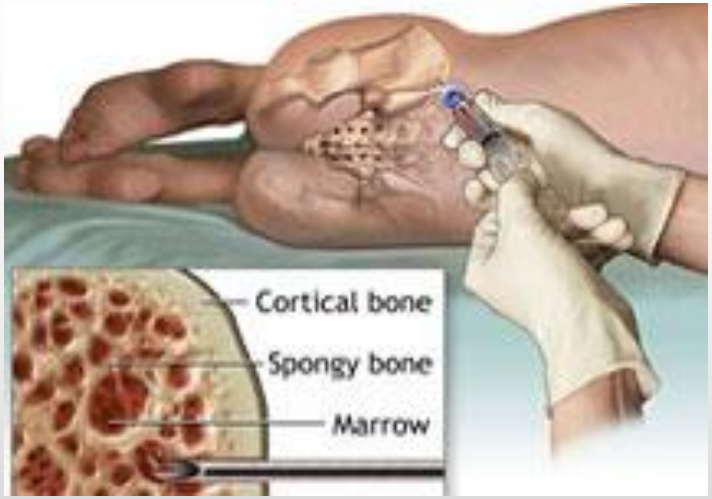
Bone Marrow Transplantation



Neda Kalhor, MD

BMT

- The collection and transplantation of hematopoietic stem cells
- 1950s and 1960s, 200 allogeneic transplants
- **1968**, first successful allogeneic transplant

Features of stem cells

- **Regenerative** capacity
- **Ability to home** to the marrow space following intravenous injection

  - Selectins (BM endothelial cells) and integrins (stem cells)
- Ability of the stem cell to be **cryopreserved**

Sources of stem cells

- **Bone marrow** stem cells
- **Peripheral blood** stem cells (**PBSC**)
- Umbilical **cord** blood

Types of transplants

- **Autologus**
- **Allogenic**
  - Syngeneic (identical twin)
  - Related
  - Unrelated

Autologous Tx

- Removal and storage of the patient's own stem cells with subsequent reinfusion after high-dose myeloablative therapy
- No risk of graft rejection
- Can be contaminated with tumor cells, leading to relapse
- No need for growth factors

Indications

1- **Replace** an abnormal but nonmalignant lymphohematopoietic system

2- **Treat malignancy** by allowing the administration of highdose chemotherapy with stem cell rescue (HDC/SCR)

Non-malignant diseases

- **Inherited immune disorders**
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome
- Chédiak-Higashi syndrome
- Chronic granulomatous disease
- Kostmann’s syndrome
- **Marrow failure states**
- Fanconi's anemia
- Severe aplastic anemia

Continued…

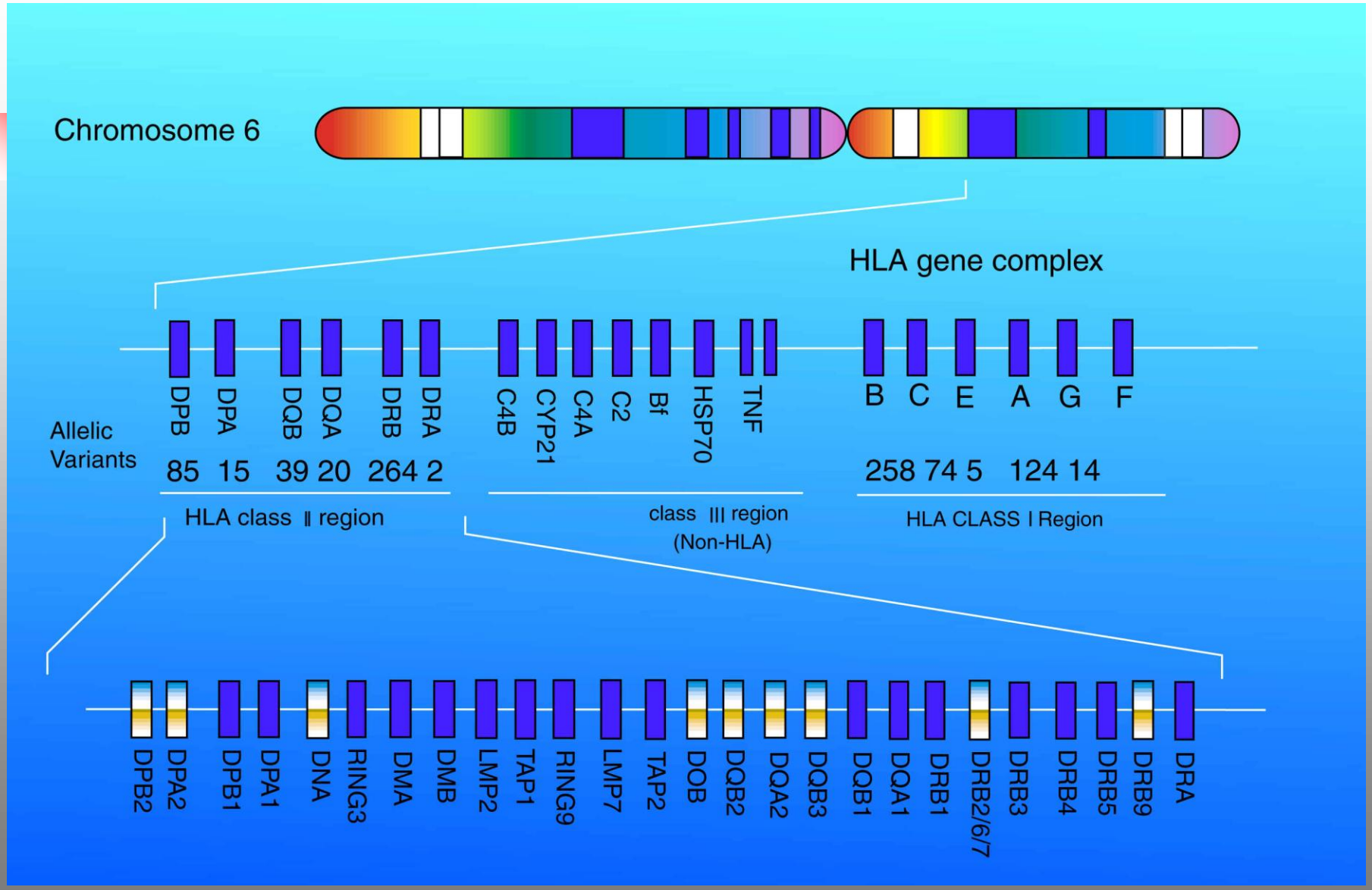
- **Inherited red cell disordes**
  - Thalassemia major
  - Sickle cell anemia
- **Autoimmune diseases** (experimental)
- **Storage diseases**
  - Gaucher's disease
  - Hurler's syndrome
  - Hunter's syndrome

Malignant disorders

- **Hematopoitic** neoplasms
  - Acute Leukemia
  - Chronic Leukemia
  - Myelodysplasia
  - Lymphoma
  - Myeloma
- **Solid Tumors**
  - **Breast** cancer
  - **Ovarian** cancer
  - **Testicular** cancer

Histocompatibility

- Human Leukocyte Antigen (HLA) typing for allogeneic transplants
  - Class I: HLA-A, -B, -C
  - Class II: HLA-DR, -DP, DQ
- Chromosome **6**
- HLA –**A**, -**B** and –**DR** are the most relevant loci
- -A and –B by **serology** and –DR by **molecular** methodology


Chromosome 6
HLA gene complex
DPB
DPA
DQB
DQA
DRB
DRA
C4B
CYP21
C4A
C2
Bf
HSP70
TNF
B
C
E
A
G
F
Allelic Variants
85 15 39 20 264 2
258 74 5 124 14
HLA class Ⅱ region
class Ⅲ region (Non-HLA)
HLA CLASS I Region
DPB2
DPA2
DPB1
DPA1
DNA
RING3
DMA
DMB
LMP2
TAP1
RING9
LMP7
TAP2
DOB
DQB2
DQA2
DQB3
DQB1
DQA1
DRB1
DRB2/6/7
DRB3
DRB4
DRB5
DRB9
DRA

HLA

- The genes encoding HLA antigens are highly polymorphic (10^{23})
- Inherited as **haplotypes**, with only rare crossovers between them
- The odds that any one **sibling** will match a patient are **one in four**
- Within different races, certain haplotypes are far more common
- More problematic for African-American to find an acceptable donor

Obtaining HLA-matched marrow

- **National Marrow Donor Program (NMDP)** with 4 million potential donors
- Identifying and typing >3 million volunteers, 50% chance of finding HLA-matched donor
- **6 cord blood banks** in the U.S. have been set up under a National Institutes of Health initiative.

Bone marrow Harvest

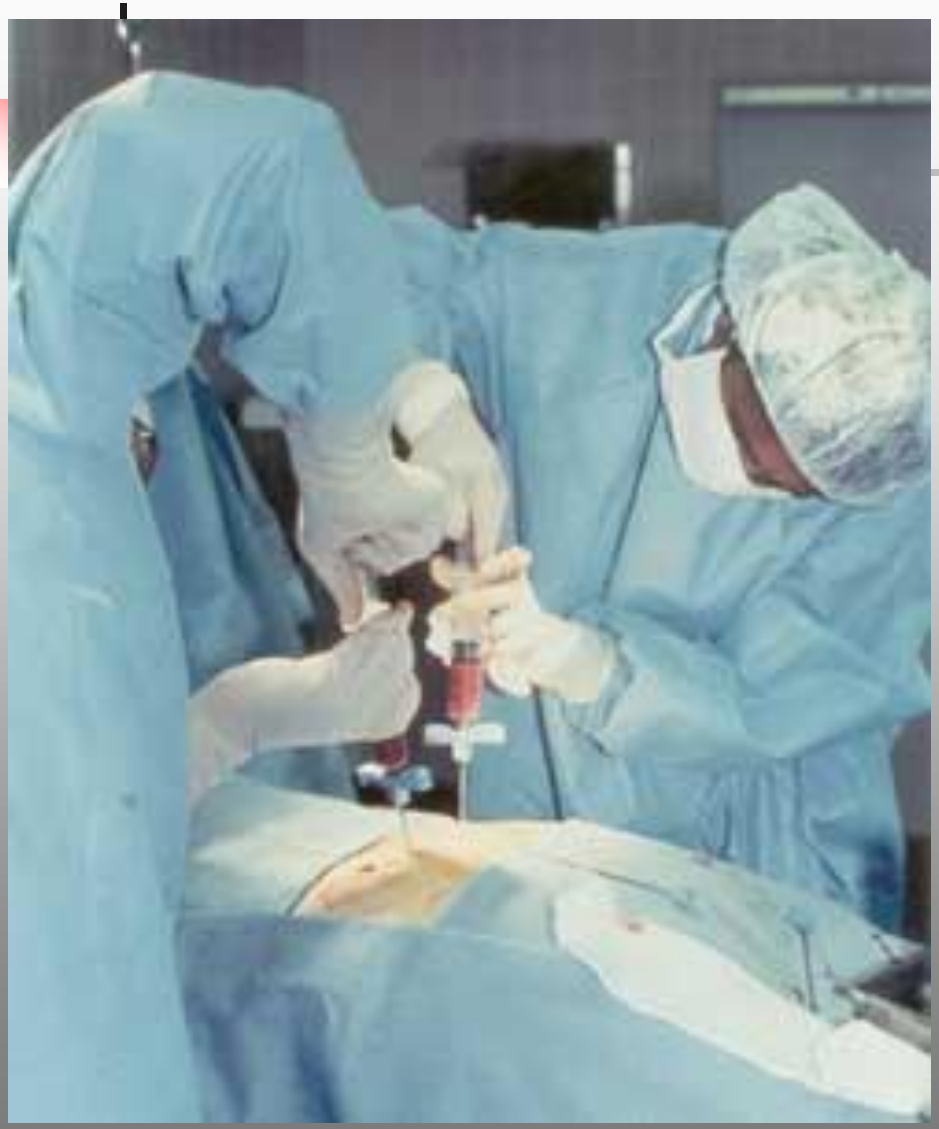
- Aspirated from the donor's iliac crests, under general or spinal anesthesia
- **5-10 mL/kg** of marrow is aspirated, placed in heparinized media, and filtered, to remove fat and bony spicules.
- 2-5% of a person's bone marrow, which the body replaces in four weeks.
- 1.5 to 5 × 10^8 nucleated marrow cells per kilogram

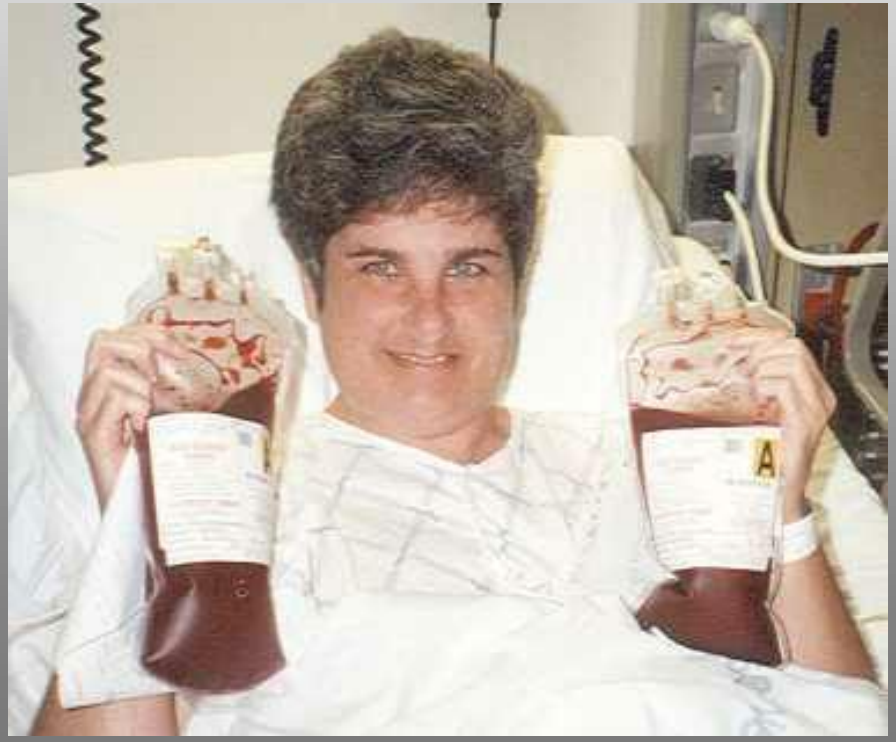
Bone marrow stem cells

- Further processings:
- Removal of red cells in ABO-incompatible transplants
- Removal of donor T cells to prevent GVHD
- Removal of contaminating tumor cells in autologous transplantation

BMT procedure

- Chemo-radiation (**conditioning or preparative regimen)**
- 1-2 days following conditioning
- In the patient's room
- Stem cells infused through a large-bore central venous catheter
- Usually well tolerated, occasionally fever, cough, or shortness of breath





Engraftment

- **2-4 weeks** post-transplant
  - 10-14 d for marrow
  - 7-12 with PBSCs
  - 24 days for cord

BMT complications

- **Early** complications:
  - Rejection
  - Acute GVHD
  - Infections; HSV, CMV, PCP
- **Late** complications:
  - Chronic GVHD
  - Prolonged immunodeficiency
  - Relapse

Graft-Versus-Host Disease

- Donor T cells transferred, reacting with host cells
- A major complication to allogenic tx
- Much less frequent in fully-matched txs

GVHD

- **Acute** (<3 months posttransplant); fever, exfoliative dermatitis, anorexia, vomititng and diarrhea, hepatitis
- Usually requires skin, liver, or GI biopsy for confirmation
- **Chronic** (>3 months); resembles an autoimmune disorder with skin, liver and GI involvement and less commonly arthritis and obliterative bronchiolitis

GVHD

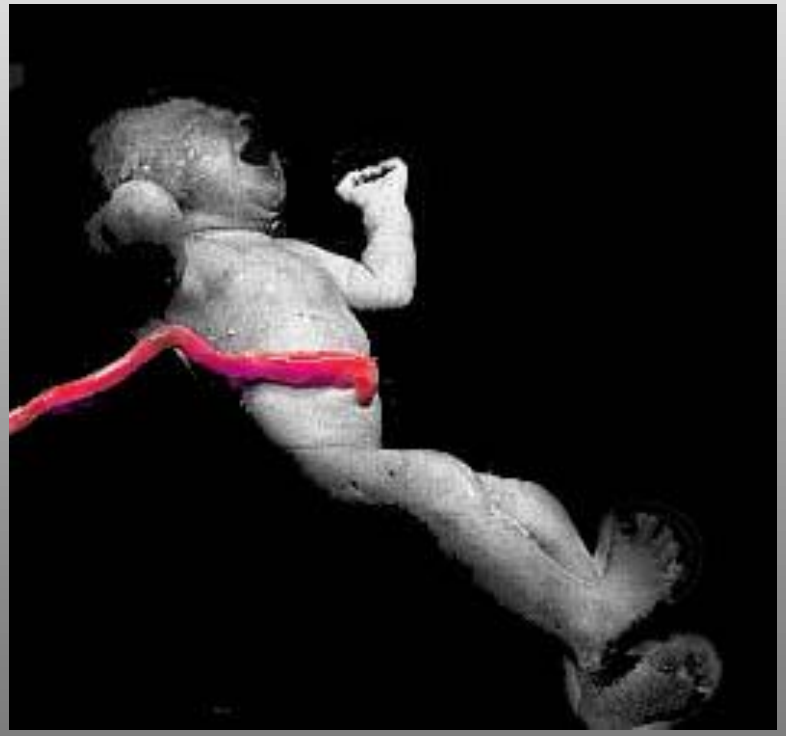
- Cyclosporine
- Removal of T cells with monoclonal Abs
- Higher incidence of engrafment failure and relapse with GVHD prevention
- Cytokines promote stem cell multiplication and maturation
- T cells involved in graft –vs.-tumor effect

Peripheral blood stem cells

- 4 or 5 days of hematopoietic growth factor, G-CSF or GM-CSF
- One or two 4-h apheresis sessions

Umbilical cord stem cells

- Related and unrelated allogeneic



Umbilical cord stem cells

- **Engraftment** at a **slower** pace than seen with a marrow
- Low cell content, limited use as a source of stem cells for adult patients.
- **Less GVHD**

Umbilical cord blood

- **Not requiring the exact match** (marrow asks that 6/6 protein markers be exact, umbilical cord blood bank needs only 4 and when the donor is a sibling of the recipient, only 3)

- If a child has a serious genetic disease, umbilical cord blood from a sibling born **within two years** may be able to correct it.