Current topic 2:

Stem cells

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LT5- Stem cell applications

Part A- Stem cells presentation

Part B- Stem cells-based therapies

Part A – Stem cells presentation

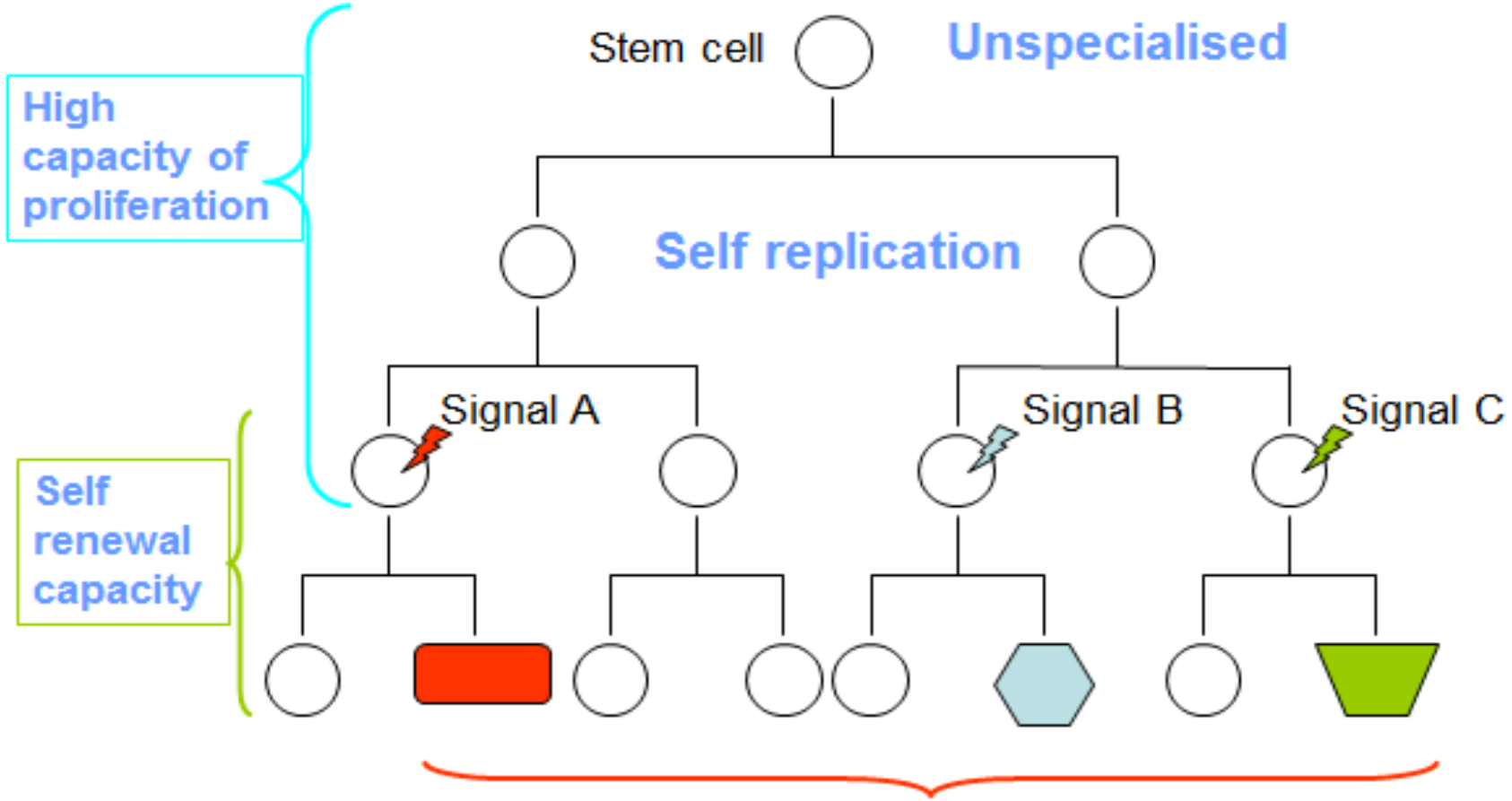
What is a stem cell?

Stem cells

1. Can proliferate
2. Can specialise

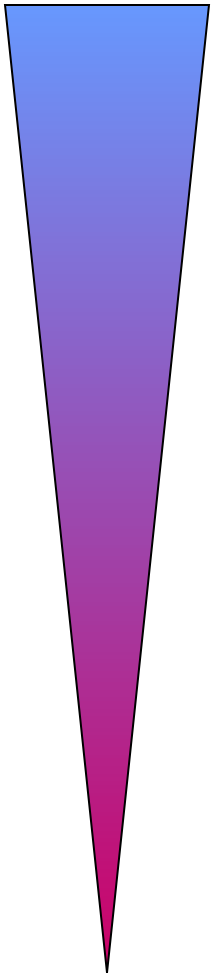
Signal =

- comes from neighbouring cells
- encoded by developmental genes
- Leads to change in gene expression

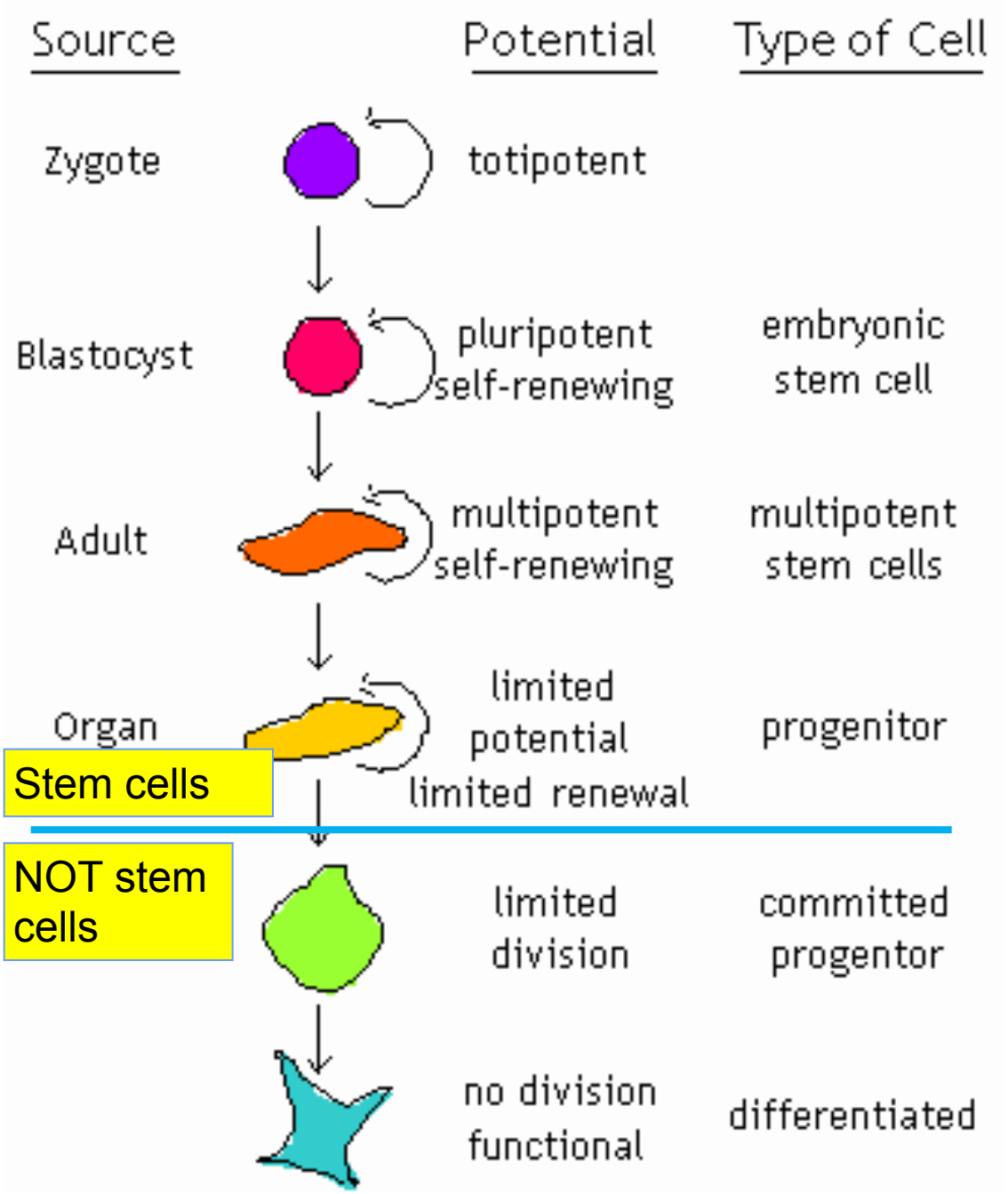


Proliferation capacity

MAXIMUM

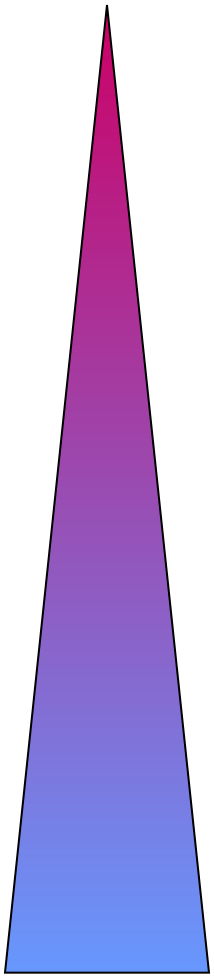


MINIMUM



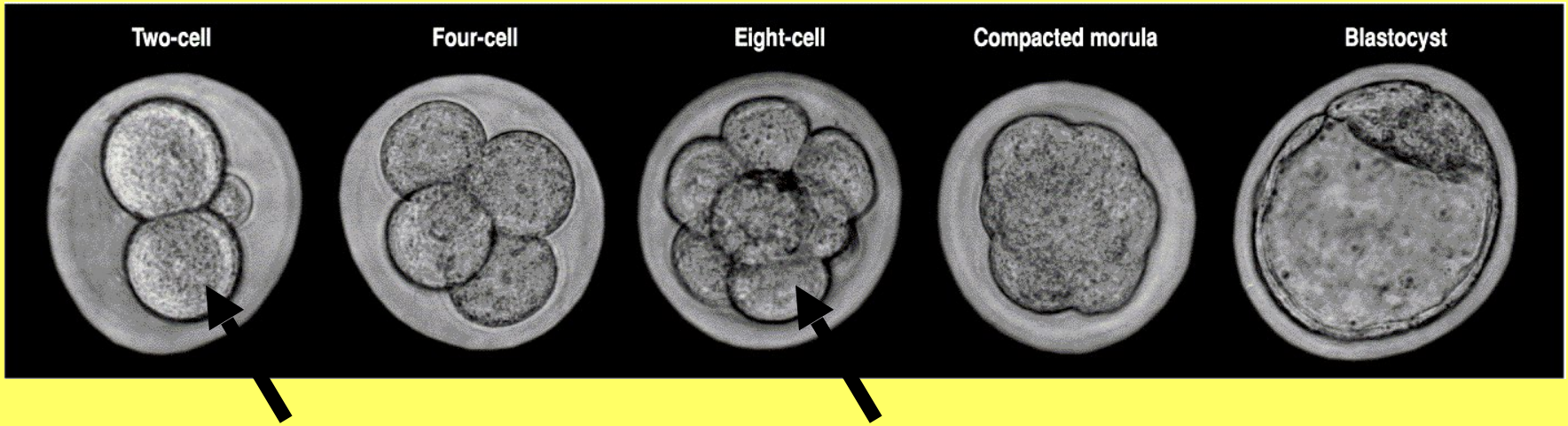
Level of specialisation

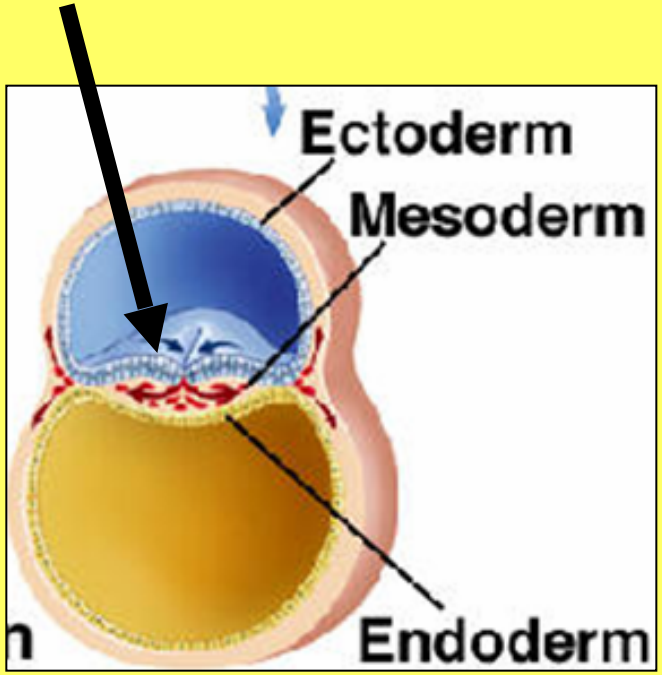
MINIMUM

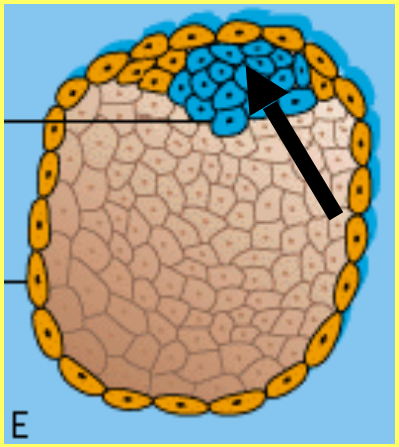


MAXIMUM

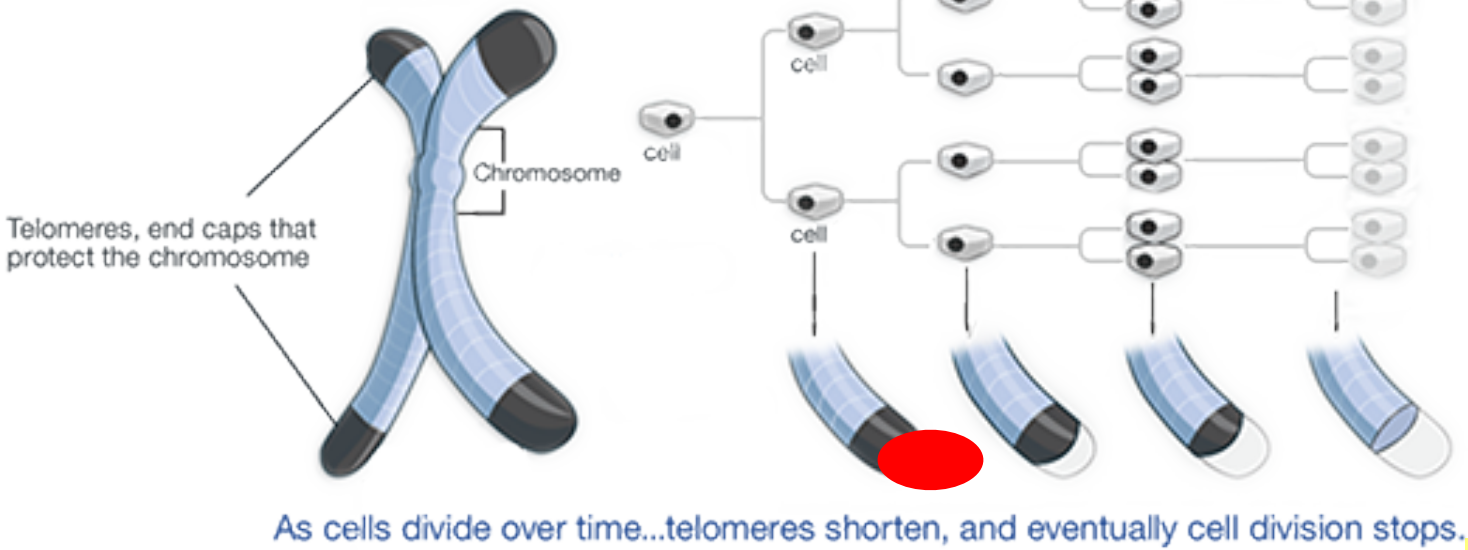
What is the potency of these cells?

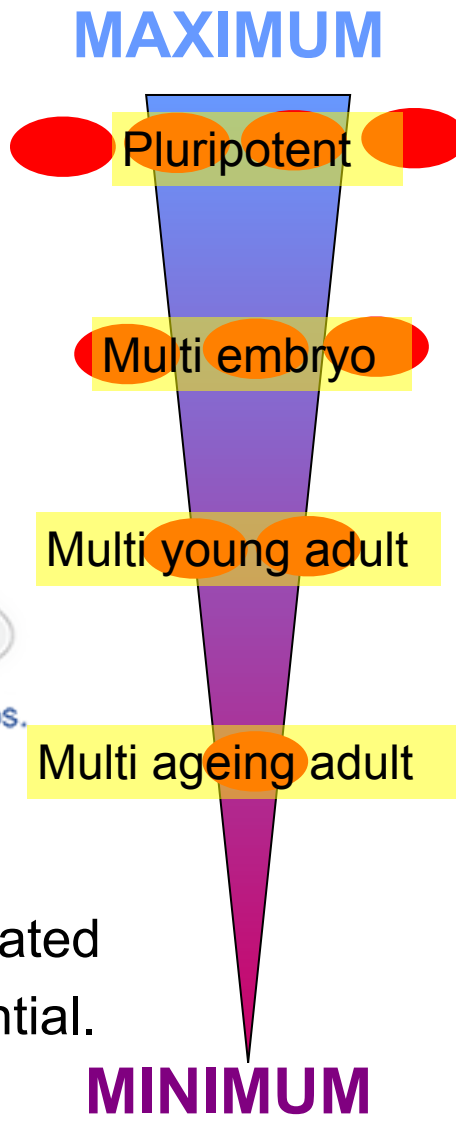






Telomeres and proliferation capacity





Telomeres are made of non-coding DNA repeats.

At each mitosis, several **telomeric repeats** do not get replicated

→ telomeres get shorter, reducing the cell proliferative potential.

→ Cells expressing **Telomerase** can protect their telomeres.

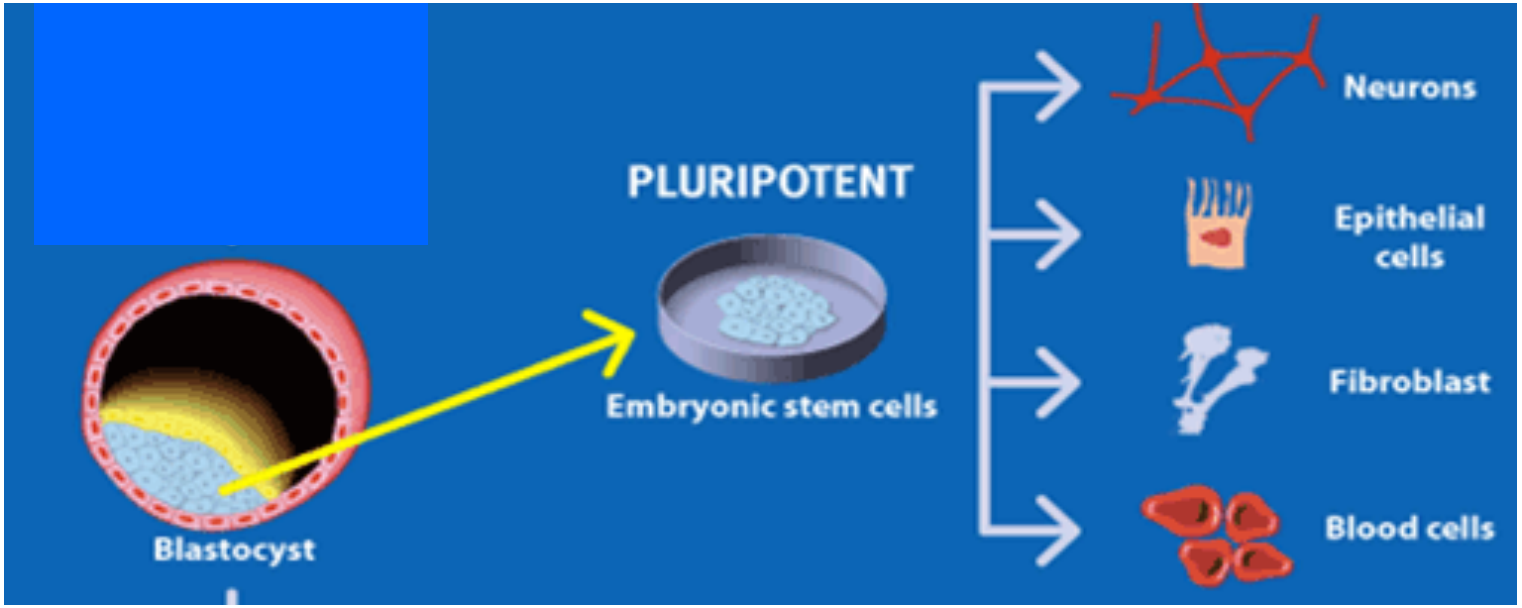
→ The level of expression of **Telomerase** influences proliferation capacity

Types of stem cells in human.

Embryonic stem cells (ESCs): immortal and pluripotent

To control ESCs differentiation *in vitro*, scientists can:

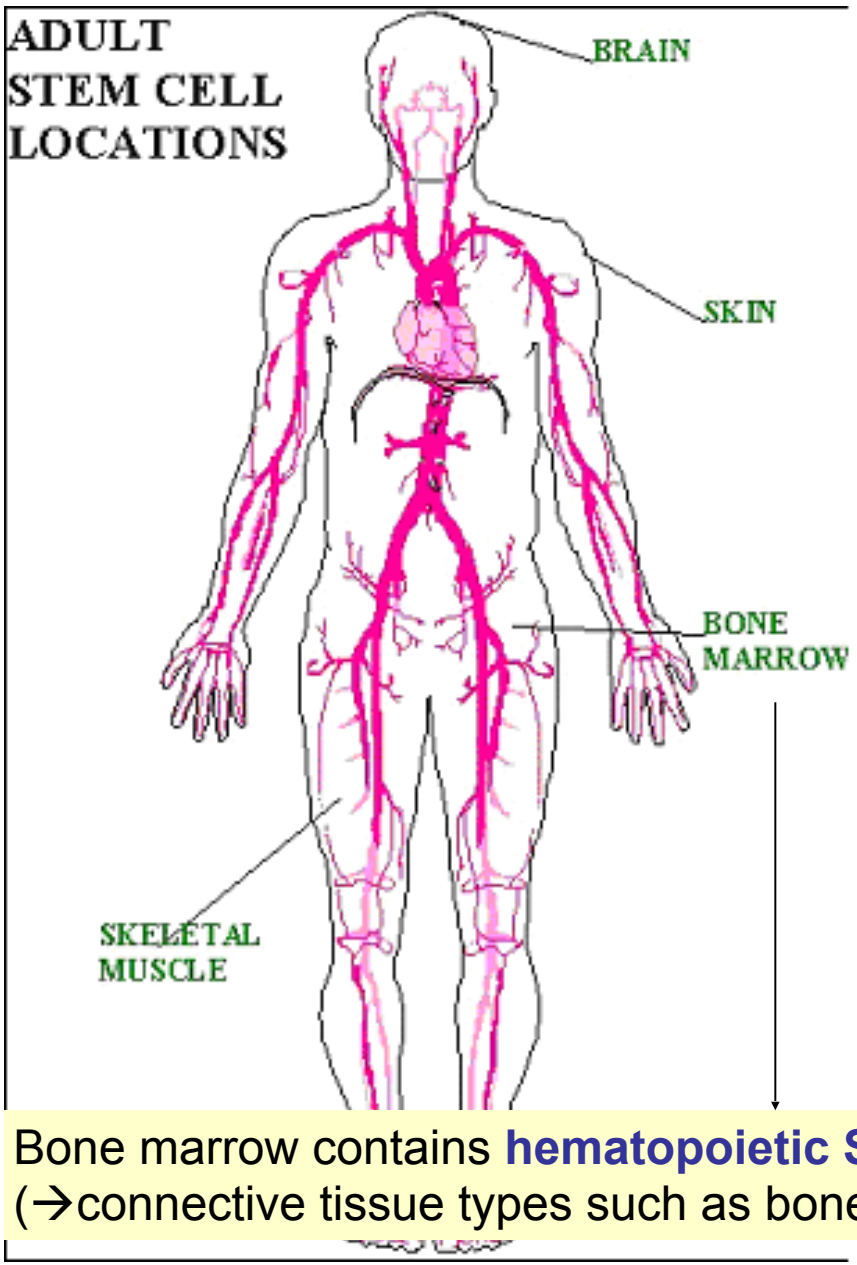
- Change the chemical composition (cocktail) of the culture medium [preferred solution].
- Insert specific genes into the cells.



can make any cells in the body

Adult stem cells (ASCs): the reservoirs

Also found in children. Sometimes called somatic stem cells



+ intestines (epithelial)

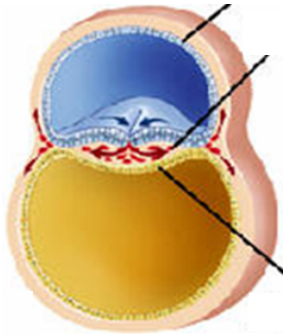
+ Fat cells (MSCs)

Etc.

- Present in many tissues but often quite rare and divide infrequently (insufficient to repair trauma)
- **Harder to grow in the lab and multipotent**, although in the lab some show plasticity

Bone marrow contains **hematopoietic SC** (→ blood) and **mesenchymal SC** (→connective tissue types such as bone, cartilage, tendons, muscle and fat.)

Plasticity of ASCs



= Capacity of most ASCs to trans-differentiate *in the lab* into cells from a different germ layer (multipotent +++).

Low efficiency process though.

The most apparently plastic cells are the Mesenchymal Stem Cells (mesoderm) = can transform into liver cells (endoderm), and brain cells (ectoderm).

Placenta and umbilical cord blood stem cells (neonatal).

Like bone marrow, they contain HSCs and MSCs

Better than bone marrow because:

Less **immunogenic**

Longer **telomeres** =longer life (express more telomerase)

Less **DNA damage**

Non invasive harvesting

Same plasticity

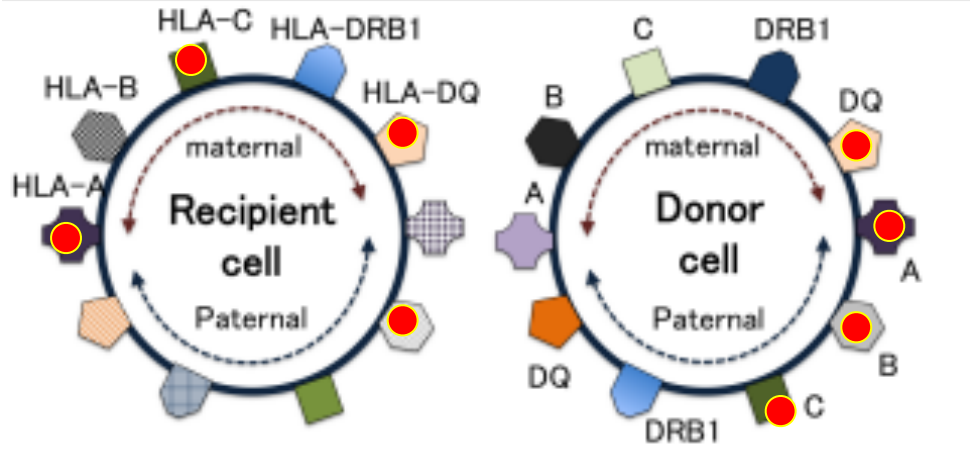
Can be privately stored for money or given at birth

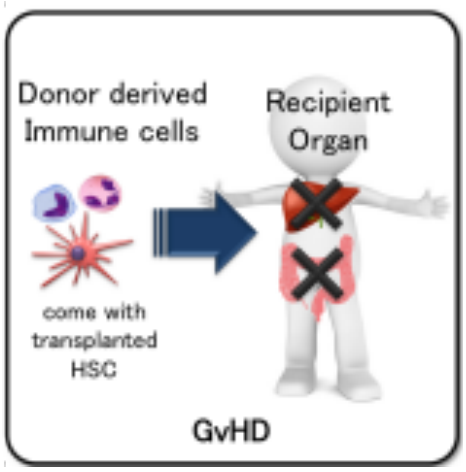
Problem: Small quantity, but in the last 2 years, protocols to expand cultures.

Immuno-compatibility in transplants

All our adult cells have the same surface proteins that are recognised as self by our immune system so that it does not attack our own cells (like an ID card).

The ID card is encoded by 5 genes with **several co-dominant alleles**, so 5 maternal proteins and 5 paternal proteins, often different.





If you introduce foreign cells in a body that do not present the same surface proteins they will be attacked by the immune system.
There is some level of tolerance, but it is limited.

Graft versus host disease: donor immune cells accidentally transferred attach recipient

Want to know more?
http://www.regimmune.com/product-pipeline/gvhd/

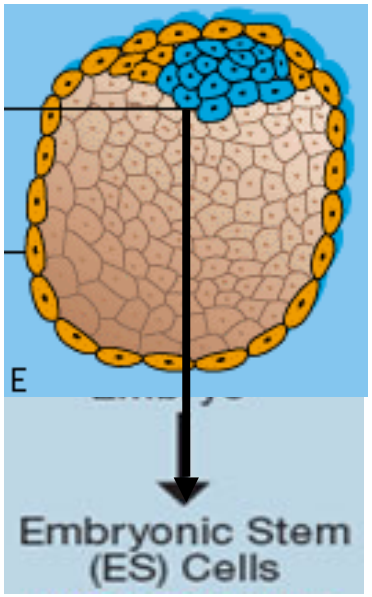
Neonatal cells are less immunogenic because

Embryos and foetuses have to evade mother's immune system. Less surface markers on cells. Easier to match with recipient and less prone to rejection.

New born babies do not have a mature immune system (no antibodies). Less chance of graft versus host disease.

Sources of human stem cells

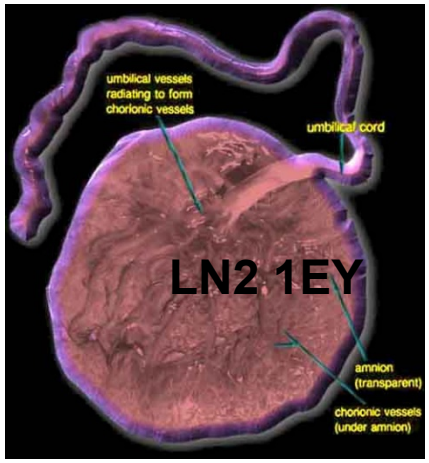
Embryonic SC



ICM of **sur-numerary IVF embryos**

BANK of ESC lines

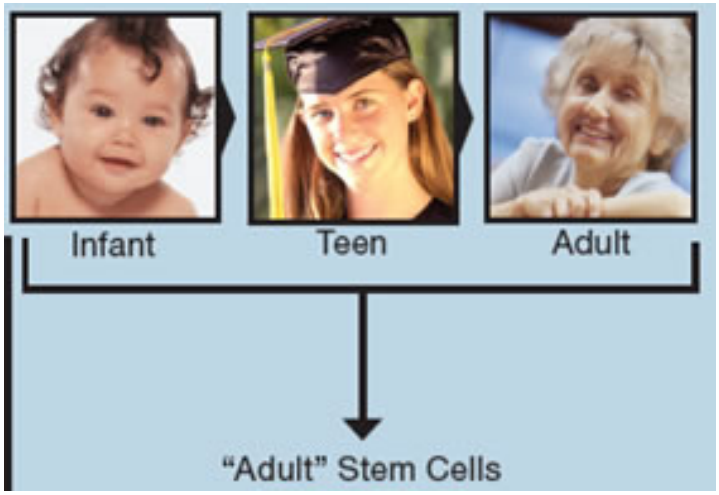
Neonatal SC



Placenta and umbilical cord

Donated at birth

Adult SC



Bone marrow, circulating blood, fat tissue (liposuction), skin.

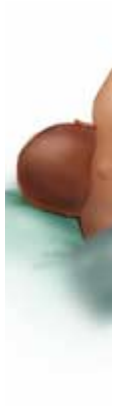
+ induced pluripotent stem cells.

Part B – Stem cells based therapies

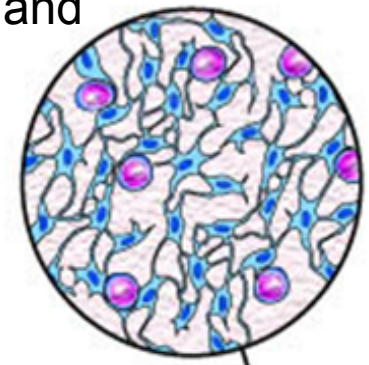
Currently approved stem cell based therapies

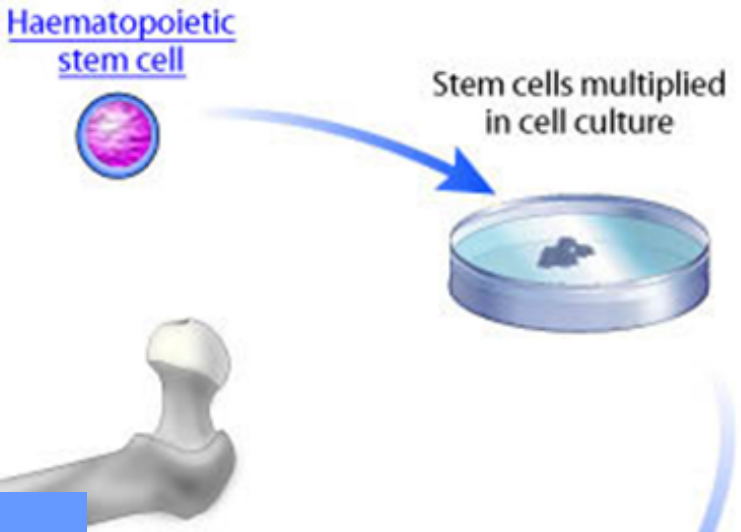
- Skin graft
- HSC transplant from adult bone marrow or neonatal cells

Current therapy: Bone marrow transplant to treat leukemia and other blood disorders.



HSCs and MSCs

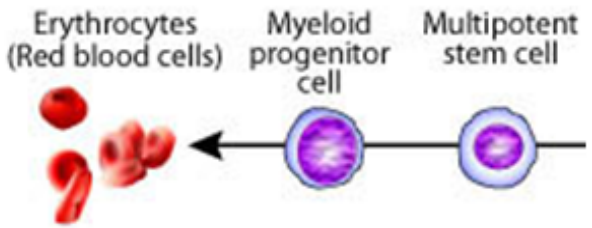


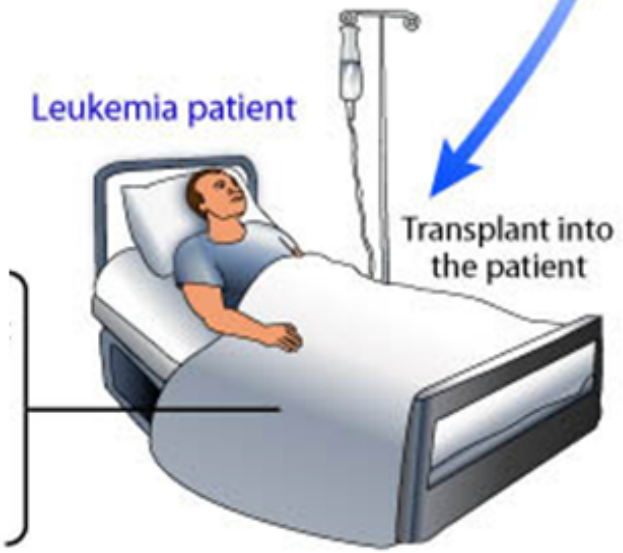


HSCs also isolated from

- Peripheral Blood Stem Cells
- Umbilical Cord Blood Stem Cells.

Better match for UCB, and both less invasive but quantity is a limitation → small patients.

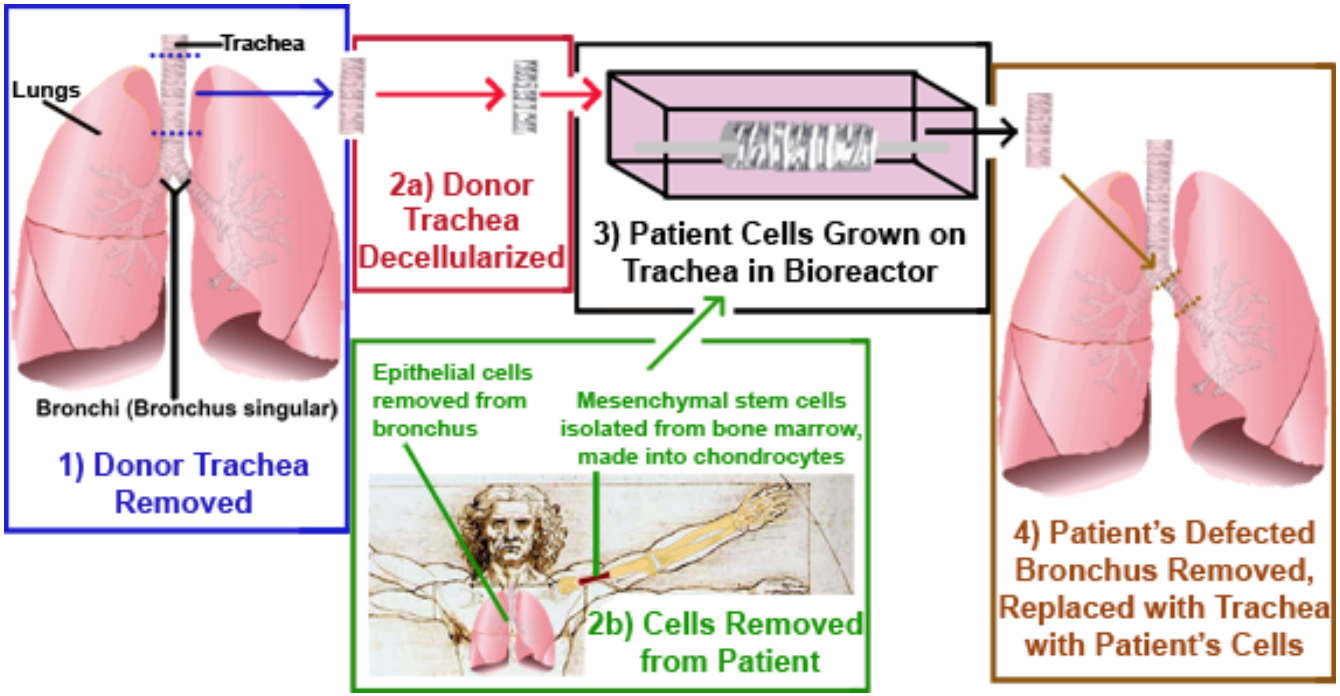




Recent advances in stem cell based therapies

Tissue engineering

Tracheal engineering with stem cells from patient – autologous transplant - 2008



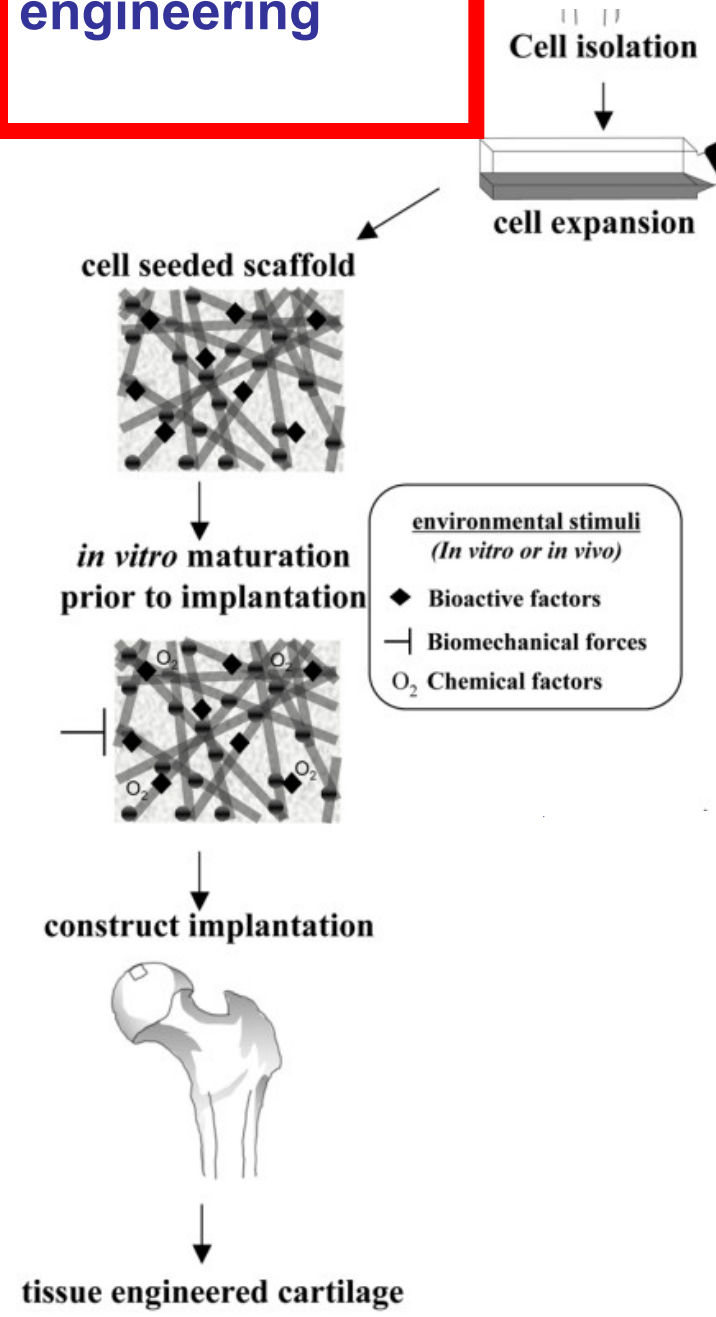
Want to know more? Follow this up: http://www.ncbi.nlm.nih.gov/pubmed/24161821

+ bladder and heart valve done or in progress.

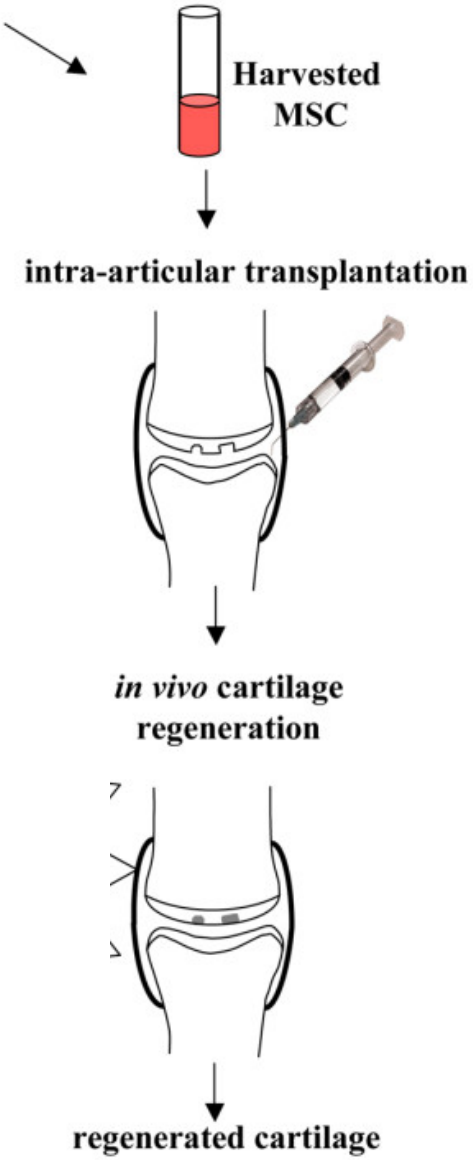
3D printing will probably give a boost in this field

Want to know more? https://www.newscientist.com/article/mg22029440-800-grow-your-own-organs-as-a-tissue-engineer/ Nov 2013.

Ex vivo cartilage engineering



In situ cartilage regeneration



MSCs for cartilage engineering or regeneration.

MSCs are isolated from patient bone marrow or fat tissue or from umbilical cord donor

MSCs regenerative functions →

- Immuno suppression

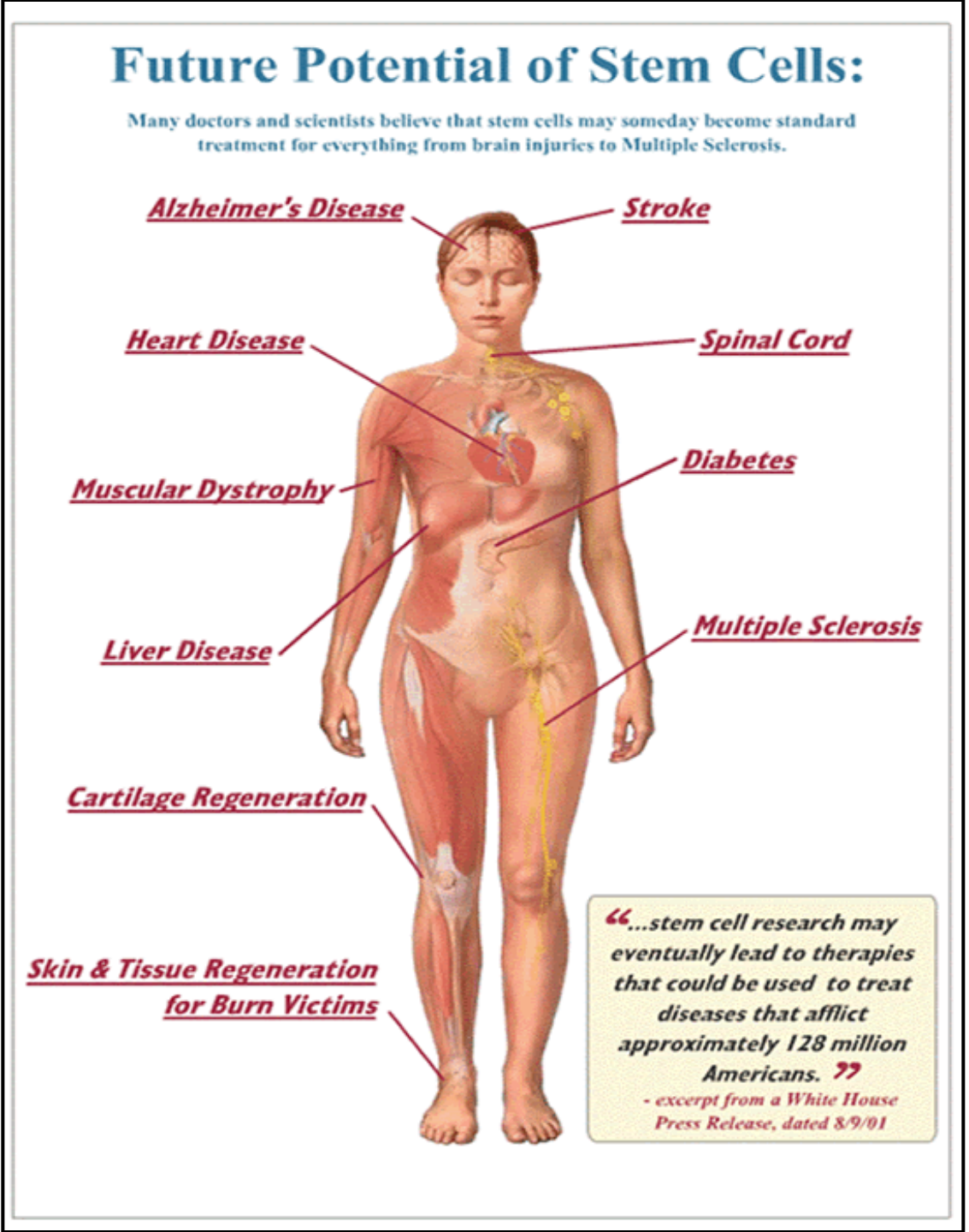
- anti inflammatory effect

-Stimulate endogeneous progenitor cells

MSCs are very promising

- Easy to isolate (BM, fat, UC) and grow in the lab→ large qty.
- Plastic in the lab → cardiac muscles, skin and nerve cells.
- Can be **frozen and thawed** without apparent damage → potential for "off-the-shelf" therapy.
- Possess potent immuno-suppression and anti-inflammation effects (protective effects on local tissue), capable of homing (going to site of injury) and stimulate regeneration (secrete repairing factors):

- Could increase tolerance to find a donor match for MSCs transplant
- Potential treatment or complement to transplant for many diseases.



Hype? Reality?

Also potential cures for Parkinson's, kidney disease, glaucoma and macular degeneration, hepatitis, blood disorders and cancer.

+ more tissue engineering

The Real situation

- To become an approved therapy, clinical trials have to occur and they take a long time (3 phases).

ClinicalTrials.gov

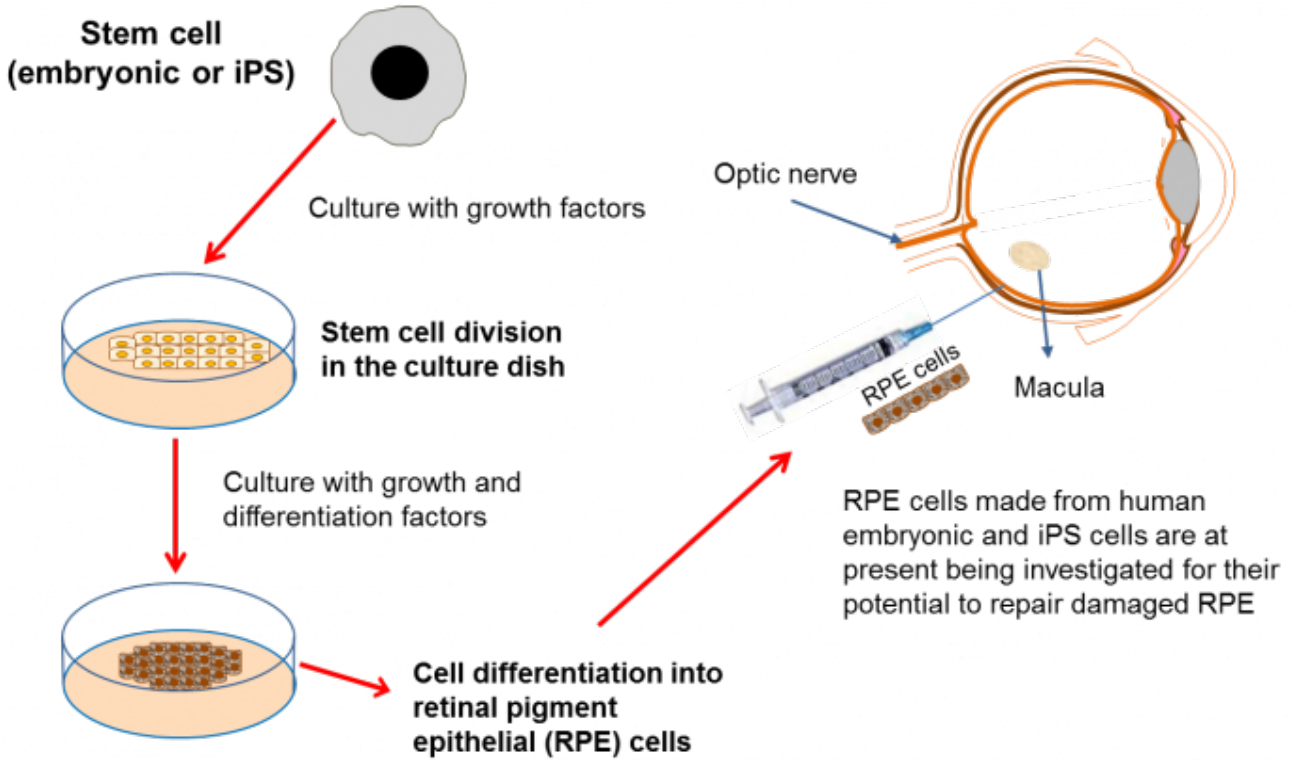
- Most trials are carried out with MSCs (~70%)

- Less than 10 therapies are now in phase III. These include trials to treat eye conditions (embryonic stem cells) and to use MSCs to repair (brain cells) and protect (avoid graft versus host disease).

- Hype? A lot of foreign clinics advertise treatments with MSCs or Umbilical cord cells. None of them have published data from clinical trials.

Want to know more? The article below is very accessible and reviews trials in terms of safety and ethics https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5765738/

Example: ESCs in phase III to cure blindness.



ESCs trials are mostly for eye conditions as these are the easiest conditions to start with.

- Few cells need to be produced
- Protocol established to produce RPEs (retinal pigmented epithelial cells) out of ESCs
- Surgery fairly easy and internal control with other eye
- Easy to check for problems or progress
- Eye is an immuno-priviledged system → unlikely to reject transplant

→ So far, no cancer, rejection and improvements in some patients

What can stem cells (SCs) be used for?

- **REPLACE (as for tissue engineering)**:
  - SCs transformed outside the body into wanted cell type and transplanted.
  - SCs transplanted with chemicals/molecules and differentiation takes place within body.
- **REPAIR**:
  - SCs transplanted and secrete molecules that promote repair (usually MSCs)
  - For monogenetic disease: SCs modified genetically outside the body and re-implanted
- **PROTECT**: MSCs transplanted → prevent inflammation or prevent immune system attacking the local or transplanted cells.

Which stem cells to use?

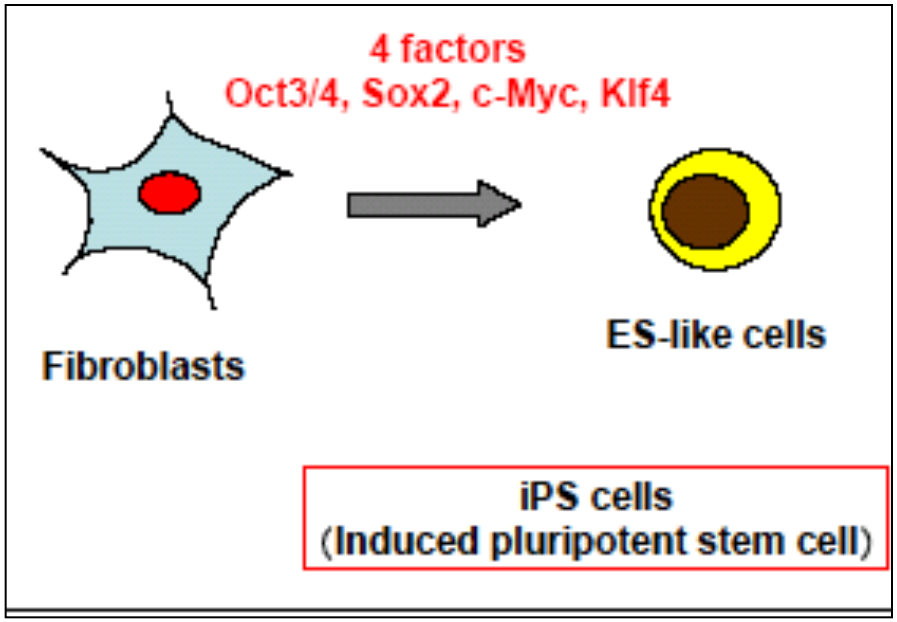
- For repair and replace, ideally use patient's own stem cell to avoid rejection (**autologous transplant**). Requires using adult stem cells plasticity. But ASCs can be hard to isolate and grow in lab
- Otherwise use donor stem cells with low immunogenicity (**allogenic transplant**): neonatal stem cells or MSCs.
- Embryonic stem cells can be used. For ethical reason, limited to a bank of about 200 lines at the moment.

Induced Pluripotent Stem Cells: The future of personalised medicine?

IPSCs: Nov 2007 (Nobel Price 2012)

Induced Pluripotent stem cells (IPSCs) = Reprogramming somatic cells.

A somatic cell (e.g. skin cell) is genetically engineered with 4 genes and goes back in development, presumably resetting the gene expression profile to the one of the embryonic stem cells.



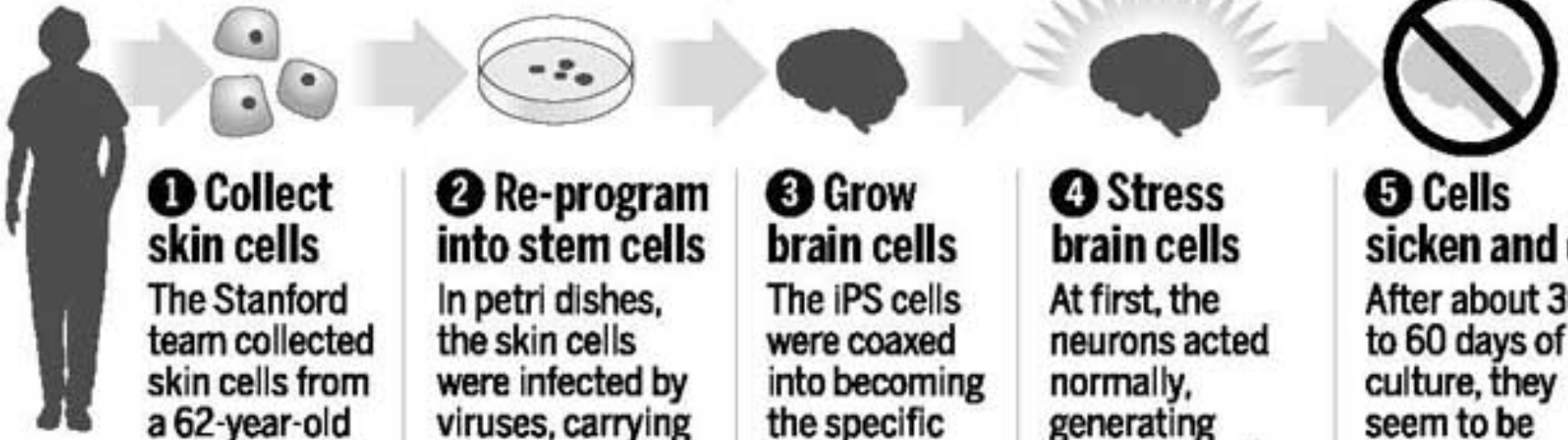
Can make IPSCs from many different somatic cells.

Many ways to provide the 4 factors which are safer.

IPSCs to model diseases

Parkinson's: Disease in a dish

Neurons derived from the skin of a woman with Parkinson's disease show key features of the condition in a petri dish.



1 Collect skin cells

The Stanford team collected skin cells from a 62-year-old woman with a genetic form of Parkinson's disease.

2 Re-program into stem cells

In petri dishes, the skin cells were infected by viruses, carrying special genes, that turned them into embryonic-like cells called **induced pluripotent stem cells.**

3 Grow brain cells

The iPS cells were coaxed into becoming the specific type of neuron involved in Parkinson's disease.

4 Stress brain cells

At first, the neurons acted normally, generating electrical and chemical signals. But when exposed to toxic agents that caused stress, trouble started.

5 Cells sicken and die

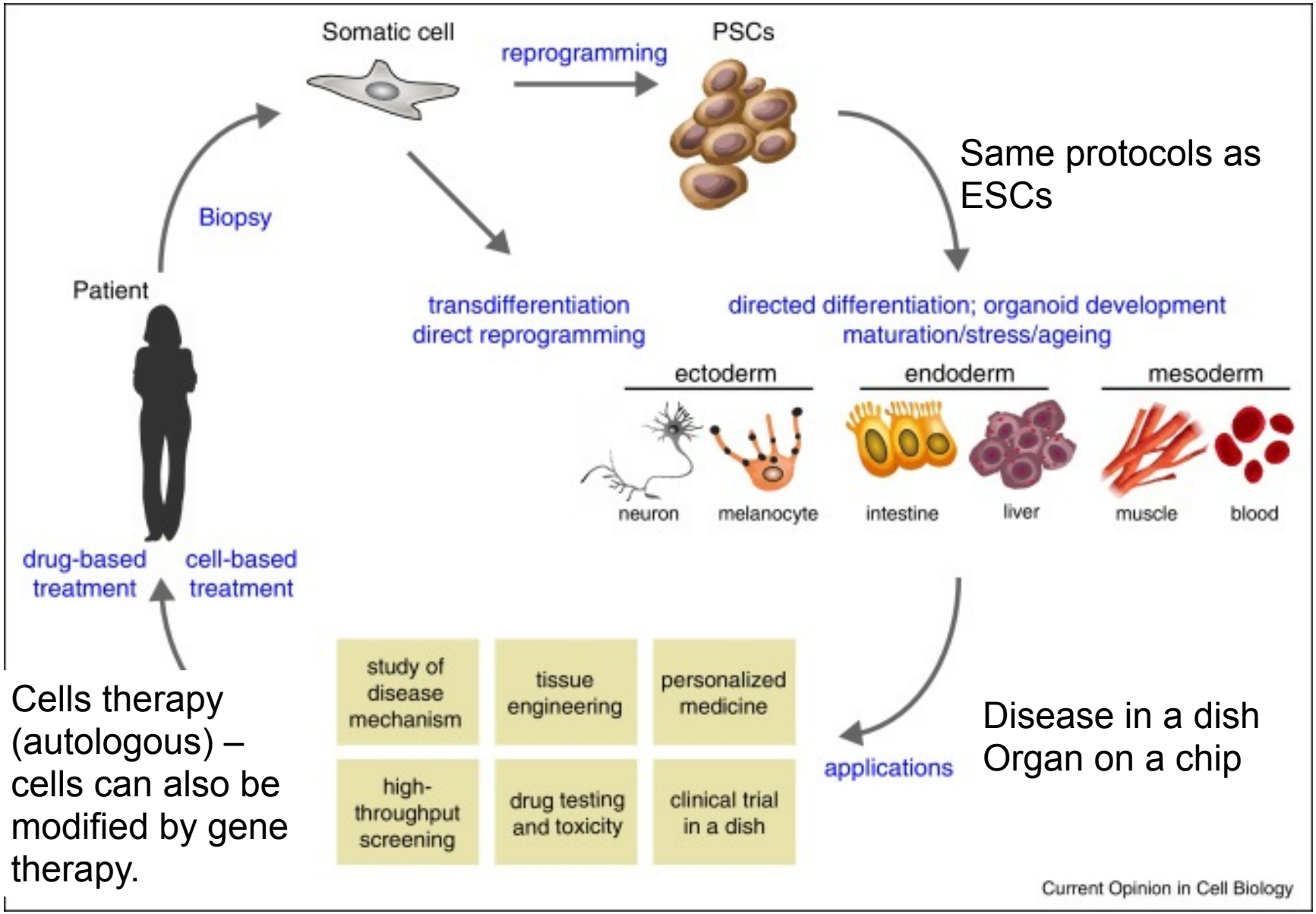
After about 30 to 60 days of culture, they seem to be replicating many of the common features of the disorder, but in a much shorter timeframe. They eventually died.

6 Next: The researchers plan to test various compounds to see if they can protect the neurons. They are also hoping to conduct the identical experiment in patients with the nongenetic form of Parkinson's disease.

Source: Stanford University School of Medicine

MERCURY NEWS

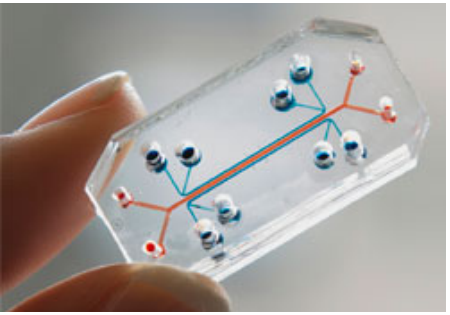
The full potential of IPSCs

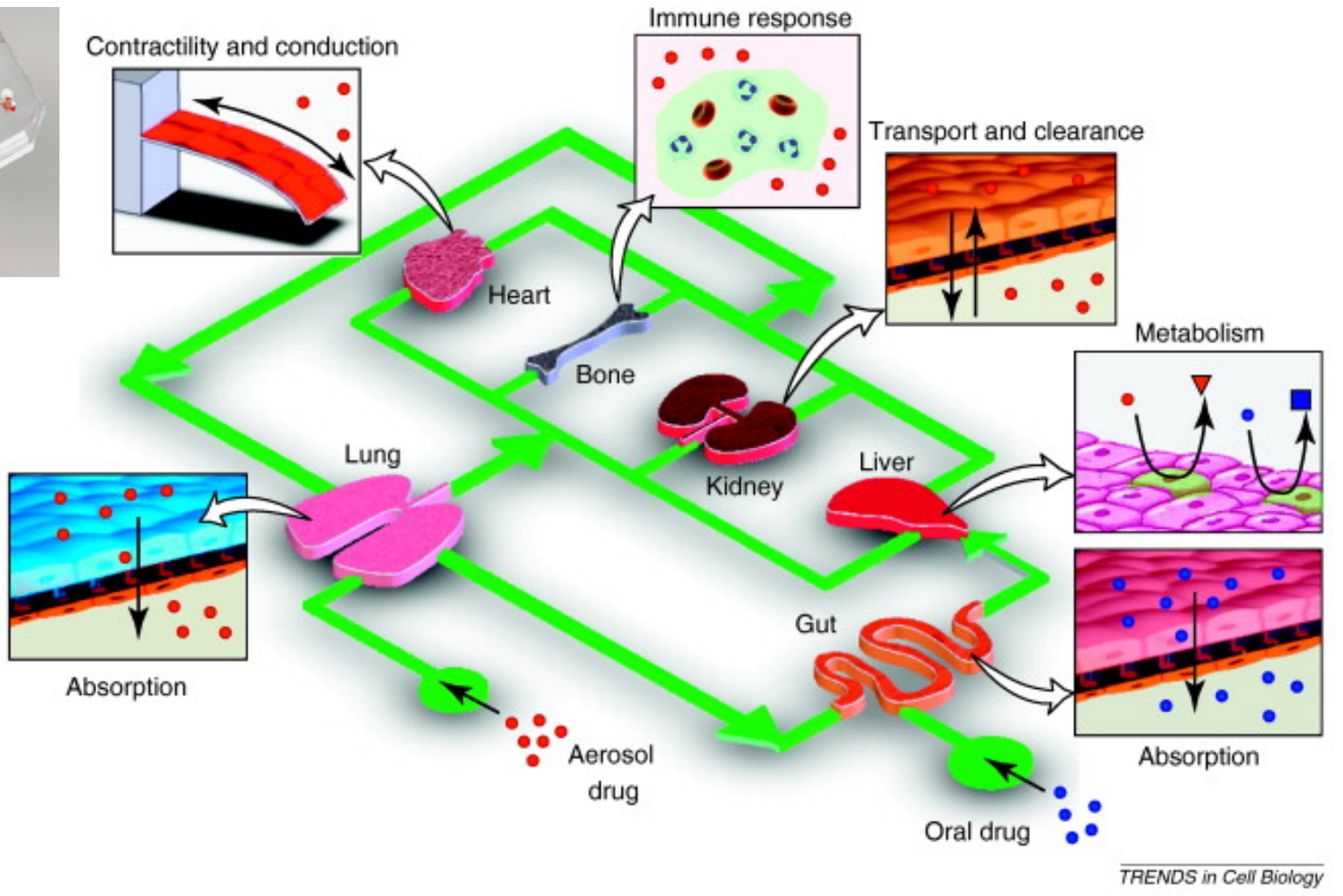


Cells therapy (autologous) – cells can also be modified by gene therapy.

Disease in a dish
Organ on a chip

Organs on a chip – could have a huge amount of humans represented if using IPSCs





D.E.Ingber, Trends in Cell Biology (2011) 21, 12, p. 745-754

Stem cells make everyday news

Go to Stem Cells News – ScienceDaily **or https://www.biosciencetoday.co.uk/ or https://www.nature.com/search?article_type=protocols,research,reviews&subject=stem-cells and search for stem cells.**

By the end of these lectures, you should understand the news items and some research papers abstracts

List of approved cell and/or gene therapy

- List of FDA Approved Stem Cell Therapies & Drugs for 2024 - The Niche (ipscell.com)
- https://www.americangene.com/blog/the-future-of-medicine-the-88-gene-therapies-in-development/
- Dog stem cell therapy: RVC Stem Cell Therapies for Dogs
- Horse stem cell therapy: RVC Stem Cell Therapies for Horses