

Exploring the Evolution of the Biotherapies Revolution

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SCHOOL OF MEDICINE

Disclosures

- No relevant financial disclosures
- Board of Directors – Association for the Advancement of Blood and Biotherapies (AABB)
- Member of apheresis working group in the NHLBI Cure Sickle Cell Initiative

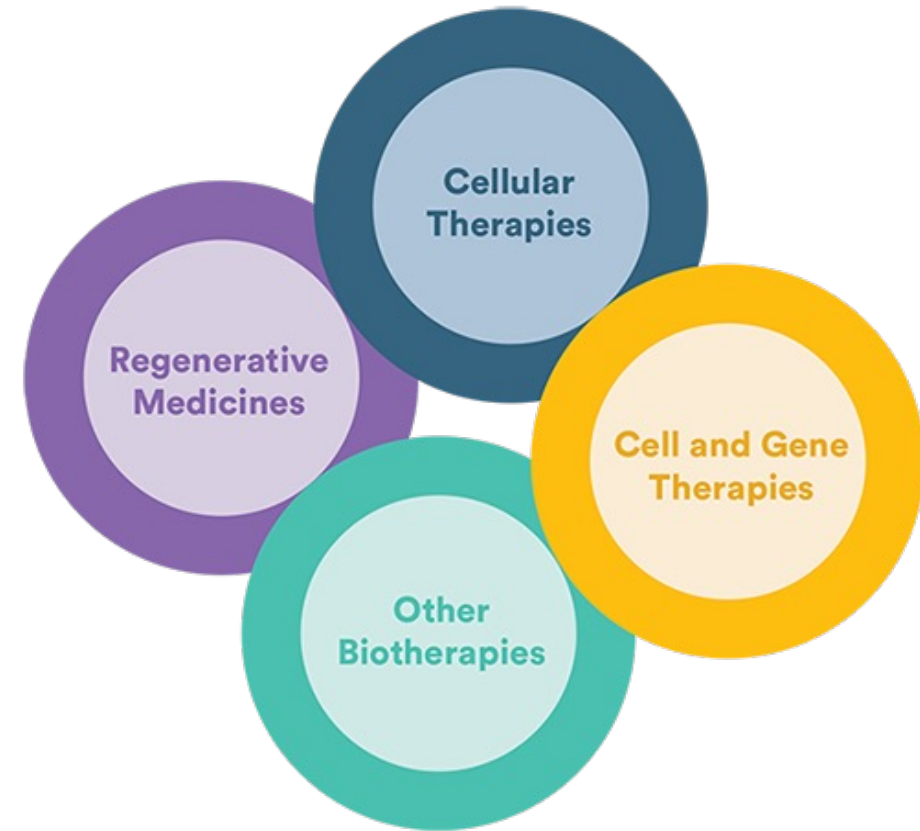
Learning objectives

By the end of this presentation, audience members should be able to:

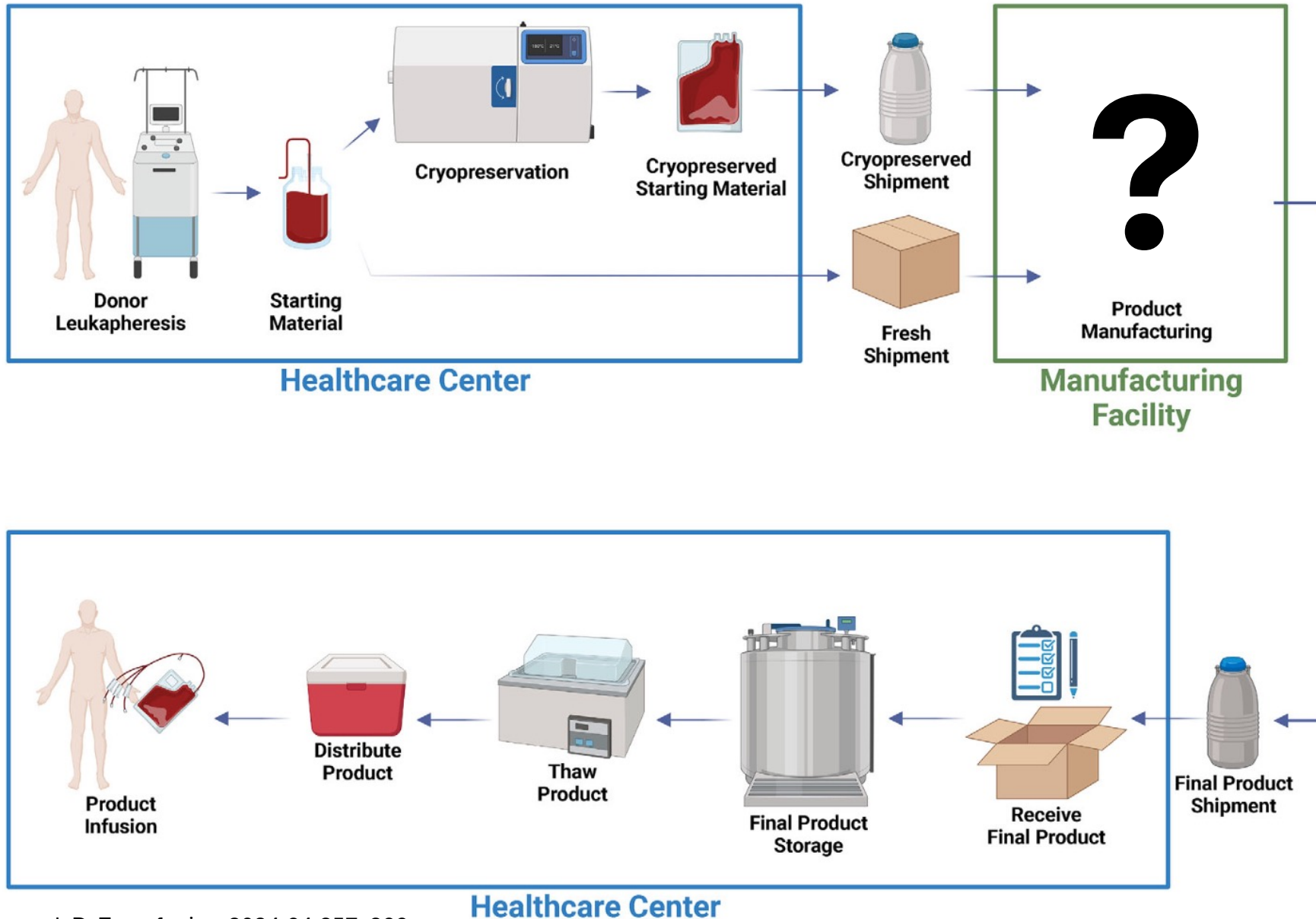
- Describe general characteristics of biotherapies in clinical use
- Compare biotherapies under development in anticipation of clinical use

Defining biotherapies

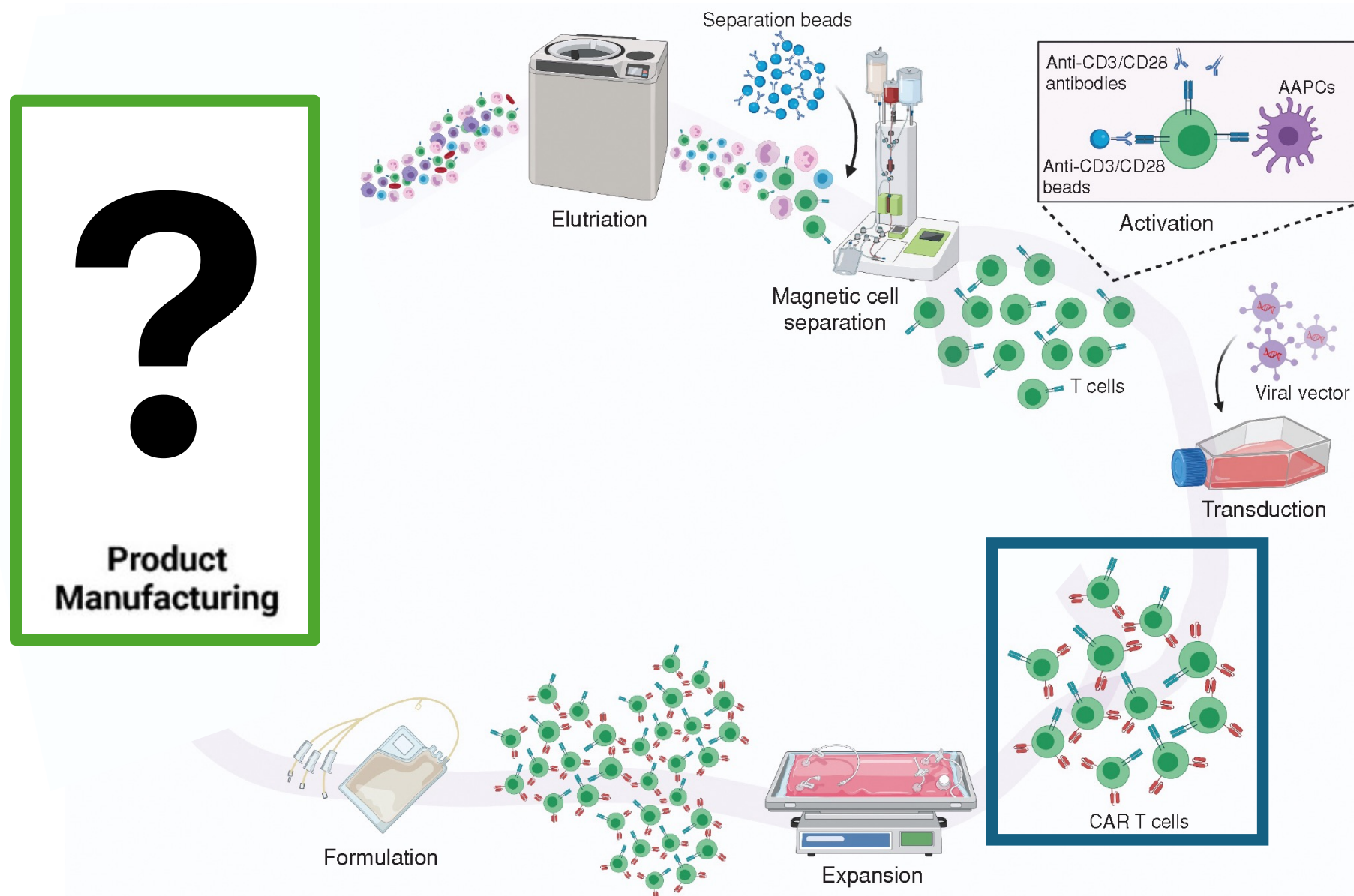
- Substances made from living organisms to treat disease that may occur naturally in the body or may be made in the laboratory
- Types of biotherapy can include (a few examples):
 - Molecules
 - cytokines
 - cancer vaccines
 - Antibodies
 - Cells
 - Blood transfusions (the original biotherapy!)
 - hematopoietic stem cell transplants
 - Genetically modified cells
 - Chimeric antigen receptor T cells
 - Genetically modified hematopoietic stem cells



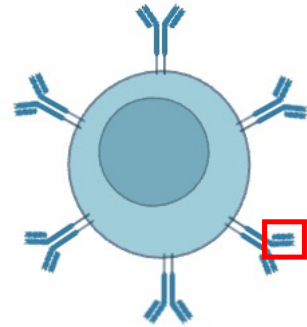
Manufacturing genetically modified cells is a complex process



Manufacturing genetically modified cells is a complex process

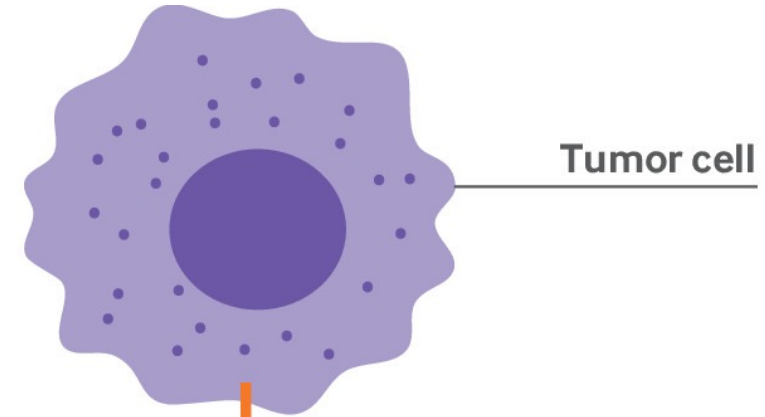
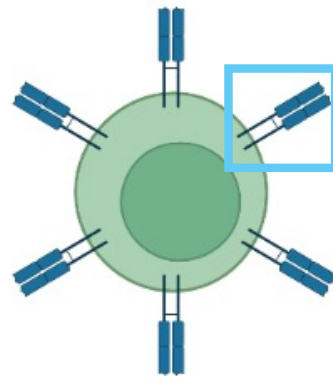


Chimeric Antigen Receptor (CAR) T cells combines the best of B cell and T cell functions

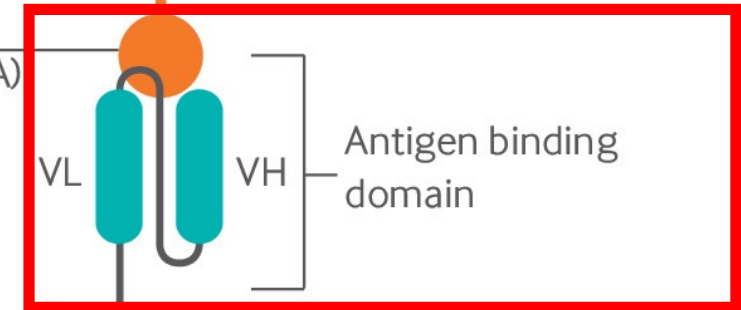


B cell (with antibodies)

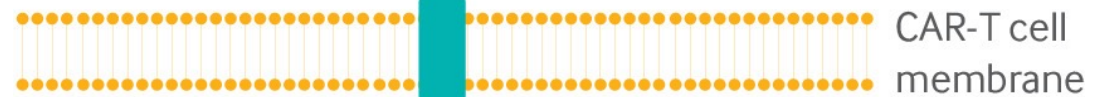
T-cell (with TCRs)



Target antigen
(eg, CD19 or BCMA)



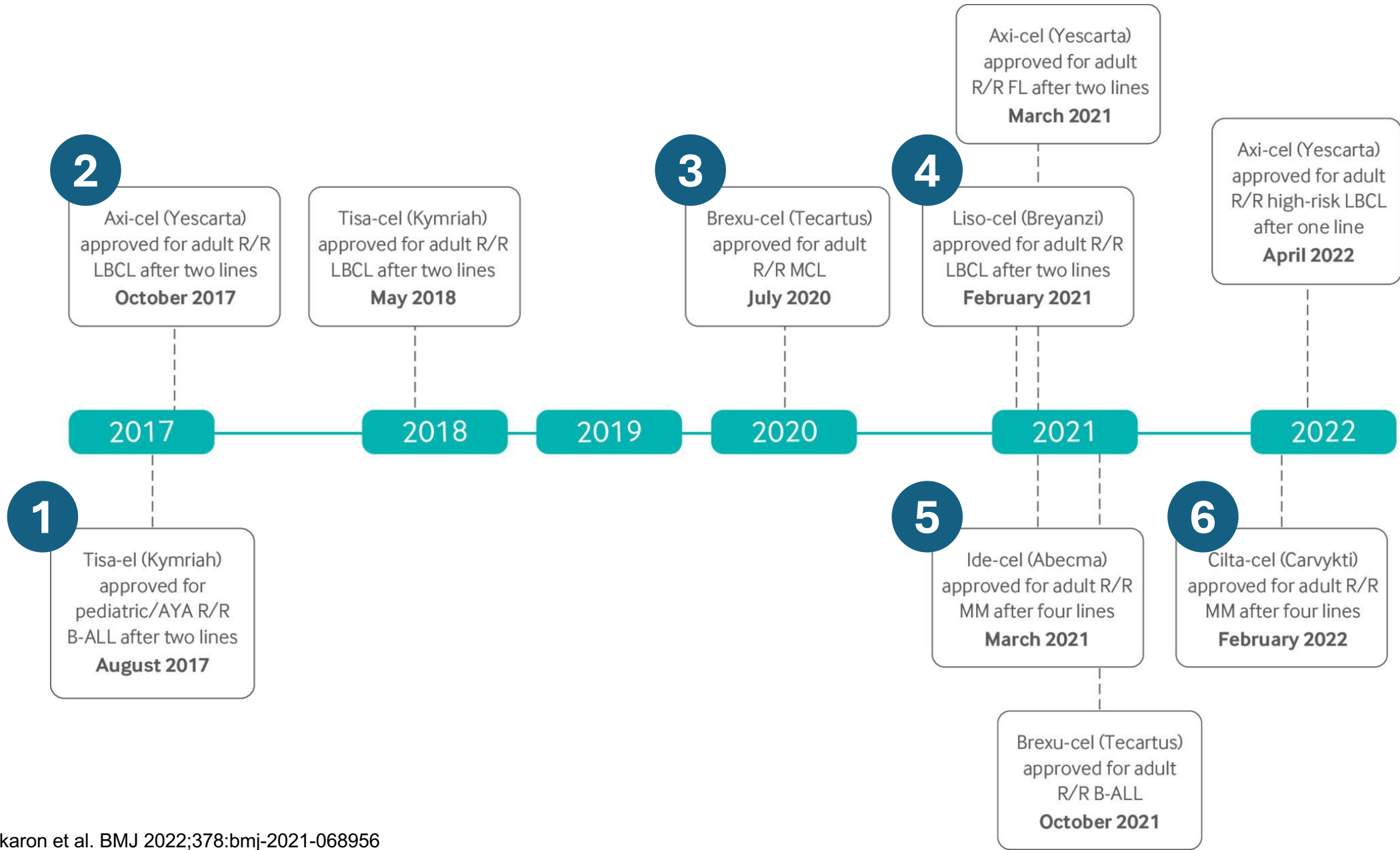
Antigen binding domain



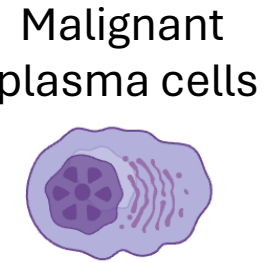
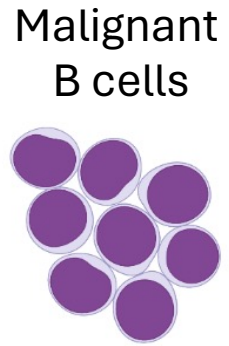
Costimulation domain
(41BB or CD28)

Activation domain
(CD37)

There are currently 6 CAR T cells approved for clinical use

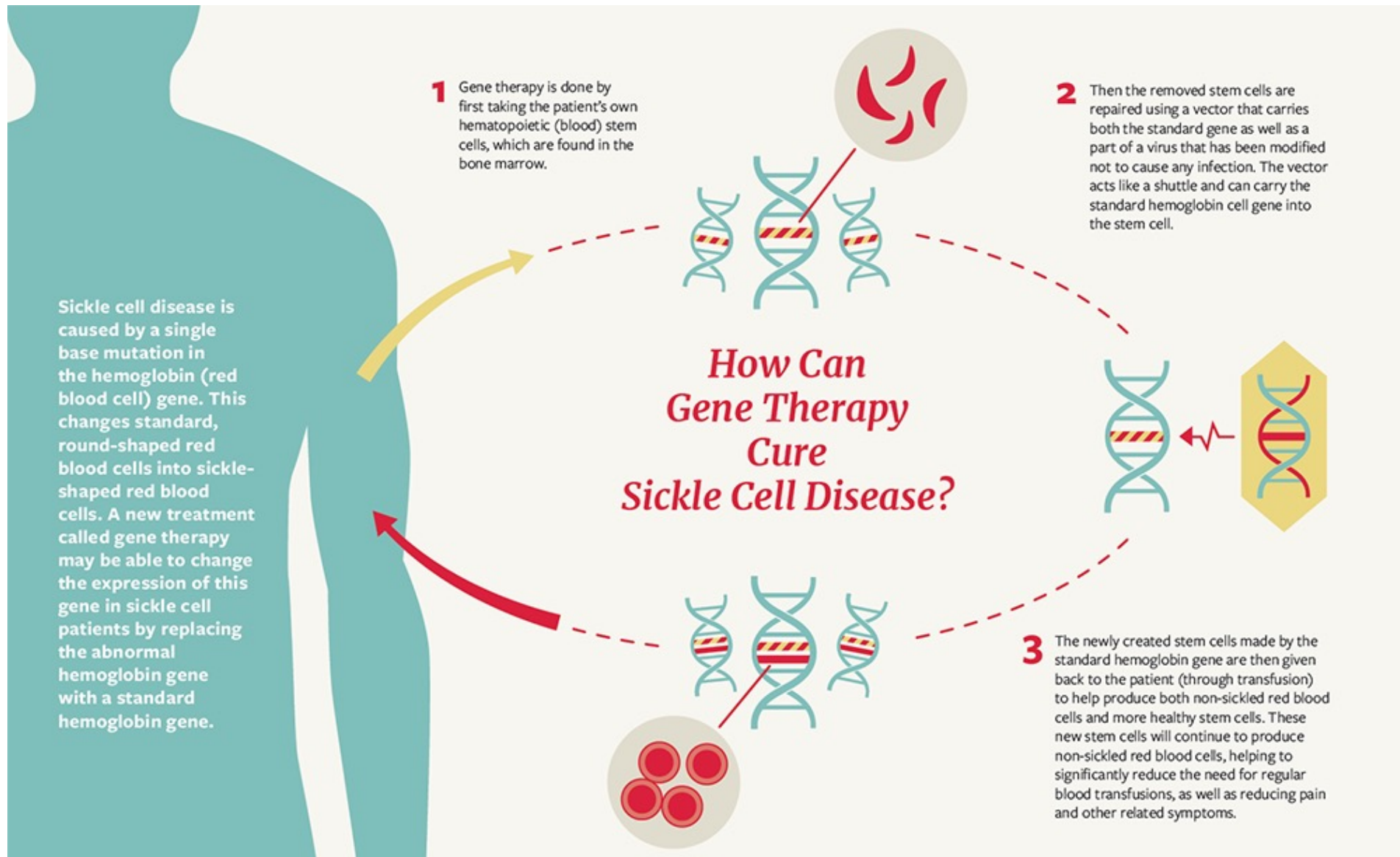


Each approved CAR T cell has unique attributes



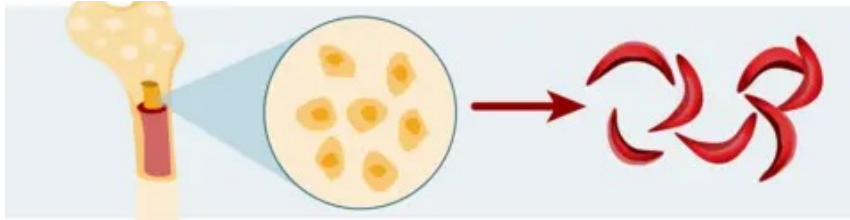
	Product	Structure of CAR construct					FDA approval (year)
		Antigen-binding domain	Hinge region	Transmembrane region	Co-stimulatory domain	T cell activation domain	
B cell lymphoma and leukaemia	2 Axicabtagene ciloleucel	Anti-CD19	CD28	CD28	CD28	CD3ζ	<ul style="list-style-type: none"> LBCL refractory to first-line therapy or relapsing at <12 months of first-line therapy (2022) Relapsed LBCL after ≥2 lines of therapy (2017) Relapsed FL after ≥2 lines of therapy (2021)
	3 Brexucabtagene autoleucel	Anti-CD19	CD28	CD28	CD28	CD3ζ	<ul style="list-style-type: none"> R/R MCL (2020) R/R B-ALL (2021)
	1 Tisagenlecleucel	Anti-CD19	CD8α	CD8α	4-1BB	CD3ζ	<ul style="list-style-type: none"> LBCL after ≥2 lines of therapy (2018) FL after ≥2 lines of therapy (2022) R/R B-ALL (2017)
	4 Lisocabtagene maraleucel	Anti-CD19	IgG4	CD28	4-1BB	CD3ζ	<ul style="list-style-type: none"> LBCL refractory to first-line or relapsing at <12 months of first-line therapy and not eligible for HSCT (2022) Relapsed LBCL after ≥2 lines of therapy (2021)
Multiple myeloma	5 Idecabtagene vicleucel	Anti-BCMA	CD8α	CD8α	4-1BB	CD3ζ	Fifth line RRMM (2021)
	6 Ciltacabtagene autoleucel	Dual anti-BCMA	CD8α	CD8α	4-1BB	CD3ζ	Fifth line RRMM (2022)

Not just CARs anymore: genetically modified hematopoietic stem cells were recently approved

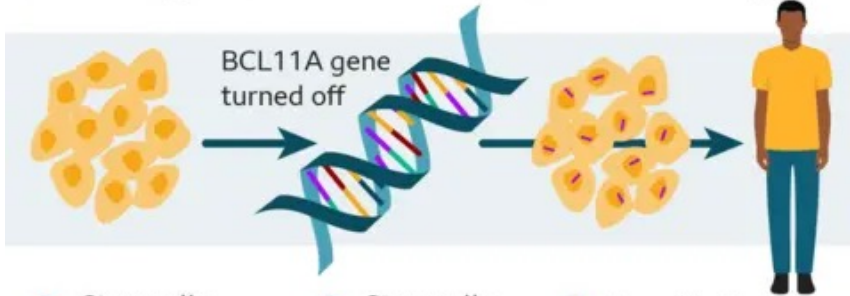


Each approved genetically modified hematopoietic stem cell has unique attributes

exagamglogene autotemcel (exa-cel)



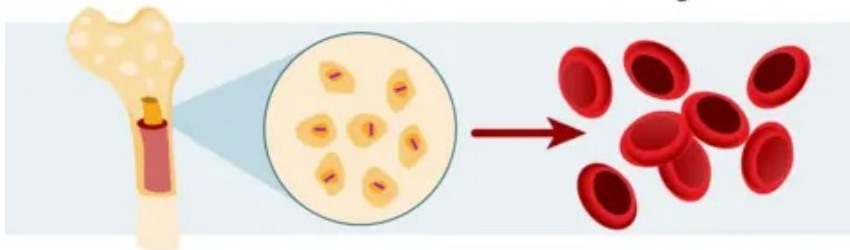
1 Jimi's stem cells in his bone marrow make diseased haemoglobin that can make red blood cells sickle-shaped



2 Stem cells extracted

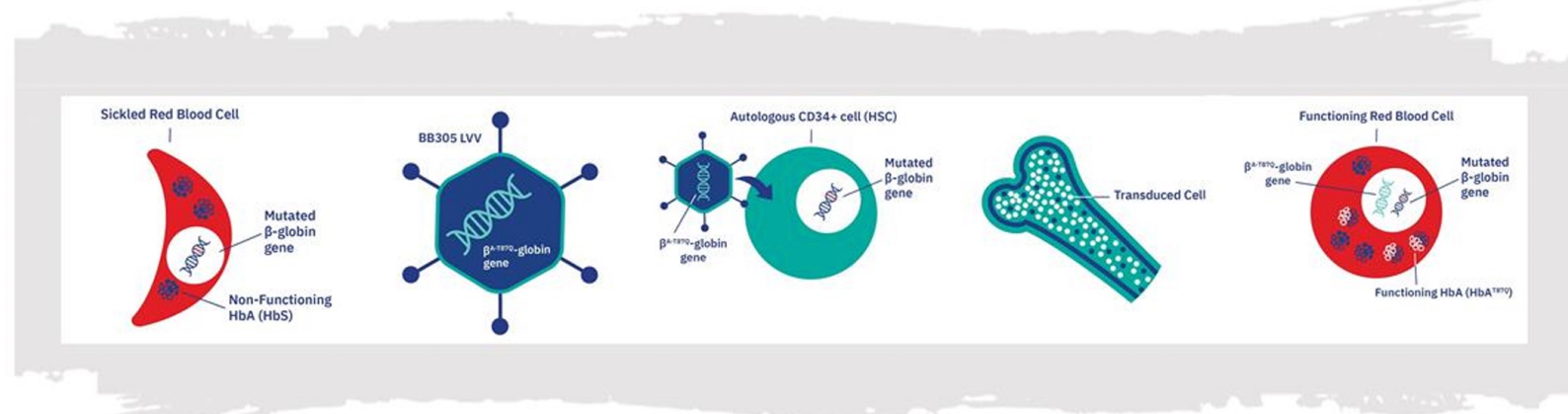
3 Stem cells genetically modified

4 Genetically engineered stem cells given



5 Engineered stem cells make healthy fetal haemoglobin and normal red blood cells

lovotibeglogene autotemcel (lovo-cel)



1

A single mutation in the beta-globin gene leads to the production of sickled hemoglobin (HbS) rather than adult hemoglobin (HbA)

2

BB305 LRV is a lentiviral vector that carries a β -globin gene (HbA^{T87Q} globin gene)

3

LYFGENIA is manufactured by transducing autologous CD34+ cells with BB305 LRV

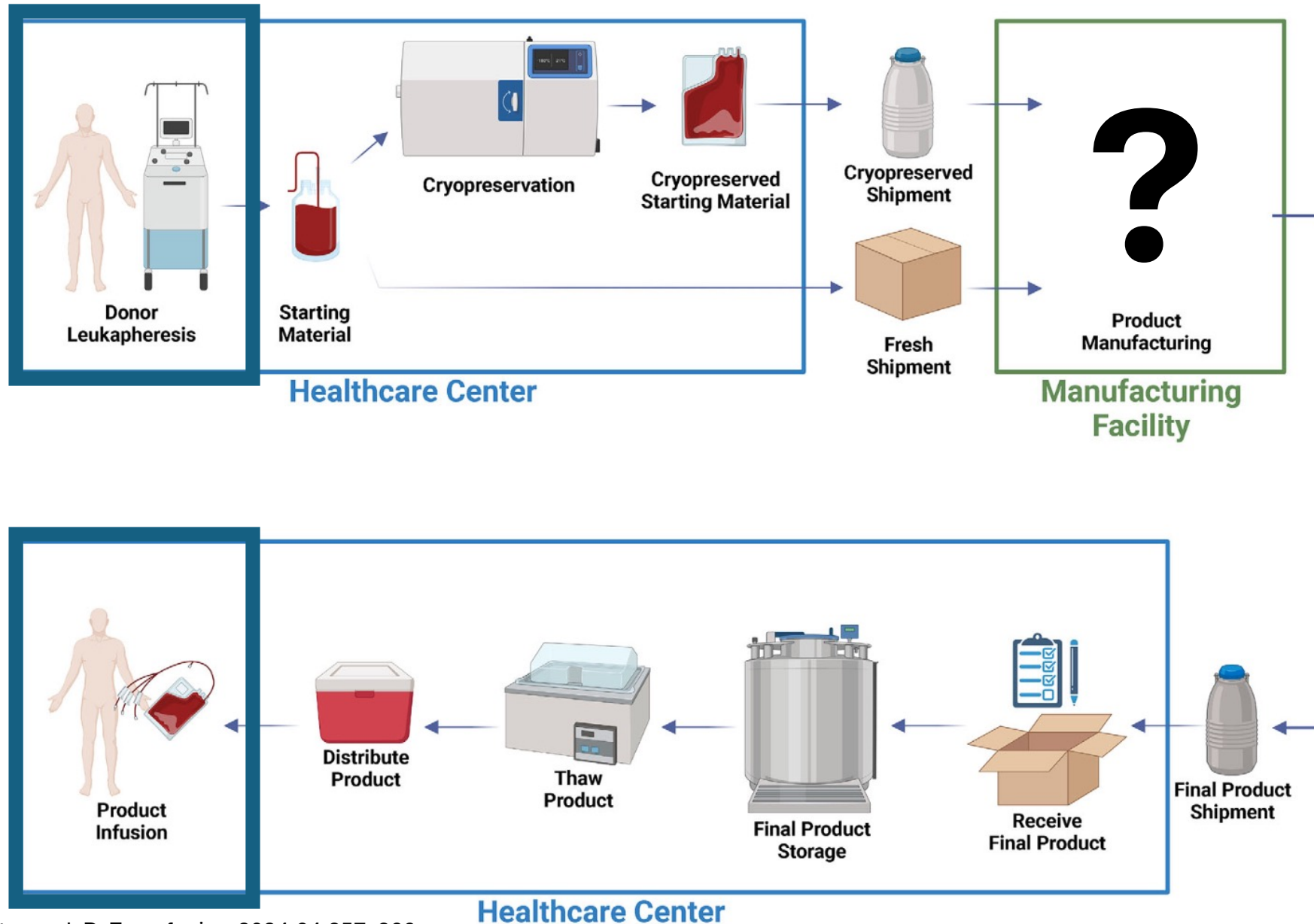
4

Following successful engraftment, red blood cells containing functioning HbA (HbA^{T87Q}) are produced

5

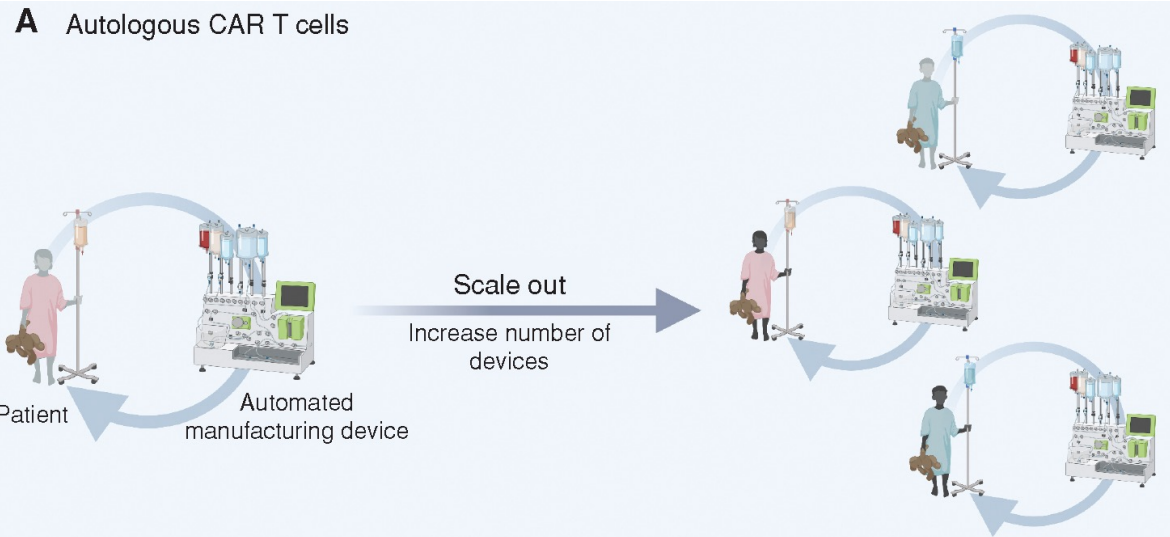
β^{A-T87Q} -globin pairs with α -globin

The future of cell and gene therapies is wide open

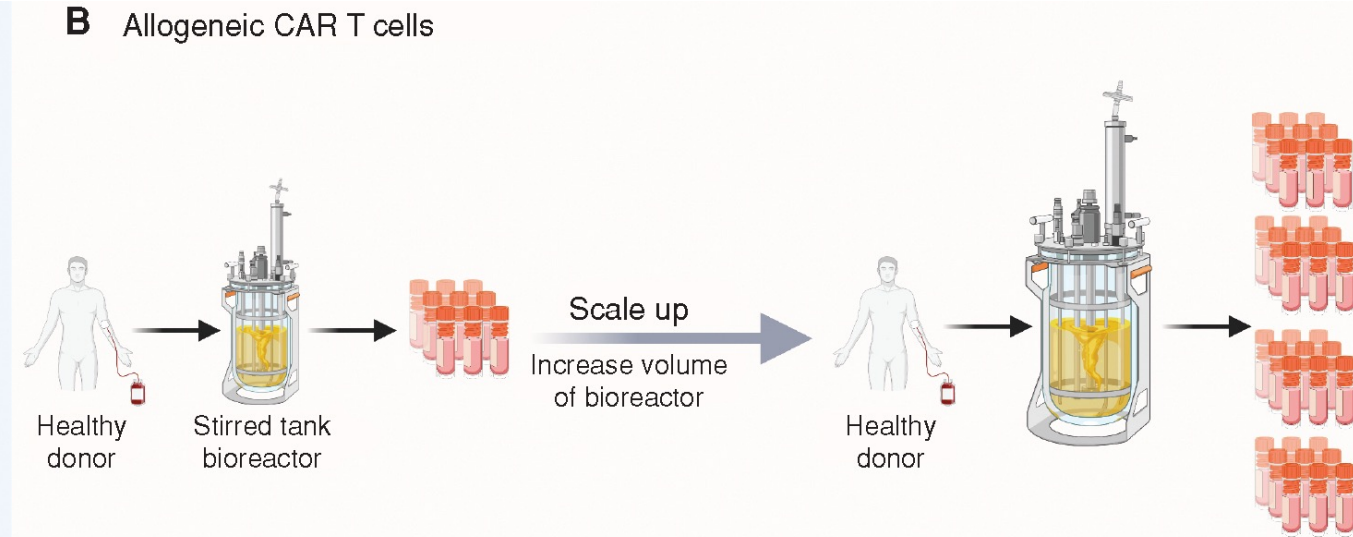


The future of cell and gene therapies is wide open

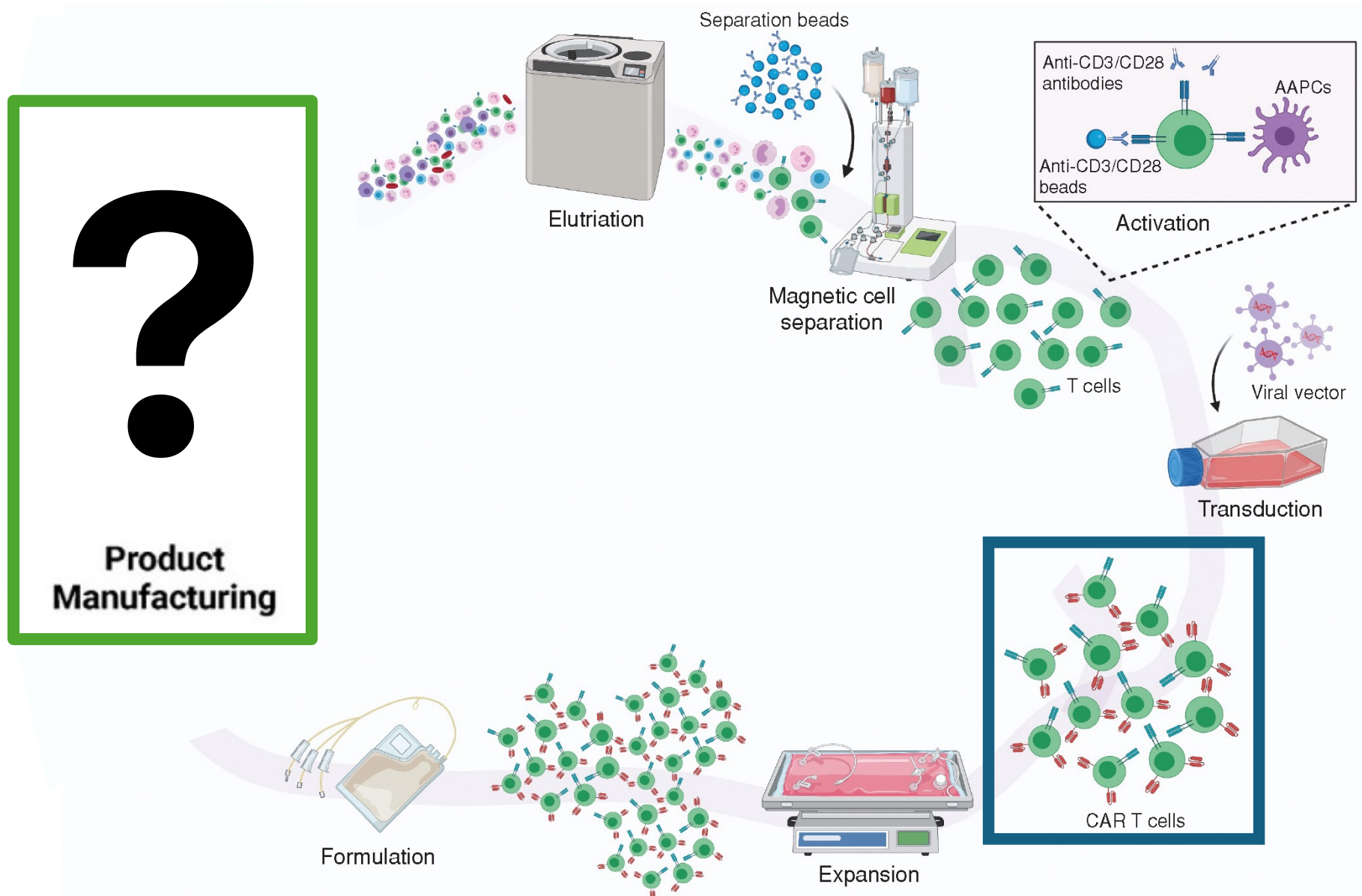
Current state



Future state?

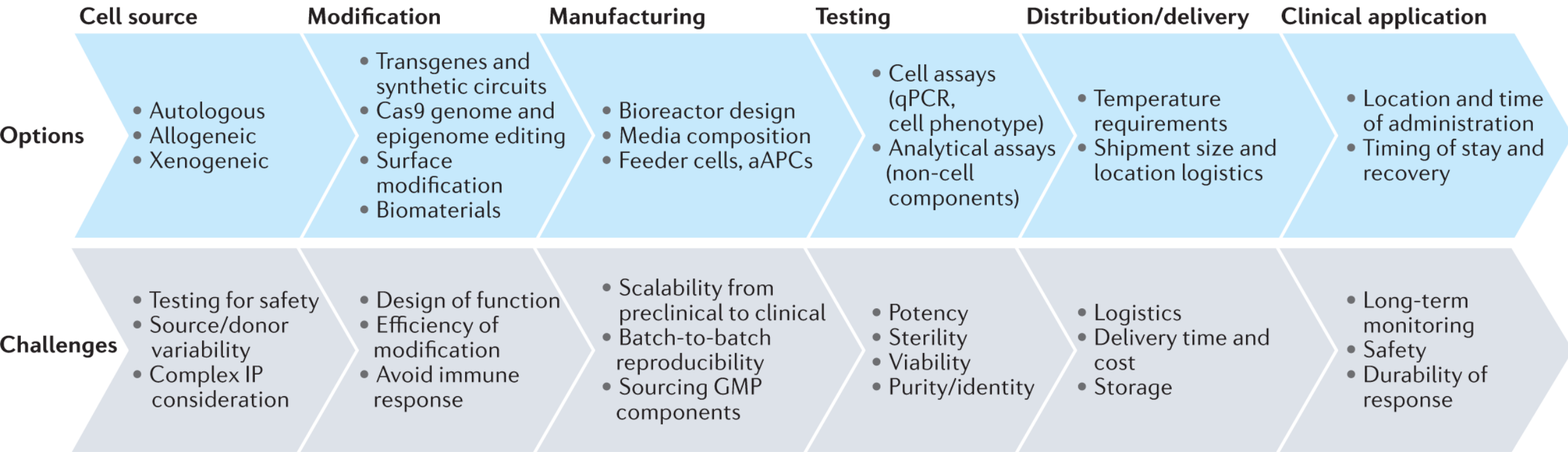


Any substantial change in the process = a new product



New products must be fully vetted at every stage of the process

Cell therapy production process



New products can take decades to reach approval

Drug Development Pipeline

■ Gene therapy

FUNDING

Academic/Grants

Venture Capital/For Profit

■ Clinical Trial Timeline

DISCOVERY

PRE-CLINICAL

IND
SUBMISSION

CLINICAL TRIAL PHASES

I

II

III

BLA
SUBMISSION
FDA
APPROVAL

COMMERCIAL
MANUFACTURING

MONITORING

YEARS

0

6

10

...

■ Traditional Pharma

FUNDING

Academic/Grants

Venture Capital/For Profit

DRUG PIPELINE

5,000-10,000
compounds

250 compounds

5 compounds

One
FDA-Approved
Drug

\$\$\$\$\$\$

No treatment is without risk

WARNING: HEMATOLOGIC MALIGNANCY

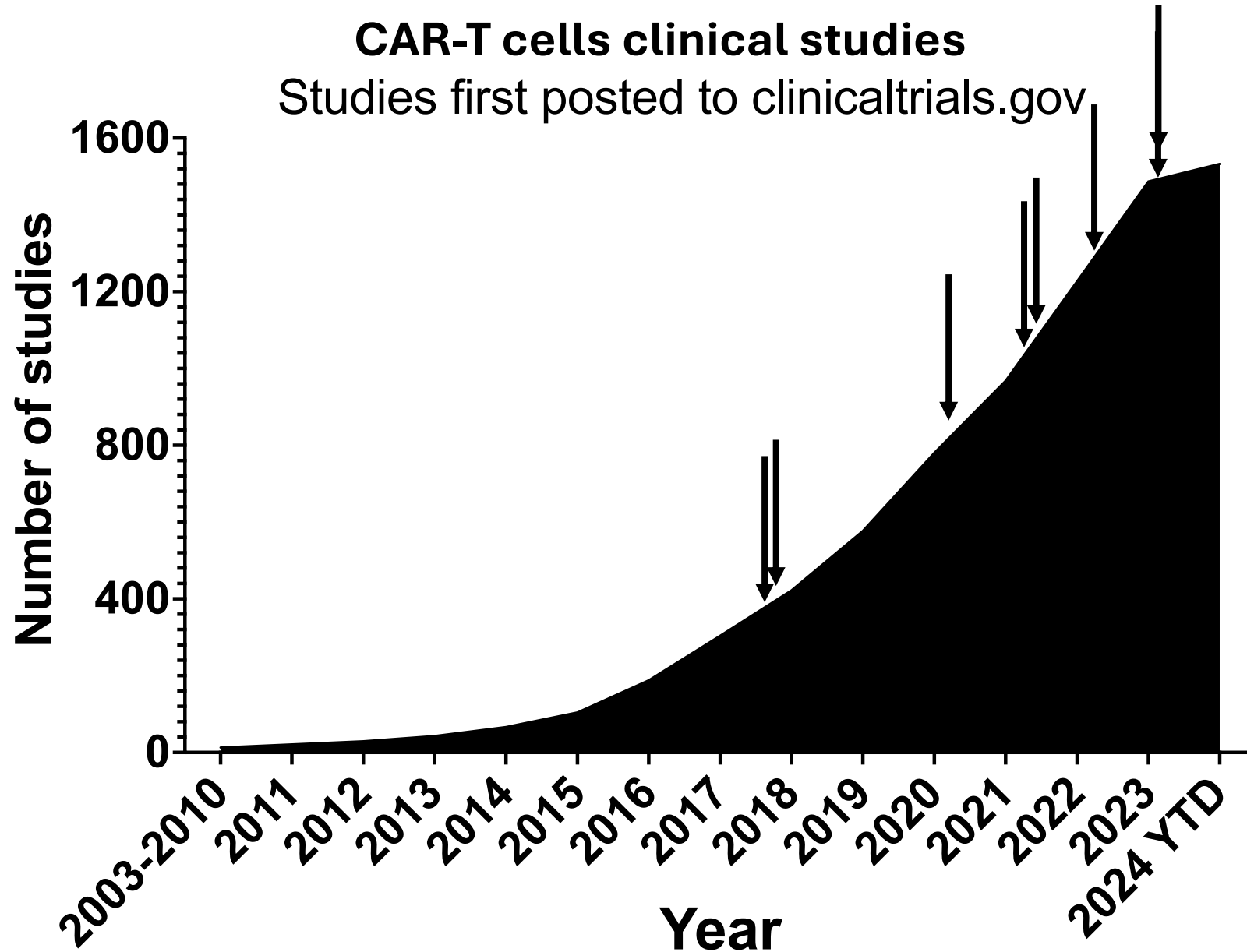
See full prescribing information for complete boxed warning.

**Hematologic malignancy has occurred in patients treated with
Monitor patients closely for evidence of malignancy
through complete blood counts at least every 6 months and through
integration site analysis at Months 6, 12, and as warranted. (5.1)**

4/18/24

**FDA Requires Boxed Warning for T cell
Malignancies Following Treatment with BCMA-
Directed or CD19-Directed Autologous Chimeric
Antigen Receptor (CAR) T cell Immunotherapies**

Cellular therapies under clinical development is exploding



Conclusions and considerations

- Genetically modified biotherapies in clinical use include:
 - CAR T cells for B cell malignancies
 - CAR T cells for multiple myeloma
 - Genetically modified hematopoietic stem cells for hemoglobinopathies
- Many parts of the process are under study for new products
 - Source of cells
 - Target
 - disease indication
 - Manufacturing process
 - Etc.

**It is an exciting time
to be in the field of
biotherapies!**

Thank you!



Heart of America Association of Blood Banks