

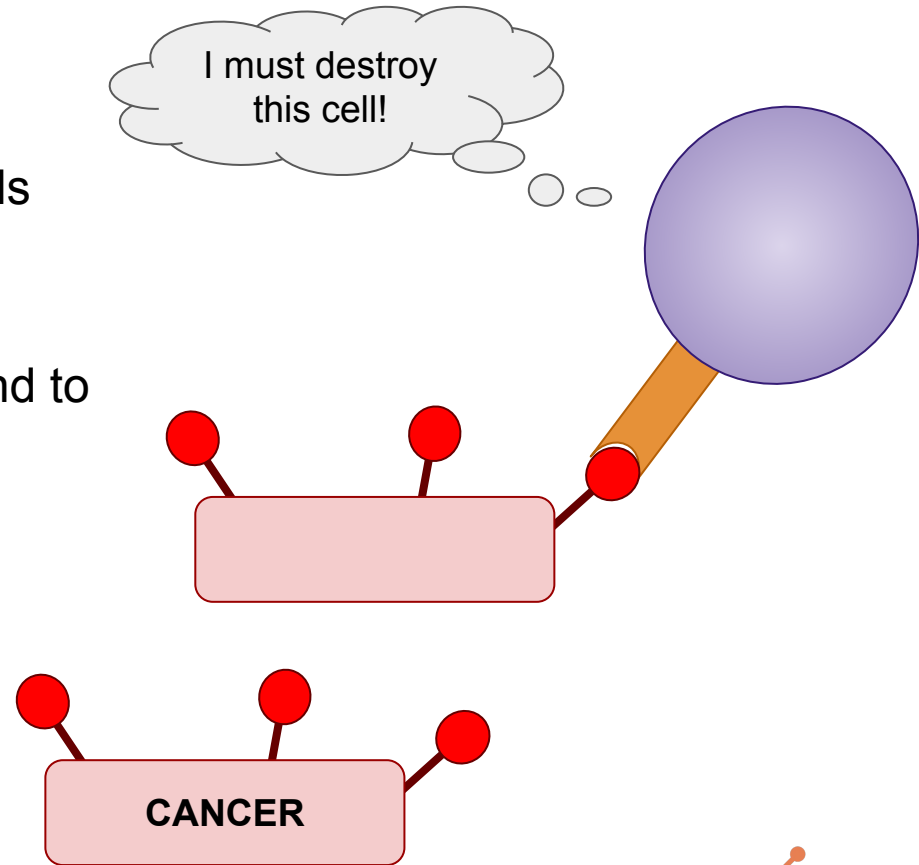
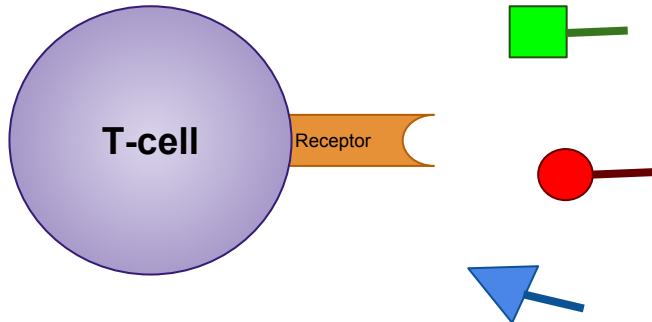
The public sector role in funding CAR T technologies

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Knowledge Ecology International
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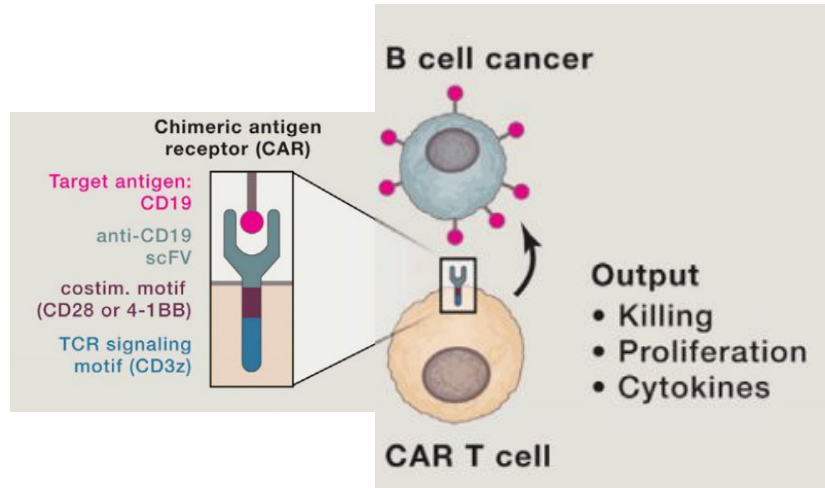


T-cells and receptors

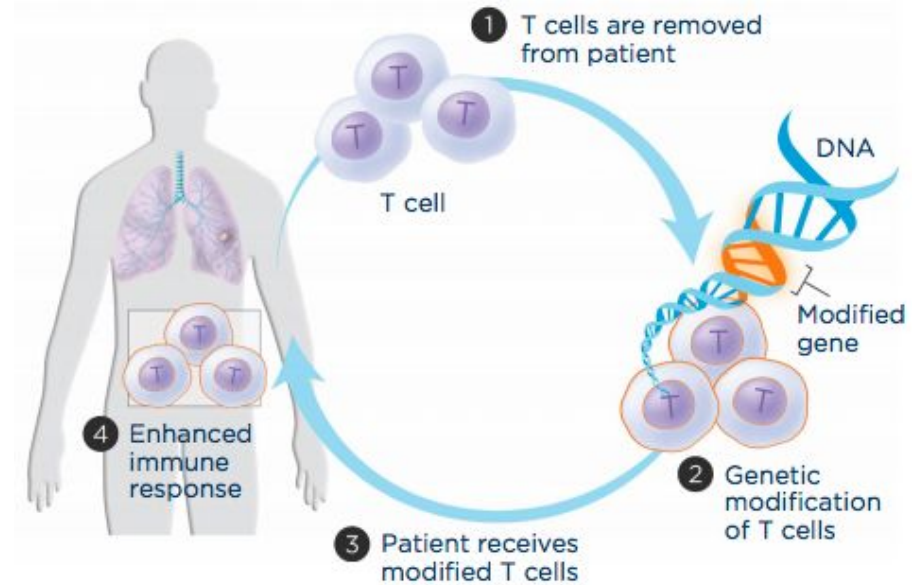
- T-cells are types of immune cells (aka: “white blood cells” or lymphocytes)
- Receptor are molecules that bind to and receive chemical signals



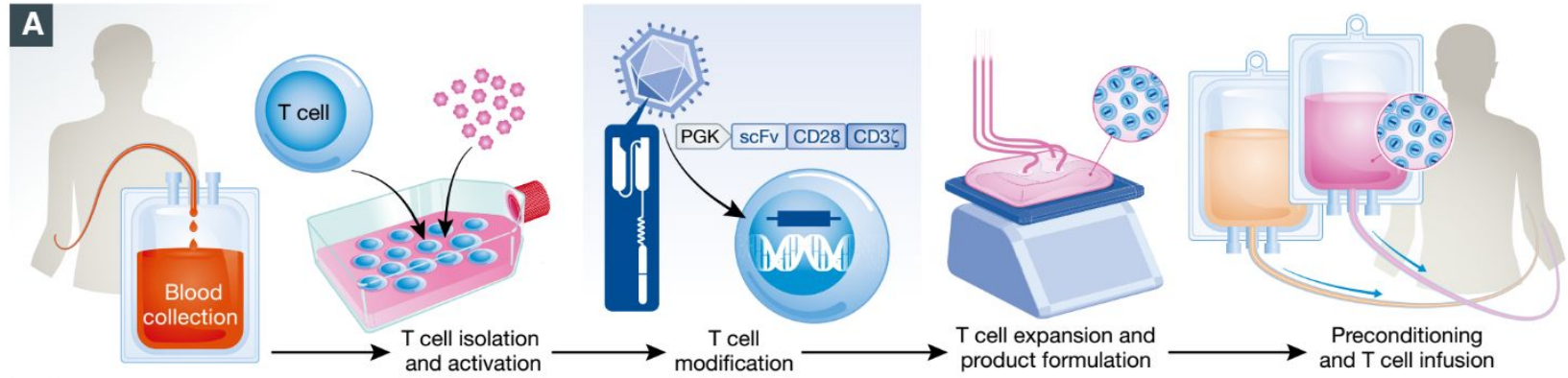
Chimeric Antigen Receptor T-cell (CAR T) Therapy



(Lim and June, 2017)



CAR T manufacturing and Treatment



Hartmann et al, 2017

▲
⋮
CRISPR

Cell manipulation core facility



(Wikipedia, 2017)



(Milteny, 2017)



Dr. Stephan A. Grupp presented "CD 19 CAR T Cells in Leukemia" at the 2017 BMT Tandem Meetings

Types of CAR T-cell Therapy

- 133 clinical trials targeting hematological malignancies:
 - 56 ongoing CD19
 - ALL- 2017, new: 5,970, deaths:1,440
 - CLL
 - NHL
- 78 solid tumors
 - Prostate cancer, Neuroblastoma, Glioma
 - Difficulties:
 - Proper T-cell infusion of Solid tumors
 - Internal environment of tumor can be immunosuppressive

CAR T and Public sector funding

- NIH Reporter database --> “chimeric antigen receptor”:
 - The records go back to 1993.
 - 356 project
 - 72 different institutions
 - 100 PIs.
 - Total NIH funding was \$204, 288, 340
- Clinical Trials
 - Only 20% of CAR T cell trials are sponsored by pharmaceutical industry (Hartmann et al. EMBO-MM, Aug 2017).
 - 91% of CAR T trials have an academic sponsor (DeWilde et al. International society for cellular therapy, March 2017).

Kite Pharma and NCI CAR T technology

- Kite Pharma Relies heavily on NCI CAR T research.
 - 3 CRADAs, 6 Exclusive license Agreements
 - 2012- NCI conducts research into various different types of TCR therapies, and Kite pays the NIH \$3 million annually.
 - Jan 2016-clinical evaluations on KTE-C19, costing \$2.5 million
 - Dr. Steven A. Rosenberg a PI with a long career at NCI and pioneer in immunotherapy as a "Special Advisor" to Kite
 - Kite reported spending \$317 million in R&D from 2012 to June 30, 201
 - Kite is selling the company for \$11.9 billion to Gilead

Kite Exclusive Licenses & CRADAs with NIH

| Date | Agreement Type* | Subject of Agreement |
|------------|-----------------|---|
| 08/31/2012 | CRADA | development of Autologous T Cell Therapy (ACT) using NCI proprietary T cell receptors (TCRs) or NCI proprietary chimeric antigen receptors (CARs) |
| 04/11/2013 | ELA | development of Autologous Cell Therapy T cell receptor (ACT TCR) product directed to synovial sarcoma breakpoint X-2 SSX2 and to epidermal growth factor receptor variant III (EGFRvIII) tumor antigens, for various types of cancers |
| 05/22/2014 | ELA | development of Autologous Cell Therapy T cell receptor (ACT TCR) product directed to treatment of New York Esophageal Antigen-1 (NY-ESO-1) expressing cancers |
| 12/31/2014 | ELA | development of Autologous Cell Therapy T cell receptor (ACT TCR) product directed to Human Papillomavirus (HPV) antigens E6 and E7 of the HPV subtype 16 |
| 10/01/2015 | ELA | development of Autologous Cell Therapy T cell receptor (ACT TCR) product directed to MAGE A3 and A6 |
| 01/04/2016 | CRADA | clinical evaluation of CD19-targeting Chimeric Antigen Receptor (CAR) therapy for the treatment of B cell lymphoma and B cell leukemia, and the development of novel CARs for B cell malignancies |
| 06/2016 | CRADA | clinical development of T cell receptor (TCR) therapy for human papillomavirus (HPV)-16 E6 and E7 oncoproteins for the treatment of HPV-associated cancers |
| 07/2016 | ELA | fully human anti-CD19 chimeric antigen receptor-based product candidate directed against B-cell malignancies |
| 09/2016 | ELA | T-cell receptor (TCR) based product candidates for the treatment of tumors expressing mutated KRAS antigens |

*CRADA = Cooperative Research and Development Agreement; ELA = Exclusive License Agreement

Zack Struver, KEI 2016

Novartis/ UPenn-Kymriah (tisagenlecleucel, CTL019)

2011- Dr. Carl June from UPenn has been working on T-cell for many years and in 2011 published an important paper using an anti-CD19 CAR T-cell therapy in CLL

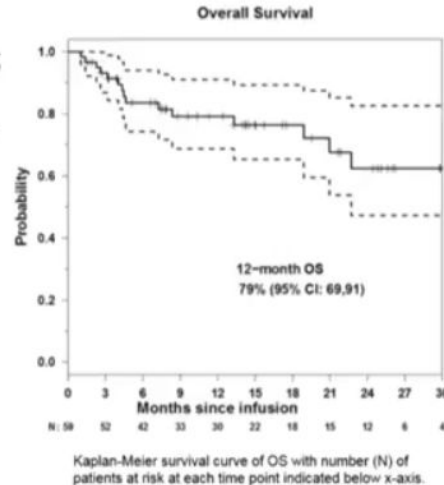
2012- Novartis and UPenn deal

- \$20 million towards a research center
- Novartis gets exclusive worldwide rights to all CARs developed through the collaboration and to CART 19, which is already in the clinic
- NIH- grants to Dr. Carl June:
 - \$30,335,306 of funding from the NIH for 39 projects relating to CAR T between 1993 and 2016.
(Dr. June received \$16,330,088, 1993 to 2011)
- August 2017, FDA approval the first CAR T-cell therapy
 - Pediatric and young adult (under 25) patients with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
- \$475,000 for one-time treatment (100% reimbursements if no response after 1 month)

CD19 CAR CTL019 in relapsed/refractory pediatric ALL: 93% complete response rate

Results presented at ASH 2015

- CR in 55 of 59 patients (93%) at 1 month; median follow-up of 12 months
- 6 patients went to subsequent transplant, 1 to DLI
- **12 month OS: 79%** (95% CI: 69, 91)
- Relapse-free survival (RFS)
 - 6 month RFS: 76% (95% CI: 65,89)
 - **12 month RFS: 55%** (95% CI: 42,73)
- No relapses past 1 year
- 18 patients in remission beyond 1 year, 13 without further therapy
- Humanized CTL119 – 22/22 CR in same population, early F/U



Thank you.

Adverse reaction

Cytokine release syndrome

Neurologic toxicities

B-cell aplasia

Current CART in clinical trial

- As of 2016,
 - 133 hematological
 - 78 solid tumors

Response is pretty good in ALL. The remission rates for ALL varies across clinicals trials ranging from 11% to 50% (for 5 trials).

Tisagenlecleucel (CTL 019)

Fda approved

Phase 2 Eliana study

Kymriah

What is a cart

Nomenclature- 1st gen, 2nd gen...

How it's done (how to get it into the cells)

Risks- crs

General clinical trials (hema vs solid pro/ cons).

Shedding light on Novartis clinical data,

Future of CarT, how to decide?