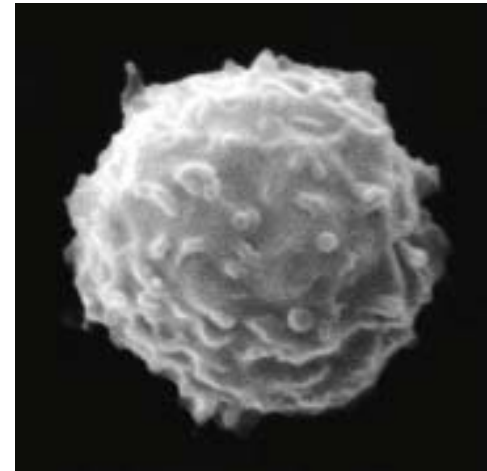


Chimeric Antigen Receptor-Modified T Cells in Chronic Lymphoid Leukemia

Kymberleigh Pagel

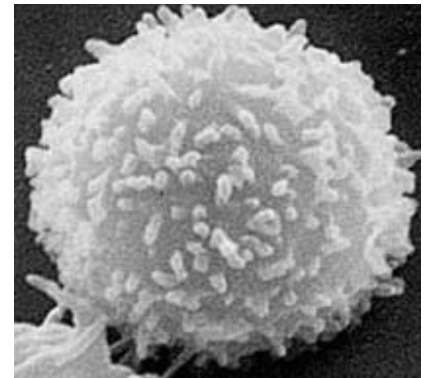
Chronic Lymphoid Leukemia

- Most common
- B cells sans antibodies
- Overproduction
- Overcrowding
- Kills healthy blood cells



Chimeric antigen receptors

- T cell = White blood cell with receptors on surface
- Redirects T cells by modification to express specific antibodies
- These cells can be generated en masse to combat a diseased particles specified by the antibodies

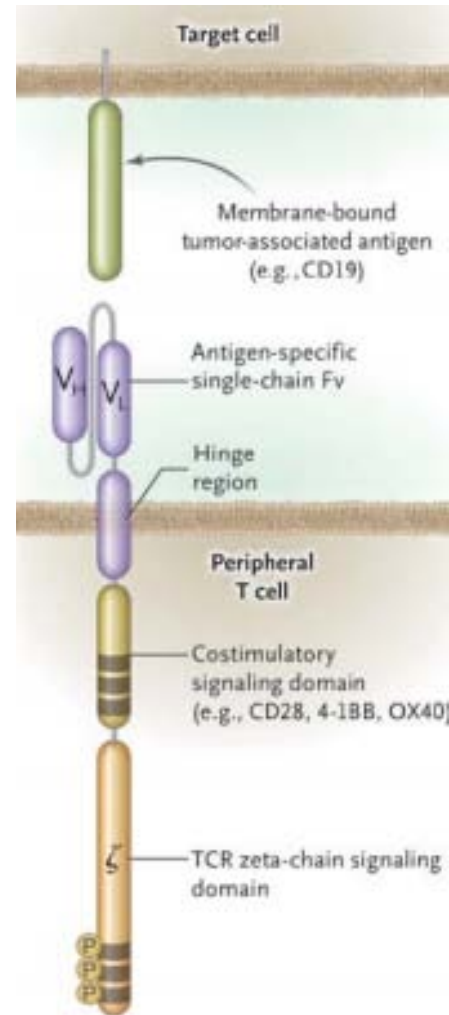


Benefits

- Reduces risk of graft versus host disease
- Produced quickly
- Same receptor can be used for multiple people
- Bind to cell-surface molecules, which broadens potential applications

Chimeric Antigen Receptor

- Specificity:
 - B cell antigen CD19
 - Normal
 - Malignant
 - Precursors
- Signaling domains
 - CD137 (4-1BB)
 - CD3-zeta chain

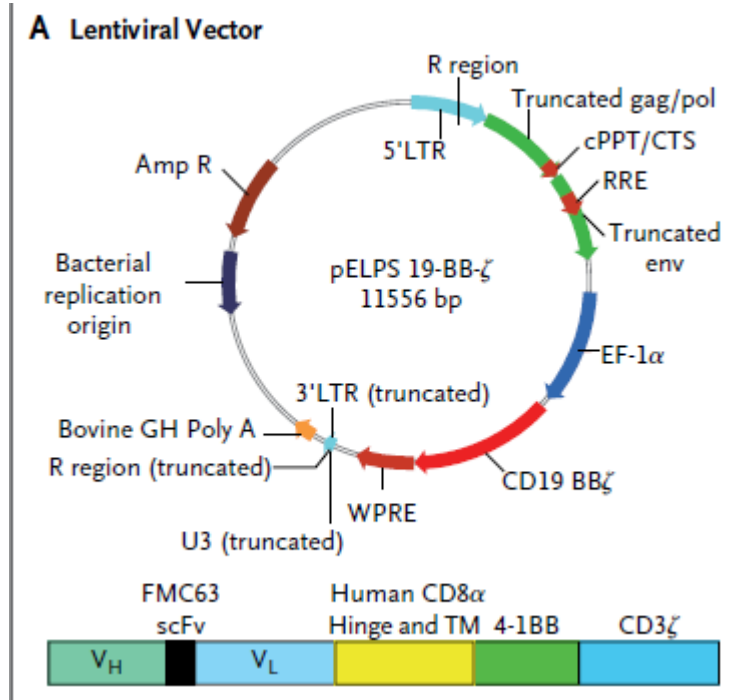


Not new, just improved.

- Old: Since at least 1986
- Improvement: Inclusion of the CD137 signaling domain
 - antitumor activity
 - in vivo persistence

Making the T cells

- Extract T cells from patient
- Replicate T cells
- Use plasmid to express the CD19 receptor



Porter et al. Chimeric Antigen Receptor-Modified T Cells in Chronic Lymphoid Leukemia. NEJM 2011 365:8 725-733

Treatment

- Four days after chemotherapy
 - Goal: Deplete lymphocytes
- 1.42×10^7 cells
 - three intravenous infusions in one day
- No immediate toxic effects

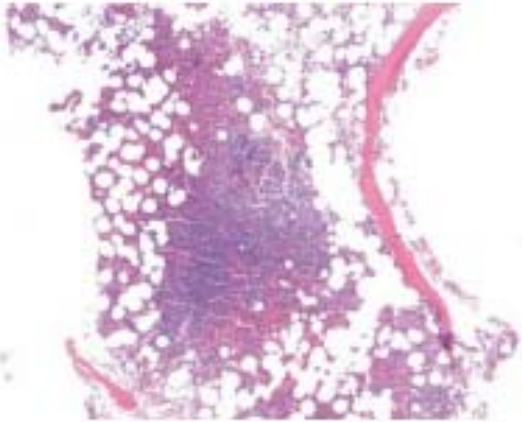
Effects

- Chills, Fever, Rigors
- Fatigue, Diaphoresis
- Anorexia, Nausea, Diarrhea
- Lymphopenia, thrombocytopenia, neutropenia
- Tumor lysis syndrome
 - High potassium, phosphate, uric acid, calcium

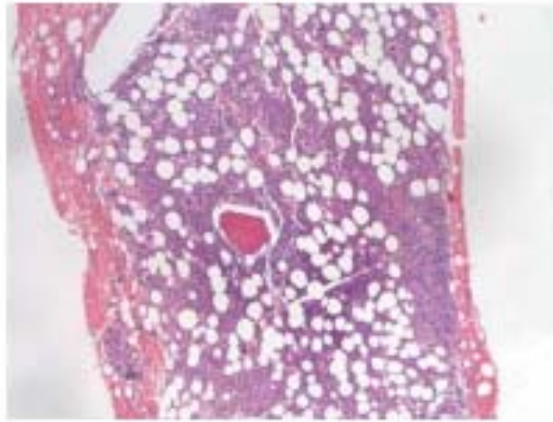
Better Effects: Bone Marrow

Bone Marrow—Biopsy Specimens

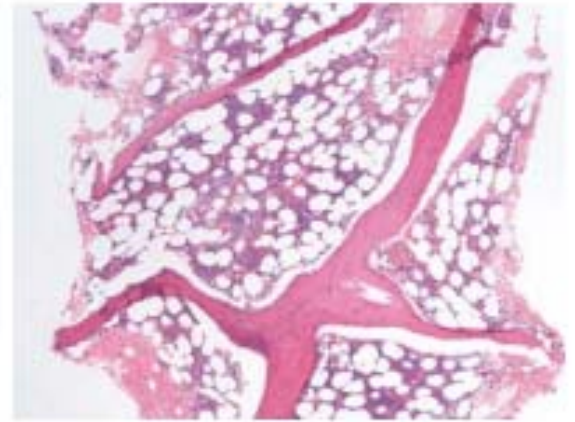
Day -1 (baseline)



Day 23



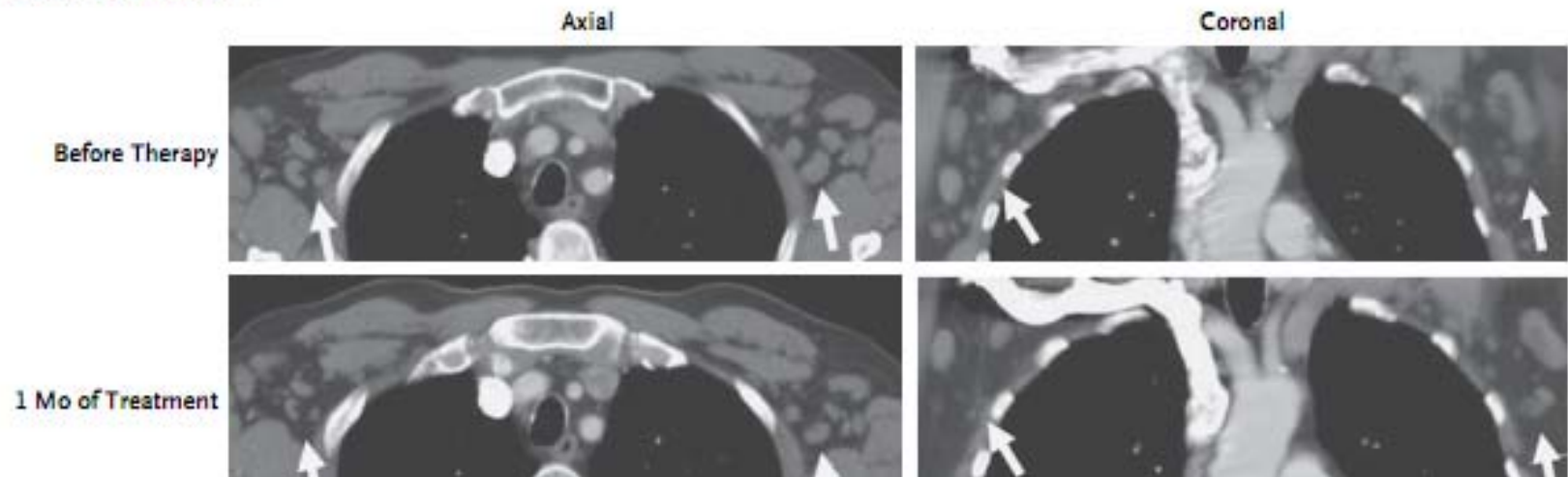
6 Mo



Porter et al. Chimeric Antigen Receptor-Modified T Cells in Chronic Lymphoid Leukemia. NEJM 2011 365:8 725-733

Better Effects: Lymph Nodes

Contrast-Enhanced CT



Porter et al. Chimeric Antigen Receptor-Modified T Cells in Chronic Lymphoid Leukemia. NEJM 2011 365:8 725-733

Wait, what?

- The relatively low dose was not expected to produce these results.
 - 1.5×10^5 per kilogram body mass
 - Caution in dosage.
- The cells persist in the bodies.
 - Could mean long term cancer control
 - Long term B cell deficiency
 - Manageable condition

Speculation

- Include exogenous cytokines
- One-Two punch:
 - Start with chemotherapy, to weaken the cancerous cells.
 - Insert modified T cells.