  (2) capacity to differentiate into at least three mesenchymal lineages: bone, fat and cartilage;
  (3) express cell markers CD73, CD90, CD105 and negative for CD11b, CD14, CD34, CD45 and HLA-DR.

- have a great potential in tissue engineering and may serve to treat chronic inflammatory and degenerative disorders due to their immunosuppressive properties

- considered 'immunoprivileged' by many researchers and may permit allo-transplantation without immunosuppressive therapy, which would become particularly useful in treating acute injuries.

- Bone marrow has been the primary source of mesenchymal stem cells; however, bone marrow collection is invasive and MSC isolation is inefficient (<0.05%)

Adipose Tissue-Derived Stem Cells (ADSCS)

- Human adipose tissue is now a widely accepted source for stem cells in regenerative medicine
- The nonlipid cell population isolated from adipose tissue is heterogeneous and contains adipose-derived stem cells (ASCs), which can be isolated and cultured.
- ASCs are of mesenchymal lineage and manifest features that are attractive for regenerative therapy approaches, including multipotency and release of growth factors that can induce tissue healing.
- These beneficial characteristics have the potential to affect cancer growth and this issue is still being investigated in preclinical and clinical studies.
- To date, 129 active clinical trials are listed in the US National Institutes of Health Web site (www.clinicaltrials.gov), spanning a broad range of applications including arthritis, intervertebral disc degeneration, autism therapy, cell-enriched fat grafting, pulmonary disease, and numerous clinical targets.

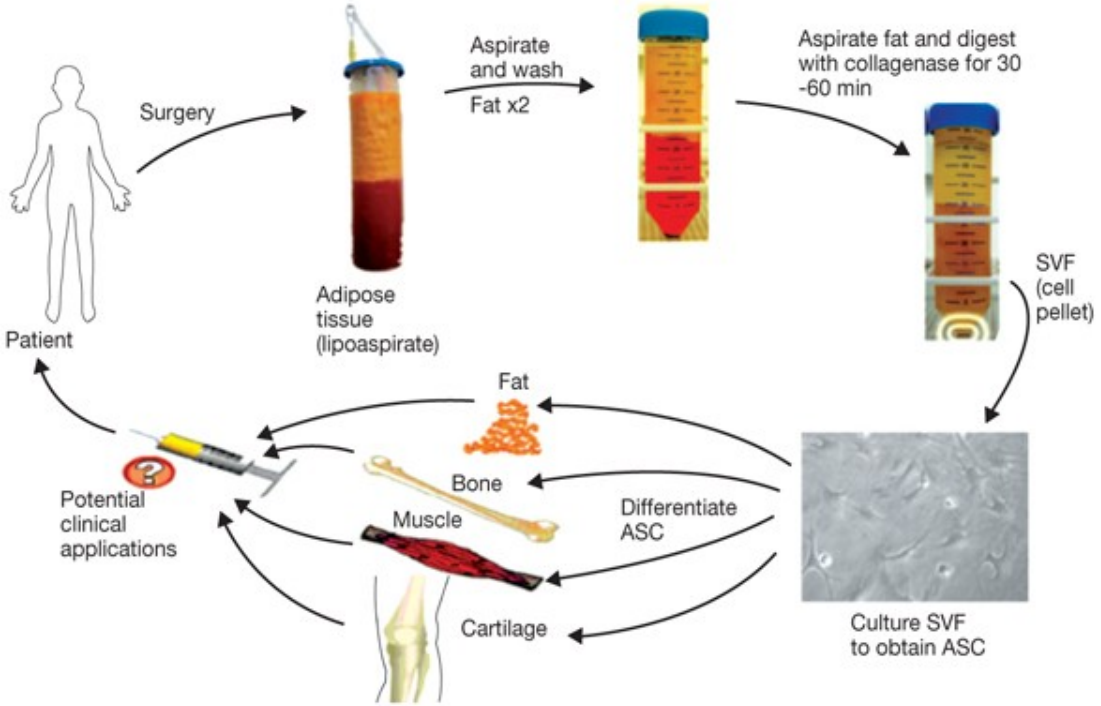
ADSCS protocol

- These non–lipid-laden stromal cells can be isolated from either suction-aspirated adipose tissue or excised human fat by enzymatic collagenase digestion.
- The freshly isolated cell pellet is highly heterogeneous and is named the stromal vascular fraction (SVF).
- If the SVF cells are placed in culture, the ASCs adhere to the surface of an untreated tissue culture flask after 6 to 8 hours' incubation at 37C and 5% CO2. Once ASCs have adhered to the culture flask surface, nonadherent cells are washed away

Data on current clinical trials:

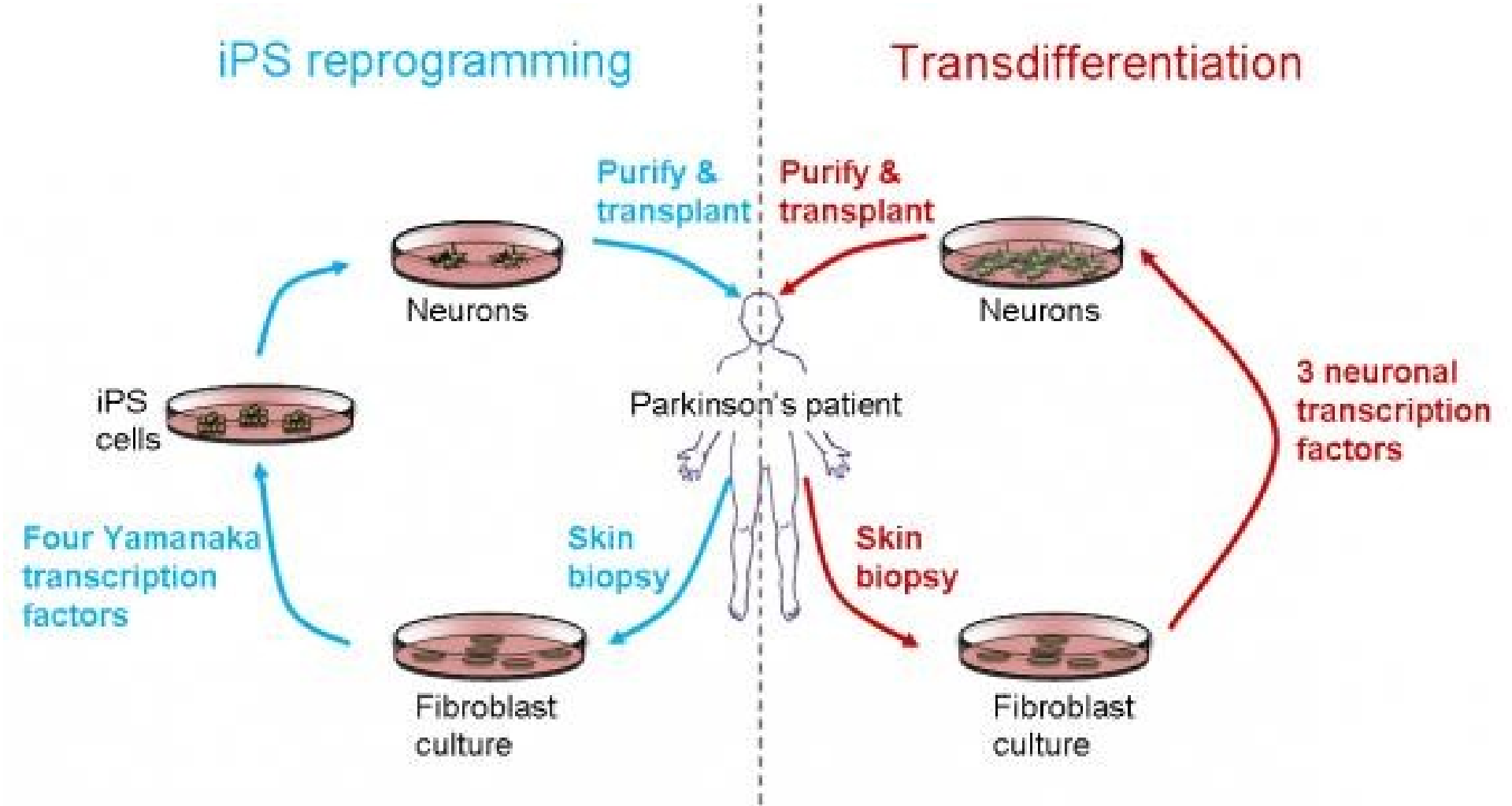
www.clinicaltrial.gov

(NIH only)

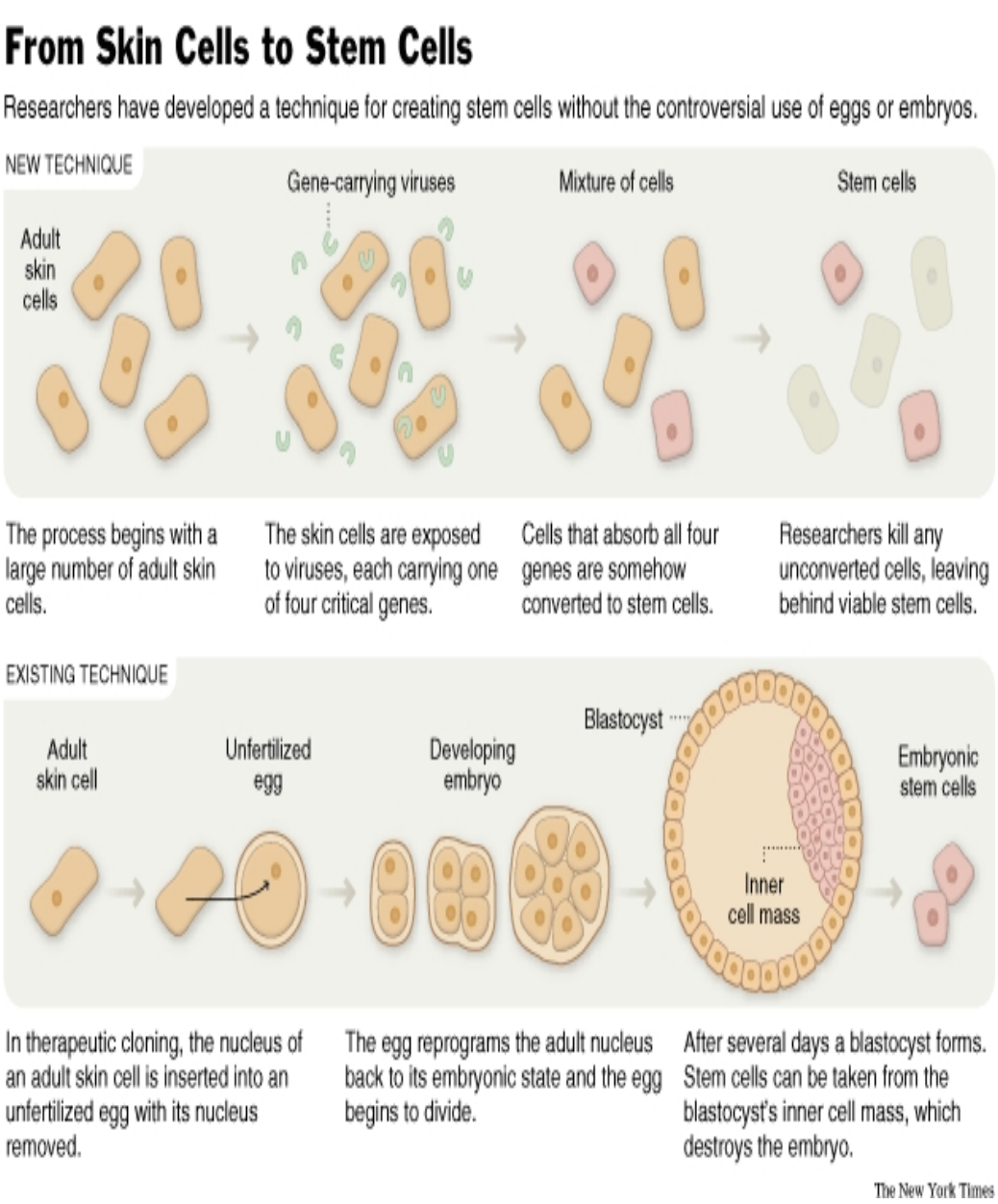


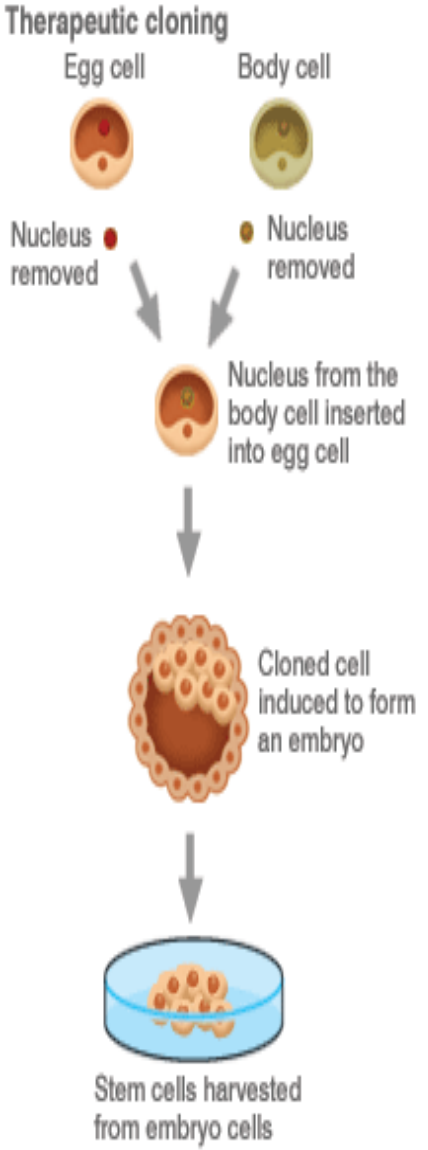
The source#3: ADULT TISSUE DERIVED STEM-LIKE CELLS

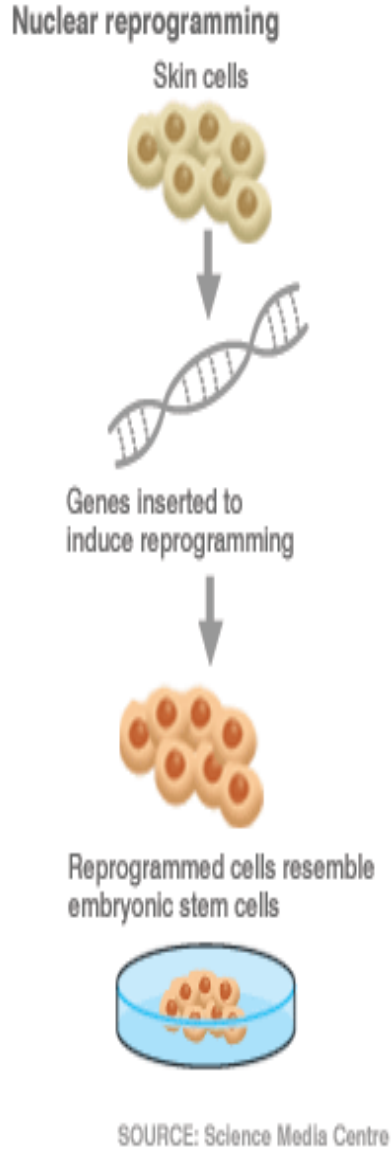
Two main techniques exist: 1) one reprograms somatic cells into pluripotent stem cells 2) converts somatic cells directly into other types of specialized cells(transdifferentiation) These techniques raise high hopes for patient-personalized cell therapies.



The source#3: INDUCIBLE PLURIPOTENT CELLS (iPS)







2006- INDUCIBLE PLURIPOTENT CELLS (iPS)

Cell

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

Myc, Oct3/4, Sox2 and Klf4

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DOI 10.1016/j.cell.2006.07.024

SUMMARY

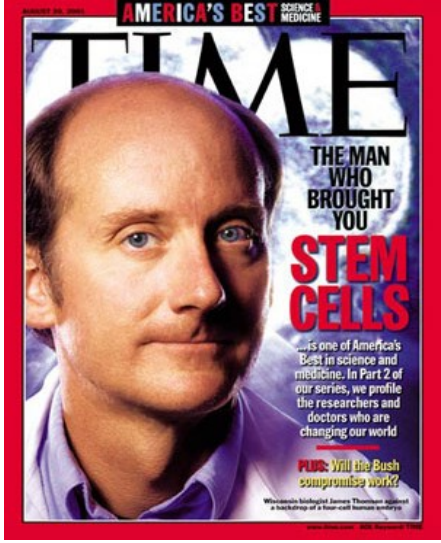
Differentiated cells can be reprogrammed to an embryonic-like state by transfer of nuclear contents into oocytes or by fusion with embryonic stem (ES) cells. Little is known about factors

or by fusion with ES cells (Cowan et al., 2005; Tada et al., 2001), indicating that unfertilized eggs and ES cells contain factors that can confer totipotency or pluripotency to somatic cells. We hypothesized that the factors that play important roles in the maintenance of ES cell identity also play pivotal roles in the induction of pluripotency in somatic cells.

Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells

Junying Yu,[1,2]* Maxim A. Vodyanik,[2] Kim Smuga-Otto,[1,2] Jessica Antosiewicz-Bourget,[1,2] Jennifer L. Frane,[1] Shulan Tian,[3] Jeff Nie,[3] Gudrun A. Jonsdottir,[3] Victor Ruotti,[3] Ron Stewart,[3] Igor I. Slukvin,[2,4] James A. Thomson[1,2,5]*

Somatic cell nuclear transfer allows trans-acting factors present in the mammalian oocyte to reprogram somatic cell nuclei to an undifferentiated state. We show that four factors (*OCT4*, *SOX2*, *NANOG*, and *LIN28*) are sufficient to reprogram human somatic cells to pluripotent stem cells that exhibit the essential characteristics of embryonic stem (ES) cells. These induced pluripotent human stem cells have normal karyotypes, express telomerase activity, express cell surface markers and genes that characterize human ES cells, and maintain the developmental potential to differentiate into advanced derivatives of all three primary germ layers. Such induced pluripotent human cell lines should be useful in the production of new disease models and in drug development, as well as for applications in transplantation medicine, once technical limitations (for example, mutation through viral integration) are eliminated.



2007 – human IPs

OCT4, SOX2, NANOG. LIN28

Today's research:

Reprogramming with Small Molecules instead of Exogenous Transcription Factors

The low efficiency (0.01%) and slow dynamics of this method posed serious potential problems for the generation of iPSCs. Besides low iPSC generation efficiency, there are some safety concerns regarding the overexpression of the four aforementioned transcription factors involving genetic mutations, gene insertions, epigenetic changes, incomplete reprogramming, and immunogenicity

First Ever iPS-Cell Trial a Go

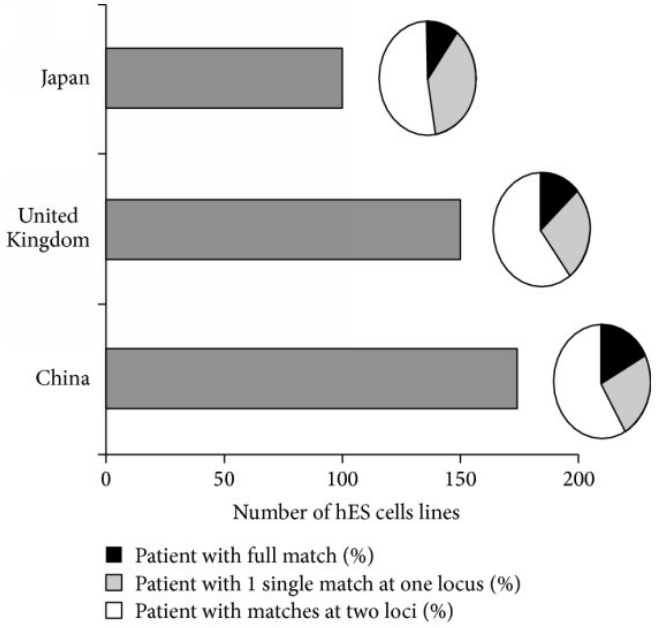
2013 - The Japanese government will allow a study of stem cell therapy using patients' own IPs cells to treat vision loss.

RIKEN - s a large research institute in Japan. Founded in 1917, it now has approximately 3000 scientists on seven campuses across Japan, the main one in Wako, just outside Tokyo.

- human IPs cell bank – 1) iPS cells derived from healthy persons
  - 2) Disease-specific iPS cells (patient-specific iPS cells) – currently › 60 diseases

Stock of IPs cells for regenerative medicine

2012 - cells from high-frequency HLA donors to generate, evaluate, and store iPS cells under conditions appropriate for eventual clinical application. The plan is to create an iPS cell stock that covers around half the Japanese population within 5 years and 80-90% within 10 years.



Summary

- Many clinics offering stem cell treatments make claims that are not supported by a current understanding of science
- Stem cells have tremendous promise to help us understand and treat a range of diseases, injuries and other health-related conditions. Their potential is evident in the use of blood stem cells to treat diseases of the blood and can be seen in the use of stem cells for tissue grafts to treat diseases or injury to the bone, skin and surface of the eye.
- **We are severely lacking the knowledge how to make stem cells to do what we want from them in our bodies – 1) derive and 2) conquer**
- Important clinical trials involving stem cells are underway for many other conditions and researchers continue to explore new avenues using stem cells in medicine.
- There is still a lot to learn about stem cells, however, and their current applications as treatments are sometimes exaggerated by the media and other parties who do not fully understand the science and current limitations, and also by "clinics" looking to capitalize on the hype by selling treatments to chronically ill or seriously injured patients.

Thank you for your attention!
Any questions?