CAR T Cell Therapy:

CAR T Cells Explained

Family Practice Oncology Network CME Day

November 23, 2019

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Disclosures

- AL
  - Financial – none
  - Consultancy – Novartis

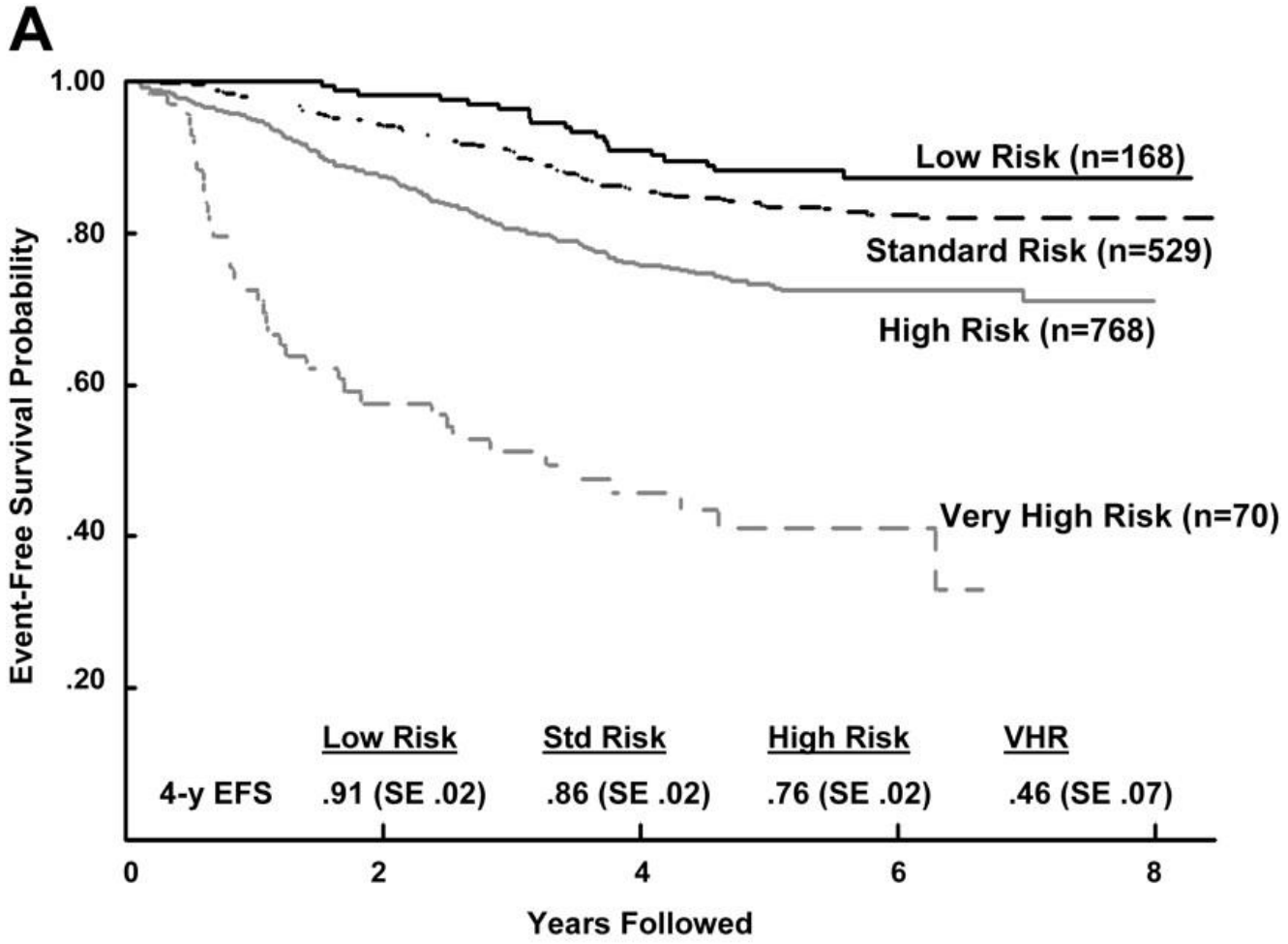
Aims

1. Described the current use of chimeric antigen receptor (CAR) T cells in pediatric cancer therapy

2. Identify unique toxicities associated with CAR T cell therapy

3. Appreciate the challenges in CAR T cell therapy delivery in British Columbia

Pediatric Acute Lymphoblastic Leukemia (ALL): Survival



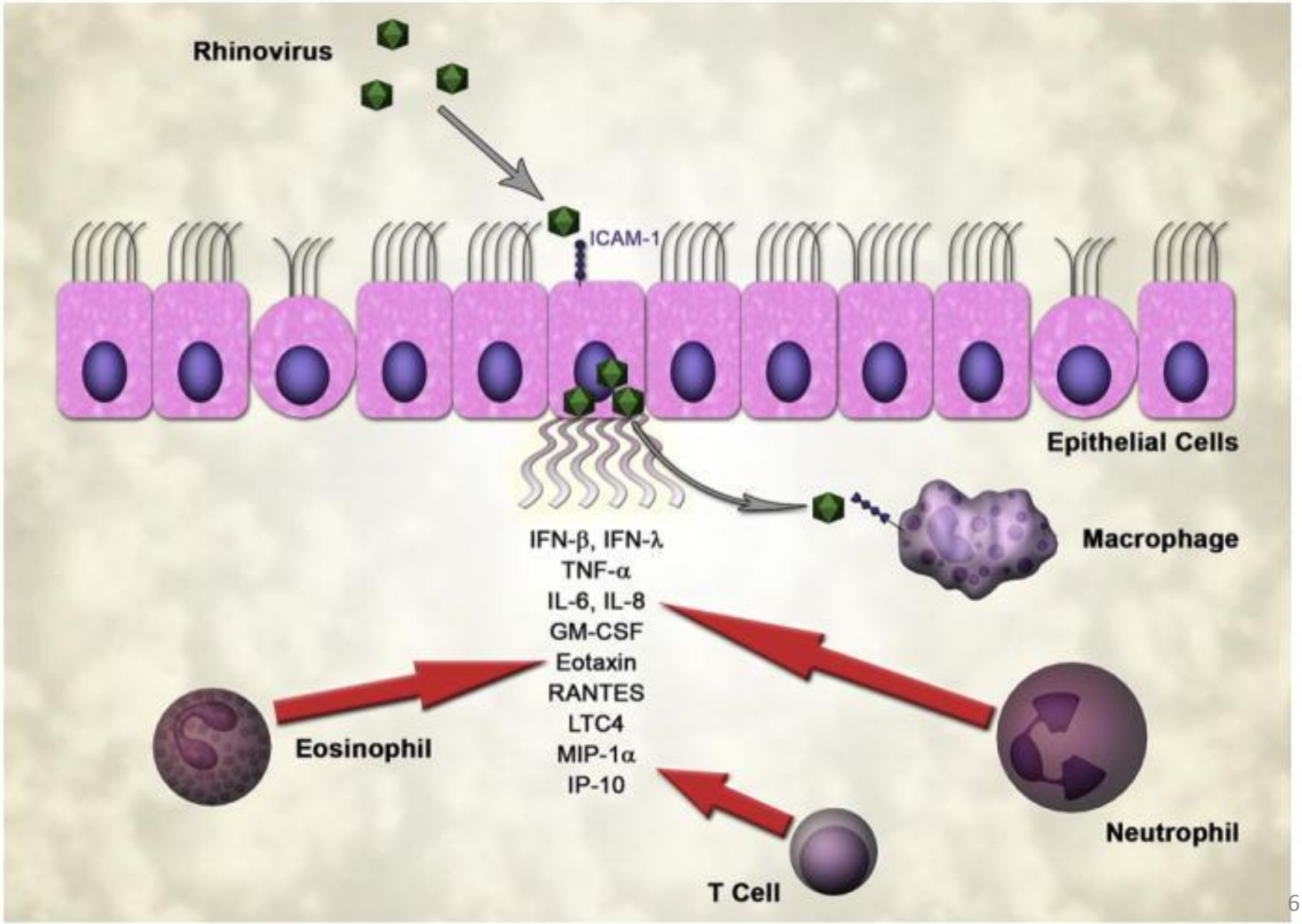
Schultz (2007) Blood

Approaches to eliminating cancer cells

- Chemotherapy
- Radiation
- Surgery

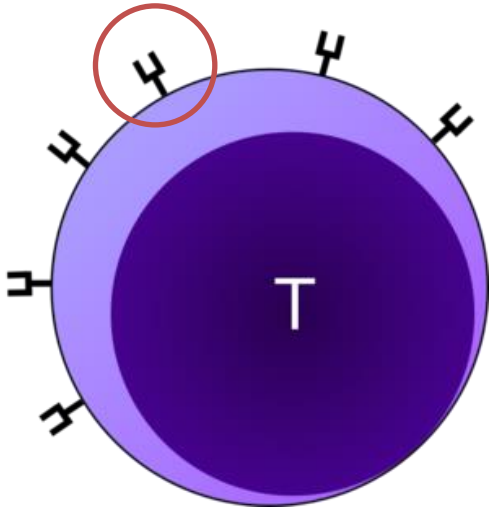
- **Immunotherapy –** generate immune response against malignancy
  - Bone Marrow Transplant
  - Bispecific antibodies (T-cell engagers)
  - Cancer vaccines
  - *Genetically modified T-cell (CAR T cell) therapy*

Why is the common cold not fatal?



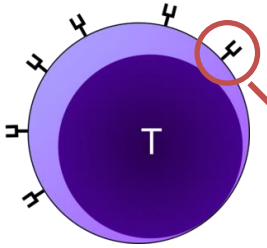
T Cell Receptor
"On Switch"

- Recognizes and binds to foreign target
  - MHC restricted
- Sends signal to activate cell
- Effector T cell killing
- Tightly regulated to prevent T cells from attacking one's own body



Hijacking the "on" switch

(Chimeric Antigen Receptor)



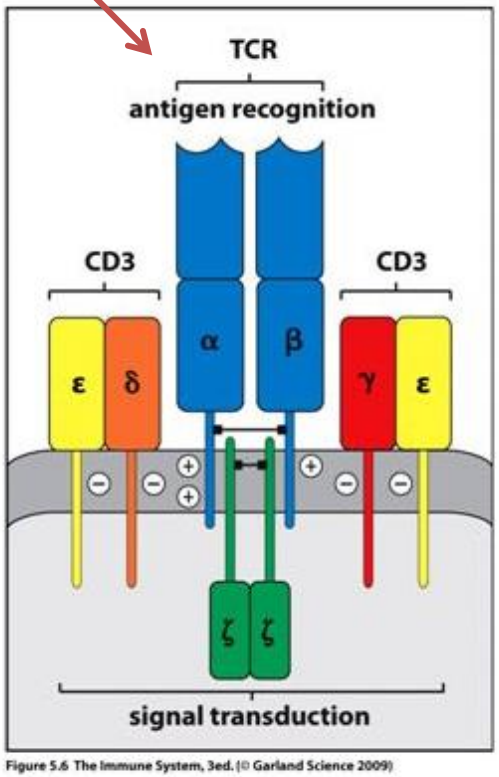
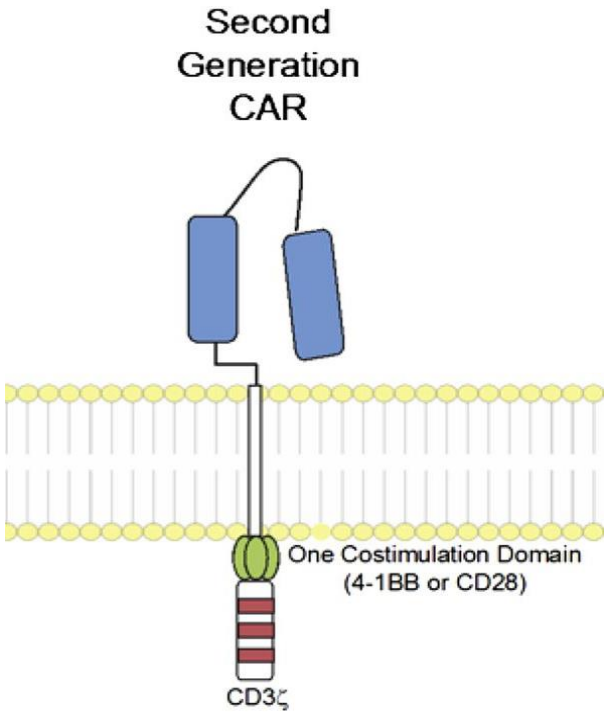


Figure 5.6 The Immune System, 3ed. (© Garland Science 2009)

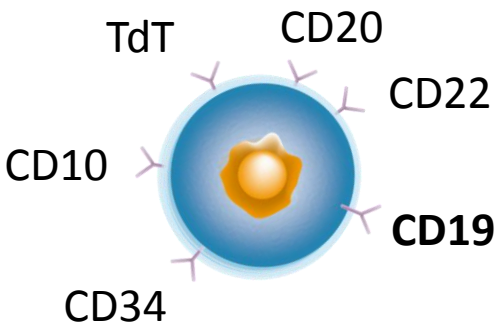


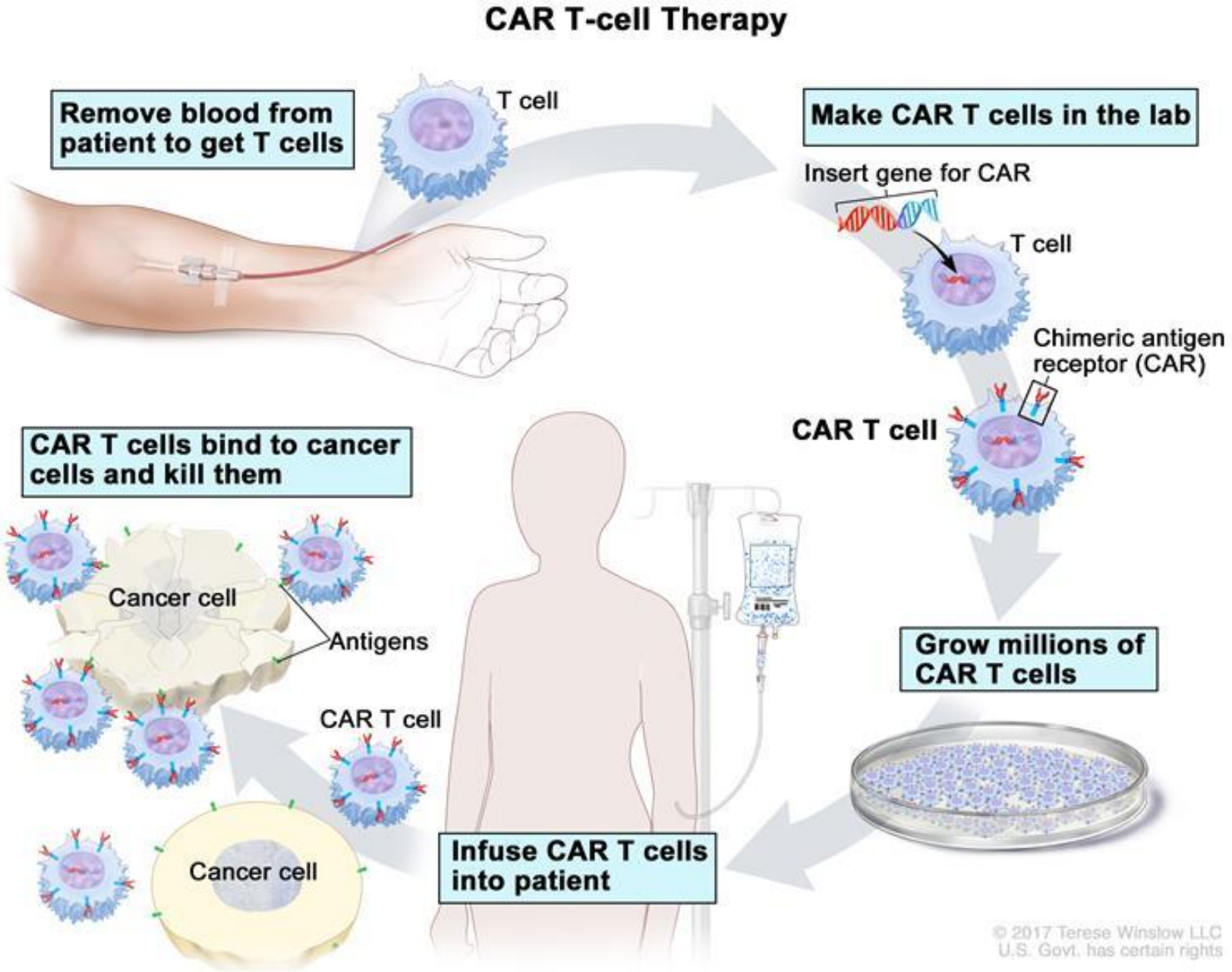
Getting the target right

Doesn’t harm healthy cells
Doesn’t kill cancer cells

Very harmful to cancer cells
Very harmful to healthy cells

B-cells




CAR T-cell Therapy
Remove blood from patient to get T cells
T cell
Make CAR T cells in the lab
Insert gene for CAR
T cell
Chimeric antigen receptor (CAR)
CAR T cell
CAR T cells bind to cancer cells and kill them
Cancer cell
Antigens
CAR T cell
Cancer cell
Infuse CAR T cells into patient
Grow millions of CAR T cells
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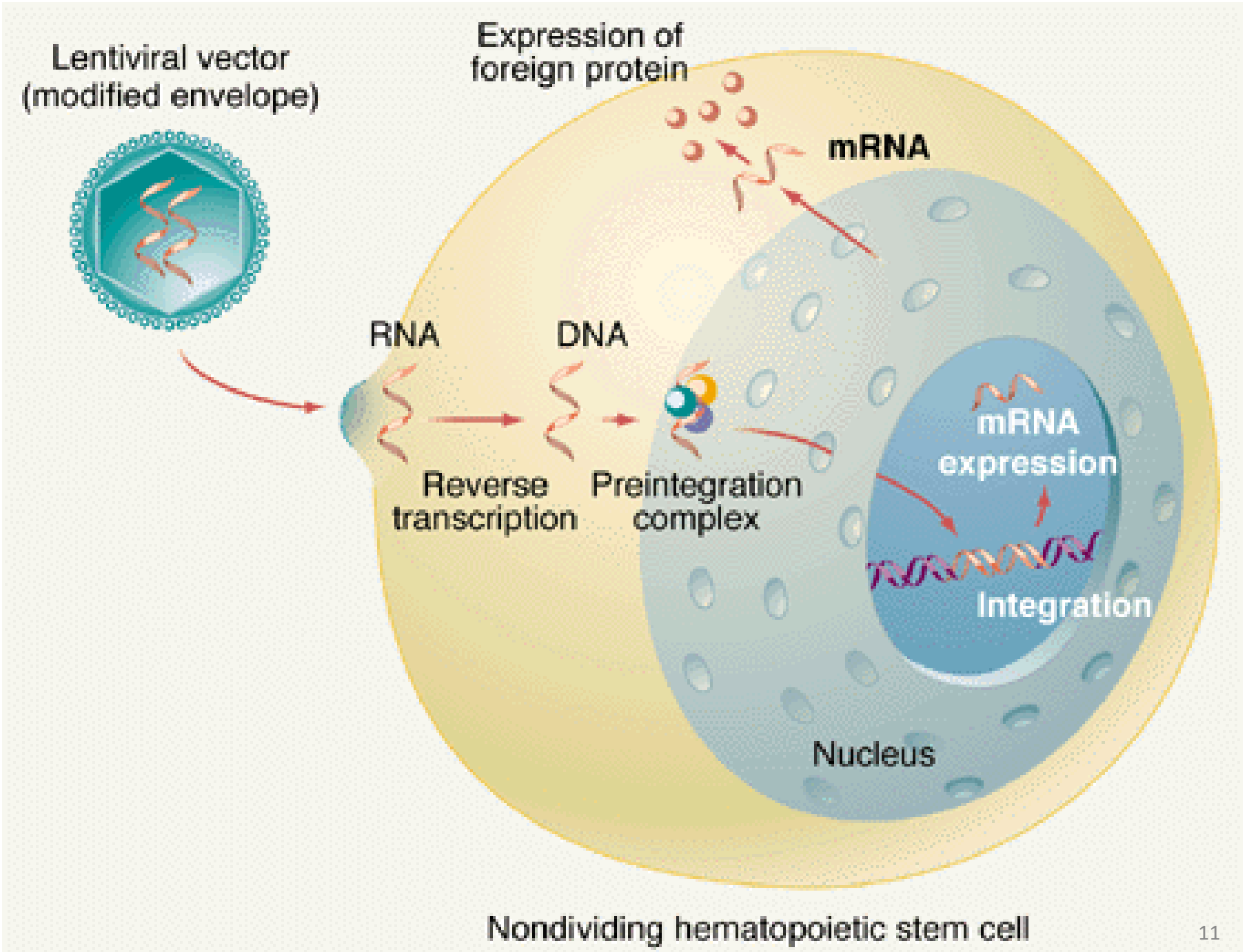


Amado (1999) Science

WSJ | OPINION

OPINION | THE WEEKEND INTERVIEW

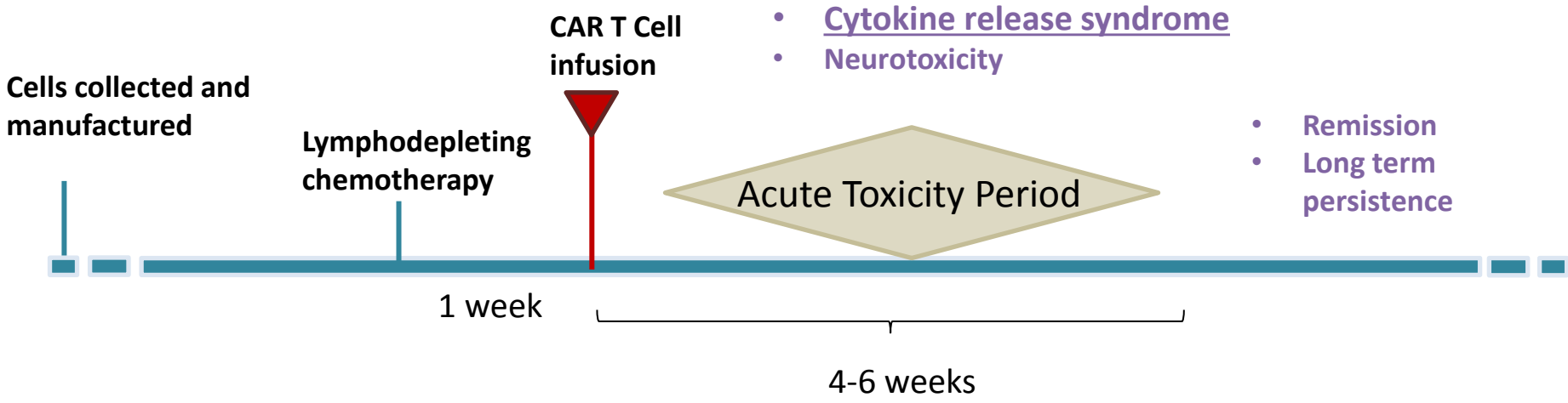
How HIV Became a Cancer Cure

The immunologist behind the revolutionary new treatment set to win approval from the FDA.

By Allysia Finley
Aug. 18, 2017 5:34 pm ET

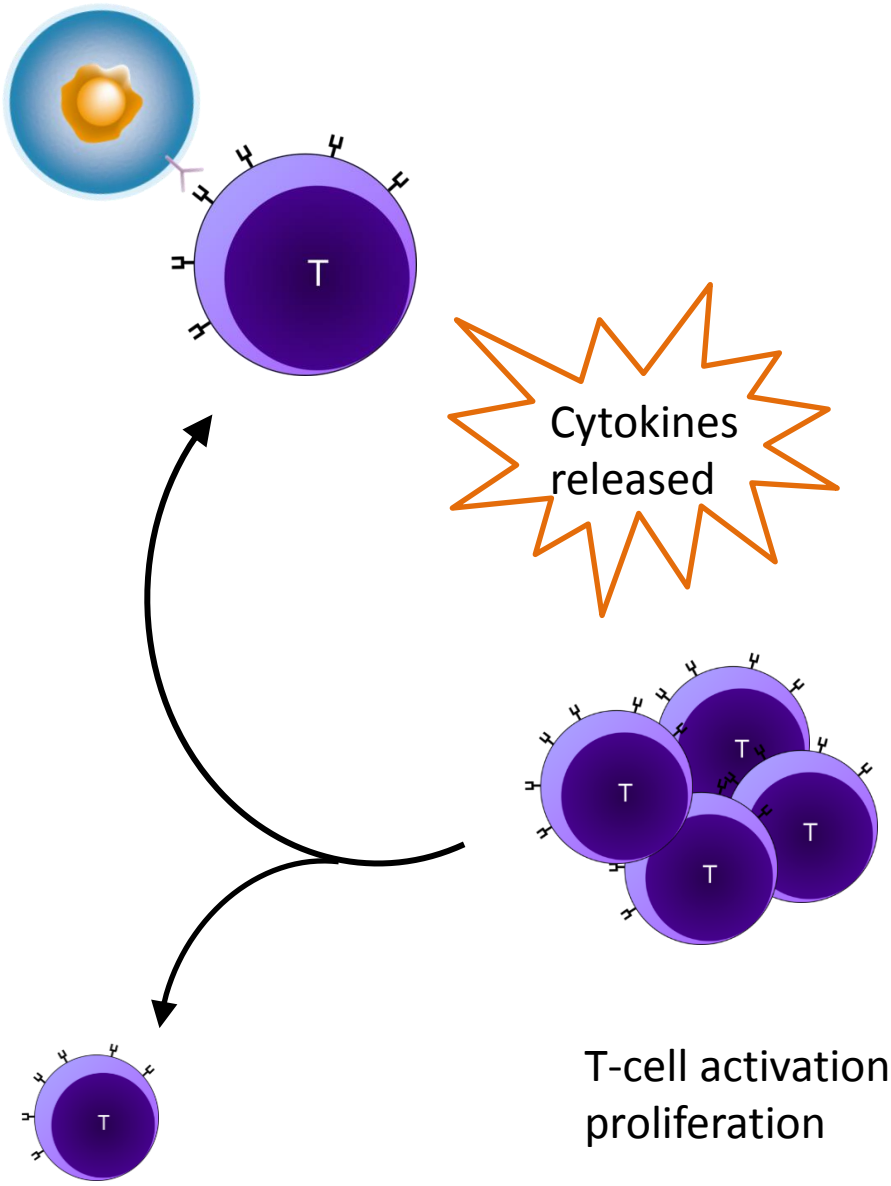
Philadelphia

When Ben Franklin proposed in 1749 what eventually became the University of Pennsylvania, he called for an academy to teach "those Things that are likely to be most useful." Today the university lays claim to having incubated the world's biggest cancer breakthrough. In 2011, a team of researchers led by immunologist Carl June, a Penn professor, reported stunning results after genetically altering the T-cells of three patients with advanced chronic lymphocytic leukemia, a cancer that affects white blood cells.



LD chemotherapy (outpatient)

- 2 days cyclophosphamide (500 mg/m2/day)
- 4 days fludarabine (30 mg/m2/day)



Tumour Lysis Syndrome

Cytokines

Fever

Flu-like symptoms

Severe Cytokine Release Syndrome

Capillary leak

Generalized edema

Low blood pressure

Respiratory insufficiency

Multi-organ failure

Neurologic Side Effects

Encephalopathy

Aphasia

Seizures

Cerebral edema

Chronic B cell aplasia

Immunoglobulin deficient

1. Cytokine Release Syndrome

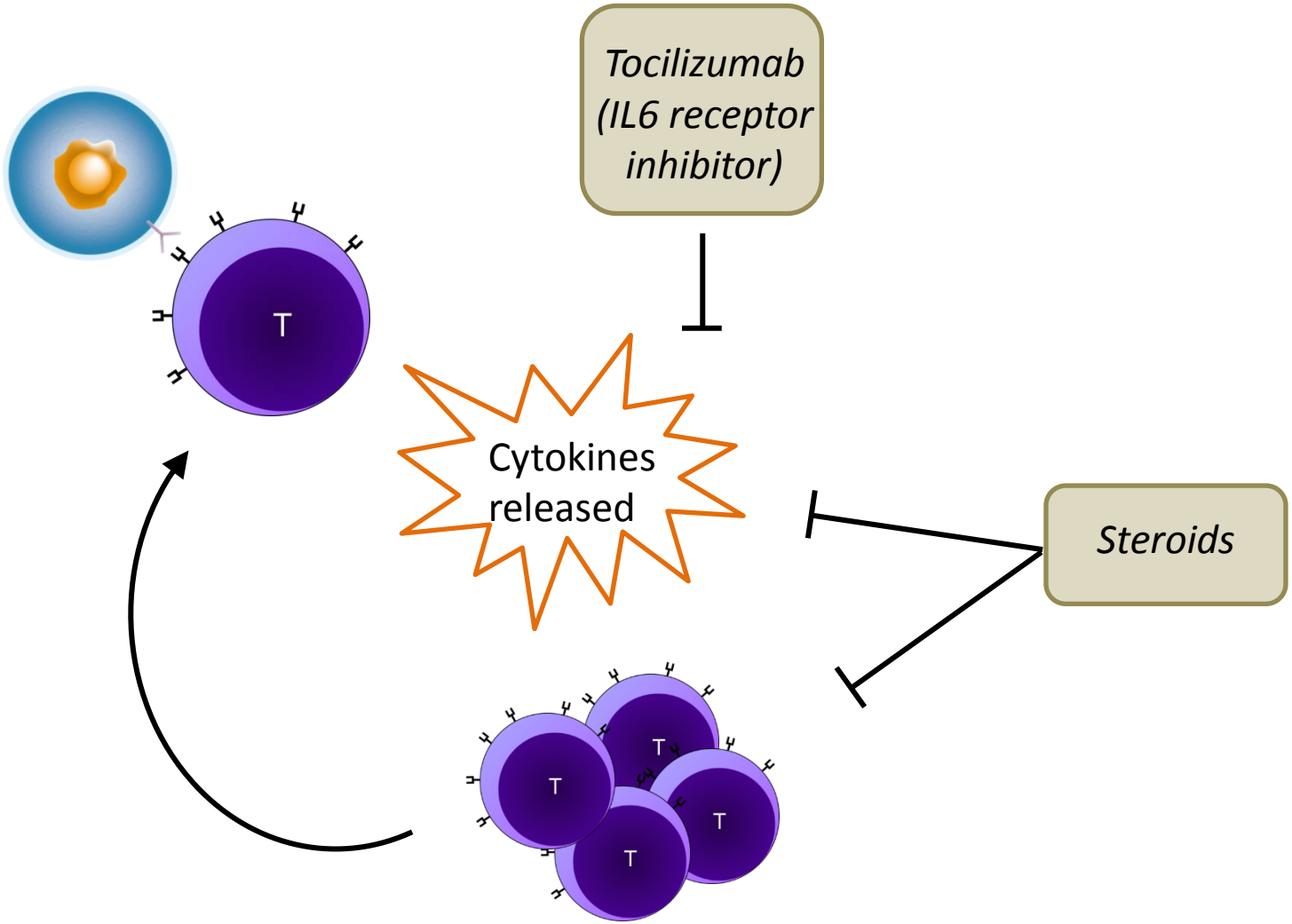
Typical onset Day 0-10

Mild

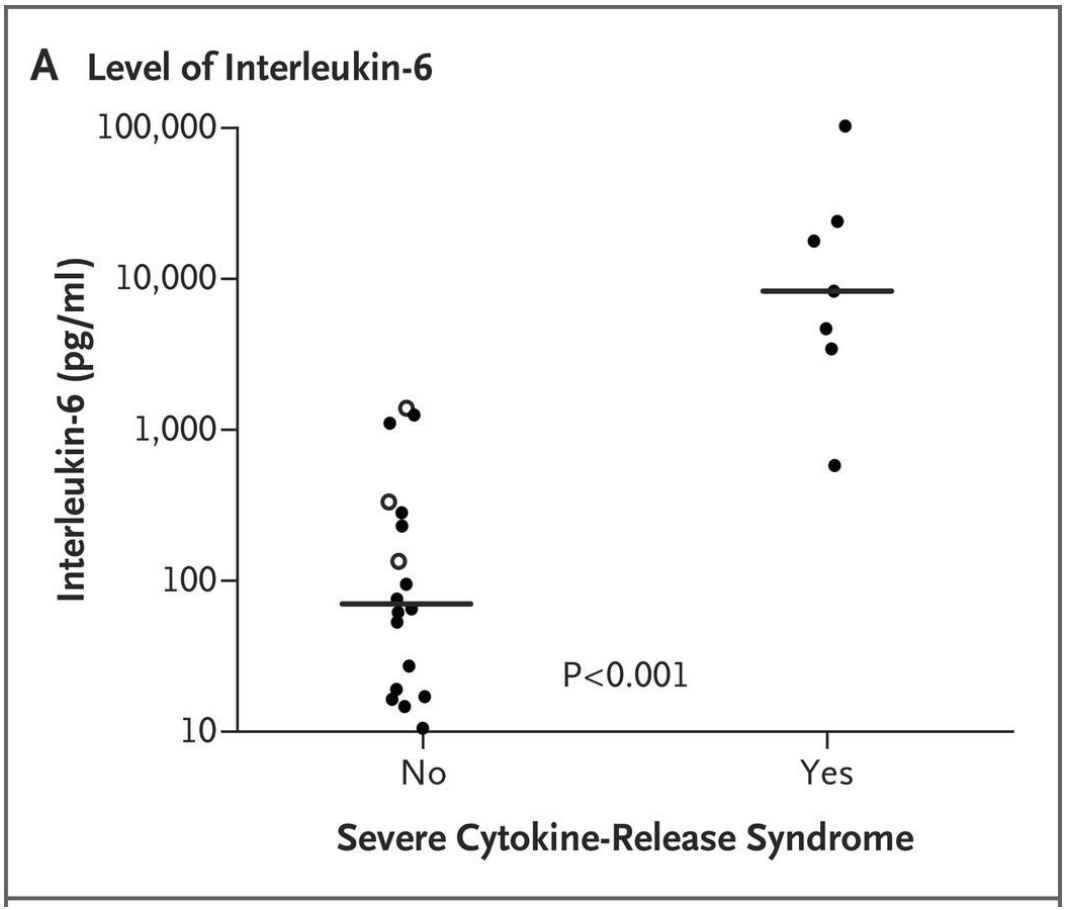
- Flu like symptoms – fatigue, myalgias, headache, poor appetite, nausea, diarrhea
- **Fever**

Severe

- High fever ($\geq$ 40^{o}C, unresponsive to antipyretics)
- Capillary Leak Syndrome
  1) Hypotension *(multiple vasopressors)*
  2) Respiratory insufficiency *(mechanical ventilation)*
  3) Fluid accumulation
  4) Renal dysfunction *(dialysis, CRRT)*
- Liver dysfunction, coagulopathy, macrophage activation syndrome *(plasma, cryoprecipitate)*
- Multi organ failure *(ECMO consideration)*



T-cell activation & proliferation



Maude et al. (2014) ***N Engl J Med***

2. Immune effector Cell Associated Neurotoxicity Syndrome (ICANS)

Typical onset Day 7-14

Encephalopathy

- Slowed thinking, confusion
- Slowed speech, aphasia
- Akinesia
- Visual and auditory hallucinations

- May or may not have imaging findings
- Not correlated to CNS disease
- All cases so far – reversible, self-limited, brief (days)
- CAR-T cells detected in CSF

- Seizures
- *Cerebral edema*

- **No impact of Tocilizumab (does not cross Blood-Brain barrier)**
- **Treat with Steroids**

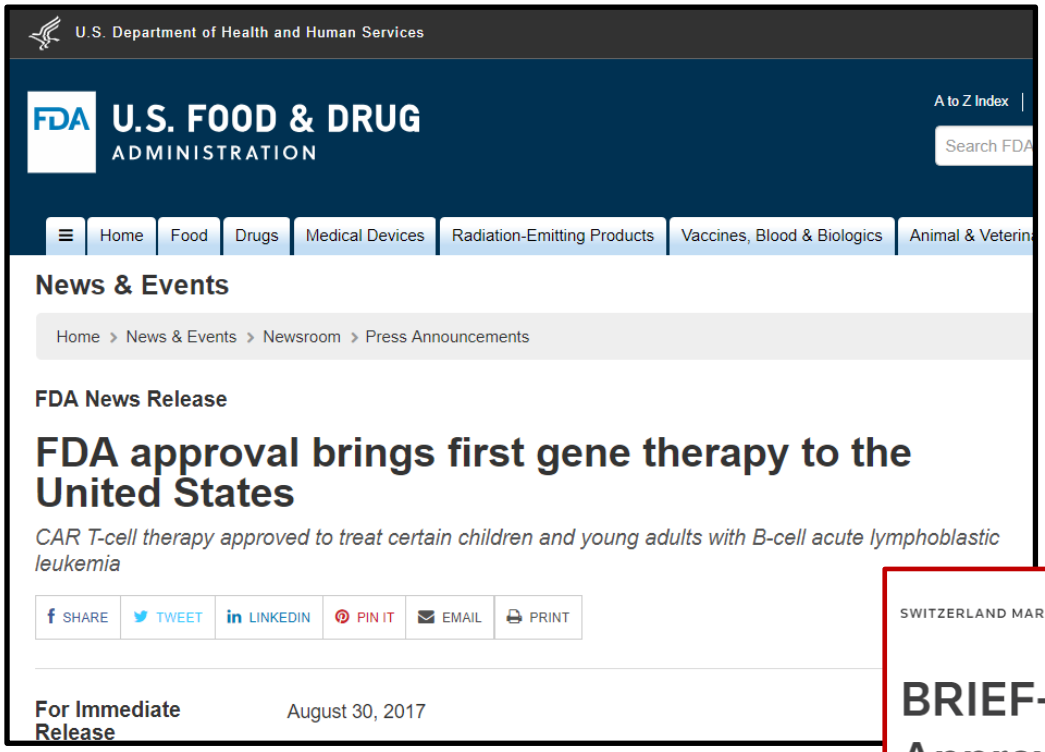
emily whitehead foundation
activate the cure

Major Pediatric/AYA CD19 Trials

Trial	CD19 scFv CD3z Costimulatory domain, vector	Population	Response of infused patients	Persistence
Children's Hospital of Philadelphia (single centre) ***Maude (2015) NEJM***	4-1BB, lentivirus	25 pediatric (5-22 years), 5 adult (26-60)	90% CR 82% MRD neg	6 months: 67% EFS, 78% OS
National Institutes of Health ***Lee (2015) Lancet***	CD28, gamma retrovirus	21 pediatric (5-27 years)	70% CR 60% MRD neg (Intent to treat)	Maximal persistence: 68 days 10 pts to BMT
Seattle Children's Hospital (single centre) ***Gardner (2017) Blood***	4-1BB lentivirus, 1:1 ratio of CD4 and CD8	45 pediatric (1-25 years)	93% MRD neg	1 yr: 50% EFS, 69% OS 11 pts to BMT
Novartis Eliana trial (multicenter) ***Maude (2018) NEJM***	4-1BB, lentivirus	75 pediatric (3-23 years)	81% MRD neg	1 yr: 50% EFS, 76% OS

Major Adult B-ALL/NHL CD19 Trials

Trial	Costimulatory domain, vector	Population	Response	Other
Memorial Sloan Kettering (single centre) Davila (2014) Sci Transl Med	CD28, Gamma retrovirus	16 adult (18-74 years) with B-ALL	88% CR 75% MRD neg	<u>Maximal Persistence:</u> 3 months 44% pts to BMT
ZUMA-1 and 2 (multicenter) Neelapu (2017) NEJM; Locke (2019) Lancet Oncol	CD28, Gamma retrovirus	101 adults With DLBCL, PMBCL, TFL	21 months: ORR 39% CR 37% 23/61 PR converted to CR after 1 month	Gilead/Kite axicabtagene ciloleucel (KTE-C19)
JULIET phase 2 (multicenter) Schuster (2018) Blood; Schuster (2019) NEJM	4-1BB, Lentivirus	167 adults (115 infused) with aggressive B-cell lymphoma	ORR 54% CR 40% 18 mo RFS: 64% 54% PR conversion to CR	Novartis tisagenlecleucel (CTL-019)
Fred Hutchinson Cancer Research Center Turtle (2017) Sci Transl Med	4-1BB lentivirus, 1:1 ratio of CD4 and CD8	34 adults with NHL	63% ORR 33% CR	Licensed to Juno Therapeutics (JCAR014)



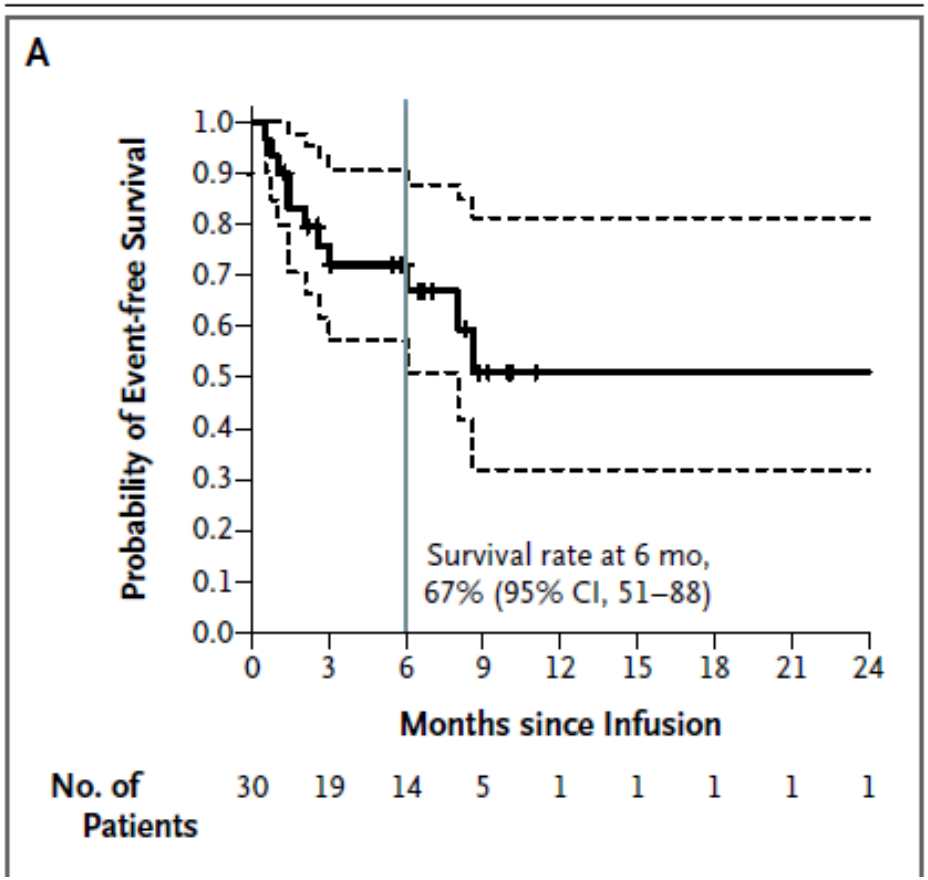
SWITZERLAND MARKET REPORT SEPTEMBER 6, 2018 / 4:14 AM / 12 DAYS AGO

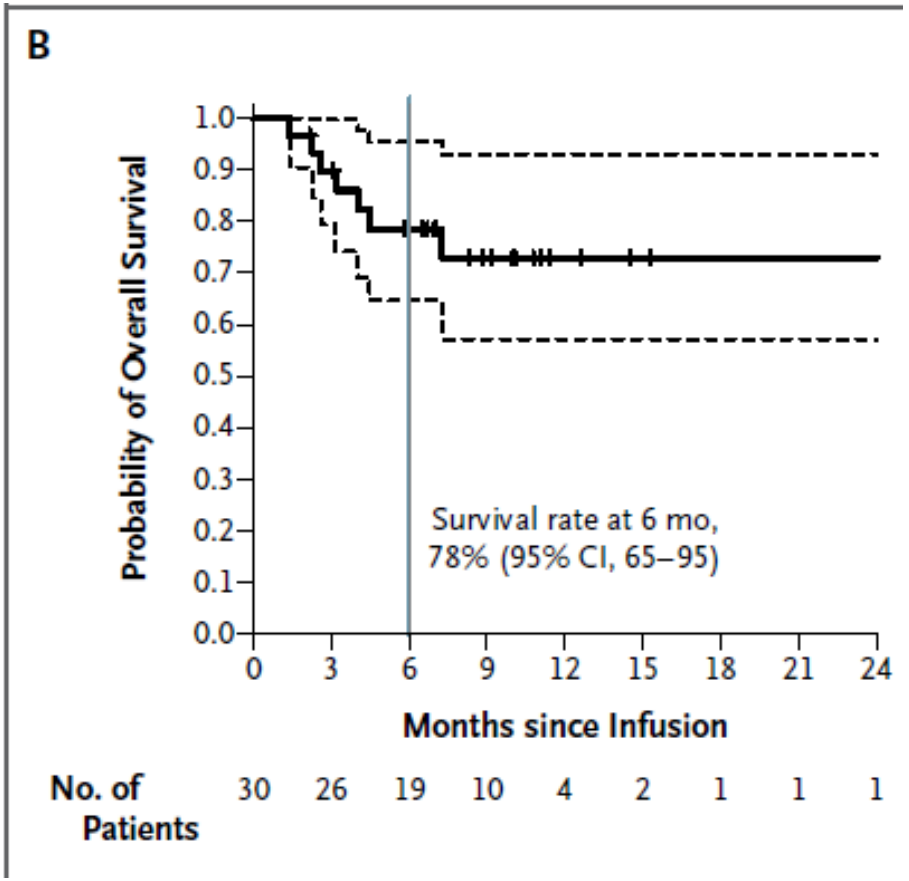
BRIEF-Novartis Receives Health Canada Approval Of Its Car-T Cell Therapy, Kymriah I

1 MIN READ

Sept 6 (Reuters) - Novartis AG:

* NOVARTIS RECEIVES HEALTH CANADA APPROVAL OF ITS CAR-T CELL THERAPY, KYMRIAH™ (TISAGENLECLEUCEL)I





1 month:	90% complete response
12 months:	60% complete response

Maude (2014) NEJM

How can CAR T cell therapy fail?

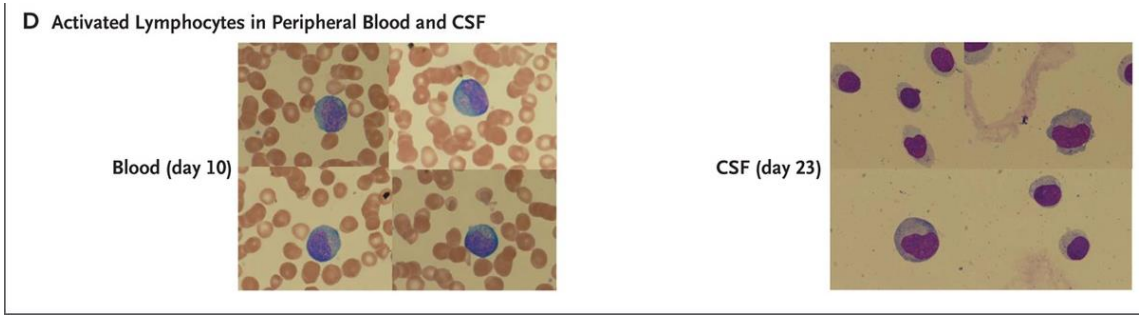
❑ **Short term persistence**

- CAR T cells are rejected by the body or become exhausted and stop working

  – *more therapy required (e.g. Bone Marrow Transplant)*

❑ **CD19-negative relapse**

- Leukemia cells evade the CAR T cell
  - *Hiding the CD19 target*
  - *Changing the leukemia type*



How is CAR T cell therapy available to BC Pediatric Patients?

1. Traveling to the U.S. for Clinical Trials

- Seattle Children's Hospital
- Children's Hospital of Philadelphia
- National Institutes of Health

2. Local Collaborative Clinical Trials

- **PLAT05 trial – Seattle Children's Hospital / CureWorks**

3. Health Canada approved product Kymriah ™ (Novartis)

- Currently not available

Summary

- CAR T cell therapy uses a patient's own T cells to create a live, targeted therapy for B-lineage ALL
- Potentially less toxic ALL therapy (particularly for long-term survivors)
- Exciting early successes but ongoing work needed to realize full potential of this approach