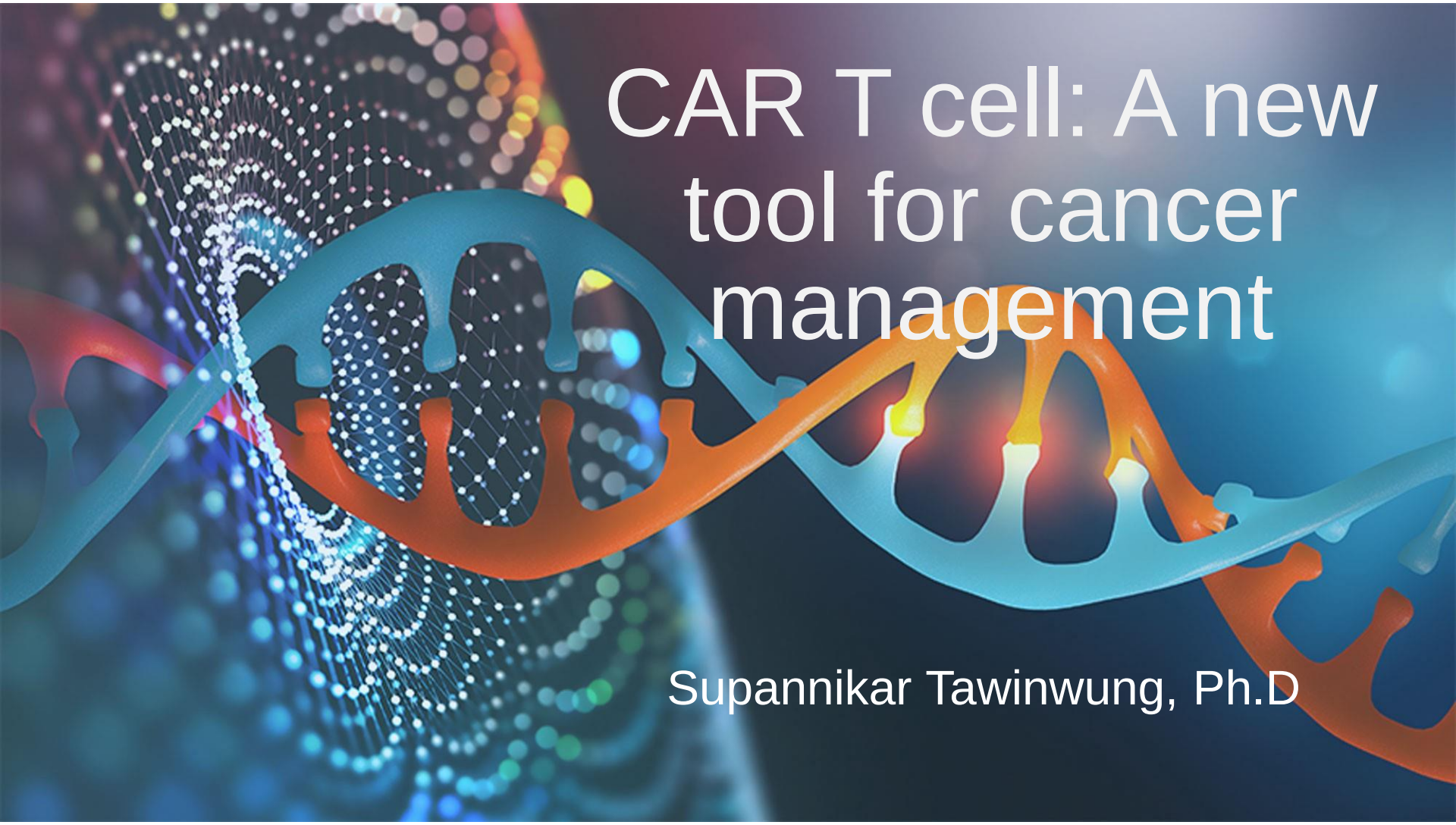
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
Faculty of Pharmaceutical Sciences, Chulalongkorn University

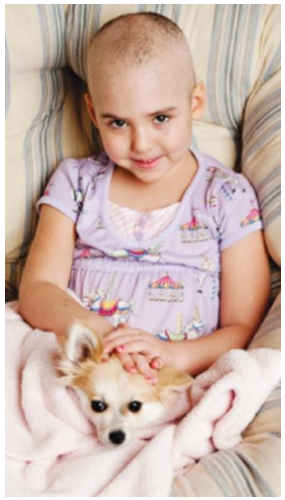
PPRx Department of Pharmacology & Physiology
Faculty of Pharmaceutical Sciences

CUCT CU Cancer Cellular Therapy
หน่วยวิจัยเซลล์บำบัดสำหรับโรคมะเร็ง



CAR T cell: A new tool for cancer management

Supannikar Tawinwung, Ph.D

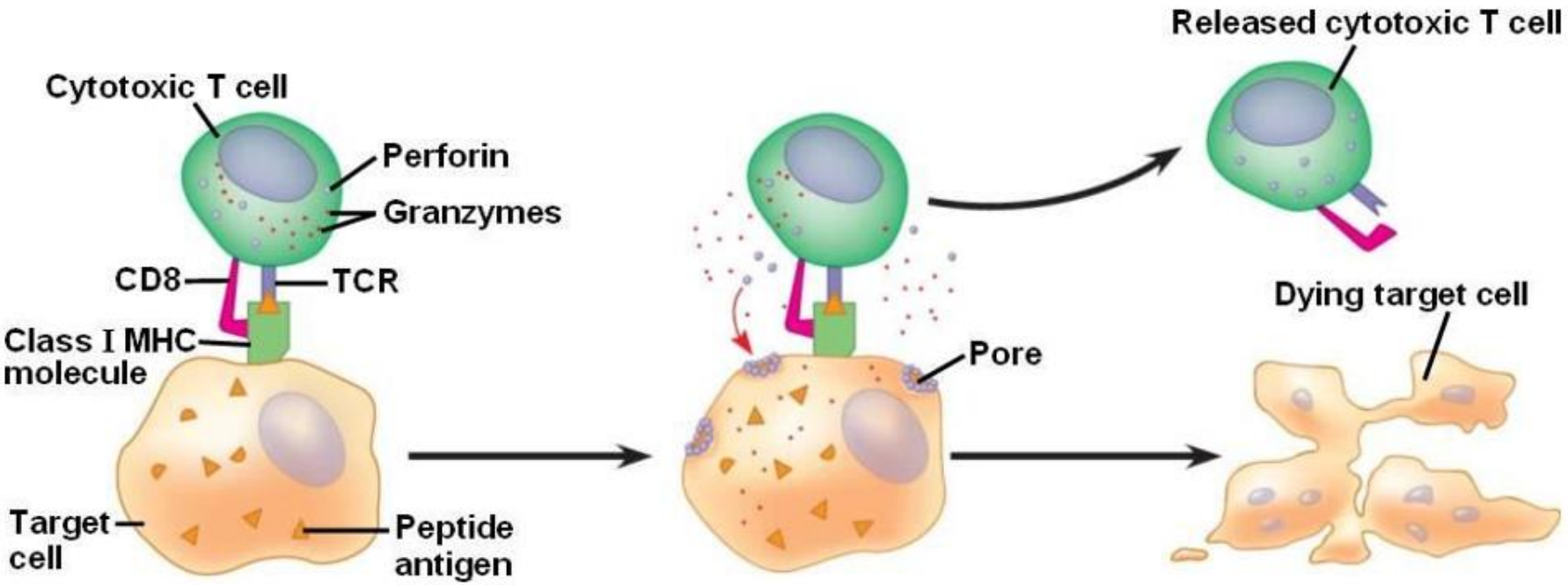


Emily Whitehead's success story in Leukemia

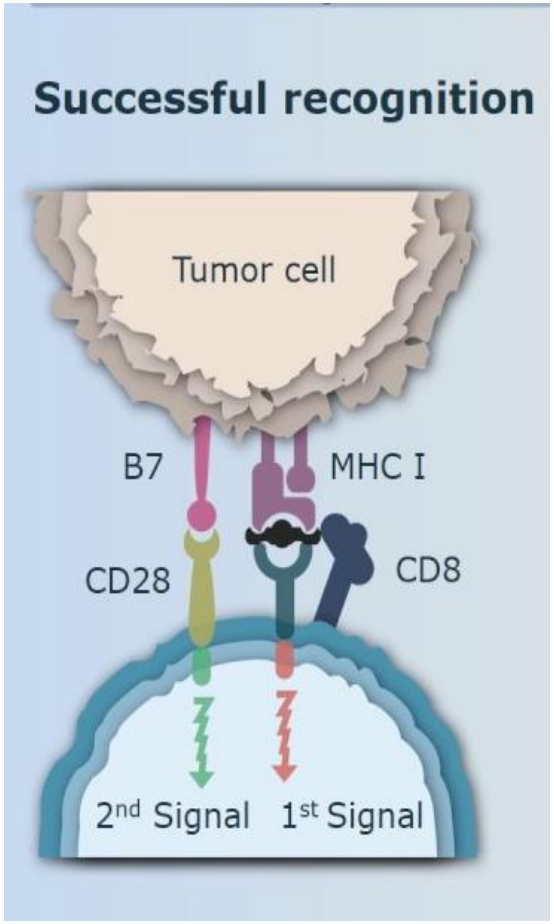
April 2012

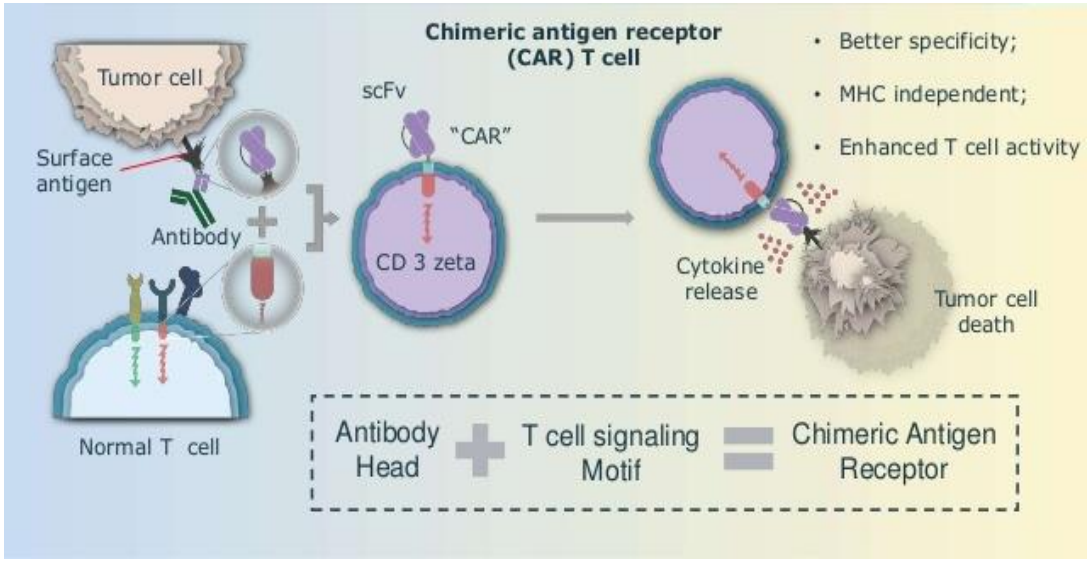
- First patient to be enrolled in a clinical trial for immunotherapy treatment, CAR T cell therapy
- Emily receives the CD19 CAR T cell treatment after her acute lymphoblastic leukemia relapsed
- Since her treatment, she has been cancer free.

Anti-tumor activity of T cells

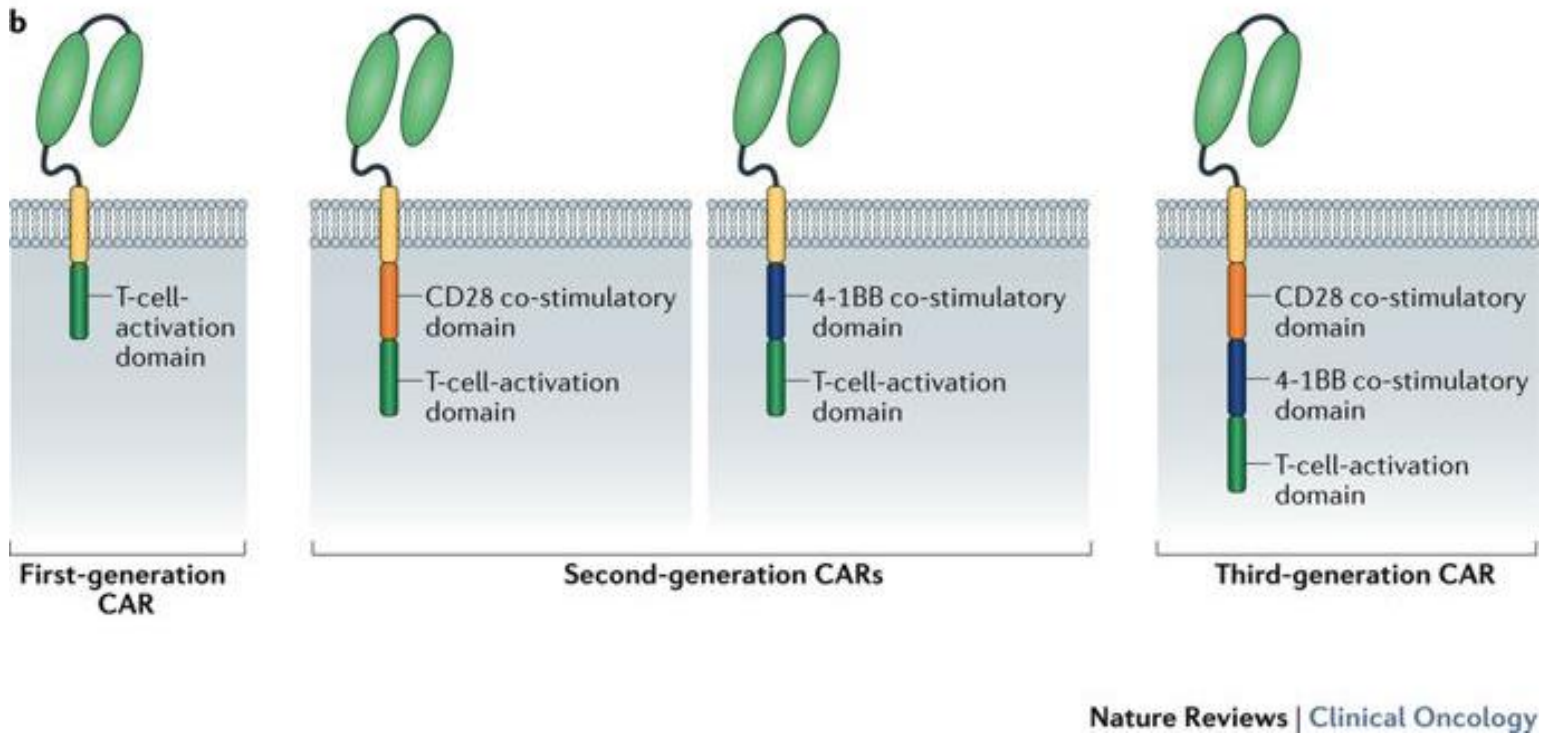


CAR: Chimeric Antigen Receptor



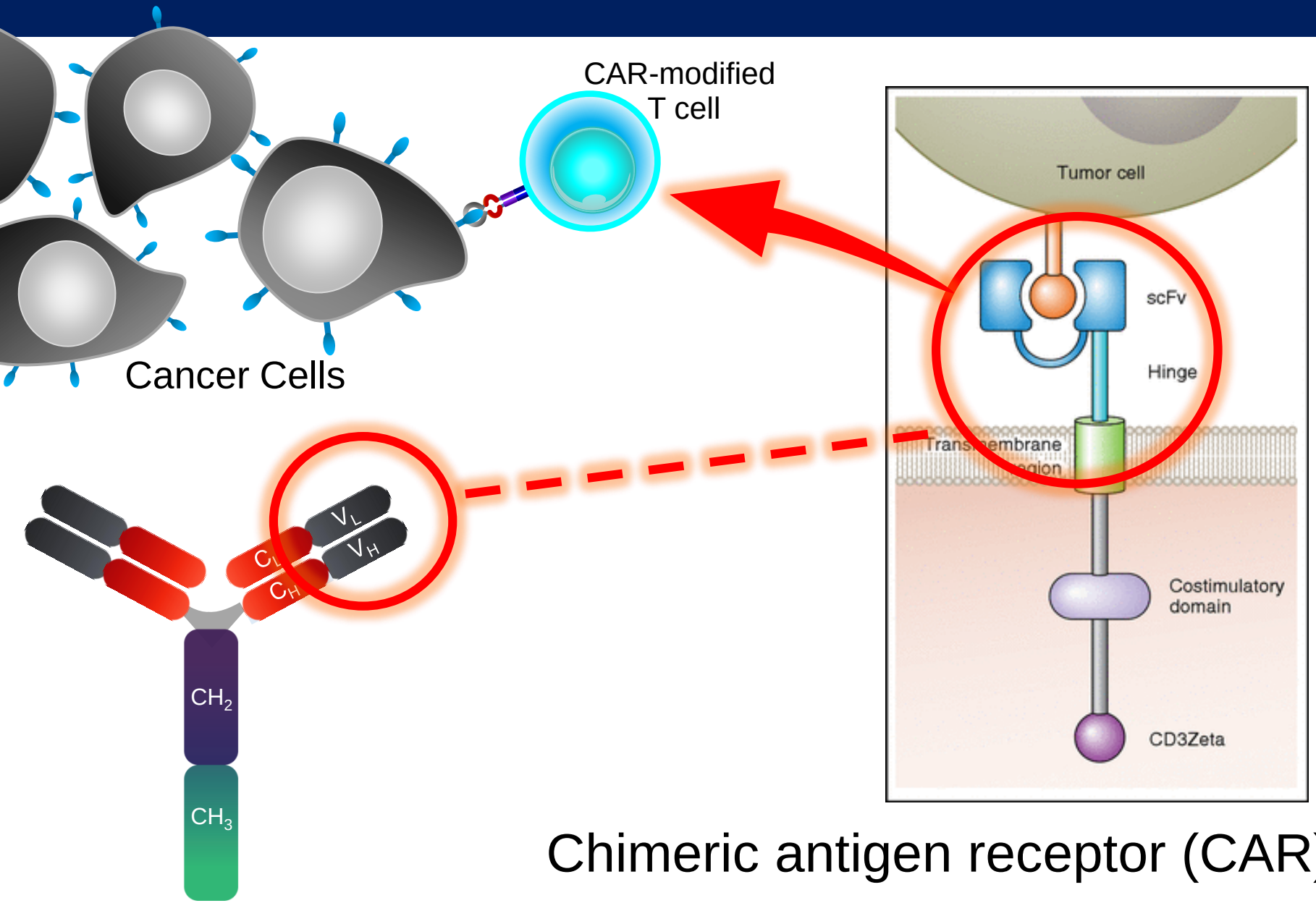


Structure of CAR generations



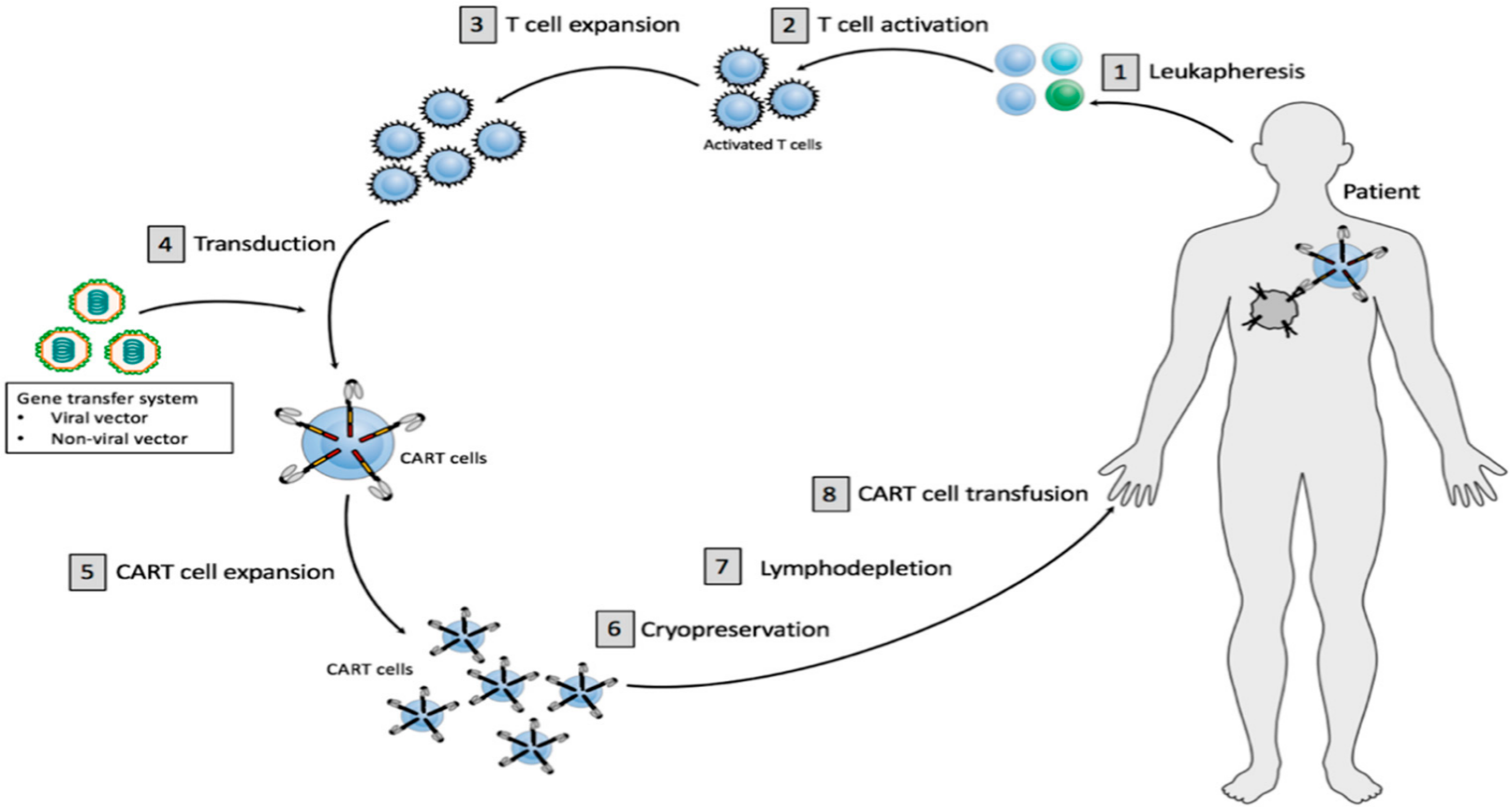
Adapted from Nature Reviews Clinical Oncology volume 15, pages 31–46 (2018)

Target tumor with CAR T cells



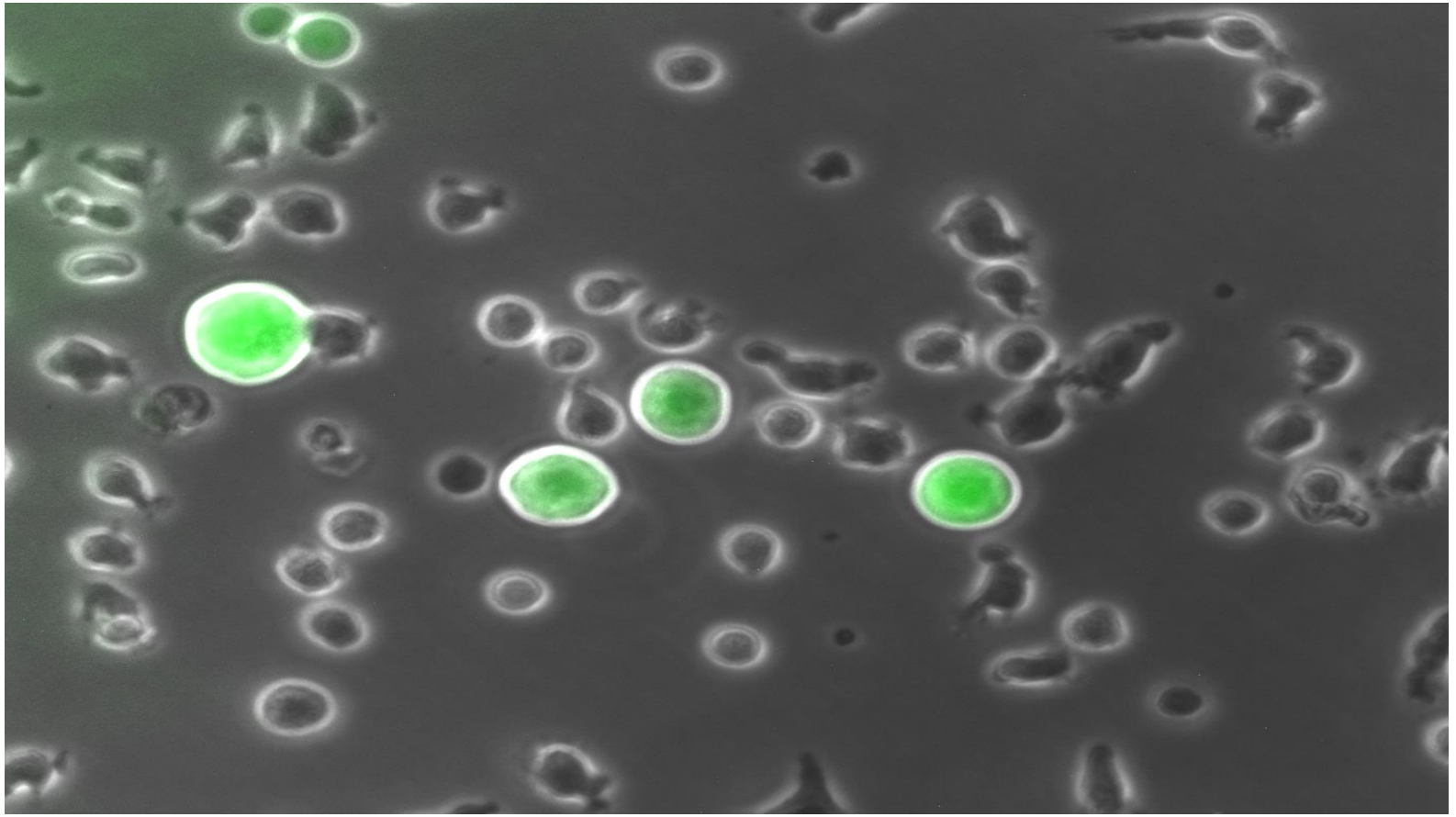
Chimeric antigen receptor (CAR)

CAR T cell manufacturing process

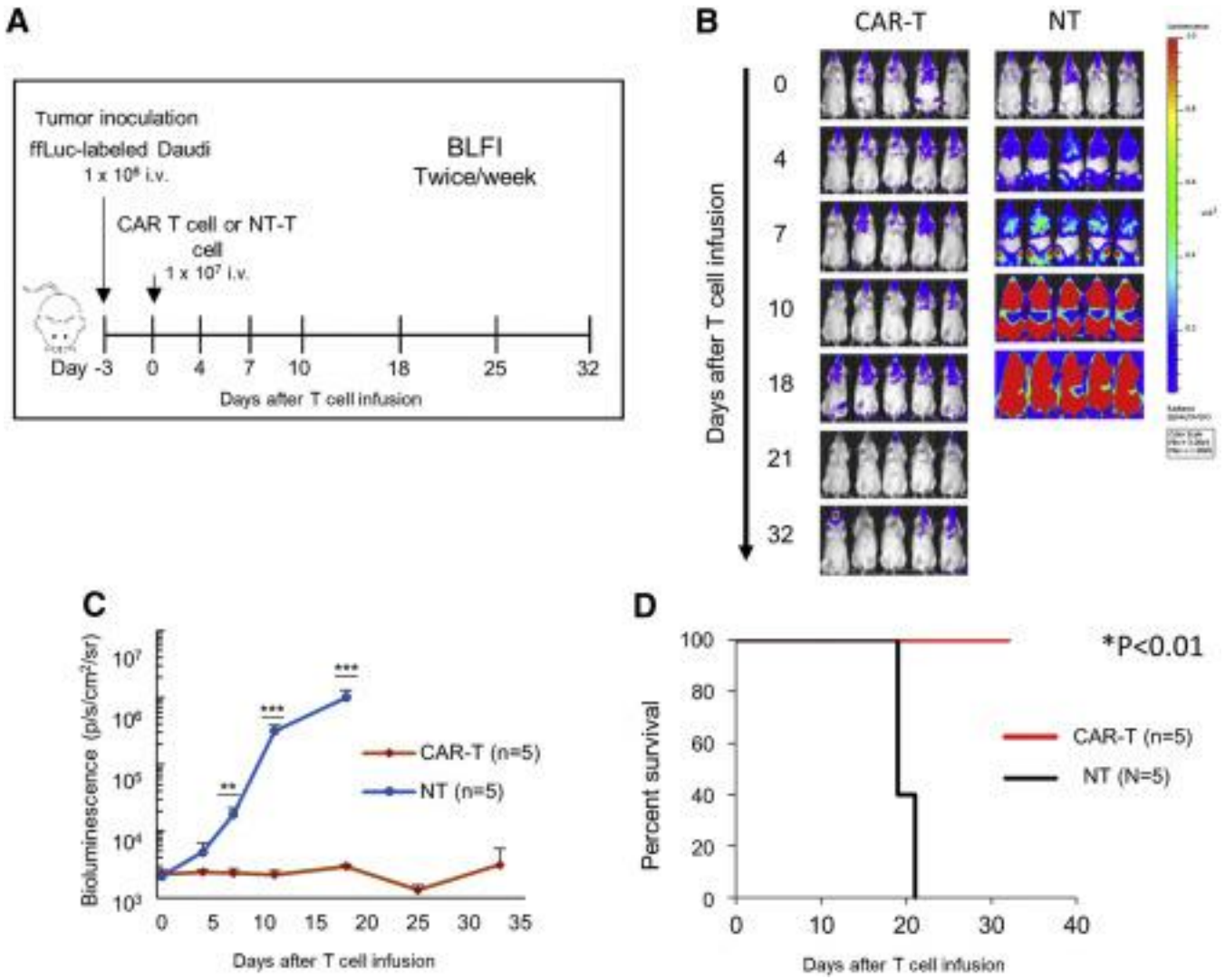


Int. J. Mol. Sci. **2019**, *20*(24), 6223

Tumor killing by CAR T cells



CAR T cells eliminate cancer cells in animal model



Data from Morita, Daisuke, et al. *Molecular Therapy-Methods & Clinical Development* 8 (2018): 131-140.

Current FDA/EMA approved CD-19 CAR T cell

- Tiagenlecleucel (Kymriah)
  - < 25 y/o c R/R B-cell ALL

    (ELIANA trial)
  - Adult c R/R large B cell lymphoma

    (JULIET trial)
- Axicabtegene ciloleucel (Yescarta)
  - Adult c R/R large B cell lymphoma

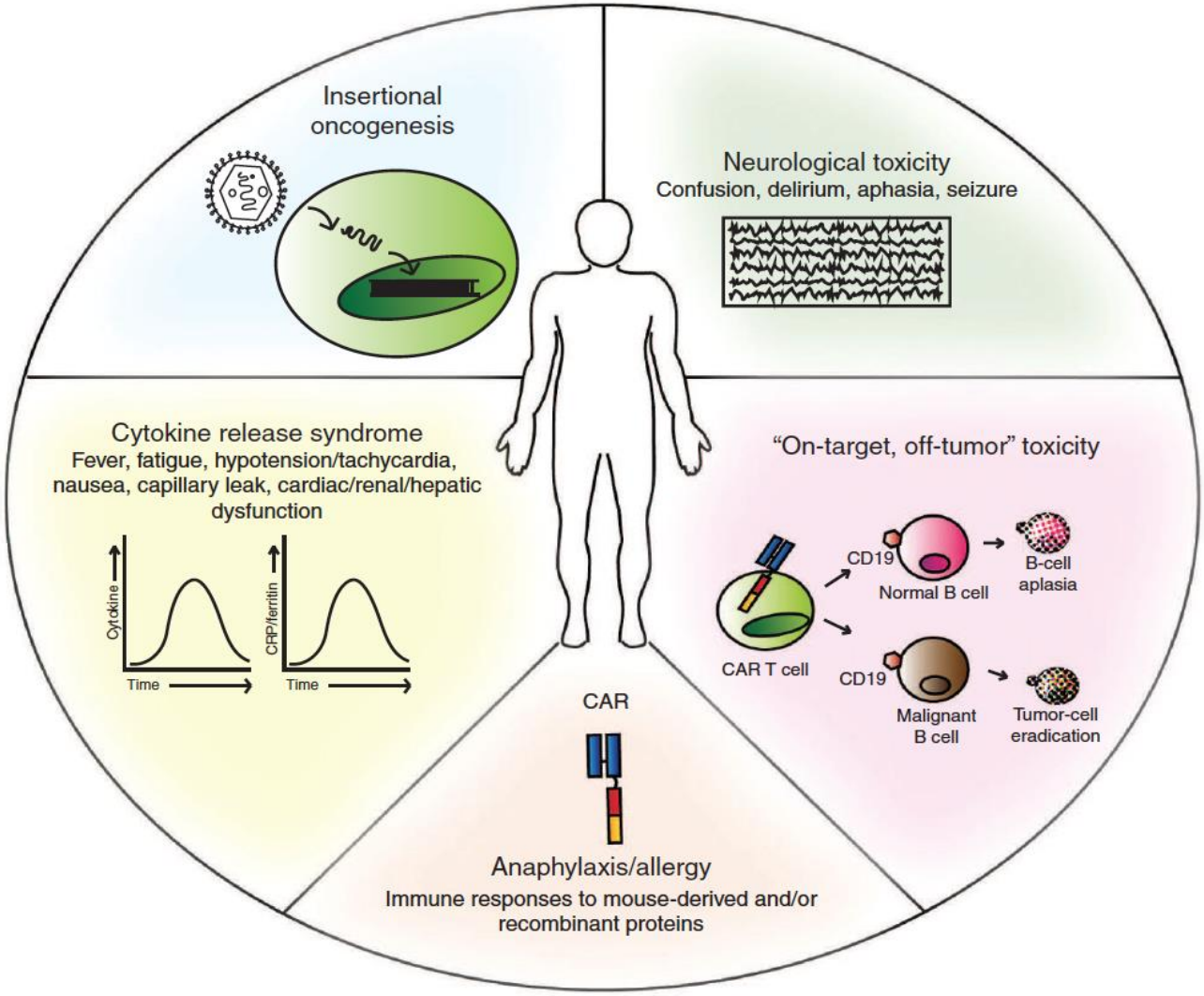
    (ZUMA-1 trial)

CD19 CAR-T cells in leukemia/lymphoma

- In less than 10 years more than 500 patients with ALL or CLL/NHL have received CD19.CAR-T cells.
- About 80% with complete responses in relapsed/refractory ALL patients.
- Below 50%, response rates in patients with NHL/CLL.
- Clinical responses are observed across multiple clinical studies and using different CD19.CAR-T cell manufacturing approaches.

	Kymriah Tisagenlecleucel **Novartis**	**Yescarta** Axicabtagene ciloleucel **Kite/Gilead**
Indication	R2R B-ALL (2017) R/R DLBCL after 1-2 lines (May 2018)	R/R DLBCL after 1-2 lines (Oct 2017)
Dosage	B-ALL - 0.2 to 5.0 x 10^6 CAR+ T cells/kg; 50 kg or less or maximum 2.5 x 10^8 CAR+ T cells/infusion DLBCL - 0.6 to 6.0 x 10^8 CAR-positive viable T cells	Cell suspension 2 × 10^6 CAR+ cells/kg in about 68 mL for infusion
Lymphodepletion	Fludarabine 30 mg/m^2 for 4 days and cyclophosphamide 500 mg/m^2 for 2 days	cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 for 3 days.
Price	$475,000/dose	$373,000/dose

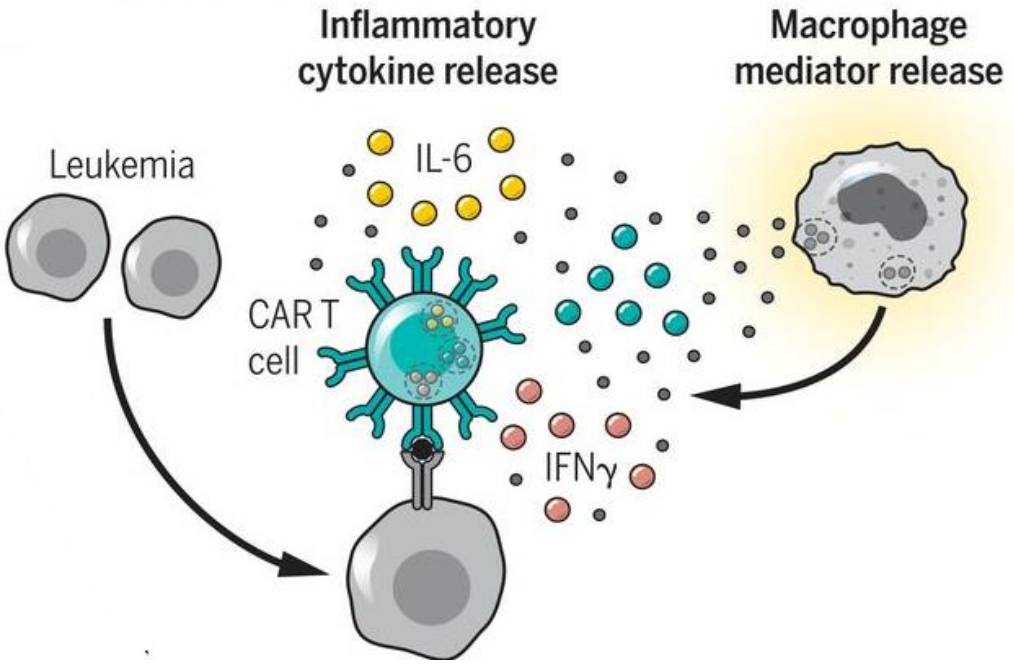
CAR T cell toxicity and management



From *Molecular Therapy-Oncolytics* 3 (2016): 16011.

Cytokine Release Syndrome (CRS)

- Most common serious SE
  - Kymriah: 77% in ALL, 57% in NHL
  - Yescarta: 93% in NHL
- Pathogenesis
  - CAR T cell-target interaction → IFN-gamma, TNF-alpha
  - Activation of monocyte and macrophage → proinflammatory cytokine (IL-1, IL-6, IL-10), Nitric oxide



Adapted from Science 23 Mar 2018: Vol. 359, Issue 6382, pp. 1361-1365

Clinical presentation of CRS

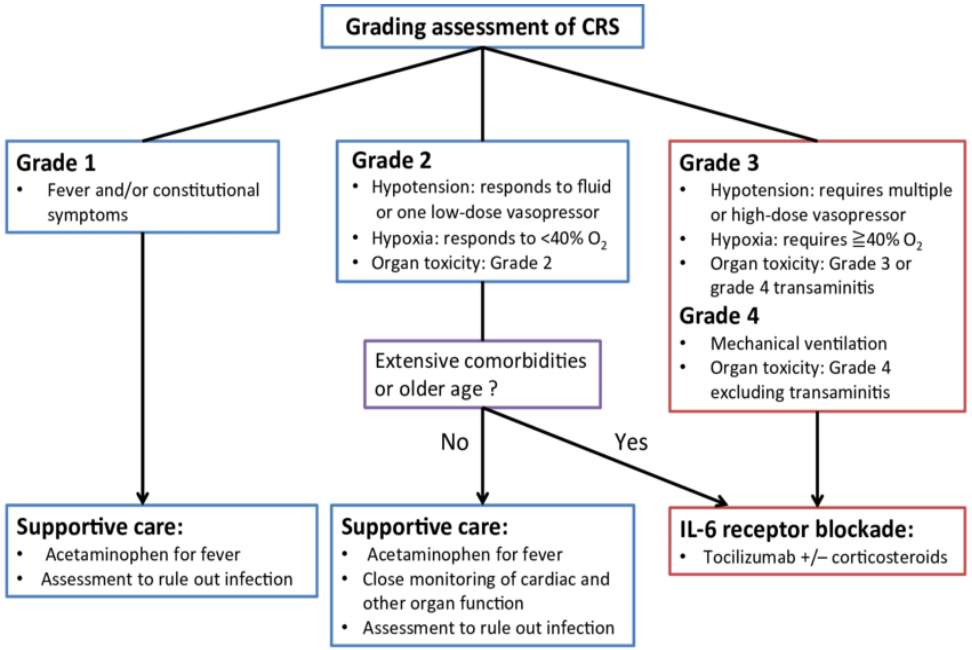
- Median onset 2-3 days and can occur up to 3 weeks
- Median time to resolution 7-8 days
- Prodromal syndrome
  - Fever usually the first presentation
  - Flu like symptoms
  - GI symptoms
- Life-threatening manifestation
  - Hemodynamic instability
  - Organ dysfunction → hypoxia, hypotension

ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[*]*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or[†]†		
Hypoxia	None	Requiring low-flow nasal cannula[‡]‡ or blow-by	Requiring high-flow nasal cannula[‡]‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

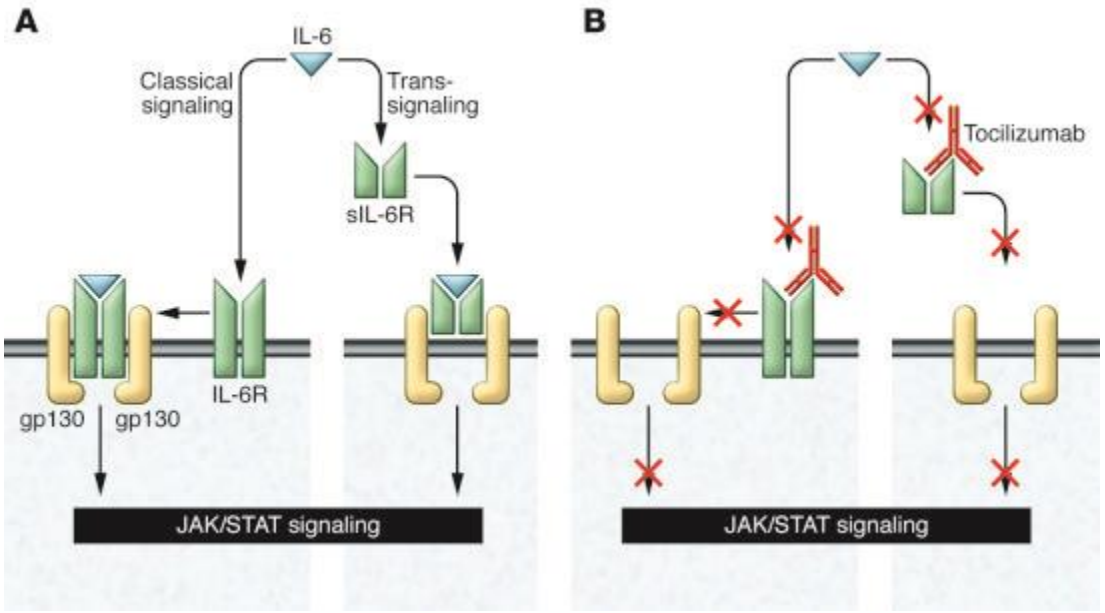
Management of CRS

- ASTCT grading system based management
- Mild CRS (Grade 1-2):
  - close monitoring and supportive care
- Severe CRS (Grade 3-4)
  - 5-30%
  - Tocilizumab: IL-6R antagonist
    - Median start time 3-4 days
    - No clinical improvement: given Q8 H x 4 doses
  - Corticosteriods
    - No clinical improvement in 12-24 H
    - Worsening symptoms
    - Started then taper over 3 days
  - Anti-TNF-alpha/IL-1R inhibitor



Tocilizumab (Actemra®)

a humanized IL-6 receptors monoclonal antibody

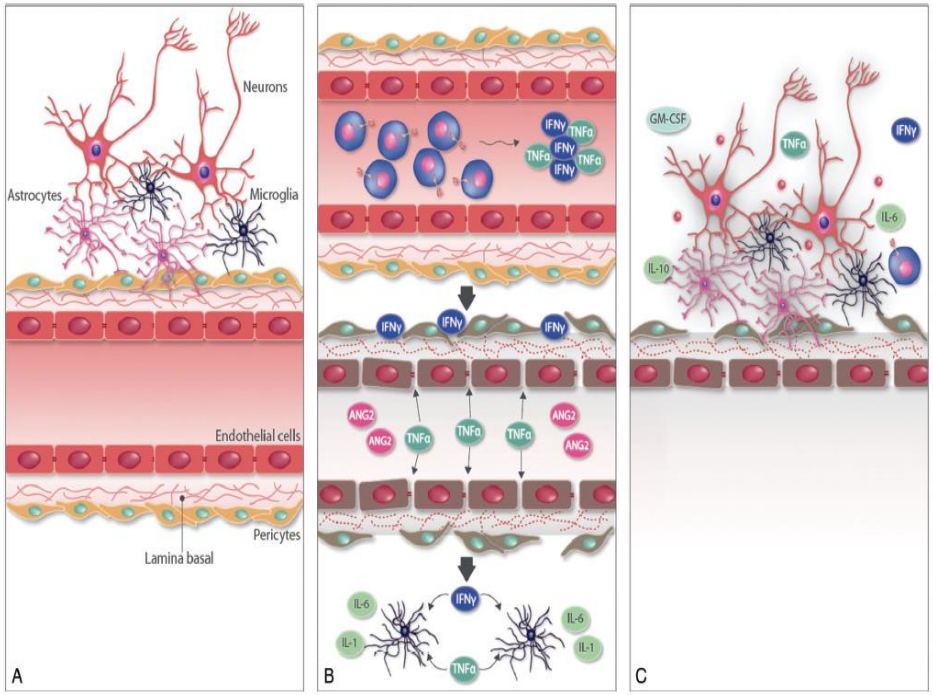


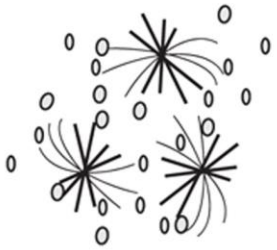
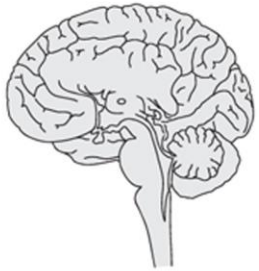
Approved for moderately to severely active RA who have failed to respond to one or more DMARDs.

2017 FDA approved for the treatment of severe or life-threatening chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome (CRS) in adults and in pediatric patients 2 years of age and older intravenous tocilizumab 8 mg/kg (12 mg/kg for patients <30 kg) for severe or life-threatening CRS

Central nervous system toxicity

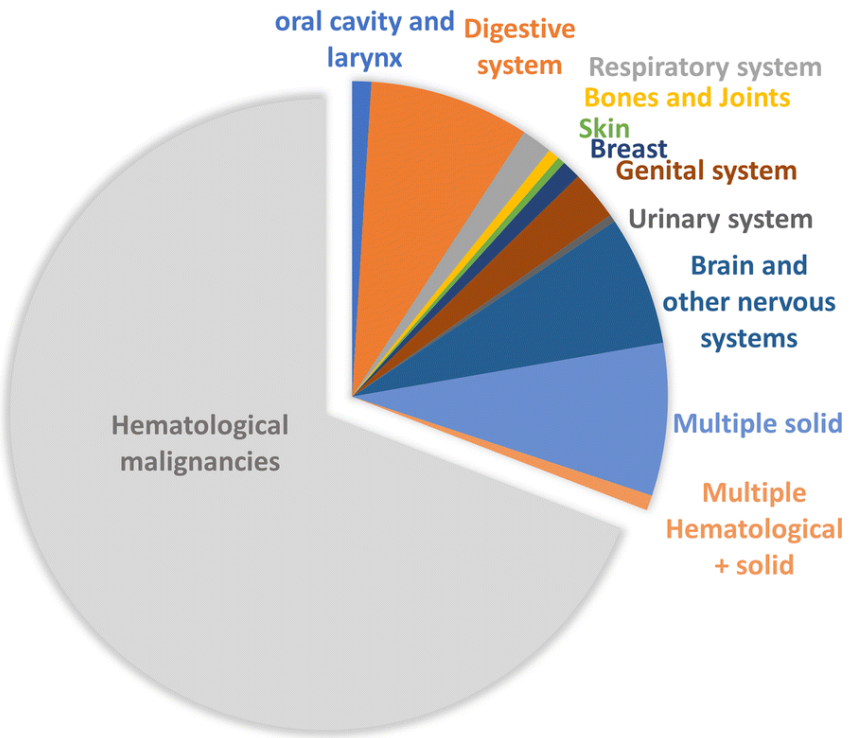
- CAR T cell related encephalopathy syndrome (CRES) → Immune effectors cell associated neurotoxicity syndrome (ICANS)
- Incidence 0-87%
- 90% appears concurrent with CRS or following CRS resolution
- Pathogenesis
  - Impair blood brain barrier from proinflammatory cytokine
  - IFN-gamma and TNF-alpha activated microglia to induced inflammatory state and brain damage



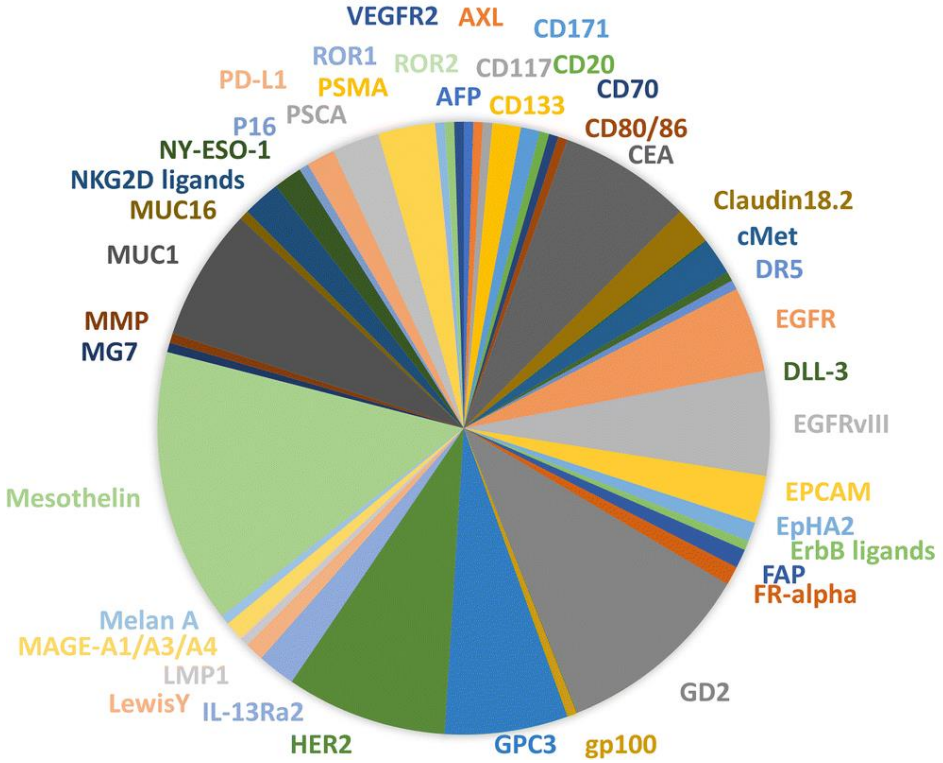
Adverse effect	Commercial CAR T	
	Tisagenlecleucel[5]	**Axicabtagene ciloleucel[8]**
Cytokine release syndrome (CRS) 	• Administer tocilizumab in patients with CRS that requires moderate to aggressive intervention. • If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high flow oxygen are no longer needed, then taper.	• Administer tocilizumab if CRS grade ≥ 2. • Administer methylprednisolone if CRS grade ≥ 3 or CRS grade 2 if no improvement within 24 hours after starting tocilizumab.
Central Nervous Toxicity (CNS) 	• No specified management in the prescribing information.	• If neurotoxicity is associated with CRS administer tocilizumab as previously described. • If neurotoxicity is grade ≥ 3 administer dexamethasone (CNS grade 3) or high dose of methylprednisolone (CNS grade 4) with the first dose of tocilizumab. • If neurotoxicity is not associated with CRS, administer dexamethasone (CNS grade 2 or 3) or high dose of methylprednisolone (CNS grade 4)

Current situation of CAR T cell therapy

CAR T TRIALS - PER ORGAN CLASS

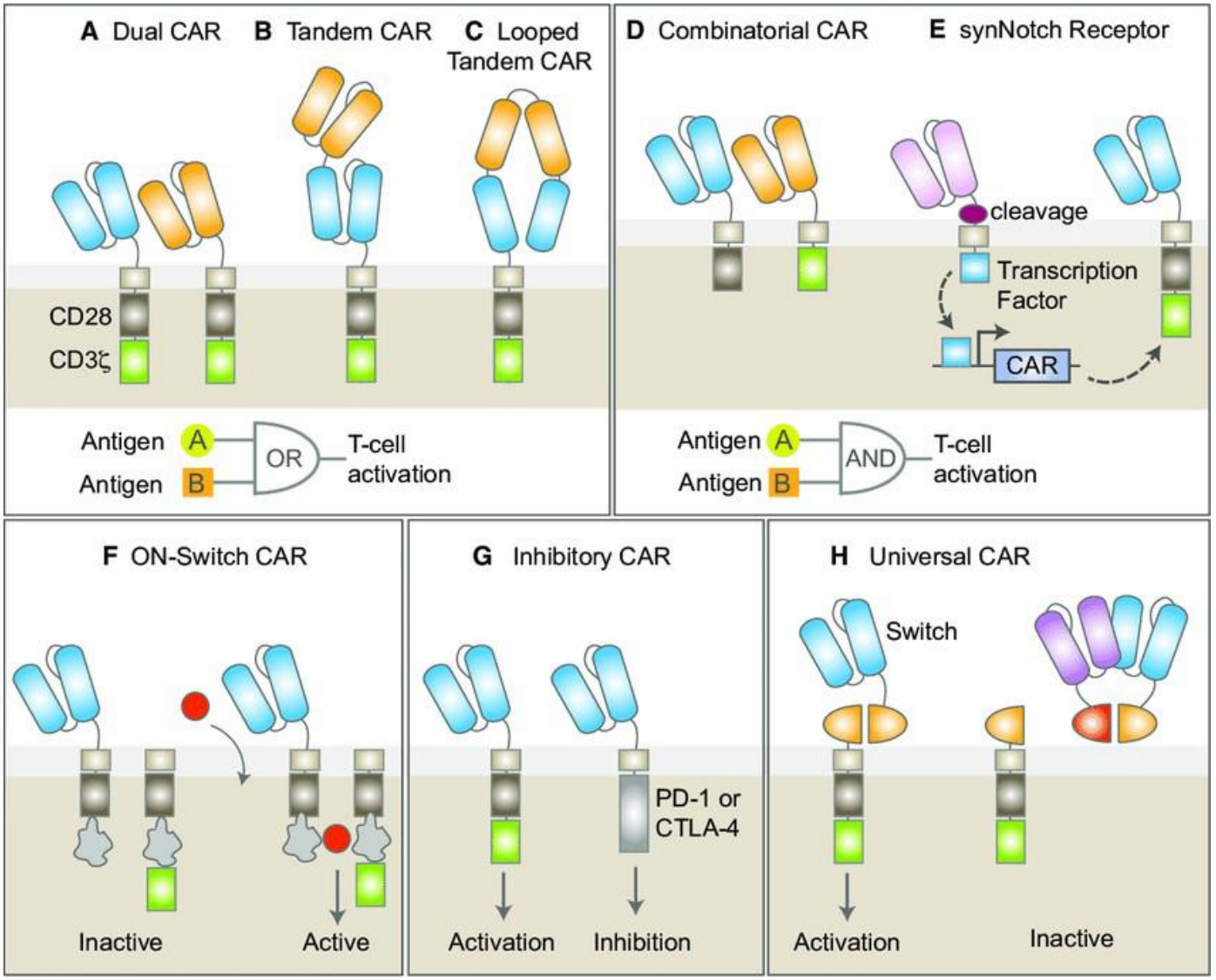


SOLID CAR T CLINICAL TRIALS - PER TARGET

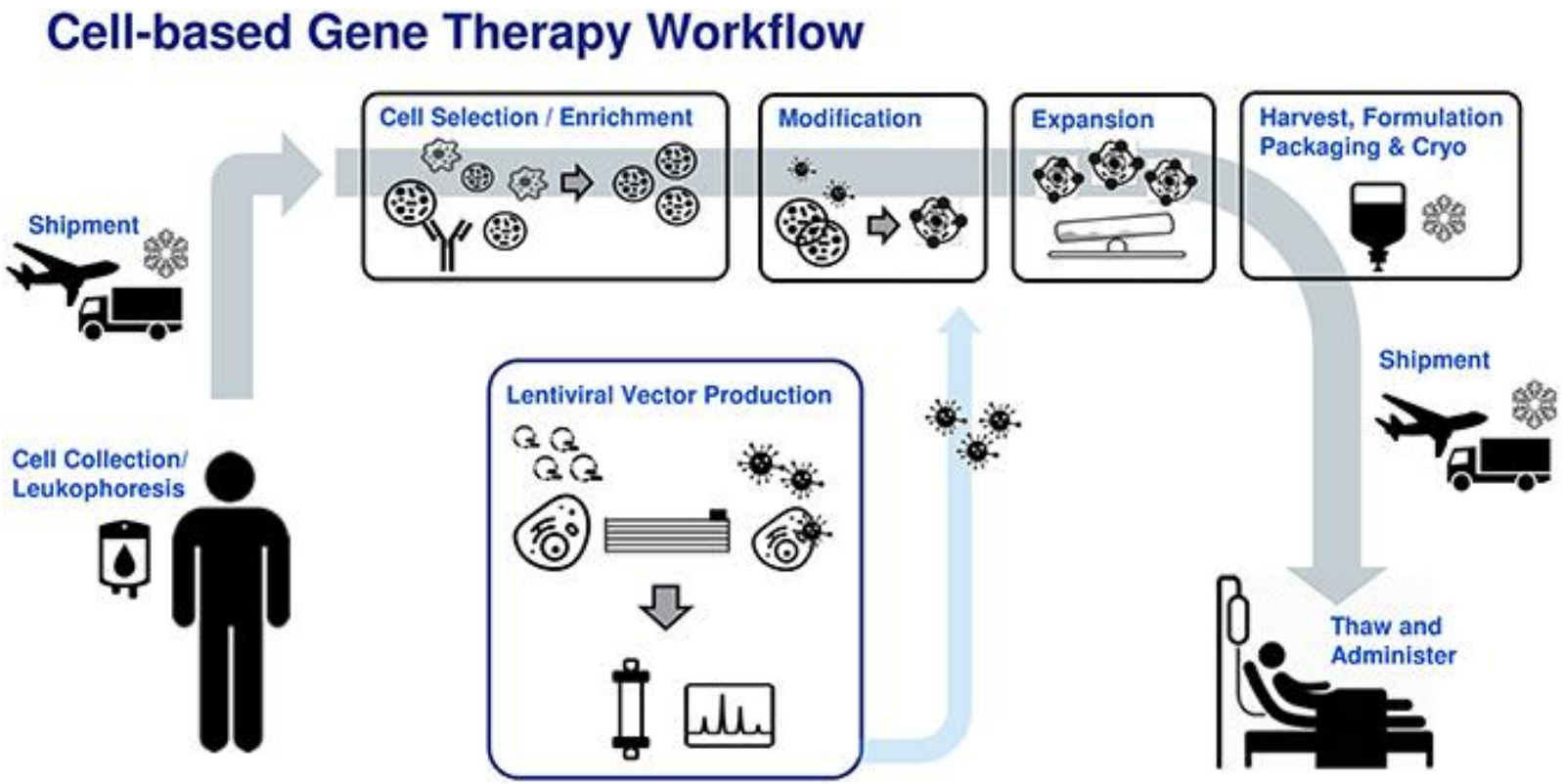


From BioDrugs **volume 33**, pages515–537(2019)

Next Generation CAR T cell therapy



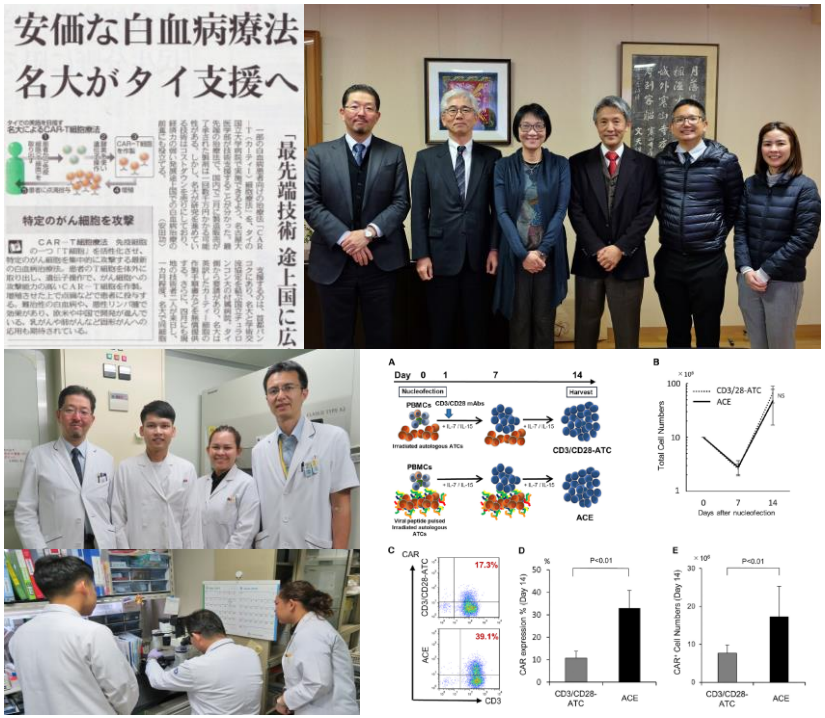
Commercial CAR T cells



Cost?
Accessibility?
Complicated manufacturing process?

Development of sustainable CAR T cell therapy for cancer patients in Thailand

Phase I clinical trial piggyBAC CD19 CAR T cell in Thai patients with relapse and refractory ALL/NHL



- Goal:
  - To Increase accessibility to CAR T cell therapy through clinical trial
  - Develop sustainable CAR T cell therapy in Thailand
- Collaboration with Nagoya University
- Clinical scale protocol validation in Thailand September to October 2562
- IRB/IBC approval on December 2562
- First patient enrolled September 2563

คณะเภสัชศาสตร์ | Faculty of Medicine Chulalongkorn University | กองทุน Cancer Immunotherapy Fund | โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย | CU Cancer Cellular Therapy หน่วยวิจัยเซลล์บำบัดสำหรับโรคมะเร็ง | NAGOYA UNIVERSITY

Thank you

Q&A