Transplantation: Stem Cells

4540-FS2017-0: Selected Topics in Clinical Immunology
27.04.2017, 16:15 -17:00

Gabriela M. Baerlocher
Hematology, University Hospital/Inselspital Bern
Experimental Hematology, Department of Clinical Research, University of Bern

Aims

- to understand the basics of hematopoiesis
- to understand the basic principles of hematopoietic stem cell transplantation

Outline

- Hematopoiesis
- Hematopoietic Stem Cell Transplantation
  - allogeneic
  - autologous

Hematopoietic Cell Production

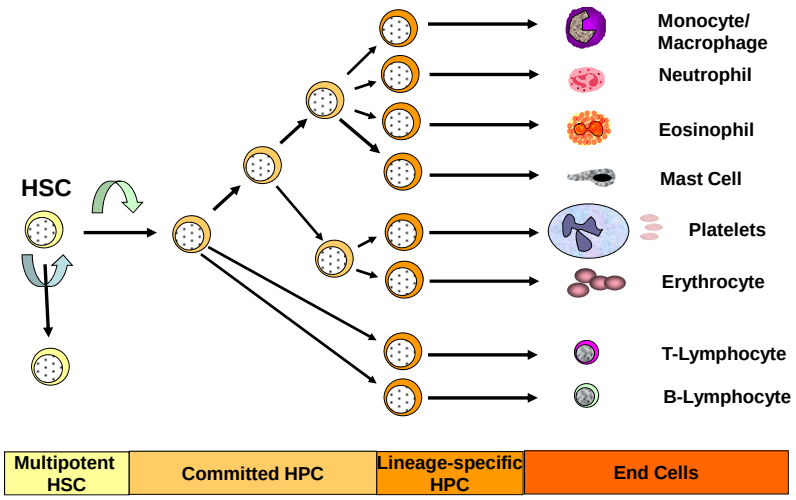
→ 70-140 x 10^6/Min

→ 180 x 10^6/Min

→ 180 x 10^6/Min

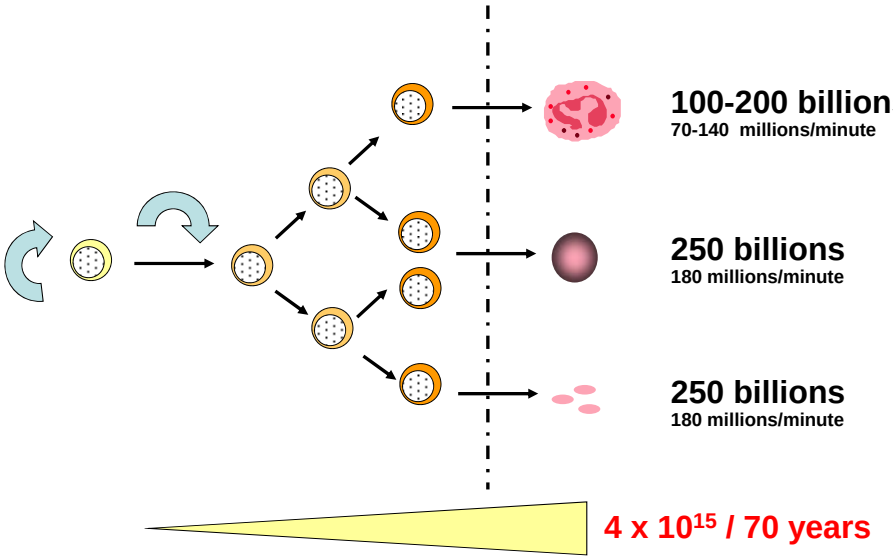
4 x 10^{15}/70 years

Hematopoiesis



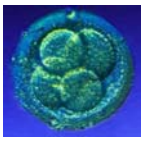
Gabriela M. Baerlocher 27.04.2017

Hematopoiesis



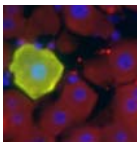
Gabriela M. Baerlocher 27.04.2017

Stem Cells



Zygote → **Totipotent Cells**
can develop to a whole organism

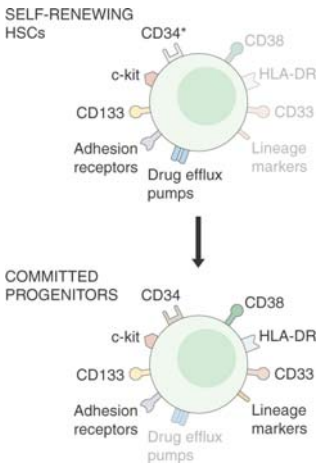
Blastocyst: Embryonic Stem Cells → **Pluripotent Cells**
can develop all tissue types of an organism



Organs: Hematopoietic Stem Cells → **Multipotent Cells**
can develop all cell types of a certain tissue

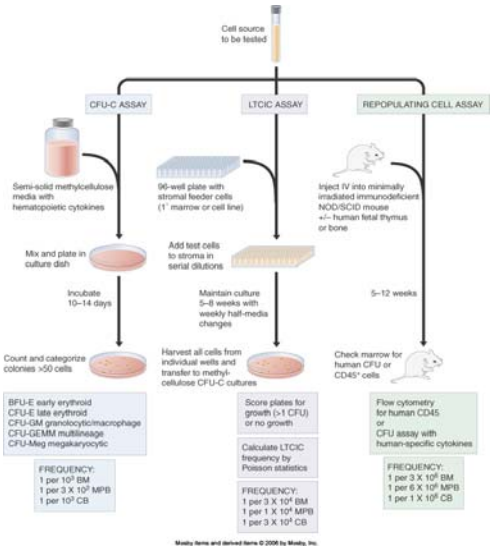
Gabriela M. Baerlocher 27.04.2017

Stem Cell Characterisation



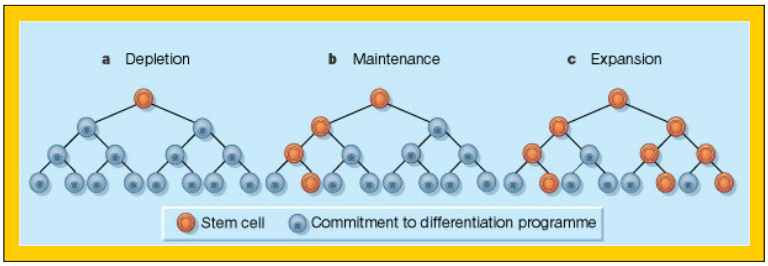
Gabriela M. Baerlocher 27.04.2017

Stem Cell Assays



Gabriela M. Baerlocher 27.04.2017

Stem Cell Concept



Nature 2003; 423: 231-233

Gabriela M. Baerlocher 27.04.2017

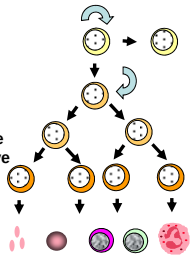
Stem Cell Regulation

Stochastic Model

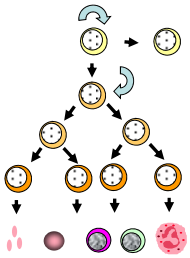
Intrinsically

properties of the stem cell

cytokines have only permissive role



Instructive Model



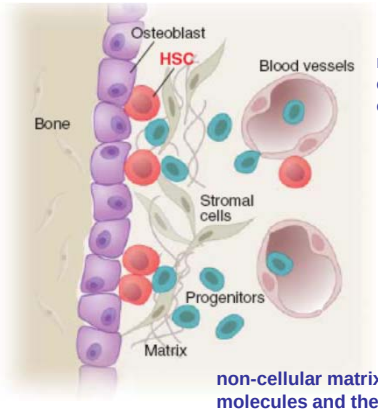
Extrinsically

hematopoietic cytokine signaling Influences cell fate

Gabriela M. Baerlocher 27.04.2017

Hematopoietic Environment

hematopoietic stem and progenitor cells and their progeny



non-hematopoietic cellular components of the environment

non-cellular matrix molecules and their complex supportive structures

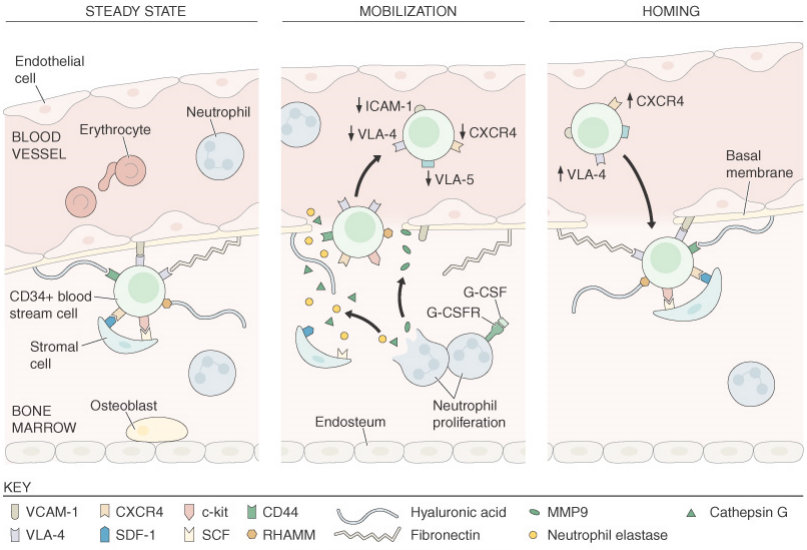
Gabriela M. Baerlocher 27.04.2017

Hematopoietic Cytokines

TABLE 1–1. Hematopoietic Cytokines

Cytokine	Site(s) of Production	Predominant Action(s)	Deficiency State
Erythropoietin	Kidney	Erythropoiesis	Anemia
Thrombopoietin	Liver	Megakaryocytopoiesis	Thrombocytopenia
Interleukin (IL)-11	Stromal cells	Megakaryocytopoiesis and erythropoiesis, acts in synergy with multiple other cytokines	None known
Granulocyte colony-stimulating factor (G-CSF)	Endothelial cells, monocytes, macrophages	Myelopoiesis; granulocyte differentiation	Neutropenia
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Endothelial cells, T cells, mast cells	Myelopoiesis; eosinophil differentiation	Infection diathesis with intracellular organisms
Stem cell factor (SCF)	Stromal cells, endothelial cells, fibroblasts	Proliferation and differentiation of primitive hematopoietic stem cells (HSCs); mast cell differentiation	Anemia and reduced stem cell content
Fetal liver tissue (FLT)-3 ligand	Stromal cells, spleen, and widely	Early hematopoiesis; synergizes with other cytokines	Decreased pre- and pro-B cells
IL-1 (two forms, α and β)	Most tissues	Pyrogenic factor; inflammatory response mediator through induction of multiple other cytokines	IL-1β demonstrates impaired febrile responses
Tumor necrosis factor (TNF)-α	B cells, natural killer (NK) cells, macrophages	Inflammatory response mediator through induction of multiple other cytokines	Lack of splenic primary B-cell follicles, follicular dendritic cell (FDC) networks, germinal centers
IL-6	Endothelial cell, T cells, macrophages	Early hematopoiesis; synergizes with other cytokines; dampens inflammation; autocrine and paracrine factor in multiple myeloma	Impaired immune and acute-phase reactions
IL-5	T cells, mast cells	Proliferation and differentiation of primitive HSCs	None known
IL-7	Stromal cells, spleen, thymus	Lymphopoiesis	Lymphopenia
IL-2	T cells	T-cell proliferation and function	Immunoproliferative syndrome
IL-15	Monocytes, macrophages, stromal cells	T-cell proliferation and function, overlap with IL-2	Absent $V\gamma5^+$ fetal thymic and dendritic epidermal T cells
IL-4	T cells	B-cell proliferation	Impaired mucosal immunity
IL-10	T cells, activated B cells	Inhibition of T_H1 cytokines with resulting immune suppression	Lethal immune responses to infection, autoimmune bowel disease
IL-12	Mononuclear phagocytes	Differentiation of naive helper T cells to T_H1 cells; stimulation of proliferation and activity of NK cells	Defective type 1 cytokine responses

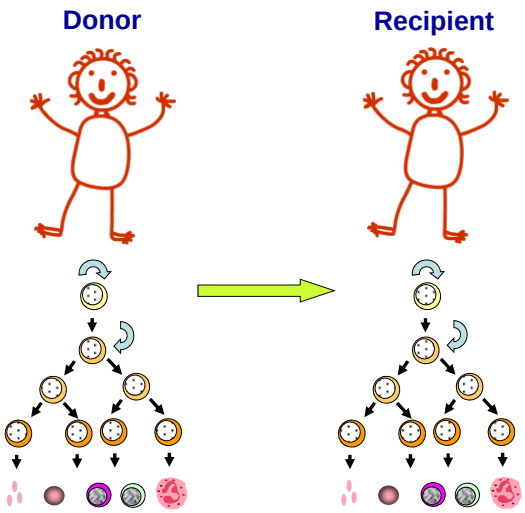
HSC Mobilization and Homing



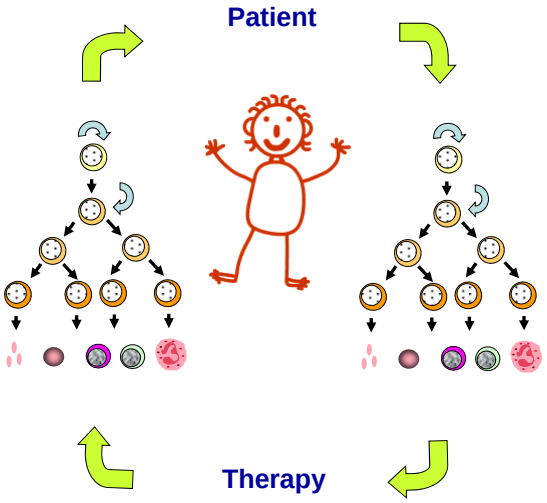
Outline

- Hematopoiesis
- Hematopoietic Stem Cell Transplantation
  - allogeneic
  - autologous

Allogeneic Transplantation

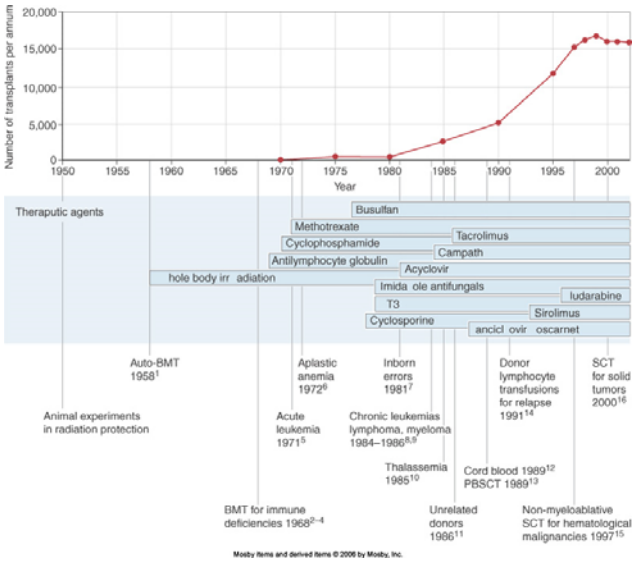


Autologous Transplantation



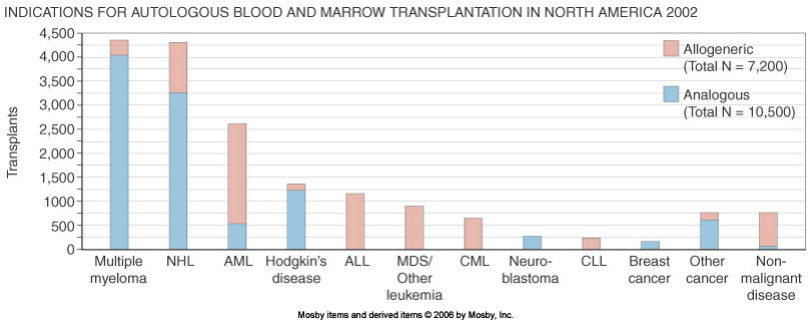
Gabriela M. Baerlocher 27.04.2017

Milestones in HSCT



Gabriela M. Baerlocher 27.04.2017

Indications for HSCT



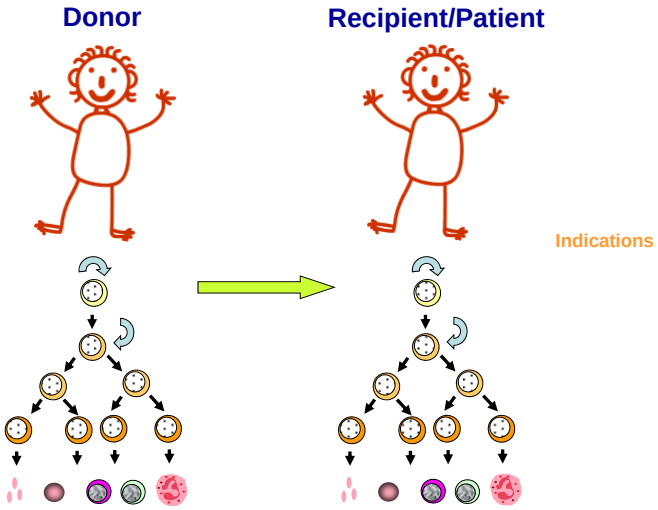
Gabriela M. Baerlocher 27.04.2017

Outline

- **Hematopoiesis**
- **Hematopoietic Stem Cell Transplantation**
  - **allogeneic**
  - **autologous**

Gabriela M. Baerlocher 27.04.2017

Allogeneic Transplantation



Gabriela M. Baerlocher 27.04.2017

Indications for Allo-HSCT

Box 94–1. Diseases Treated by Stem Cell Transplantation (SCT)

Corrected by SCT

Immune Deficiencies

- Severe combined immune deficiency disease (SCID), SCID with adenosine deaminase deficiency, Wiskott-Aldrich syndrome, lymphocyte function-associated antigen-1 deficiency, reticular dysgenesis, other rare T-cell disorders
- Chronic granulomatous disease, congenital neutropenia, Chédiak-Higashi syndrome, other rare granulocyte disorders
- Chronic Epstein-Barr virus infection

Bone Marrow Disorders

- Aplastic anemia
- Fanconi's aplastic anemia
- Dyskeratosis congenita
- Schwachman-Diamond syndrome
- Histiocytoses
- Osteopetrosis

Red Cell Disorders

- Thalassemia syndromes
- Sickle cell anemia
- Diamond-Blackfan syndrome
- Pure red cell aplasia
- Paroxysmal nocturnal hemoglobinuria
- Dyserythropoietic anemias
- Sideroblastic anemia
- Severe inherited and acquired hemolytic anemias
- Congenital erythropoietic porphyria

Platelet Disorders

- Glanzmann's thrombasthenia
- Congenital amegakaryocytic thrombocytopenia

Metabolic Disorders

- Mucopolysaccharidoses: type I (Hurler), type V (Maroteaux-Lamy)
- GM_1 gangliosidosis, metachromatic leukodystrophy
- Cerebrosidosis types 1, 2, and 3 (Gaucher)

Not Corrected by SCT

Variable or No Significant Benefit—Not Standard Indications for SCT

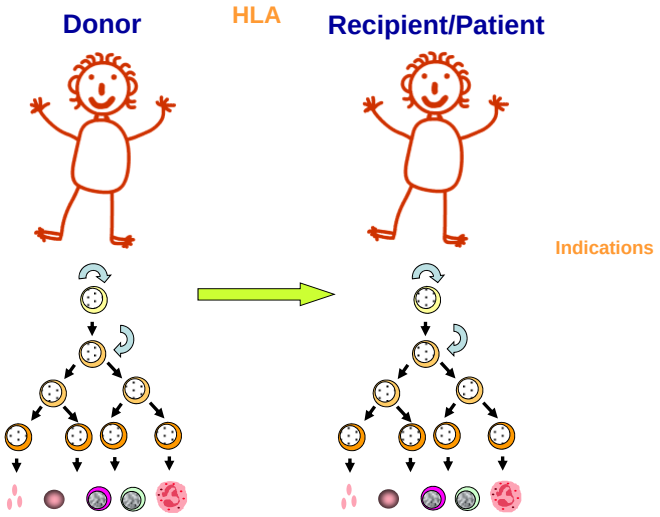
- Mucopolysaccharidosis type II (Hunter syndrome), type III (San Filippo disease), type IV (Morquio disease)
- Osteogenesis imperfecta

No Benefit

- Hypoxanthine-guanine phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome)
- Type IIA glycogen storage disease (Pompe's disease)
- Niemann-Pick disease
- Infantile globoid cell leukodystrophy (Krabbe's disease)

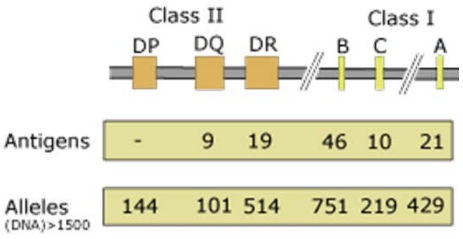
Gabriela M. Baerlocher 27.04.2017

Allogeneic Transplantation



Gabriela M. Baerlocher 27.04.2017

Human Leukocyte Antigens (HLA)

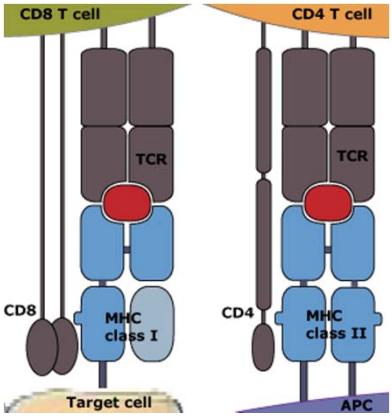


Schematic representation of HLA class I and II loci in the MHC that comprises >200 genes on the short arm of chromosome 6. The corresponding number of antigens (as defined by serology) and alleles (as defined by nucleotide sequence) are indicated for each locus.

Gabriela M. Baerlocher 27.04.2017

http://medweb2.unige.ch/immunologie/

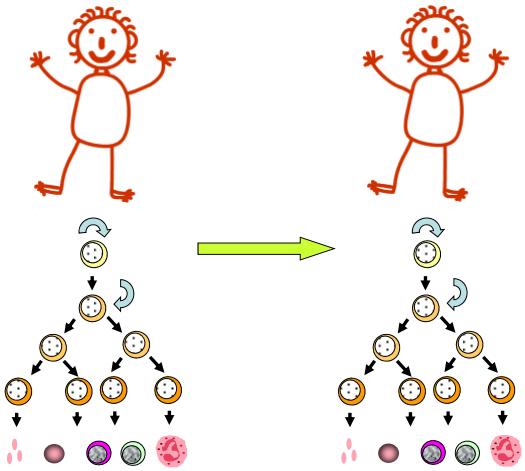
Human Leukocyte Antigens (HLA)



http://medweb2.unige.ch/immunologie/

Allogeneic Transplantation

Donor HLA Recipient/Patient



Sources of Stem Cells

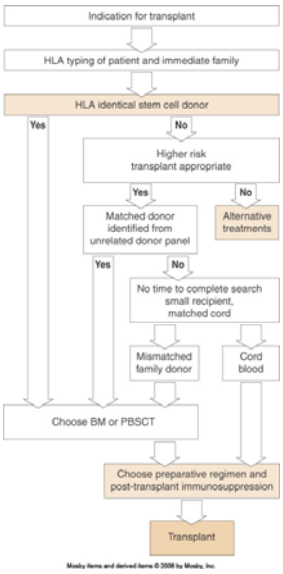
Indications

Sources of Stem Cells

Bone Marrow	Peripheral Blood	Cord Blood
• donation requires surgery under general anesthesia; growth factors	• donation requires apheresis and growth factors	• donation poses no risk to mother and infant
• larger dose of stem cells/rapid engraftment	• larger dose of stem cells/rapid engraftment	• smaller dose of stem cells/slower engraftment
• after a formal search is begun, takes average of 4 months to transplant, if a donor is available	• after a formal search is begun, takes average of 4 months to transplant, if a donor is available	• when a match is found, can take only a few days for confirmatory and special testing and shipment to the Transplant Center
• donor may be available to give a second transplant or to donate T-cells if necessary	• donor may be available to give a second transplant or to donate T-cells if necessary	• donor is not available for a second transplant
• must be used fresh	• can be stored frozen for over 10 years	• can be stored frozen for over 10 years
• latent viral infection in the donor common (CMV > 50%)	• latent viral infection in the donor common (CMV > 50%)	• latent viral infection in the donor rare (CMV < 1%)
• severe GVHD common	• severe GVHD common	• GVHD less frequent and usually less severe
• generally requires a perfect match between donor and recipient for 6/6 HLA-A, -B and DRB1 antigens	• generally requires a perfect match between donor and recipient for 6/6 HLA-A, -B and DRB1 antigens	• HLA-mismatched cord blood transplants are possible, making it easier to find a suitable match

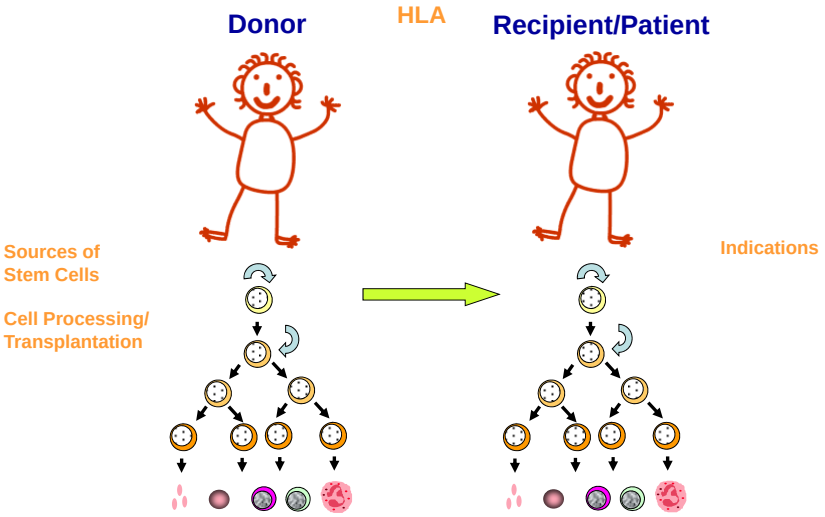
Gabriela M. Baerlocher 27.04.2017

Decision Tree for Allo-HSCT



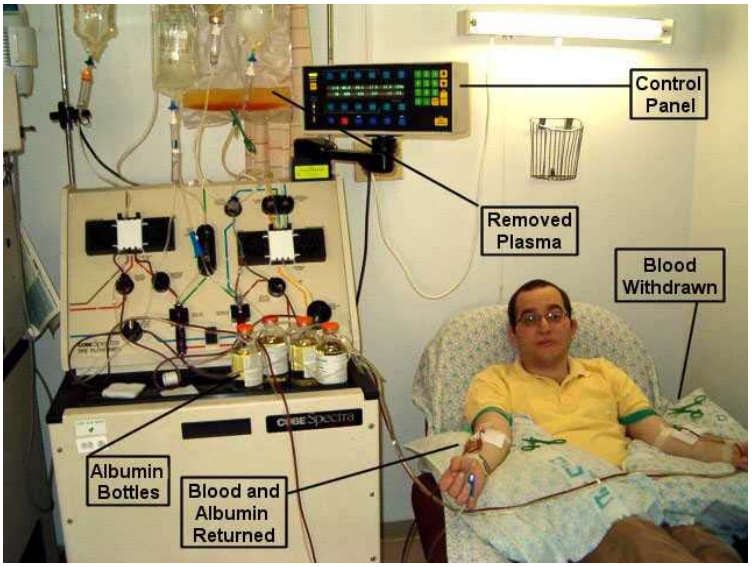
Gabriela M. Baerlocher 27.04.2017

Allogeneic Transplantation



Gabriela M. Baerlocher 27.04.2017

Stem Cell Collection



Gabriela M. Baerlocher 27.04.2017

Stem Cell Selection

Gabriela M. Baerlocher 27.04.2017

Stem Cell Freezing

Gabriela M. Baerlocher 27.04.2017

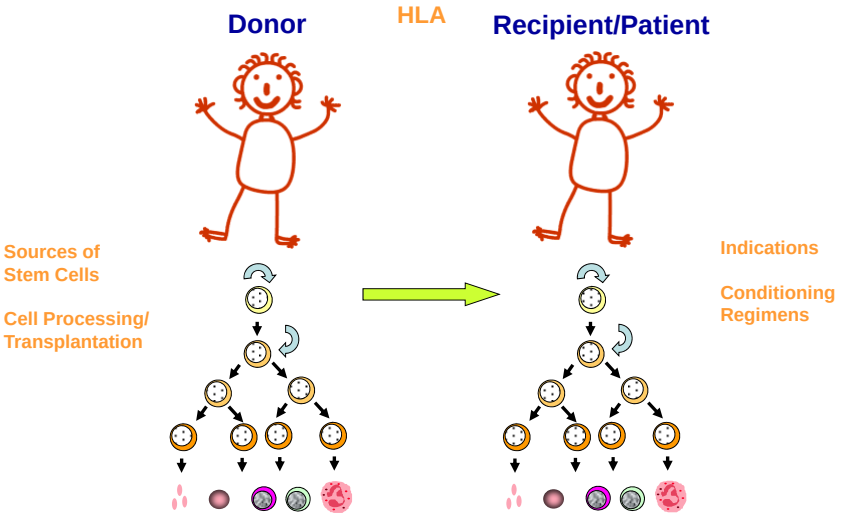
Stem Cell Thawing

Gabriela M. Baerlocher 27.04.2017

Stem Cell Transplantation

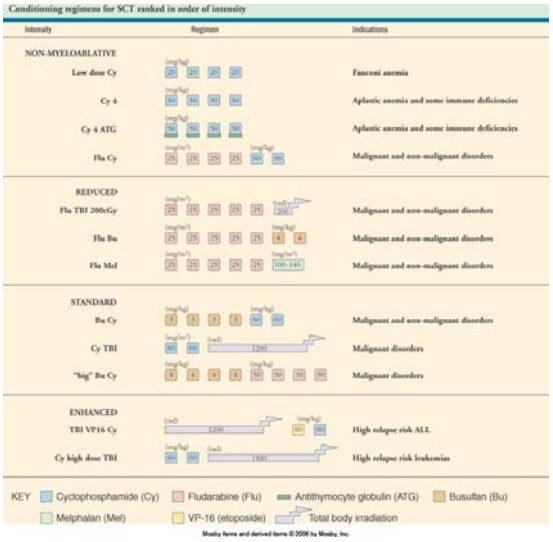
Gabriela M. Baerlocher 27.04.2017

Allogeneic Transplantation



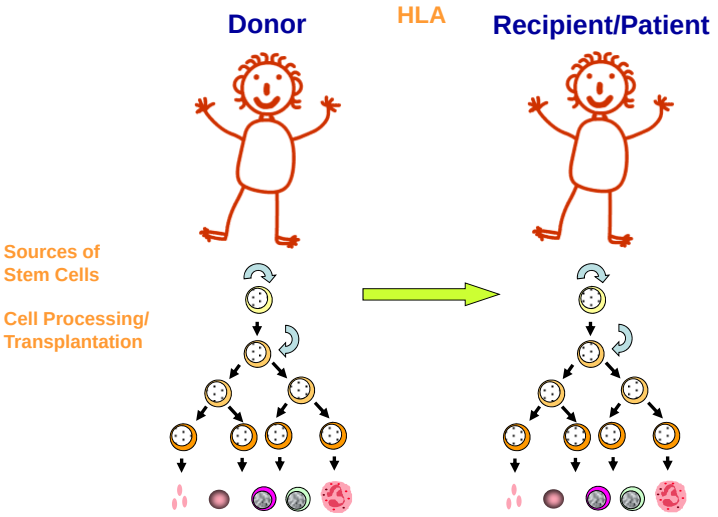
Gabriela M. Baerlocher 27.04.2017

Conditions for Allo-HSCT



Gabriela M. Baerlocher 27.04.2017

Allogeneic Transplantation



Sources of Stem Cells

Cell Processing/ Transplantation

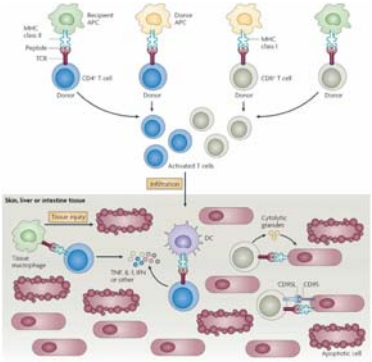
Indications

Conditioning Regimens

Preventing GVHD

Gabriela M. Baerlocher 27.04.2017

GVHD

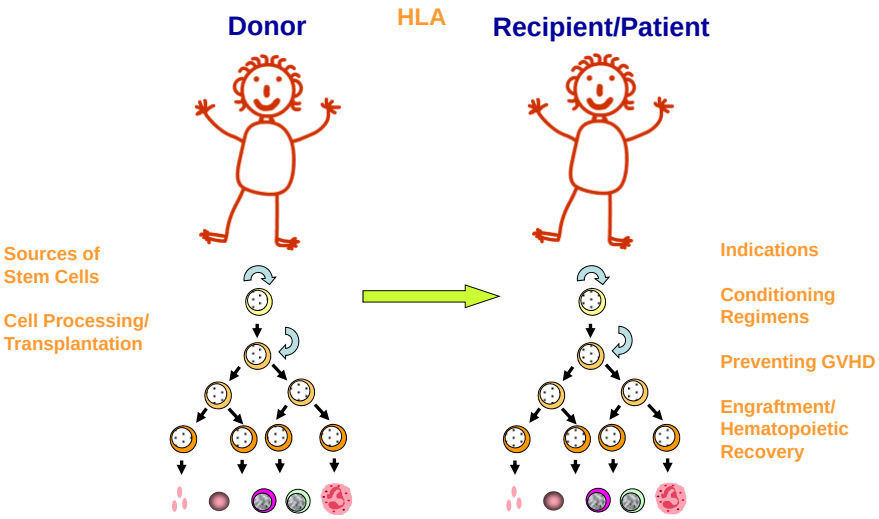


Nature Reviews Immunology 2007, 7:340-52

- presence of immunologically competent cells in the graft
- the recipient is unable to mount an effective response to destroy the transplanted cells
- the donor and recipient express different histocompatibility antigens

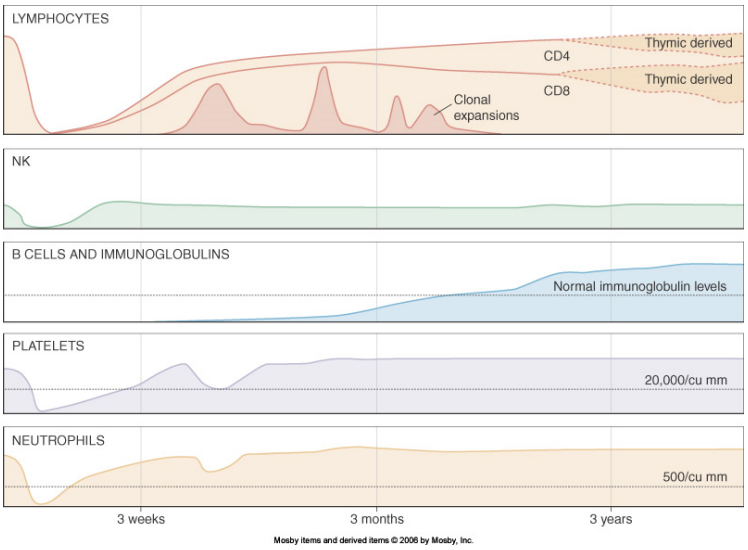
Gabriela M. Baerlocher 27.04.2017

Allogeneic Transplantation



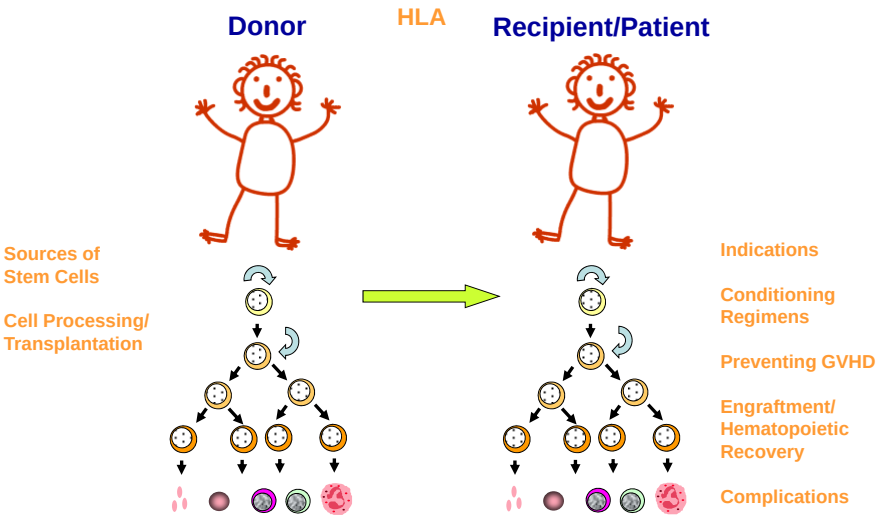
Gabriela M. Baerlocher 27.04.2017

Kinetics of Cell Recovery after Allo-HSCT



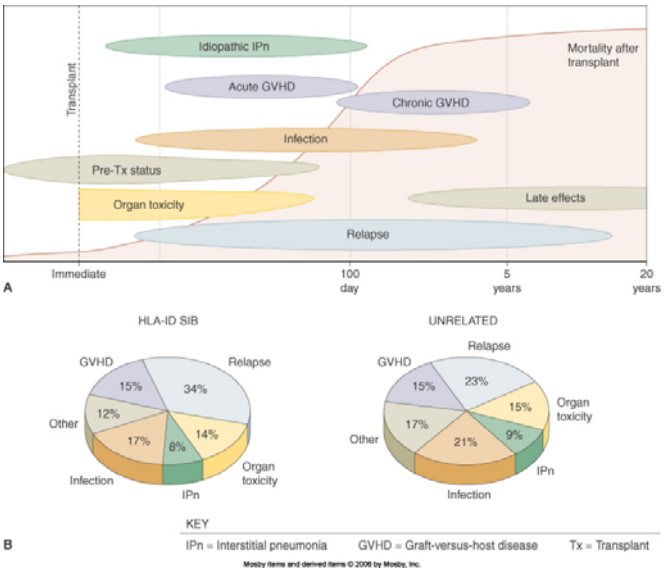
Gabriela M. Baerlocher 27.04.2017

Allogeneic Transplantation



Gabriela M. Baerlocher 27.04.2017

Complications after Allo-HSCT



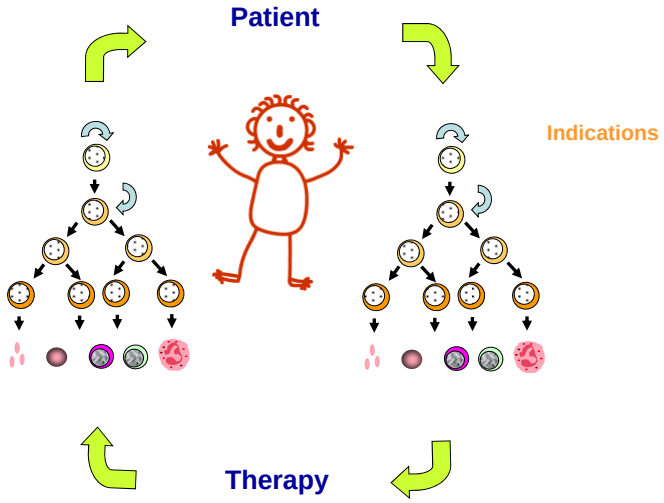
Gabriela M. Baerlocher 27.04.2017

Outline

- Hematopoiesis
- Hematopoietic Stem Cell Transplantation
  - allogeneic
  - autologous

Gabriela M. Baerlocher 27.04.2017

Autologous Transplantation



Gabriela M. Baerlocher 27.04.2017

Indications for Auto-HSCT

Box 95–1. Evidence-Based Indications for Autologous Stem Cell Transplantation

Level 1: At Least One Comparative Clinical Trial Shows Survival Benefit

- Multiple myeloma
- Intermediate-grade non-Hodgkin's lymphoma (NHL)
- Hodgkin's disease

Level 2: Multiple Noncomparative Trials Consistently Show Survival Benefit (standard of care)

- Germ cell cancer
- Neuroblastoma
- Acute myeloid leukemia
- Amyloidosis
- Low-grade NHL

Level 3: Multiple Noncomparative Trials Show Promise for Survival Benefit

- Acute lymphocytic leukemia
- High-grade NHL
- Mantle cell lymphoma
- Ovarian cancer

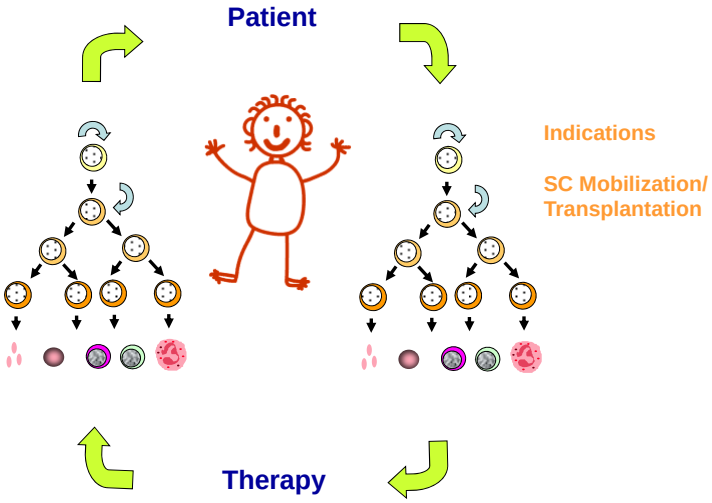
Level 4: Small Series and Case Reports Suggest Possible Survival Benefit

- Primitive neuroectodermal tumors
- Autoimmune disease
- Chronic myeloid leukemia
- Chronic lymphoid leukemia
- Small-cell lung cancer

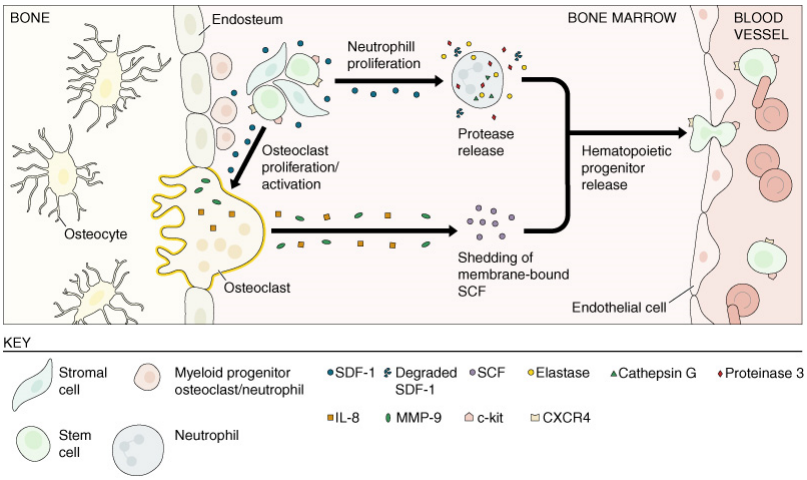
Level 5: Numerous Series Show No Clear Survival Benefit

- Breast cancer
- Glioma

Autologous Transplantation



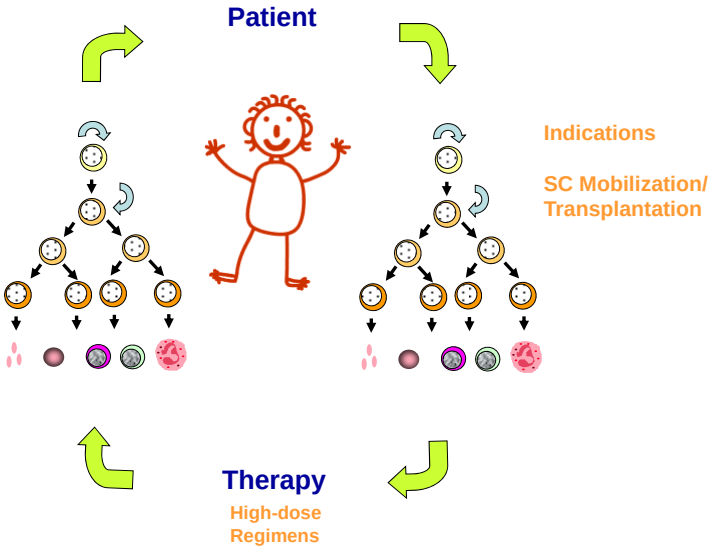
HSC Mobilization



(From Cottler-Fox MH, Lapidot T, Petit I, et al: Stem cell mobilization. Hematology [Am Soc Hematol Educ Program] 419–437, 2003, with permission.)

Gabriela M. Baerlocher 27.04.2017

Autologous Transplantation



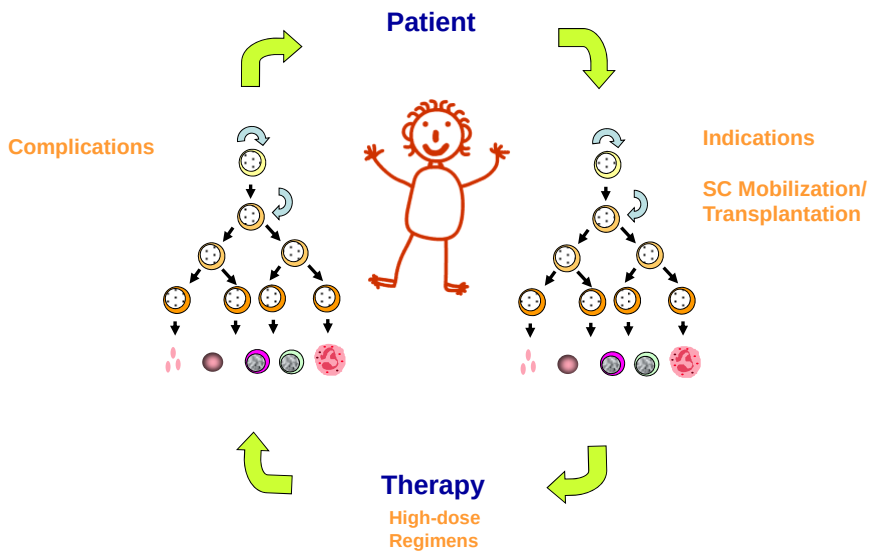
Gabriela M. Baerlocher 27.04.2017

High-dose Regimens

TABLE 95–1. Agents Used in High-Dose Therapy Regimens with Dose-Limiting Toxicity

Agent	Dose-Limiting Toxicity
Total-body irradiation	Mucositis, hepatitis, pneumonitis
Busulfan	Mucositis, hepatitis, pneumonitis
Carmustine (BCNU)	Pneumonitis, hepatitis
Melphalan	Mucositis
Thiotepa	Encephalopathy, mucositis
Cyclophosphamide	Myocarditis
Ifosfamide	Cystitis, encephalopathy
Etoposide	Mucositis
Carboplatin	Neuropathy, hepatitis, renal failure

Autologous Transplantation



Complications after Auto-HSCT

Box 95–4. Common Toxicities Associated with Hematopoietic Stem Cell Infusion

- Anaphylactic/allergic reaction
- Histamine release
  - Hypotension
  - Skin flushing
  - Dyspnea
  - Abdominal cramps
  - Nausea
  - Diarrhea
- Cardiovascular effects
  - Hypertension
  - Bradycardia
  - Heart block
- Headache
- Hemoglobinuria

Summary

- **Hematopoiesis occurs in a specialized bone marrow microenvironment, composed of cellular and non-cellular elements critical to localization and control of blood cell production**
- **Hematopoietic stem cells can be defined by the expression pattern of specific cell surface proteins, cell cycle quiescence, and telomerase activity**
- **The process of stem cell mobilization and homing are governed by modulation of interactions between primitive hematopoietic cells and their microenvironment**

Summary

- Allogeneic bone marrow transplantation involves transfer of stem cells and lymphocytes from bone marrow, peripheral blood, or umbilical cord blood
- Bone marrow transplantation is used to treat a wide spectrum of hematologic malignancies and non-malignant hematologic disorders as well as rare inborn errors of metabolism and storage diseases
- Progress in understanding allograft immunology and stem cell biology and the introduction of new antimicrobial and immunosuppressive agents over the last 30 years has resulted in continuing improvement in transplant outcome
- Major limitations are availability of suitably matched donors, complications of GVHD, slow recovery of immune function, and recurrence of advanced malignant diseases after transplant

Summary

- Autologous hematopoietic stem cell transplantation is based on the dose-response relationship of many chemotherapy agents and radiation: the greater the dose, the greater the response. Infusion of autologous stem cells allows for substantial dose escalation of these agents
- Successful autologous stem cell transplantation requires proper patient selection, adequate stem cell harvest, processing and storage, appropriate high-dose therapy, intravenous stem cell reinfusion and supportive care and follow-up
- Autologous stem cell transplantation improves survival for selected groups of patients with multiple myeloma, non-Hodgkin‘s and Hodgkin‘s lymphoma, acute myeloid leukemia and germ cell cancer

Literature

http://edweb2.unige.ch/immunologie/

Clinical Hematology by N.S. Young, S.L. Gerson, K.A. High
Mosby, Elsevier