Stem cell transplantation

Contents

History of HSCT

Mouse

Dog

Human patients

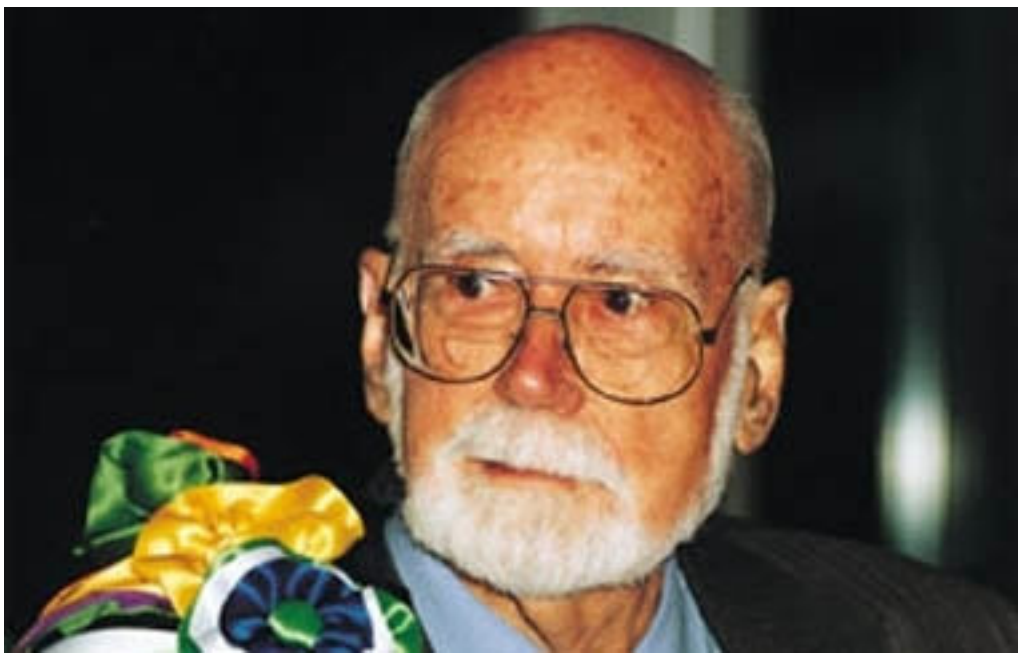
- 1959–1963 : first allogeneic HSCT in humans

First successful bone marrow transplant

- 1956
- Dr E Donnall Thomas in New York
- Patient- leukaemia
- Donor-identical twin

The Nobel Prize, 1990

E. Donnall Thomas

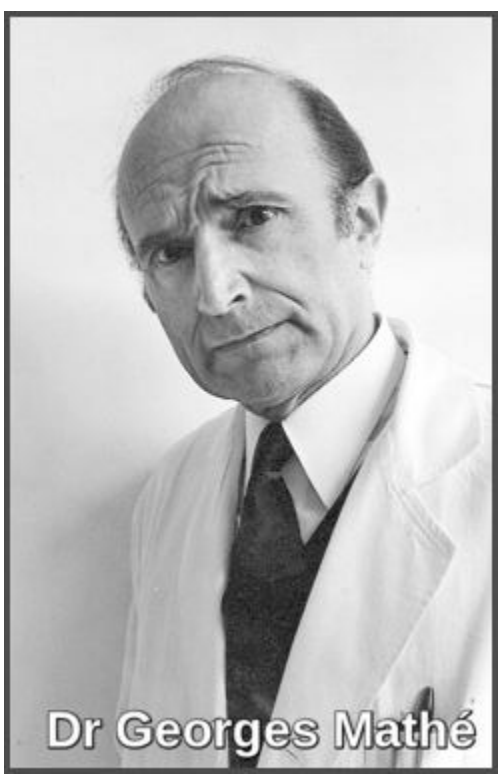


first succsessful HSCT in treatment of acute leukemias

Thomas ED, Lochte HL, Lu WC, Ferrebee JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. N. Engl. J. Med. 1957; 257: 491.

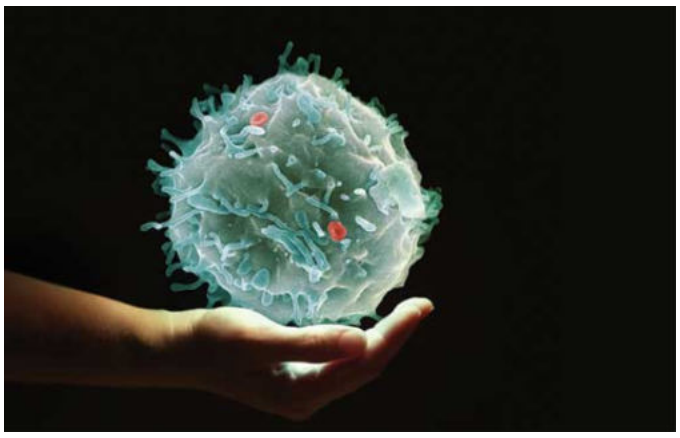
1958

- Dr Georges Mathé
- Defined the 'graft versus host' disease



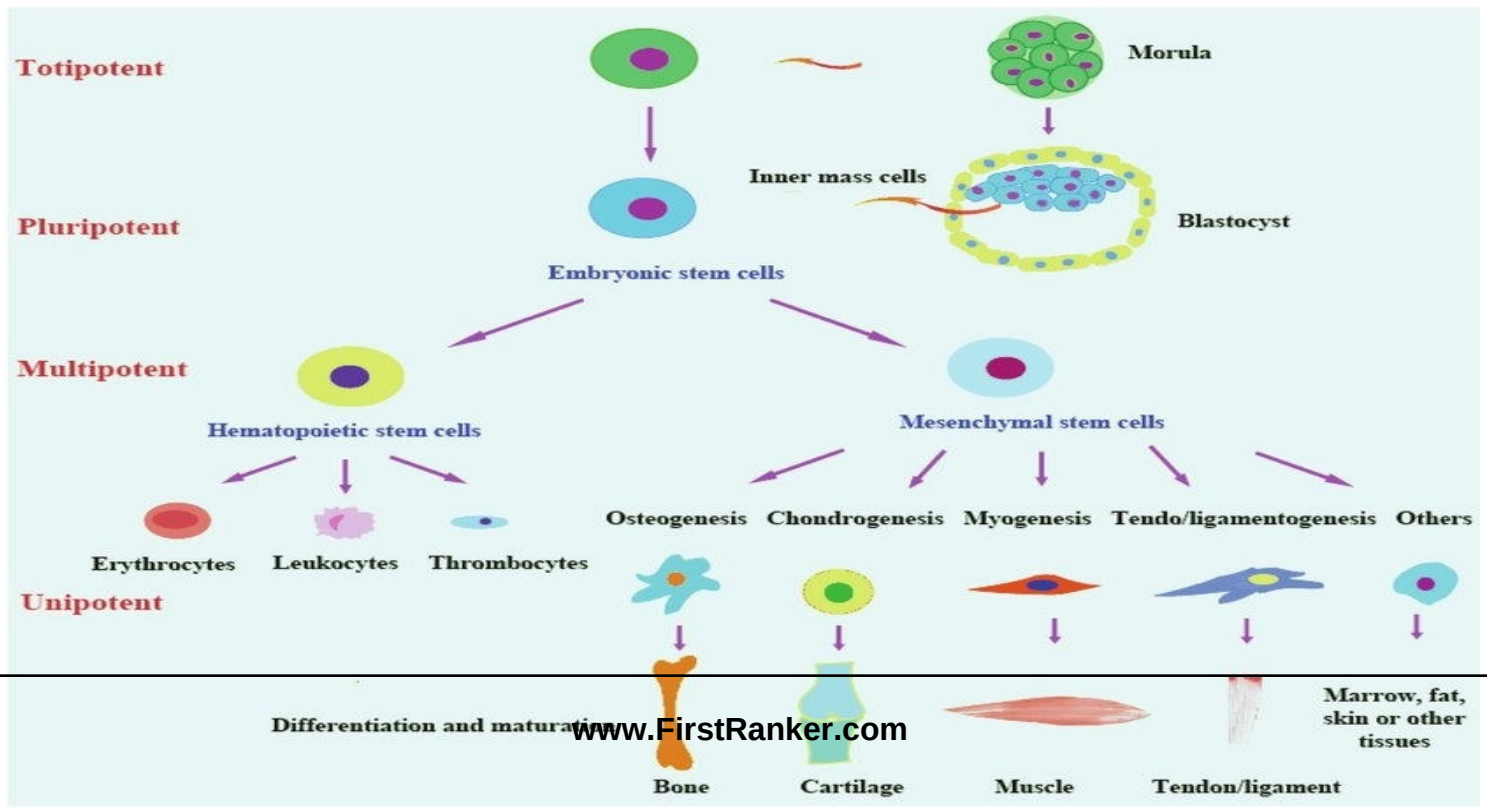
1968

- Major landmark year for BMT in immunodeficiency disorders
  - Children with X-linked lymphopenic immune deficiency
  - Wiskott-Aldrich syndrome
  - Aplastic anemia



Stem cells

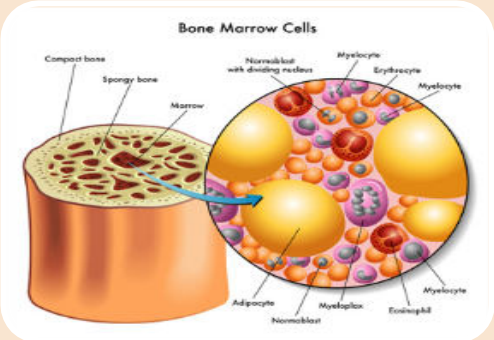
- **undifferentiated cells which are able**
  - **to divide for indefinite period**
  - **to self renew**
  - **to generate a functional progeny of highly specialised cells**

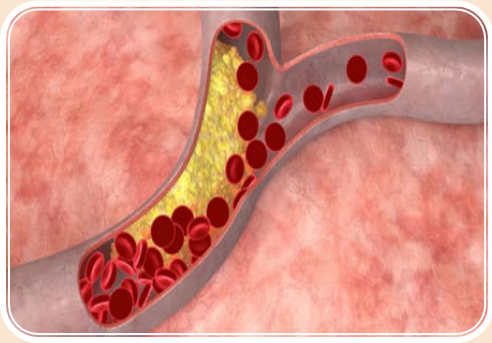


HSCT

- **Allogeneic HSCT**
  - Syngeneic-identical twin
  - from sibling/related donor
  - from unrelated donor
- **Autologous HSCT**

Sources of stem cells



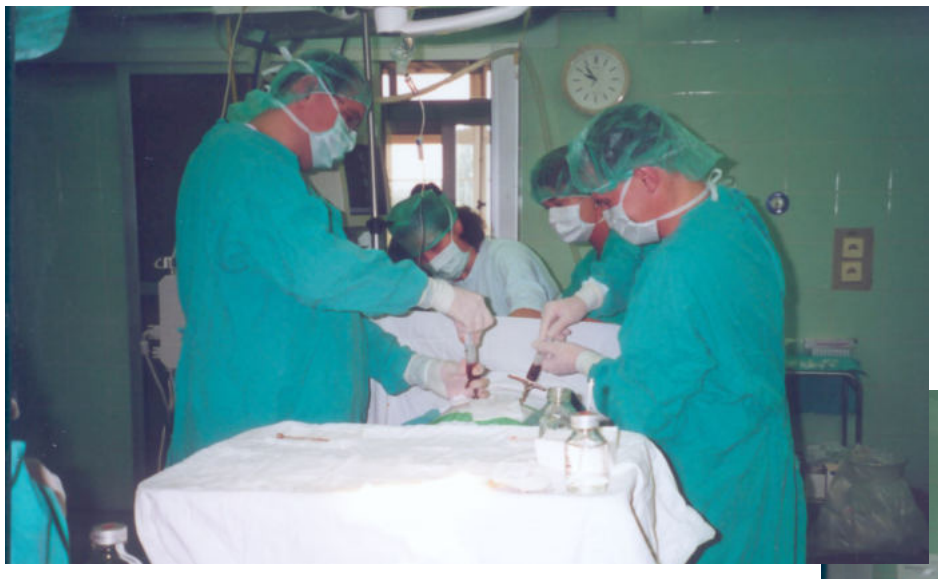


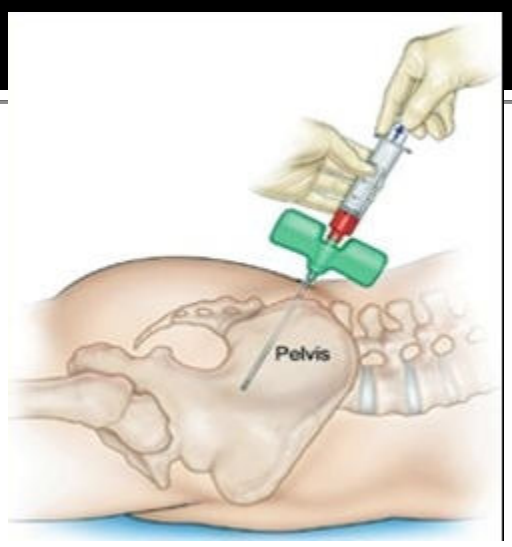
Bone marrow

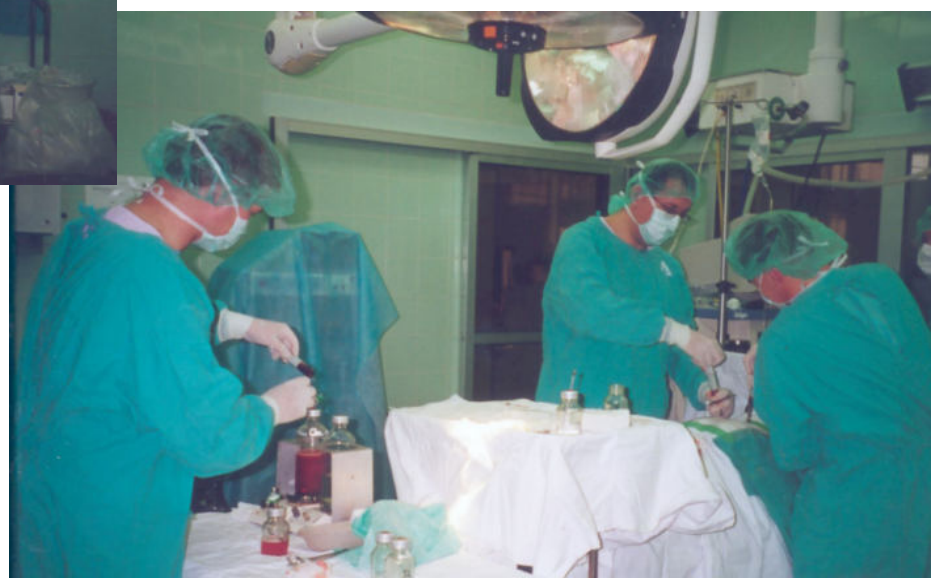
Peripheral blood

Umbilical cord blood

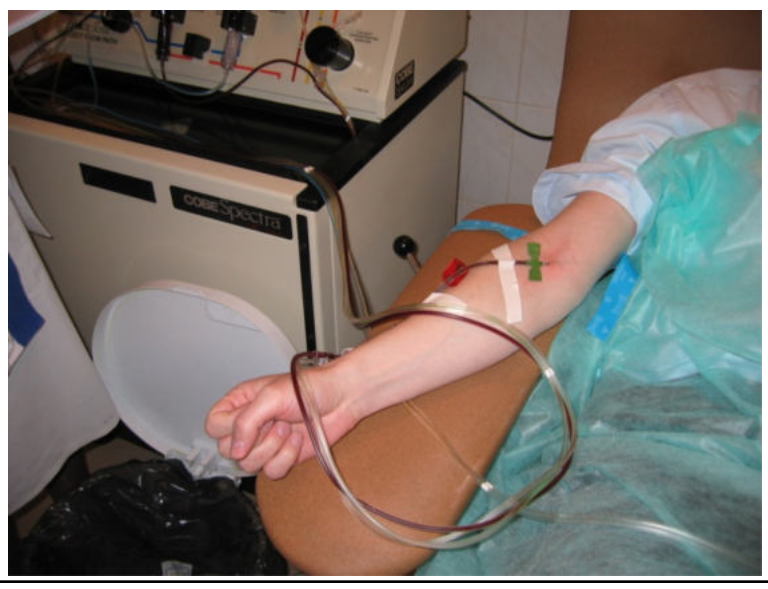
Bone marrow







Peripheral blood



Umbilical Cord

Umbilical Cord Blood

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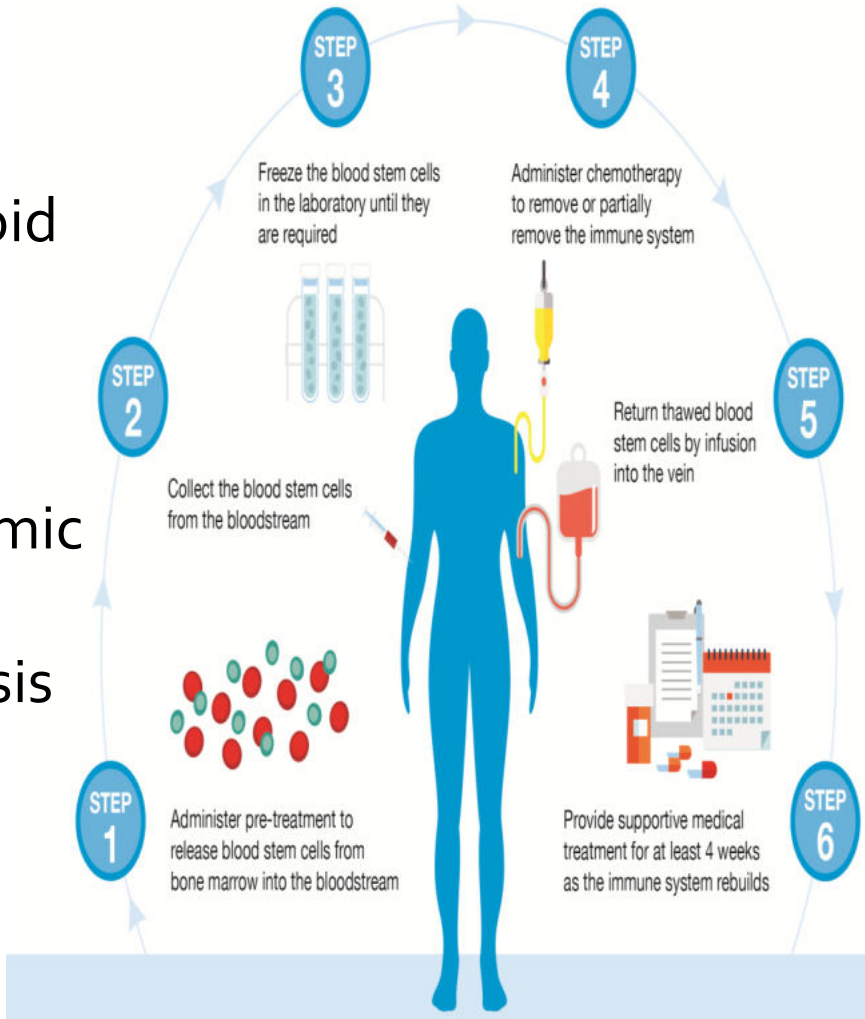
Placental blood directly drained into bag

Indications for HSCT

- **Neoplastic disorders**
  - Hematological malignancies
    - Lymphomas
    - Leukemias
    - Multiple myeloma
  - Solid tumors
- **Non-neoplastic disorders**
  - Aplastic anemia
  - Autoimmune diseases
  - Immunodeficiency
  - Inborn errors of metabolism

Indications -Autologous HSCT

- **Multiple myeloma**
- **Non-Hodgkin lymphoma**
  Hodgkin disease, Acute myeloid leukemia
- Neuroblastoma, Germ cell tumors
- Autoimmune disorders (systemic lupus erythematosus [SLE], systemic sclerosis), Amyloidosis



Indications - Allogeneic HSCT

- **Acute myeloid leukemia**
- **Acute lymphoblastic leukemia**
- **Chronic myeloid leukemia**
- **Chronic lymphocytic leukemia**
- Myeloproliferative disorders
- Myelodysplastic syndromes
- Multiple myeloma
- Non-Hodgkin lymphoma
- Hodgkin disease
- Aplastic anemia
- Pure red-cell aplasia
- Paroxysmal nocturnal hemoglobinuria
- Fanconi anemia
- **Thalassemia major**
- Sickle cell anemia
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome
- Hemophagocytic lymphohistiocytosis
- Inborn errors of metabolism
- Epidermolysis bullosa
- Severe congenital neutropenia
- Shwachman-Diamond syndrome
- Diamond-Blackfan anemia
- Leukocyte adhesion deficiency
- HSCT-related morbidity and mortality

Major steps

Selection of donor
Based on tissue typing -HLA antigens

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Harvest of stem cells from donor
Bone marrow harvest or pheresis of peripheral blood

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Preparative regimen
Chemo-radiation for ablation and immune suppression

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Stem cell infusion

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Post-transplant supportive care

Autologous 100 days	Allogeneic 180 days or longer

Stem cell donors

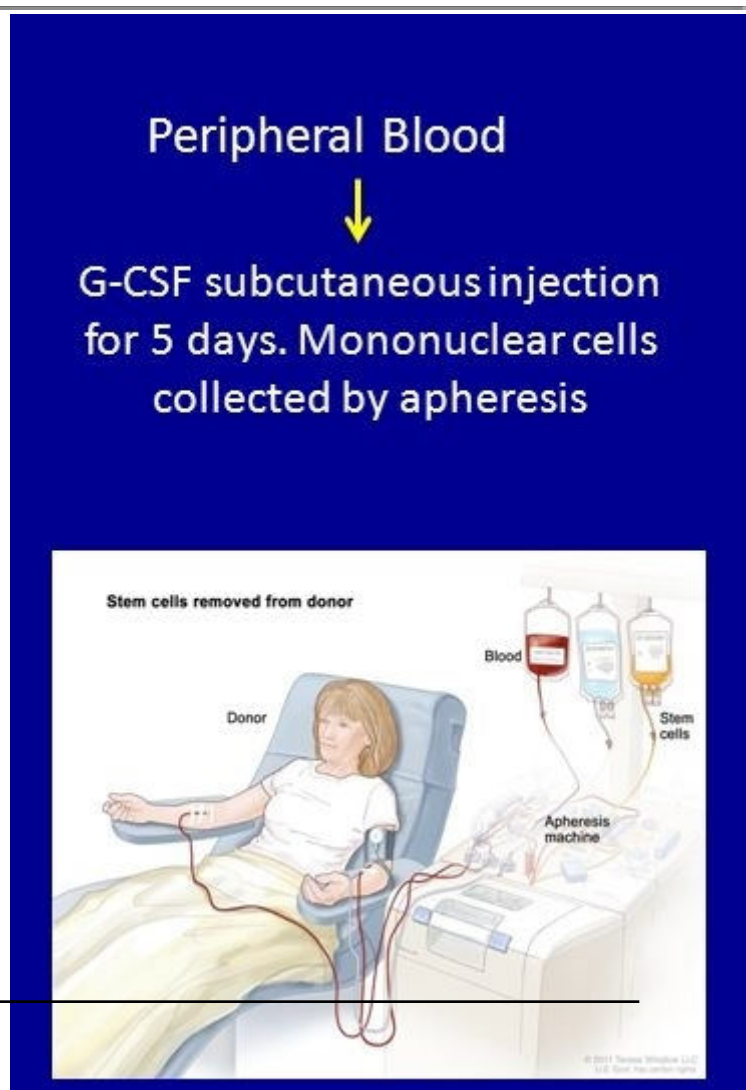
- Identical twins
- Matched related or unrelated donors
- Mismatched related donors
- Haploidentical donors
- Umbilical cord blood donors

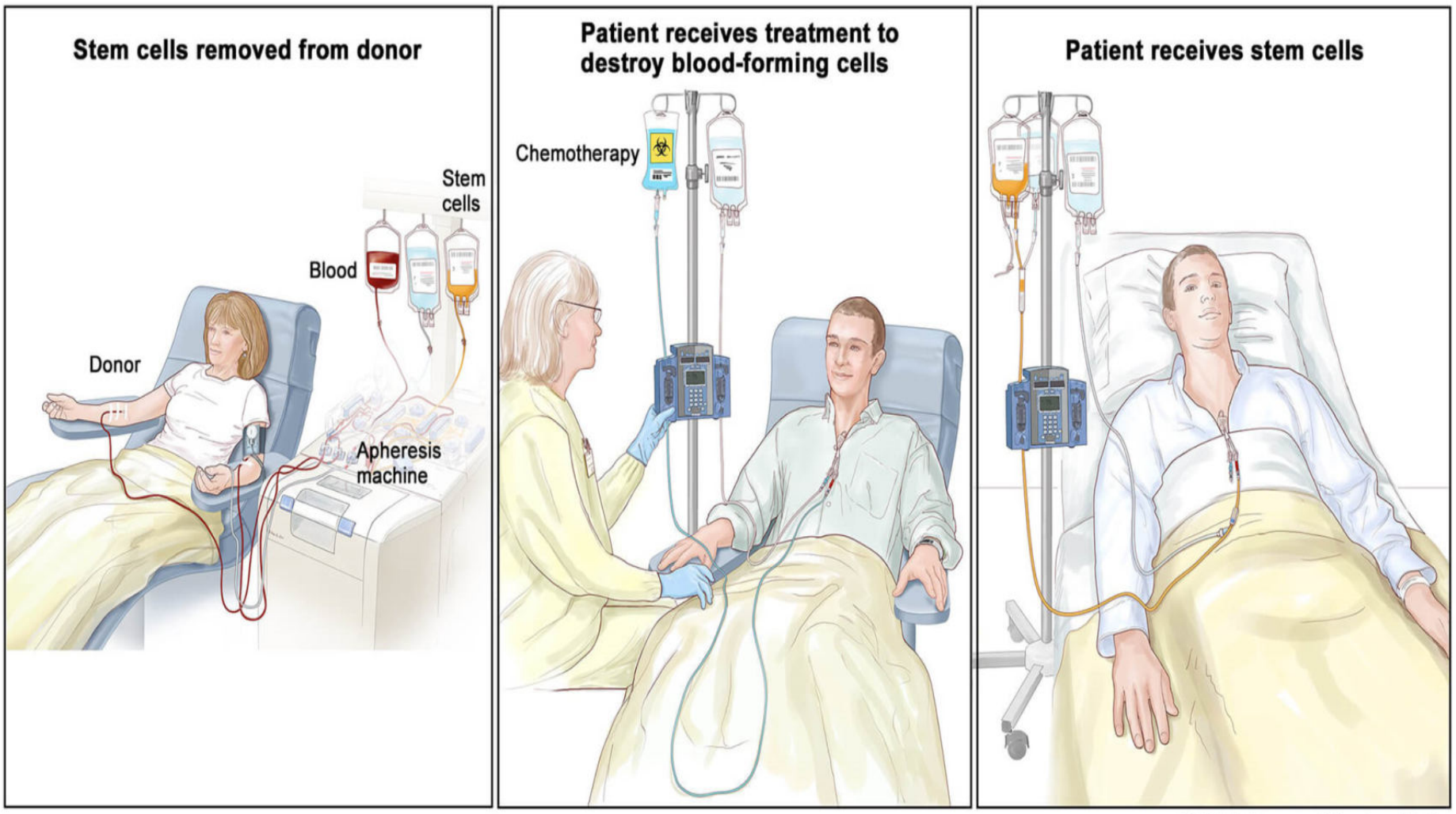
Donor selection

- History and physical examination
- Investigations
  - Serum creatinine, electrolyte, and liver function studies.
  - Serologic studies
    - cytomegalovirus (CMV), herpes virus, HIV RNA, anti-HIV antibodies, hepatitis B and C viruses, syphilis (VDRL)
  - ABO blood typing
  - Human leukocyte antigen (HLA) typing
  - Chest radiography
  - Electrocardiography (ECG)

Mobilization of stem cells

- Mobilization of peripheral blood **stem cells** (PBSC) in healthy volunteers with granulocyte colony-stimulating factor (**G-CSF**)





Stem cell procurement

- Amount of stem cells collected is based on recipients body weight
- Minimal number
  - 2 x 10^8/kg nucleated cells
  - 2 x 10^6/kg CD 34 + cells

Procedure

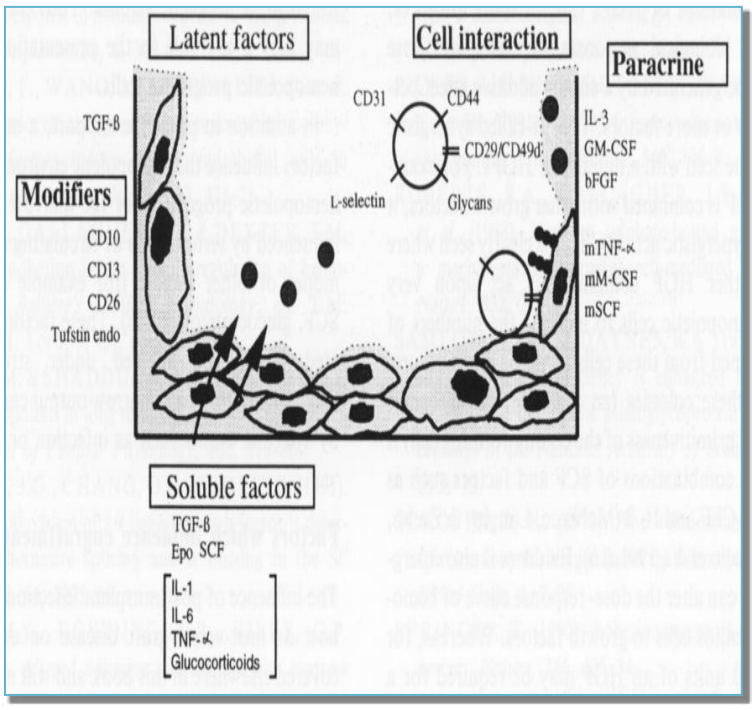
- Recipient undergoes myeloablative conditioning
  - high-dose radiotherapy and immunosuppressive agents

Recipient preparation

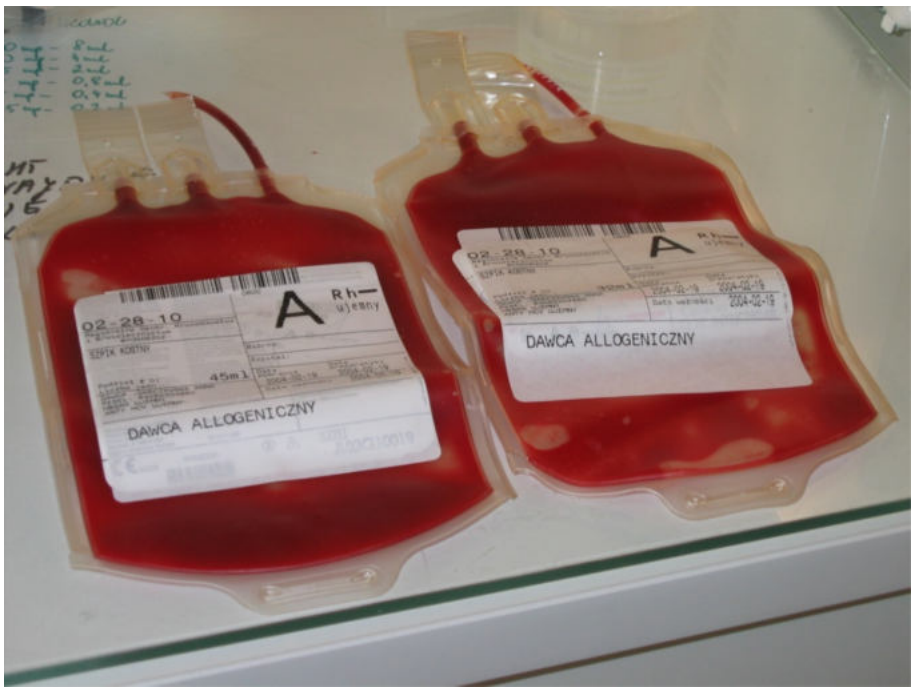
- Cyclophosphamide 60 mg/kg/day
  During two days and Toal body irradiation
- Busulfan 4mg/kg/day for four days and
  Cyclophosphamide without irradiation
- Etoposide ,Cytarabine as a maximizer antitumor properties,myeloblation,immunosuppression

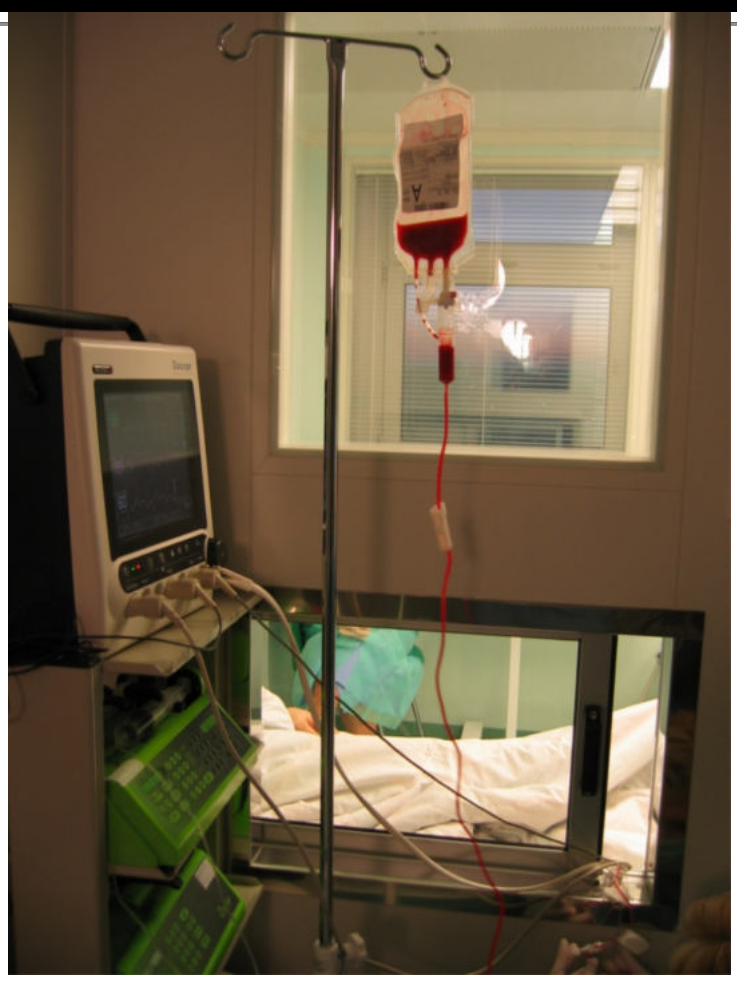
Procedure

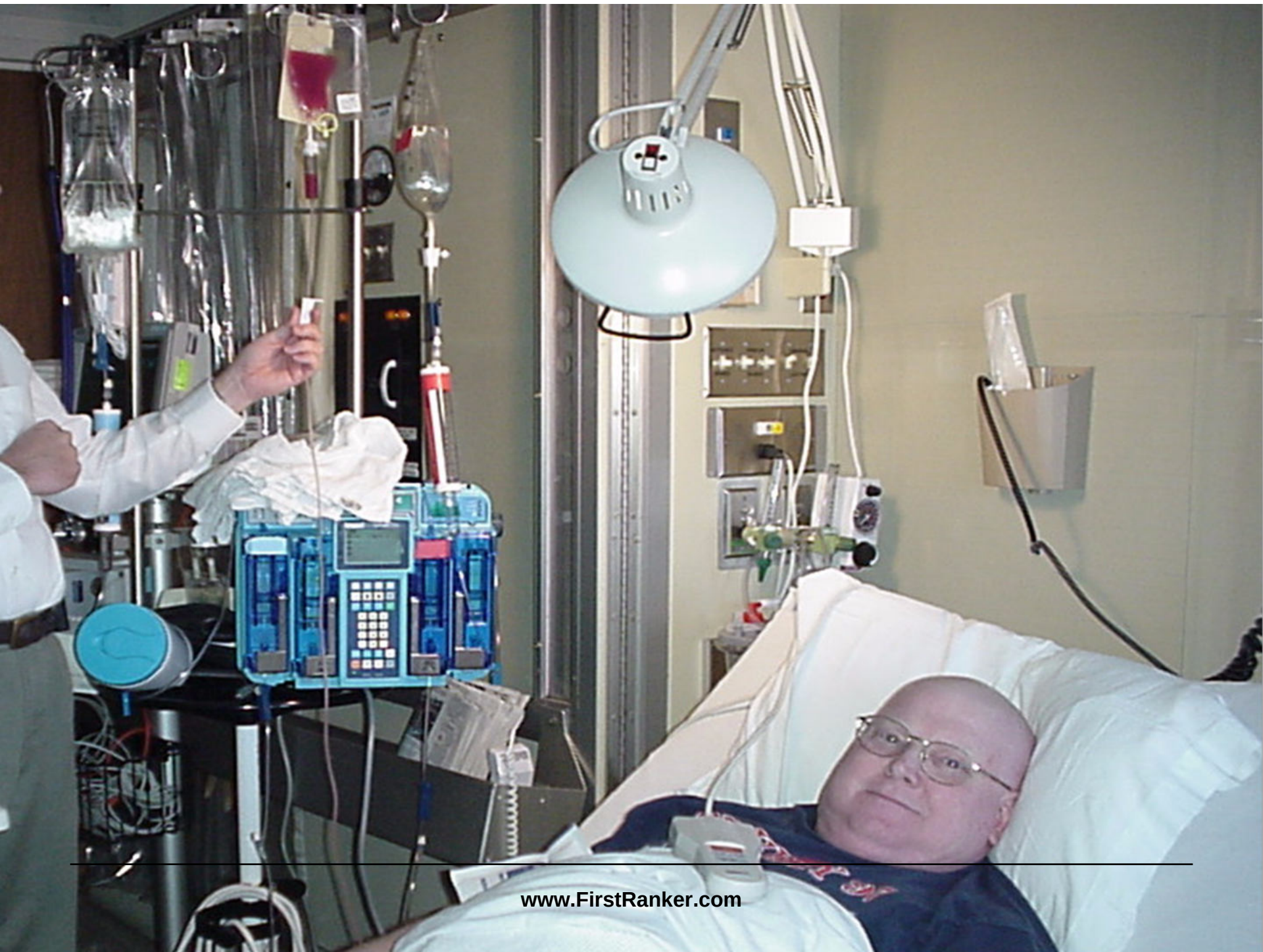
- Donor stem cells are infused
- Migrate to the bone marrow to repopulate the immune system
- "Home" to micro-environment niches in marrow and spleen



Hematopoietic stem cell infusion







Special Blood Requirement

- Irradiated
- CMV Negative
- Leukocyte-Reduced
- Saline-washed or volume reduced

ABO compatibility

- **Is not a MUST!!**
- **major or minor ABO incompatibility?**

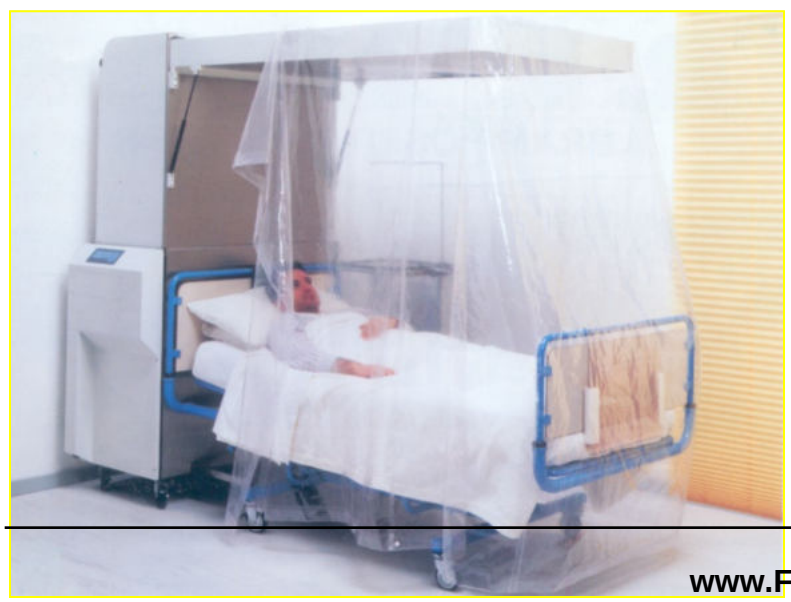
- **patient's /donor's antibody titers**

Post HSCT

- Infection prophylaxis is essential
  - Care in HEPA-filtered, positive-air-pressure accomodation, with strict hand hygiene
  - Antibacterial and antifungal prophylaxis

Bone marrow transplantation unit






Outcome is influenced by:

- **Stage of disease**
- **Patient - related factors:** age, comorbidity
- **Donor - related factors:** Histocompatibility (HLA)
- **Peri-transplant factors:**Conditioning
- **Post-transplant factors:**GVHD

Complications

- **Early**
  - Infection, aGVHD, bleeding, toxicity, graft failure
- **Late**
  - chGVHD, infection, relapse, gonadal failure, secondary malignancy, toxicity

Cord Blood

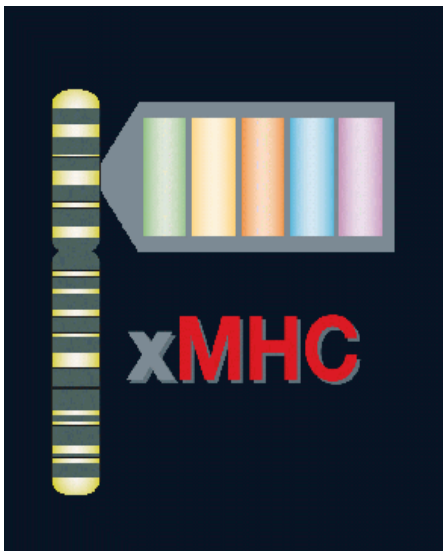
Less prone to rejection than either bone marrow or peripheral blood stem cells.

Limitations of Allogeneic HSCT

- Scarcity of suitable donors
- Graft versus Host Disease
- Infections

HLA Typing
Human Leukocyte Antigen

- HLA are proteins found on short arm of chromosome 6
- 3-antigens important in HSCT- one set of 3 from each parent
  - HLA-A
  - HLA-B
  - HLA-DR
- Brings to a total of six antigens to match
- A full match is "6/6" or "perfect" match



HLA or Tissue Typing

- Rate of GVHD

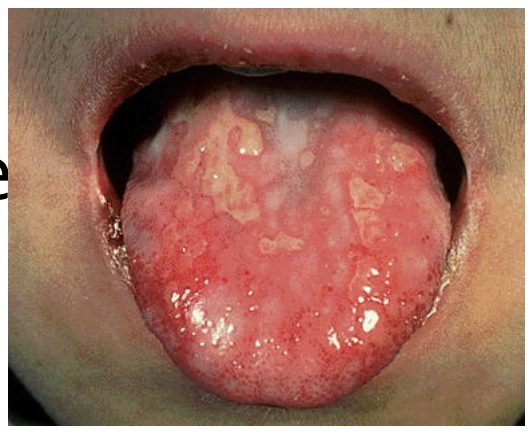
Donor	Incidence
6/6	40%
5/6	50%
4/6	80%
3/6	90%

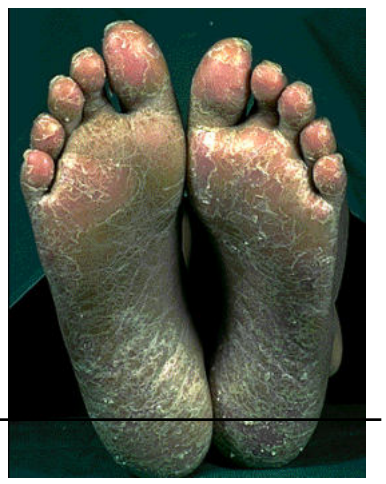
Graft-versus-host disease

- Donor immune cells attack recipient tissues, often skin, gut and liver.
- It can be very debilitating or even fatal.

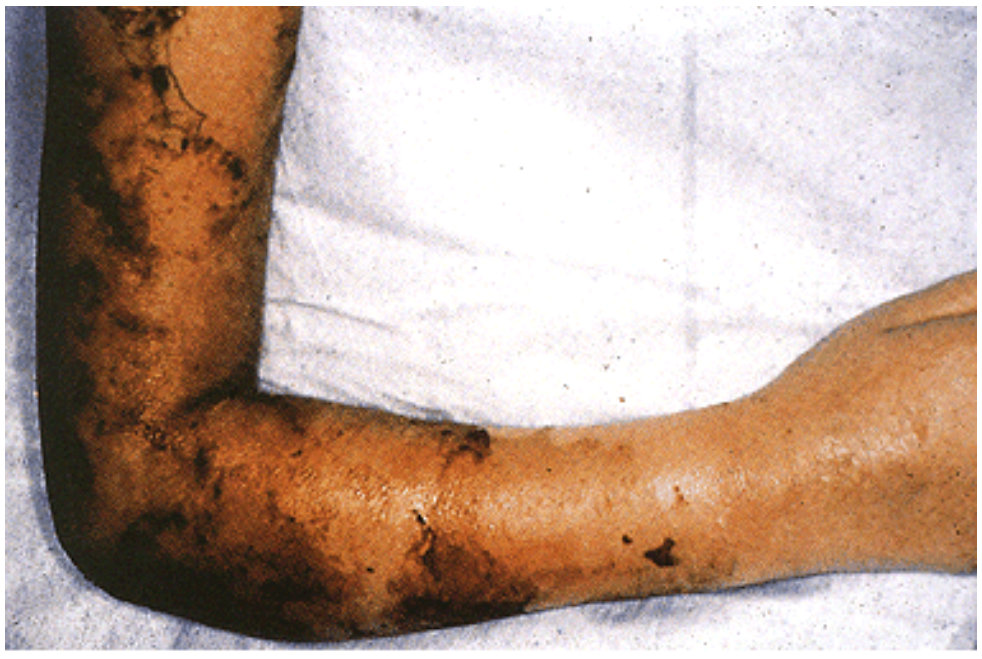
Acute GVHD

- Within the first 100 days after the procedure
- It starts as an erythematous, macular skin rash, blistering, abdominal pain, profound diarrhea, and hyperbilirubinemia.





Acute GVHD: Skin



Skin manifestations of acute GVHD Skin lesions in a patient with severe acute graft-versus-host disease (GVHD). There is swelling, generalized erythroderma, and bullous formation.

Acute GVHD

- Stage I disease is confined to the skin and is mild
- Stage II-IV have systemic involvement
- Stage III and IV acute GVHD carry a grave prognosis

Acute GVHD

- Risk factors for acute GVHD
  - HLA-mismatched grafts
  - MUD grafts (Matched unrelated donor)
  - grafts from a parous female donor
  - advanced patient age

Acute GVHD

- Prophylaxis
  - imunosuppressive agents
- Treatment
  - high-dose steroids and antithymocyte globulin (ATG)

Chronic GVHD

- Risk factors
  - peripheral blood stem cell transplants
  - mismatched or unrelated donors
  - second transplant
  - donor leukocyte infusions (DLIs)
  - acute GVHD

Chronic GVHD

- approximately 40-80% of long-term survivors
- 2-12 months after HSCT
- almost any organ in the body

- Treatment- Immunosuppression

- **Graft-versus-leukaemia (GvL)-** is essential to prevent relapse when treating malignant disease.
- **Graft failure -**failure to establish hematologic engraftment
  - Graft failure is associated with increased risk of infection and peritransplant mortality.

Cost of BMT

- Variable due to several factors:
  - Complications: hospital days, blood products
  - Stem cell source: PBSC<Marrow (faster engraftment)
  - Preparative regimen: TBI expensive
  - Unrelated>>Allogeneic>Autologous

Outcome

- Nonmalignant disease- more favorable
  - 70-90% if the donor is a matched sibling
  - 36-65% if the donor is unrelated.
- Transplants for acute leukemias (eg- ALL, AML) in remission
  - 55-68% if the donor is related
  - 26-50% if the donor is unrelated.

Donor registries- datri

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Jeevan Stem Cell Foundation

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About The Registry

Every year over 120,000 Indians are diagnosed with blood cancers and another 10000 children are born with diseases like Thalassemia. They can hope for a 60 to 80% chance of cure, if they find matching stem cell donors. The chance of finding a donor in the family is less than 30%. The match is highly ethnicity dependent and hence the chance of finding a match in an Indian registry is over 70%..

Stem Cells from donated cord blood can help children with a body weight less than 30 Kg. Other patients will need a larger number of cells and that can only be obtained from a donor either as Peripheral Blood Stem Cell (PBSC) donation or Bone Marrow Donation.

Bone Marrow Registry is a database of potential stem cell donors, whose Human Leucocyte Antigen (HLA) is typed by Jeevan and stored in a server. When a patient needs a donor, the matching donor is identified from the database. He / she is then counseled, medically examined and then encouraged to donate stem cells. These stem cells are used for the treatment of patients.

Eligibility

- You must be between the ages of 18 and 50

(+91 80) 2529 3486 bloodbank@bmstindia.org FCRA Report

BMST Bangalore Medical Services Trust

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SCRI STEM CELL REGISTRY INDIA

INITIATED BY BMST - SUPPORTED BY DKMS

The Stem Cell Registry India (SCRI) was initiated by BMST in 2008 and re-launched with the cooperation of the international NGO, DKMS Germany (the single largest network of stem cell donor centres in the world), in 2014. The aim of the SCRI project is to improve the chances of recovery and the health outcomes of patients suffering from Leukemia, Thalassemia and other blood disorders for whom a stem cell (bone marrow) transplant offers a second chance at life. To do this the SCRI educates, recruits and registers voluntary potential blood stem cell donors. The project aims to recruit over 10,00,000 potential stem cell donors by 2020. To know more please click here www.bmstindia.org.in.

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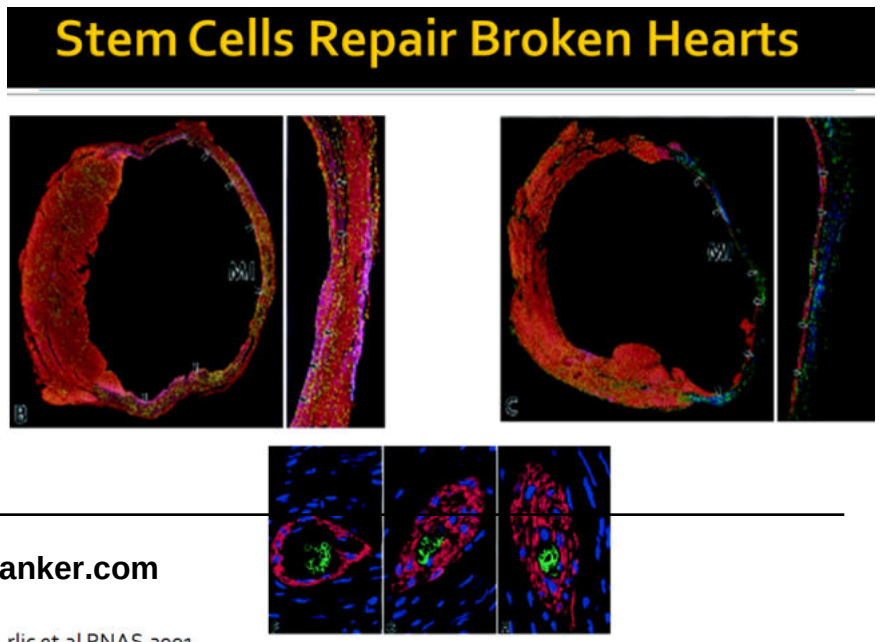
Developing Applications II

- Damaged Heart muscle
  - Injection of stem cells into area of dead heart muscle regenerates viable muscle
  - Promotes formation of new blood vessels in injured heart muscle

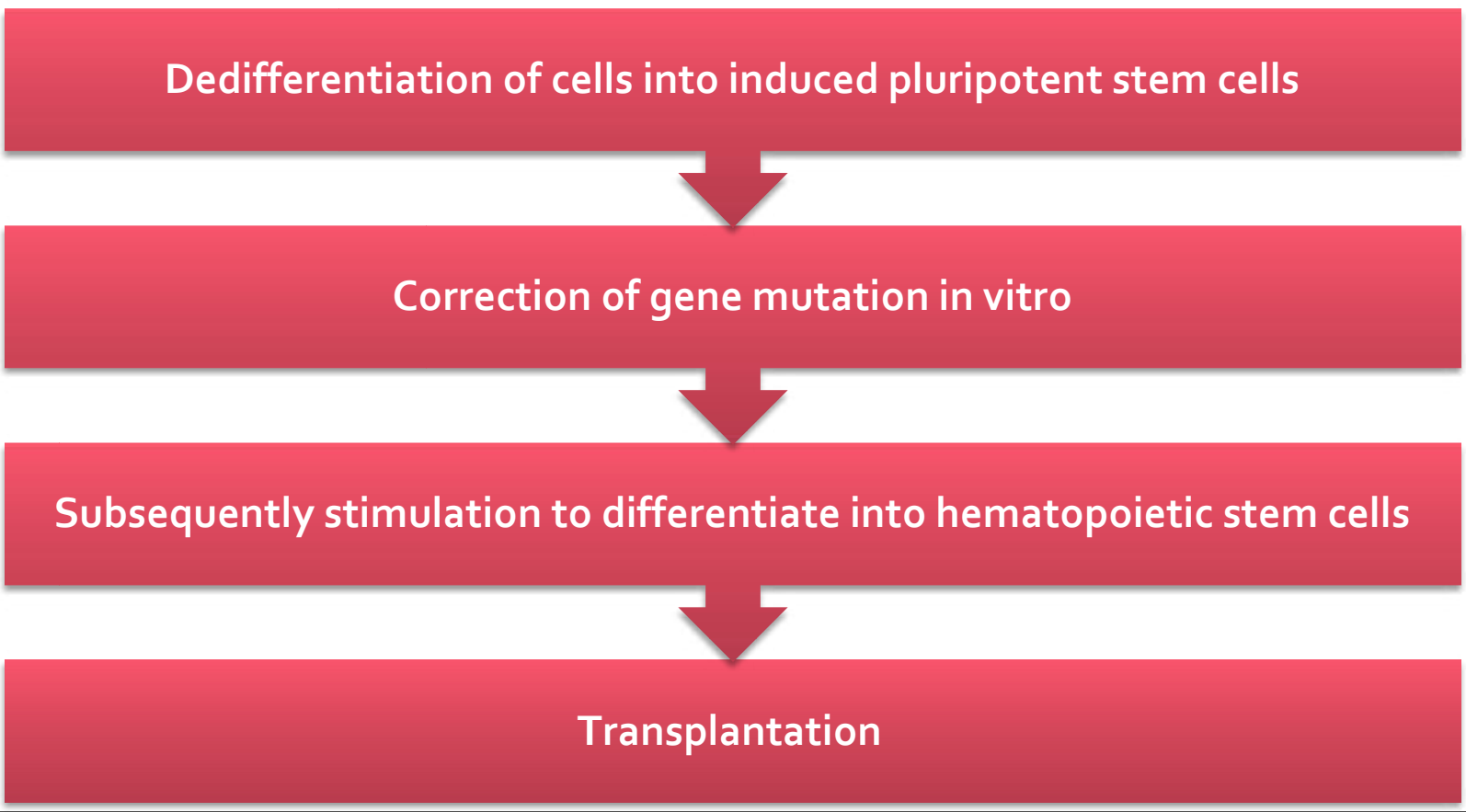


rlic et al PNAS 2001

Gene therapy

- Deficiency in a patient's own hematopoietic stem cell is rectified by gene correction or addition and is reinfused
  - similar to autologous HSCT
    - HIV infection
    - Beta-thalassemia
    - Sickle cell disease

iPS- induced pluripotent stem cells



Conclusions

- Stem cells can be derived from adult, cord blood and embryonic stem cells
- Bone marrow transplantation (BMT) is rapidly expanding as a therapeutic modality with the advancements in techniques, indications, and supportive therapy