An Overview of Chimeric Antigen Receptor T-cells:

"CAR-T-ing Away Cancer"

Maxwell Brown, PharmD

Clinical Pharmacy Manager, Hematopoietic Stem Cell Transplantation

NewYork-Presbyterian/Weill Cornell Medical Center

Conflict of Interest Disclosure

I have no actual or potential conflicts of interest to disclose regarding this presentation.

Objectives

1. Discuss the structure and mechanism of action of chimeric antigen receptor (CAR) T-cells.

2. Describe the pathophysiology and management of cytokine release syndrome (CRS) and CAR-T related encephalopathy syndrome (CRES)

3. Summarize key clinical trials assessing the use of CAR-T cell therapy in acute lymphoblastic leukemia (ALL) and B-cell lymphomas

Audience Response Question #1

What does CAR-T cell stand for?

1. Carrier T cell
2. Chemotherapy/antibody receptor T cell
3. Chimeric antigen receptor T cell
4. Chimeric antibody receptor T cell

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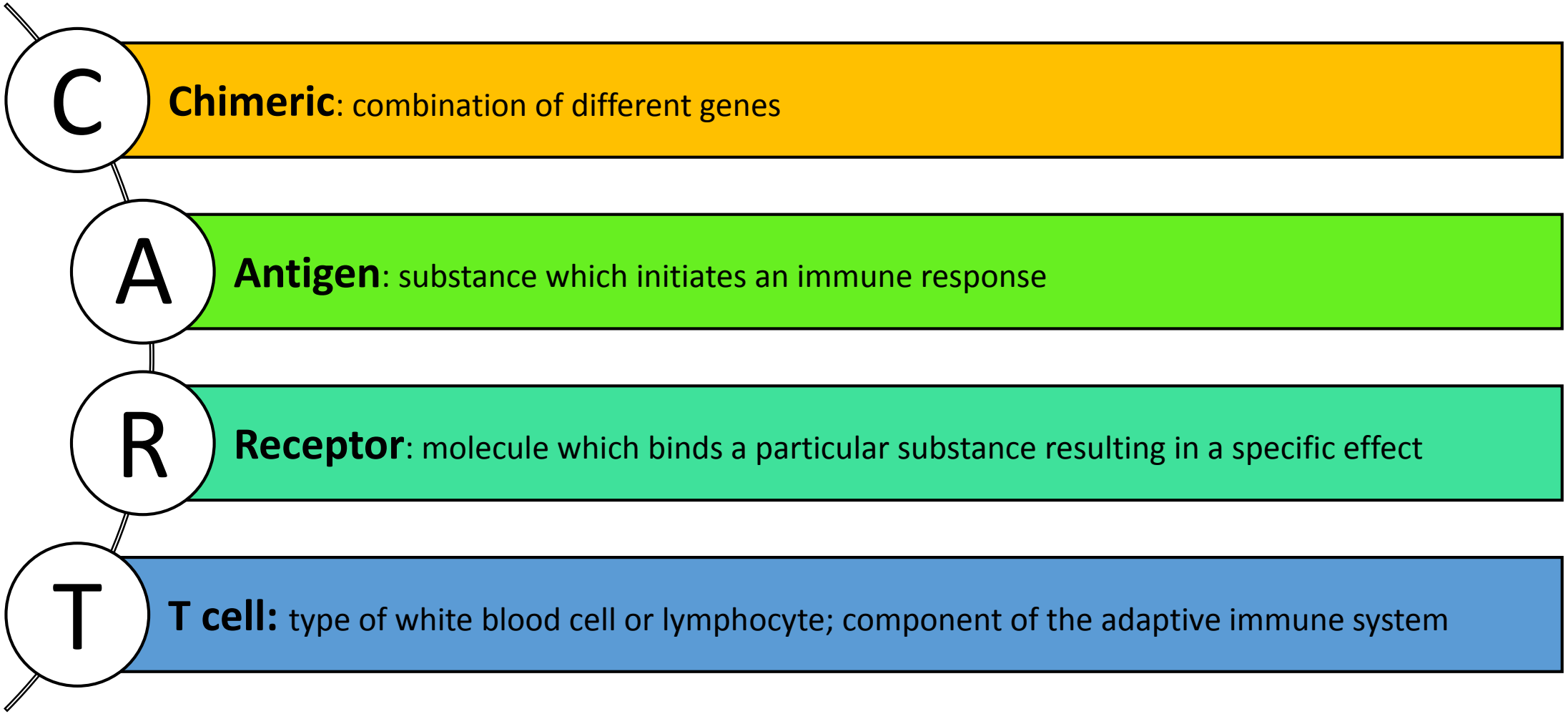
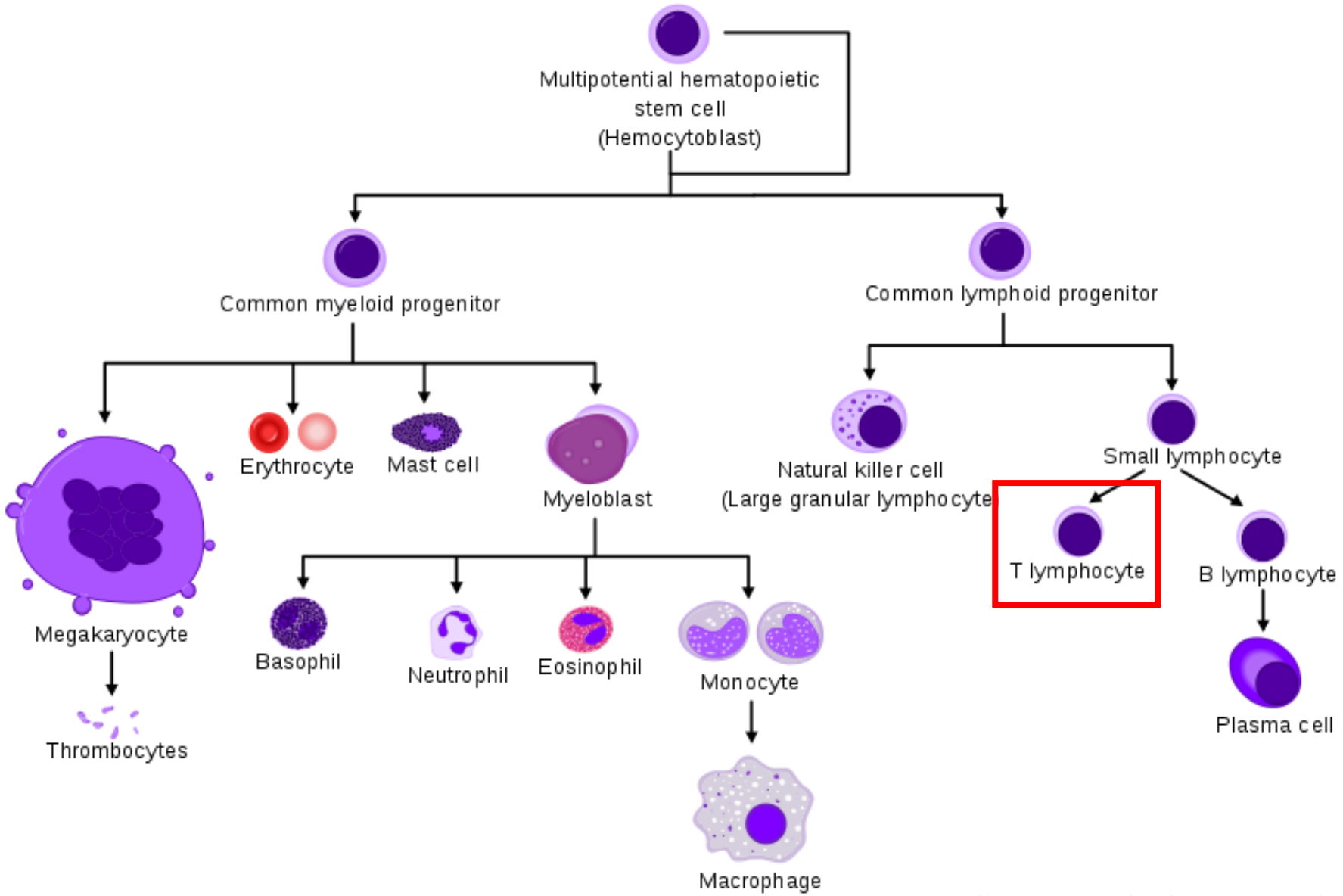
CAR-T cells


C
Chimeric: combination of different genes
A
Antigen: substance which initiates an immune response
R
Receptor: molecule which binds a particular substance resulting in a specific effect
T
T cell: type of white blood cell or lymphocyte; component of the adaptive immune system

What is a CAR-T cell?

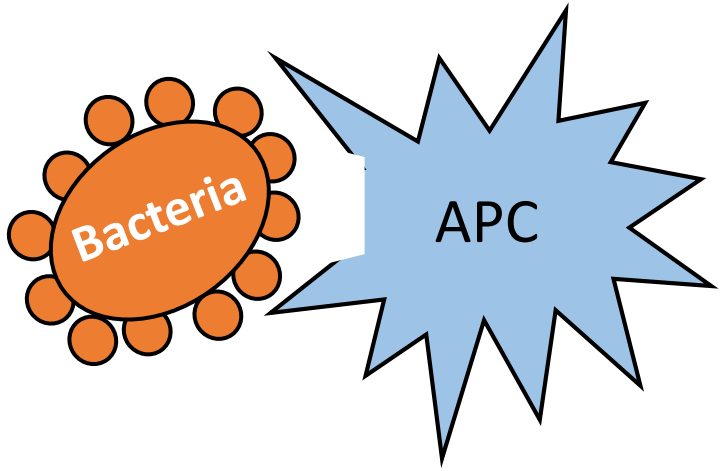
Hematopoiesis

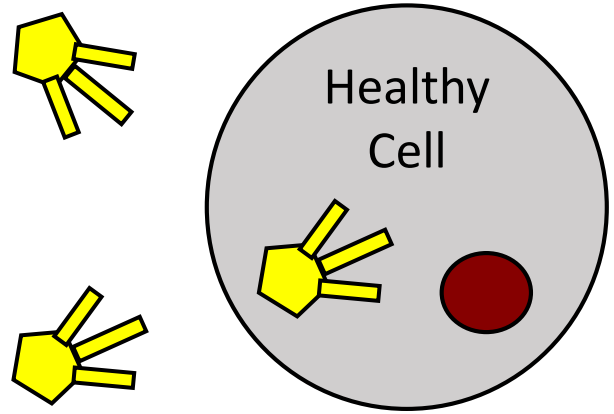


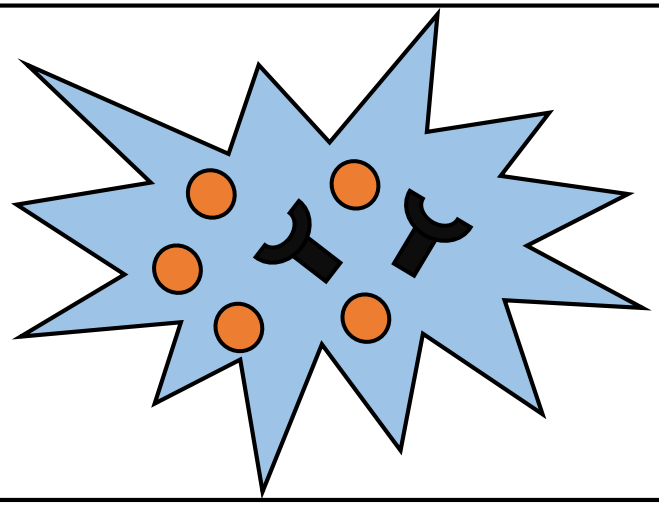
https://en.wikipedia.org/wiki/Haematopoiesis#/media/File:Hematopoiesis_simple.svg

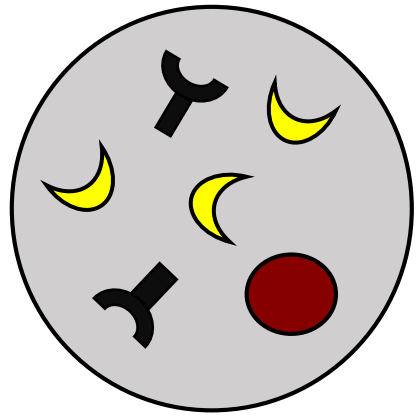
Antigen Recognition and Processing

Bacteria	Viruses
Phagocytosis of bacterial cells by antigen presenting cells (APC).	Virus invades healthy cell and begins replicating.
Antigen processing into peptide fragments for presentation via the major histocompatibility complex (MHC).	Degradation of viral proteins by the proteasome for presentation via the MHC.



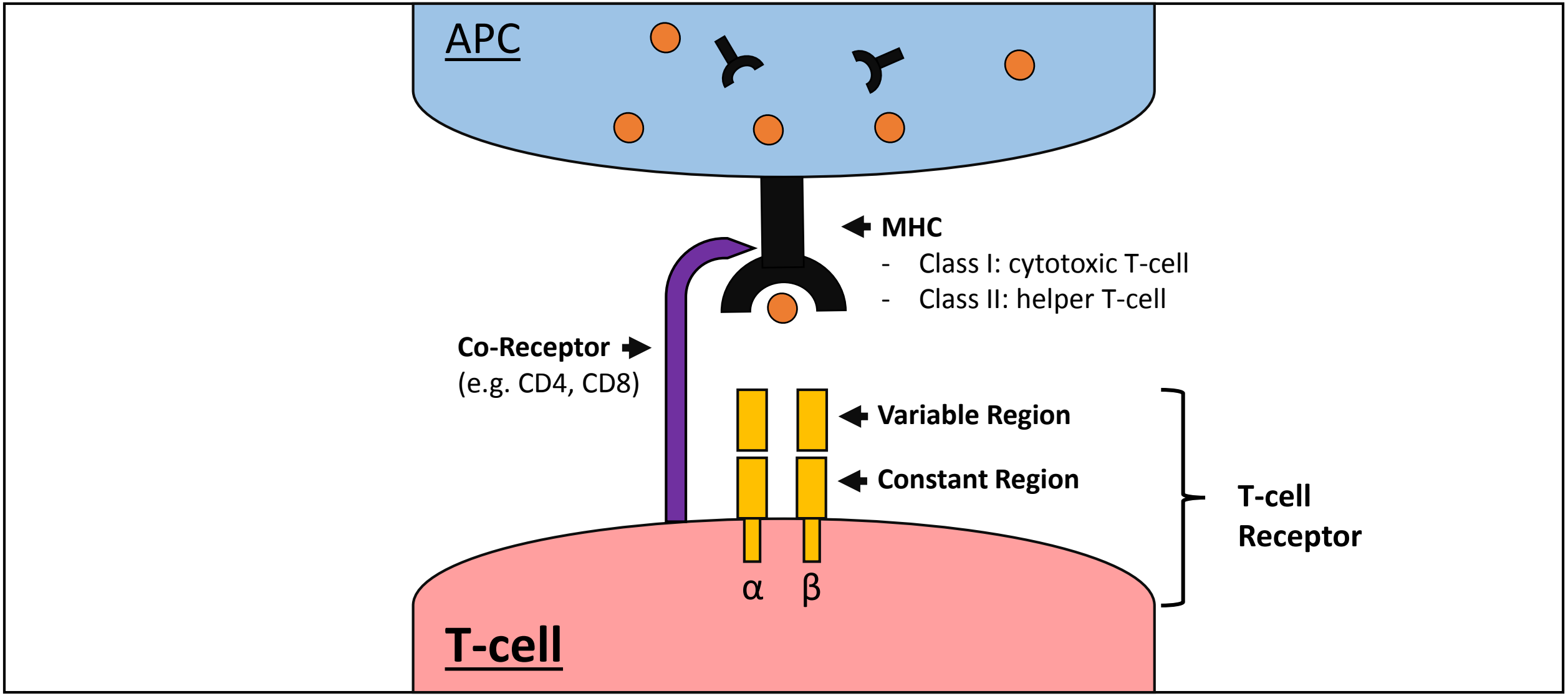






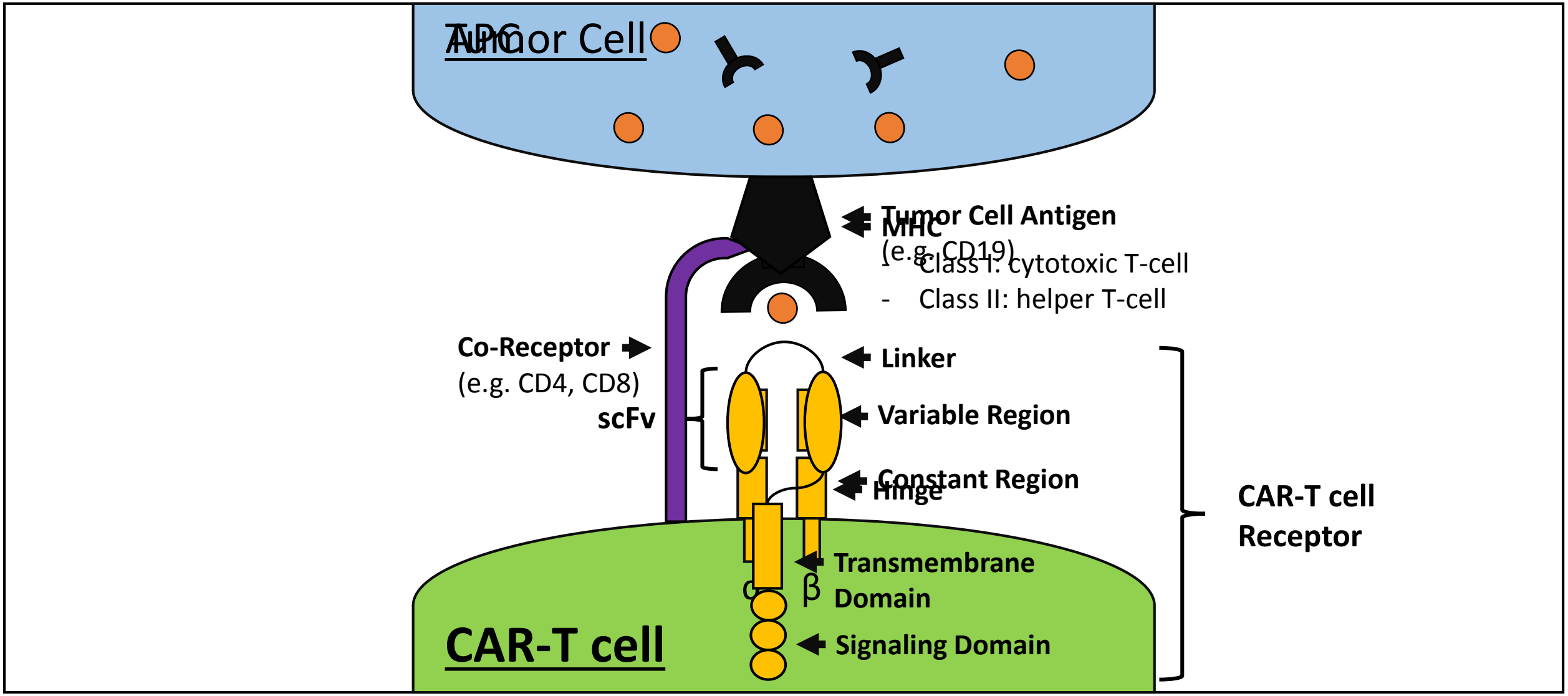
Curr Res Transl Med. 2017;65(3):93-102.

Endogenous T-cell Activation



Curr Res Transl Med. 2017;65(3):93-102.

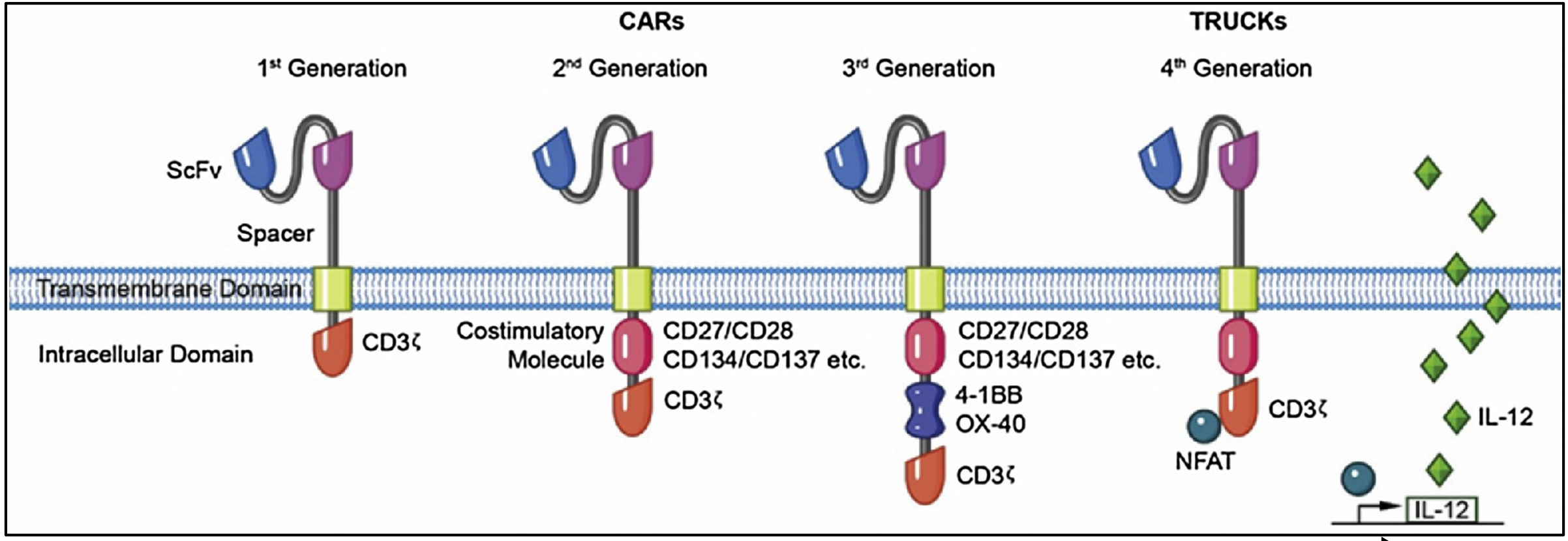
CAR-T cell Activation



scFv = single chain fragment variable

Curr Res Transl Med. 2017;65(3):93-102.

Engineering of CAR-T cells



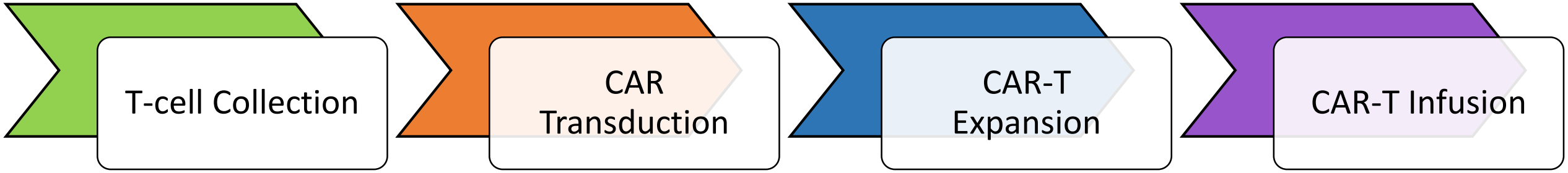
- Cytotoxicity
- Proliferation & Persistence
- Cytokine Production

TRUCK =T cell redirected for universal cytokine-mediated killing

Curr Res Transl Med. 2017;65(3):93-102.

CAR-T cell Manufacturing and Administration

CAR-T cell Manufacturing Process



- ❑ Apheresis
- ❑ T-cell selection

- ❑ Lentiviral/retroviral DNA vectors
- ❑ Gene transfer
- ❑ CAR expression

- ❑ APCs, activation reagents, antibody-coated microbeads
- ❑ Cryopreservation

- ❑ Administration of lymphodepleting chemotherapy
- ❑ Infusion of CAR-T product

Autologous versus Allogeneic?

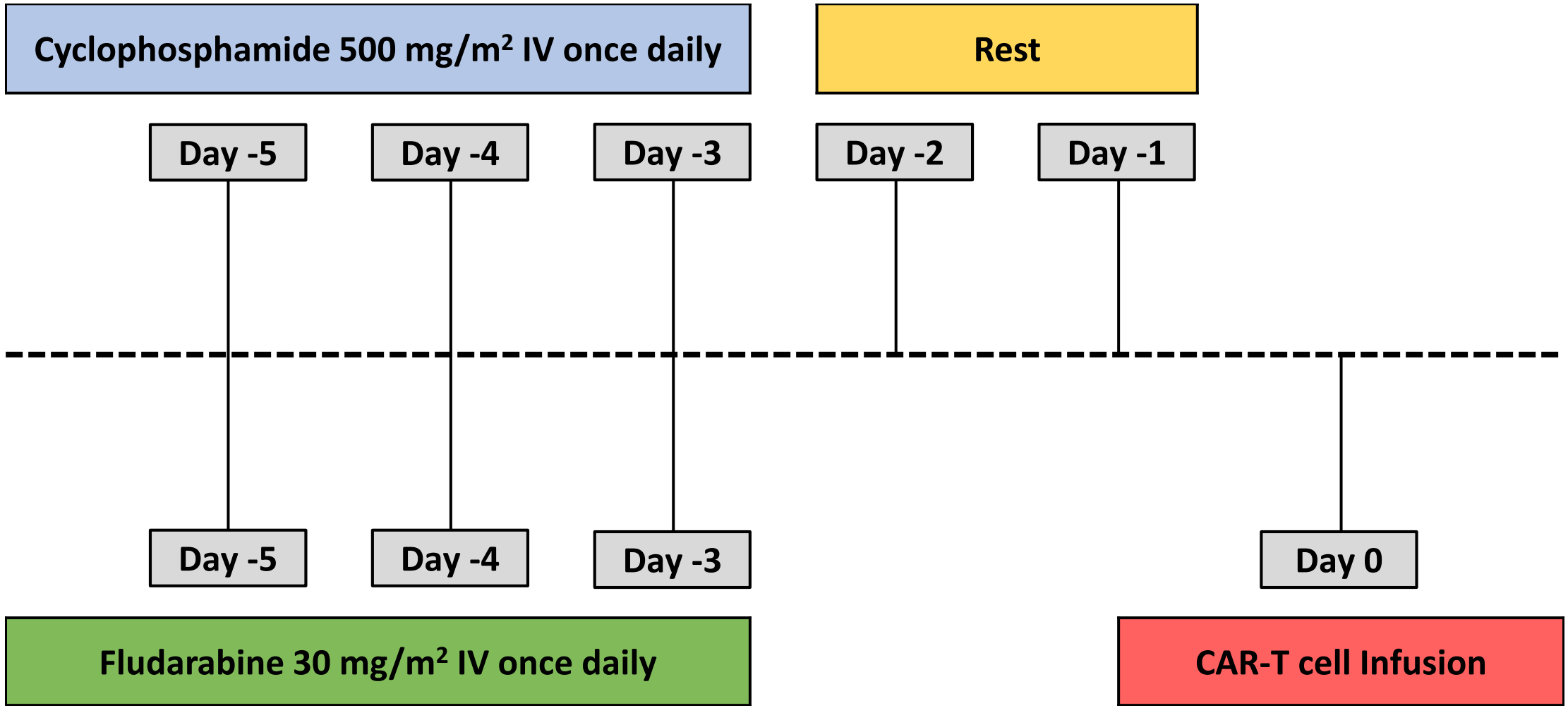
Mol Ther Oncolytics. 2016;3:16015.

Autologous versus Allogeneic CAR-T cells

Autologous	Allogeneic
Ability to collect	Persistence of CAR-T cells
Quality & functionality	Risk of graft-versus-host disease
Production time	
Delays in treatment	

Curr Opin Hematol. 2015;22(6):509-15.

Lymphodepleting Chemotherapy



YESCARTA (axicabtagene ciloleucel suspension) [package insert].

Commercially Available CAR-T Products

Audience Response Question #2

For which disease states are CAR-T cells currently FDA approved?

1. Acute lymphoblastic leukemia (relapsed or refractory)
2. Large B-cell lymphoma (relapsed or refractory)
3. Acute myeloid leukemia (relapsed or refractory)
4. Both A and B
5. All of the above

Audience Response Question #2

For which disease states are CAR-T cells currently FDA approved?

1. Acute lymphoblastic leukemia (relapsed or refractory)
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3. Acute myeloid leukemia (relapsed or refractory)
4. **Both A and B**
5. All of the above

Currently Available CAR-T cell Products

YESCARTA (axicabtagene ciloleucel)

- FDA Approval: treatment of adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
- Autologous CAR-T cell product targeting CD19

KYMRIAH (tisagenlecleucel)

- FDA Approval: treatment of patients up to 25 years of age with relapsed or refractory B-cell precursor acute lymphoblastic leukemia
- Autologous CAR-T cell product targeting CD19

YESCARTA (axicabtagene ciloleucel suspension) [package insert].
KYMRIAH (tisagenlecleucel) [package insert].

What’s in a name?

axicabtagene ciloleucel

- First Word: corresponds to gene component
- Second Word: corresponds to vector and cell component

World Health Organization 2017.

What's in a name?

axicabtagene ciloleucel

Prefix is random

World Health Organization 2017.

What's in a name?

axi**cabta**gene cilo**leu**cel

First Word Infix identifies the gene component

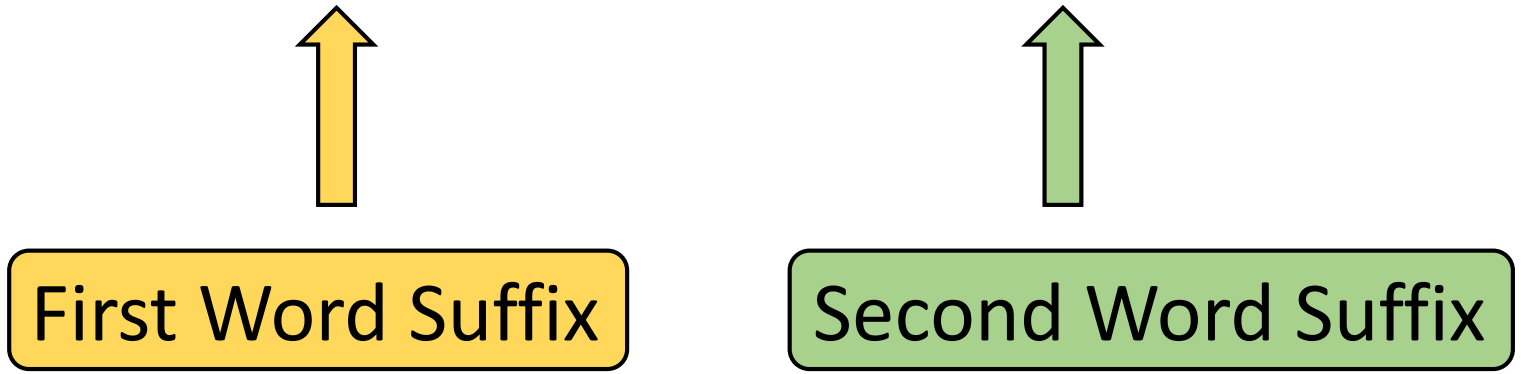
'cabta' = cell expressed antibody and T cell activation

Second Word Infix identifies the cell type

'leu' = lymphocytes/monocytes/APC (white cells)

What's in a name?

axicabtagene ciloleucel



Designate the product as a genetically modified cell-based therapy

World Health Organization 2017.

ZUMA-1 Trial

Design	▪ Multicenter, phase II clinical trial
Population	▪ n = 111 ▪ Adult patients with relapsed or refractory B cell lymphomas*
Intervention	▪ Axicabtagene ciloleucel

Efficacy	▪ ORR = 82%; CR = 52%; median duration of response = 8.1 months
	▪ At 15 months:
	  ○ Median PFS = 44%
	  ○ Median OS = 52%

Safety	▪ CRS occurred in 93% of patients, 13% of grade 3 or higher ▪ Neurotoxicity occurred in 64% of patients, 28% of grade 3 or higher

*diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma

ORR = overall response rate; PFS = progression-free survival; OS = overall survival; CRS = cytokine release syndrome

N Engl J Med 2017; 377:2531-44.

ELIANA Trial

Design	▪ Multicenter, phase II clinical trial
Population	▪ n = 92 ▪ Pediatric and young adults (≤25 years) with CD19+ relapsed or refractory B-cell ALL
Intervention	▪ Tisagenlecleucel

Efficacy	▪ ORR = 81%; CR = 45%; CRi = 21%; Median duration of response not reached
	▪ At 12 months:
	  ○ Median EFS = 50%
	  ○ Median OS = 76%

Safety	▪ CRS occurred in 77% of patients, 46% of grade 3 or higher ▪ Neurotoxicity occurred in 40% of patients, 10% of grade 3

CRi = complete response with incomplete hematologic recovery; EFS = event free survival

N Engl J Med 2018; 378:439-48.

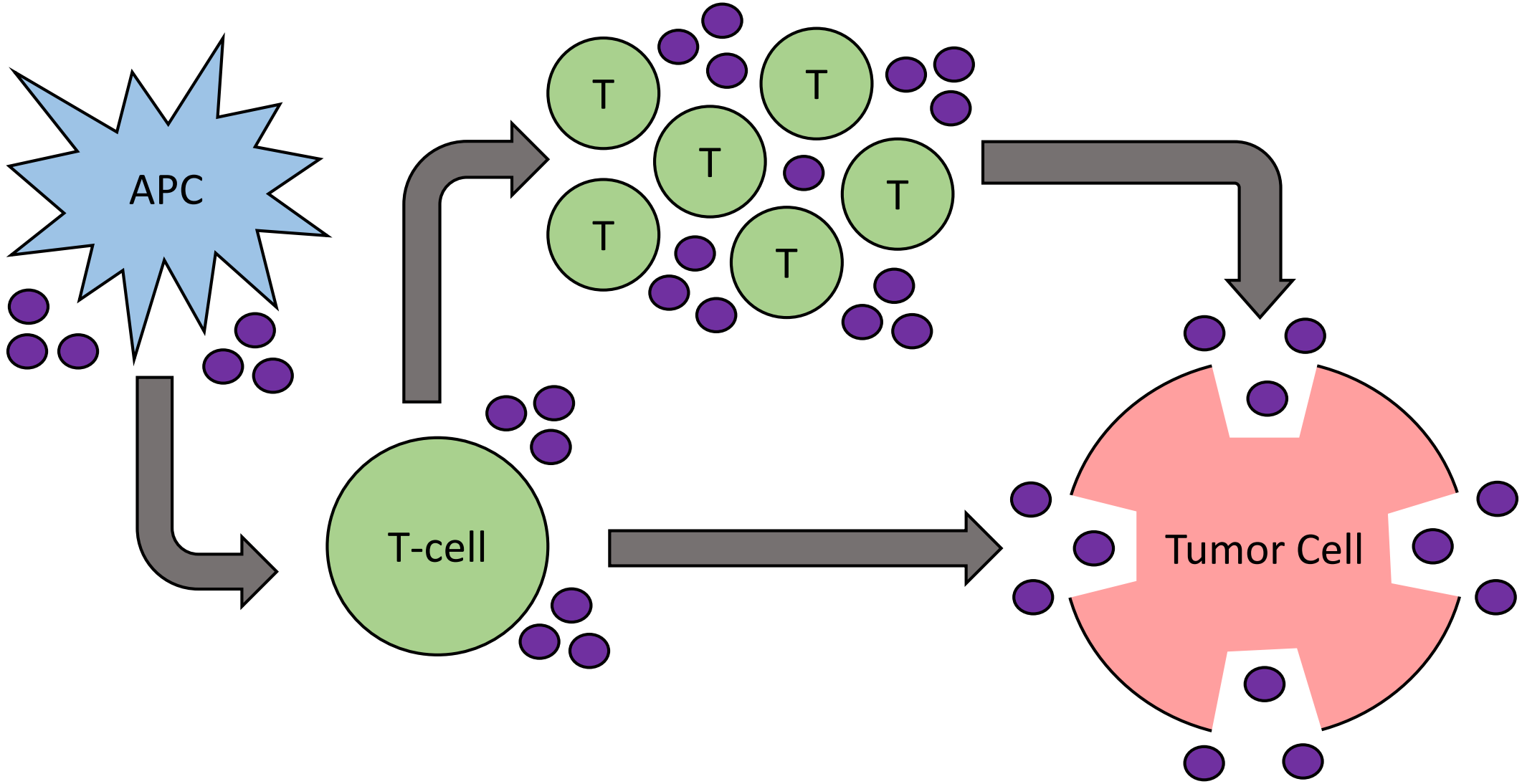
Black Box Warnings

Cytokine Release Syndrome	• Fever, hypoxia, hypotension, coagulopathy, acute kidney injury, transaminitis, hyperbilirubinemia
Neurologic Toxicities	• Headache, encephalopathy, delirium, anxiety, tremor
REMS Program	• Patient wallet card • Minimum of two doses of tocilizumab available for each patient

YESCARTA (axicabtagene ciloleucel suspension) [package insert].
KYMRIAH (tisagenlecleucel) [package insert].

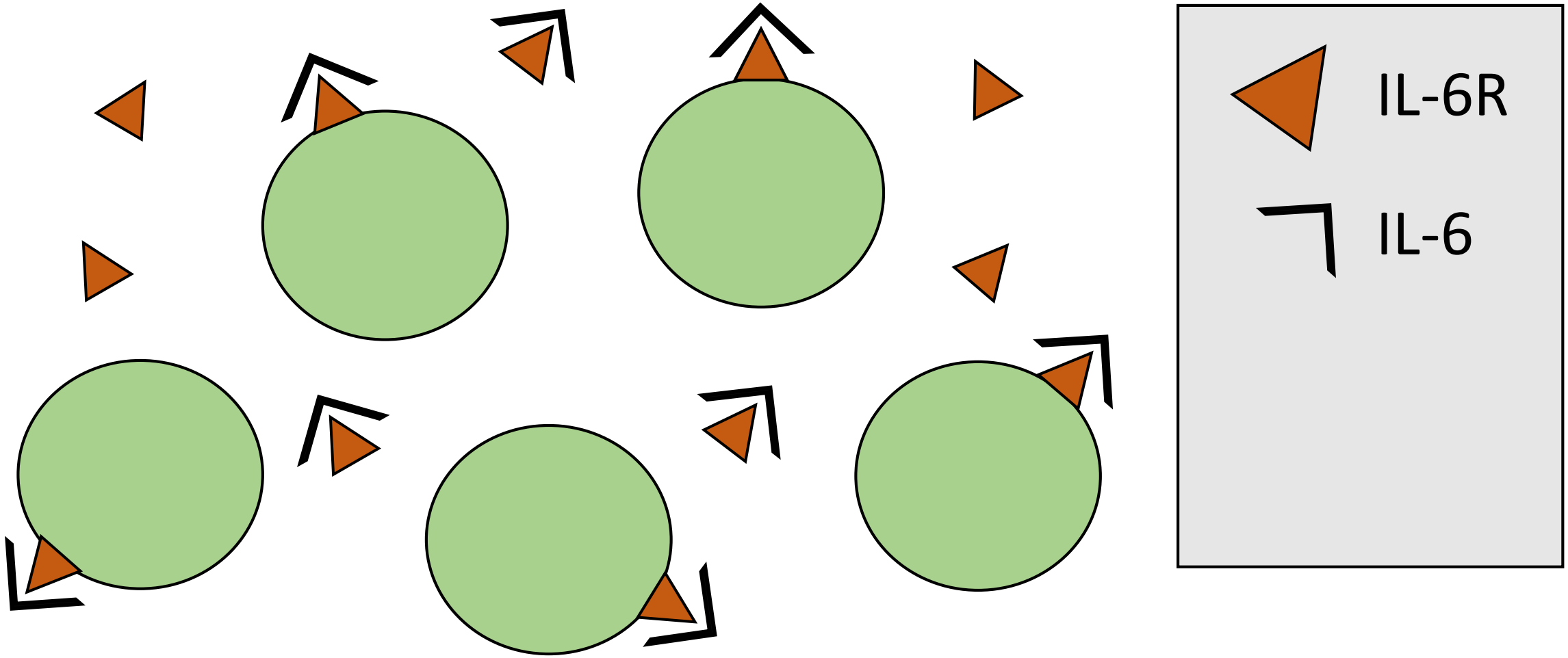
Cytokine Release Syndrome (CRS)

Pathophysiology of CRS



Blood. 2014;124(2):188-95.

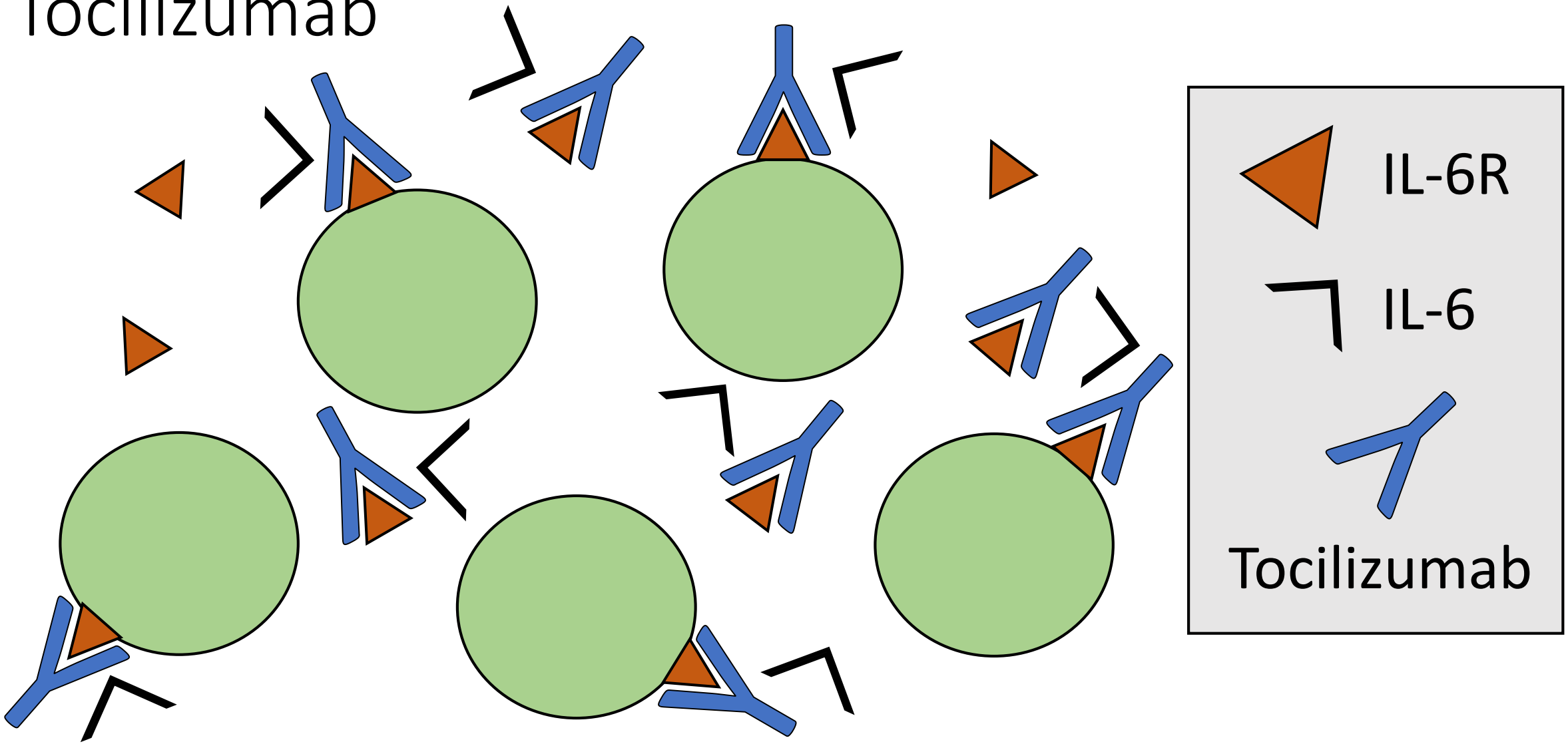
Tocilizumab



IL-6R = interleukin-6 receptor; IL-6 = interleukin-6

Blood. 2014;124(2):188-95.

Tocilizumab



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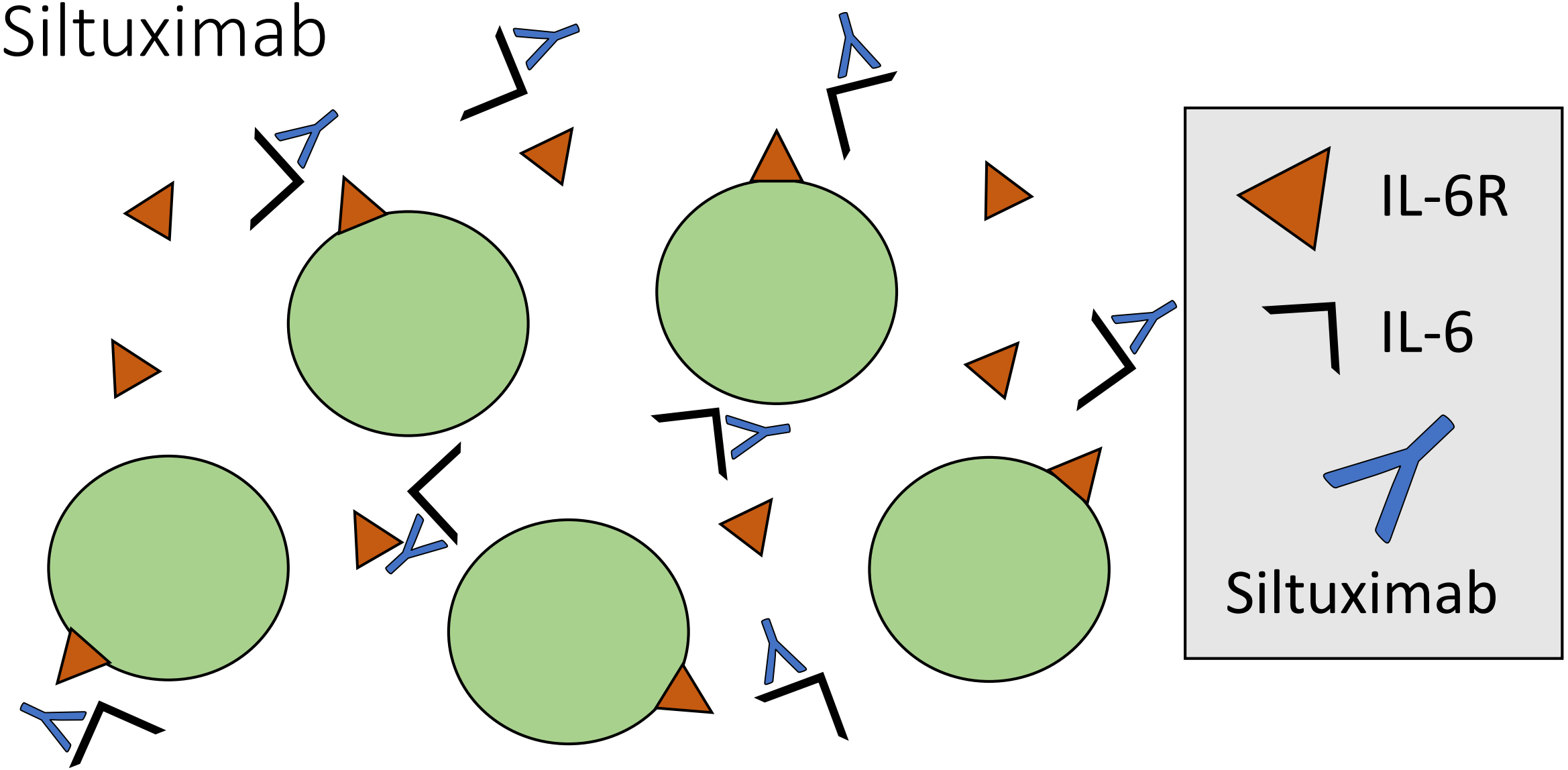
Siltuximab



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Conclusion

- CAR-T cells are a novel therapeutic approach to cancer therapy
- Over 200 clinical trials actively recruiting participants
- Proper management of CAR-T cell toxicities is critical
  - CRS / Neurotoxicity
  - “On-target, off-tumor” toxicities

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References

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