

Stem cells from the ground floor

What happens when we get injured?

- Immune cells come in and clear away the debris and any infection
- Tissue can repair themselves, filling the void with non-functional material using the scar
- Regeneration is the complete restoration of the original tissue. Damaged tissue is replaced by new functional cells.

What happens when we get injured?

Tissues regenerate new functional cells by

- Either dividing the existing functional cells, ...
- ... or by activating an adult stem cell population
- A stem cell must make more copies of itself (self-renew) and give rise to more capable offspring (differentiate)

What is a stem cell?

Different tissues turn over and are renewed at different rates

- Nerves may last a lifetime
- Bone is completely eaten away by osteoclasts and replaced by osteoblasts every 10 years
- Blood cells are generated in the bone marrow and may last 120days.
- Large doses of ionizing radiation prevent cell division and prevent renewal - so within a few days the lining of the intestine is deprived of cells and massive diahorrea and water loss occurs.

What is a stem cell?

- Stem cells generate a continuous supply of *terminally differentiated* cells
- Terminally differentiated cell are unable to divide - eg. gut, skin and red blood cells.
- They are generated from a stock of precursor cells - the stem cells.

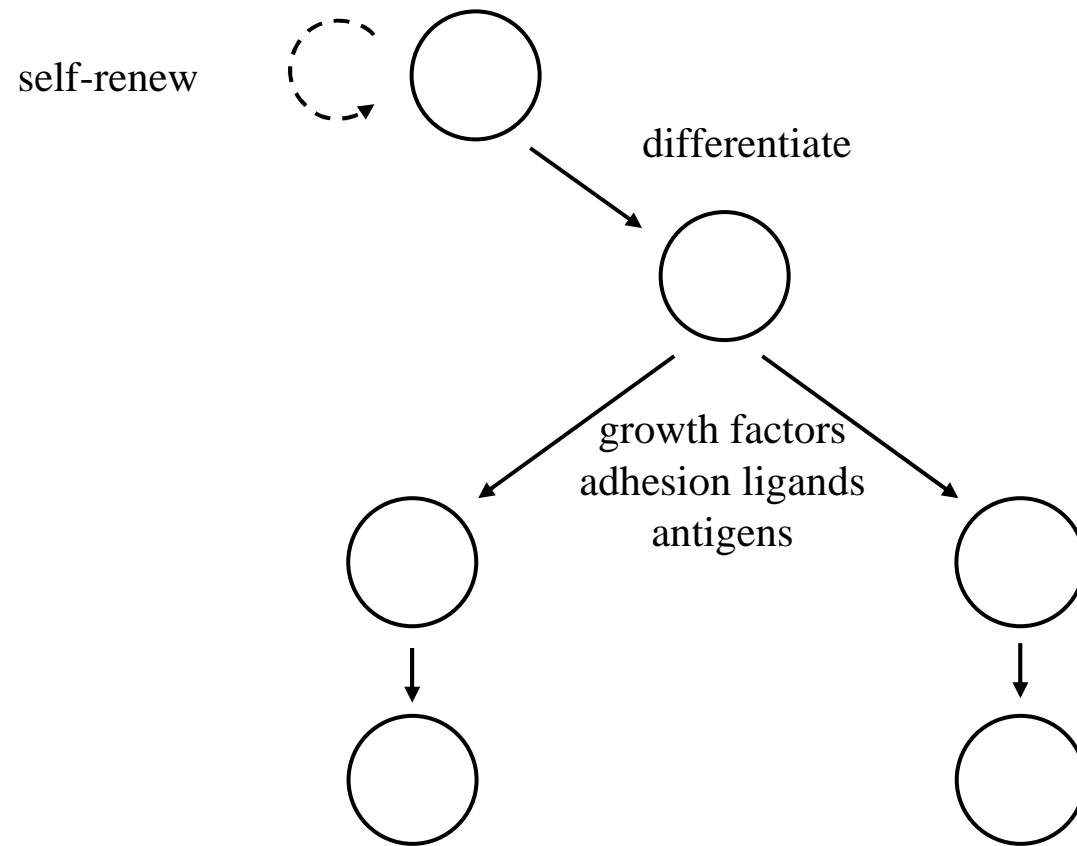
What is a stem cell?

- Stem cells are not terminally differentiated and can divide without limit.
- When a stem cell divides, each daughter either remains a stem cell or becomes terminally differentiated.
- Stem cells do not carry out the functions of mature differentiated cells, but produce the cells that will do this
- They are not terminally differentiated but many are *determined* - this means they stably express sets of gene regulatory proteins that ensure their offspring will be of a specific cell types

What is a stem cell?

- Because stem cells can proliferate or generate differentiated daughter cells, they provide for growth and tissue repair as well as normal tissue maintenance
- Transfusing a few hemopoetic stem cells into a mouse whose own stem cells have been destroyed by irradiation will fully restore a new blood system and rescue the mouse from death by anaemia.
- This approach is the basis for treatment of leukemia in humans through the use of bone marrow transplants

Stem cell replication



Stem Cell Classifications

Totipotent stem cells: *can differentiate into any cell type in the body; generally cells from the first few divisions after fertilization;*



Pluripotent stem cells: *descendants of totipotent stem cells which develop by about Day 4 after fertilization; can differentiate into any cell type other than totipotent cells*



Multipotent stem cells: *descendants of pluripotent stem cells and antecedents of specialized cells in particular tissues; Ex: hematopoietic stem cells found in bone marrow give rise to all forms of blood cells*



Progenitor cells “unipotent stem cells”: *can produce only one cell type; Ex: erythroid progenitor cells differentiate into only red blood cells*

Cellular proliferation

Tissues of the body are divided into three groups

- **Continuously dividing (labile) tissues**
- **Stable tissues**
- **Permanent tissues**

Cellular proliferation

Continuously dividing (labile) tissues

- Cells are continuously proliferating
- Can easily regenerate after injury
- Contain a pool of stem cells
- Ex.: bone marrow, skin, GI epithelium

GI epithelium

- Stem cells in the gut lie near the bottom of the crypts.
- Newborn absorptive and goblet (secretory) cells are generated from these and move up in the plane of the epithelium.
- they reach the tip of the villi and are shed within about 5 days

Bone marrow

- The more capable the cell becomes, the fewer types of cells it can become

Cellular proliferation

Continuously dividing (labile) tissues

Stable tissues

- Cells have limited ability to proliferate
- Limited ability to regenerate (except liver!)
- Normally in G₀-phase, but can proliferate if injured
- Examples: liver, pancreas, kidney

Cellular proliferation

Continuously dividing (labile) tissues

Stable tissues

Permanent tissues

- Cells can't proliferate
- Can't regenerate (so injury always leads to a scar)
- Examples: neurons, cardiac muscle

Die besonderen Eigenschaften der ersten Zellen

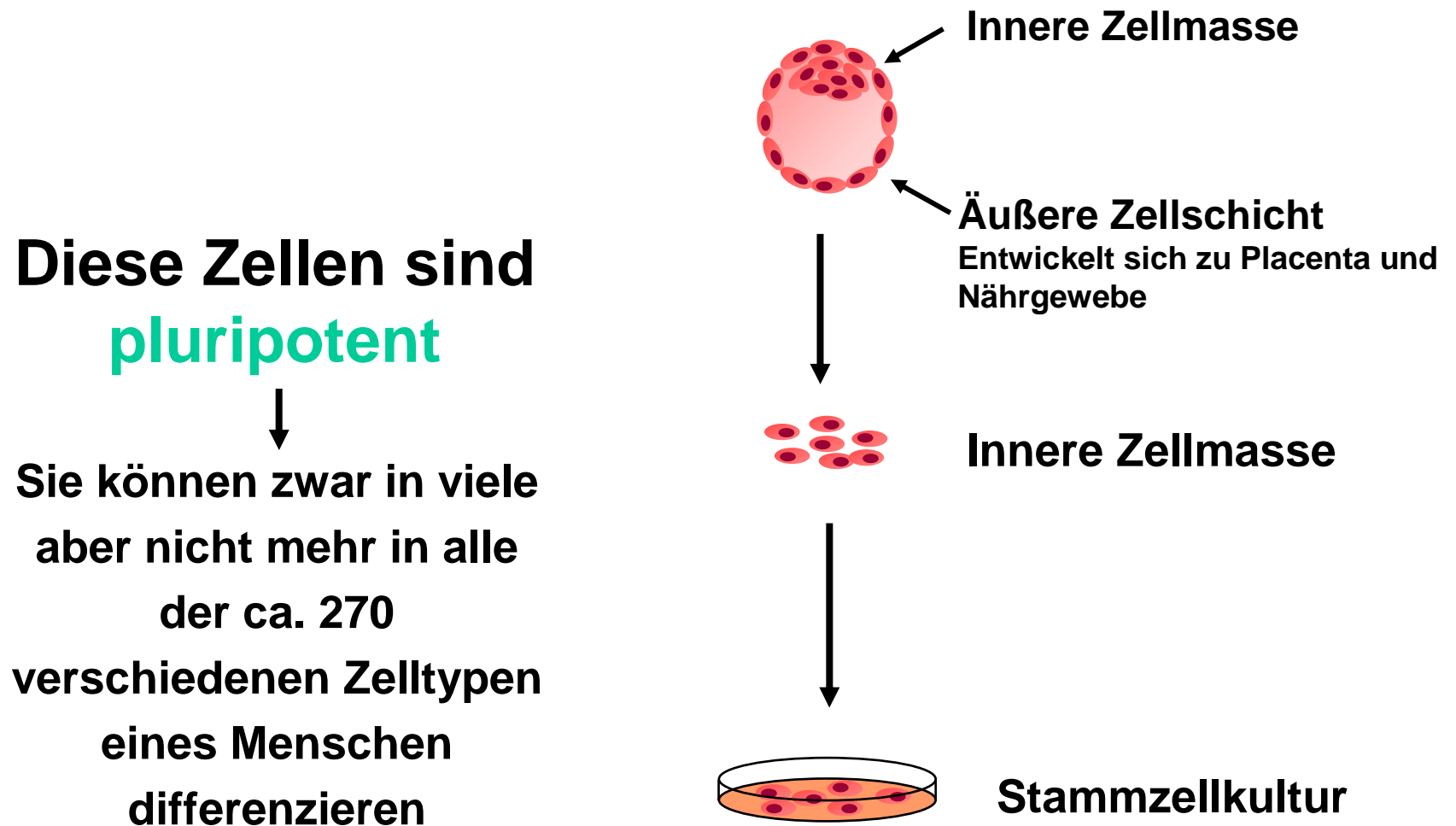
Diese Zellen sind
totipotent



Jede dieser Zellen kann
in jede der ca. 270
verschiedenen Zelltypen
eines Menschen
differenzieren

Die "eingeschränkten" Eigenschaften der folgenden Zell-Generationen

Die Blastocyste





**Neuronen
Nervenzellen**

Parkinson-Patienten

Schlaganfall-Opfer und Demente



**Pankreatische
Inselzellen**

Typ-I-Diabetiker

Infarkt-Patienten



Herzmuskelzellen

Noch mutiger?

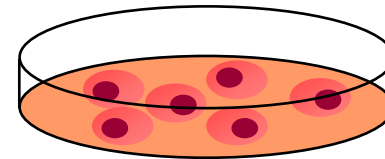
Niere



Herz



Leber



Mit dem Organmangel in der Transplantationsmedizin soll es endgültig vorbei sein!

Worum geht es?

Worum geht es nicht?

Stammzellen

- embryonale Stammzellen
- adulte Stammzellen
- Nabelschnur-Stammzellen

Stammzellforschung

Stammzelltherapie

Gentechnik

- Gentherapie
- "Designerbiologie"

Prä-Implantationsdiagnostik

Klonen

Humane Stammzellen

**Embryonen bis 8-Zell-Stadium
(totipotente Stammzellen)**

- Differenzierung in jede Körperzelle möglich
- Induktion einer Immunabwehr des Empfängers
- Ethisch umstritten, derzeit verboten

**Therapeutisches Klonen
(totipotente Zellen)**

- Empfänger ist gleichzeitig sein eigener Spender
- Daher keine Immunreaktion
- Hohe ethische Barrieren

**Späte Embryonen
(100-Zell-Stadium,
pluripotente Zellen)**

- Differenzierung in fast jede der vielen Körperzellen möglich
- Induktion einer Immunabwehr des Empfängers
- Ethisch umstritten, derzeit verboten

Humane Stammzellen

**Fötale Gewebe
(pluripotente Zellen)**

- **Eingeschränkte Differenzierungspotenz, hohe Proliferationspotenz**
- **Induktion einer Immunabwehr des Empfängers**
- **Ethisch umstritten aber nicht verboten**

**Adulte Stammzellen
(pluripotente Zellen)**

- **Eingeschränkte Differenzierungs- und Proliferationspotenz**
- **Keine Induktion einer Immunabwehr bei autologer Anwendung**
- **Induktion einer Immunabwehr bei heterologer Anwendung**
- **Keine ethischen Hürden**

**Nabelschnur-Stammzellen
(pluripotent)**

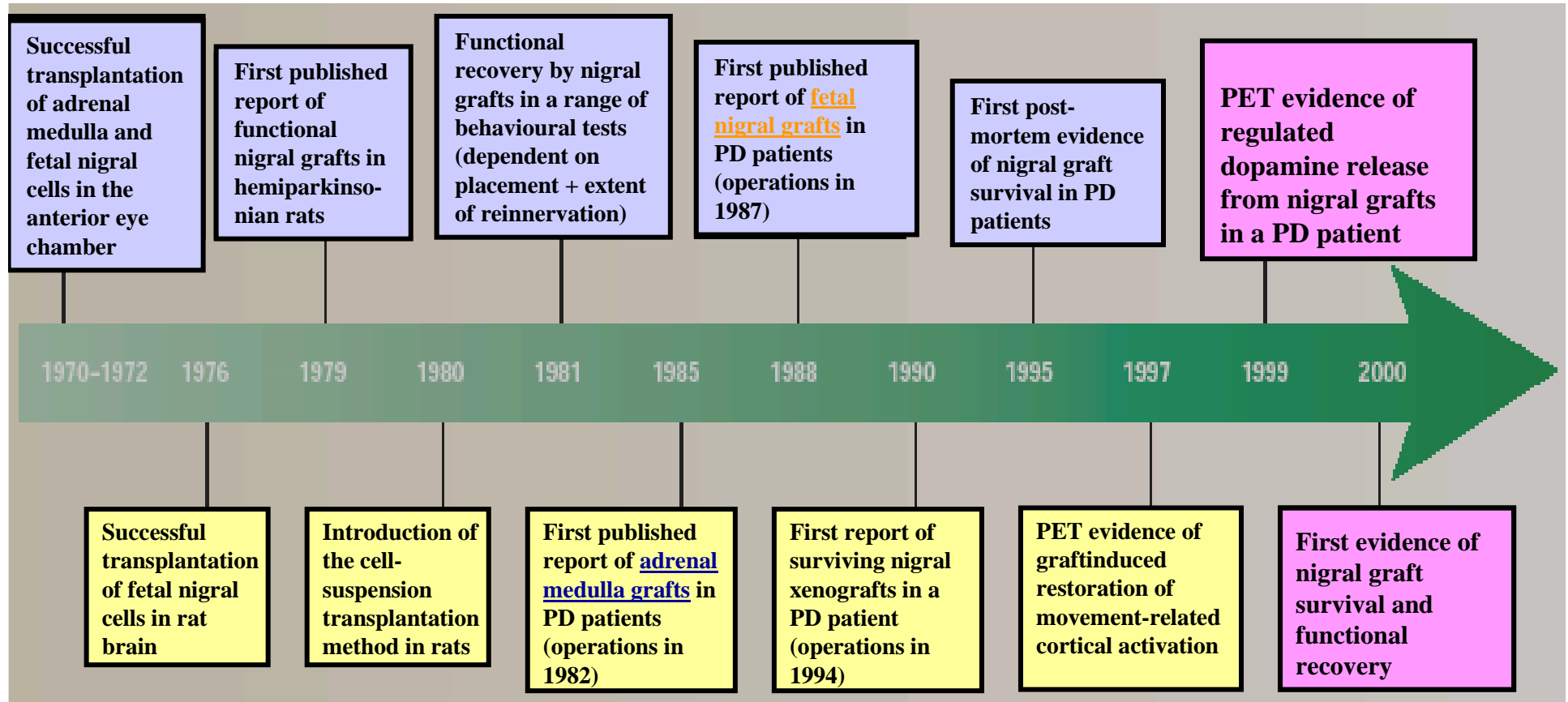
- **Potential noch nicht beurteilbar**
- **Keine Induktion einer Immunabwehr bei autologer Anwendung**
- **Keine ethischen Hürden**

Mögliche Anwendungen pluripotenter Stammzellen

Grundlagenforschung

- **Regulation früher Entwicklungsprozesse**
 - Spezifizierung und Differenzierung
 - Genregulation
 - Pathologie der Differenzierung und Genregulation
- **Rationale Wirkstoffentwicklung**
 - Wirksamkeit
 - Sicherheit
 - Zellkultur vs. Tierversuche
- **Stammzell-Therapie**
 - Differenzierung pluripotenter Stammzellen in einer ausdifferenzierten Matrix
 - Ersatz bei Ausfall oder Zerstörung verschiedener Zellen oder Organe

Cell transplantation in PD – an old story



Modified from S. Dunnett et al., Nature Reviews, 2001