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HEALTHY ARIZONA WORKSITES PROGRAM (HAWP) PRESENTS:

EMERGING OPTIONS FOR CANCER TREATMENT (PART 1)

Presented by:

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WEBINAR HOUSEKEEPING

WELCOME

All lines have been muted.

Please type any questions into the chat or Questions panel and we will do our best to answer them all at the end.

All handouts and a copy of the presentation slides are available in the Handouts panel.

Please complete the survey that will be emailed out after the presentation

A recording will be added to the library of HAWP webinars on our website within 48 hours.

Special thanks to our supporting partner Dignity Health for their generous support in making this webinar possible.

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Q&A

PLEASE ENTER YOUR QUESTIONS IN THE CHAT.

Emerging Options for Cancer Treatment (Stem Cell and Cellular Therapies) Part 1

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Cellular Therapy
Clinical Program
Director
July 23, 2020

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Emerging Options for Cancer Treatment (Stem Cell)

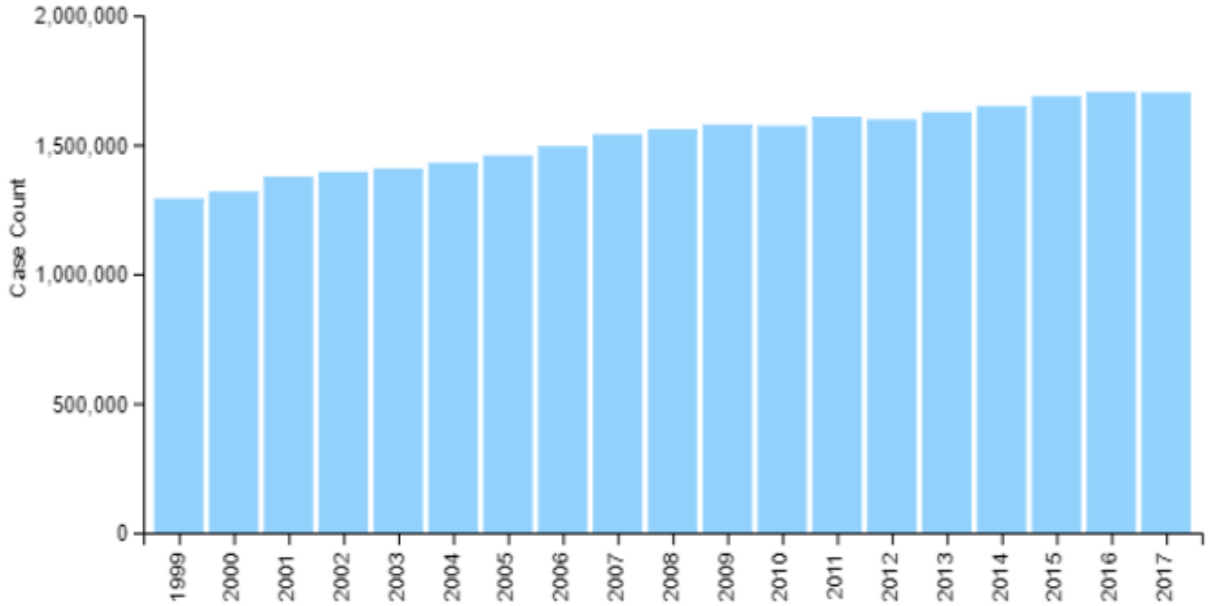
Objectives

- Understanding cellular therapies
- Know the different types of cellular therapies
- Understand the differences between emerging therapies
- Indications for using cellular therapies
- Future direction for innovative cancer treatment

Emerging Options for Cancer Treatment (Stem Cell)

Annual Number of New Cancers, 1999-2017

All Types of Cancer, United States



Data source – U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2019 submission data (1999-2017): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz , June 2020.

Emerging Options for Cancer Treatment (Stem Cell)

- Conventional methods of cancer treatment include surgery, radiation and chemotherapy.
- These modalities have made a some difference in improving outcomes, but most of the patients with cancer continued to have limited survival.
- Later on targeted agents and Immunotherapies have made a significant difference in the survival of cancer patients in general.
- Cellular therapies and Gene Therapies of the most recently developed modalities now being used clinically are not showing significant improvement in the survival of patients who have not responded to all of the above modalities.

Emerging Options for Cancer Treatment (Stem Cell)

Objectives

- **Understanding cellular therapies**
- Know the different types of cellular therapies
- Understand the differences between emerging therapies
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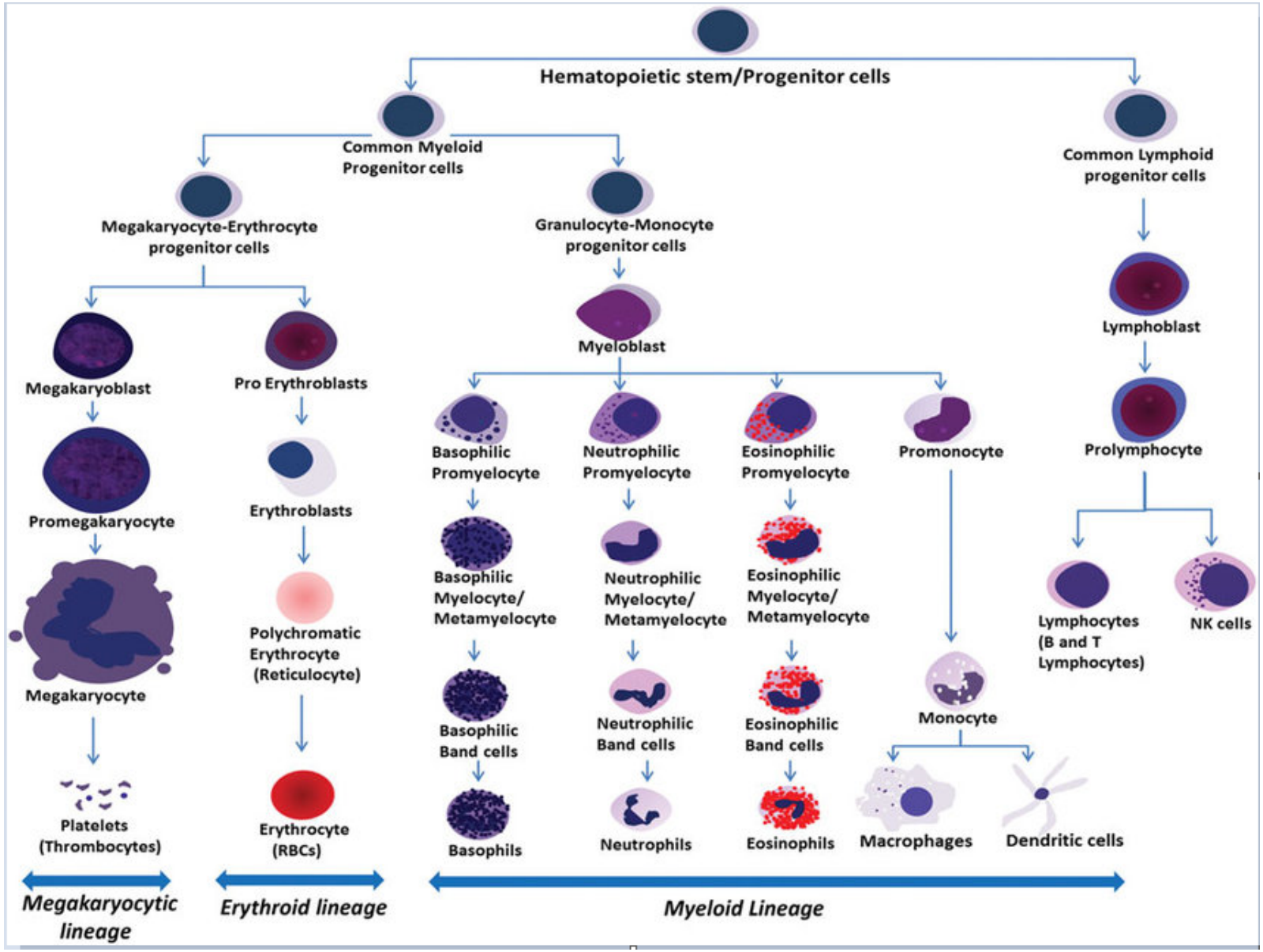
Understanding Cellular Therapies

- In adults **Bone Marrow** is the niche for producing all of the normal cells circulating in blood.
- All the cells in the blood are produced from **hemopoietic stem cells.**
- Hemopoietic stem cells or special cells that are formed during the embryonal development to produce blood cells.
- Blood production from hemopoietic stem cells started 3 months of gestation (6 months before birth for humans).

Understanding Cellular Therapies



Understanding Cellular Therapies (Continued)

Hemopoietic stem cells have 2 special characteristics:

1. They are **self regenerating**
   - This is important to maintain a population of hemopoietic stem cells in the bone marrow to be able to regenerate blood cells.

2. They **can differentiate to produce all of the different types of blood cells**
   - This differentiation process is an one way process.
   - This means that the differentiated cells cannot produce the stem cells that they are formed from.

Understanding Cellular Therapies (Continued)

- Bone Marrow Transplant vs Stem Cell Transplant
- Transplantation is the process by which an organ is taken out of a person and placed back in the same person or a different person.
  - In this case the organ being transplanted is the blood system.
- **Bone marrow transplant** is mainly to transplant the **Hemopoietic stem cells** located in the bone marrow.
- **They are the same for all practical purposes**

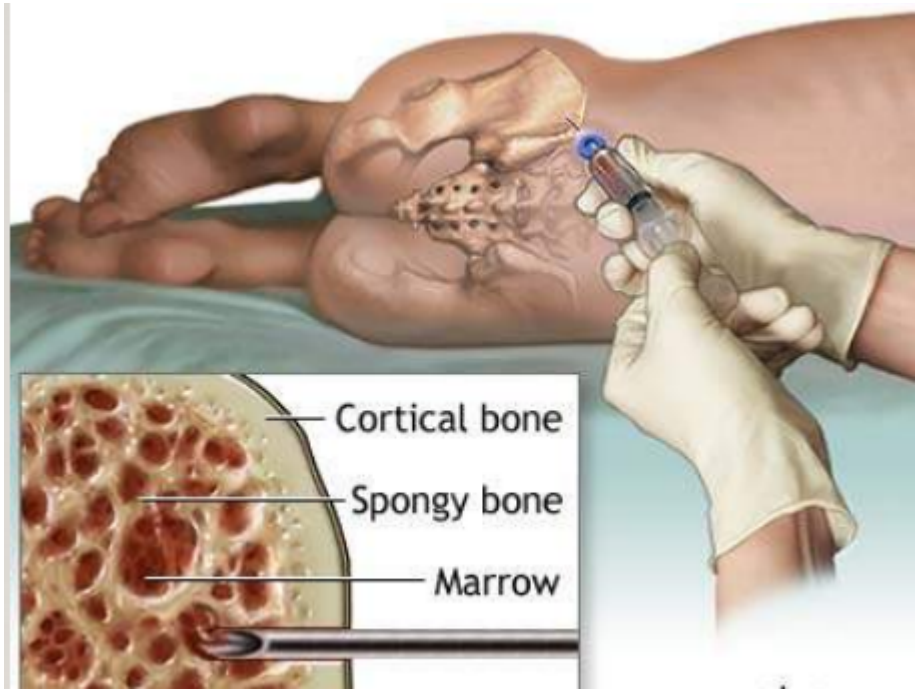
Understanding Cellular Therapies (Continued)

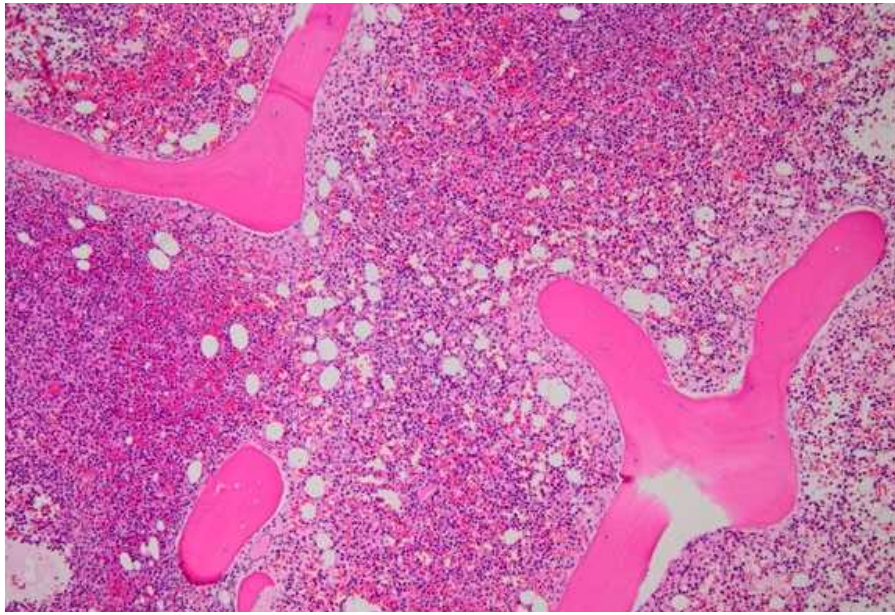
- Hemopoietic stem cells are necessary for keeping the bone marrow well populated and functional for producing all types of blood cell.

- **Damage to the bone marrow (hemopoietic stem cells) can lead to serious and life-threatening problems.**

- Chemotherapy or radiation treatment of cancers is dose adjusted to avoid damage to the bone marrow.

Understanding Cellular Therapies (Continued)
Bone Marrow Architecture

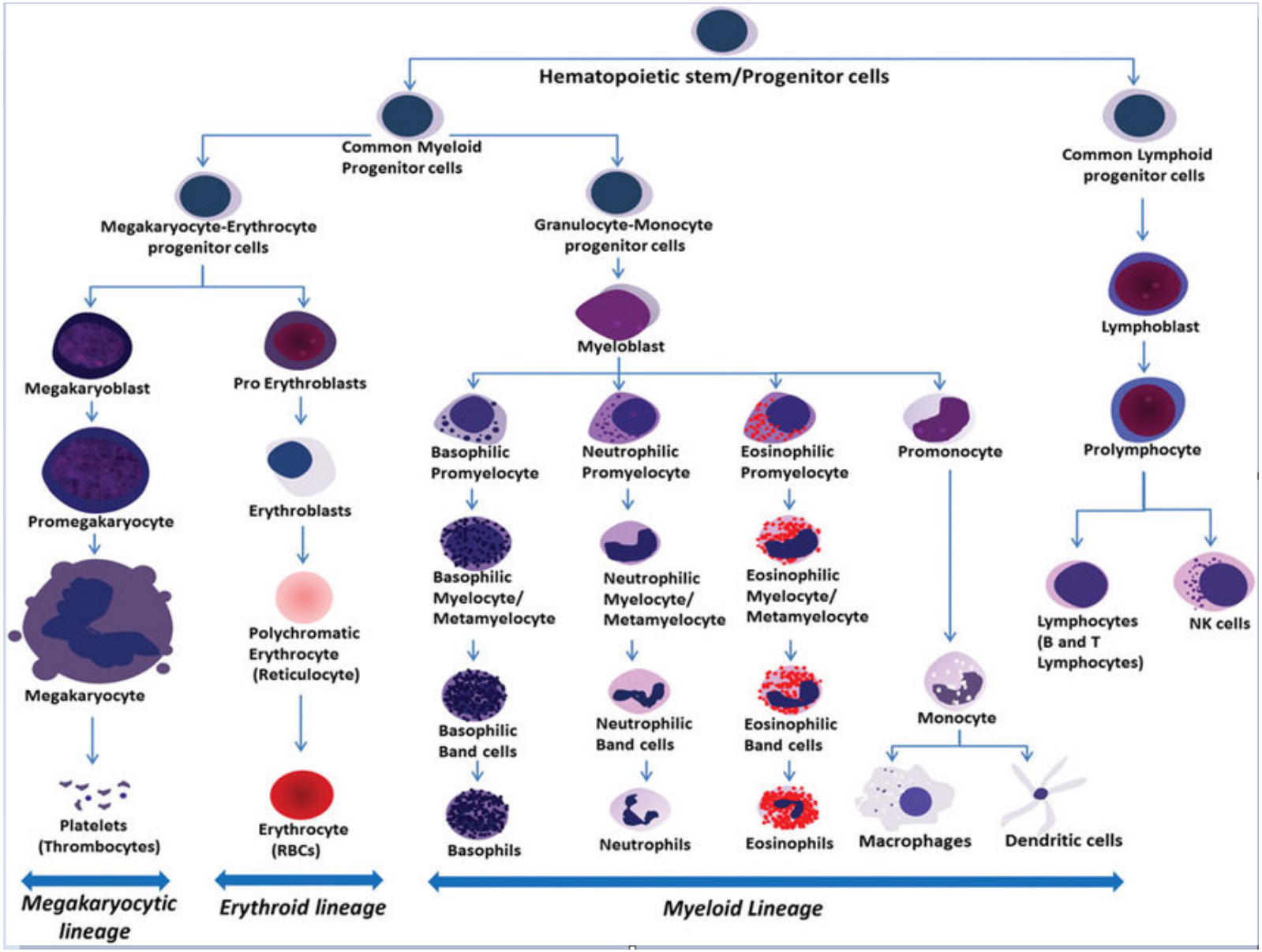




Understanding Cellular Therapies (Continued)

- Types of cells used for the treatment of cancer
- Hemopoietic stem cells
- T Lymphocytes
- Engineered T Lymphocytes
- NK cells
- Hemopoietic stem cells with treated gene (Gene Therapy)

Understanding Cellular Therapies



Understanding Cellular Therapies – Quick Recap

- Hemopoietic stem cells are essential for a person to live.
- Hence it is essential to preserve hemopoietic stem cells which is practiced in Autologous Stem Cell Transplantation.
- Hemopoietic stem cells generate all of the blood cells, including immune cells which are essential for Allogeneic stem cell transplantation.
- Chemotherapy or radiation treatment of cancers is adjusted to avoid damage to the bone marrow.

Emerging Options for Cancer Treatment (Stem Cell)

- Learning Objectives
- Understanding cellular therapies
- **Know the different types of cellular therapies**
- **Understand the differences between emerging therapies**
- **Indications for using cellular therapies**
- Future direction for innovative cancer treatment

Types of Cellular Therapies used for Cancer Treatment

- Stem cell transplantation
- Genetically engineered cellular therapies
- Gene therapies
- Indications for these treatments

Stem Cell Transplantation

Where are the stem cells collected from:

- Bone marrow
- Peripheral blood

Sources of Hemopoietic stem cells:

- Autologous
- Allogeneic

Stem Cell Transplantation: **Apheresis Process**

Used for Peripheral Blood Stem Cells Collection

Stem Cell Transplantation: **Harvested Bone Marrow**

- Performed in the operating room under general anesthesia.
- Bone marrow is extracted using bone marrow biopsy needles and syringes from the iliac crest of the pelvic bones bilaterally.
- Since the needles would be introduced repeatedly into the iliac crest to extract bone marrow with the syringes this would be a painful process and requires general anesthesia.
- The bone marrow extracted includes red blood cells and other blood cells so the donor will need close monitoring.
- Sometimes patients would need a blood transfusion if they are symptomatic from the blood removal during Bone Marrow Harvestation.

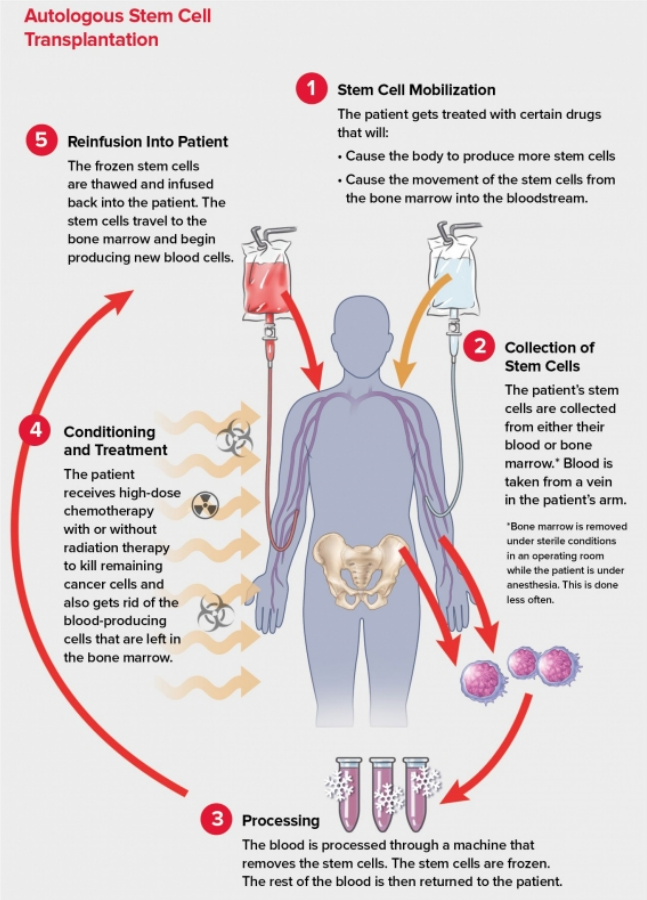
Stem Cell Transplantation: **Where are the stem cells collected from?**

- **Peripheral Blood Stem Cells (PBSC)**
  - CD34+ 2 ~ 5 x 10^6 /kg –Stem Cells
  - CD3+ 150 ~ 600 x 10^6 /kg –**T Lymphocytes**

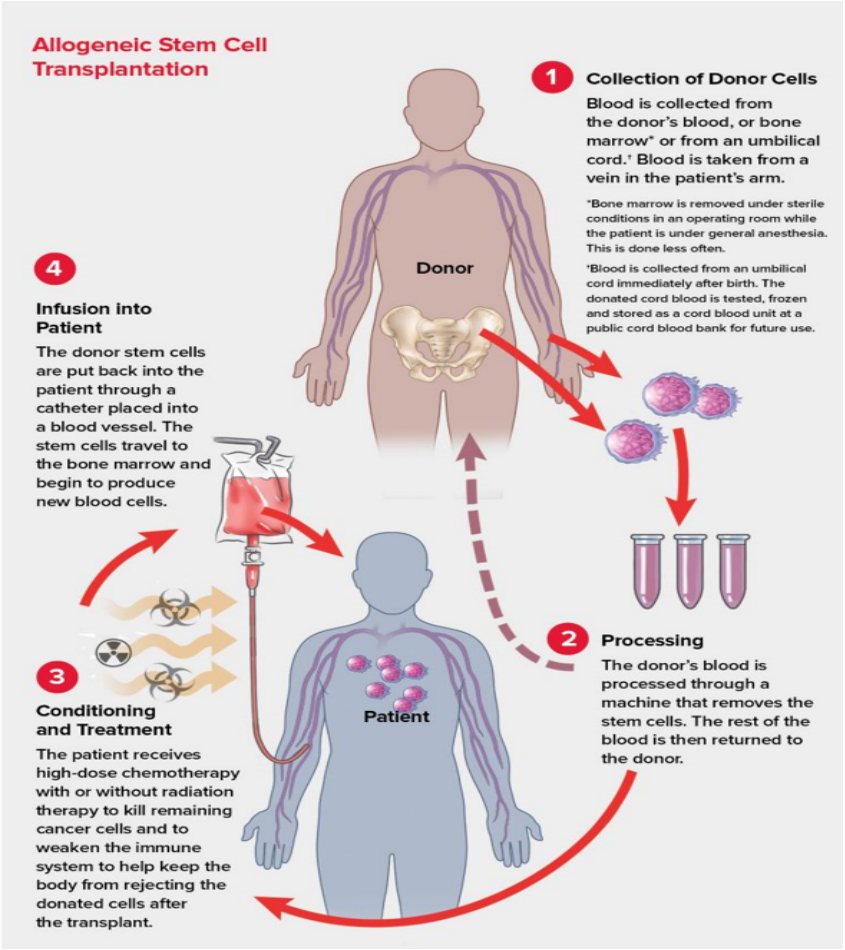
- **Harvested Bone Marrow**
  - CD34+ 2 ~ 4 x 106 /kg –Stem Cells
  - CD3+ 30 ~ 100 x 106 /kg –T Lymphocytes

Stem Cell Transplantation: **Sources of Hemopoietic Stem Cells**

Autologous



Allogeneic



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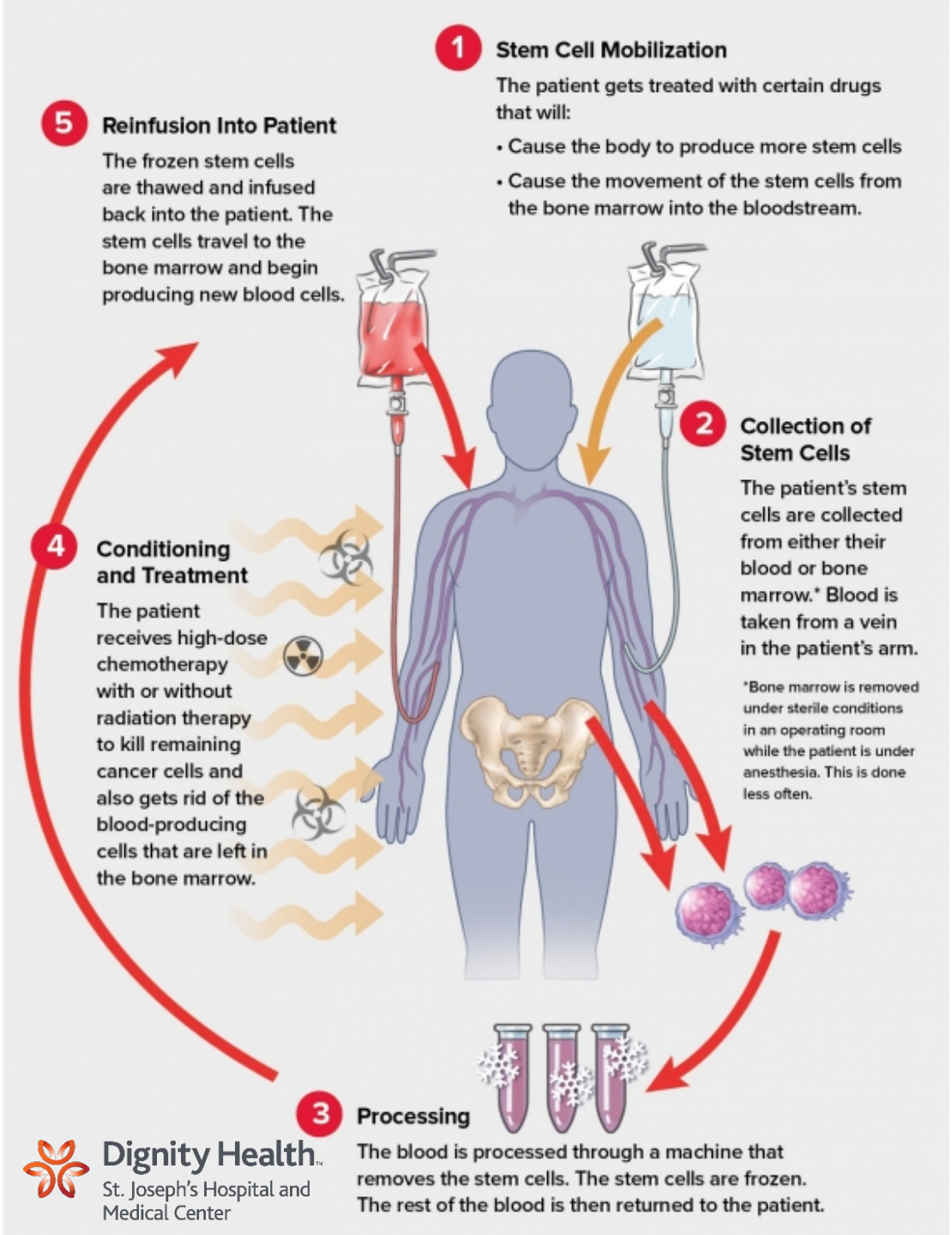

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Autologous Stem Cell Transplantation

Courtesy: LLS

Stem Cell Transplantation: **Pre-Treatment Testing**

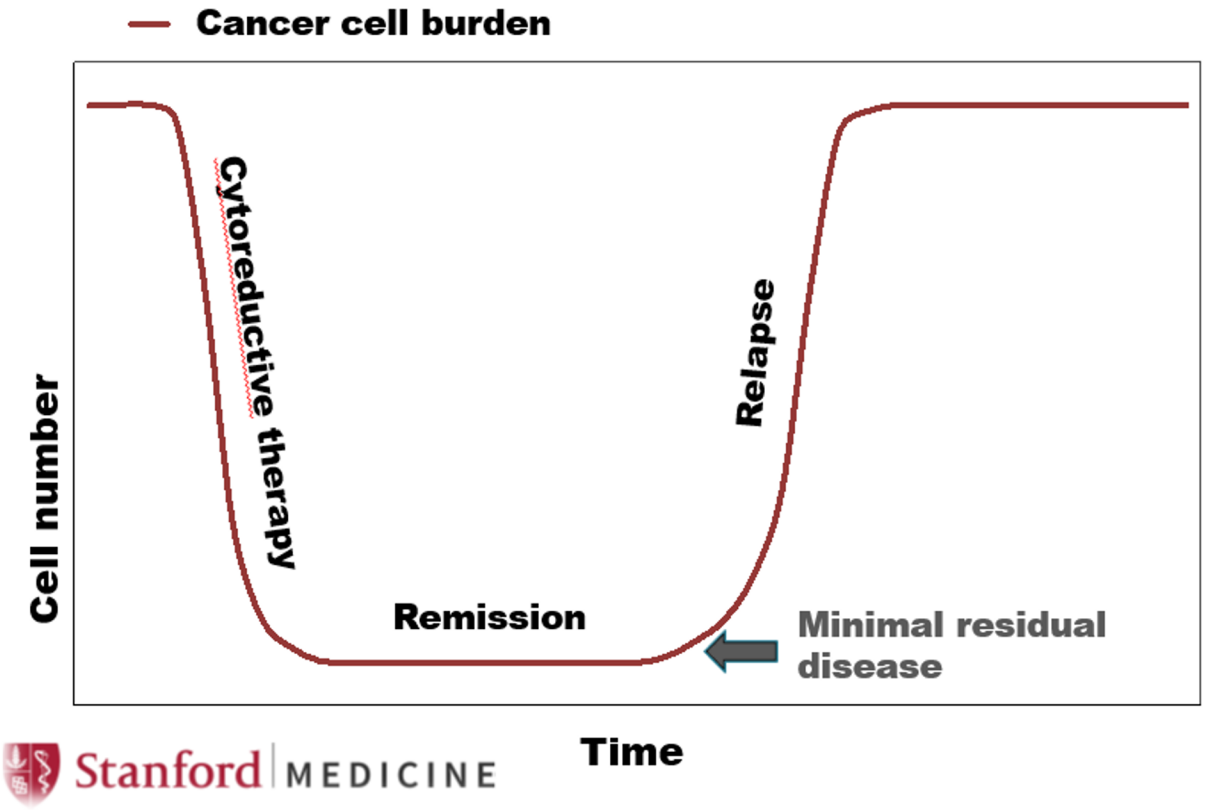
- Any cellular therapy process involves extensive testing to identify the suitable candidates.
- This testing would involve checking:
  - For any infectious markers of latent infections
  - Pulmonary function
  - Cardiac function
  - Bone marrow function.
  - *Depending on the patient's comorbidities additional testing may also be performed.

Stem Cell Transplantation : **Autologous Stem Cell Transplantation**

- Basic Principles:
  - When chemotherapy works to induce a remission we know that sometimes the disease can come back (recurrence).
  - The reason for that is during remission the disease burden decreases to undetectable levels because of her testing limitations.
  - So after the chemotherapy is stopped the disease starts to grow back to detectable levels at which point we realize that the disease has come back or relapsed.
  - If the chemotherapy is continued or given at a higher dose it can sometimes cause permanent bone marrow damage by destroying all of the hematopoietic stem cells.

Stem Cell Transplantation : **Autologous Stem Cell Transplantation (Continued)**

- Graph of the Disease level in Remission.

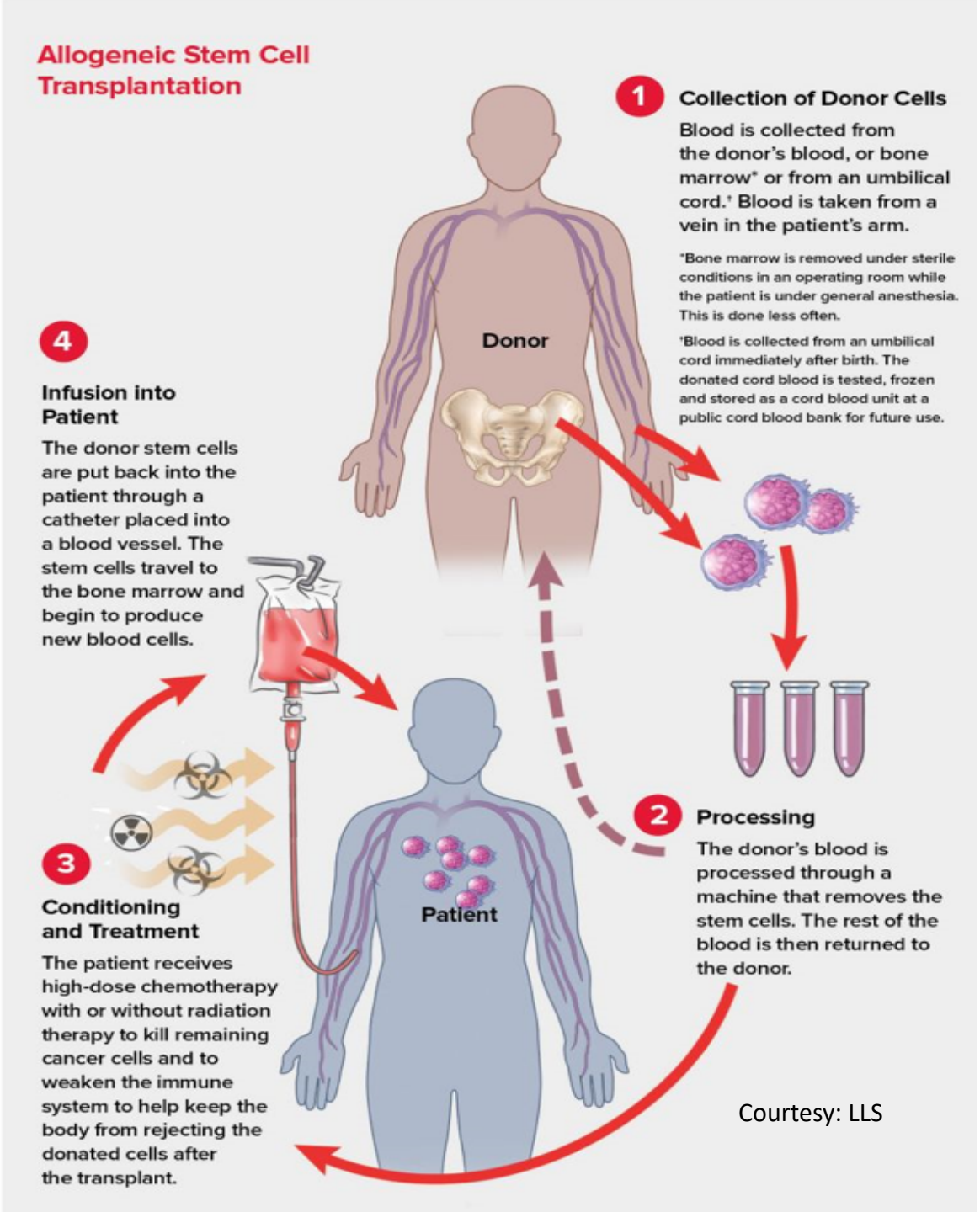


Stem Cell Transplantation: **Autologous Stem Cell Transplantation (Continued)**

- If regular dose of chemotherapy can achieve remission without completely ablating the patient's bone marrow a higher dose of chemotherapy might actually cure the disease but would ablate the bone marrow.
- This would mean that the patient would never be able to produce blood which ultimately means that.
- Objective of autologous stem cell transplantation is to give an extremely high dose of chemotherapy safely.

Stem Cell Transplantation: **Autologous Stem Cell Transplantation (Continued)**

- This is achieved by collecting and storing the hemopoietic stem cells prior to administering the high dose of chemotherapy.
- After the extremely high dose of chemotherapy is administered the stem cells can be infused to the patient which would allow marrow to regenerate and repopulate the blood cells.
- Patient would need to be closely monitored in the appropriate specially designed inpatient or outpatient setting for safe recovery from the process.



Courtesy: LLS

Allogeneic Stem Cell Transplantation

Stem Cell Transplantation : **Allogeneic Stem Cell Transplantation**

- This kind of transplantation involves using an appropriate donor of hemopoietic stem cells.
- HLA matching process is used to select the appropriate donor.
- This has a different mechanism than autologous stem cell transplantation in treating cancer.
- Allogenic stem cell transplantation uses the donor immune system to stop the cancer from coming back. This is called Graft Versus Tumor Effect.

Stem Cell Transplantation : **Allogeneic Stem Cell Transplantation (Continued)**

- Appropriate preparative regimen : Conditioning regimen
- What does the conditioning regimen do ?

A. Reduces disease burden

  - Appropriate regimen for the disease is chosen

B. Immunosuppression of the recipient

  - Facilitates engraftment and avoids graft rejection

- **Myeloablative:** Does both A and B
- **Reduced-intensity**: B and a little bit of A
- **Non-myeloablative:** Mostly B

Stem Cell Transplantation: **Allogeneic Stem Cell Transplantation (Continued)**

Efficacy depends on:

- Appropriate preparative regimen : Conditioning regimen
- Chemotherapy sensitivity
- Disease status at the time of transplant
- Sensitivity to graft-versus-tumor effect

Stem Cell Transplantation: **Allogeneic Stem Cell Transplantation (Continued)**

- Sensitivity to graft-versus-tumor effect
- (In order of decreasing efficacy)

CML

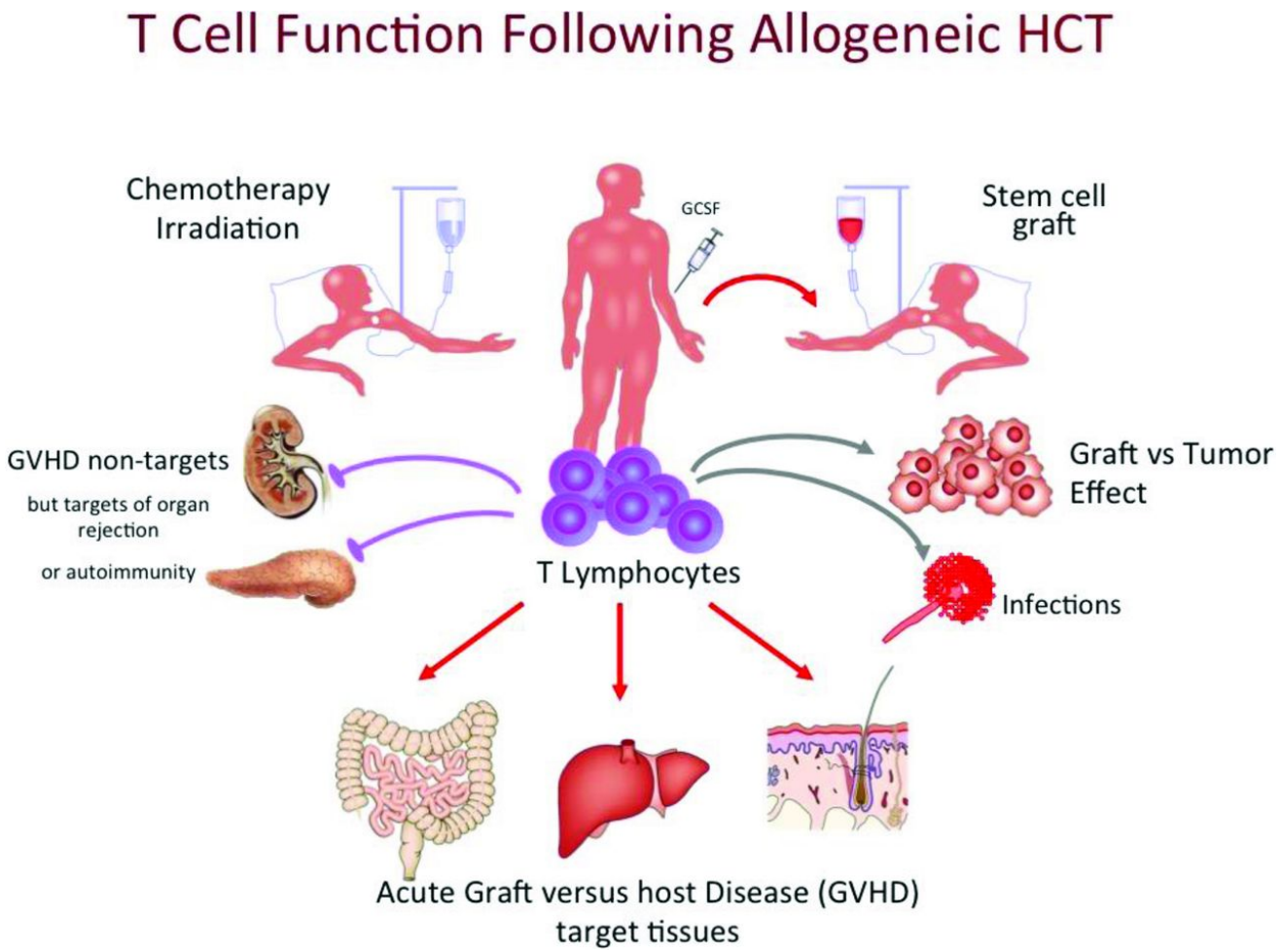
NHL or CLL

AML

ALL

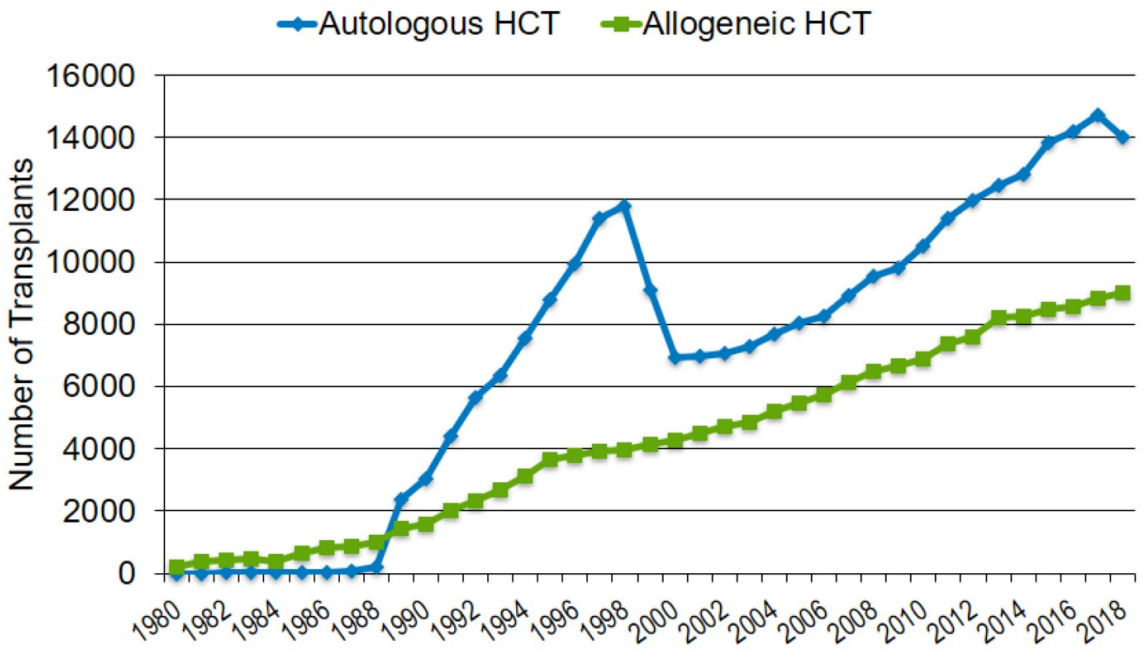
MM

Stem Cell Transplantation: **Allogeneic Stem Cell Transplantation (Continued)**



Stem Cell Transplantation: **By Numbers**

Annual Number of HCT Recipients in the US by Transplant Type



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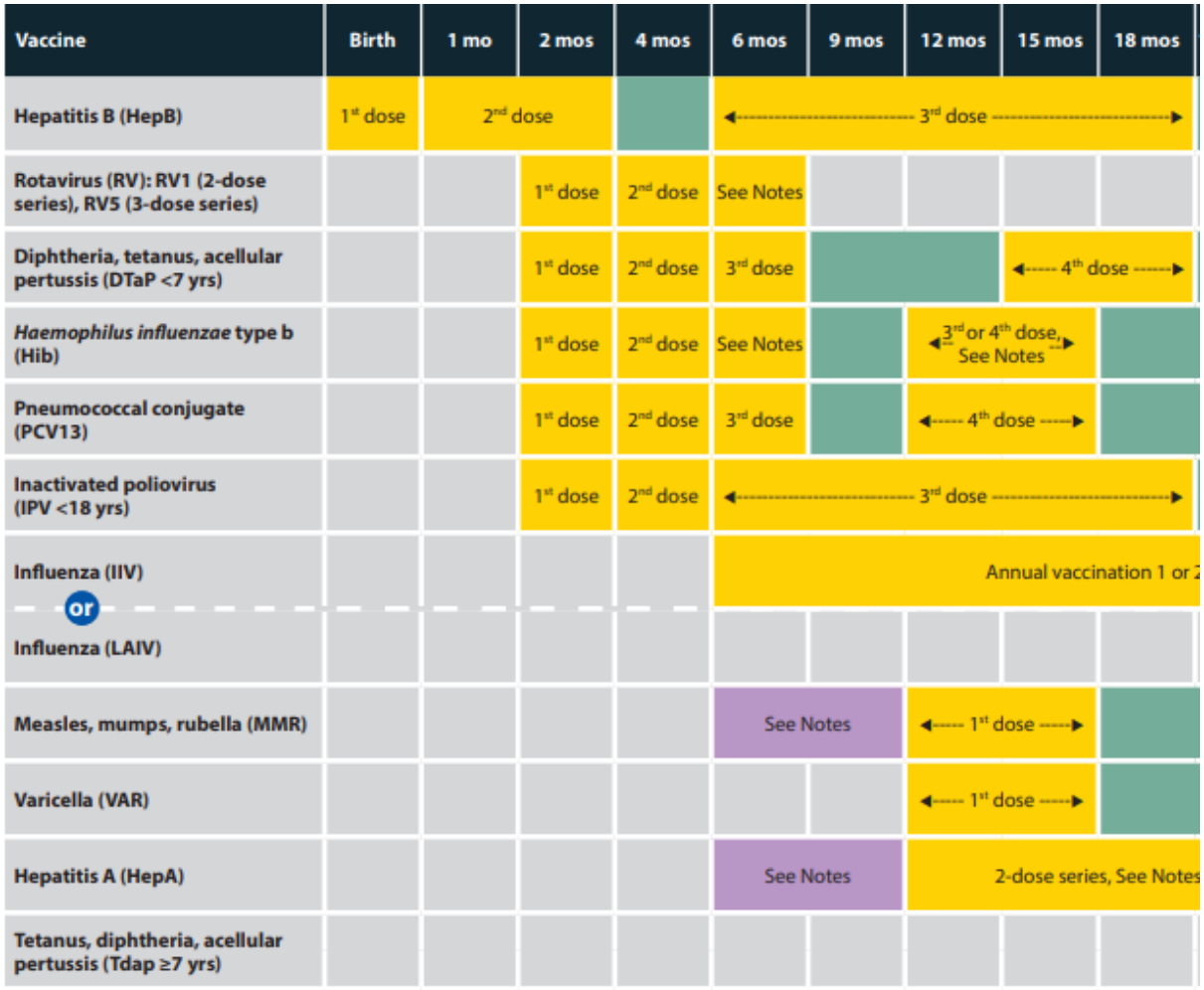
Stem Cell Transplantation: **By Numbers**

Autologous Stem Cell Transplantation	**Allogenic Stem Cell Transplantation**
➢ Less transplant related complications ➢ Need about 3-6 months of time off from work ➢ Less than 5% mortality from the transplant	➢ Higher rate of transplant related complications ➢ Need immunosuppressive medications for at least up to 6 months after transplant ➢ Need longer time off from work typically up to 1 year ➢ Typically about 20% mortality from the transplant

- **Will need to avoid situations that could result in high rate of infections**
- **Will need to get immunizations at about 6 months to 1 year after transplantation extending up to 2 years after transplantation.**

Childhood Immunization Schedule



Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos
Hepatitis B (HepB)	1st dose	2nd dose			3rd dose				
Rotavirus (RV): RV1 (2-dose series), RV5 (3-dose series)			1st dose	2nd dose	See Notes				
Diphtheria, tetanus, acellular pertussis (DTaP <7 yrs)			1st dose	2nd dose	3rd dose			4th dose	
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See Notes		3rd or 4th dose, See Notes		
Pneumococcal conjugate (PCV13)			1st dose	2nd dose	3rd dose		4th dose		
Inactivated poliovirus (IPV <18 yrs)			1st dose	2nd dose	3rd dose				
Influenza (IIV)					Annual vaccination 1 or 2				
or									
Influenza (LAIV)									
Measles, mumps, rubella (MMR)					See Notes		1st dose		
Varicella (VAR)							1st dose		
Hepatitis A (HepA)					See Notes		2-dose series, See Notes		
Tetanus, diphtheria, acellular pertussis (Tdap ≥7 yrs)									

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Post Transplant Immunization Schedule

POST-TRANSPLANT VACCINATION SCHEDULE										
Vaccine:	6 Months	8 Months	10 Months	12 Months	14 Months	16 Months	18 Months	24 Months	25 Months	60 Months
Inactivated Influenza (September to March)										
Pneumococcal conjugate (Prevnar 13)										
Acellular Pertussis-Tetanus-Diptheria (Tdap)										
Haemophilus influenza conjugate (HiB)										
Meningococcal conjugate (Menactra)										
Inactivated Polio (IPV)										
Recombinant Hepatitis B (Engerix)										
23-valent polysaccharide pneumococcal (Pneumovax)										
Live Vaccines:										
Measles-mumps-rubella (MMR) - live vaccine and uses 2-1-8 rule										
Varicella Zoster (Varivax) (seronegative ONLY and uses the 2-1-8 rule)										
High-Titer Varicella-zoster (Zostavax) for seropositive ONLY and Adults >60 yo ONLY and 5-1-8 Rule										
*2-1-8 Rule: Safe to give live attenuated vaccine when recipients are ≥2 years out from transplant, ≥1 year off all systemic IST and ≥8 months out from any prior IVIG dose										
*5-1-8 Rule: Safe to give live attenuated vaccine when recipients are ≥5 years out from transplant, ≥1 year off all systemic IST and ≥8 months out from any prior IVIG dose										

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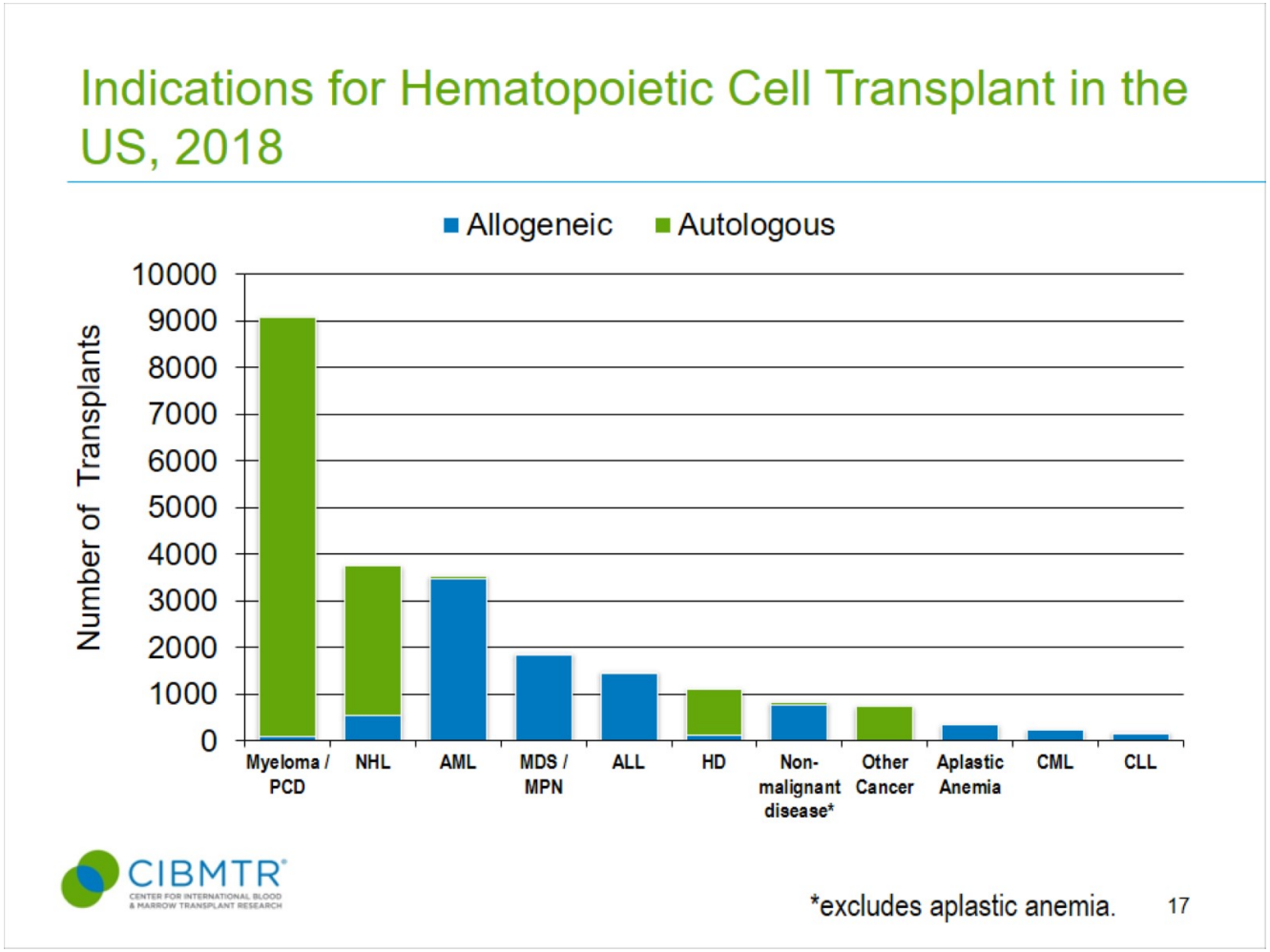
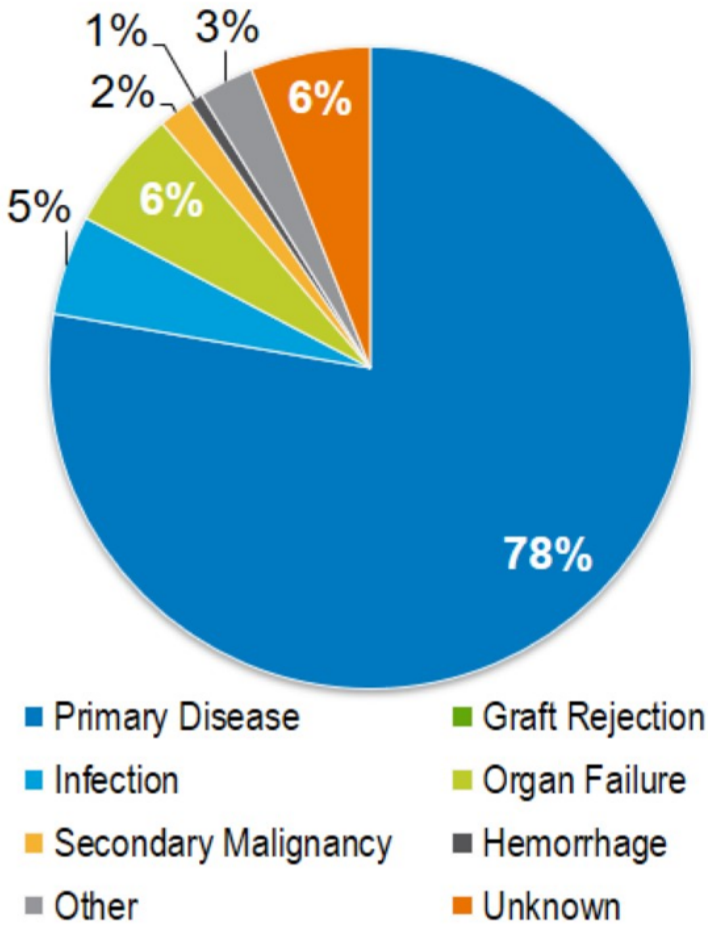
Stem Cell Transplantation: **By Numbers (Continued)**

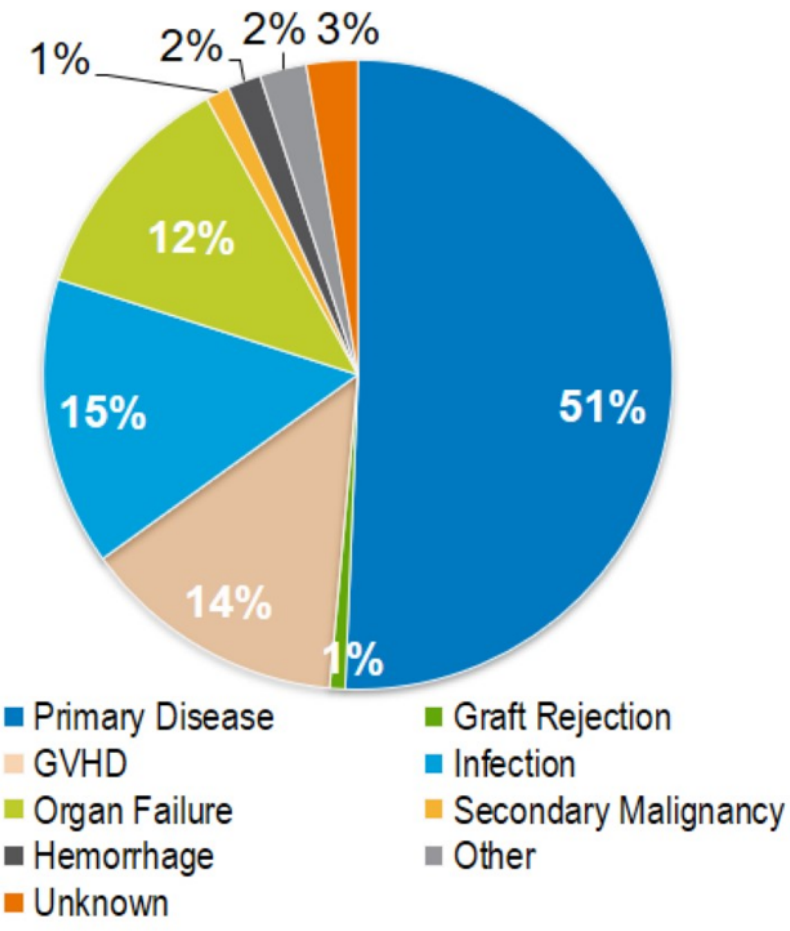


Stem Cell Transplantation: **By Numbers (Continued)**

Autologous Stem Cell Transplant



Allogeneic Stem Cell Transplant



*Data reflects 3-year mortality

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Types of Cellular Therapies used for Cancer Treatment

- Stem cell transplantation
- Genetically Engineered Cellular Therapies
- Gene therapies
- Indications for these emerging treatments

Genetically Engineered Cellular Therapies

- Chimeric Antigen Receptor –T Lymphocytes (CAR-T)
- Engineered NK cells (In clinical trials)

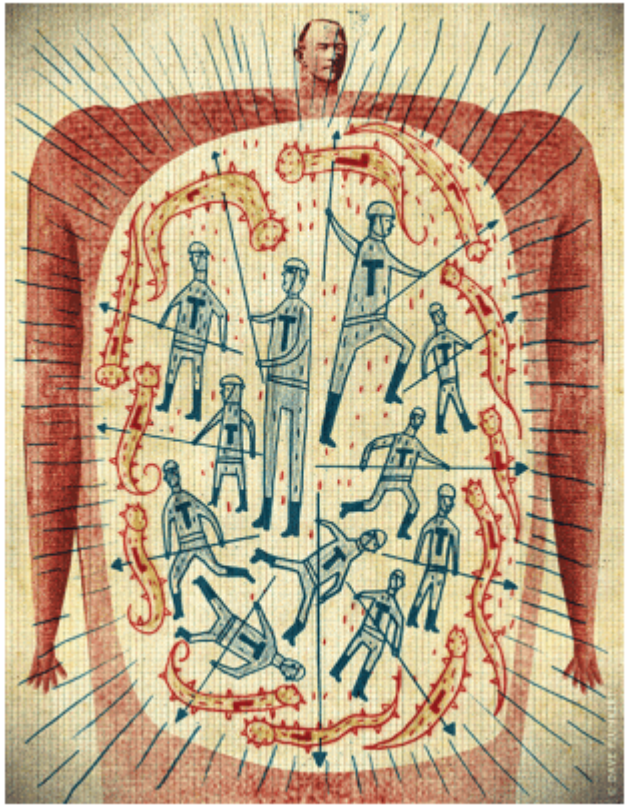
Genetically Engineered Cellular Therapies - (CAR-T)

The T-Cell Warriors

26 Feb 2015 5

Four years after a tentative but tantalizing breakthrough against leukemia, Carl June and Bruce Levine C'84 have gone from the fringes of gene therapy to the center of a revolutionary approach to cancer treatment. But first they had to run out of money, conquer skeptics, and turn a 12-year exile from cancer research to their advantage.

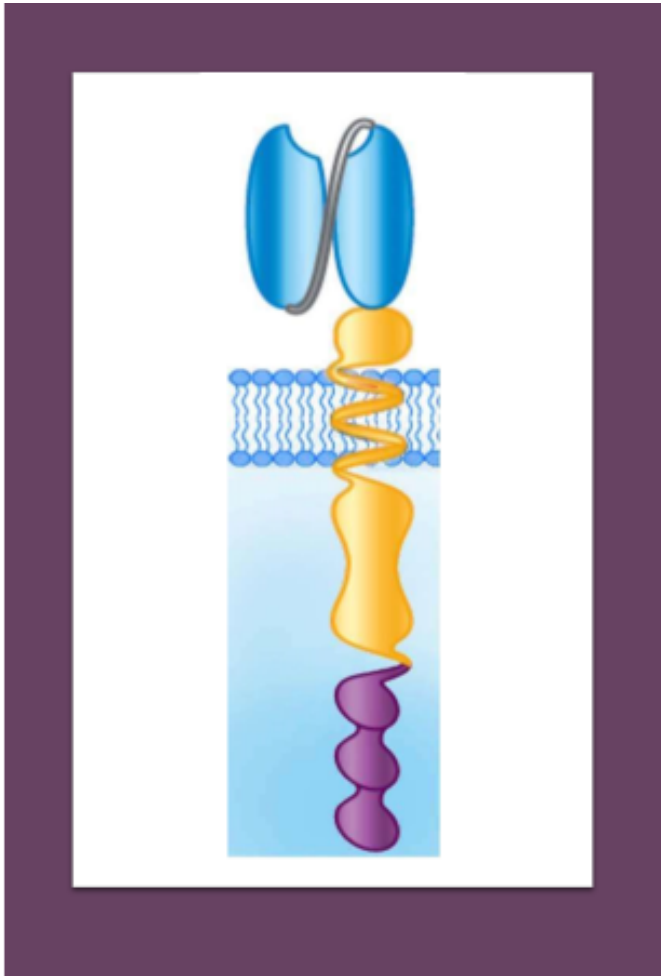
26 Feb 2015



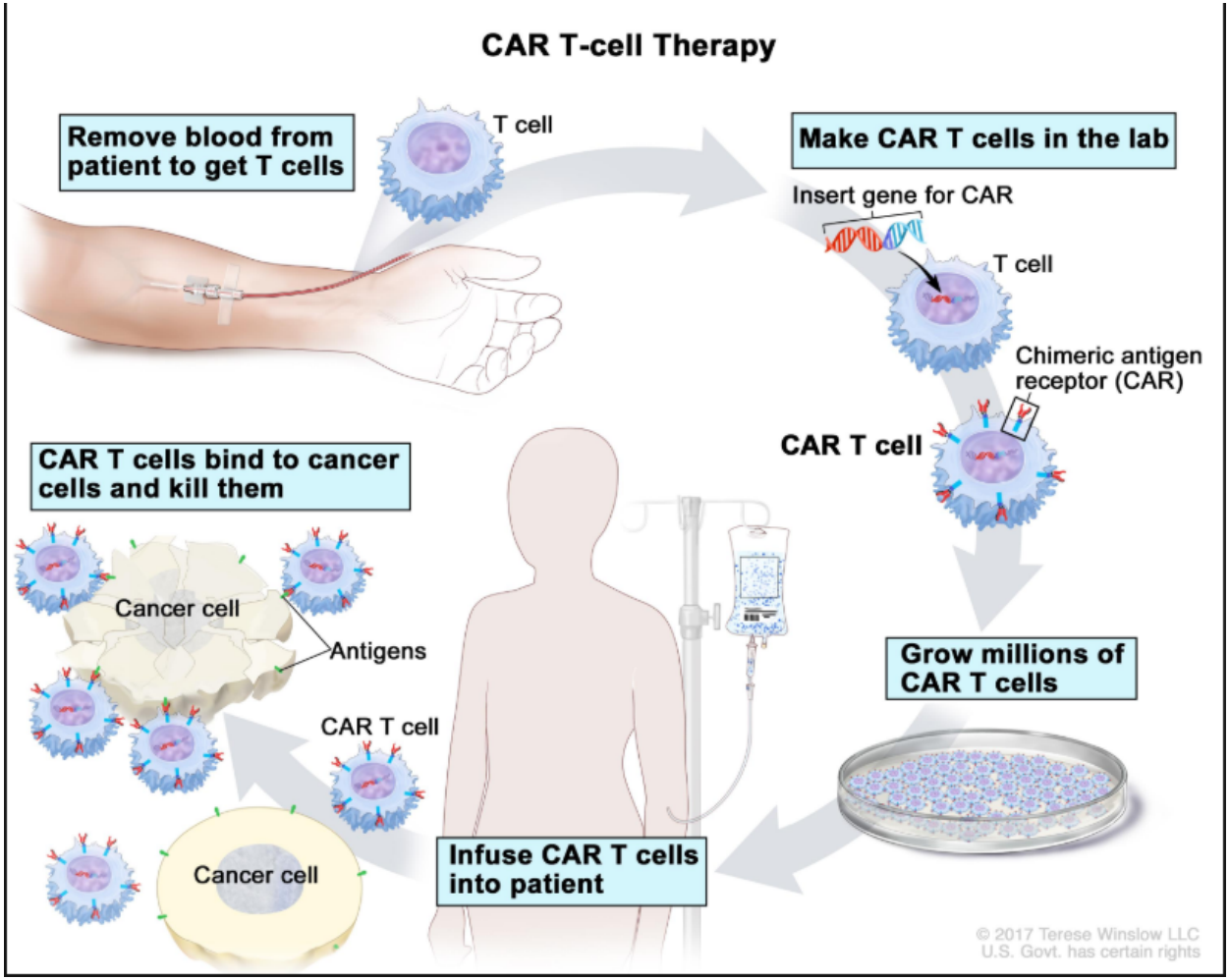
Genetically Engineered Cellular Therapies – CAR-T Cells

Chimeric Antigen Receptor – T cell

- **Extracellular domain** – TCR-pMHC Complex
- **Hinge** – Provides flexibility for appropriate CAR-epitope binding and function
- **Transmembrane domain** – Stable and high level expression on T cell surface
- **Costimulatory** signaling domain
- **Essential CD3 zeta** signaling domain



Genetically Engineered Cellular Therapies – CAR-T Cells



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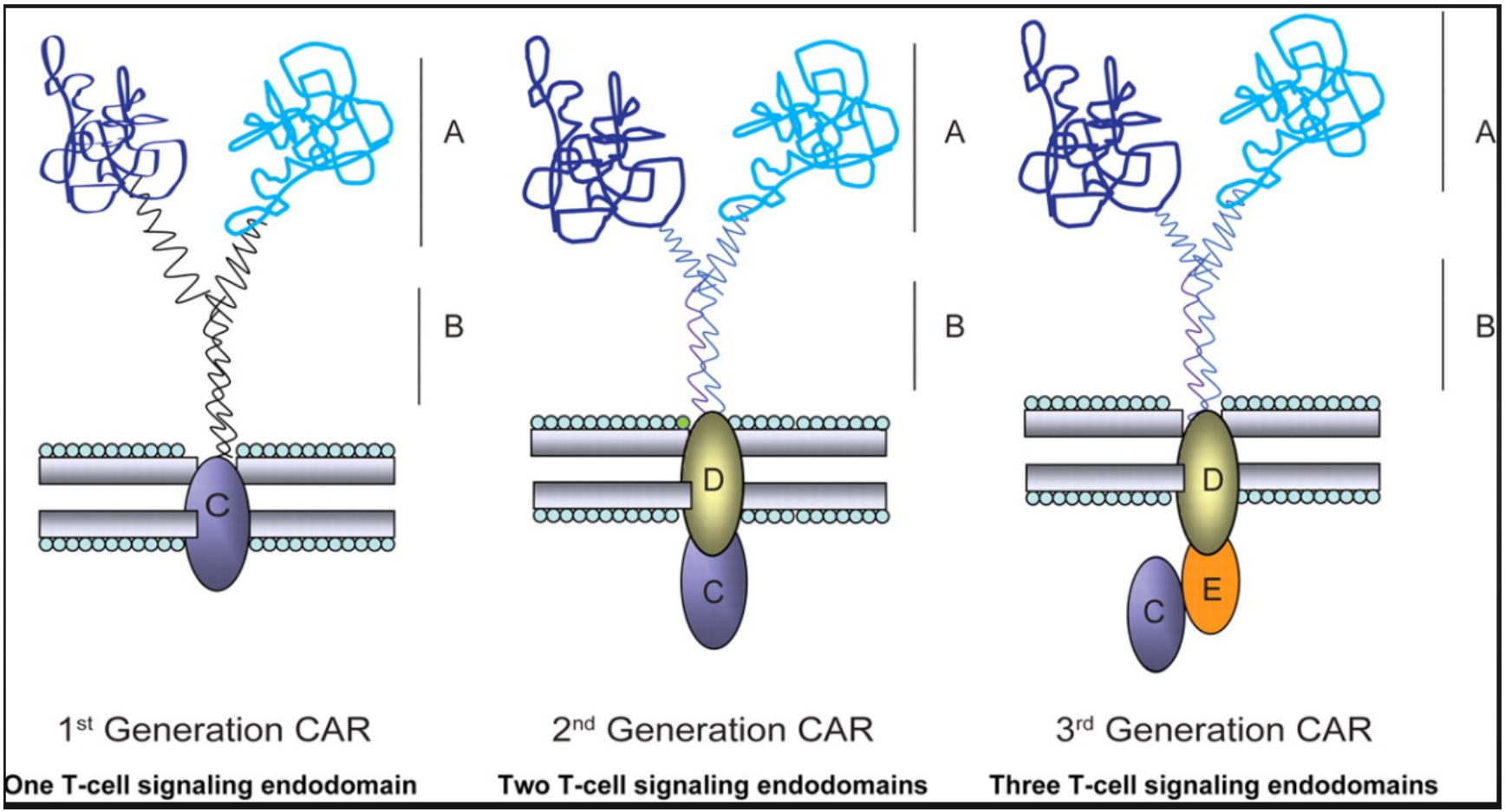
Genetically Engineered Cellular Therapies – CAR-T Cells



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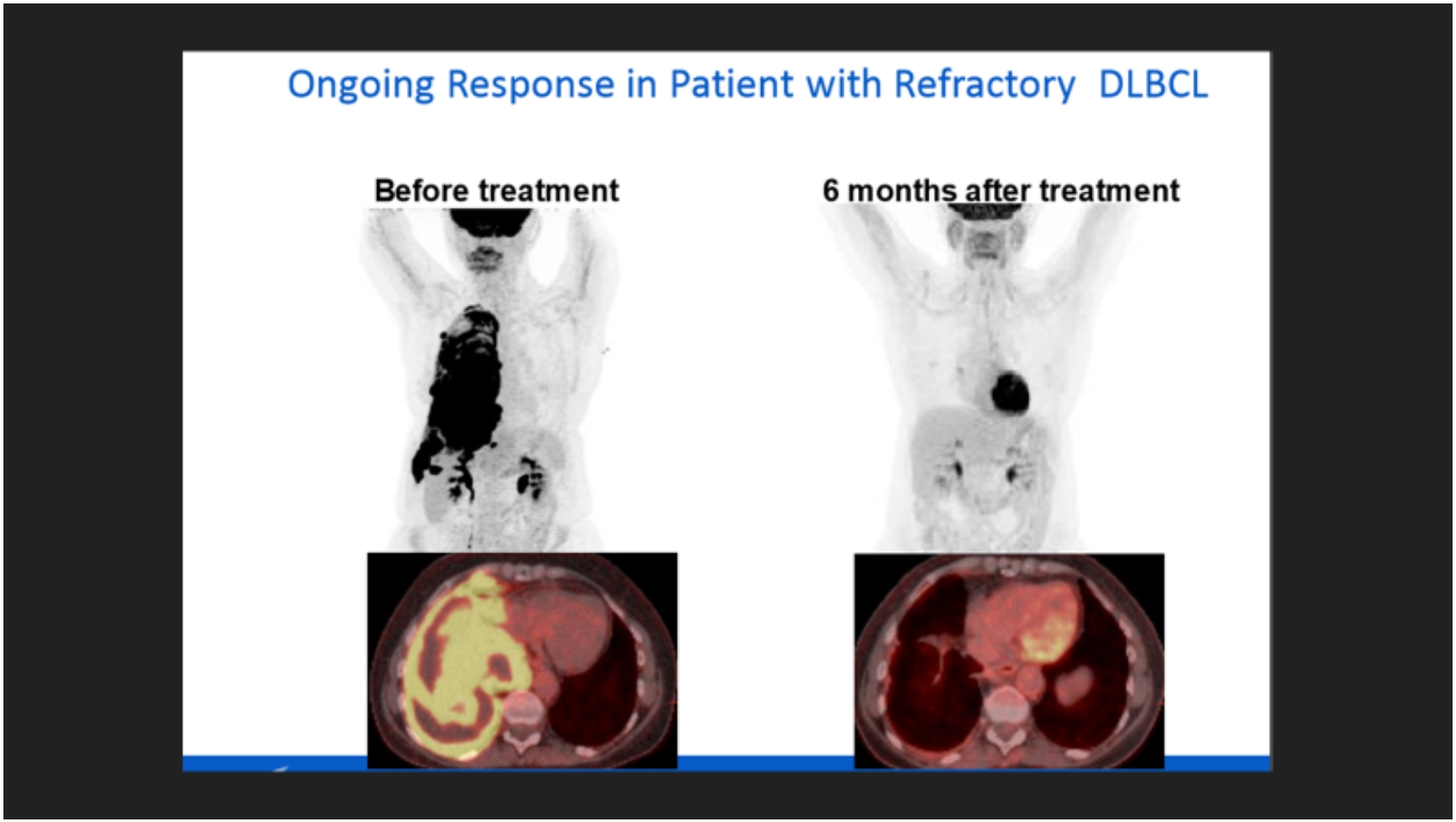
Genetically Engineered Cellular Therapies – CAR-T Cells

- **Co-stimulatory Domain**
- Function: Provides a second signal to stimulate full T cell activation.
- **4-1BB co-stimulatory domain :**
- Slow, Sustained and Persistent

- **CD28 co-stimulatory domain:**
- Rapid and Short lived

- **Costimulatory Domain can influence the activity of CAR-T cells**

Genetically Engineered Cellular Therapies – CAR-T Cells



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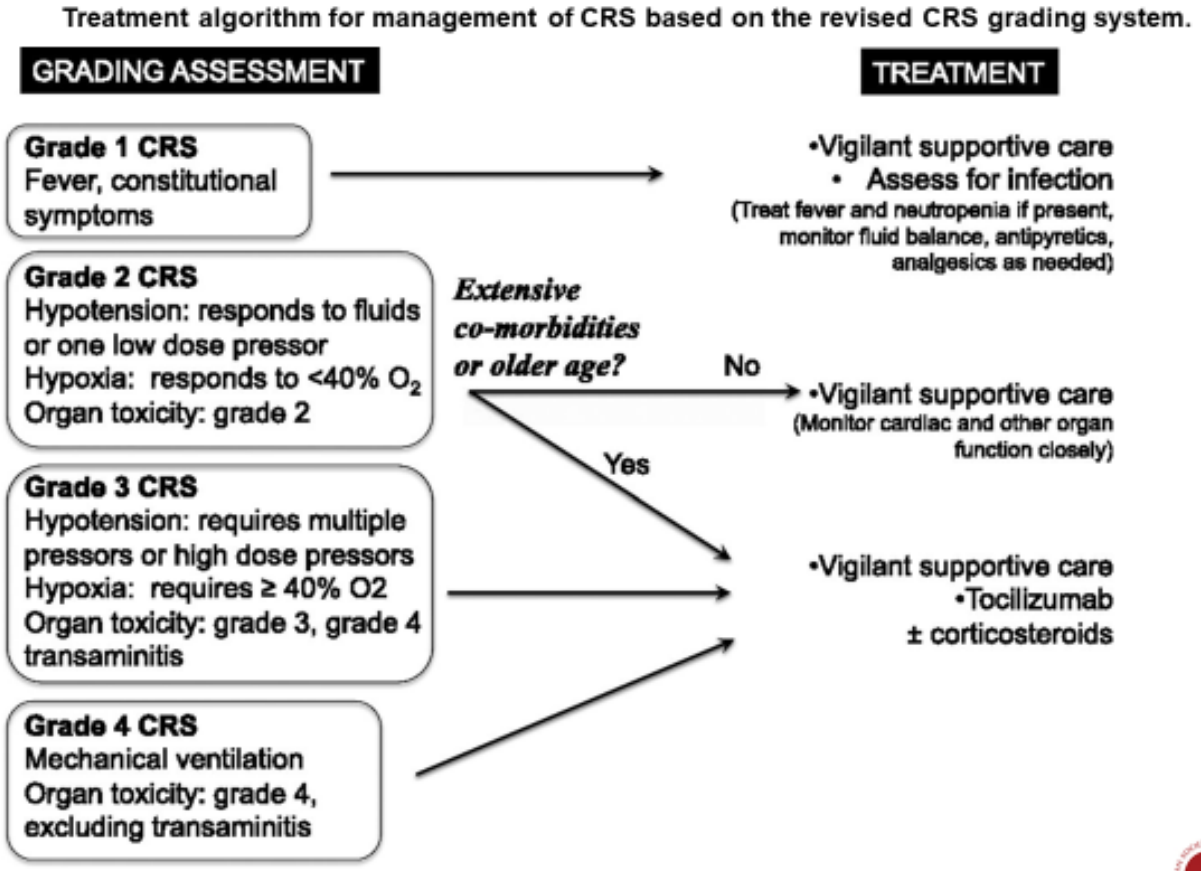
Genetically Engineered Cellular Therapies – CAR-T Cells



Daniel W. Lee et al. Blood 2014;124:188-195

blood

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Types of Cellular Therapies used for Cancer Treatment

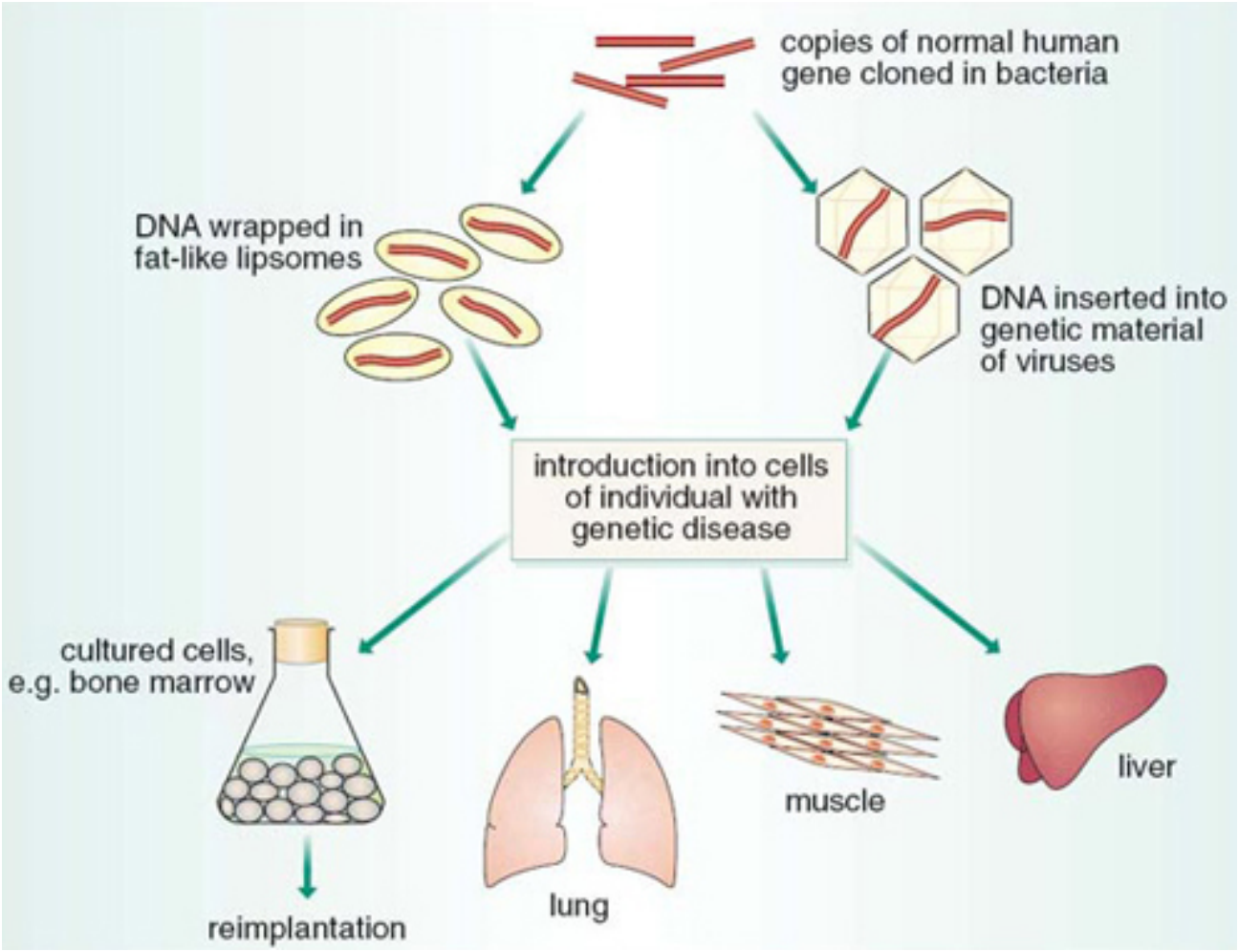
- Stem cell transplantation
- Genetically Engineered Cellular Therapies
- Gene Therapies
- Indications for these Treatments

Genetically Engineered Cellular Therapies – CAR-T Cells

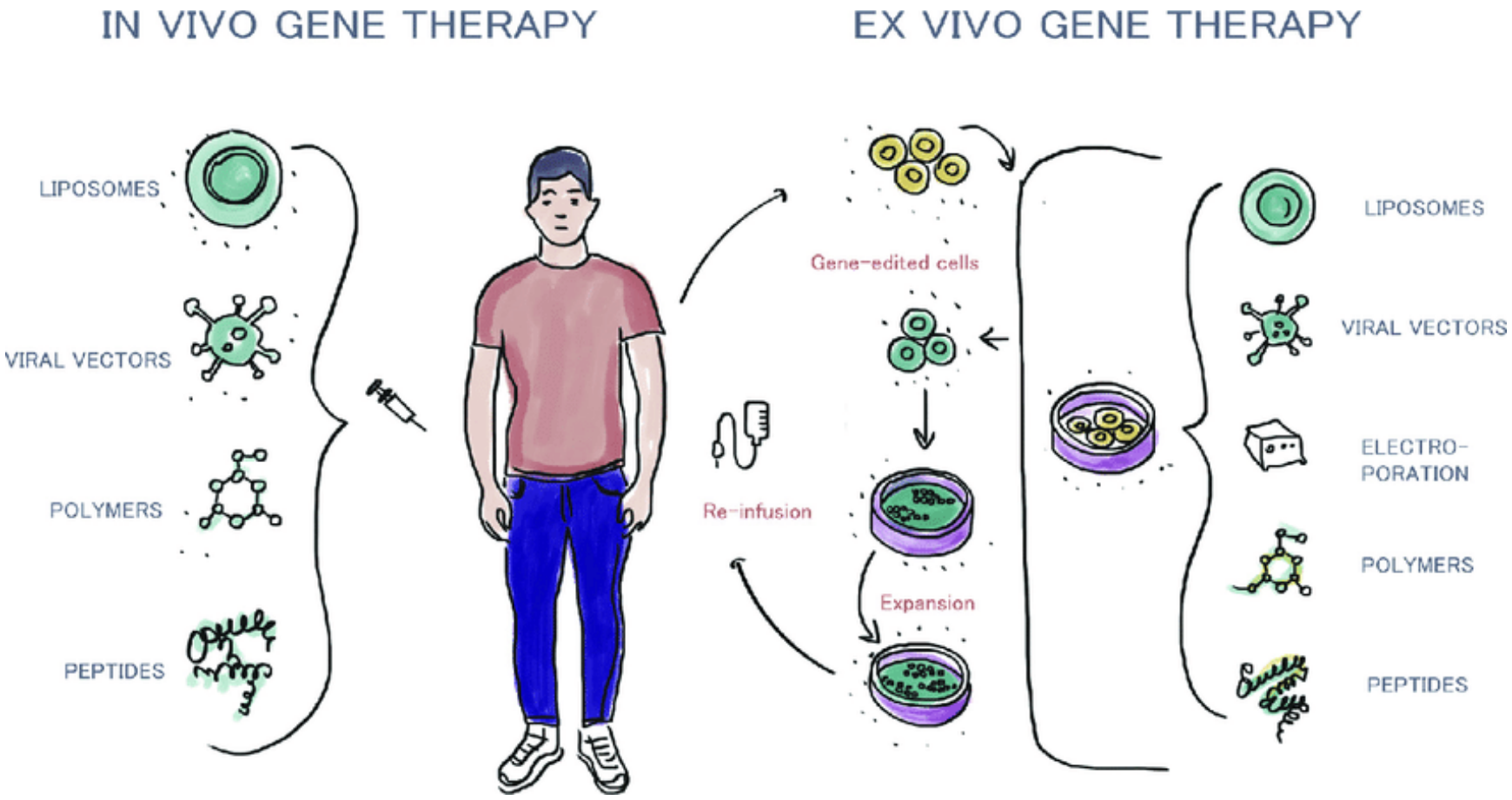
- Gene therapy is a process by which a gene is inserted into the patient's cell is up to restore a normal function or to modify an expression.

- Gene therapy of thalassemia and sickle cell anemia all examples of the therapy restoring the normal function.

Gene Therapies



Gene Therapies



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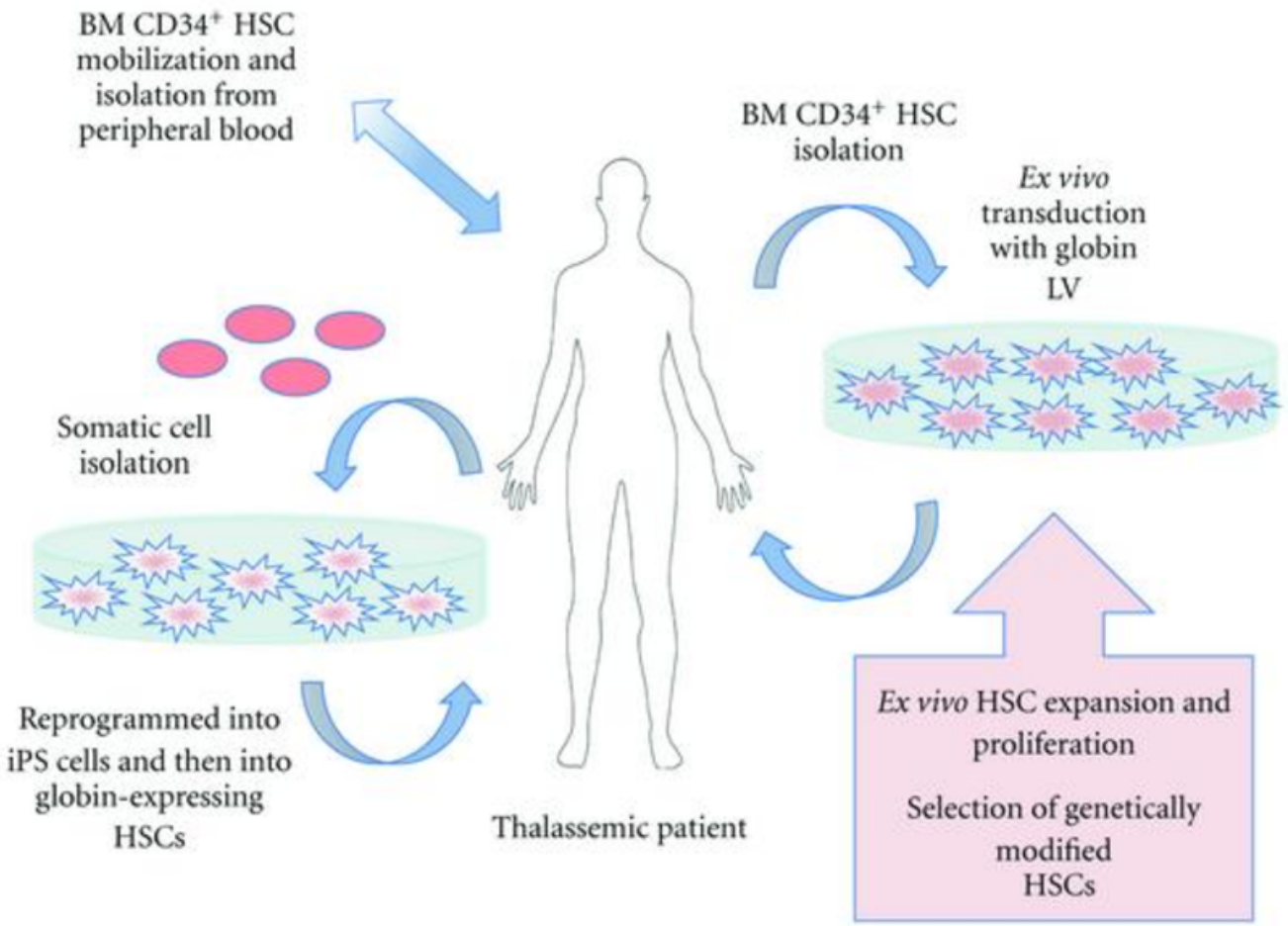
Gene Therapies



Indications for Cellular Treatments

Indications for Stem Cell Transplantation:

Multiple Myeloma

- Higher risk for early relapse

Lymphoma

- Relapsed or Refractory

Leukemia

- Higher risk Acute leukemias(AML and ALL)
- Chronic leukemias refractory to treatment (CML and CLL)

Indications for Cellular Treatments

Indications for CAR – T cell Therapy:

- Relapsed or Refractory Lymphoma
- Acute Lymphocytic Leukemia

Indications for Gene Therapy:

- Sickle Cell Anemia and Thalassemia

Future Direction for Innovative Cancer Treatment

Stem Cell Transplantation for:

- Rheumatologic disorders
- Neurologic disorders

T cell Therapy for:

- Multiple Myeloma
- AML
- Solid tumors
- Infections
- Autoimmune Conditions

Gene Therapy for:

- Coagulation disorders
- Multiple inherited disorders

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Everyone and Everything You Need In One Place

Hematology Oncologists

Murali Kodali, MD
Cellular Therapy and Hematologic Oncology

Soyoung Park, MD
Malignant Hematologic Oncology

Genetic Counselors

Karen Dirrigl, MS
Genetic Counselor

Kimberly Brussow, MS, CGC
Genetic Counselor

Pain and Palliative Care

Kerry Tobias, DO
Supportive Care and Survivorship

Radiation Oncology

Nitika Thawani, MD
Radiation Oncology

Medical Oncology

Mital Patel, MD
Gastrointestinal Oncology

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Other services involved in all decisions: Radiology and Pathology
When needed: Gynecologic Oncology and Urologic Oncology

Thank You!

For more information about cancer prevention, treatment, screening, or to request a speaker for your worksite on any cancer-related topic, **call:**

602.699.3366

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St. Joseph's Cancer Center - We are Here for You and Your Family!

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THANK YOU FOR WATCHING!

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