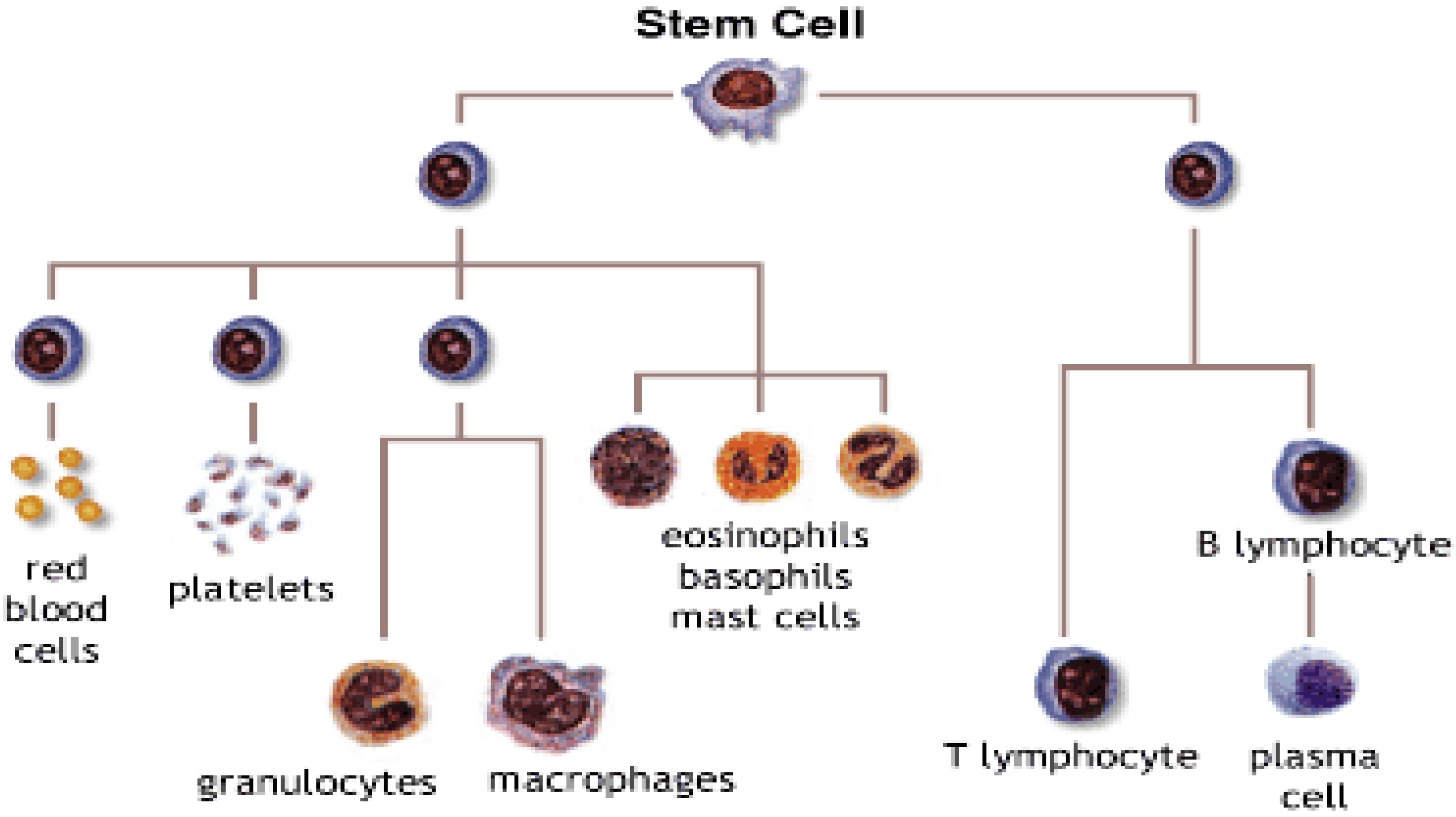
Stem Cell Transplantation

By Dr Dina El Dahshan

Pluripotent hematopoetic stem cell

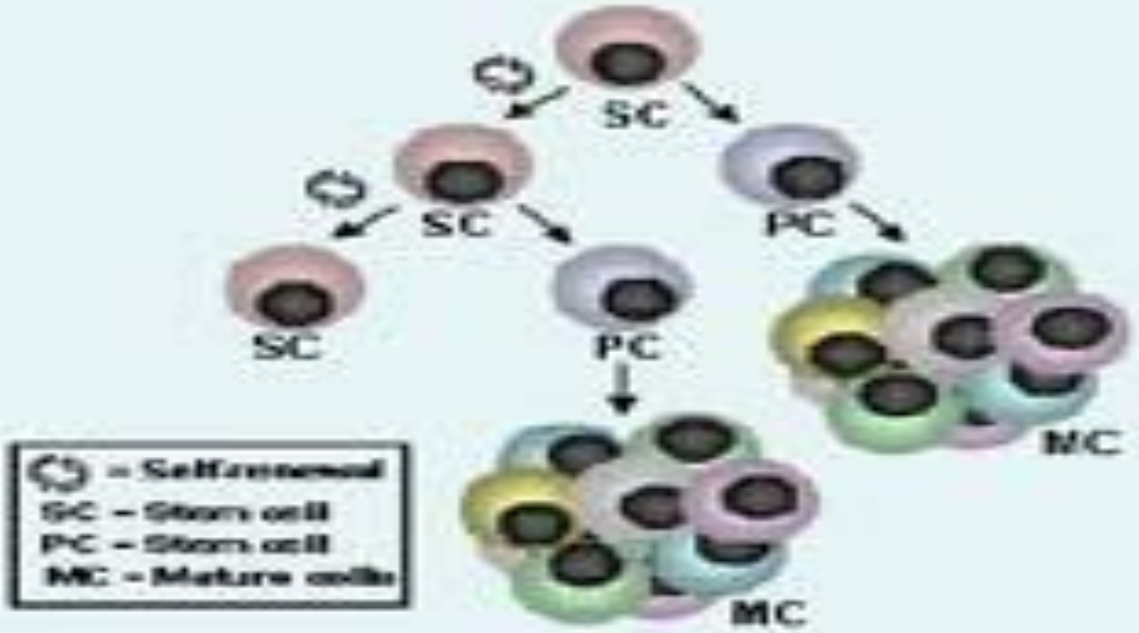


Pluripotent hematopoetic stem cell

- HSCs have the ability of long term reconstitution of hematopoeisis after myeloablative therapy, of both myeloid and lymphoid lineages.
- To fullfill this it must be able to self renew.
- CFU colony forming units (CFU granulocyte macrophage, BFU megakaryocyte,BFU erythroid) are unable to do this function.

Self renewal

- Essential characteristic of SC
- On division at least one daughter cell remains a SC

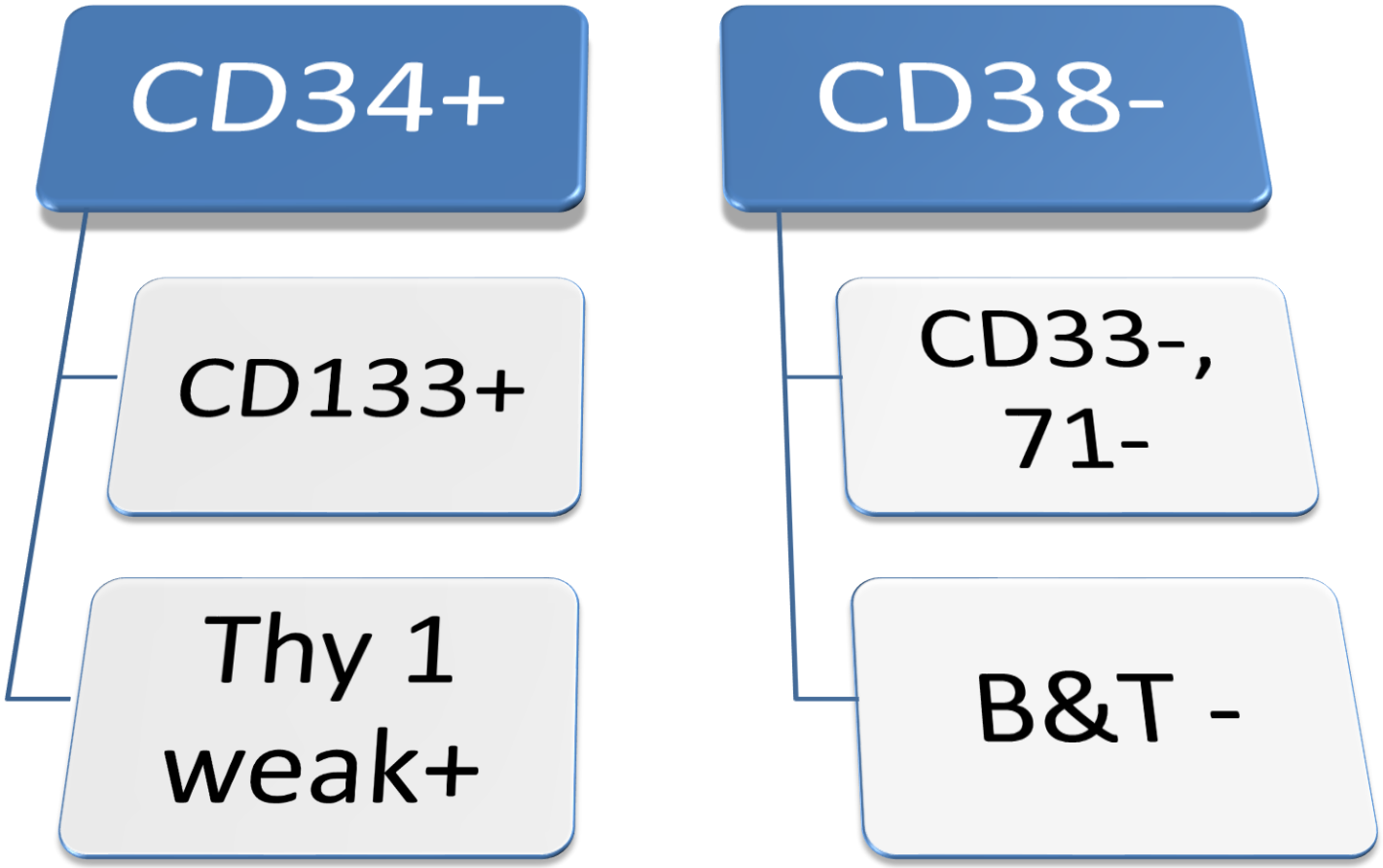


- SC pool is maintained and progenitor cells differentiate into mature tissue
- Avoids exhaustion and loss of SC

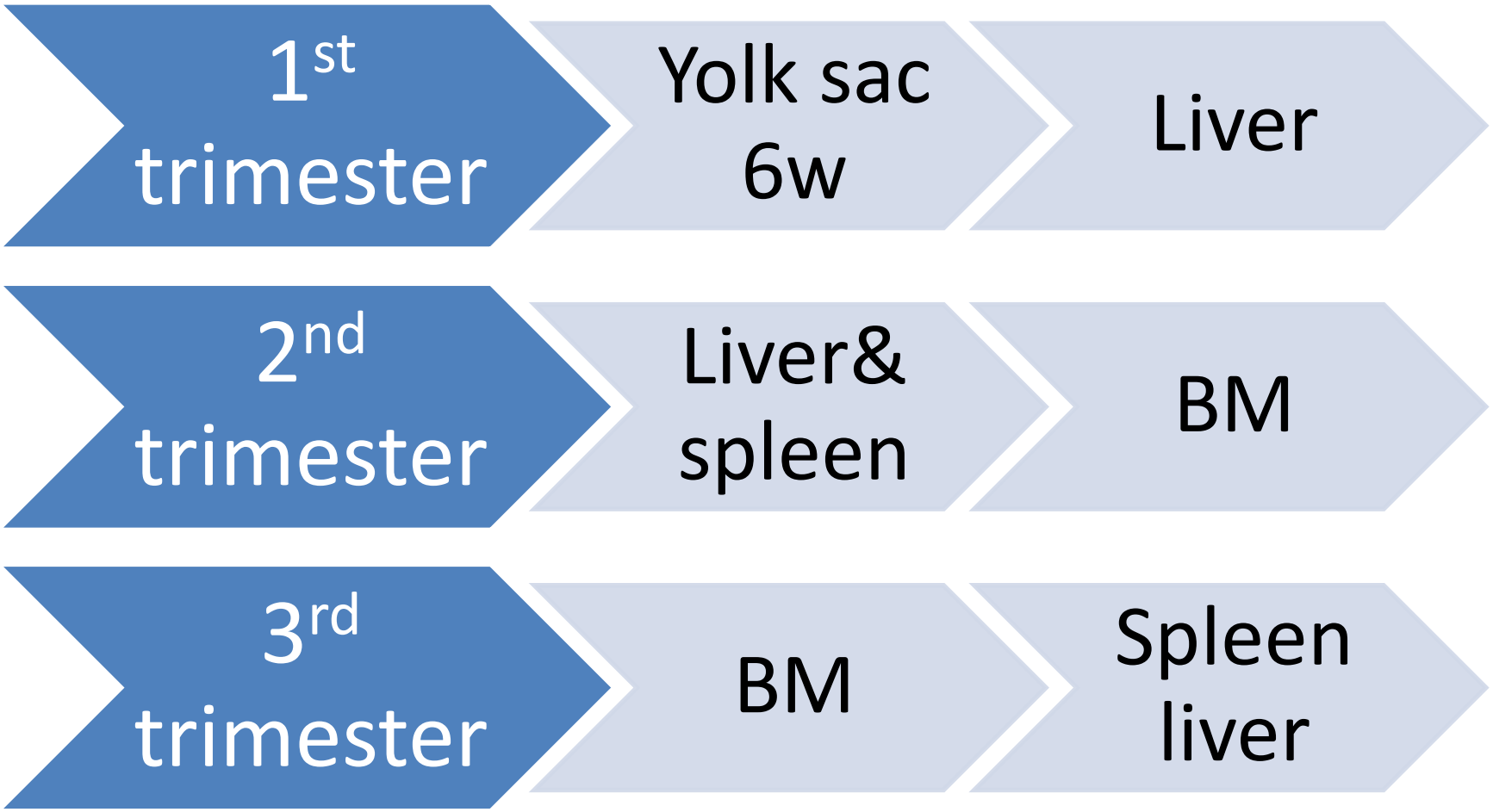
Hematopoetic stem cell

- The CD 34 antigen is expressed on hematopoeitic progenitor cells and vascular endothelium.
- The CD 34 antigen is expressed on 1-5% of normal human adult marrow cells

Hematopoetic stem cell



Sites of hematopoeisis



Sources of HSC

1-Bone marrow

2-Peripheral Blood

3-Cord blood

Hematopoetic stem cell Transplantation

Bone Marrow	• Allogeneic • Autologous
Peripheral Blood	• Allogeneic • Autologous
Cord Blood	• Allogeneic • Allogeneic

Selection of stem cell source

1-The availability

-Autologous SCT is available for most patients, except if *extensive prior cytotoxic therapy or heavy involvement of BM with malignant cells.*

-Allogeneic HLA matched sibling is prefered but only available in 30% of cases.

-Syngenic donors are available in less 1% of cases.

-Phenotypically HLA matched or one antigen mismatched haploidentical family donors in 5% of cases.

-HLA matched Unrelated donor in 50% of cases.

Selection of stem cell source

2-Type of the disease

-Autologous or allogeneic can support the hematopoeitic recovery in hematological disease

-Acquired marrow disorders Aplastic anemia,

-Congenital hematopoeitic defects as thalassemia require *allogeneic stem cells*

Indications of HSCT

Acquired

- Malignancies
  - Hematological
    - Leukemias
      - Acute lymphoblastic leukemia (ALL)
      - Acute myeloid leukemia (AML)
      - Chronic lymphocytic leukemia (CLL)
      - Chronic myelogenous leukemia (CML), accelerated phase or blast crisis
    - Lymphomas
      - Hodgkin's disease
      - Non-Hodgkin's lymphoma
    - Myelomas
      - Multiple myeloma

Indications of HSCT

- Solid tumors
  - Neuroblastoma
  - Ewing's sarcoma
  - Choriocarcinoma
- Hematologic disease
- Myelodysplasia
  - Anemias
    - Paroxysmal nocturnal hemoglobinuria (PNH; severe aplasia)
    - Aplastic anemia
    - Acquired pure red cell aplasia
  - Myeloproliferative disorders
    - Polycythemia vera
    - Essential thrombocytosis
    - Myelofibrosis

Indications of HSCT

- Metabolic disorders
  - Amyloidoses
    - Amyloid light chain (AL) amyloidosis
- Environmentally-induced diseases
  - Radiation poisoning
- Viral diseases
  - HIV

Indications of HSCT

Congenital

- Lysosomal storage disorders
  - Lipidoses (disorders of lipid storage)
    - Sphingolipidoses
      - Niemann-Pick disease
      - Gaucher disease
  - Mucopolysaccharidoses
      - Hurler syndrome (MPS I H, α-L-iduronidase deficiency)
      - Scheie syndrome (MPS I S)
      - Hurler-Scheie syndrome (MPS I H-S)
  - Glycoproteinoses
      - Mucolipidosis II (I-cell disease)
      - Alpha-mannosidosis
  - Other
      - Wolman disease (acid lipase deficiency)

Indications of HSCT

- Immunodeficiencies
  - T-cell deficiencies
    - Ataxia telangiectasia
  - Combined T- and B-cell deficiencies
    - Severe combined immunodeficiency (SCID), all types
  - Well-defined syndromes
    - Wiskott-Aldrich syndrome
  - Phagocyte disorders
    - Kostmann syndrome
    - Shwachman-Diamond syndrome
  - Innate immune deficiencies
    - NF-Kappa-B Essential Modulator (NEMO) deficiency (Inhibitor of Kappa Light Polypeptide Gene Enhancer in B Cells Gamma Kinase deficiency)

Indications of HSCT

- Hematologic diseases
  - Hemoglobinopathies
  - Sickle cell disease
  - β thalassemia major (Cooley's anemia)
  - Anemias
    - Aplastic anemia
      - Diamond-Blackfan anemia
      - Fanconi anemia
  - Cytopenias
    - Amegakaryocytic thrombocytopenia
  - Hemophagocytic syndromes
    - Hemophagocytic lymphohistiocytosis (HLH)

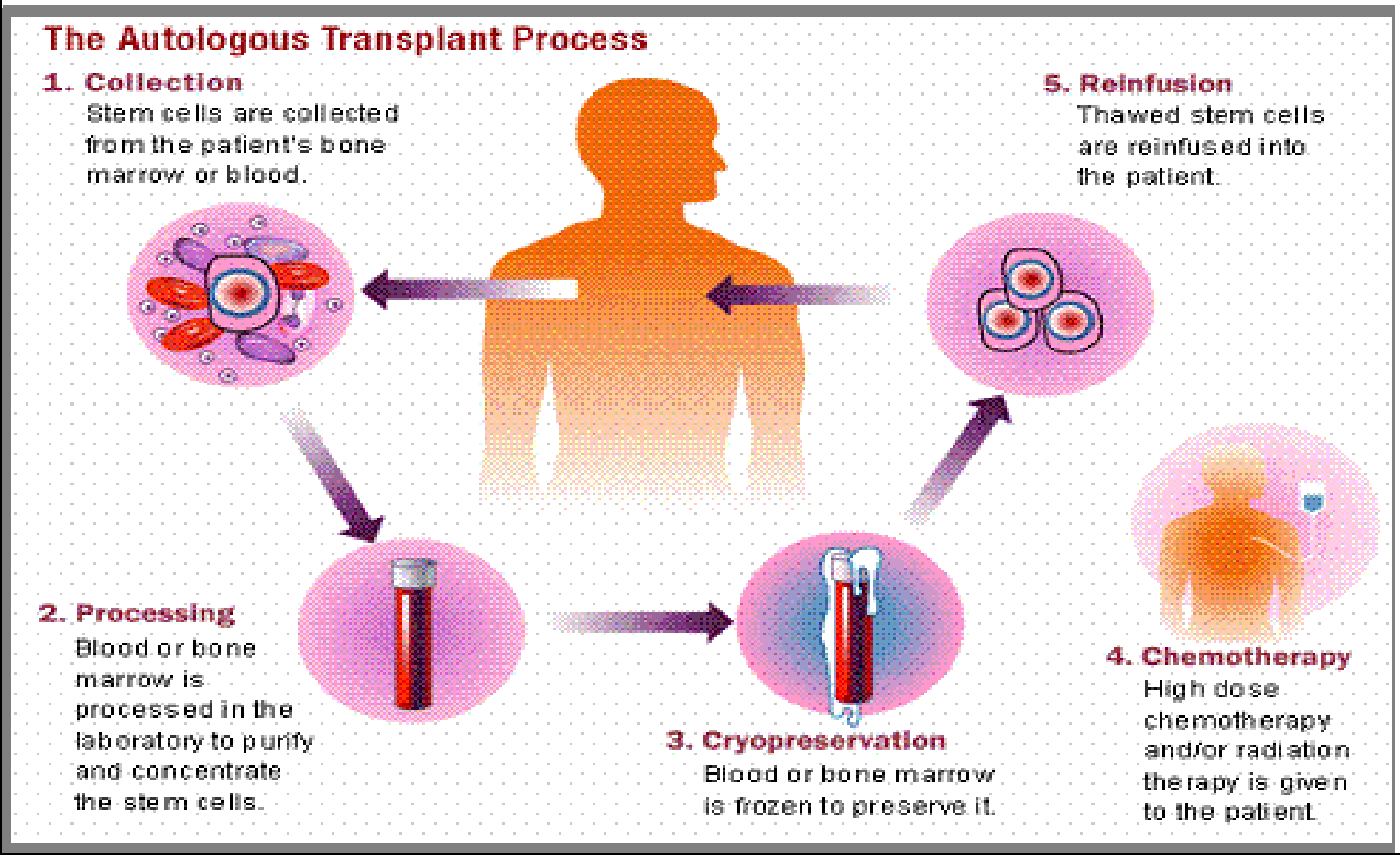
Autologous HSCT

- Autologous HSCT requires the extraction of haematopoietic stem cells (HSC) from the patient and storage of the harvested cells in a freezer.
- The patient is then treated with high-dose chemotherapy with or without radiotherapy with the intention of eradicating the patient's malignant cell population at the cost of partial or complete bone marrow ablation (destruction of patient's bone marrow function to grow new blood cells).

Autologous HSCT

- The patient's own stored stem cells are then returned to his/her body, where they replace destroyed tissue and resume the patient's normal blood cell production

Autologous SCT



Advantages of Autologous SCT

- Lower risk of infection during the immune-compromised portion of the treatment.
- No use of immunosuppressive drugs.
- Rapid hematological recovery
- Recovery of immune function is rapid.
- Incidence of patients experiencing rejection (graft-versus-host disease) is very rare due to the donor and recipient being the same individual.
- Lower cost

Advantages of Autologous SCT

NB: These advantages have established autologous HSCT as one of the standard second-line treatments for such diseases as lymphoma.

NB: For others such as Acute Myeloid Leukemia, the reduced mortality of the autogenous relative to allogeneic HSCT may be outweighed by an increased likelihood of cancer relapse and related mortality, and therefore the allogeneic treatment may be preferred for those conditions

Allogeneic SCT

- Allogeneic HSCT involves two people: the (healthy) donor and the (patient) recipient.
- Allogeneic transplant donors may be *related* or *unrelated* or syngenic transplantation.
- Allogeneic transplants are also performed using umbilical cord blood as the source of stem cells.
- Allogeneic HSC donors must have a tissue (HLA) type that matches the recipient.

Allogeneic SCT

- Even if there is a good match at these critical alleles, the recipient will require immunosuppressive medications to reduce graft-versus-host disease.

Allogeneic SCT

- In general, by transplanting healthy stem cells to the recipient's immune system, allogeneic HCSTs appear to improve chances for cure or long-term remission once the immediate transplant-related complications are resolved

HLA matching (Allogeneic)

- HLA Matching :

  - is performed before transplantation.

  - A compatible donor is found by doing additional HLA-testing from the blood of potential donors.

The HLA genes fall in two categories (Type I and Type II).

-Mismatches of the Type-I genes (i.e. HLA-A, HLA-B, or HLA-C) increase the risk of graft rejection.

-A mismatch of an HLA Type II gene (i.e. HLA-DR, or HLA-DQB1) increases the risk of graft-versus-host disease

-A perfect match at these loci is preferred.

Bone Marrow Transplantation

I - Patient selection

II - Donor Preparation

III-Stem cell collection (Harvest)

IV-Stem cell quantitation

V -Stem cell purification

VI- Stem cell storage

VII- Conditioning regimen

VIII-Reinfusion

IX-Engraftment

X-Complications

Bone Marrow Transplantation

I - Patient selection

A-Patient consent

B-Through a complete workup of patient or donor:

healthy BM, unaffected marrow if autologous, free from infections, not feverish, HCV ab-ve, HIV-ve, CMV, TORCH, Blood culture, gynecological and dental examination,CT chest, abdominal US.

Bone Marrow Transplantation

II - Donor Preparation

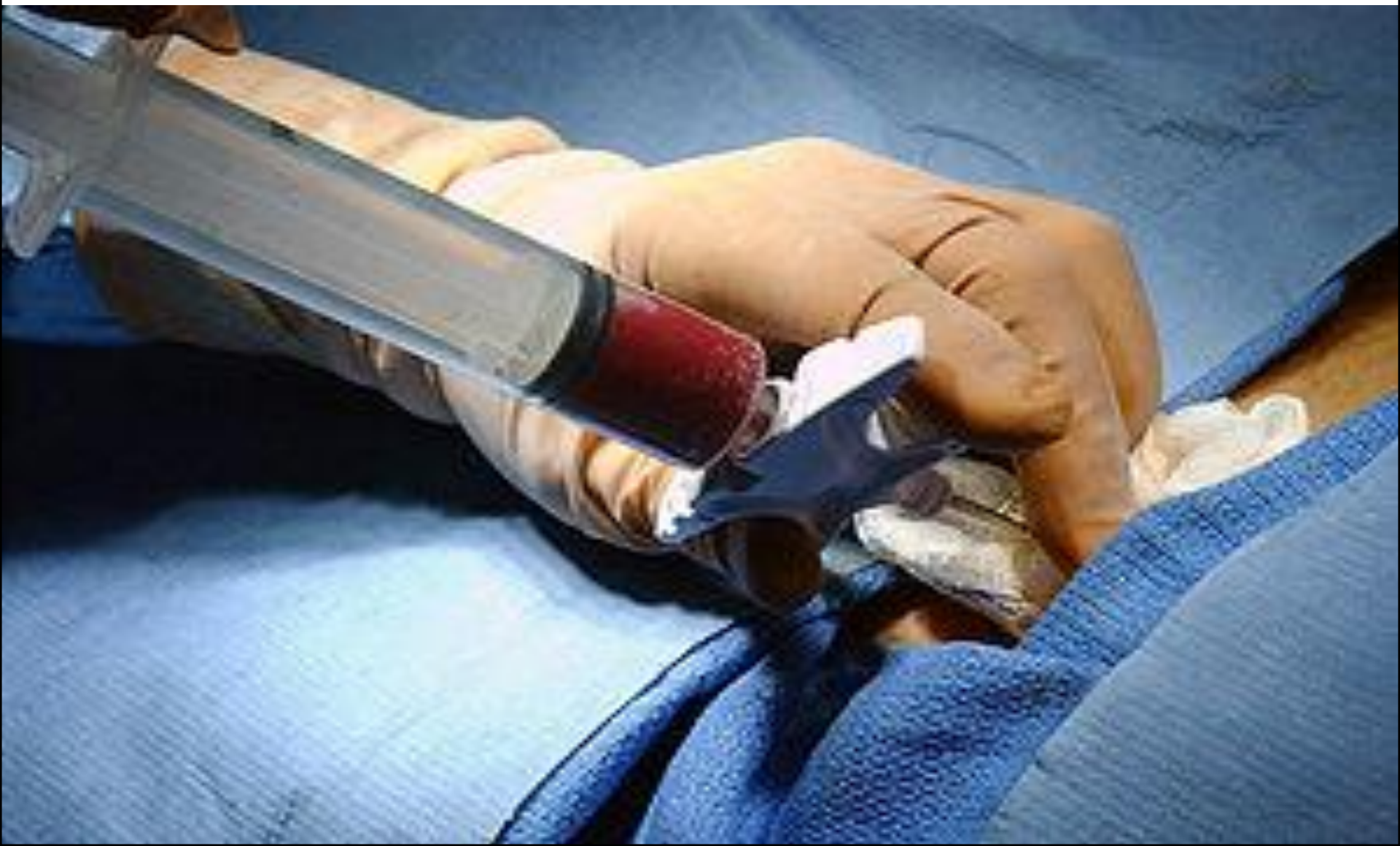
If autologous ensure free BM

If allogeneic nothing to do

III-Stem cell collection (Harvest)

- Under general anaesthesia
- multiple BM punctures from PS iliac spine collect about 50- 200ml

Bone Marrow Transplantation



Bone Marrow Transplantation

IV-Stem cell quantitation

Flow cytometric assessment of the amount of CD34+ve cells in the harvest.

The accepted amount is not less than $2x10_6$ CD34 + cells enough for a successful transplantation

Bone Marrow Transplantation

V -Stem cell purification

-Removal of bony debris , RBCs and unwanted cells

-+ve selection of CD 34 cells by magnetic beads

--ve selection of stromal and mature cells

Bone Marrow Transplantation

VI- Stem cell storage(cryopreservation)

-To cryopreserve HSC a preservative,DMSO (dimethyl sulfoxide), must be added and the cells must be cooled very slowly in a control rate freezer to prevent osmotic cellular injury during ice crystal formation.

- HSC may be stored for years in a*cryofreezer* which typically utilizes liquid nitrogen because it is non-toxic and it is very cold (boiling point -196°C.)

Bone Marrow Transplantation

-HSC can be frozen for prolonged periods (cryopreserved) without damaging too many cells.

-This is necessary for autologous HSC because the must be harvested months in advance of the transplant treatment.

- In the case of allogeneic transplants fresh HSC are preferred in order to avoid cell loss that might occur during the freezing and thawing process.

-Allogeneic cord blood is stored frozen at a cord blood bank because it is only obtainable at the time of childbirth.

Bone Marrow Transplantation

VII- Conditioning regimen

Myeloablative transplants

- The chemotherapy or irradiation given immediately prior to transplant
- to help eradicate the patient's disease prior to the infusion of HSC
- to suppress immune reactions.
- The bone marrow can be *ablated* with dose-levels that cause minimal injury to other tissues.
- In allogeneic transplants a combination of cyclophosphamide with busulfan or total body irradiation is commonly employed.
- *Autologous* transplants may also use similar conditioning regimens, but many other chemotherapy combinations can be used depending on the type of disease.

Bone Marrow transplantation

Non-myeloablative (or "mini") allogeneic transplants

- This is a newer treatment approach using lower doses of chemotherapy and radiation which are too low to eradicate all of the bone marrow cells of a recipient.
- Instead, non-myeloablative transplants run lower risks of serious infections and transplant-related mortality while relying upon the *graft versus tumor* effect to resist the inherent increased risk of cancer relapse.[
- Also significantly, while requiring high doses of immunosuppressive agents in the early stages of treatment, these doses are less than for conventional transplants.[22] This leads to a state of mixed chimerism early after transplant where both recipient and donor HSC coexist in the bone marrow space.
- Decreasing doses of immunosuppressive therapy then allows donor T-cells to eradicate the remaining recipient HSC and to induce the graft versus tumor effect.

Bone Marrow transplantation

- This effect is often accompanied by mild graft-versus-host disease, sustained treatment with low levels of immunosuppressive agents.
- Because of their gentler conditioning regimens, these transplants are associated with a lower risk of transplant-related mortality and therefore allow patients who are considered too high-risk for conventional allogeneic HSCT to undergo potentially curative therapy for their disease.
- These new transplant strategies are still somewhat experimental, but are being used more widely on elderly patients unfit for myeloablative regimens and for whom the higher risk of cancer relapse may be acceptable.

Bone Marrow Transplantation

VIII-Reinfusion

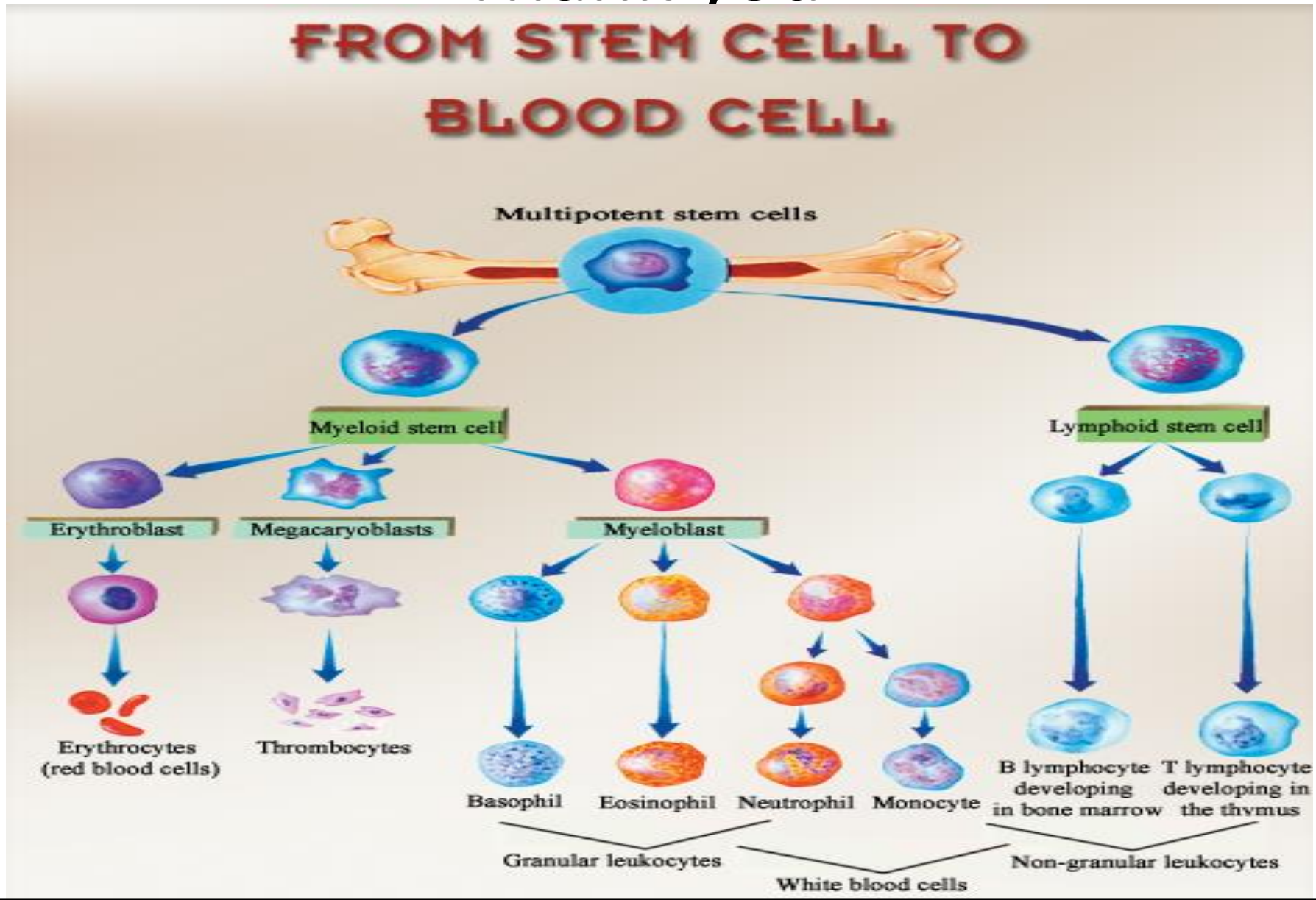
Thawing of the harvest gradually

IV introduction when it reaches 37c

IX-Engraftment

X-Complications

Thank you


FROM STEM CELL TO BLOOD CELL
Multipotent stem cells
Myeloid stem cell
Lymphoid stem cell
Erythroblast
Megacaryoblasts
Myeloblast
Erythrocytes (red blood cells)
Thrombocytes
Basophil
Eosinophil
Neutrophil
Monocyte
B lymphocyte developing in bone marrow
T lymphocyte developing in the thymus
Granular leukocytes
White blood cells
Non-granular leukocytes