Foundations of Cancer Therapeutics Crash Course –CTTP, Aug 19, 2021

Chimeric Antigen Receptor T cell (CAR-T) based immunotherapy

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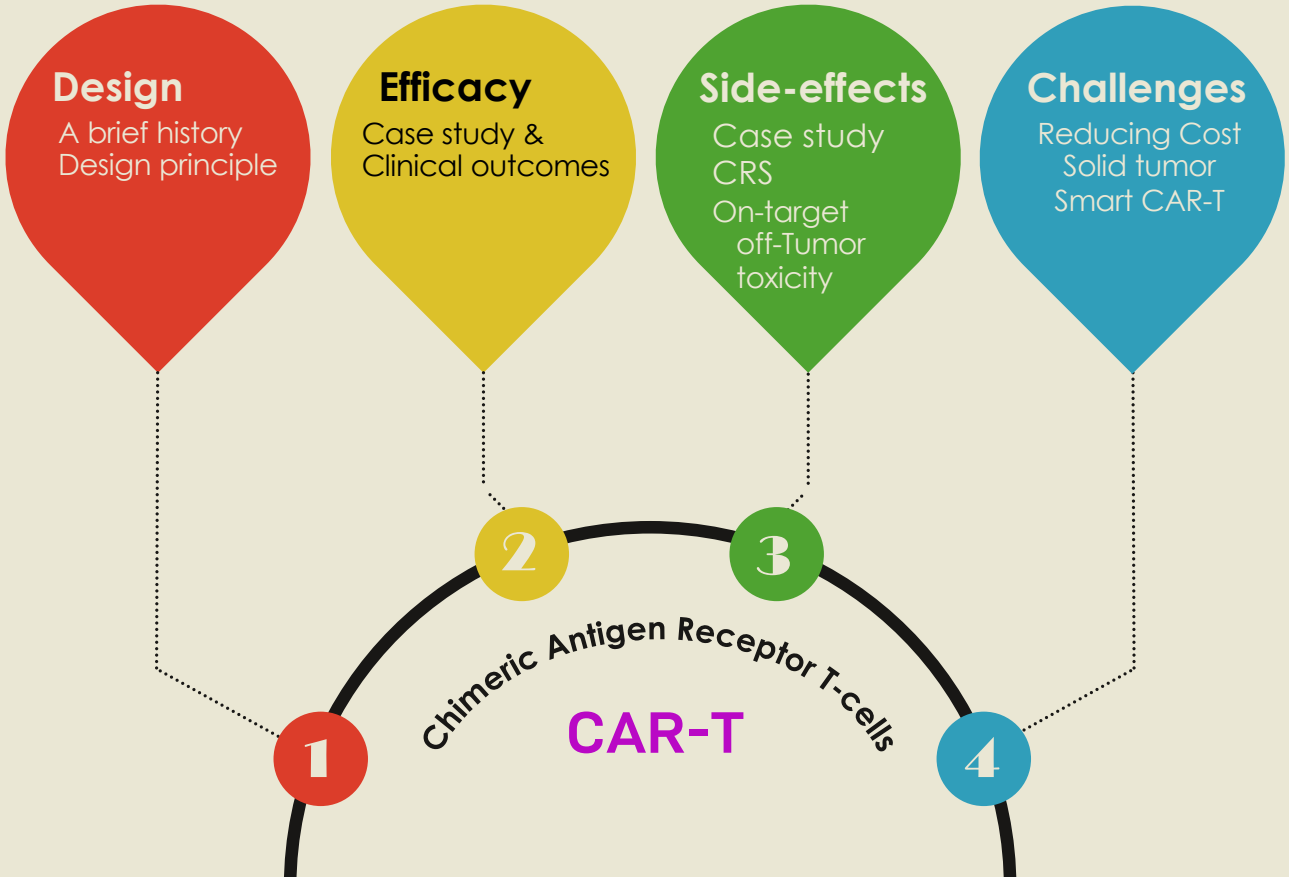
Gas pedal:

Activating **CAR T-cells** to boost anti-tumor immunity

Release the **brake** by immunocheckpoint blockers (**ICBs**) to restore anti-tumor immunity

Overview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Solid tumor
Smart CAR-T
1
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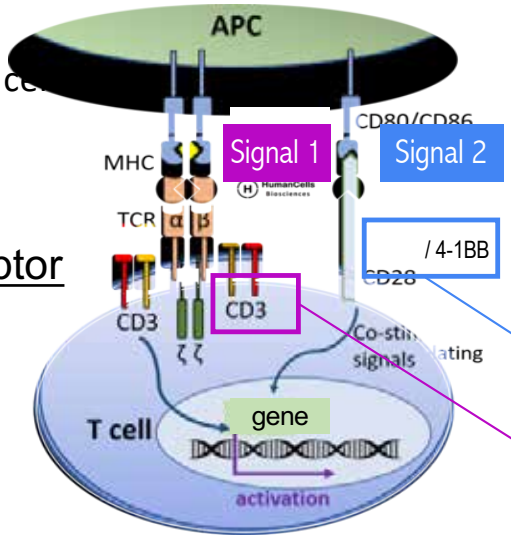
Chimeric Antigen Receptor T-cells
CAR-T

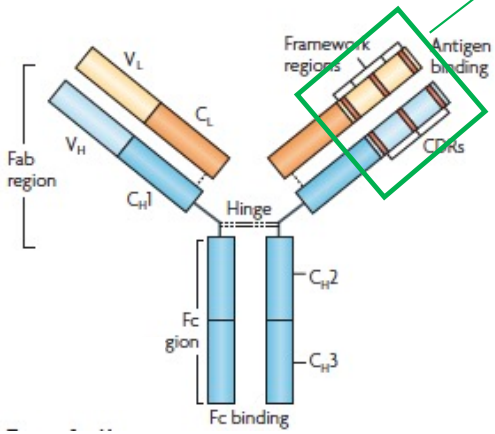
Chimeric Antigen Receptor (CAR) T-cell engineering

Antigen-presenting ce
(dendritic cell etc.)

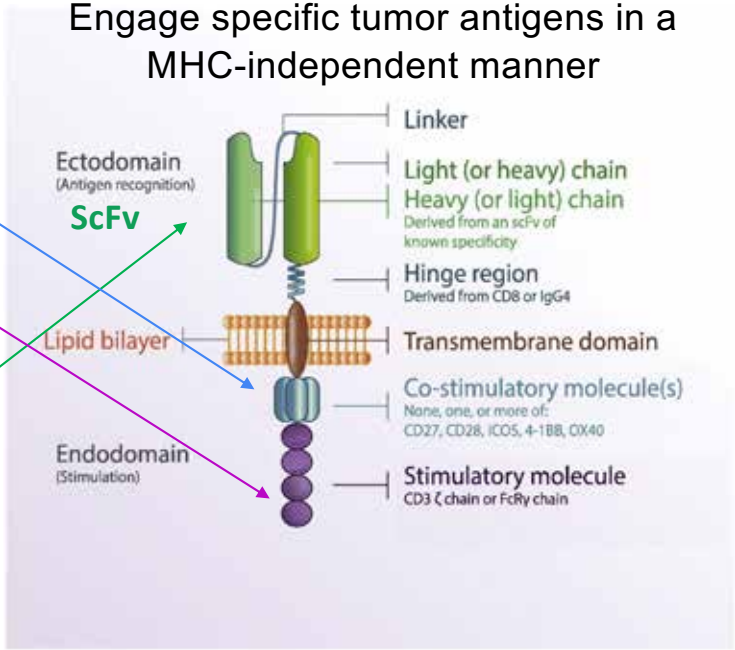


T cell receptor

Antibody structure



Engage specific tumor antigens in a MHC-independent manner

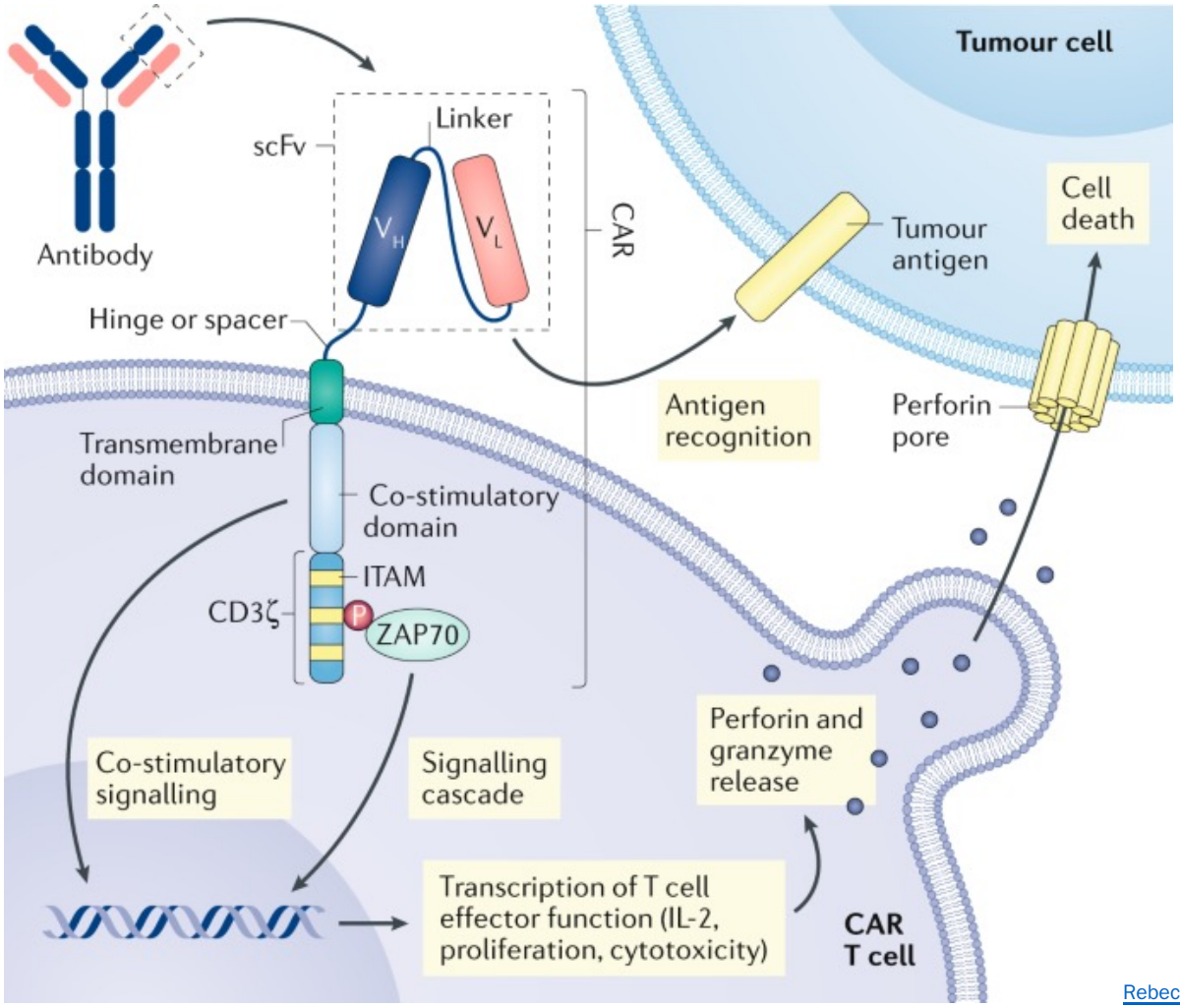


ScFv: single chain fragment variable

2017
YESCARTA
KYMRIAH
FDA approved **CD19+ CAR T-cell therapy** for hematological malignancies

Chen R, Jing J, et al, Curr Opin Biotech 2020
Nicholas R. J. Gascoigne (2008). Nat Rev Immunol 8, 895–900.
Hansel TT, et al. (2010) Nat Rev Drug Discov 9(4):325–338

How CAR T-cell works



- Engineered to express a chimeric antigen receptor
- Reprograms T cells to target tumor cells
- T cell effector function: Release of perforin and granzyme to kill tumor cells

Rebecca C. Larson & Marcela V. Maus. Nature Reviews Cancer **21**, pages145–161 (2021)

30+ years' bench-to-bedside research on CAR-T

1980-1990s:
Altering T-cell receptor can lead to targeted cell killing

1990s:
First Generation CARTs – slow tumor growth in mice

2000s:
Second Generation CARTs – improved in vitro killing and persistence in mice

2012:
Adult studies begin showing promise of CD19 CAR (Seattle, NCI,

2013:
2 children with refractory ALL, achieve remission

2017:
FDA Approves first two CAR-T products
- Kymriah
- Yescarta

2020-2021:
FDA Approves 3 new CAR-T products
- Tecartus
- Breyanzi
- Abecma

First

Second

Third Generation

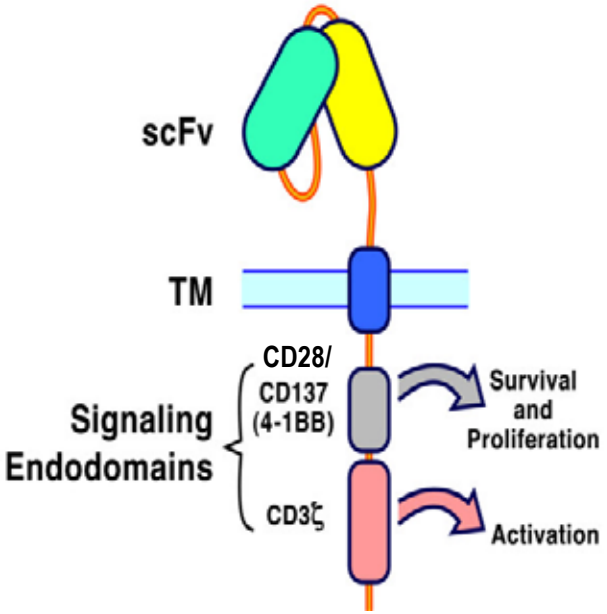
Grupp et al. New Eng J Med. 2013 Maude, S et al. New Eng J Med. 2014

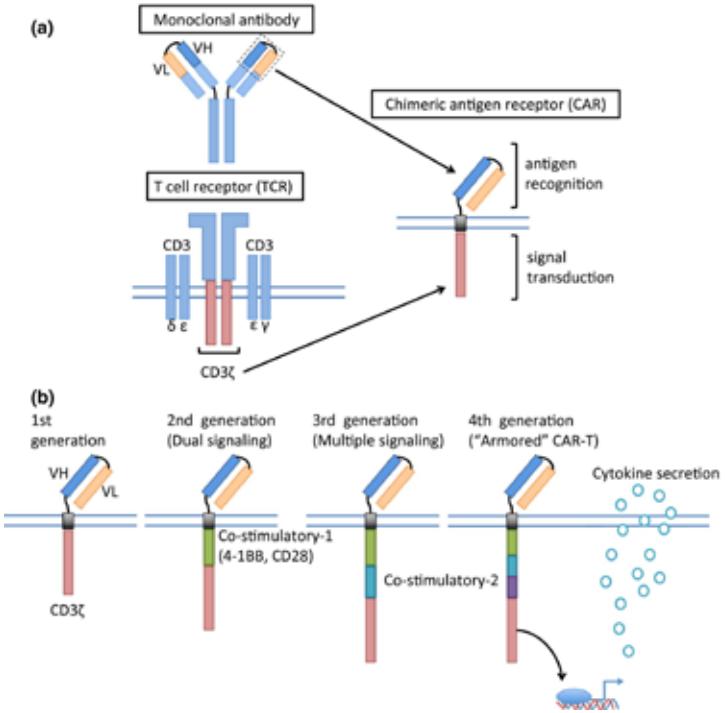
C Chimeric

A Antigen

R Receptor

T T cell





Advantages of CAR-T

"Live drug"	MHC-independent tumor recognition	Multiple anti-tumor immuno-modulators can be engineered	Target a variety of antigens (protein, carbohydrate, glycolipid)

Maus M V et al. Blood 2014;123:2625-2635

CAR T-cell therapy: where we are?

FDA-approved CAR T-cell Therapies

Chimeric antigen receptor (CAR) T-cell therapy is a type of immunotherapy that uses a patient's own genetically modified T cells to find and kill cancer. UPMC Hillman Cancer Center currently offers two types of FDA-approved CAR T-cell therapy.

KYMRIAH™ ***Anti-CD19 [***approved in 2017; Norvatis, Inc***]***

UPMC Hillman Cancer Center is part of the network of certified treatment centers providing KYMRIAH™ (tisagenlecleucel), an FDA-approved CAR T-cell therapy for:

- Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)
- Young adult patients up to age 25 with relapsed or refractory acute lymphoblastic leukemia (ALL)

YESCARTA™ ***Anti-CD19 [***approved in 2017; Kite Pharma, Inc***]***

UPMC Hillman Cancer Center is the first center in western Pennsylvania providing YESCARTA™ (axicabtagene ciloleucel), the first FDA-approved CAR T-cell therapy for adult patients with certain types of B-cell lymphoma.

The FDA has approved this treatment for patients with the following conditions that have either not responded to or have relapsed following two or more lines of systemic therapy:

- Diffuse large B-cell lymphoma (DLBCL)
- Primary mediastinal B-cell lymphoma
- High grade B-cell lymphoma
- DLBCL that results from follicular lymphoma
- Follicular lymphoma

Patients will undergo an extensive evaluation to determine their eligibility for this highly specialized treatment. To learn more, please call 1-833-UPMC-CART.

ABECMA® (idecabtagene ***Anti-BCMA*** [approved in 2021; BMS, Inc]

UPMC Hillman Cancer Center was one of the first in the United States certified to provide ABECMA® (idecabtagene vicleucel) for adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an antidCD38 monoclonal antibody.

BREYANZI® ***Anti-CD19 [***approved in 2021; Bristol Myers Squibb, Inc***]***

Hillman was the first of 10 centers in the United States to offer BREYANZI® (lisocabtagene maraleucel), an FDA-approved CAR T-cell therapy for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including:

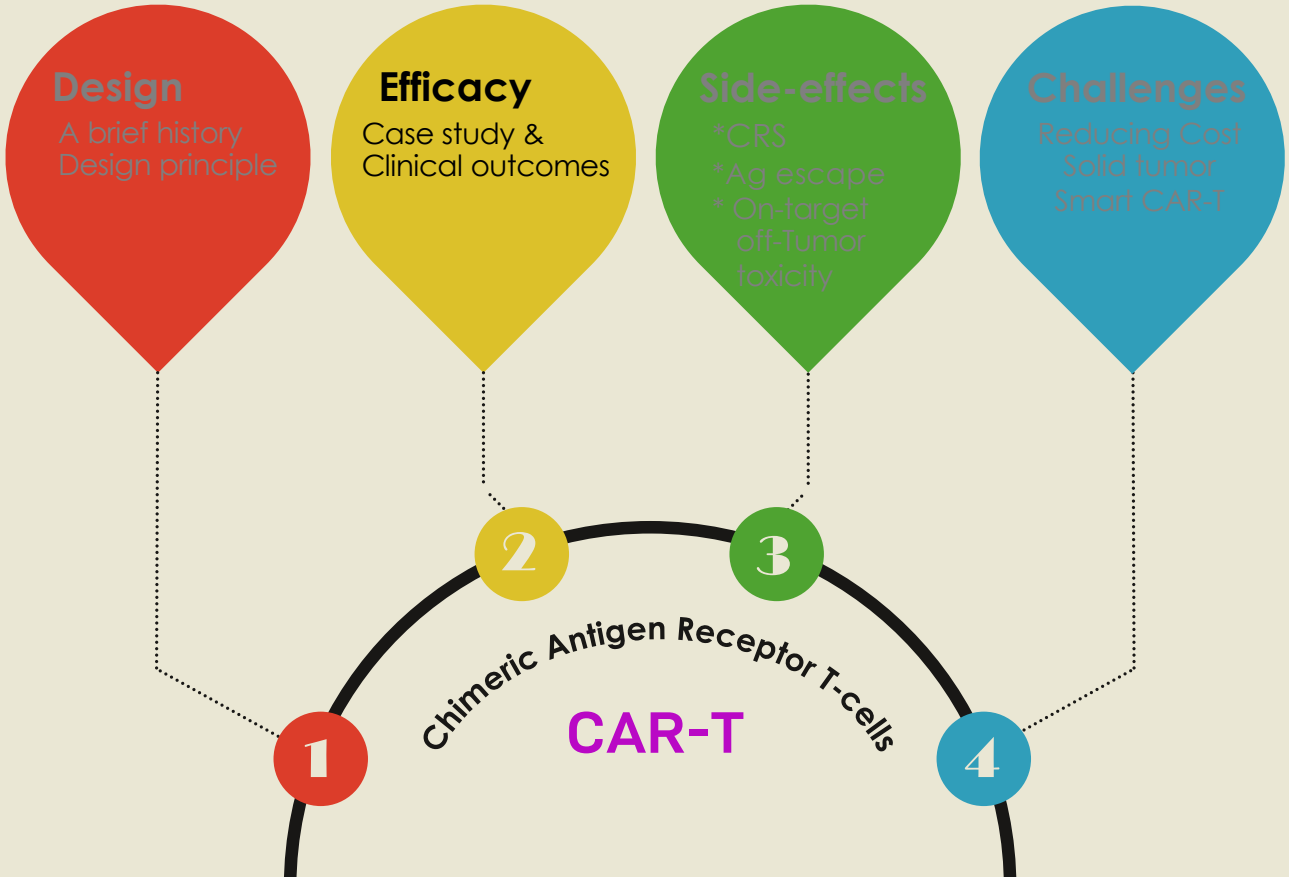
- Diffuse large B cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma)
- High-grade B-cell lymphoma
- Primary mediastinal large B-cell lymphoma
- Follicular lymphoma grade 3B

TECARTUS™ ***Anti-CD19 [***approved in 2020; Kite Pharma, Inc***]***

UPMC Hillman Cancer Center is the first in western Pennsylvania to provide TECARTUS™ (brexucabtagene autoleucel), an FDA-approved CAR T-cell therapy for patients with relapsed or refractory mantle cell lymphoma.

*BCMA: B-cell maturation antigen

Overview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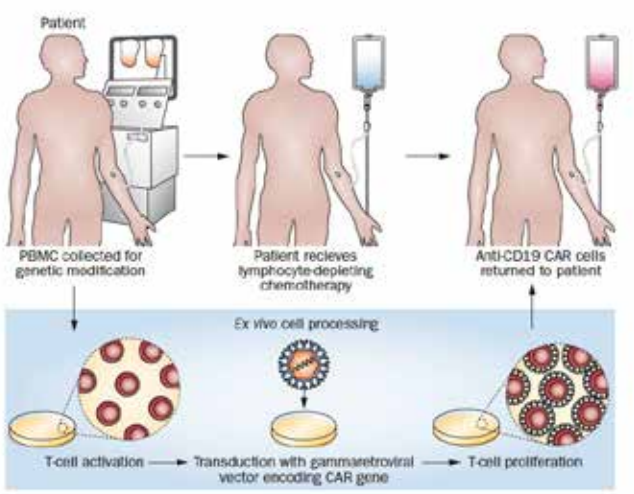
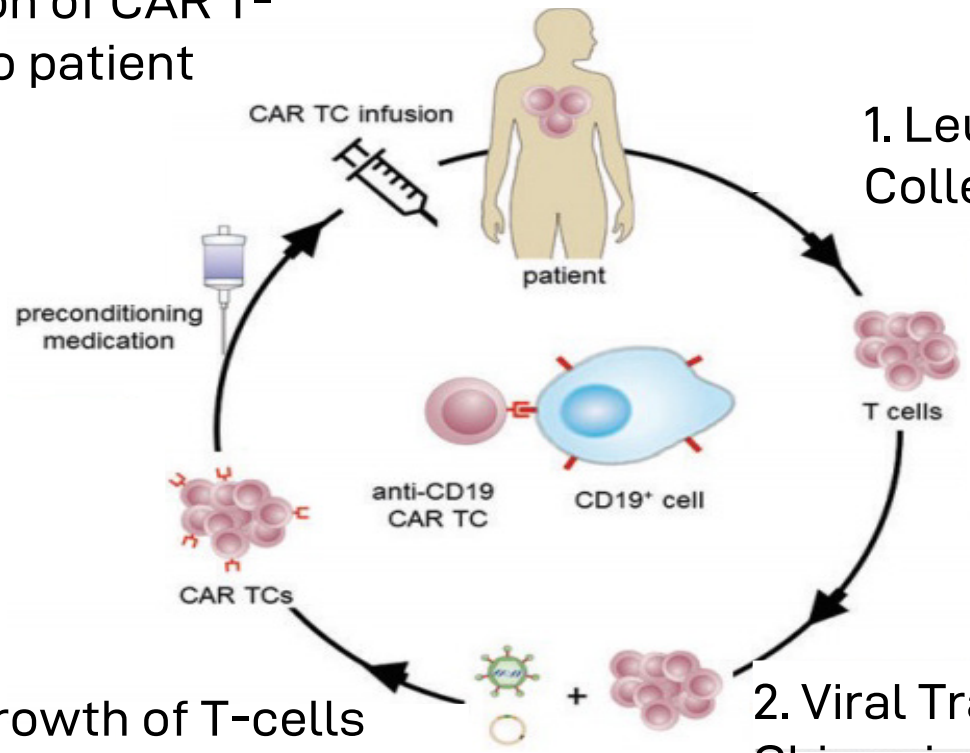
FDA Approval of the first 2 CART agents

- Tisagenlecleucel
  - Aka **Kymriah**
  - Novartis Inc.
  - $475,000
  - Approved for pediatric patients with of refractory or 2nd or later relapse of B-cell ALL
- Axicabtagene
  - Aka **Yescarta**
  - Kite Pharma Inc.
  - $373,000
  - Approved for adults with relapsed or refractory large B-cell lymphoma

Creating autologous CAR T-cells to target CD19+ leukemia

4. Infusion of CAR T-cells into patient





1. Leukapheresis Collect T-cells

2. Viral Transduction: Chimeric antigen receptor transferred into T-cells

3. Growth of T-cells expressing the Chimeric Receptor

Shubert et al, Human Gene Therapy. 2016; Frey, NV and Porter, DL. Am J Hematol. 2016

Kochenderfer, J. N. & Rosenberg, S. A. (2013) Nat. Rev. Clin. Oncol.

Curative potential in certain blood cancer patients

cure

Friday Frontline: First Patient to Receive CAR-T Cell Therapy Dies, Cancer Organizations Appeal to President for COVID-19 Vaccine Priority Access, and More

February 19, 2021
Jessica Skarzynski

First clinical trial in July of 2010

From the death of Bill Ludwig, the first patient to receive CAR-T cell therapy to treat his end-stage CLL, to a letter to the President urging him to grant patients with cancer and survivors priority access to the COVID-19 vaccine, here's what's happening in the cancer space this week.

Bill Ludwig, the first patient to receive CAR-T cell therapy for treatment of end-stage chronic lymphocytic leukemia, died of COVID-19 pneumonia.

After being diagnosed in 2000, Ludwig managed to control his disease for years with intermittent chemotherapy. But it became increasingly more debilitating until he discovered the clinical trial examining the use of a patient's own genetically engineered T cells to fight cancer. While treatment was by no means easy, Ludwig eventually became the first person to receive the therapy and went on to have his cancer "wiped out" by it.

https://www.pennmedicine.org/cancer/about/patient-stories/leukemia-bill

https://www.chop.edu/news/five-years-later-first-pediatric-recipient-car-t-cell-therapy-remains-ca

Celebrating 9 Years Cancer Free

May 10, 2021

Share

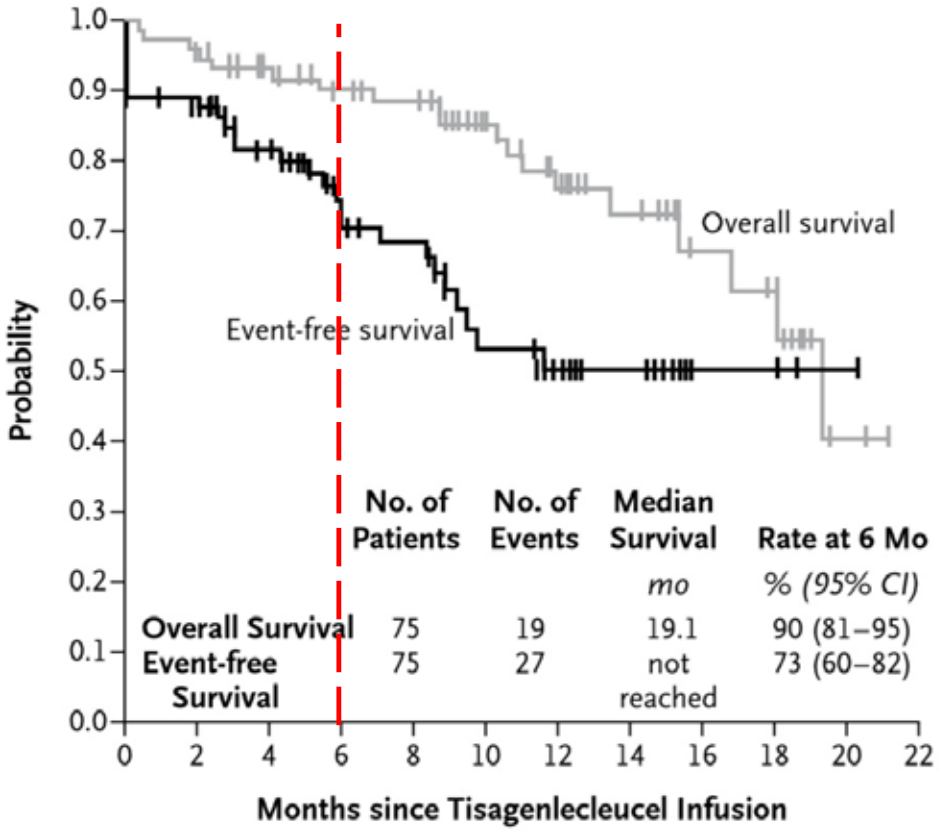
Today, Emily is 9 years cancer free!

Emily recently celebrated her 16th birthday and is currently finishing up her sophomore year of high school. Nine years post CAR T-cell therapy, cancer is thankfully a distant memory for her.

CAR-T therapy efficacy: Validated in an international trial

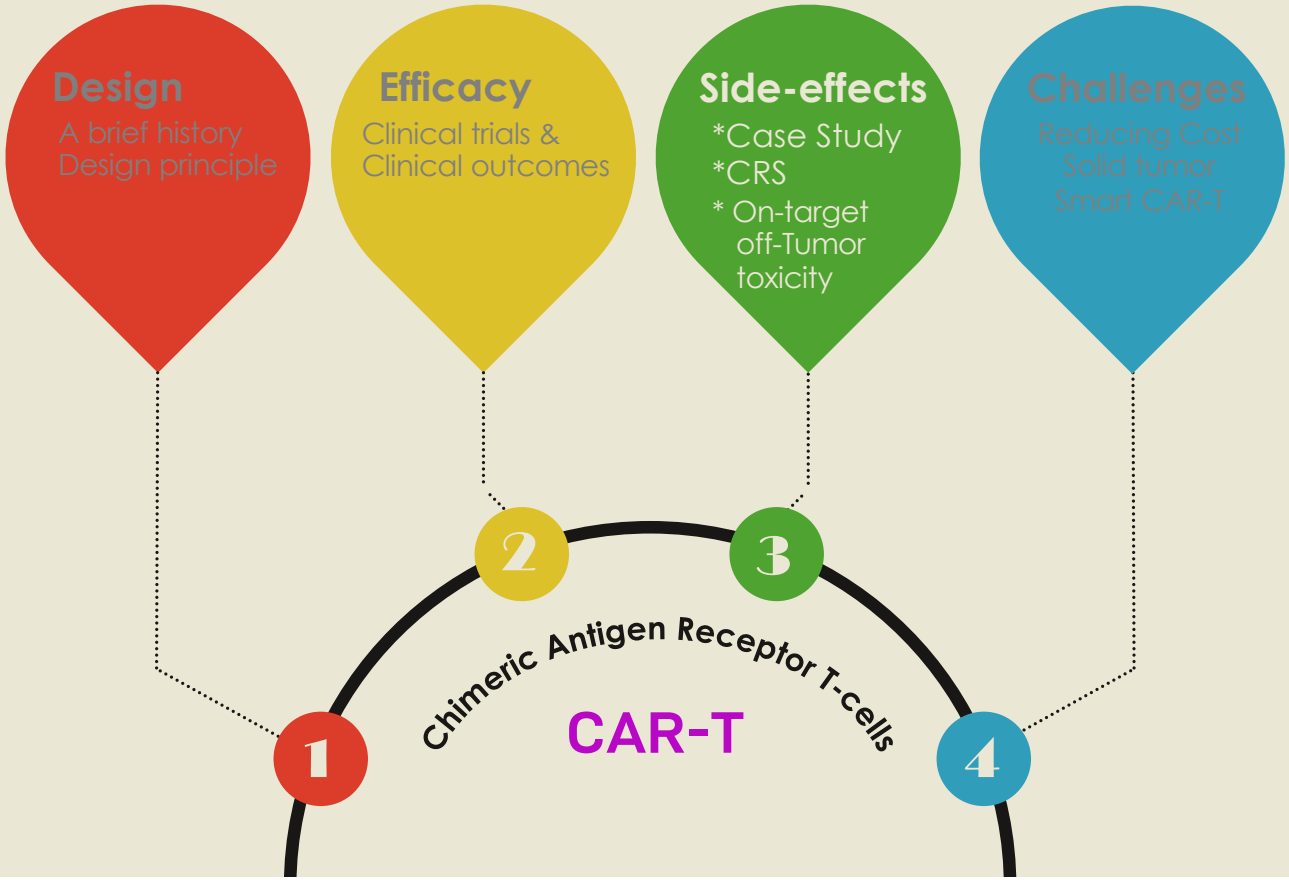
- International trial
- N=75 received CAR-T cell therapy
- 81% of patients achieved remission
- 59% relapse free survival at 12-month
- 22 patients relapsed, 68% were CD19 negative at time of relapse

[issue: Tumor antigen escape]



Maude et al. NEJM. 2018

Overview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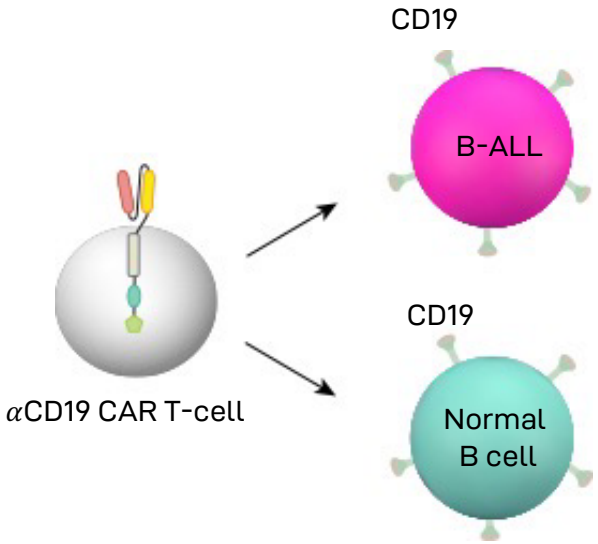
Challenge: prominent side effects associated with CAR T-cell therapy



Side effects (ZUMA-5; occurred in 86% patients):

- Grade >=3 cytokine release syndrome (CRS; 7%)
- Grade >=3 neurological events (NE; 19%)

Potential On-target/Off-tumor toxicity:

- B cell aplasia (depletion of healthy $CD19^{+}$ B cells)
- Neutrapenia (27%) and anemia (23%)

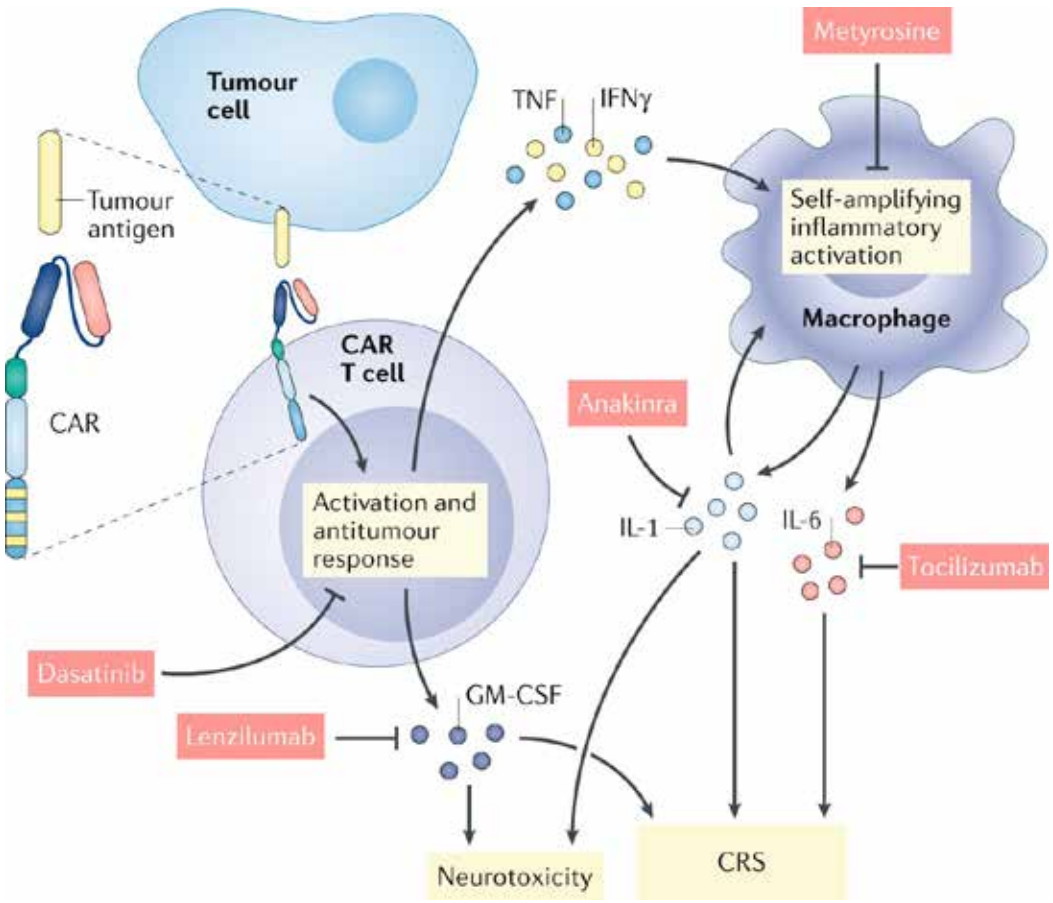
Tisagenlecleucel (KYMRIAH) in patients with B-Cell Lymphoblastic Leukemia:

- 61/75 patients with complete remission
- **All patients with a response to treatment had B-cell aplasia**

*Zuma-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL)

Tasian, et al. Ther Adv Hematol. 2015
Maude, et al. N Engl J Med. 2019

Challenges facing CAR T-cell therapy



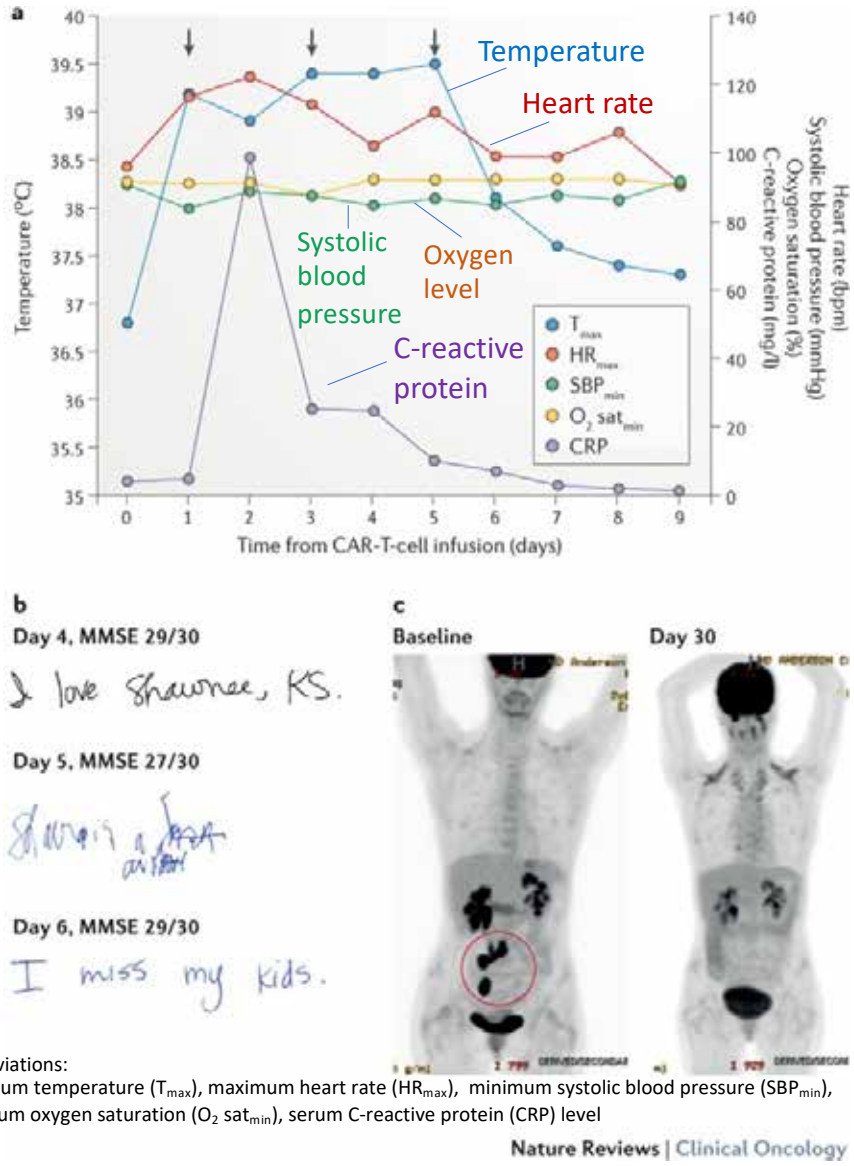
- CAR-T activation → activation of innate immune cells owing to secretion of inflammatory cytokines such as granulocyte–macrophage colony-stimulating factor (GM-CSF), tumour necrosis factor (TNF) and interferon-γ (IFNγ).
- A self-amplifying inflammatory activation loop in macrophages causing release of IL-1 and IL-6.
- Therapeutic intervention at various stages of this response can mitigate neurotoxicity and cytokine release syndrome (CRS).
- Therapeutics targeting GM-CSF (lenzilumab), the IL-6 receptor (tocilizumab) and the IL-1 receptor (anakinra) have been used for this purpose clinically. The tyrosine kinase inhibitor dasatinib affects T cell signalling to reduce CRS, and metyrosine inhibits macrophage inflammatory activation to achieve a similar effect.

Dasatinib: an ATP-competitive protein tyrosine kinase inhibitor (targeting BCR/Abl)
Metyrosine: suppressing massively secreted catecholamines to disrupt the self-amplifying loop

Case Study. CAR T-cell-related CRS + neurotoxicity

34-yo female presented with refractory diffuse large-B-cell lymphoma (DLBCL) that had progressed following extensive chemotherapy

Signs/symptoms	Treatment
Day 1. Fever 39.5 ^{0}C and Hypotension (systolic blood pressure 84 mmHg) – Grade 1 CRS–	acetaminophen/ibuprofen/ cooling blanket + IV tocilizumab (8 mg/kg)
Day 3. Hypoxia – Grade 2 CRS (cytokine storm)	IV bolus and nasal oxygen 3 l/min + IV tocilizumab (8 mg/kg)
Day 5. dysgraphia, disorientation – Grade 2 confusion - neurotoxicity	IV tocilizumab (8 mg/kg) Symptom resolved after 12 h Corticosteroids were not administered due to concurrent CRS and fever
Day 9. mild symptoms	
Day 30. complete remission >12 month CR	



Abbreviations:
maximum temperature (T_{max}), maximum heart rate (HR_{max}), minimum systolic blood pressure (SBP_{min}), minimum oxygen saturation (O_2 sat_{min}), serum C-reactive protein (CRP) level

Nature Reviews | Clinical Oncology

Tocilizumab: anti human IL-6R monoclonal antibody

Neelapu, S. S. *et al.* (2017) Chimeric antigen receptor T-cell therapy — assessment and management of toxicities *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2017.148

Toxicity Management Algorithm

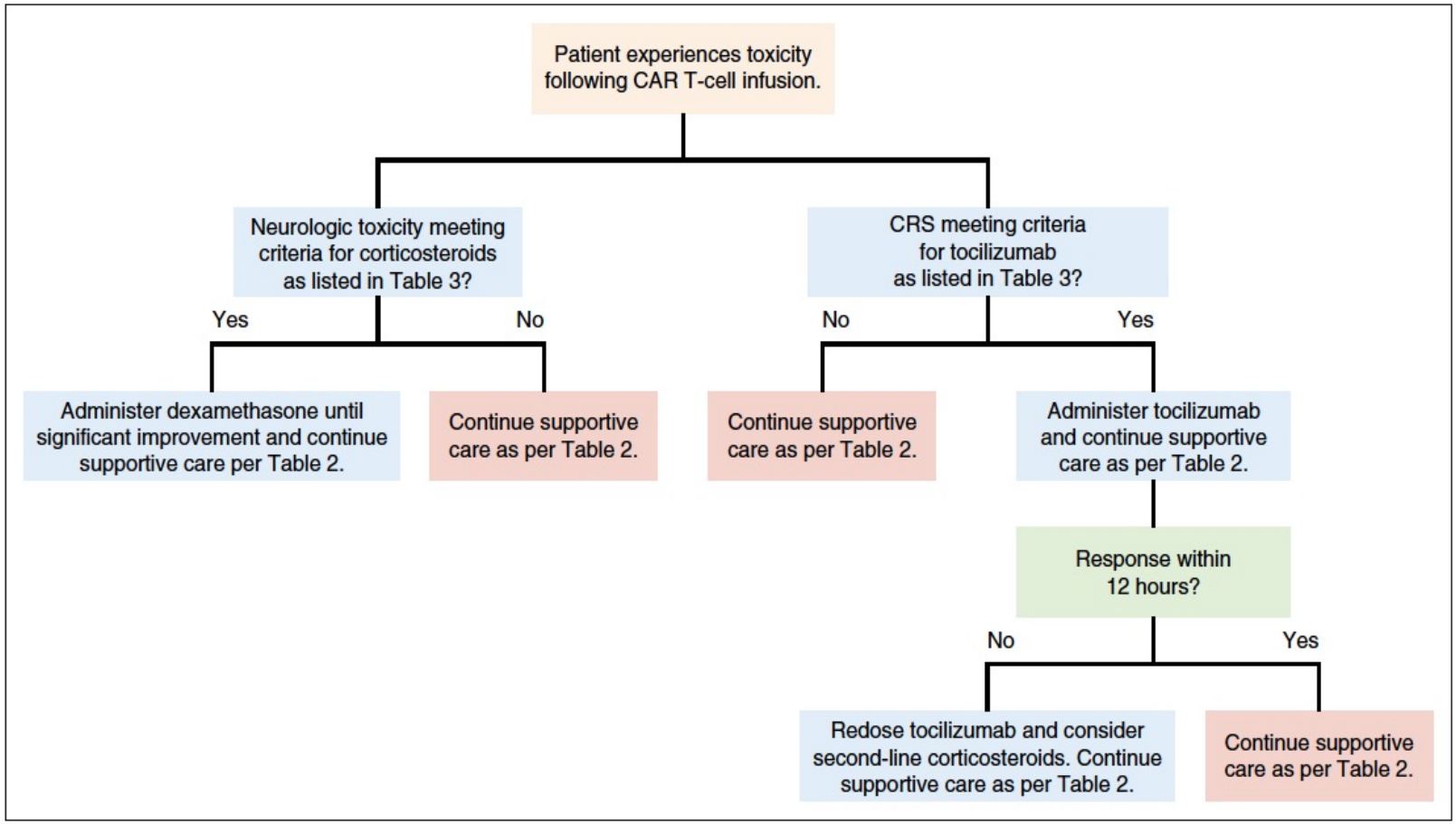


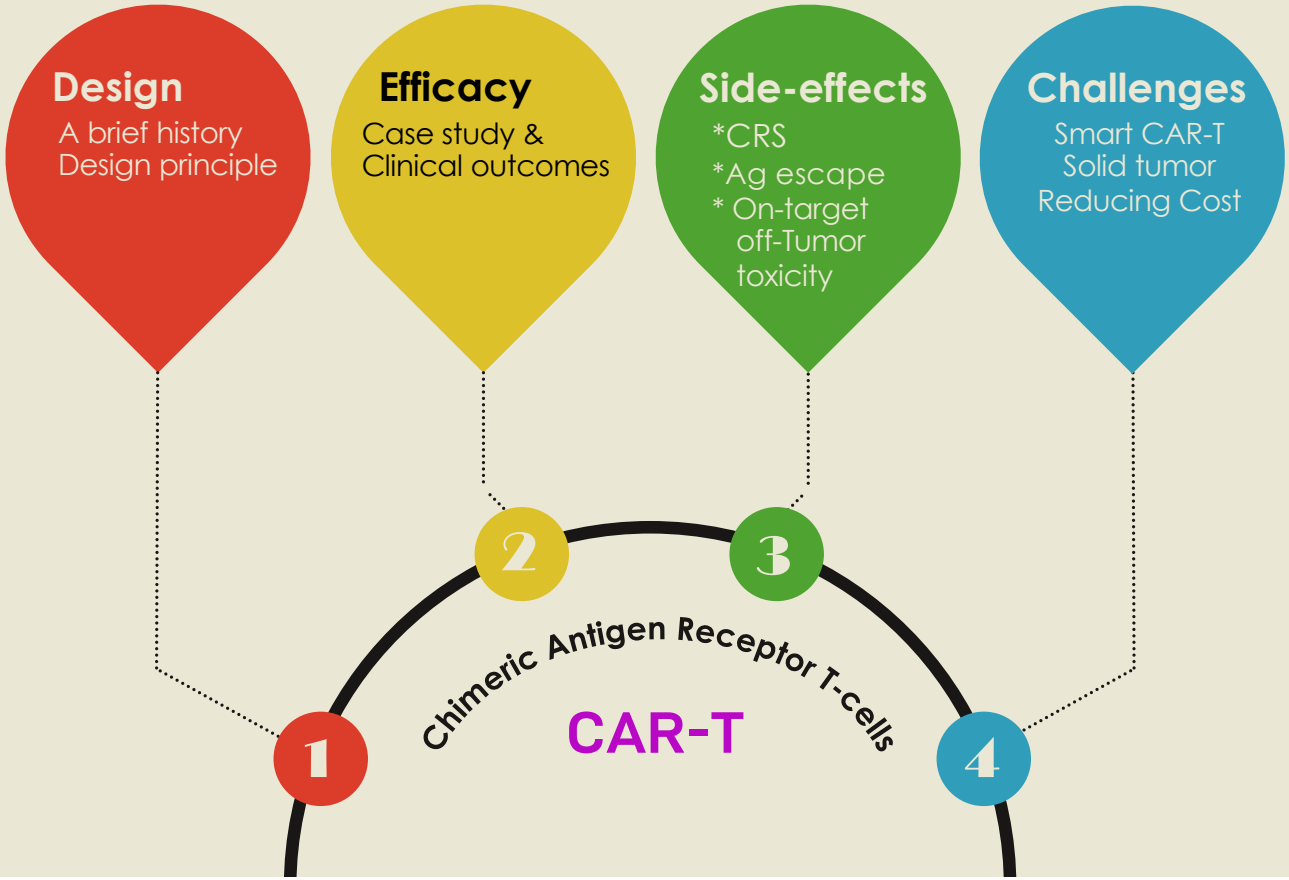
Figure 3. General treatment algorithm for CRS and neurologic toxicities. A general algorithm used for treatment of CAR T-cell toxicity occurring in patients at the NCI Experimental Transplantation and Immunology Branch is shown. Professional illustration by Patrick Lane, ScEYEnce Studios.

Toxicity Management: supportive care for CRS

Toxicity	Preventive/supportive measure
Fevers	• Acetaminophen • Cooling blankets • Avoid NSAIDs, steroids and meperidine
Cardiovascular	• At least q 4 hour vitals, q 2 if HR > 115 • IV fluid boluses for hypotension if SBP < 80% baseline and < 100 mm Hg; or if SBP < 85 mm Hg • IVF to replace insensible losses; keep net positive • ECG, troponin, and Echo if patients require > 1 fluid bolus for hypotension or are in the ICU
Infectious diseases	• Bactrim and acyclovir prophylaxis • Pan-culture for any fever • Pan-culture and broad spectrum antibiotics for neutropenic fever
Heme	• Allopurinol for tumor lysis syndrome prophylaxis • Goals: Hb > 8, platelets > 20, ANC > 500 (with filgrastim) • Goals: PTT normal; give FFP if > 1.5 x ULN; give cryoprecipitate for goal fibrinogen > 100.
Neurologic	• Neurology consult for all patients • Brain MRI and lumbar puncture whenever possible

Ther Clin Risk Manag. 2019; 15: 323–335.

Overview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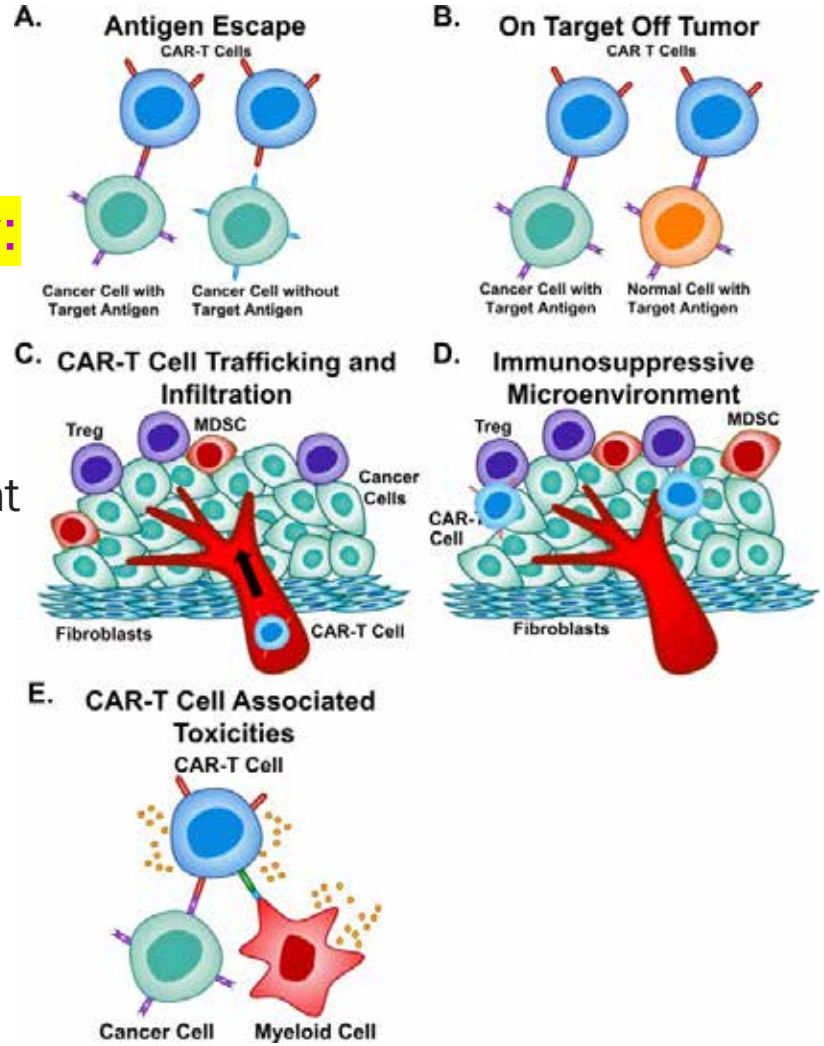
Current challenges in CAR-T cell therapy:

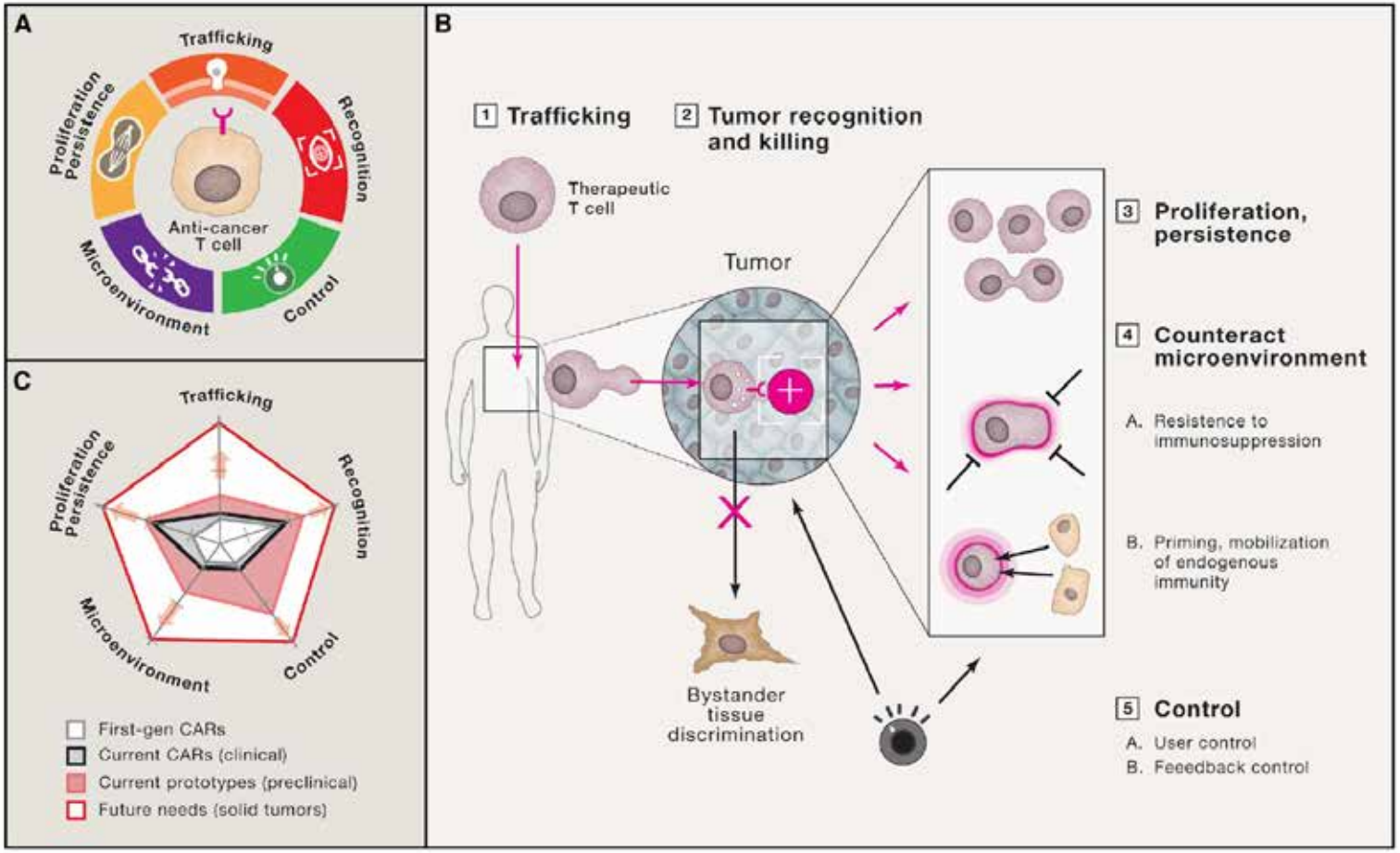
- Antigen escape
- Trafficking and infiltration of tumors
- The immunosuppressive tumor microenvironment
- CAR-T cell-associated toxicities -

    CRS & on-target off-tumor effects



https://www.nature.com/articles/s41408-021-00459-7

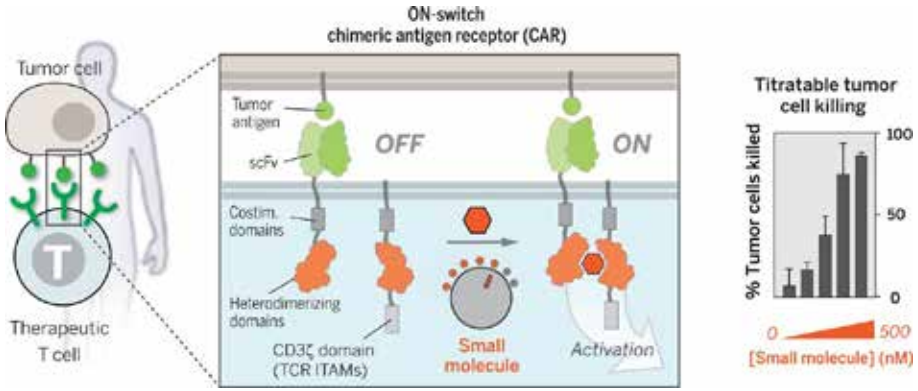
Toward the development of optimized next-generation Smart CAR T-cell therapy



1. Neoantigen & recognition
2. Precise control
3. TME
4. Proliferation/persistence (avoid exhaustion)
5. Trafficking to tumor sites

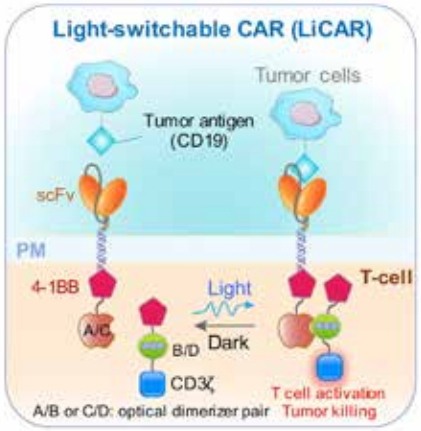
How to better CONTROL CAR-T?

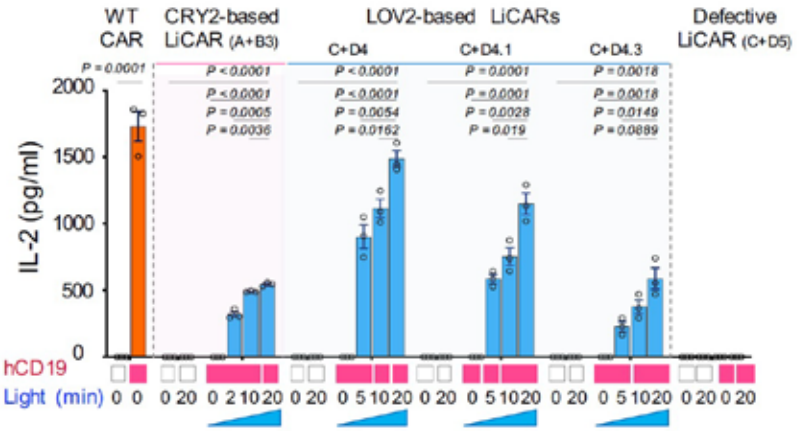
Small molecule-controllable CAR-T



Wu CY et al., Science 350 (6258): aab4077 (2015)

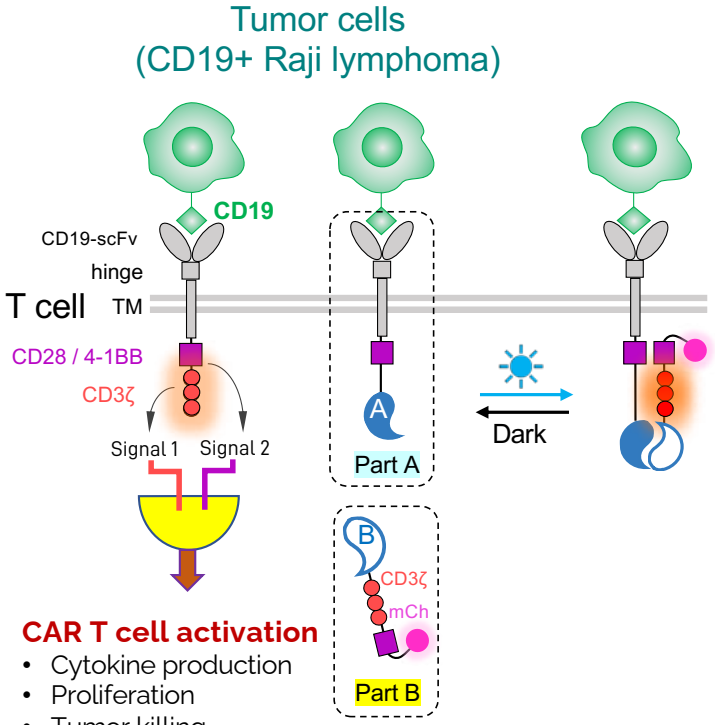
Light-switchable CAR-T

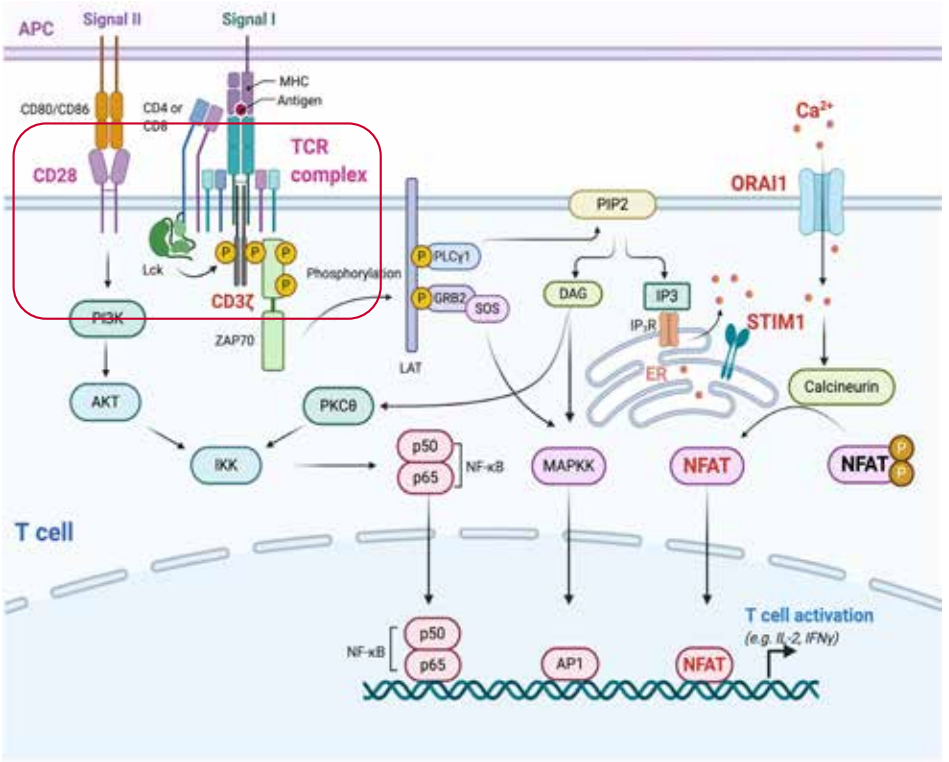




He L et al., Nat Chem Biol; ; 17, pages 915–923 (2021) | Nguyen NT, et al., Nature Nano 2021 (accepted)

Optogenetic engineering of CAR T-cells





Traditional CAR

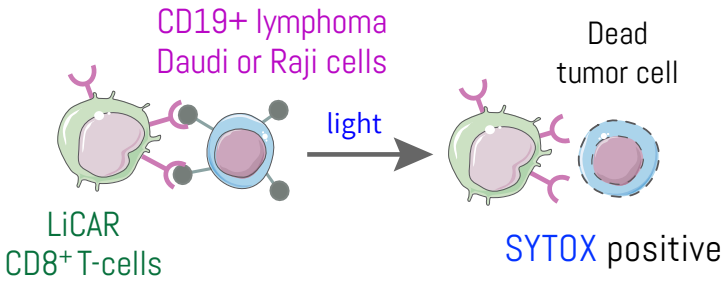
LiCAR
Light-switchable
CAR T cell

A/B: optical dimerizer

He L et al., Nat Chem Biol 21 (online)
Nguyen, et al. Nat Nano (accepted)

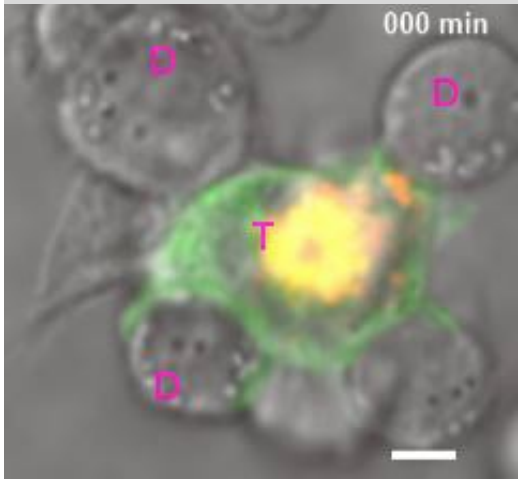
Precise control over the **time, location** and **duration** of CAR T-cell activation to mitigate side effects

LiCAR-mediated photo-tunable tumor killing ex vivo

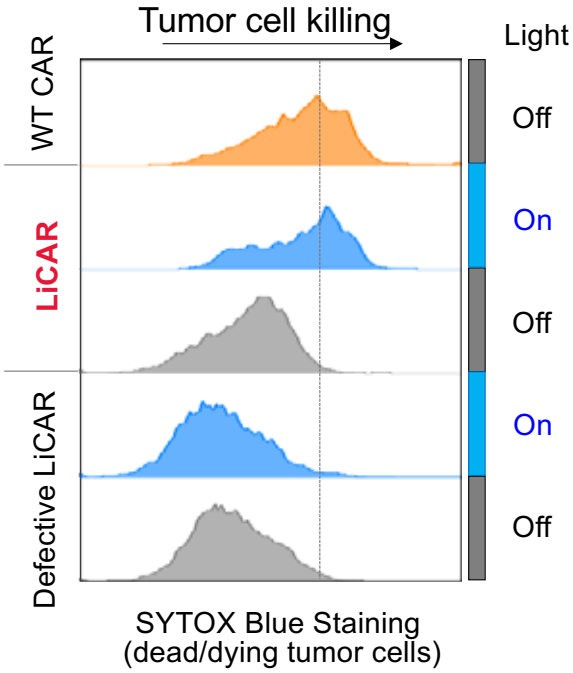


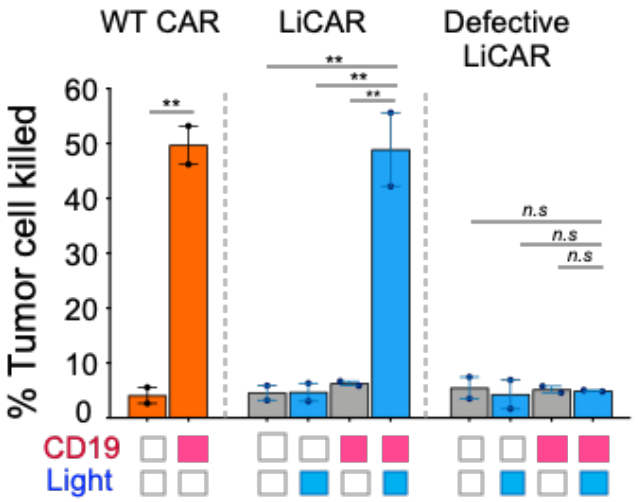
Antigen and Light dually gated CAR T-cells for precise tumor killing

light-triggered tumor killing



T: engineered LiCAR T-cell (green)
D: Daudi lymphoma cells with
SYTOX blue (Cell death indicator)





Nguyen, et al. Nat Nano (accepted)

Addressing the recognition issue: the synNotch idea

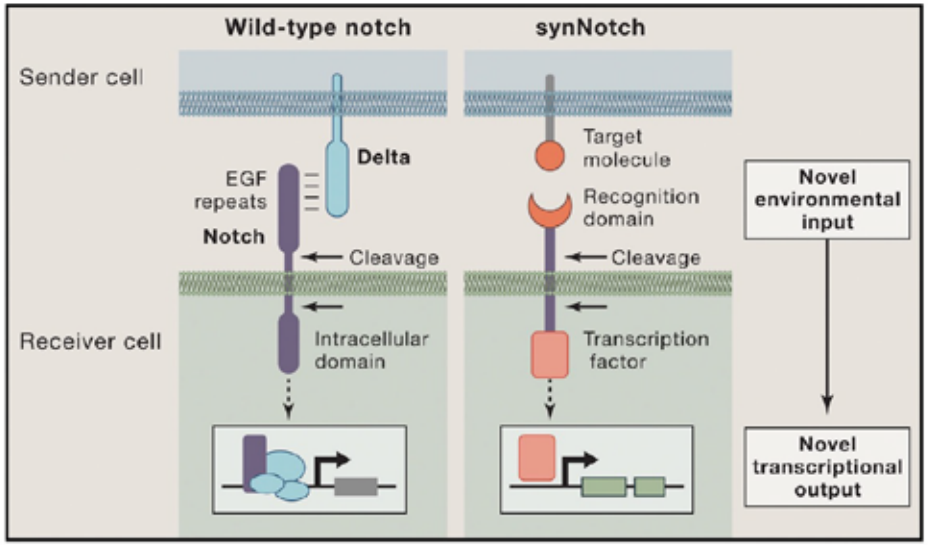
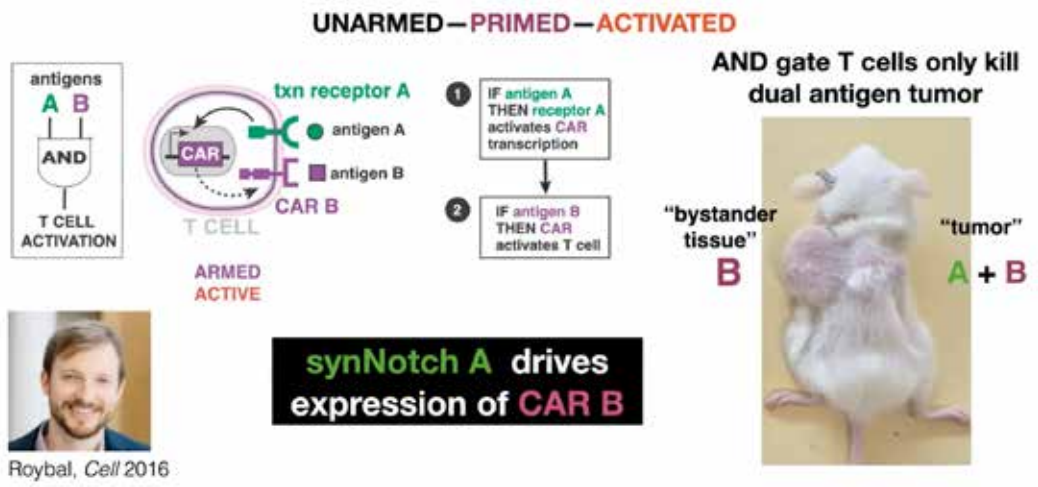


Figure 1. Design of SynNotch Receptors
Schematic structure/function relationships for endogenous Delta-Notch interactions (left) and engineered synNotch receptors (right).



Kole T. Roybal, … Wendell A. Lim., Volume 164, Issue 4, 11 February 2016, Pages 770-779
Leonardo Morsut, …, Wendell A. Lim. Cell, Volume 164, Issue 4, 11 February 2016, Pages 780-791

Addressing the tumor escape issue: multiple Ag targeting

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CAR T cells with dual targeting of CD19 and CD22 in adult patients with recurrent or refractory B cell malignancies: a phase 1 trial

Jay Y. Spiegel, Shabnum Patel, [...]David B. Miklos

Nature Medicine **27**, 1419–1431 (2021) | Cite this article

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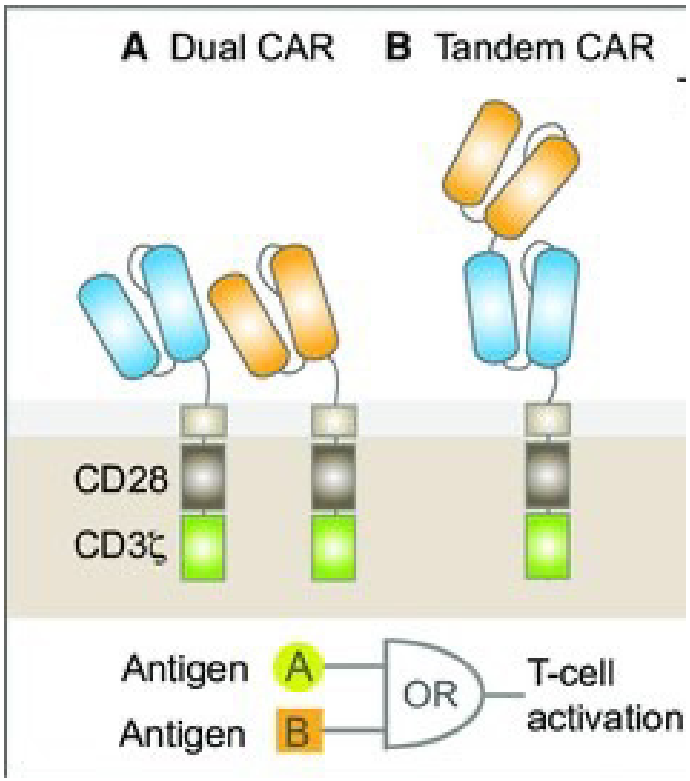


Addressing the Trafficking issue

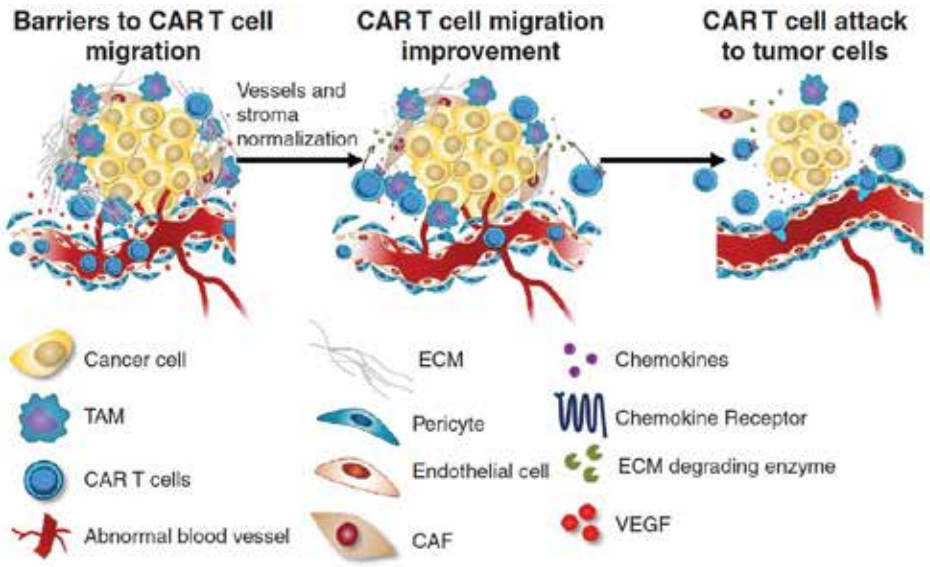


FIGURE 2 **Barriers and improvements to chimeric antigen receptor (CAR) T cell migration.** CAR T cells should overcome the barriers to cell migration at tumor sites in order to perform their cytolytic effector function. Obstacles to T cell trafficking toward tumors might occur due to abnormal tumor blood vessels with pericyte detachment, dysregulation of chemokine-chemokine receptor interaction, deposition of extracellular matrix (ECM) proteins by cancer-associated fibroblasts (CAF), as well as encounter with tumor-associated macrophages (TAM). Therefore, targeting of tumor micro-environmental components represents an important approach for CAR T cell therapy improvement. The combination of chemokine-chemokine receptor signaling with co-expression of ECM degrading enzymes could be determinant for T cell function, as well as enhancing the therapeutic efficacy of CAR T cells

- One preclinical model showed that **chemokine receptor type 2b** (CCR2b) expression on GD2-CAR T cells improved homing to neuroblastoma tumor cells and pleural mesotheliomas.

- Blocking **protein kinase A** in T cells from reaching the immunological synapse improved T cells' ability to infiltrate tumors with increased expression of CXC motif chemokine receptor 3 (CXCR3) on T cells. [Clinical trial NCT03602157]

1.Moon EK, Carpenito C, Sun J, et al. Clin Cancer Res. 2011;17(14):4719–4730.
2.Newick K, O'Brien S, Sun J, et al. Cancer Immunol Res. 2016;4(6):541–551.
3.Brown CE, Alizadeh D, Starr R, et al. N Engl J Med. 2016;375(26):2561–2569.

Addressing the TME/Persistence issue

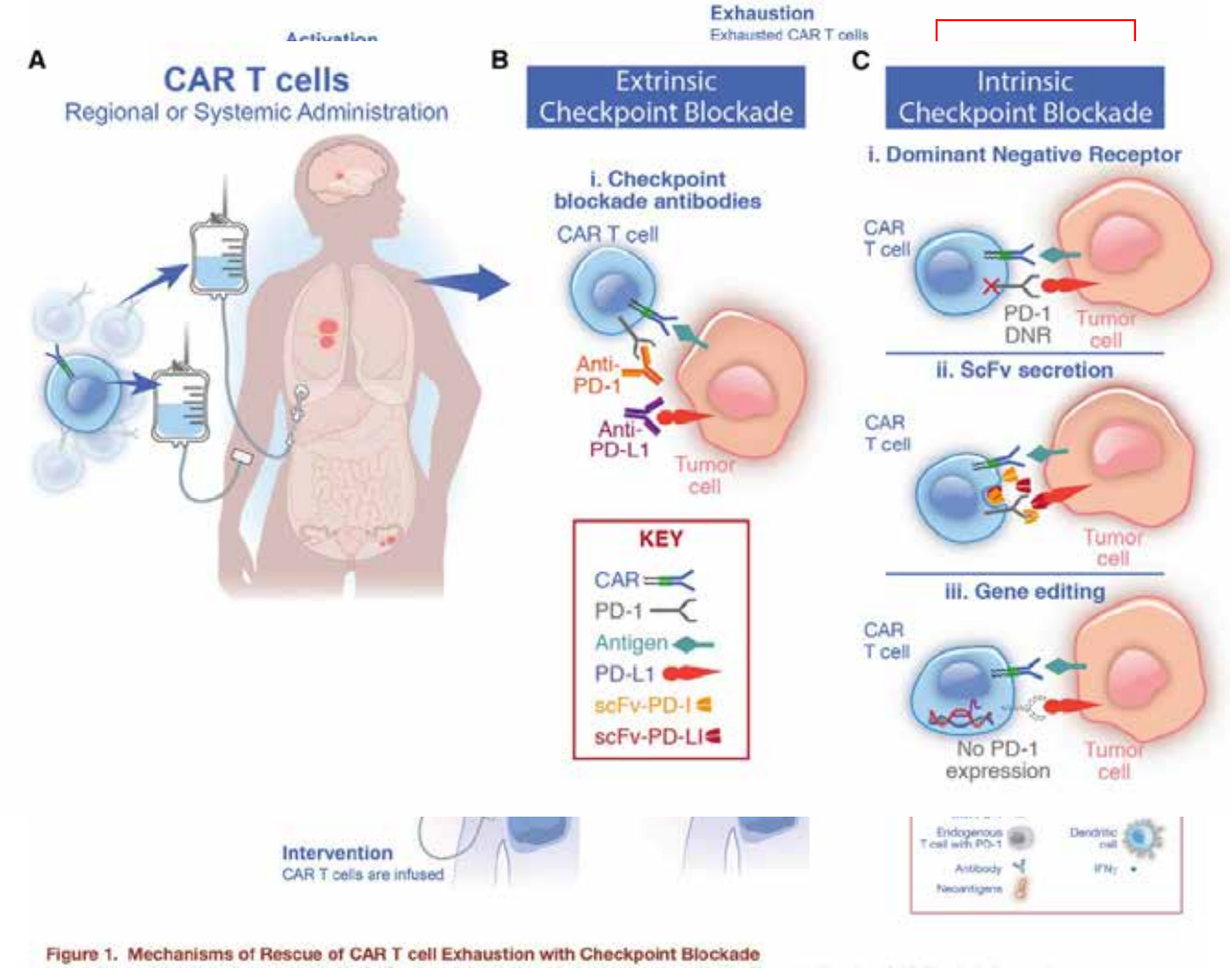


Figure 1. Mechanisms of Rescue of CAR T cell Exhaustion with Checkpoint Blockade

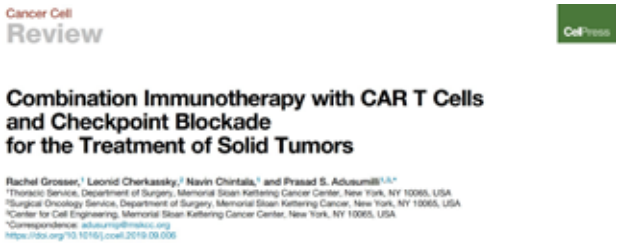
Exhaustion: in response to IFN-g, tumor cells upregulate programmed death-ligand 1 (PD-L1), which interacts with programmed cell death protein 1 (PD-1) on the surface of exhausted CAR T cells.

Checkpoint blockade (CPB) intervention and reactivation: on administration of CPB, CAR T cell and endogenous T cell function is rescued to enable killing of tumor cells.

Ab, antibody;

DNR, dominant negative receptor;

scFv, single chain variable fragment


Cancer Cell
Review

Combination Immunotherapy with CAR T Cells and Checkpoint Blockade for the Treatment of Solid Tumors

Rachel Grosser,[1] Leonid Cherkassky,[2] Navin Chintala,[1] and Prasad S. Adusumilli[1,3,*]
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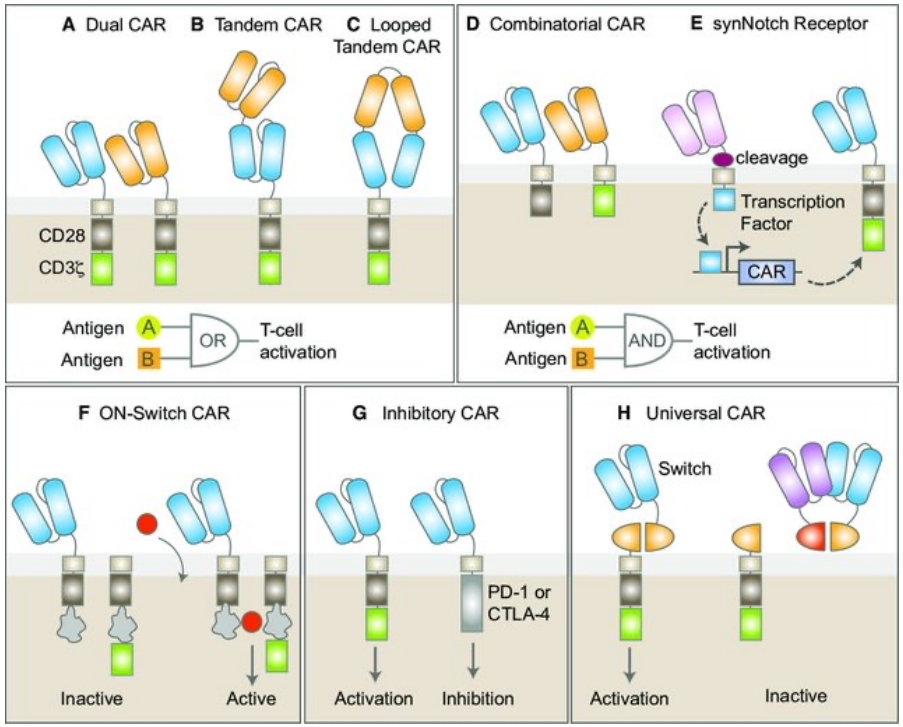
https://doi.org/10.1016/j.ccell.2019.09.006

Combining CAR-T with Immunocheckpoint blockade

Table 1. Clinical Trials Exploring Combination Therapy with CAR T Cells and Checkpoint Blockade

Trial	Launch	Phase	Center(s)	CPB Agent	CAR Target/Design	Cancer Diagnosis
NCT00586391	2009	I	Baylor	ipilimumab	CD19/CD19CAR-28-zeta T cells	B cell lymphoma, chronic lymphocytic leukemia, acute lymphocytic leukemia
NCT01822652	2013	I	Baylor	pembrolizumab	GD2/iC9-GD2-CD28-OX40 (iC9-GD2) T cells	neuroblastoma
NCT02650999	2016	I/II	University of Pennsylvania	pembrolizumab	anti-CD19 CARs	$CD19^+$ diffuse large B cell lymphoma, follicular lymphoma, mantle cell lymphoma
NCT02706405	2016	I	Fred Hutchinson	durvalumab	autologous anti-CD19CAR-4-1BB-CD3ζ-EGFRt-expressing $CD4^+$/$CD8^+$ central memory T lymphocytes JCAR014	diffuse large B cell lymphoma
NCT02926833	2016	I/II	City of Hope, Stanford, Moffitt, Dana Farber, MD Anderson	atezolizumab	CD19/KTE-C19	diffuse large B cell lymphoma
NCT03310619	2017	I/II	City of Hope, Northwestern University, Massachusetts General, University of Nebraska, University of Pennsylvania, MD Anderson	durvalumab	JCAR017	lymphoma, non-Hodgkin lymphoma, diffuse large B cell lymphoma, follicular lymphoma
NCT03726515	2018	I	University of Pennsylvania	pembrolizumab	CART-EGFRvIII T cells	glioblastoma

More intelligent CAR-T therapies on the way



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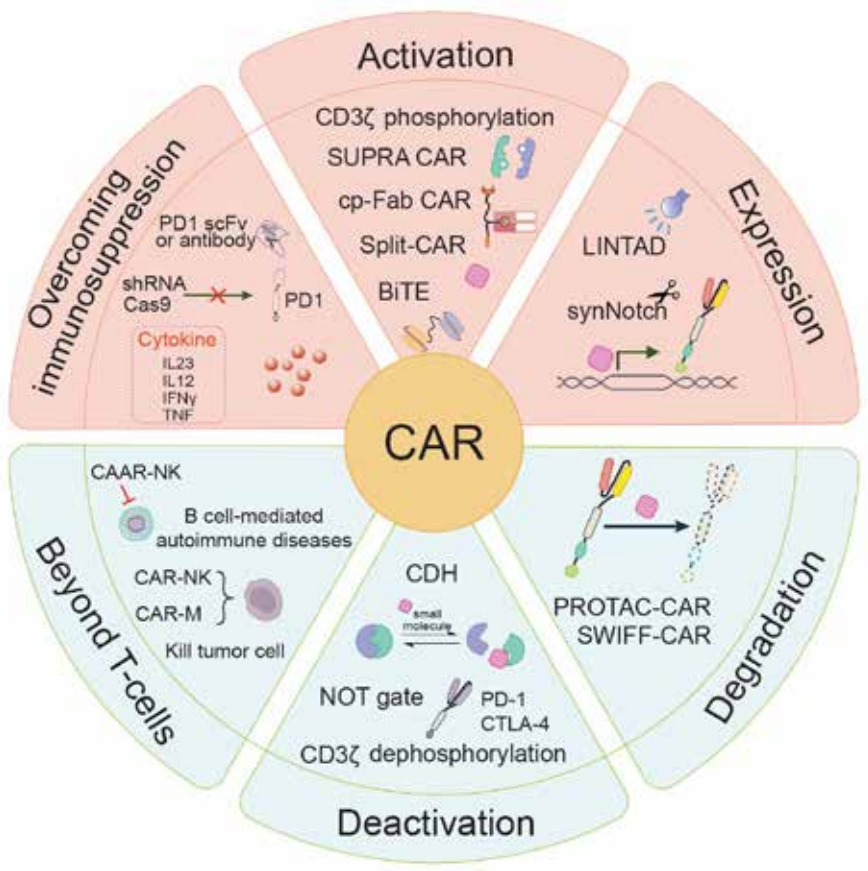
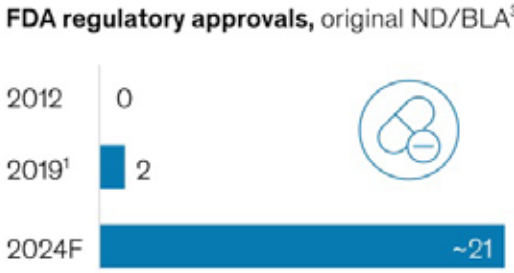
Intelligent cell-based therapies for cancer and autoimmune disorders

Rui Chen[1,4], Ji Jing[1,4], Stefan Siwko[1], Yun Huang[2,3] and Yubin Zhou[1,3]



Current Opinion in Biotechnology 2020, **66**:207–216

Over the past seven years, multiple measures show that CAR-T activity, and its impact on patients, have increased.

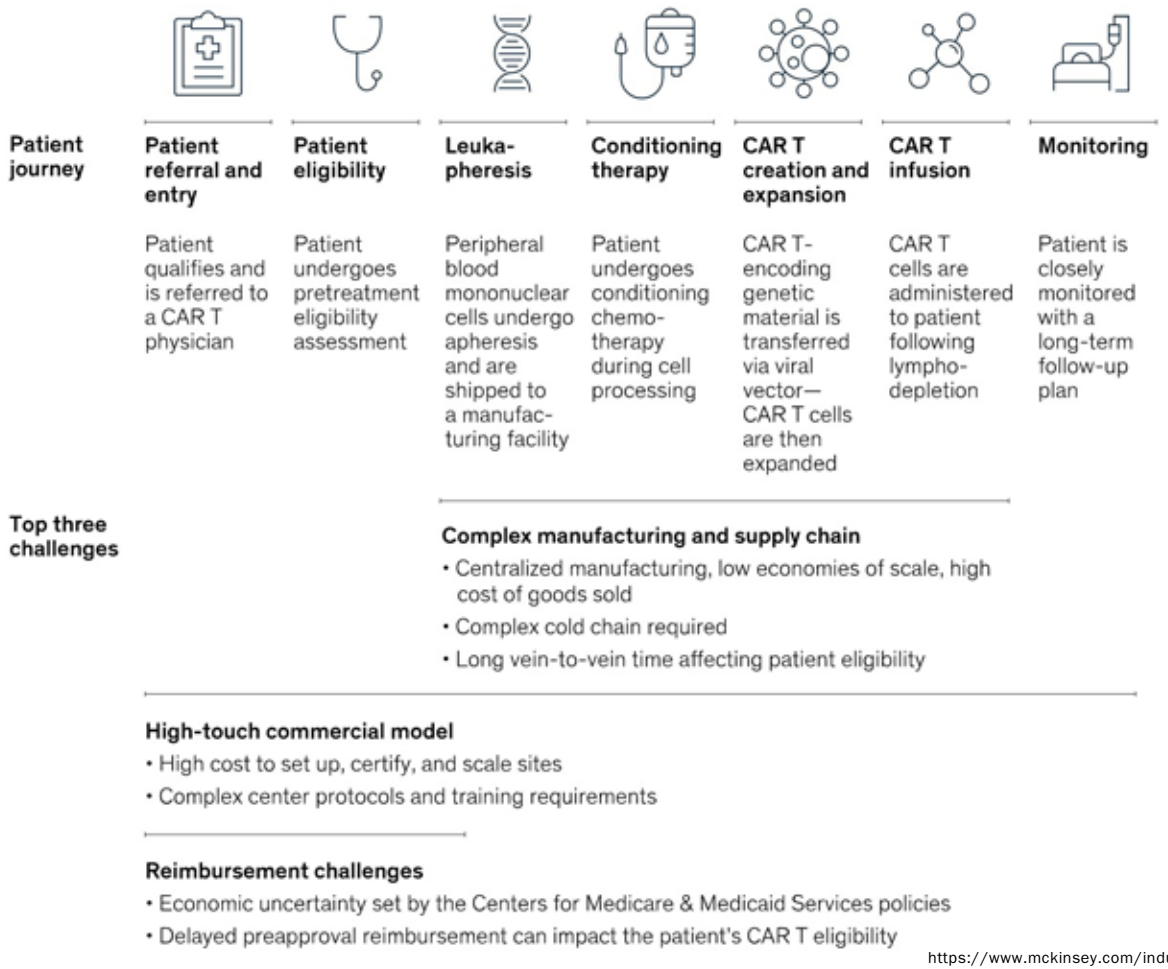


A growing need for CAR-T

https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/driving-the-next-wave-of-innovation-in-car-t-cell-therapies#

Addressing the COST challenge

Commercialization faces major challenges on the CAR T patient journey.



1. Industrialize and automate cell production to scale-out manufacturing.

Automation is needed- The high operating cost of CAR T therapy is driven largely by labor (about 25 percent of operating expenses).

2. Shift from centralized to decentralized manufacturing.

"Bedside manufacturing" at the hospital.

3. Develop allogeneic products.

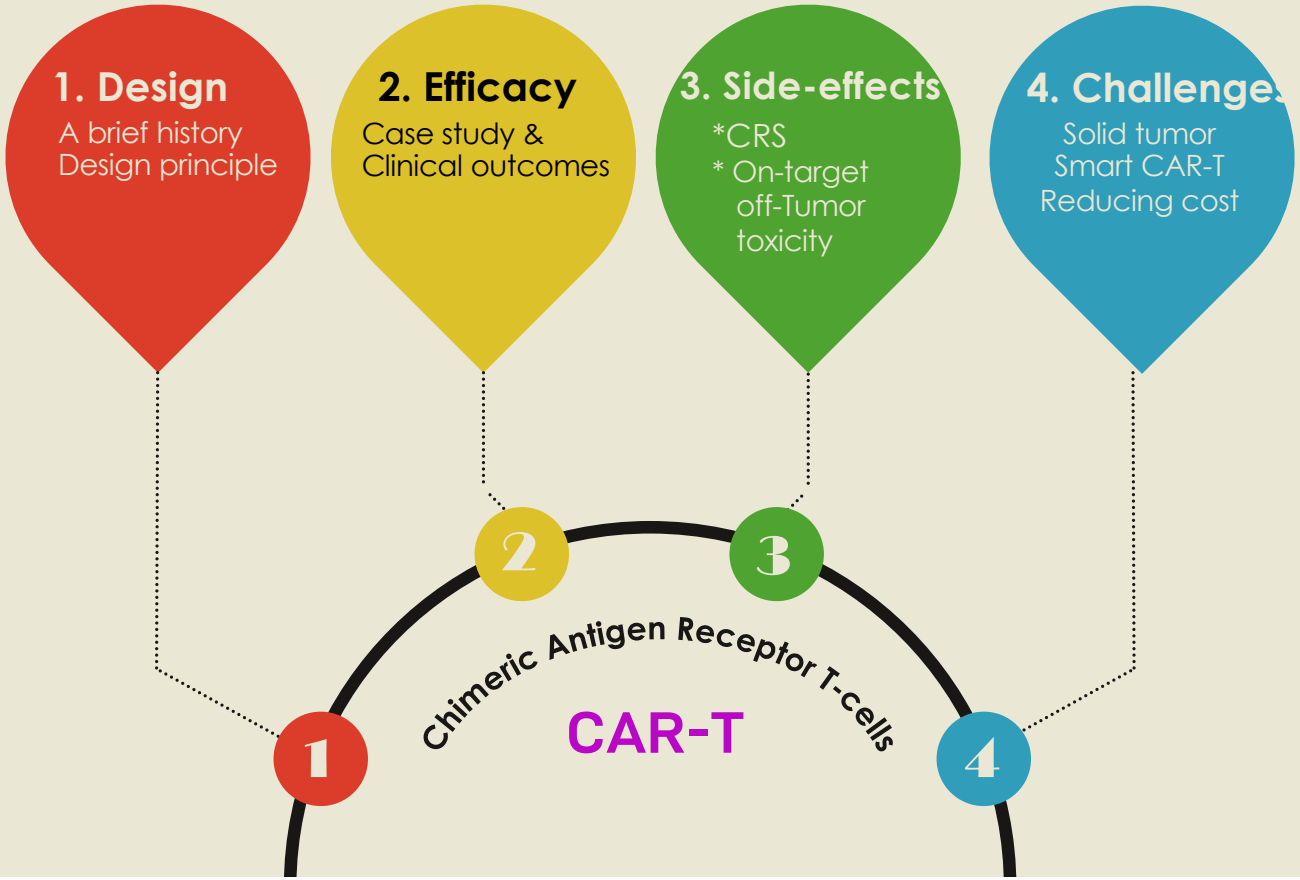
- Reduced cost of goods sold; a simplified supply chain;
- Avoidance of issues with autologous CAR T cells
- Lack of graft-versus-host disease and clearance of allogeneic cells.

4. Advanced gene-transfer and modifying tools.

- Removing donor T-cell receptors
- Adding on-off switches that can turn off the CAR T to prevent toxicity
- Secreted factors

https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/driving-the-next-wave-of-innovation-in-car-t-cell-therapies#

Learning Objectives



Further reading

1. **Recent advances and discoveries in the mechanisms and functions of CAR T cells.**
   Nat Rev Cancer. 2021;21(3):145-161. doi: 10.1038/s41568-020-00323-z. Epub 2021 Jan 22.

2. **A Milestone for CAR T Cells.**
   N Engl J Med. 2017 Dec 28;377(26):2593-2596. DOI: 10.1056/NEJMe1714680

3. **Intelligent cell-based therapies for cancer and autoimmune disorders.**
   Curr Opin Biotechnol. 2020 Dec;66:207-216. DOI: 10.1016/j.copbio.2020.08.012

4. **Chimeric antigen receptor T-cell therapy — assessment and management of toxicities.**
   Nature Reviews Clinical Oncology volume 15, pages47–62 (2018)

5. **The Principles of Engineering Immune Cells to Treat Cancer.**
   Cell, 2017 Feb 9;168(4):724-740.