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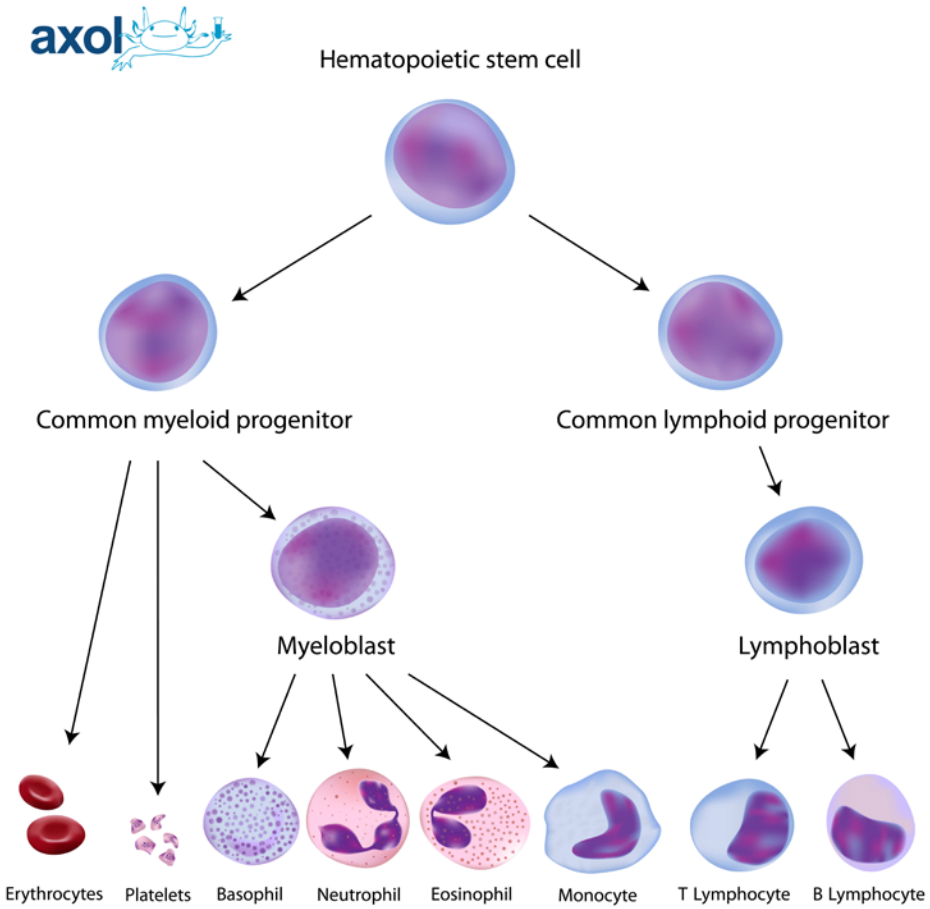
Cellular Therapy in the Hematopoietic Transplant Setting

Andrea Nadas, MLS(ASCP)

Hematopoiesis

- Process of formation and development of cells of the blood and immune system from a common hematopoietic stem cell
- Hematopoietic progenitor cells (HPCs):
  - Divide into RBCs, WBCs, platelets
  - Have CD34 surface protein
  - Transplanted to replace or regenerate bone marrow

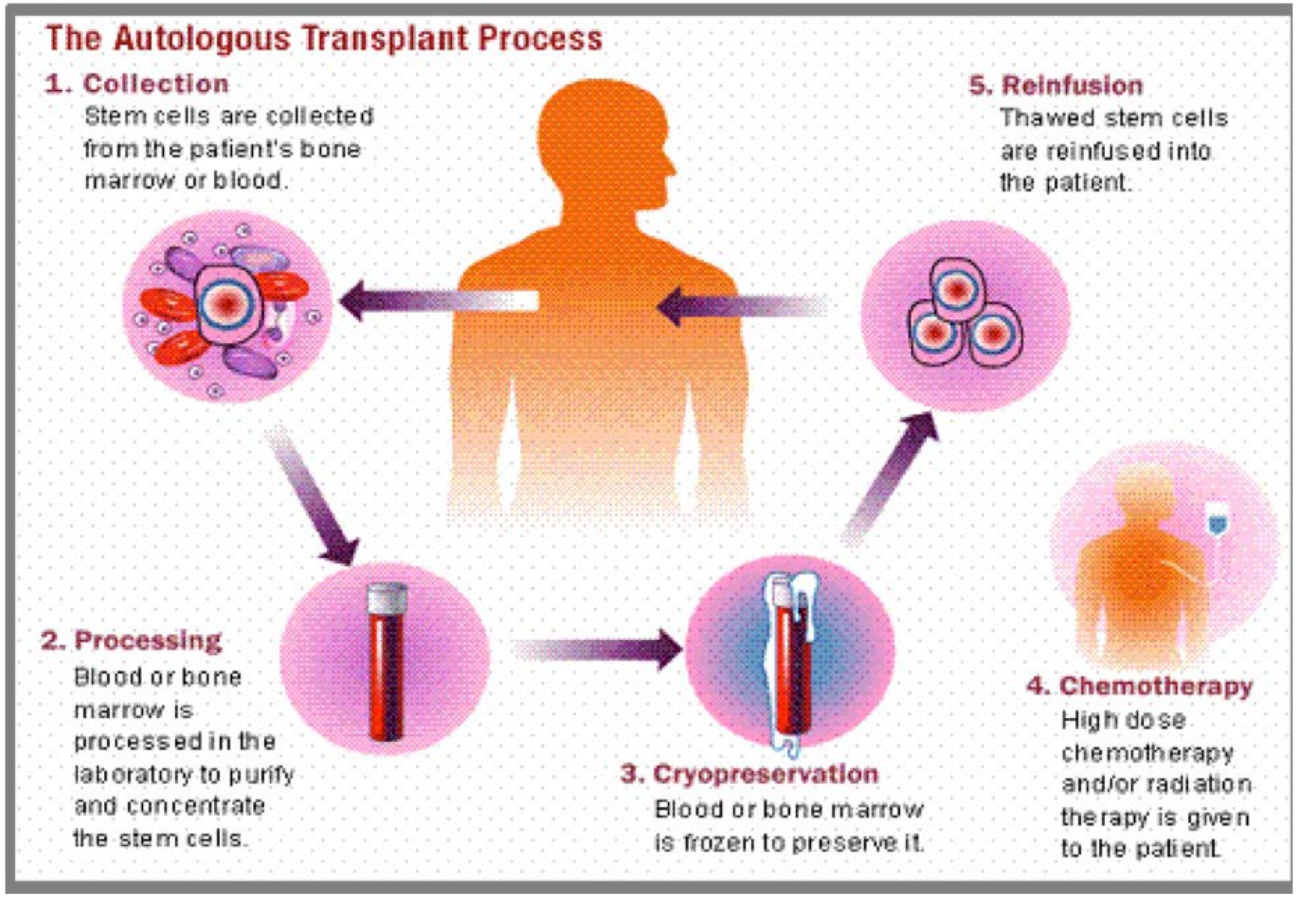


Transplantation of HPCs

- Transplant centers collect, process, store, and infuse HPCs
- Two types of Transplantation:
  - Autologous HPC Transplantation
  - Allogeneic HPC Transplantation

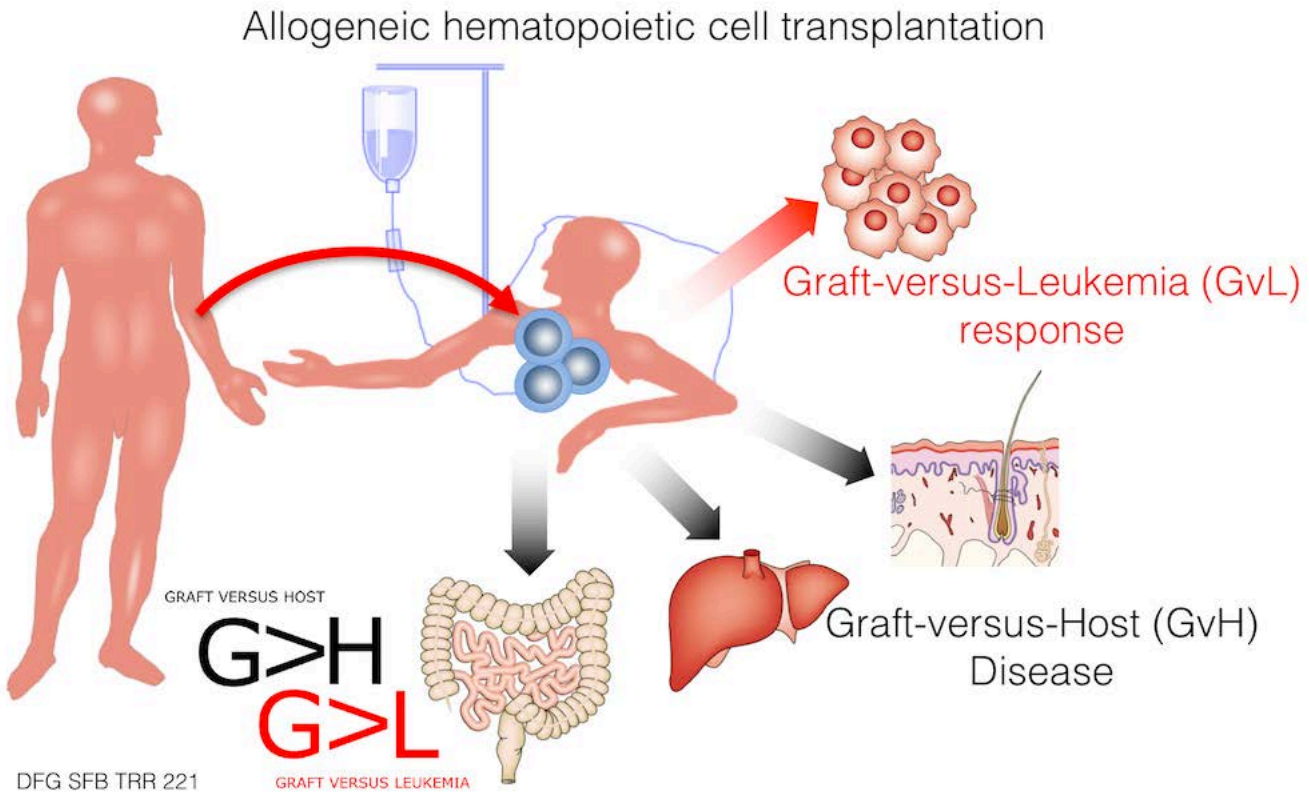
Autologous HPC Transplantation

- Use of own HPCs for transplant
- Reasons for autologous transplant:
  - Adults with lymphoproliferative or plasma cell disorders
  - Children with solid tumors
  - Rescue bone marrow after high-dose chemotherapy



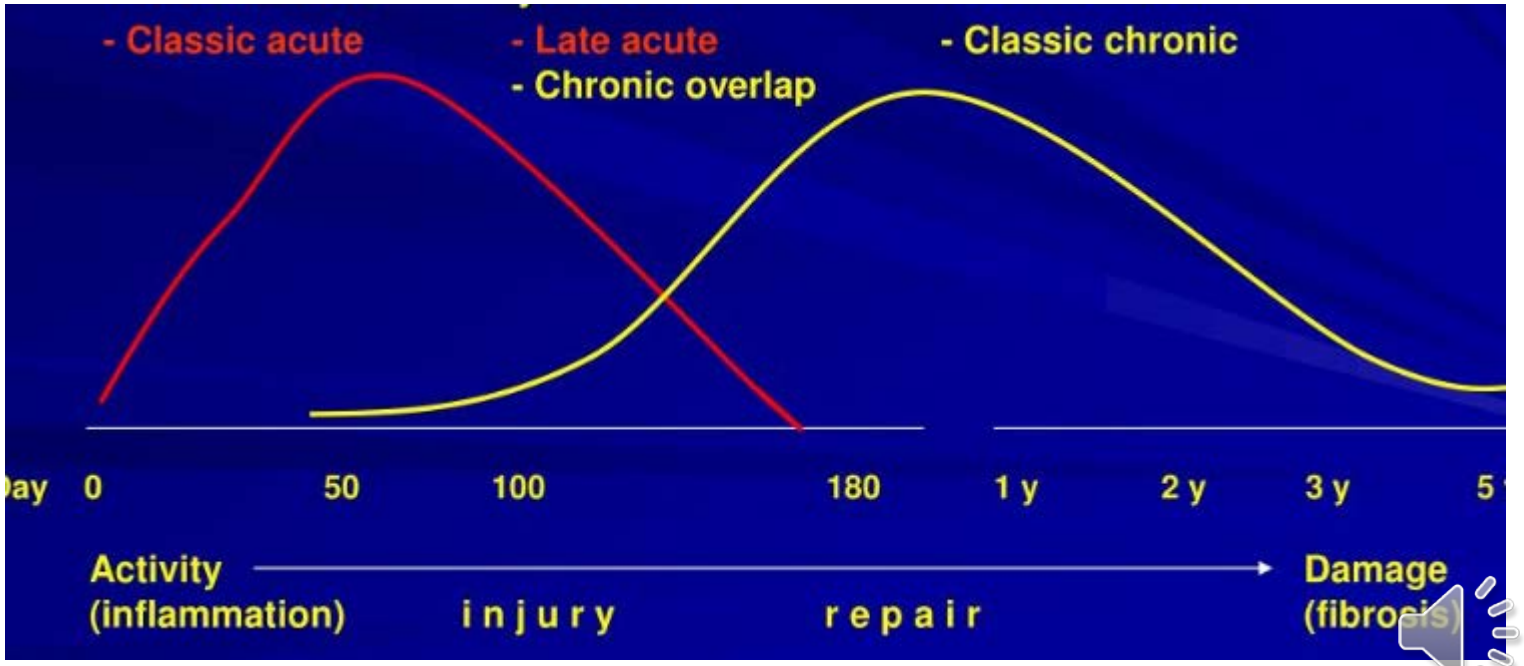
Allogeneic HPC Transplantation

- HPCs from another individual used for transplant
- Reasons for Allogeneic transplant:
  - Malignant myeloproliferative processes
  - Sickle Cell Anemia
  - Congenital immune deficiencies
- Allogeneic transplants can lead to graft-vs-host-disease
  - Donor cells recognize recipient as foreign and attack
  - Need HLA matching
  - Graft-vs-leukemia (GVL)



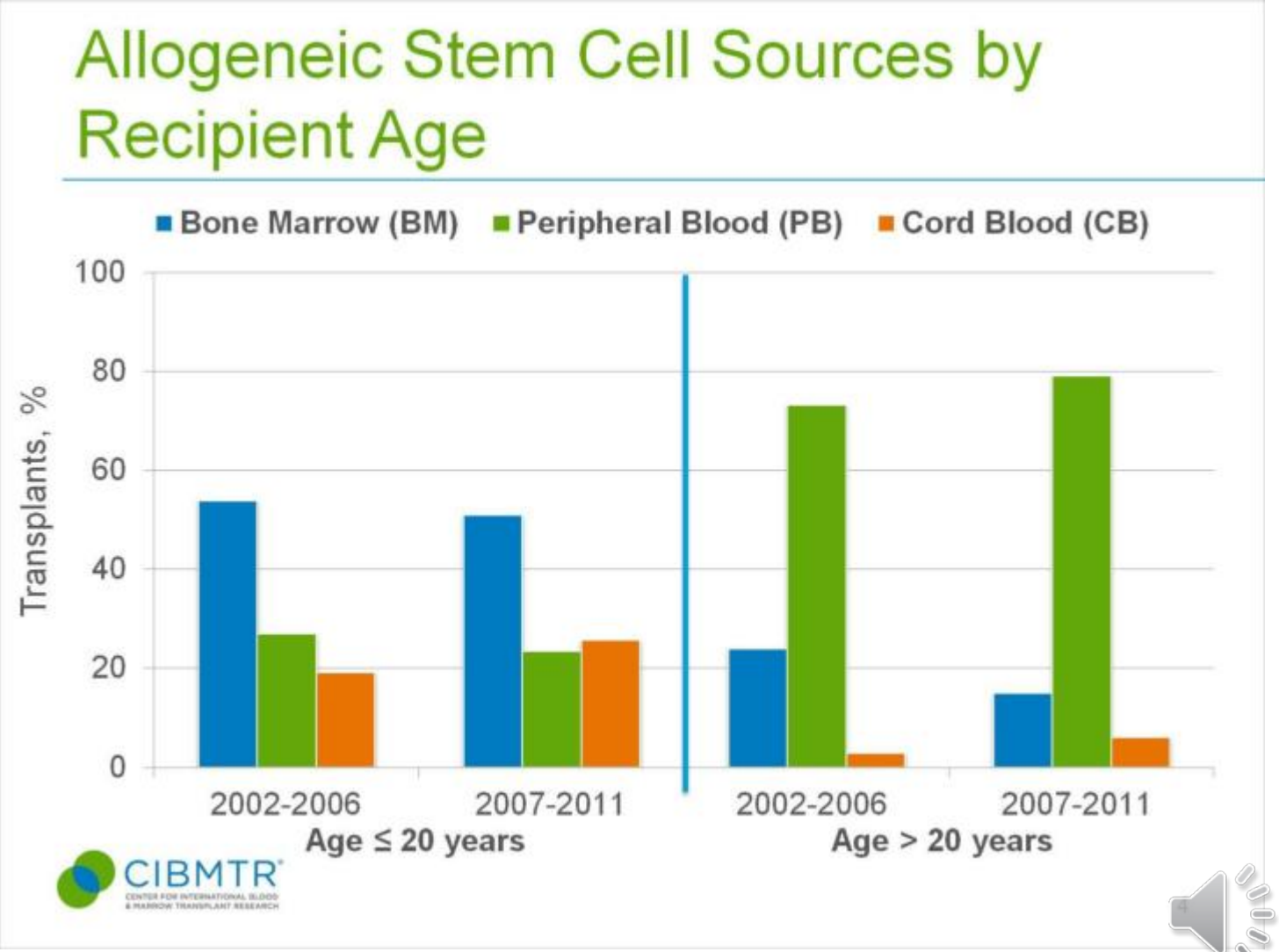
Graft-vs-Host Disease (GVHD)

- Incidence of GVHD is 30-50% with high mortality rate
- Acute GVHD
  - Symptoms: skin rash, transaminitis, gastroenteritis
  - Occurs within 100 days of HPC Transplant
- Chronic GVHD
  - Symptoms: Dry eyes and mouth, joint contractures and reduced mobility, scleroderma-like changes in skin, lung damage



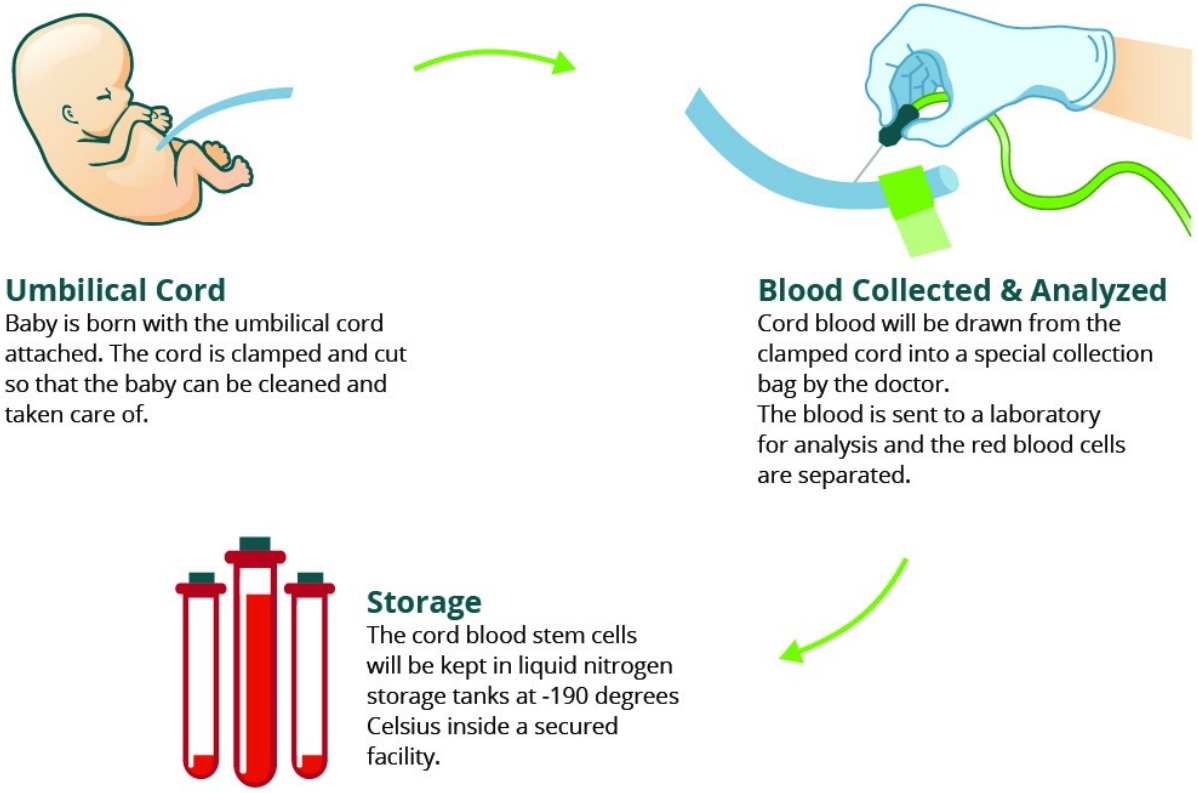
Sources of HPC Products

- Umbilical **Cord** Blood (HPC-C)
- Bone **Marrow** (HPC-M)
- Peripheral blood stem cells collected by **apheresis** (HPC-A)



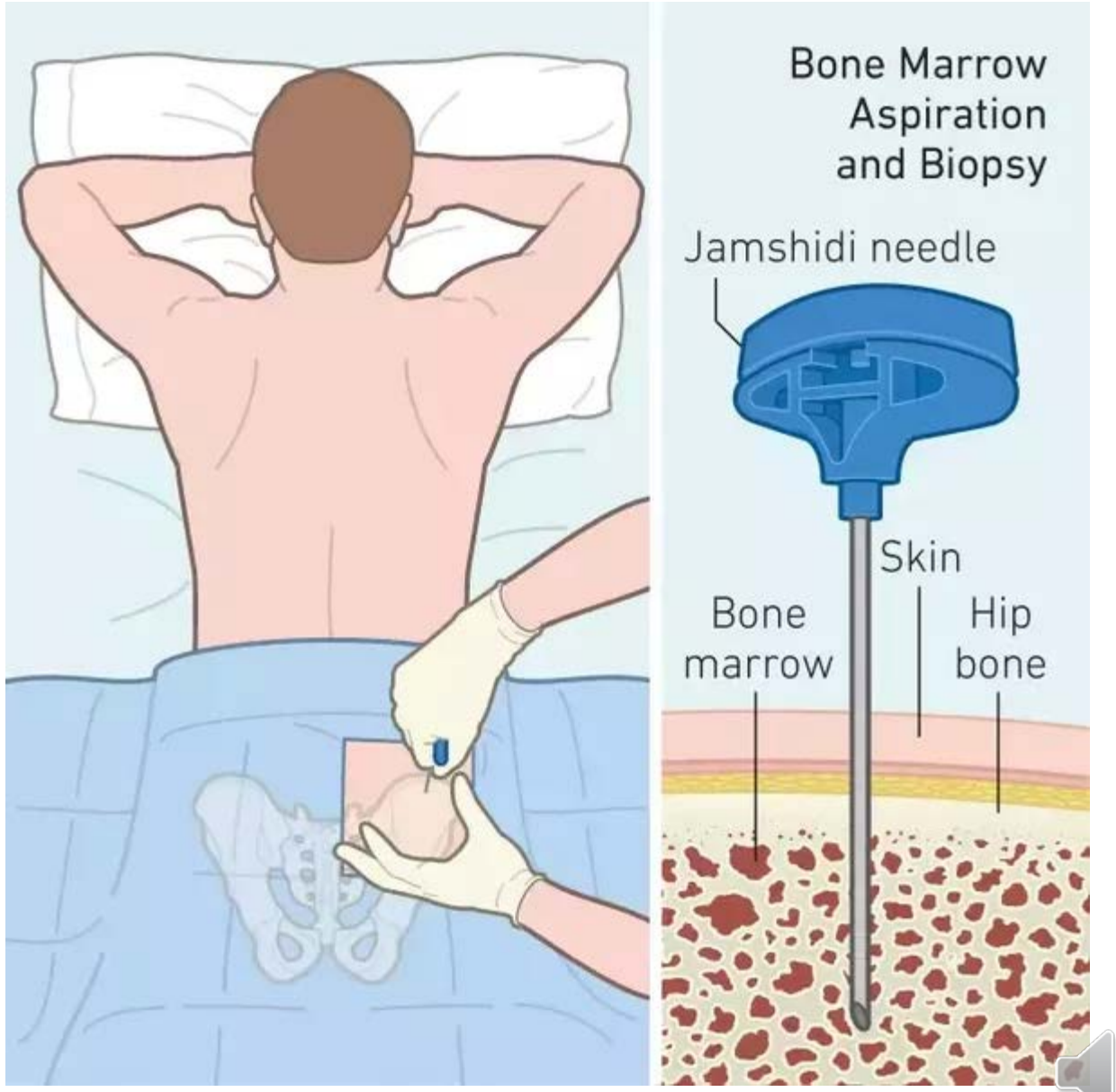
HPC-C

- Collected from placenta and umbilical cord at delivery
- Collected with anticoagulant CPD
- Wash before use - remove RBCs/Plasma
- Freeze with 10% DMSO (dimethyl sulfoxide cryoprotectant)
- Greater tolerance of HLA disparity
- Lower risk of GVHD
- Longer time until engraftment



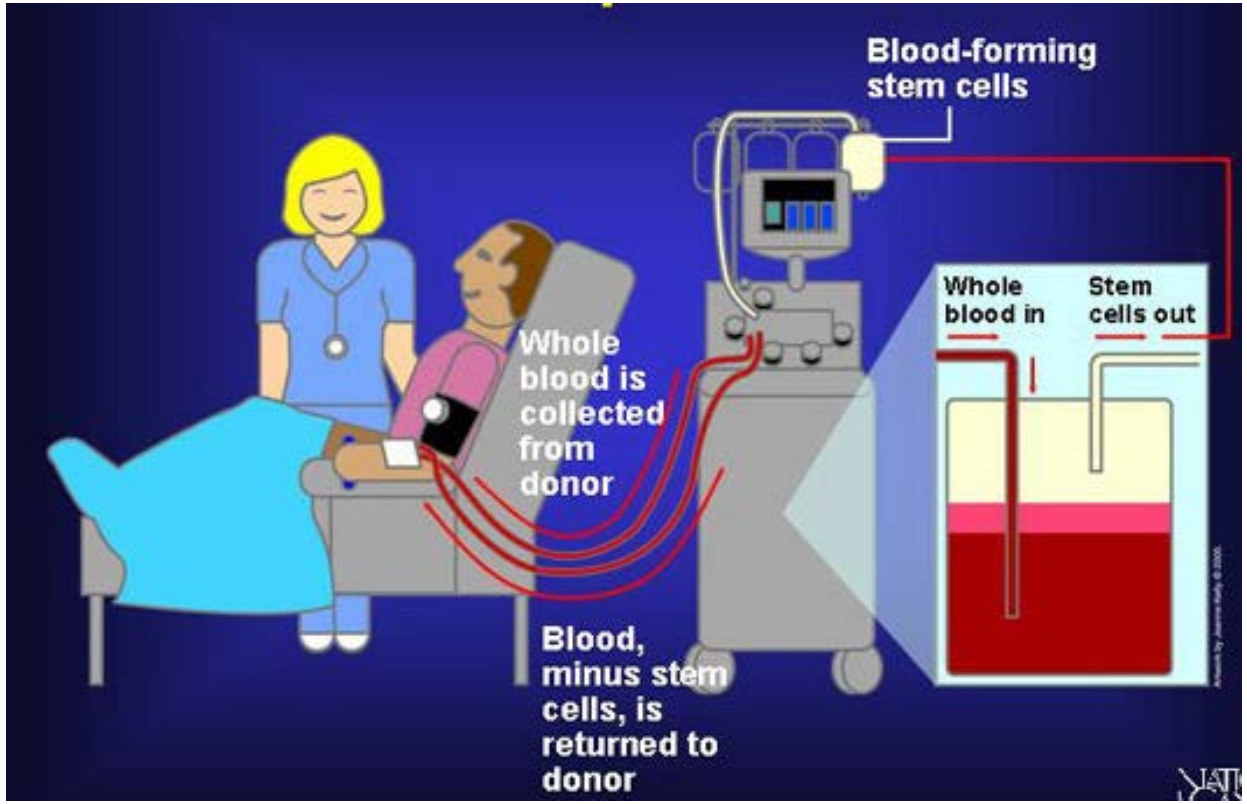
HPC-M

- HPCs collected from bone marrow under anesthesia
- Done using needle to access posterior iliac crest
- Placed into sterile container with anti-coagulant and electrolyte solution
- Lower risk of GVHD than HPC-A
- Higher risk for donor



HPC-A

- Most common product used
- Collected through apheresis
- Growth factors administered before – increase # of HPCs in peripheral blood before collection
- Number of HPCs collected monitored by flow cytometry
- Faster engraftment of neutrophils and platelets than HPC-M
- Better graft-vs-leukemia effect than HPC-M

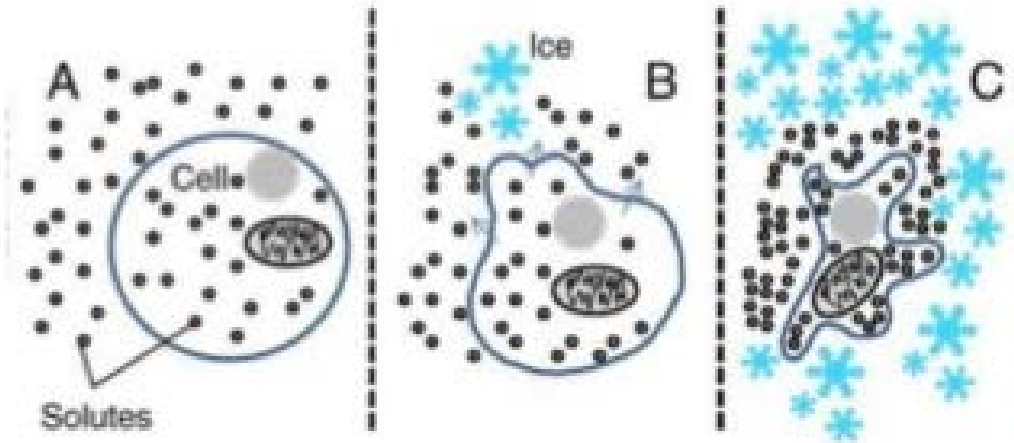


Requirements for HPC Donors

- Pass screening questionnaire
- Physical exam
- Review of medical records
- Infectious disease testing
  - HIV, Hepatitis B and C, HTLV-I, II, Syphilis, CMV
- HLA testing
  - HLA-A, HLA-B, HLA-C, HLA-DRB1

HPC Processing and Storage

- Initial testing: CBC, WBC Differential, CD34 enumeration, viability studies
- Require 2 x 10^6 – 6 x 10^6 CD34+ cells/kg of recipient body weight
- Long term storage:
  - Cryopreservation with addition of cryoprotectant DMSO
  - Store in liquid nitrogen freezer (-196°C)



Cryoprotectant

- Macromolecules, like Glycerol, are used to protect tissues from freezing
- As ice forms outside the cell, water leaves the cell to dilute the higher concentrations of solutes
- Cryoprotectants prevent all the water from leaving by increasing the concentration of solutes inside the cell

HPC Infusion

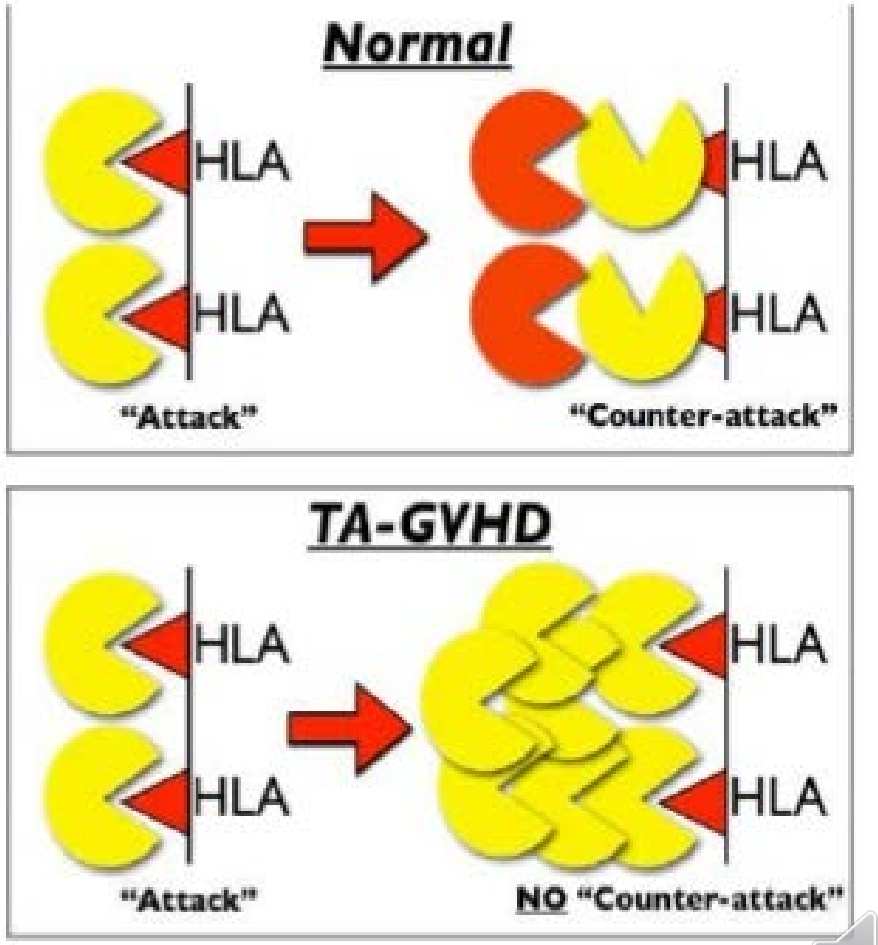
- Thaw in 37°C waterbath
- May be washed to remove DMSO
- Infusion through central venous catheter
- Circulating HPCs enter bone marrow through CD34+ cells reacting with bone marrow stroma
- Most common complication: DMSO toxicity
  - Coughing, flushing, rash, nausea, vomiting, cardiovascular instability, wheezing

Special Transfusion Requirements for HPC Transplantation

- Transfusion Associated Graft-vs-Host Disease
- ABO Incompatible HPC Transplantation
- Rh Transplant Incompatibility
- Passenger Lymphocyte Syndrome (PLS)
- Platelet Refractoriness

Transfusion-Associated Graft-vs-Host Disease

- Recipient's immune system unable to destroy donor lymphocytes
- Lymphocytes divide and attack recipient tissues
- Symptoms: skin rash, fever, increased liver enzymes, pancytopenia, diarrhea
- Reduce risk with irradiation
- BMT patients always get irradiated products



ABO Incompatible HPC Transplantation

- HPCs lack ABO antigens
- Three different ABO mismatches possible:
  - Major ABO Mismatch – Recipient is O, Donor is A, B, or AB
  - Minor ABO Mismatch – Recipient is A, B, or AB, Donor is O
  - Bidirectional ABO Mismatch – Recipient is A, Donor is B

Major ABO Mismatch

- Recipient: O, Donor: A, B, or AB
- Recipient: A or B, Donor: AB
- 20-25% of transplants

- Potential Complications:
  - Acute Hemolysis of RBCs in HPC product
  - Delayed RBC production after transplant
  - Delayed granulocyte and platelet production
  - Pure red cell aplasia

Selecting Blood for Transfusion

	RBCs	FFP	Platelets
Pre-transplant	Recipient ABO	Recipient ABO	Recipient ABO
During Transplant	Recipient ABO	Donor ABO	Donor ABO
Post-transplant*	Donor ABO	Donor ABO	Donor ABO

*Switch to Donor ABO at post transplant if recipient antibodies are no longer detected

Minor ABO Mismatch

- Recipient: A or B, Donor: O
  Recipient: AB Donor: A, B, or O
- 20-25% of transplants

- Potential Complications:
  - Acute hemolysis if donor plasma in HPC product has high ABO titer
  - Hemolysis of recipient RBCs due to passenger lymphocyte syndrome

Selecting Blood for Transfusion

	RBCs	FFP	Platelets
Pre-transplant	Donor ABO	Recipient ABO	Recipient ABO
During Transplant	Donor ABO	Recipient ABO	Recipient ABO
Post-transplant*	Donor ABO	Donor ABO	Donor ABO

*The patient should receive FFP and Platelets compatible to the recipient until the recipient's RBCs are no longer detected in forward type

Bidirectional ABO Mismatch

- Recipient: A, Donor: B
- Recipient: B, Donor: A
- 1-5% of transplants

- Potential Complications:
  - Hemolysis of RBCs in HPC product
  - Acute hemolysis if donor plasma in HPC product has high ABO titer
  - Hemolysis of recipient RBCs due to passenger lymphocyte syndrome

Selecting Blood for Transfusion

	RBCs	FFP	Platelets
Pre-transplant	Group O	Group AB	Group AB
During Transplant	Group O	Group AB	Group AB
Post-transplant*	Donor ABO	Donor ABO	Donor ABO

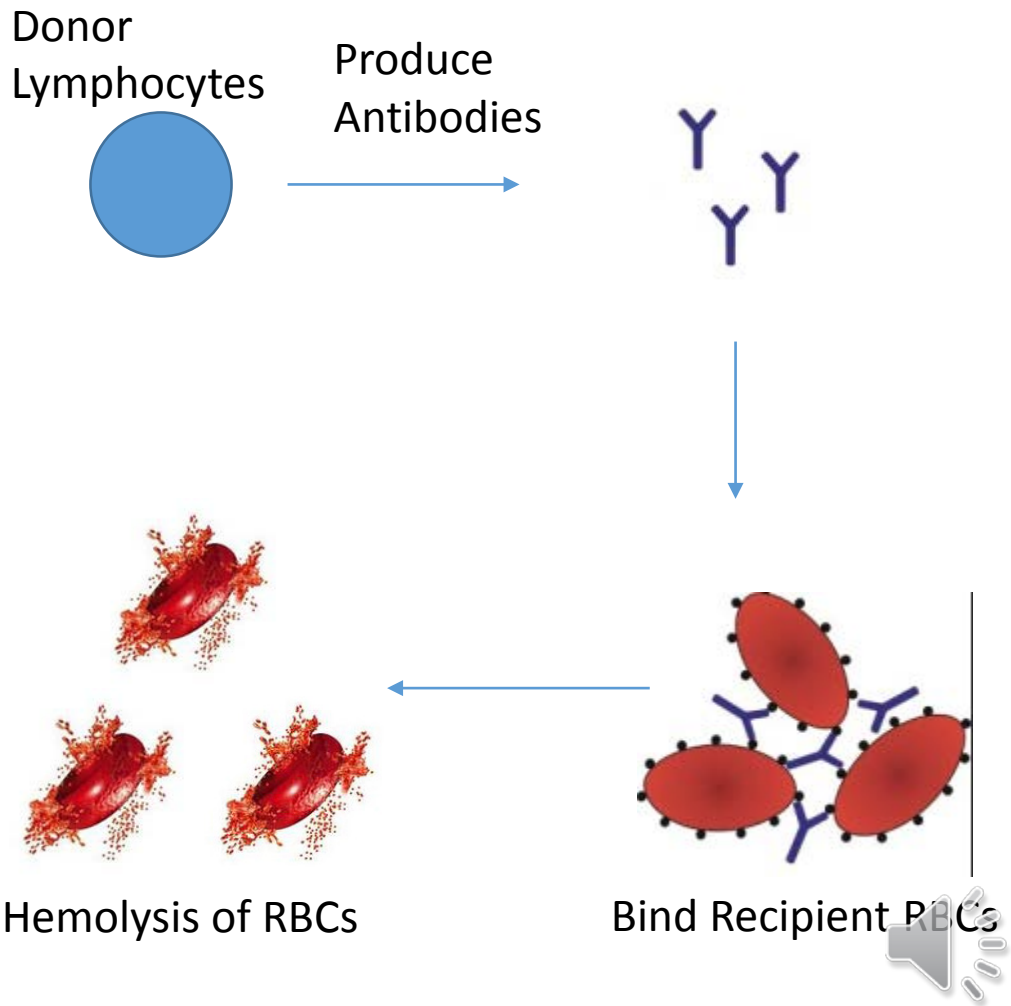
*The patient can receive the Donor ABO after transplant when both the recipient's antibodies and antigens are no longer present

Rh Transplant Incompatibility

- Major Rh Mismatch:
  - Recipient = Rh negative
  - Donor = Rh positive
  - Complication – Recipient could be sensitized and form anti-D
- Minor Rh Mismatch:
  - Recipient = Rh positive
  - Donor = Rh negative
  - Complication – donor may have anti-D which is passively transferred to patient
- Both cases should receive Rh negative RBCs and platelets

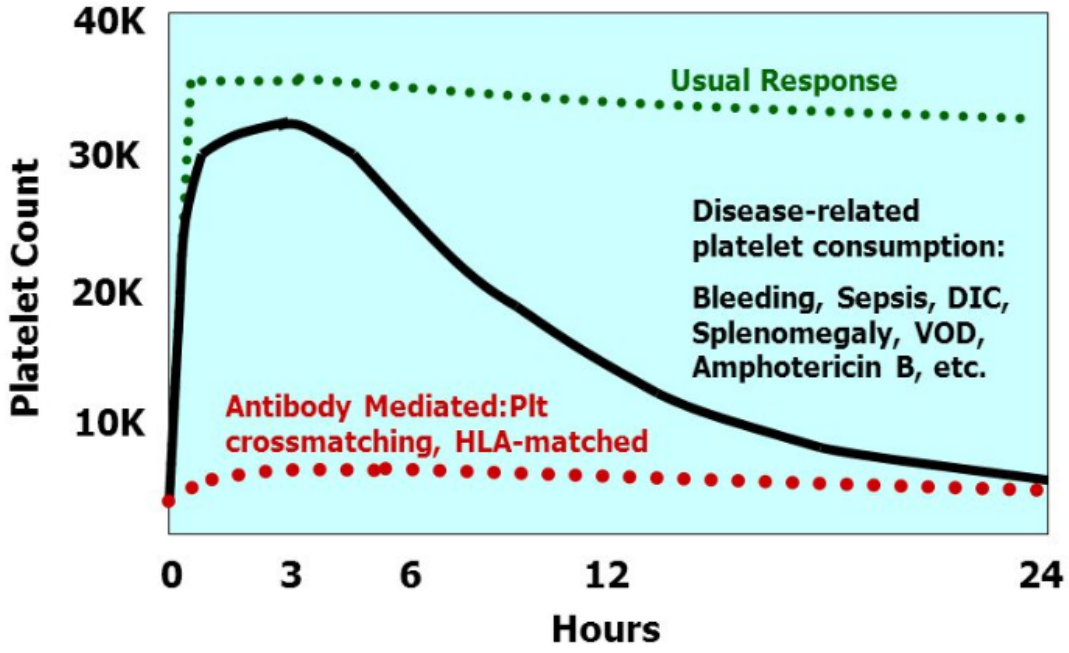
Passenger Lymphocyte Syndrome (PLS)

- Donor lymphocytes infused recognize foreign RBC antigens in recipient
- Donor lymphocytes manufacture antibodies against recipient RBCs
- Result is hemolysis of recipient RBCs
- 9-16 days post transplant
- DAT is positive
- Eluate will be positive for antibody
- Provide RBCs negative for target of PLS



Platelet Refractoriness

- Immune mediated platelet refractoriness
  - Recipient makes antibodies against HLA antigens
  - Platelets positive from antigen removed from circulation
  - Post transfusion platelet counts don't increase
  - Transfuse HLA matched platelets
- Non-immune platelet refractoriness
  - Due to splenomegaly, sepsis, fever, DIC, medications, or GVHD
  - Difficult to overcome



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