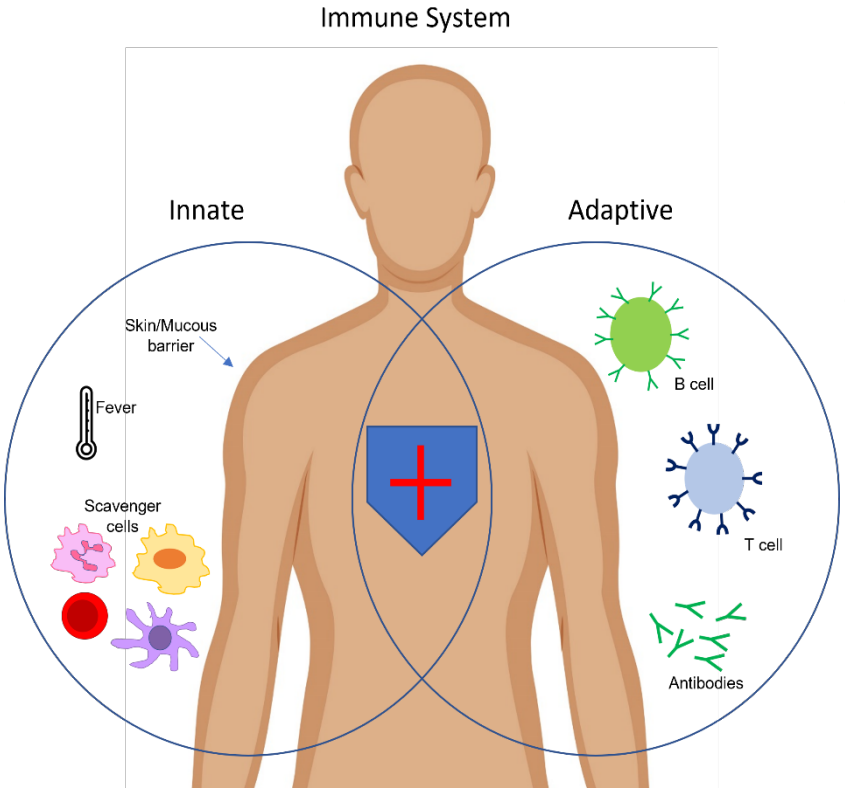
Chimeric Antigen Receptor (CAR)-Based Therapies: A New Vision in Treating Rare Diseases

Kelly Mercer, Ph.D.
Division of Systems Biology
Innovative Safety and Technology Branch
National Center for Toxicological Research

Disclosure

- This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred
- The materials presented are available in the public domain

Your Immune System Keeps You Healthy



Credit: in part, Vecteezy

- **Immunity** is the ability of the body to defend itself against disease-causing organisms.
- **Immunotherapy** is the prevention or treatment of a disease with substances that **stimulate** a response.
- **Examples:**

Allergy Shots

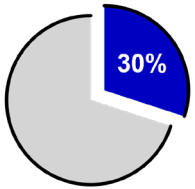
Credit: Macrovector

Cancer treatment

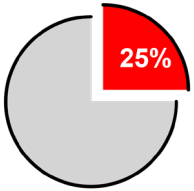
Rare Diseases

Rare Cancers and Immunotherapy

- Rare cancers are a group of 200 cancers that occur at extremely low frequencies.
  - 15 per 100,000 people in the United States
  - Collectively make up a significant portion of disease burden

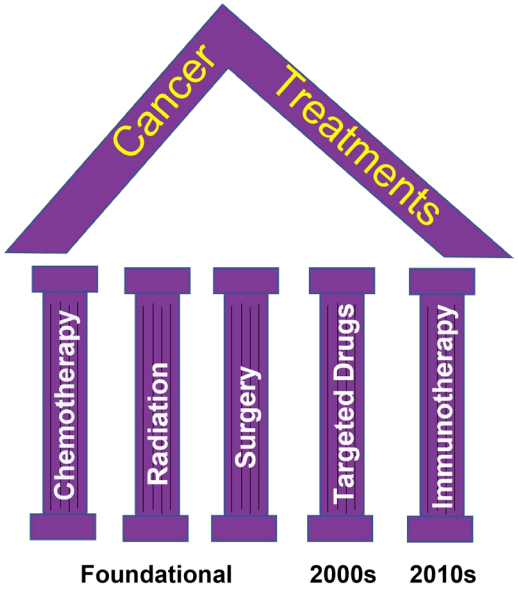


~ Rare Cancers diagnosed



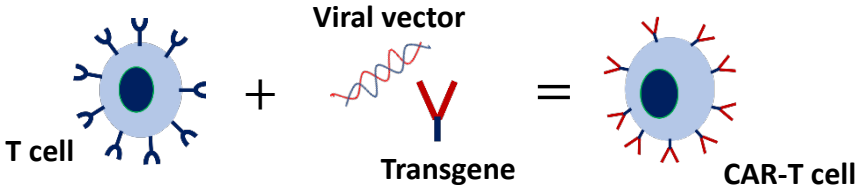
~Rare Cancer deaths

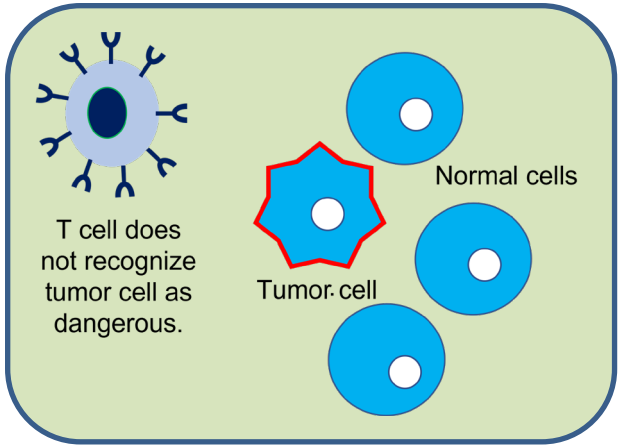
- Treatment options are limited; however, **immunotherapies** have greatly improved clinical outcomes for several rare cancers.
- Most Impact:
  - Immune cell checkpoint inhibitors (ICIs)
  - Chimeric Antigen (CAR)-T receptor therapy



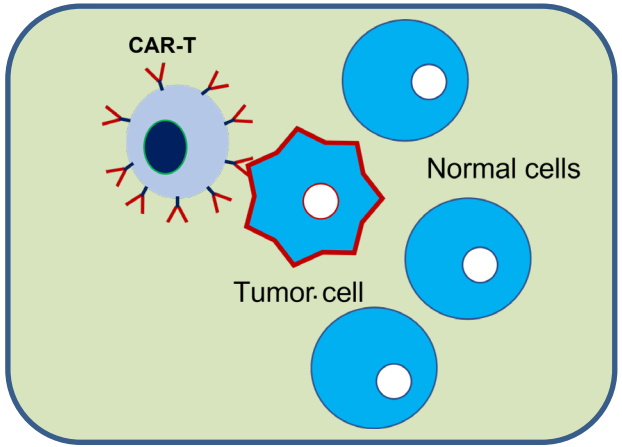
What is CAR-T Therapy?

- Made from patient's own immune cells
- Re-engineer the T cell to recognize tumor cells, attack and kill them



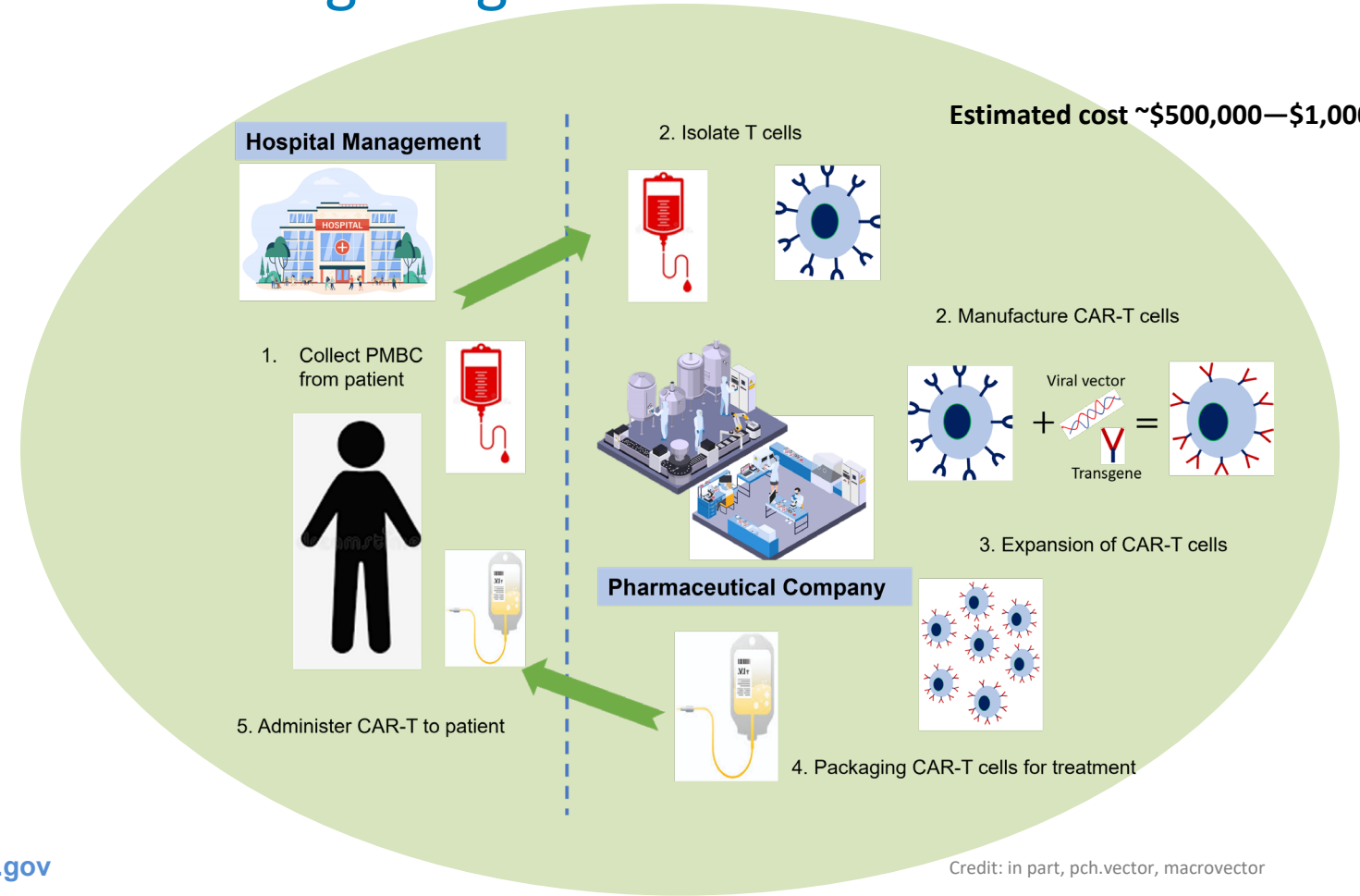


VS.



- Clinical Trials
  - Very successful "last resort" treatment for adult and pediatric refractory/relapse [R/R] B-cell lymphomas and leukemias
  - Overall response rates (ORR), 92-93%
  - Long-term remission
  - Two CD19-directed CAR-T therapies received FDA approval 2017

CAR-T: The “Living Drug”



Credit: in part, pch.vector, macrovector

CAR-T Therapies are Effective

US FDA has approved CAR-T therapies for certain Rare Cancers

- CD19-directed CAR-T
  - B cell acute lymphocytic leukemia (ALL)
  - Mantle cell leukemia
  - B cell non-Hodgkin lymphoma
  - Follicular lymphoma
- B cell maturation antigen(BMCA)-directed CAR-T
  - Multiple myeloma

Patient Outcomes

- CD19- CAR-T
  - Leukemia: long-term remission when combined with allogenic hematopoietic stem cell transplantation (allo-HSCT)
  - Lymphoma: likely curative in a subset of patients
- BMCA CAR-T
  - Multiple myeloma: long-term remission is observed, maybe curative?

Factors linked to successful remission

- Deep initial response to treatment
- Malignancy type
- Low baseline tumor volume or burden
- Lymphodepleting chemotherapy

Nature Reviews Clinical Oncology. https://doi.org/10.1038/s41571-023-00754-1

Post-Treatment Toxicities

ACUTE

Cytokine Release Syndrome (CRS)

Occurs within 2 weeks following treatment

Reversible with supportive interventions

Symptoms: Mild (fever) to severe (SIRS)

R/R Lymphoma and leukemia patients more likely to have a serve CRS response (≥50%)

Much less serve in non-Hodgkin lymphoma and multiple myeloma, chronic leucitic leukemia

Neurotoxicity

Occurs within 2 weeks following treatment

Reversible with supportive interventions

Symptoms: Mild (impaired speech) to Severe (seizures)

Severity may depend on the co-stimulatory construct used.

LONG-TERM

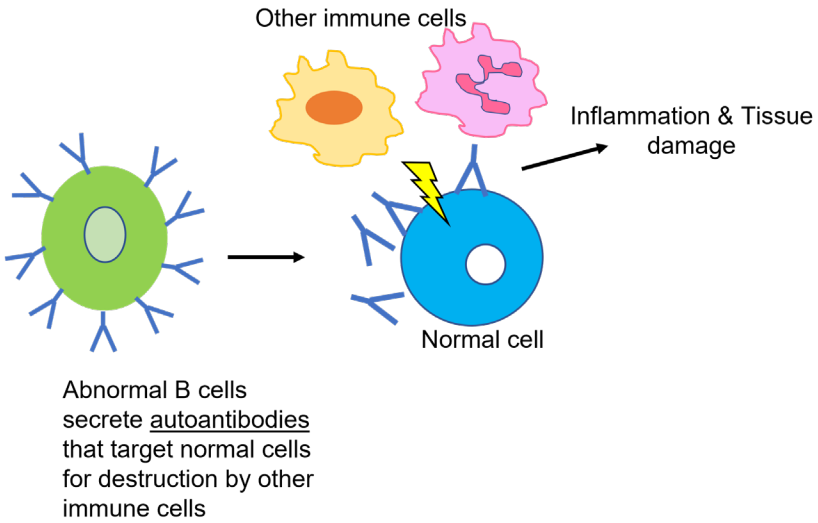
Post-treatment development of T cell malignancies, including CAR+ lymphoma

Risk is applicable to all approved CD19- and BMCA-directed CAR-T therapies

Future Direction: Autoimmune Diseases

Systemic lupus erythematosus (SLE)

- Inflammatory disease where immune system attacks its own tissue
- Effects multiple tissues
- Symptoms managed by medicine



One Small Study

Will depletion of these abnormal B cells using CAR-T therapies provide a "reset" for the immune system, relieving symptoms?

- 5 Patients with treatment-resistant SLE, multiple organs effected
- Received CD19-directed CAR-T following lymphodepleting chemotherapy
- At 3 months post-therapy, all patients achieved disease remission
- 2023 Update, 7 patients, remission of 4-22 months
- 2023 FDA approves clinical trials for CAR-T therapies for treatment-resistant SLE

Nature Medicine. 2022, 28:2124, https://doi.org/10.1038/s41591-022-02017-5.

Recent CAR-T Clinical Trials for SLE

Table 1 | Select list of CAR T cell therapies in clinical development for lupus

Drug	Target	Sponsor	Lupus trial phase
MB-CART19.1	CD19	Academic study[a]	Phase I
Rapcabtagene autoleucel/YTB323	CD19	Novartis	Phase I/II
CC-97540/BMS-986353	CD19	Bristol Myers Squibb	Phase I
CABA-201	CD19	Cabaletta Bio	Phase I
KYV-101	CD19	Kyverna Therapeutics	Phase I
Relmacabtagene autoleucel	CD19	JW Therapeutics	Phase I
BRL-301	CD19	Bioray Laboratories	Phase I soon
GLPG5101	CD19	Galapagos	Phase I soon
Obecabtagene autoleucel	CD19	Autolus	Phase I in 2024
SC291, donor-derived CAR T cells	CD19	Sana Biotechnology	IND submitted[b]
IMPT-514	CD19 and CD20	ImmPACT Bio	Phase I/II in 2024
GC012F	CD19 and BCMA	Gracell	Phase I
BCMA-CD19 compound CAR T cells	CD19 and BCMA	iCell Gene Therapeutics	Phase I
Descartes-08, RNA CAR T cells	BCMA	Cartesian Therapeutics	Phase II soon

[a]CAR T cell vector provided by Miltenyi Biomedicine. [b]Trial expected to recruit patients with multiple autoimmune diseases, including lupus. IND, investigational new drug application.

Nature Reviews Drug Discovery. https://doi.org/10.1038/d41573-023-00166-x

Key Points

- These therapies are engineered from the patient's own immune cells (T cells), called a "living drug."
- CAR-T therapies have dramatically impacted survival of several rare hematological or "blood borne" diseases.
- CAR-T therapies may achieve long-term remission from symptoms of rare autoimmune diseases.
- CAR-T therapies potentially can be engineered to recognize and kill any type of diseased cell.

References

- **CAR T cell therapies raise hopes — and questions — for lupus and autoimmune disease**.
  Mullard A.
  Nature Reviews Drug Discovery. 2023, 22:859, https://www.nature.com/articles/d41573-023-00166-x.

- **Immunotherapies in Rare Cancers**.
  Vivekanandhan S., et al.
  Molecular Cancer. 2023, 22:23, https://doi.org/10.1186/s12943-023-01720-2.

- **Long-Term Outcomes Following CAR T Cell Therapy: What We Know so Far**.
  Cappell K.M. and Kochenderfer J.M.
  Nature Reviews Clinical Oncology. 2023, 20:359, https://doi.org/10.1038/s41571-023-00754-1.

- **Systematic Review on CAR-T Cell Clinical Trials Up to 2022: Academic Center Input**.
  Wang V., et al**.**
  Cancers. 2023, 15:1003, https://doi.org/10.3390/cancers15041003.

- **Anti-CD19 CAR T Cell Therapy for Refractory Systemic Lupus Erythematosus**.
  Mackensen A., et al.
  Nature Medicine. 2022, 28:2124, https://doi.org/10.1038/s41591-022-02017-5.

- **CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers**.
  National Cancer Institute. 2022, *https://www.cancer.gov/about-cancer/treatment/research/car-t-cells*.

Image Credits

- **Slide 3** — https://www.vecteezy.com/vector-art/418279-human-body-outline-in-three-colors
- **Slide 3** — https://www.freepik.com/free-vector/allergy-concept-with-symptoms-treatment-common-allergens-symbols-cartoon_13768287.htm
  - Image by Macrovector on Freepik
- **Slide 6** — https://www.freepik.com/free-vector/isometric-pharmacy-composition_26798070.htm#query=pharmaceutical&position=15&from_view=keyword&track=sph&uuid=76b39402-1e27-4c29-b4c7-e8cd656e200f%22%3EImage%20by%20macrovector%3C/a%3E%20on%20Freepik
  - Image by Macrovector on Freepik
- **Slide 6** — https://www.freepik.com/free-vector/people-walking-sitting-hospital-building-city-clinic-glass-exterior-flat-vector-illustration-medical-help-emergency-architecture-healthcare-concept_10613398.htm#query=hospital%20cartoon&position=2&from_view=keyword&track=ais&uuid=e45a6d97-b342-42eb-be54-f04a58823564
  - Image by Pch.vector on Freepik


FDA
U.S. FOOD & DRUG
ADMINISTRATION