

Stem Cell Biology and Technology

Prof. David Suter
Gene regulation and cell identity

BIO-447 2025/2026

Other teachers



Prof. David Suter

Gene regulation & Cell identity

Introduction, plasticity; tools; neural stem cells



Prof. Wouter Karthaus

Endocrine therapy resistance and molecular genetics

Adult stem cells; niche of adult stem cells; stem cell bioengineering



Prof. Freddy Radtke

ES, iPS, cloning and nuclear reprogramming; Intestinal stem cells; Cancer stem cells



Prof. Olaia Naveiras

CHUV, UNIL

Clinical impact of Stem cells



Dr. Jean-Francois Mayol

Flow cytometry Facility UNIL

Flow cytometry and FACS

	Subject	Teacher
Week 1	Introduction to Stem Cells	David Suter
Week 2	Plasticity	David Suter
Week 3	Neural Stem Cells	David Suter
Week 4	Tools in Stem Cell Biology	David Suter
Week 5	Adult Stem Cells	Wouter Karthaus
Week 6	Flow Cytometry and FACS	Jean-Francois Mayol
Week 7	Niches of Adult Stem Cells	Wouter Karthaus
Week 8	Stem Cell Bioengineering (Mimicking the Niches)	Wouter Karthaus
Week 9	ES, iPS, Cloning and nuclear reprogramming	Freddy Radtke
Week 10	Intestinal Stem Cells	Freddy Radtke
Week 11	Clinical Impact of Stem cells I	Olaia Naveiras
Week 12	Clinical Impact of Stem cells II	Shukry James Habib
Week 13	Cancer Stem Cells	Freddy Radtke
Week 14	free	free

Enrollment key: IPS&Co

Exercises and exam

Exercise time

- **No exercises**
- **But teachers might ask you to read something**

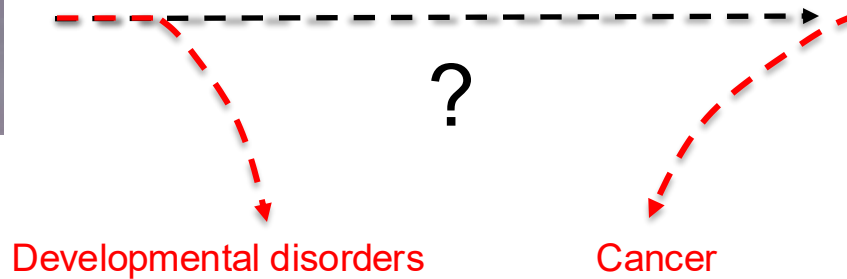
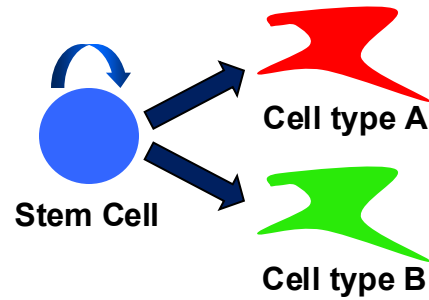
Exam

- **Multiple choice**
- **Might be some short open answer questions**

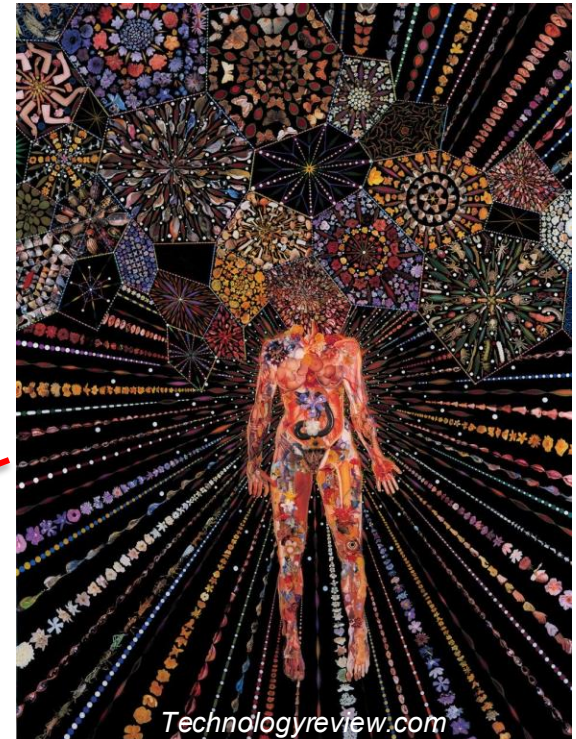
Stem cell definition

One genome, from one to hundreds cell types

1 genome, 1 cell



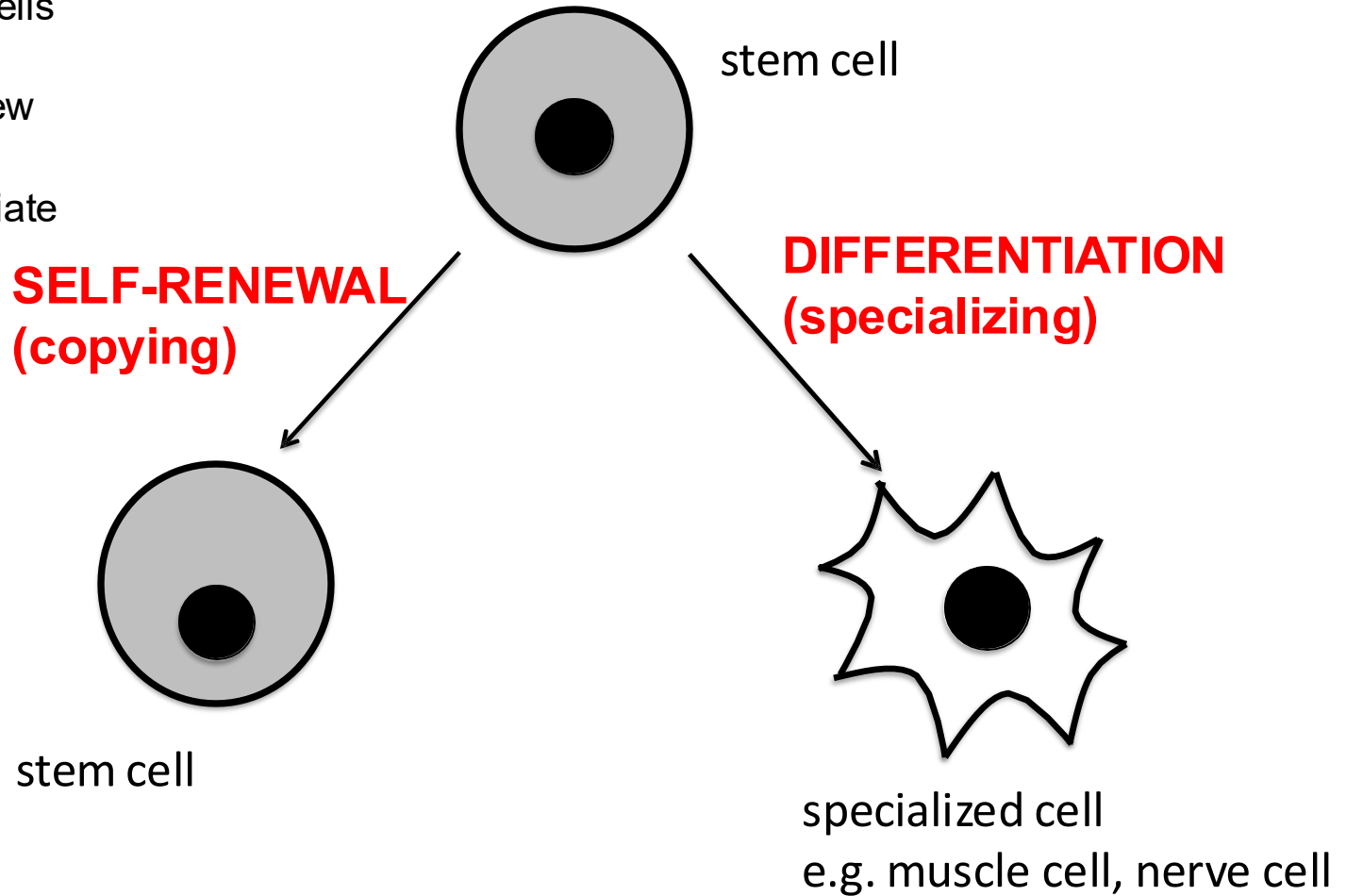
1 genome, >200 cell types



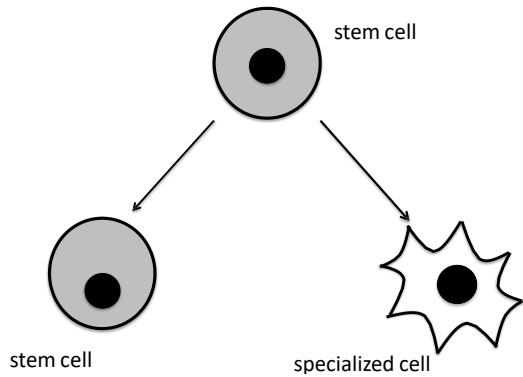
What is a stem cell?

Stem cells are:

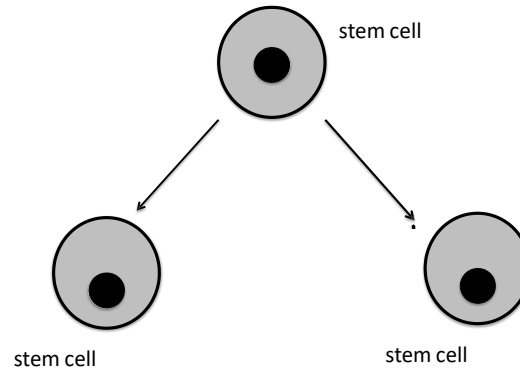
- Unspecialized cells
- Able to self-renew
- Able to differentiate



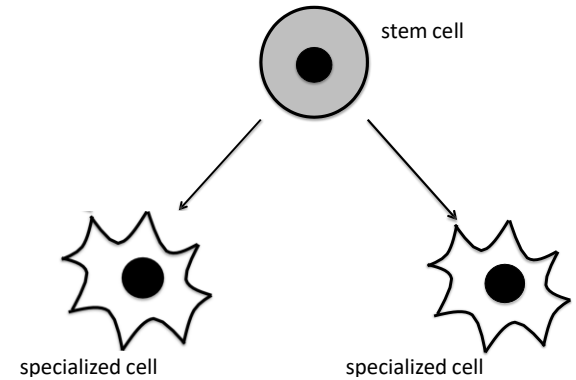
Different types of stem cell divisions



Asymmetric division

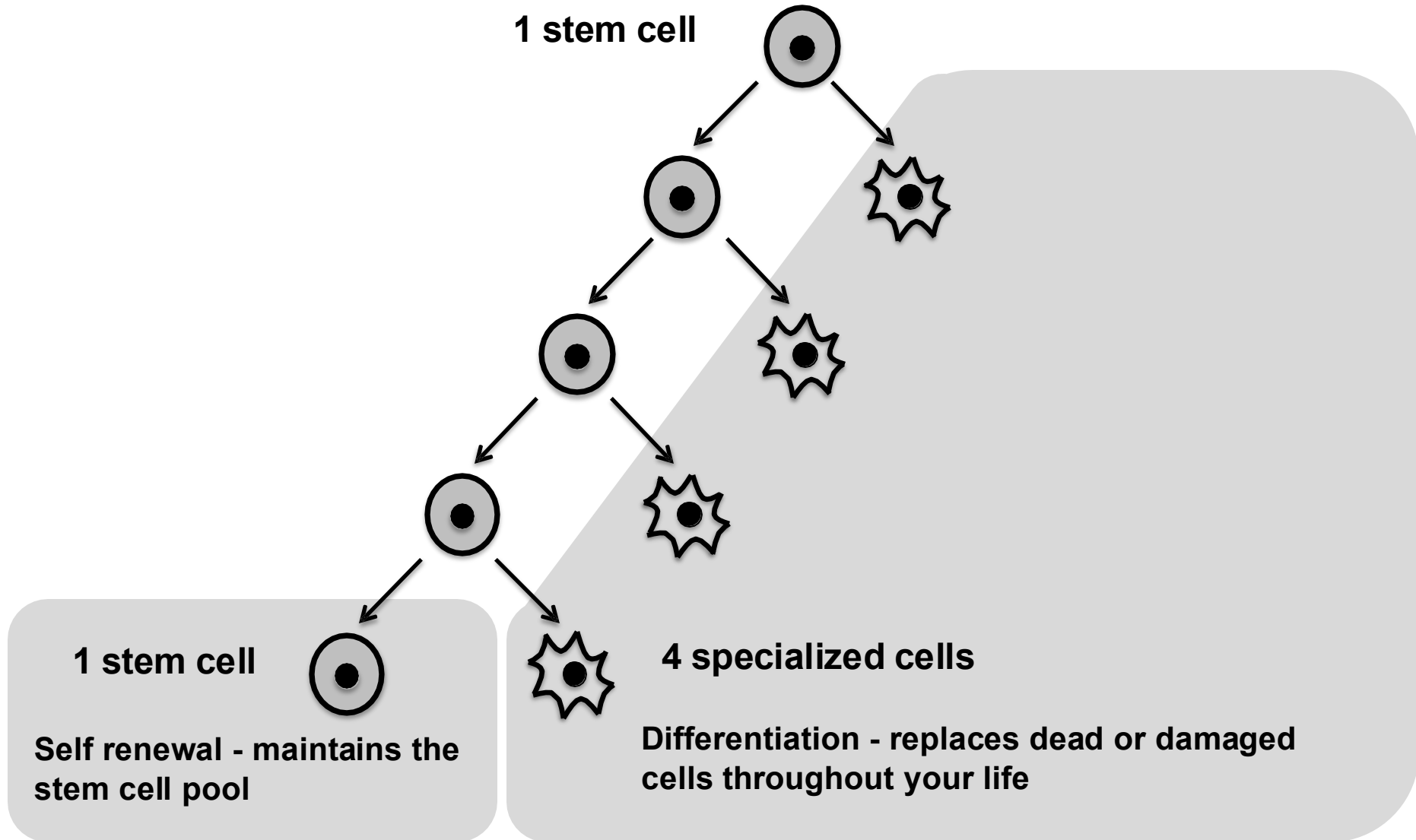


Symmetric self-renewal division



Symmetric differentiation division

Why self-renewal and differentiation?



History of stem cell research

Stem cell research was born in the aftermath of Hiroshima and Nagasaki (6. and 9. August 1945)



1961-63: Till & McCulloch → “colony forming cells” in the bone marrow self-renew and differentiate

1962: J.D.Gurdon → cell specialisation is reversible (2012 Nobel prize)

1981: Evans & Kaufman → first embryonic stem cells (ESCs) isolated from mouse blastocysts (2007 Nobel prize)

1989: Smithies & Capecchi → first knock-out mice (2007 Nobel prize)

1996: Wilmut → first mammal cloned from adult cells

1998: Thomson → derivation of first human ESC line

2006: Takahashi & Yamanaka → generation of induced pluripotent stem (iPS) cells (2012 Nobel prize)

A bit of early history:

Ramalho-Santos & Willenbring 2007: [https://www.cell.com/cell-stem-cell/fulltext/S1934-5909\(07\)00019-7](https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(07)00019-7)

Maehle 2011: <https://royalsocietypublishing.org/doi/10.1098/rsnr.2011.0023>

The experiments of Till and McCulloch 1961-1963



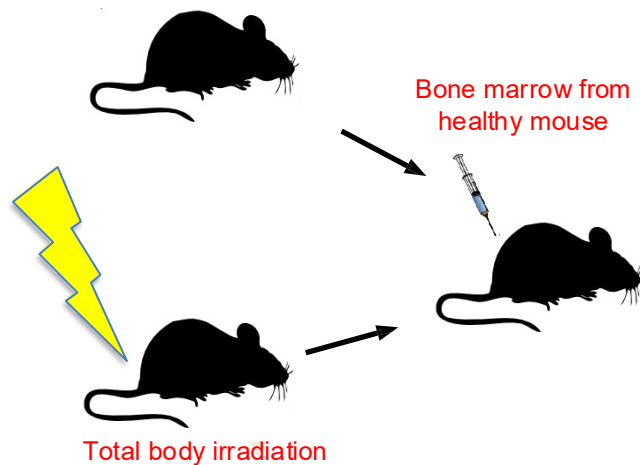
RADIATION RESEARCH 14, 213-222 (1961)

A Direct Measurement of the Radiation Sensitivity of Normal Mouse Bone Marrow Cells¹

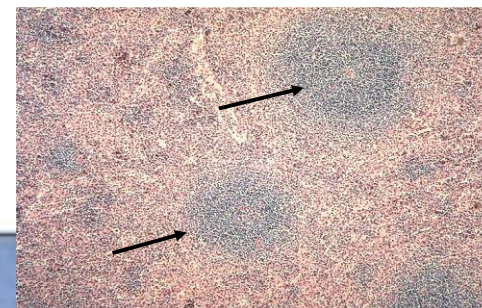
J. E. TILL AND E. A. McCULLOCH

Department of Medical Biophysics, University of Toronto, and the Divisions of Biological Research and Physics of the Ontario Cancer Institute, Toronto, Ontario

Cells with **differentiation** capacity, “colony forming cells” are present in the bone marrow



7-10 days



Myeloid, erythroid, lymphoid precursors

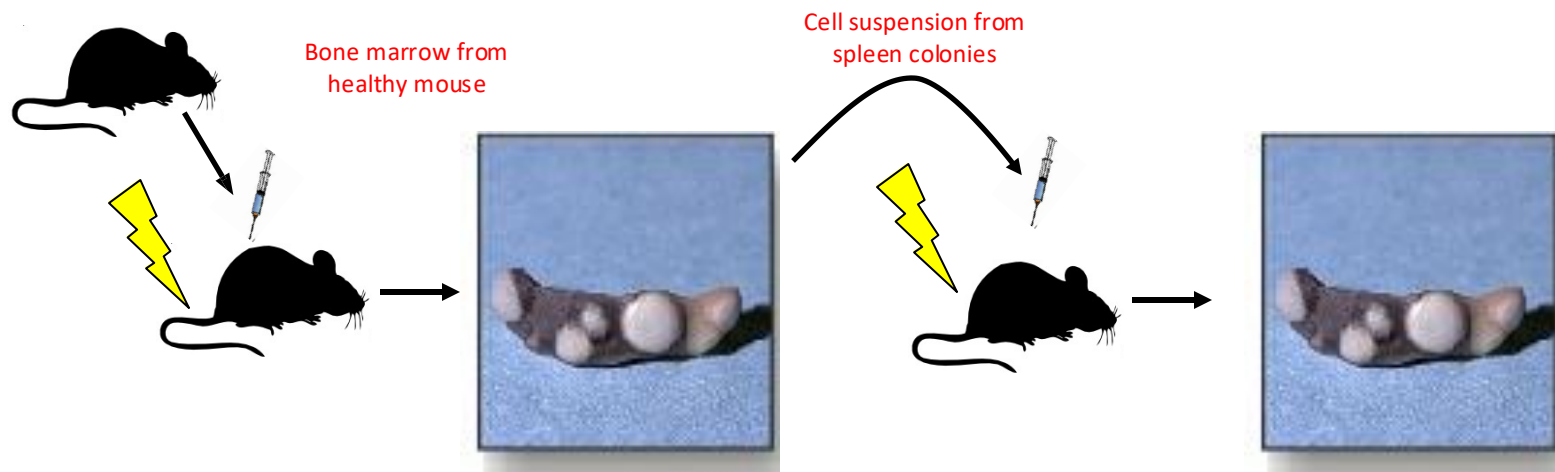
The experiments of Till and McCulloch 1961-1963

The Distribution of Colony-forming Cells Among Spleen Colonies

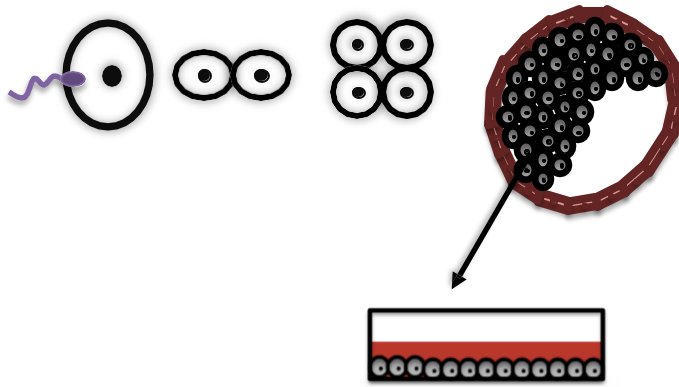
L. SIMINOVITCH, E. A. McCULLOCH AND J. E. TILL
*Department of Medical Biophysics, University of Toronto, and
The Ontario Cancer Institute, Toronto, Ontario*

JOURNAL OF CELLULAR AND COMPARATIVE PHYSIOLOGY
Vol. 62, No. 3, December 1963

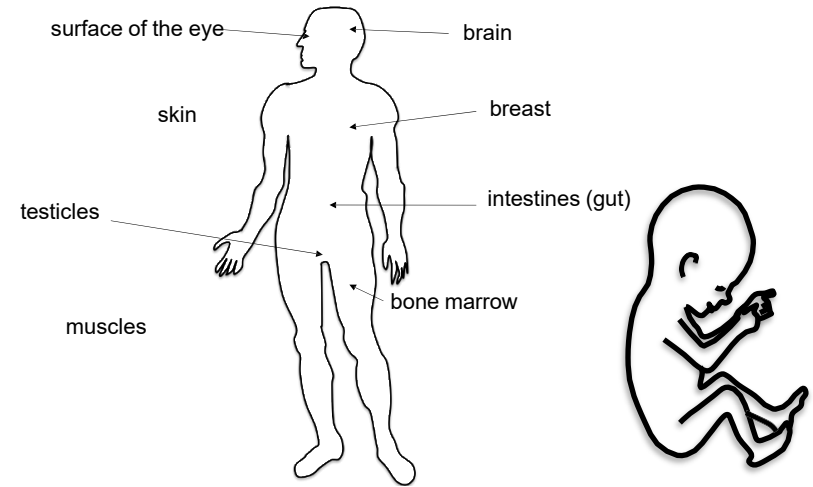
- Perform serial transplantation
- The “colony-forming cells” can renew themselves and form new “colony-forming cells”
- First assay to test **self-renewal** capacity



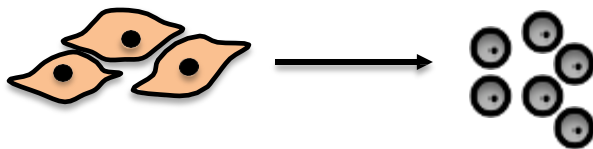
Different types of stem cells exist



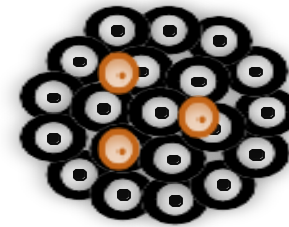
Embryonic stem cells



Tissue stem cells



Induced pluripotent stem cells



Cancer stem cells

Stem cell definition - Potency

Potency

A measure of how many types of specialized cells a stem cell can make

Totipotent

Can make **all** types of cells in the body and placenta
Note: The zygote is totipotent, but it is not a stem cell!

Pluripotent

Can make **all** types of cells in the body, but not placenta
Embryonic stem cells are pluripotent

Multipotent

Can make **multiple** types of specialized cells, but not all types
Tissue stem cells are multipotent

Unipotent

Can make **a single** type of specialized cells
Spermatogonial stem cells are unipotent

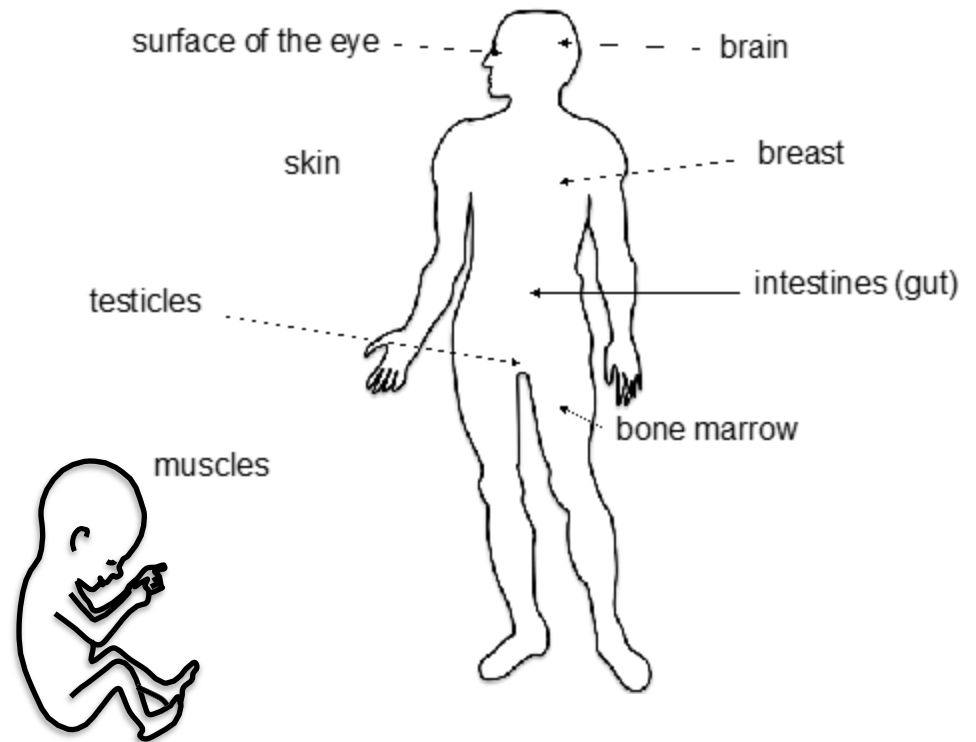
Types of stem cells

1. Tissue stem cells

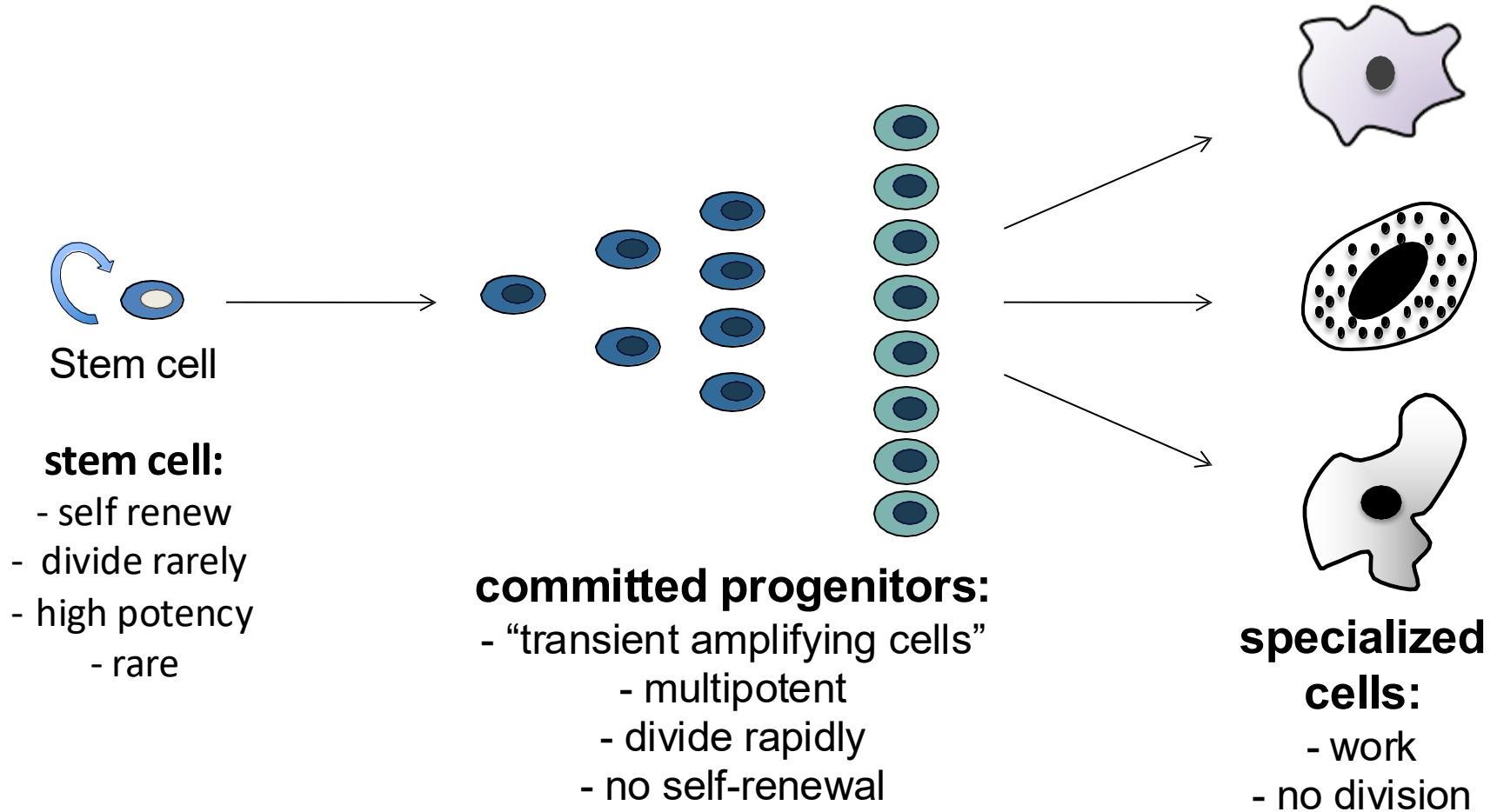
Tissue stem cells - characteristics

- Found in adult and fetal tissues
- **Multipotent** (can make multiple types of specialized cells, but not all types)
- Usually rare
- Rarely divide

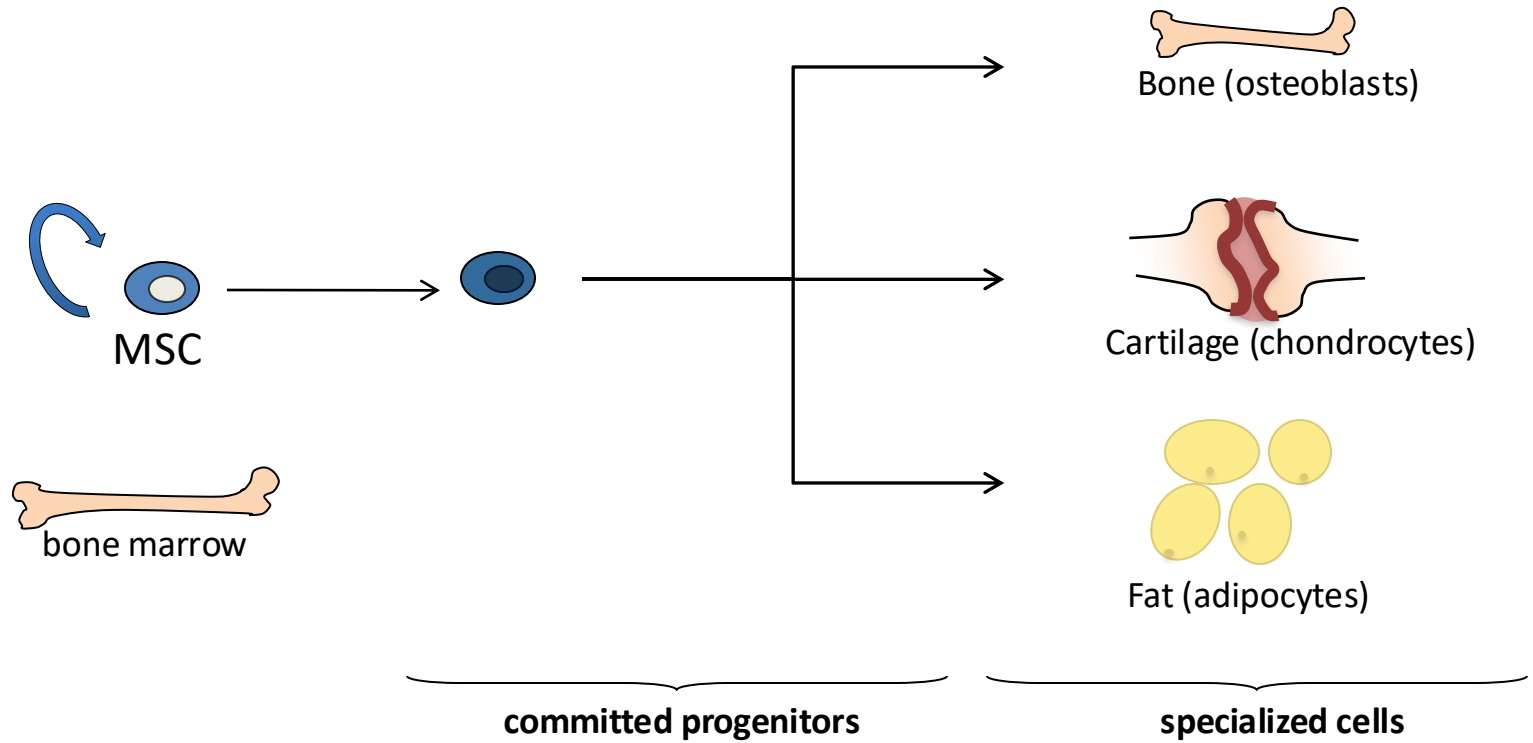
→ how can tissues still be renewed?



Principles of renewing tissues - stem cell hierarchies

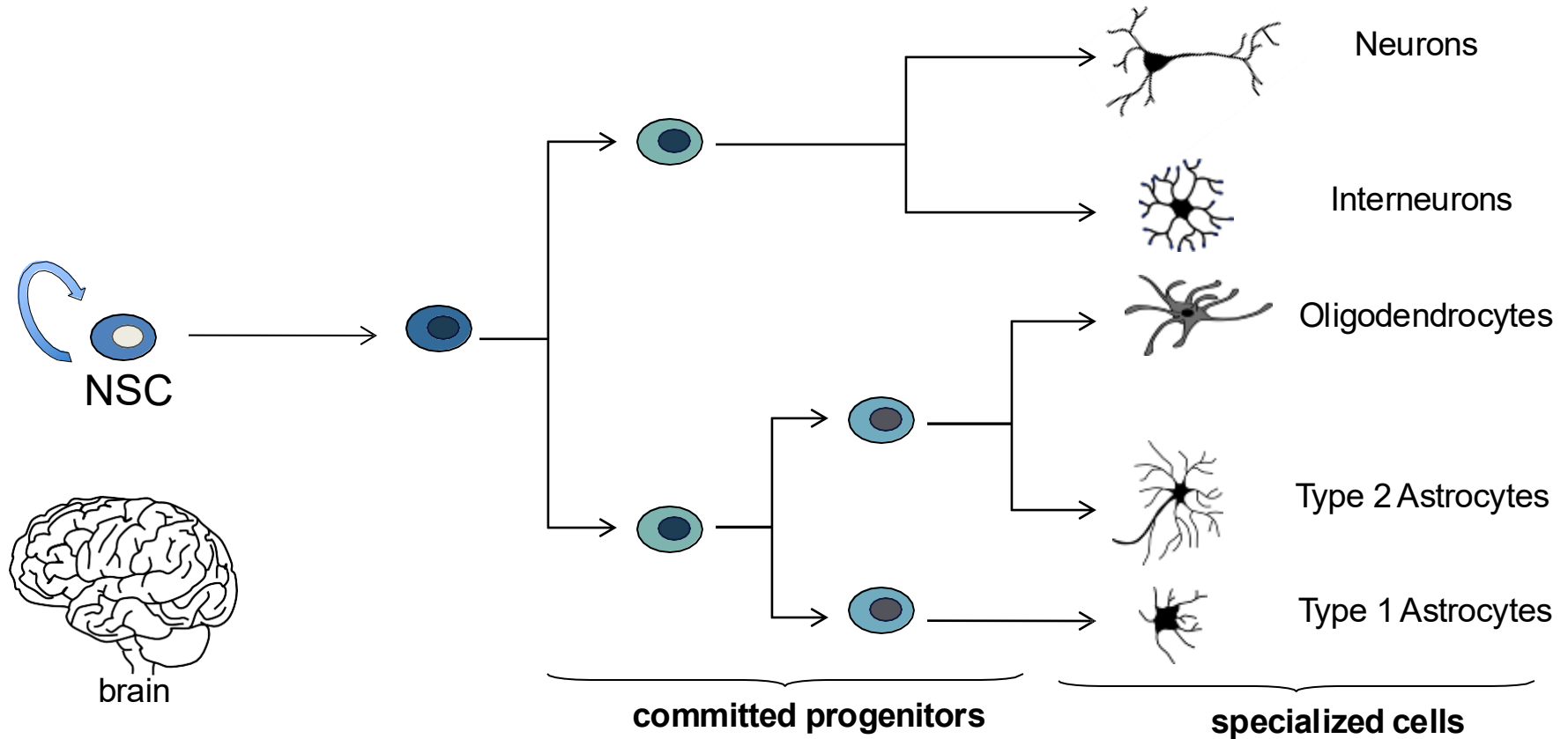


Mesenchymal stem cells (MSCs)



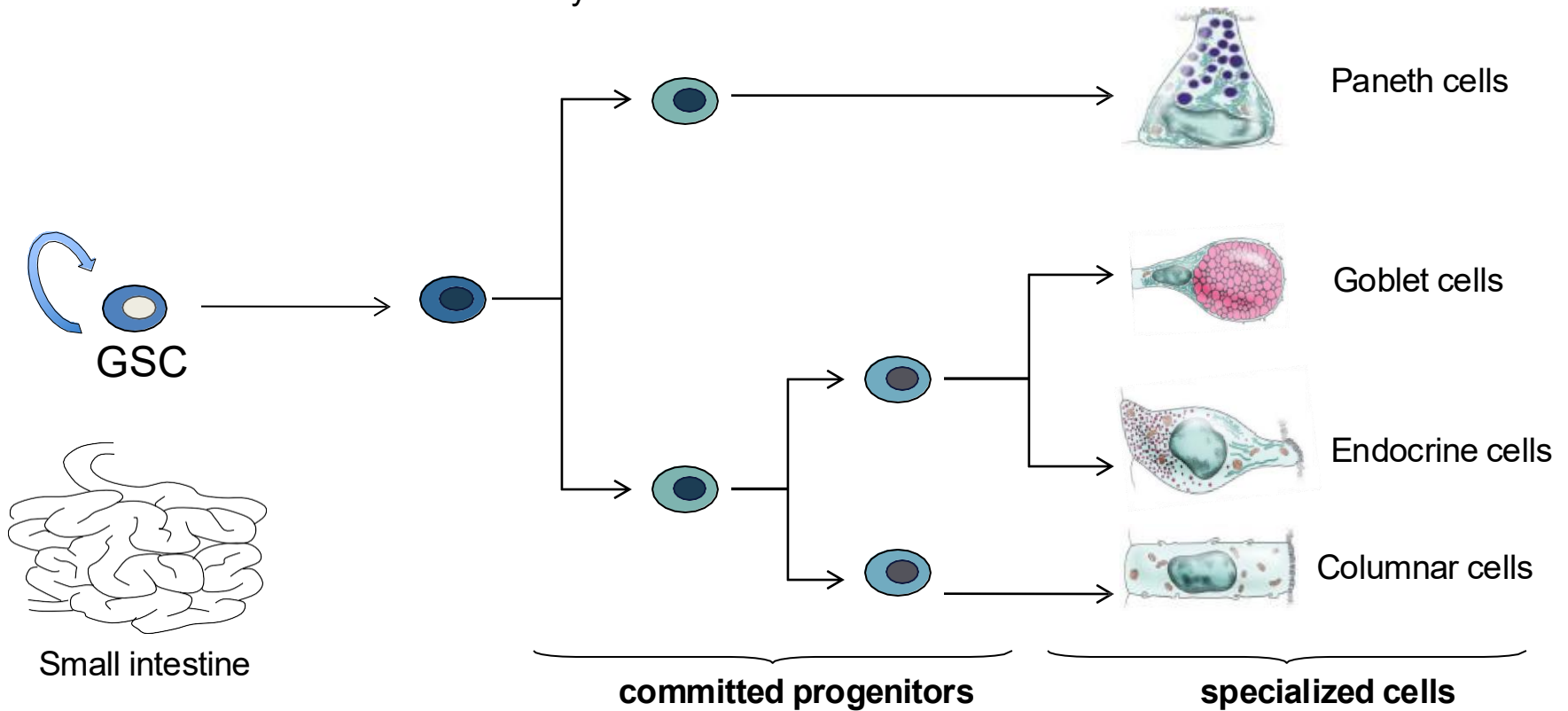
Neural stem cells (NSCs)

- See lecture “NSCs”



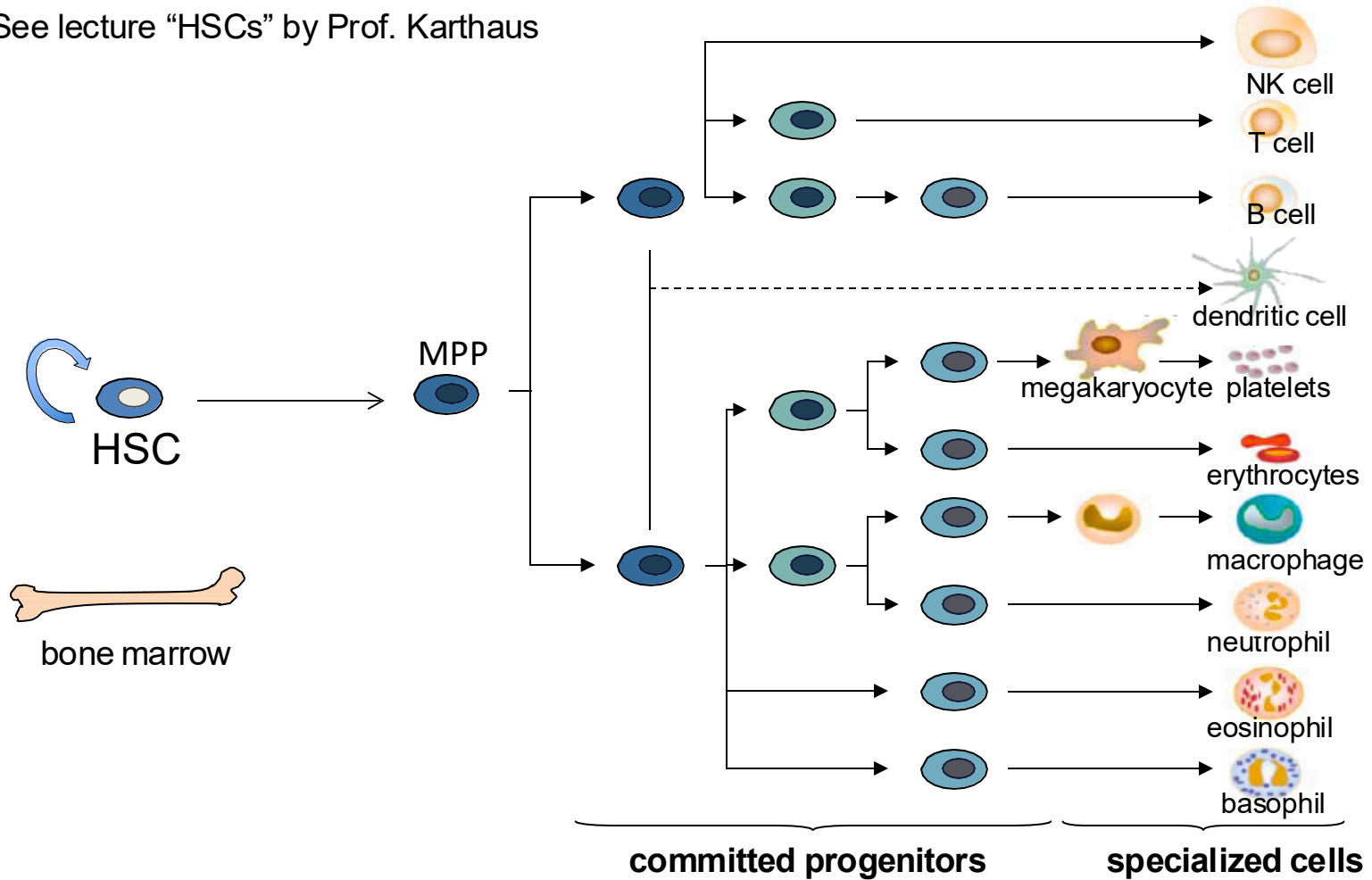
Gut or intestinal stem cells (GSCs)

- See lecture “intestinal stem cells” by Prof. Radtke



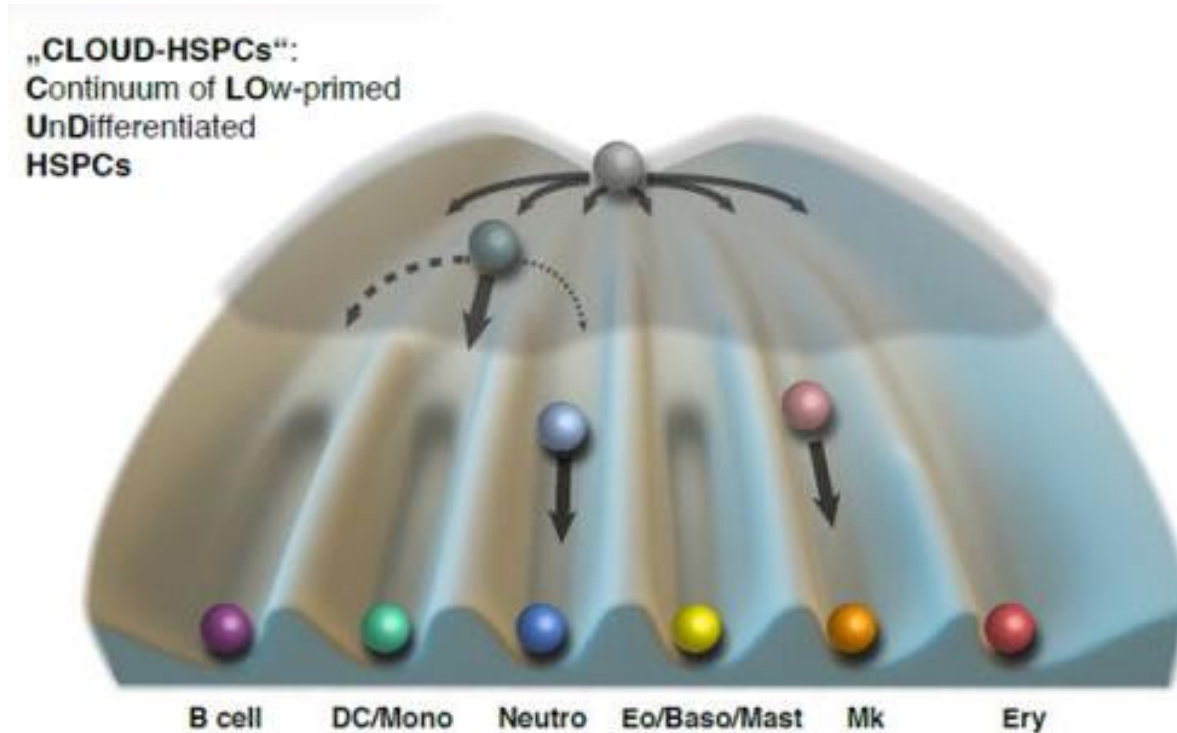
Hematopoietic stem cells (HSCs)

- See lecture "HSCs" by Prof. Karthaus



Tissue stem cell hierarchies are debated

ScRNAseq and other single cell techniques reveal a continuum of committed progenitors



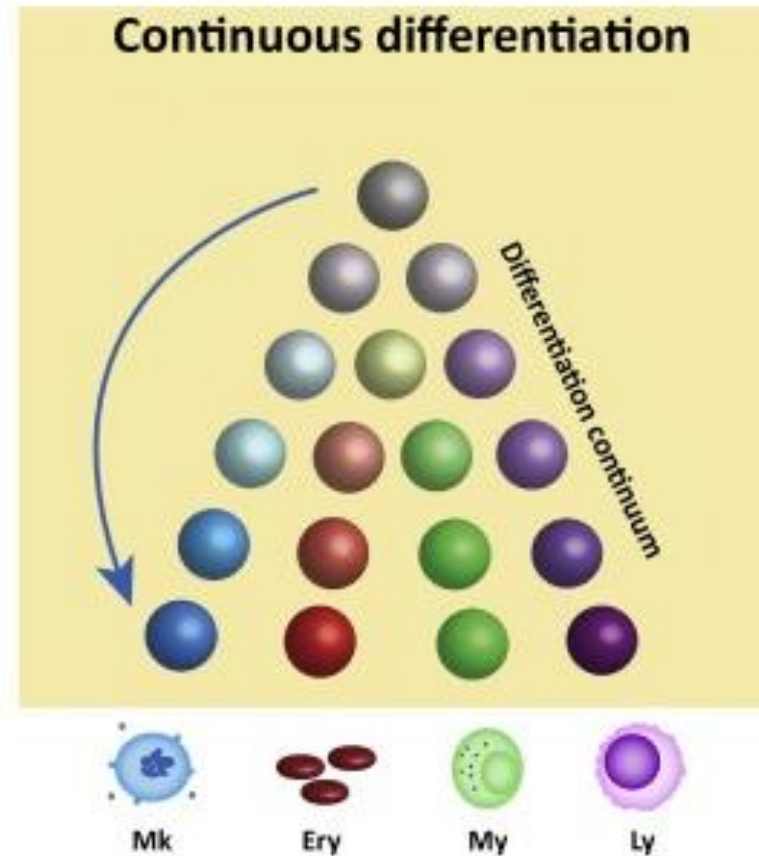
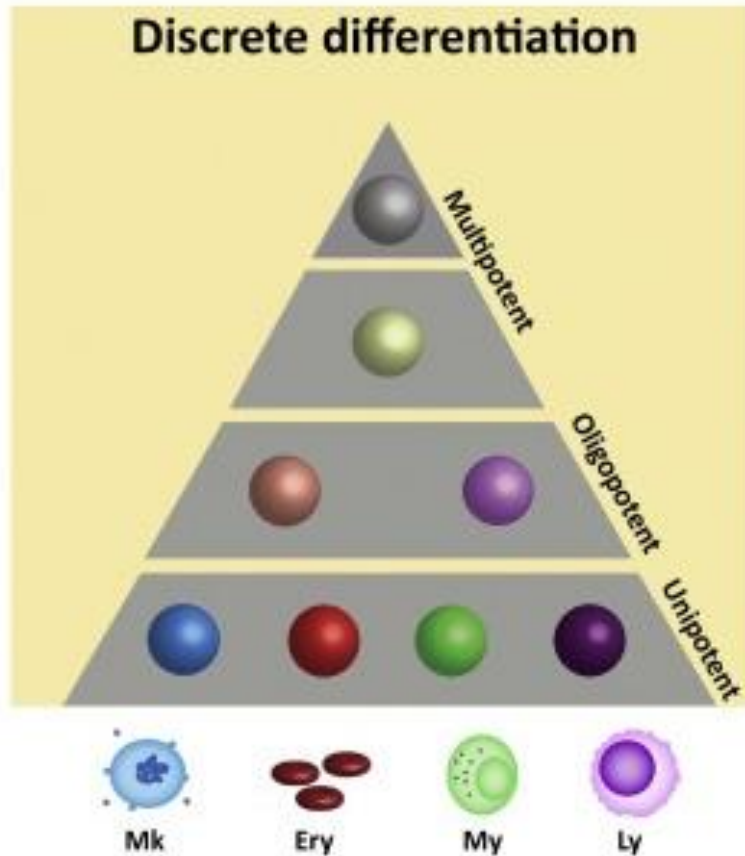
> [Nat Cell Biol.](#) 2017 Apr;19(4):271-281. doi: 10.1038/ncb3493. Epub 2017 Mar 20.

Human haematopoietic stem cell lineage commitment is a continuous process

Lars Velten ¹, Simon F Haas ^{2 3 4}, Simon Raffel ^{2 4 5}, Sandra Blaszkievicz ^{2 3}, Saiful Islam ⁶, Bianca P Hennig ¹, Christoph Hirche ^{2 3}, Christoph Lutz ⁵, Eike C Buss ⁵, Daniel Nowak ⁷, Tobias Boch ⁷, Wolf-Karsten Hofmann ⁷, Anthony D Ho ⁵, Wolfgang Huber ¹, Andreas Trumpp ^{2 4 8}, Marieke A G Essers ^{2 3}, Lars M Steinmetz ^{1 6 9}

Distinct lineages emerge directly from CLOUD-HSPCs without passing through a series of discrete, stable progenitors

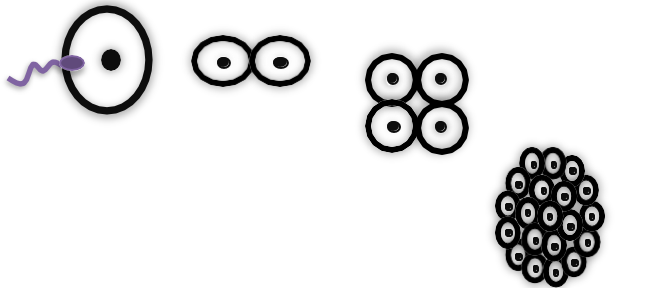
Tissue stem cell hierarchies are debated



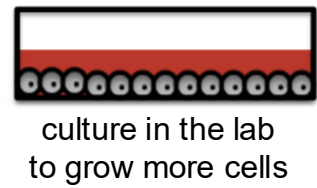
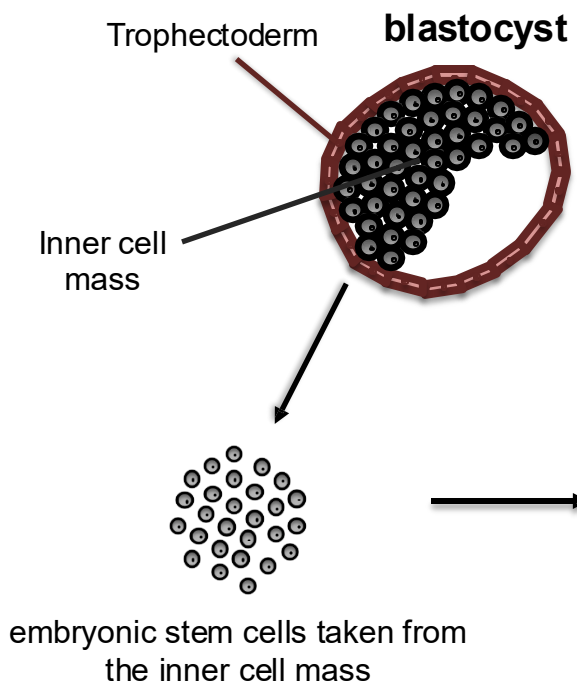
Zhang et al., Trends in Cell Bio 2018

2. Embryonic stem cells (ESCs)

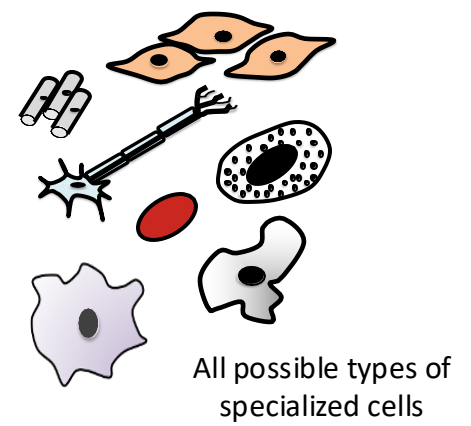
Embryonic stem cells - characteristics



- Derived from the inner cell mass of a blastocyst
- **Pluripotent** (can differentiate in all types of cells in the body, but not placenta)
- Ability to self-renew indefinitely
- Divide rapidly
- Can be grown in the lab in a defined medium

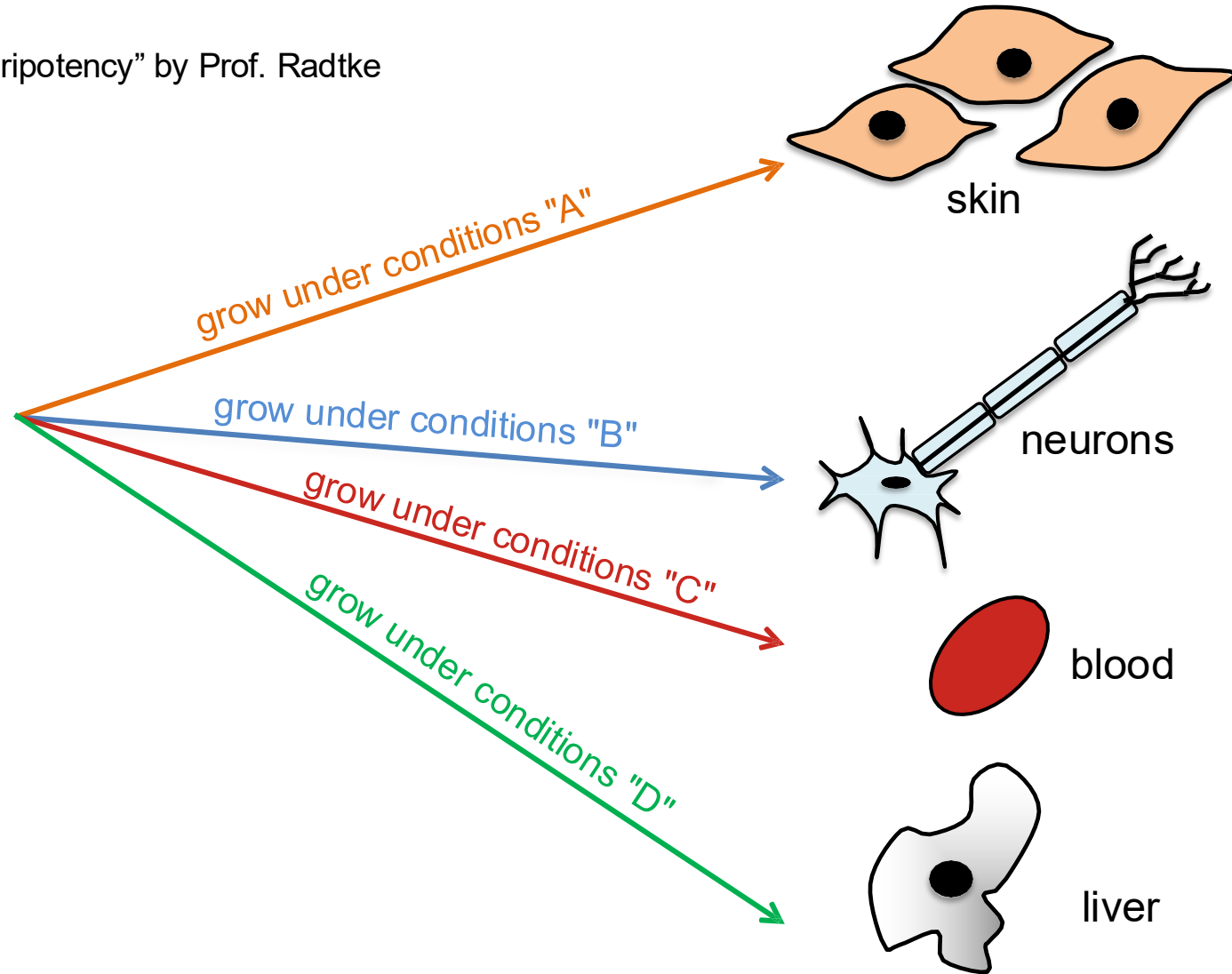
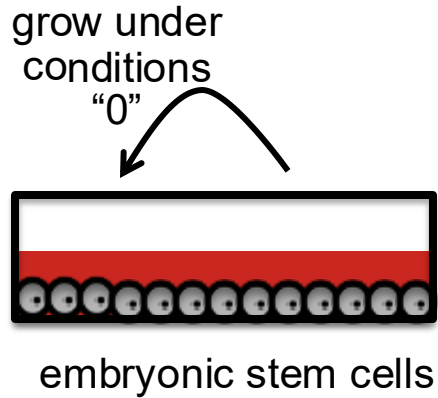


differentiation



Embryonic stem cell differentiation

- See lecture "ESCs and pluripotency" by Prof. Radtke



Nobel Prize in Physiology or Medicine 2007

Medicine



The Nobel Prize in Physiology or Medicine 2007

"for their discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells"



Photo: Tim Roberts/PR Newswire, © HHMI

Mario R. Capecchi

🕒 1/3 of the prize

USA

University of Utah
Salt Lake City, UT, USA;
Howard Hughes Medical
Institute

b. 1937
(in Italy)



Photo: The Press Association Limited

Sir Martin J. Evans

🕒 1/3 of the prize

United Kingdom

Cardiff University
Cardiff, United Kingdom

b. 1941



Photo: Scanpix/Dan Sears

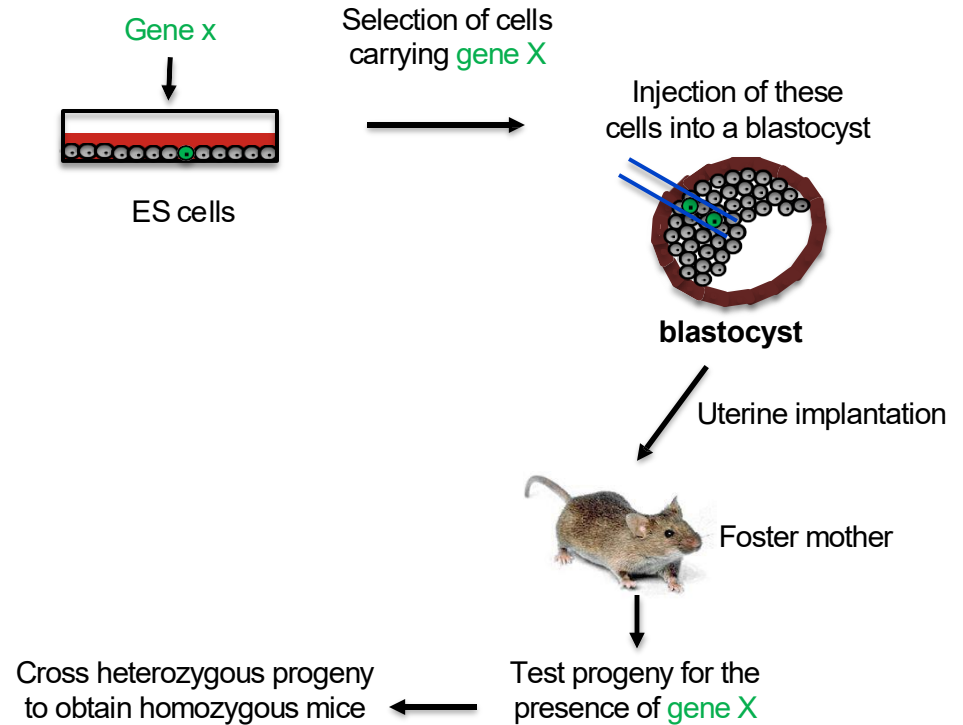
Oliver Smithies

🕒 1/3 of the prize

USA

University of North
Carolina at Chapel Hill
Chapel Hill, NC, USA

b. 1925
(in United Kingdom)

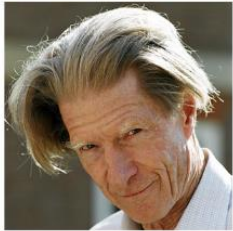


3. Induced pluripotent stem cells (iPS)

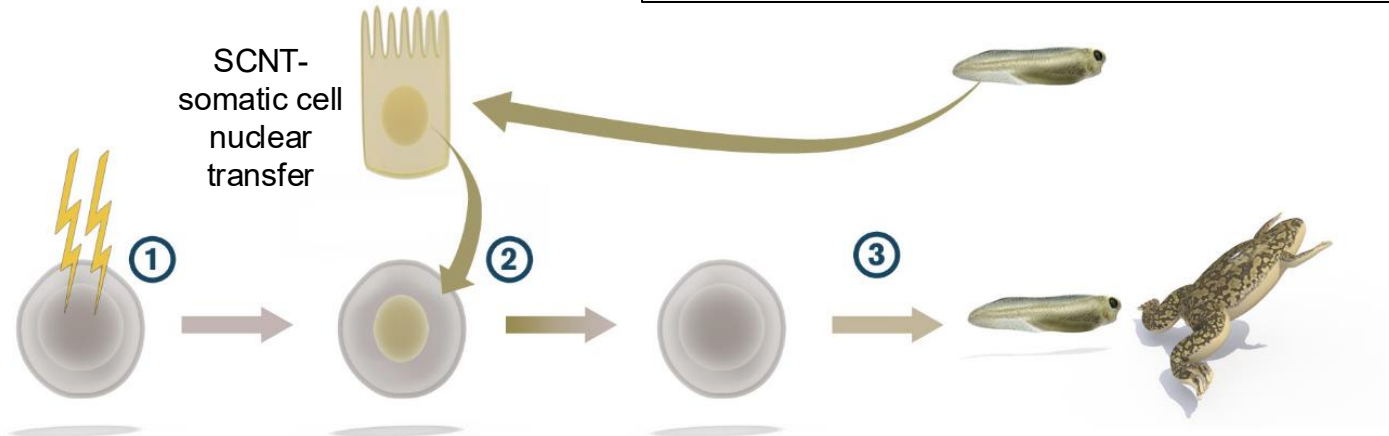
Nuclear reprogramming

- 1962: Sir John B Gurdon challenged dogma that specialised cells are irreversibly committed to their fate

[J. Embryol. exp. Morph., Vol. 10, Part 4, pp. 622-40 December 1962]
The Developmental Capacity of Nuclei taken from Intestinal Epithelium Cells of Feeding Tadpoles
by J. B. GURDON¹
From the Embryology Laboratory, Department of Zoology, Oxford



John B. Gurdon



John B. Gurdon eliminated the nucleus of a frog egg cell (1) and replaced it with the nucleus from a specialised cell taken from a tadpole (2). The modified egg developed into a normal tadpole (3). Subsequent nuclear transfer experiments have generated cloned mammals (4).



nobelprize.org/pressrelease

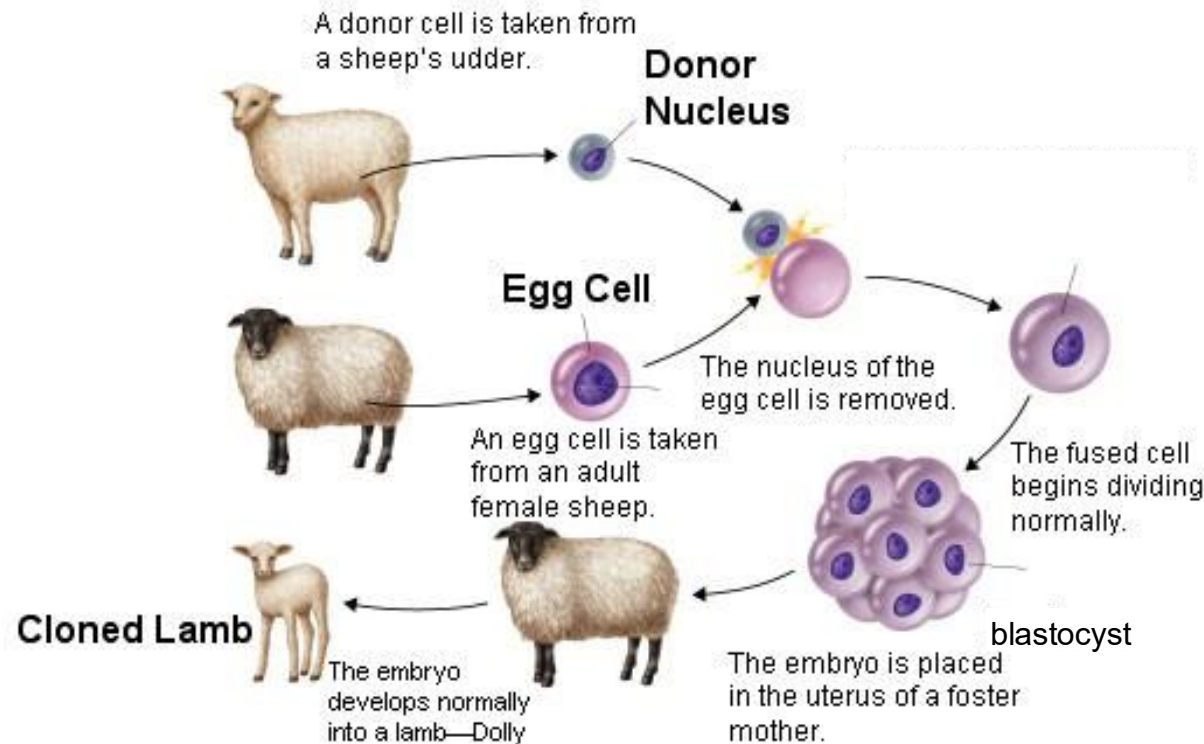
Reproductive cloning: e.g. Dolly the sheep

NATURE | VOL 385 | 27 FEBRUARY 1997

Viably offspring derived from fetal and adult mammalian cells

I. Wilmut, A. E. Schnieke*, J. McWhir, A. J. Kind* & K. H. S. Campbell

Roslin Institute (Edinburgh), Roslin, Midlothian EH25 9PS, UK
** PPL Therapeutics, Roslin, Midlothian EH25 9PP, UK*



July 5, 1996: First mammal cloned from adult cells

Since Dolly: Used in cows, mice, rats, goats, pigs, rabbits, cats, mule, horse and dog, etc.

Reproductive cloning: e.g. Dolly

SINOGENE PET CLONING SERVICE



Losing a pet is heartbreaking, but SINOGENE provides technological solutions to clone your pets by using a procedure of somatic cell nuclear transfer. As the science of pet cloning has progressed from the past years, SINOGENE provides a platform of gene edition technology, DNA preservation, DNA preservation, and cloning of cat, dog and horse. We are complied with EU regulatory standards and China Animal Welfare Legislation to maintain trust and ensure integrity with customers and society.



Cat Cloning

[READ MORE](#)



Dog Cloning

[READ MORE](#)



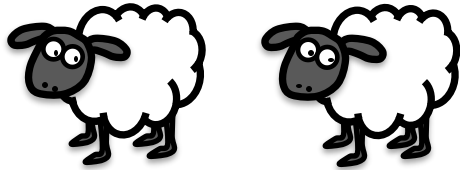
Horse Cloning

[READ MORE](#)

Careful!

There are two VERY different types of cloning:

Reproductive cloning

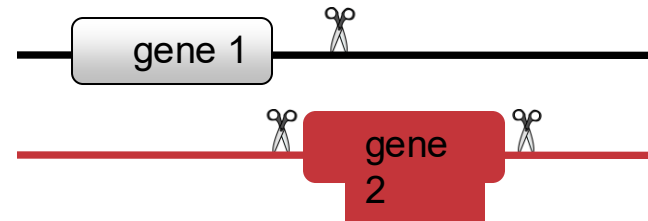


Use to make two identical individuals

Very difficult to do

Illegal to do on humans

Molecular cloning

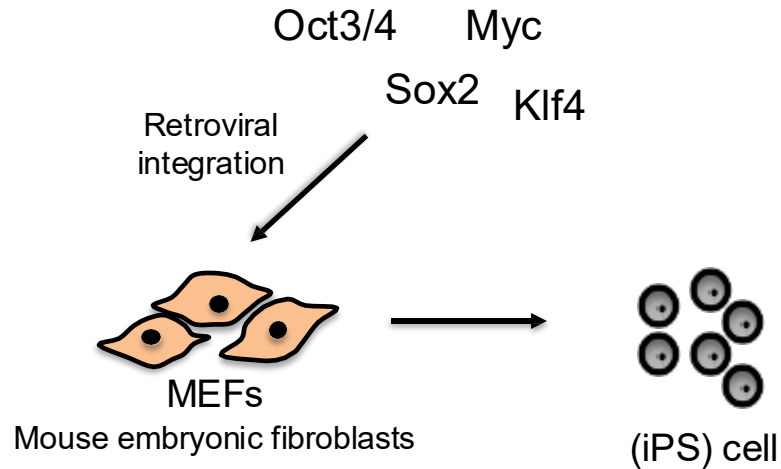


Use to study what a gene does

Routine in biology labs

Induced pluripotent stem cells discovery

- See lecture “nuclear reprogramming and iPS” by Prof. Radtke



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

Kazutoshi Takahashi¹ and Shinya Yamanaka^{1,2,*}

¹Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan

²CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan

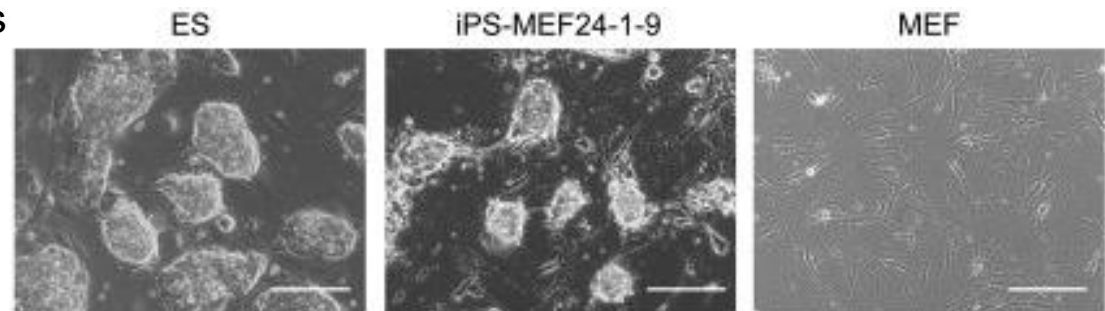
*Contact: yamanaka@frontier.kyoto-u.ac.jp

DOI 10.1016/j.cell.2006.07.024

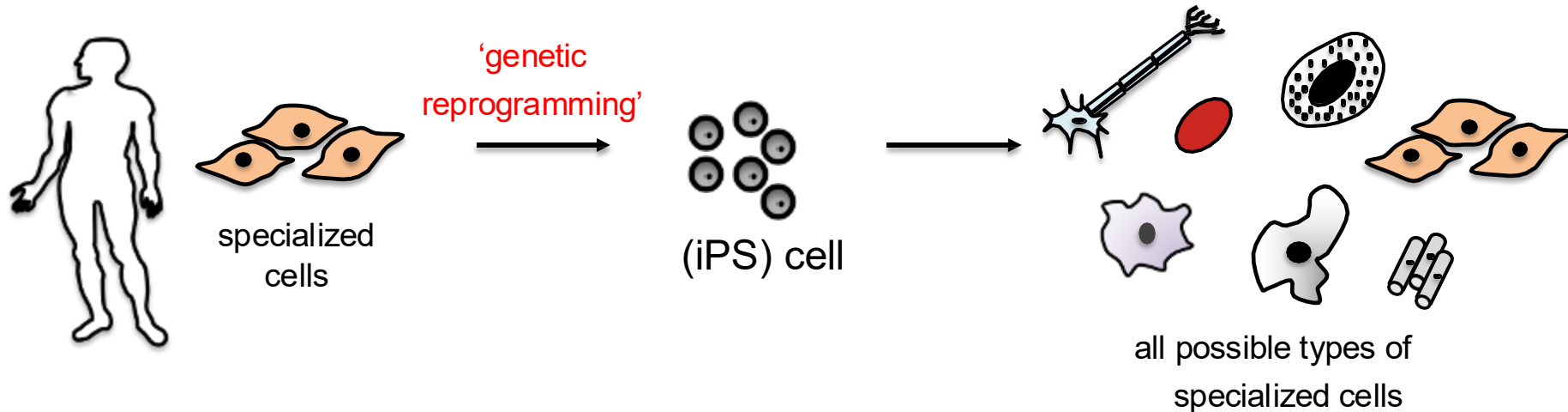


Shinya Yamanaka

- From an original set of 24, 4 factors were sufficient to generate pluripotent cells from MEFs
- Reprogramming still long and inefficient process



Induced pluripotent stem cells (iPS) - characteristics



- Behave like ESCs
- **Pluripotent** (can make all types of cells in the body, but not placenta)
- Divide rapidly
- Self-renew indefinitely
- Artificial system
- No embryonic stem cells are needed

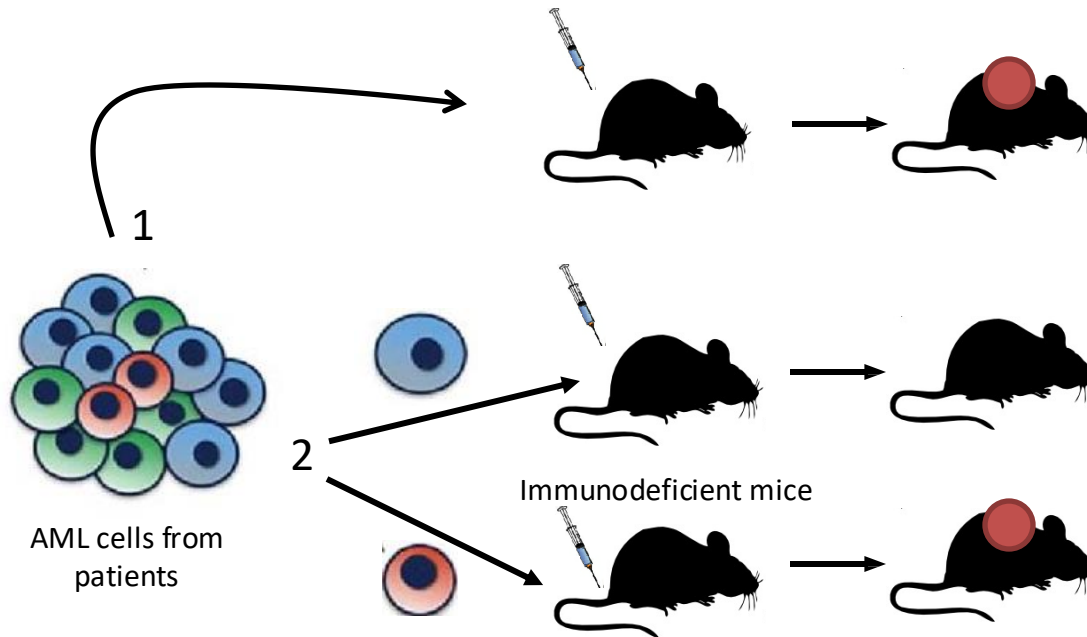
To summarize

	Embryonic stem cells (ESCs)	Tissue stem cells	Induced pluripotent stem cells (iPS)
Artificial system	yes	no	yes
Pluripotent	yes	no	yes
Efficient differentiation	no	yes	no
Efficient expansion in culture	yes	no	yes
Rare cell type	no	yes	yes*
Immune-compatible	no	no	yes
Teratoma risk	yes	no	yes

*rare in the sense that reprogramming is inefficient

4. Cancer stem cells

Cancer stem cell model - key experiment



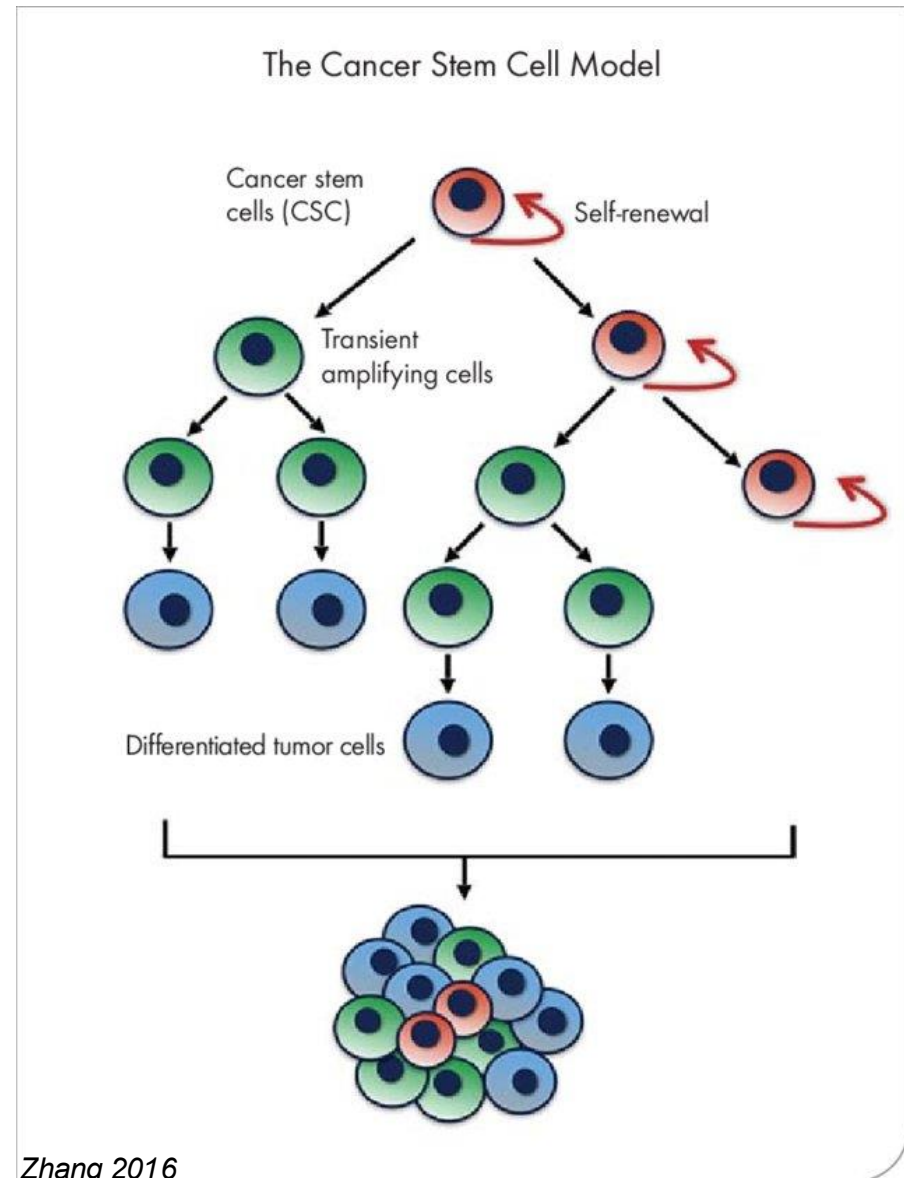
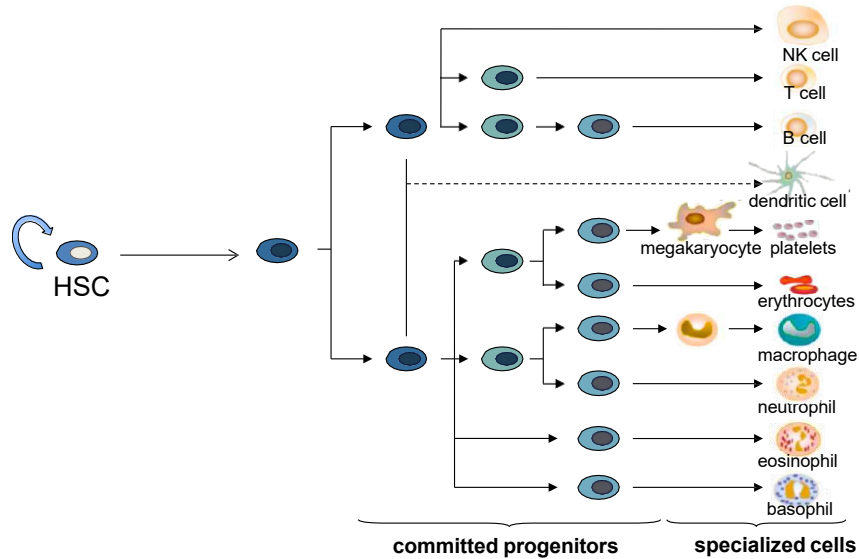
A cell initiating human acute myeloid leukaemia after transplantation into SCID mice

Tsvee Lapidot, Christian Sirard, Josef Vormoor, Barbara Murdoch, Trang Hoang*, Julio Caceres-Cortes*, Mark Minden†, Bruce Paterson‡, Michael A. Caligiuri§ & John E. Dick||

NATURE VOL 367 · 17 FEBRUARY 1994

- Only a very low fraction of tumour cells can reinitiate the disease
- Cancer stem cells have a high self-renewal capacity
- They share features of tissue stem cells:
 - Rare
 - Rare division
 - Self-renewal
 - Differentiation capacity

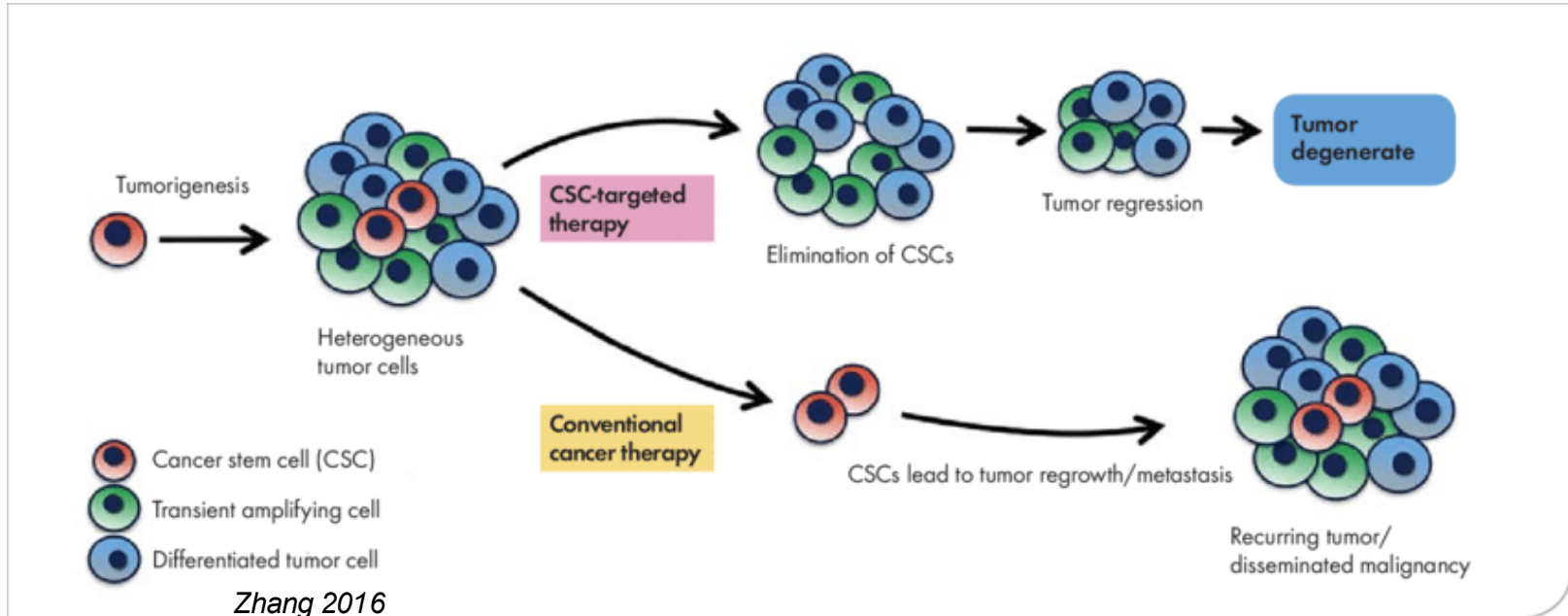
Cancer stem cell model explaining tumor heterogeneity



- The cancer stem cell model postulates that cancer cells form a hierarchy similar to the one of tissue stem cells, progenitors, and specialized cells

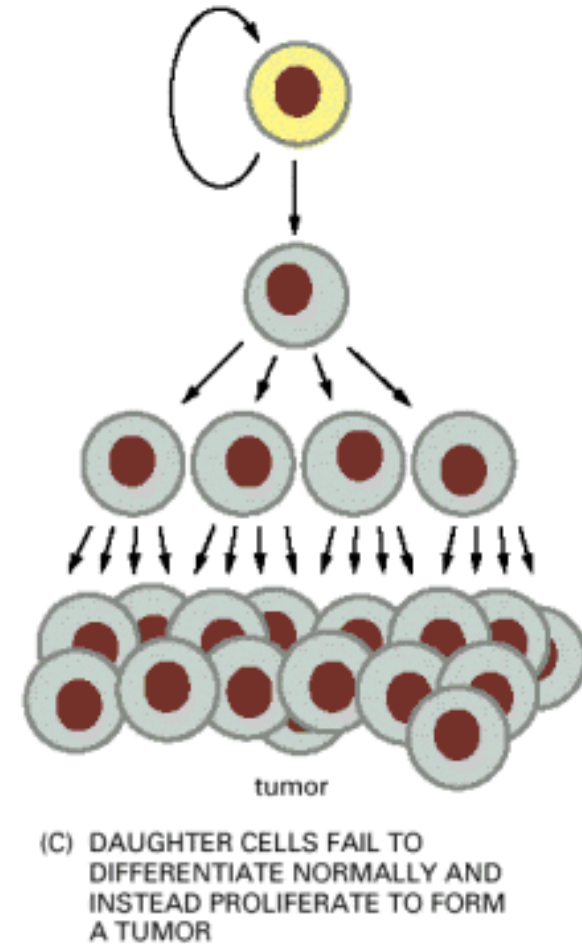
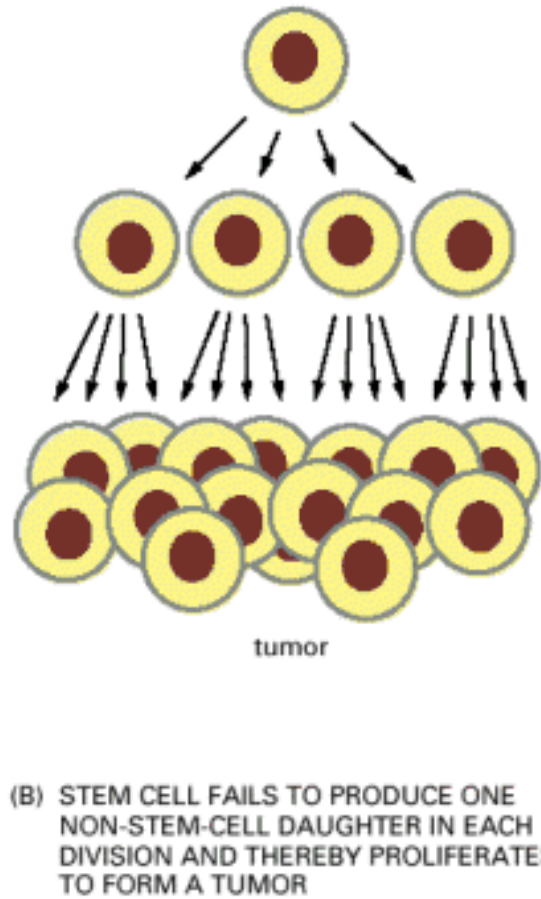
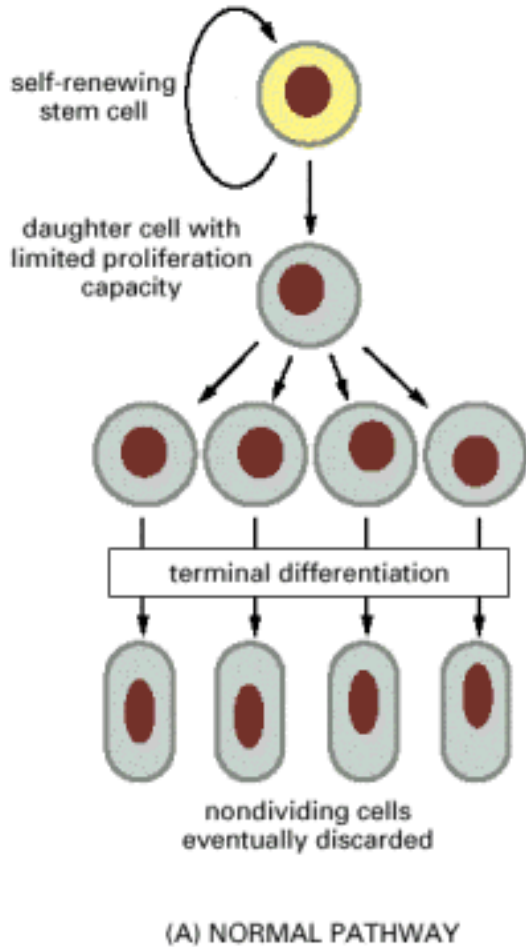
Cancer stem cell model - implications for therapy

- See lecture “Cancer stem cells” by Prof. Radtke



- CSCs are prognostic markers
- Often resistant to classical therapies and can cause relapses
- New therapies aim at specifically targeting them

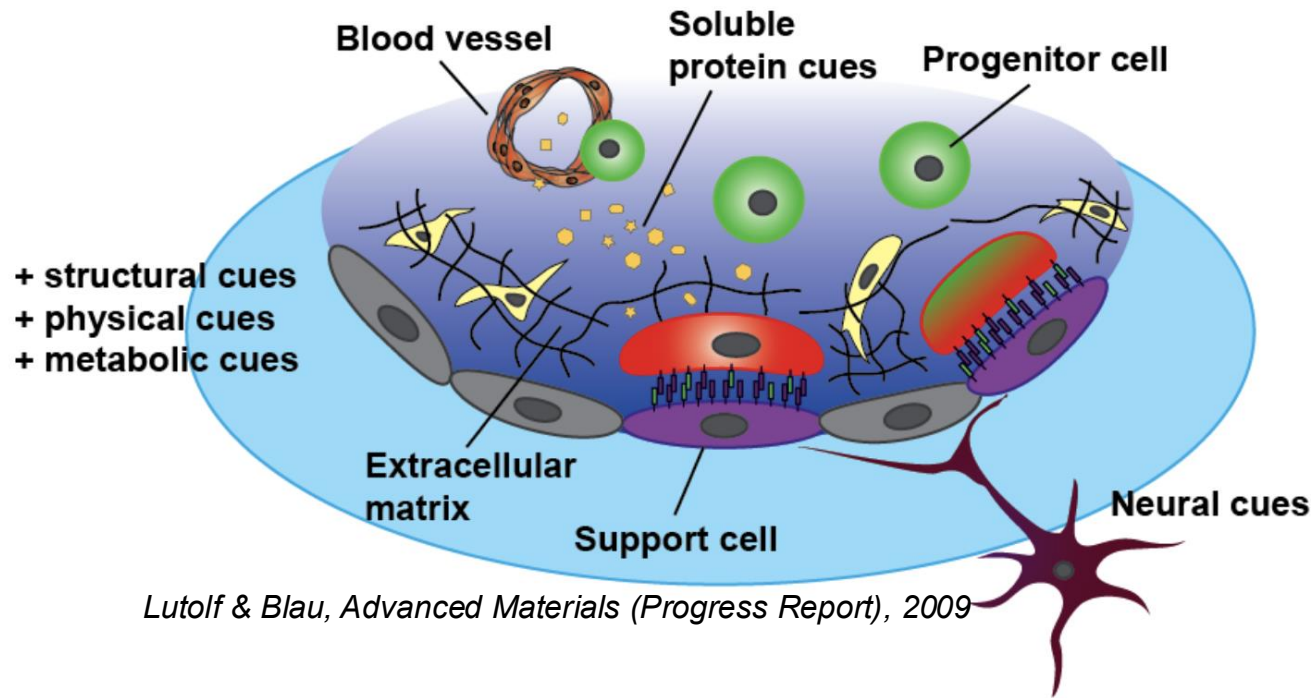
Balancing self-renewal and differentiation is crucial



How is this balance regulated ?

The stem cell niche

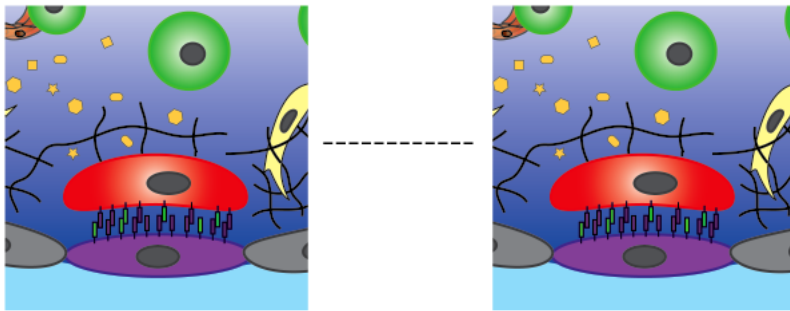
- See lecture “Stem cell niche” by Prof. Karthaus



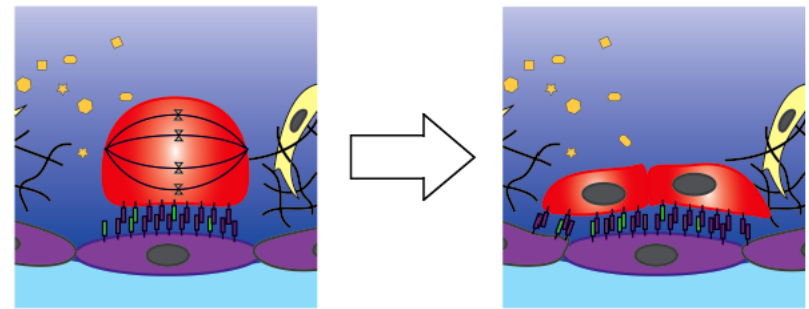
- Defined location and architecture
- Biochemical stem cell-niche crosstalk
- Physical interaction with support cells
- Protects stem cells from differentiation
- Regulates their renewal

Possible stem cell "fates" in the niche

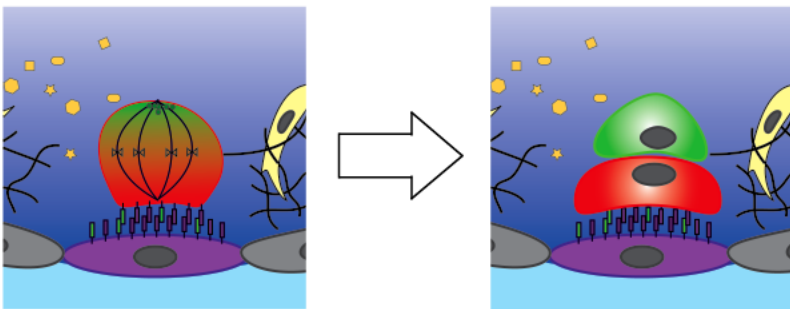
Quiescence



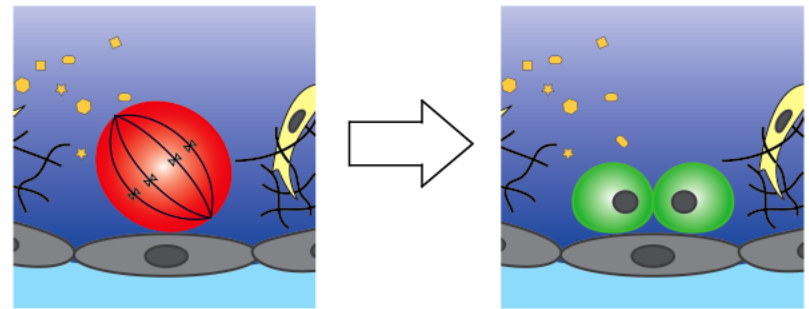
Symmetric self-renewal division



Asymmetric self-renewal division



Differentiation division



**What makes stem
cells so interesting?**

Stem cells play crucial roles

Stem cells play crucial roles during:

- Embryogenesis
- Maintenance of regenerative tissues such as skin, intestine and the hematopoietic system
- Tissue repair after injury (skin, muscle, bone, gut, ...)
- Cancer (Cancer stem cells)

→ Many potential clinical applications

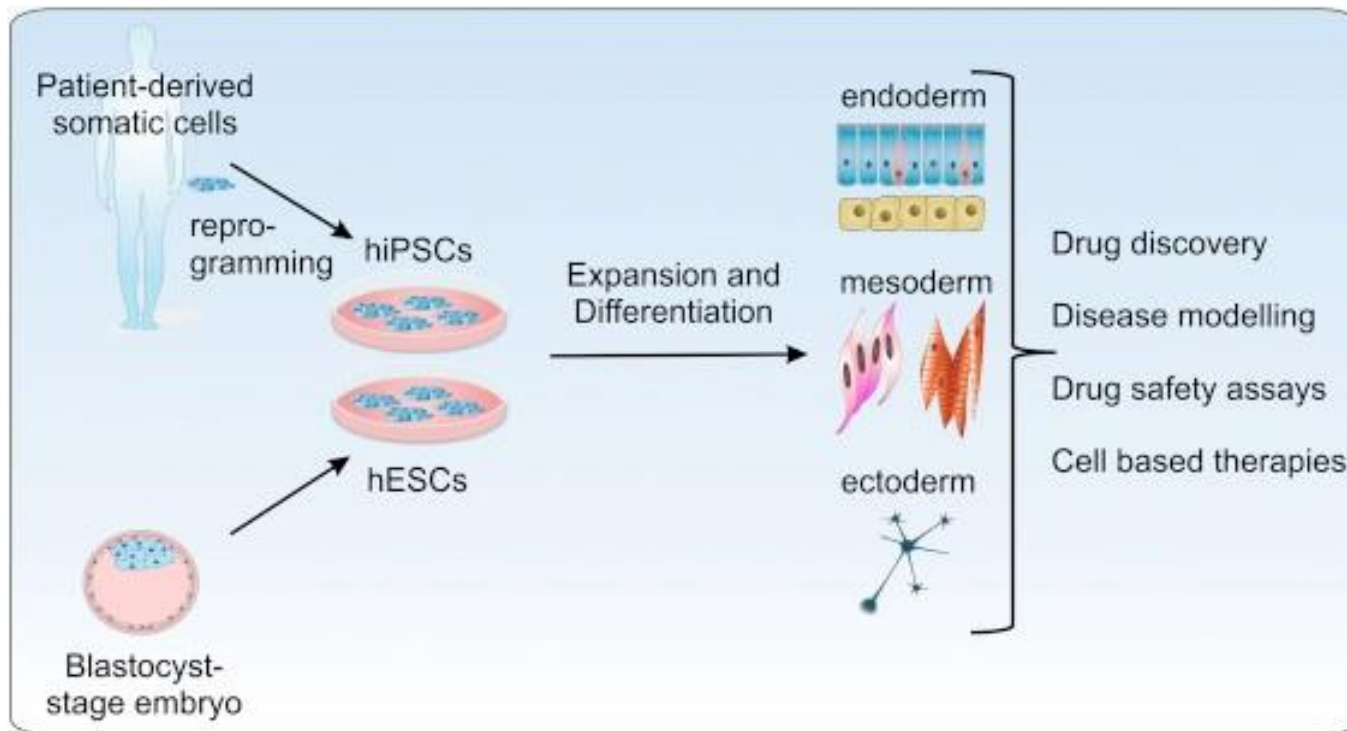
Stem cell - based therapy

- Differentiation of stem cells to produce tissues to replace
 - hESCs
 - iPSCs
 - Tissue stem cells in vitro
- Gene therapy on stem cells
- Disease modelling, drug screenings

Stem cell - based disease modelling

- In vitro disease model
- Drug discovery
- Drug safety assays

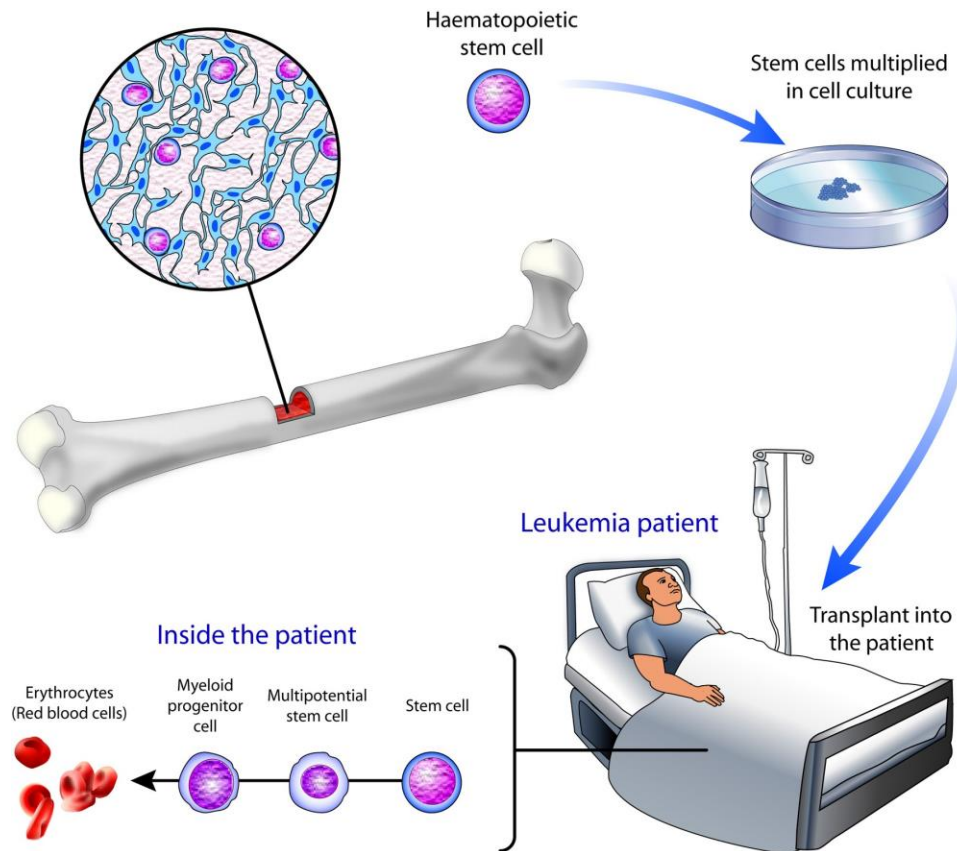
- See lectures “Clinical application” by Prof. Naveiras



Kropp et al., Process biochem. 2017

Stem cell based therapy – an example

- Bone marrow transplantation



EBMT Activity Survey in 2018: Patient and transplant numbers

Indication	Allogeneic HSCT	Autologous HSCT	Total
1st allo/1 st auto HSCT	18,483	24,418	42,901
Additional HSCT	1,147	3,420	4,567
TOTAL	19,630	27,838	47,468

Teams: 701(of 720)

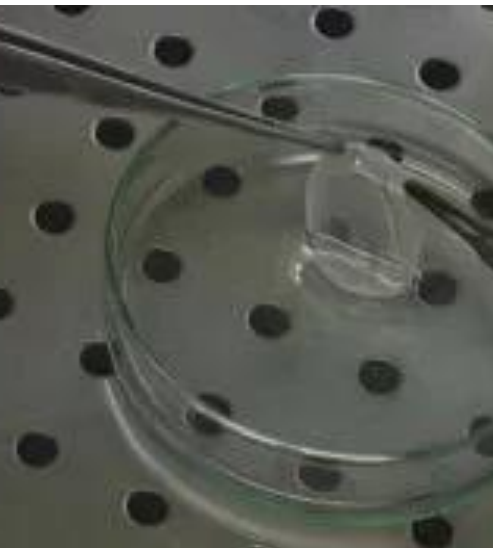
Countries reporting: 50

EBMT Activity Survey 2018: Main indications

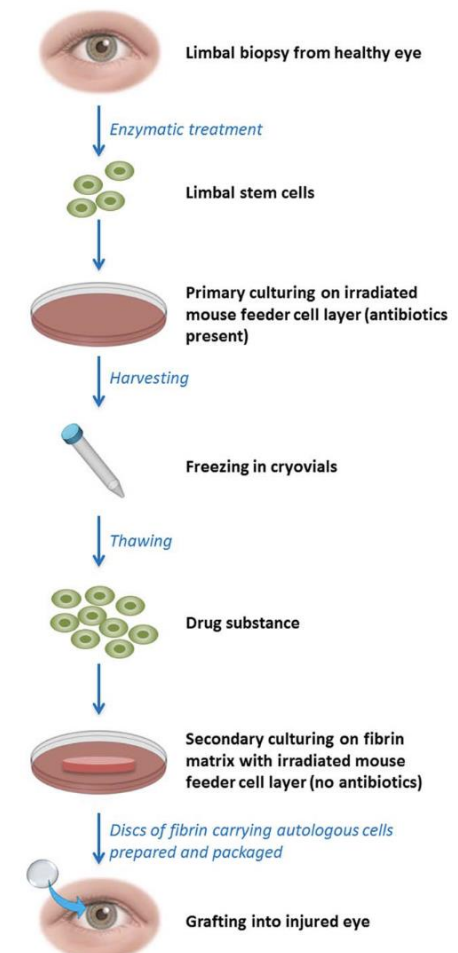
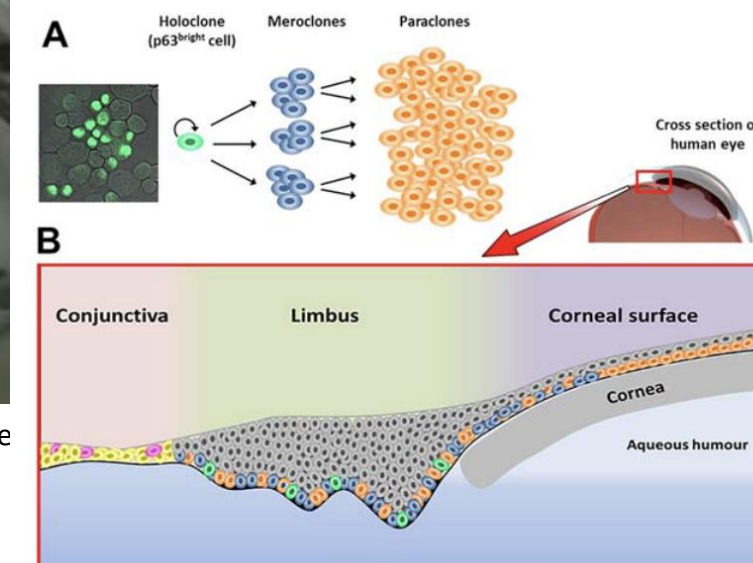
Indication	Allogeneic 1 st HSCT	Autologous 1 st HSCT	Total
Myeloid (AML, CML, MDS/MPN)	10,385	294	10,679
Lymphoid (ALL, CLL, HL, NHL)	4,953	8,803	13,756
Plasma cell disorder	416	13,146	13,562
Solid tumor	47	1,578	1,625
Non-malignant disorders	2,487	576	3,063
<i>bone marrow failure</i>	954	5	959
<i>auto immune disease</i>	20	550	570
Other	195	21	216
Total Patients	18,483	24,418	42,901

Stem cell-based therapy – first ATMP containing stem cells

- Holoclar is the first EMA-approval as first advanced therapy medicinal product containing stem cells in Europe
- To replace damaged cells on the surface of the cornea



<https://www.eurostemcell.org/de>



ATMP: Advanced Therapy Medicinal Product
EMA: European Medicines Agency

Stem cells open questions/hurdles

- Very rare (dispersed and virtually invisible)
- Markers?? (with exception of the HSCs) → purity??
- *In vivo* and *in vitro* systems to assay SC activity
- Difficulty to culture stem cells in vitro (ESCs and iPS: differentiation, TSCs: self-renewal)
- In vivo use: survival?, rejection?, tumor formation?

A Stem Cell Story

[https://www.youtube.com/watch?v=2-3J6JGN- Y](https://www.youtube.com/watch?v=2-3J6JGN-Y)

Next lecture 19.09
(Stem) Cell Plasticity