T cells Recognizing Antigen Through Native or Chimeric Receptors

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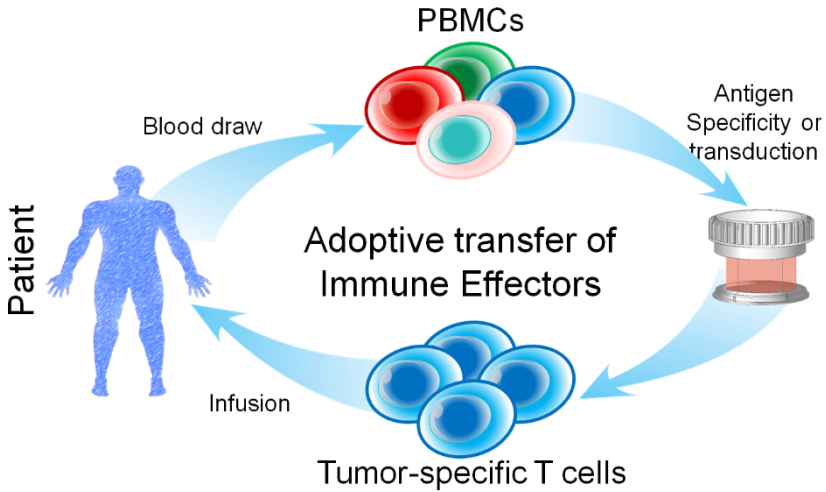
Disclosure

Interest	Company	Topic
Founder with equity	Marker Therapeutics Allovir	TAA specific T cells Third party VSTs
Advisory Boards	Novartis Gilead Biosciences Kiadis Tessa Therapeutics PACT Pharma	
Research support	Tessa Therapeutics Cell Medica	Third party EBVSTs CAR- NKT cell studies

Adoptive Cellular Therapies for Cancer

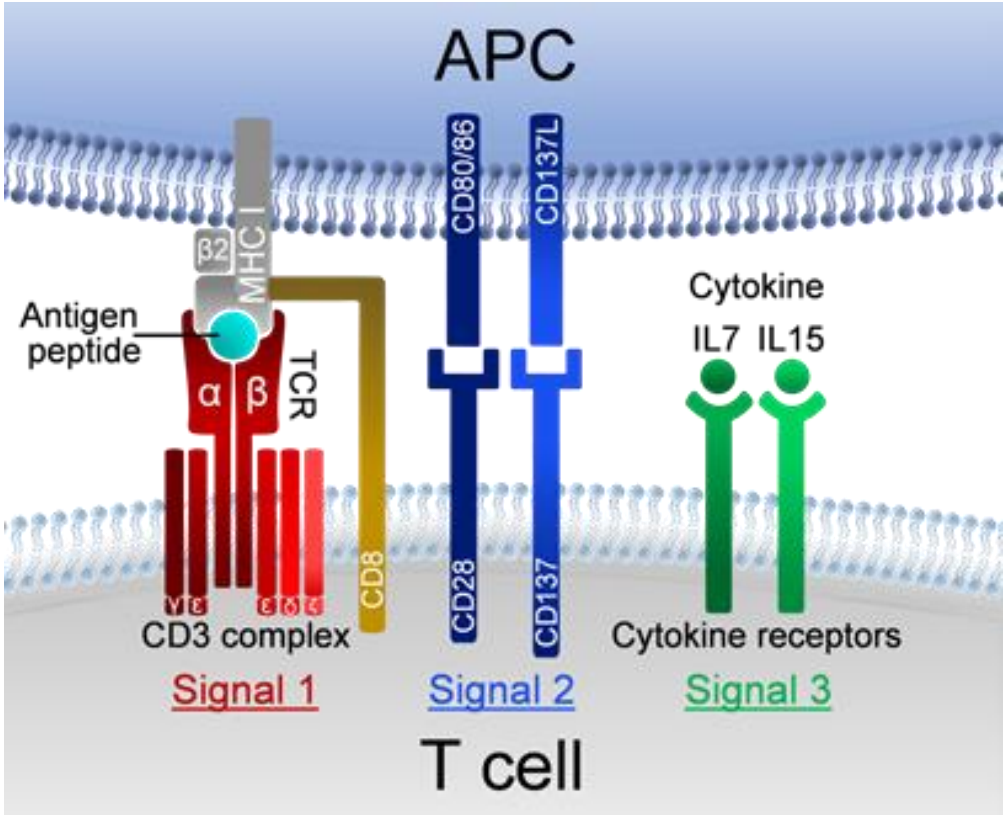
- Manipulation of the immune system to treat or prevent disease
  - Innate immunity
    - Immediate defense
    - Alerts and guides adaptive immunity
  - Adaptive immunity
    - Specific
    - Expands
    - Memory



Benefits of T Cell Therapies

- Specific receptors give high targeting ability
- Recognize internal antigens (if processed)
- Good bio-distribution - traffic through multiple tissue planes
- Multiple effector mechanisms
- Self amplifying

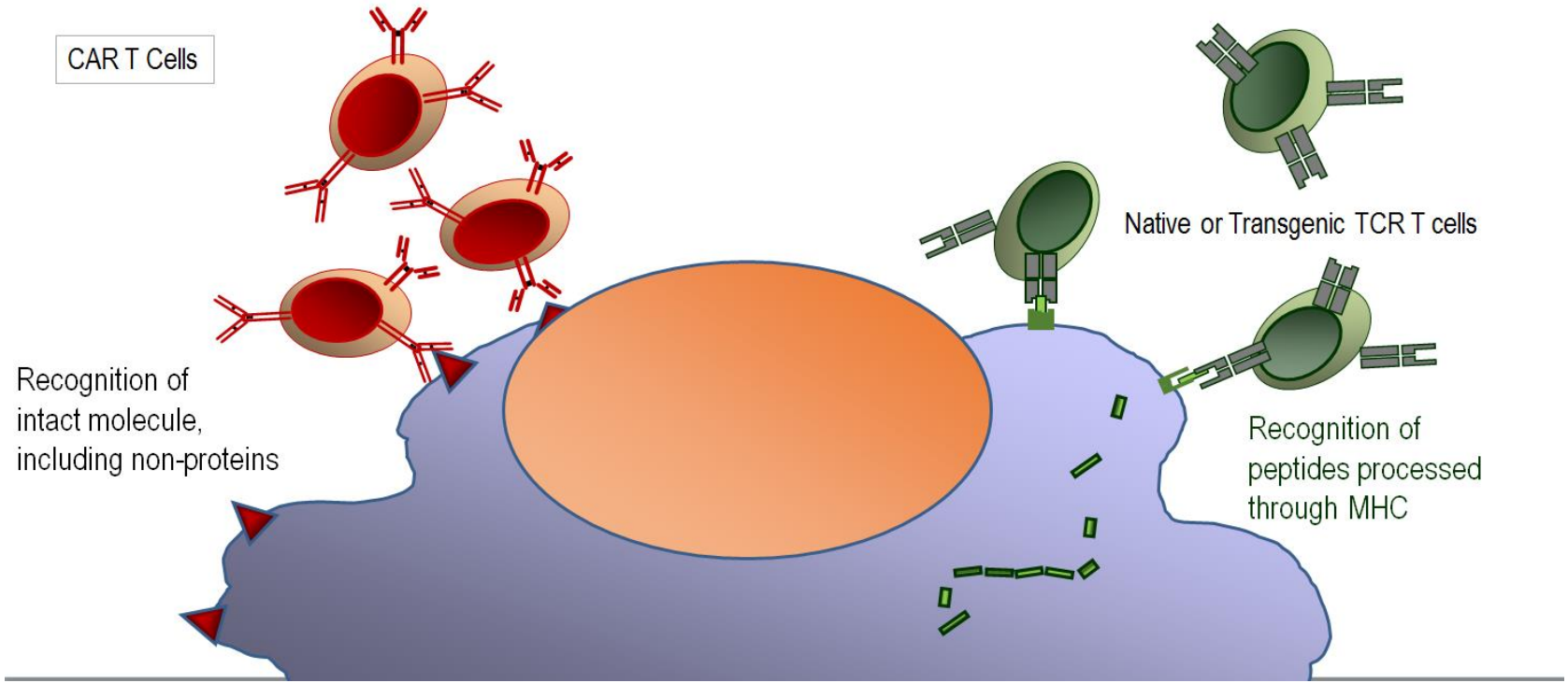
T Cell Activation



Complex process

Regulated by stimulatory and inhibitory signals

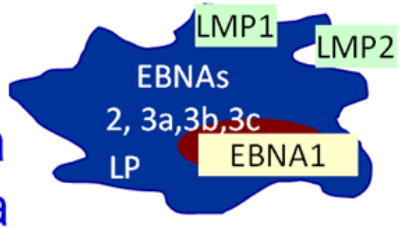
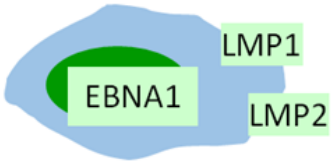
Chimeric versus Native Receptors



Requirements for T cell Targets

- Possess target antigens
  - Viral antigens e.g. EBV, CMV, HPV
  - Tumor-associated antigens e.g. survivin, PRAME
  - Neoantigens

EBV-associated Malignancies

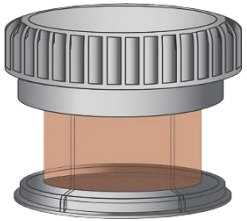
Latent Malignancy	Latent Gene Expression	Immunogenicity
Type 3 Post transplant lymphoma HIV-associated lymphoma		
Type 2 Hodgkin's lymphoma NHL		
Type 1 Burkitt's lymphoma		

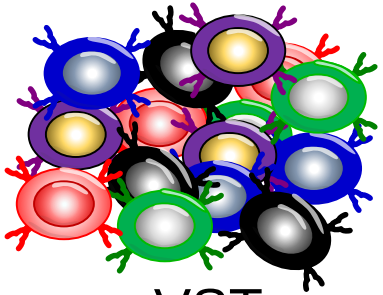
VST Manufacture

ADV – HEXON, PENTON
EBV – EBNA1, LMP2, BZLF1
CMV – IE1, PP65
BKV – LT, VP1
HHV6 – U11, U14, U90

Ulrike Gerdemann
Ann Leen

+IL4/7

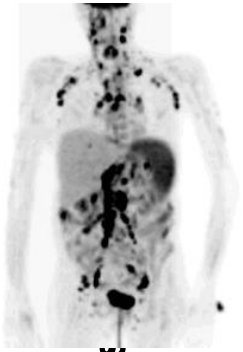


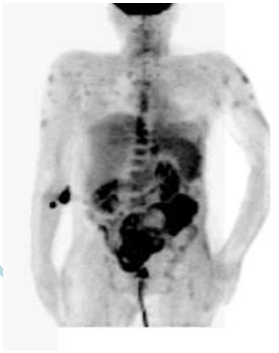


mVSTs
(multivirus VSTs)

T cell stimulation/ expansion
10 days

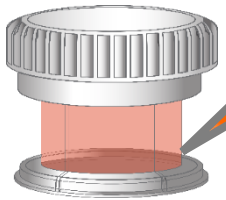
Activity in EBV-PTLD





Multi- TAA T Cell Therapy

PRAME
MAGEA4
SSX2
Survivin
NYESO1



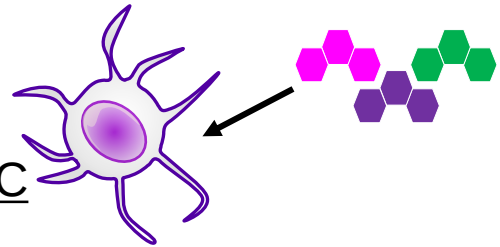
MultiTAA
T cells

Heterogeneous
tumor

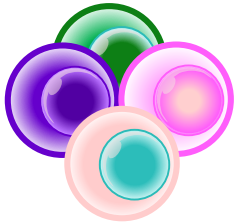
MultiTAA-T Cell Manufacture

Pepmix spanning full length
WT1, PRAME, Survivin, NyESO, SSX2

Ann Leen



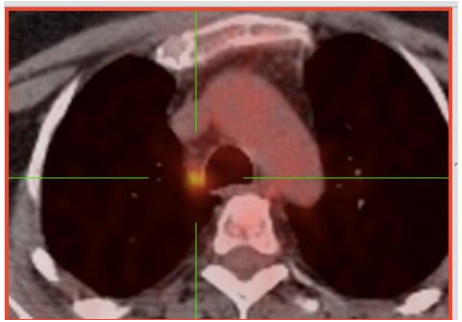
DC



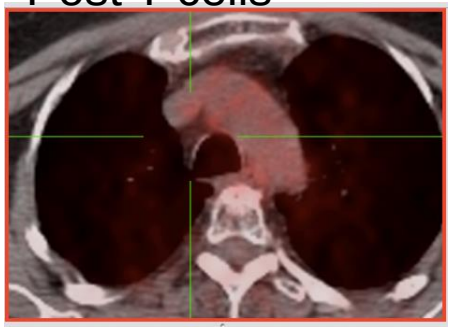
PBMCs

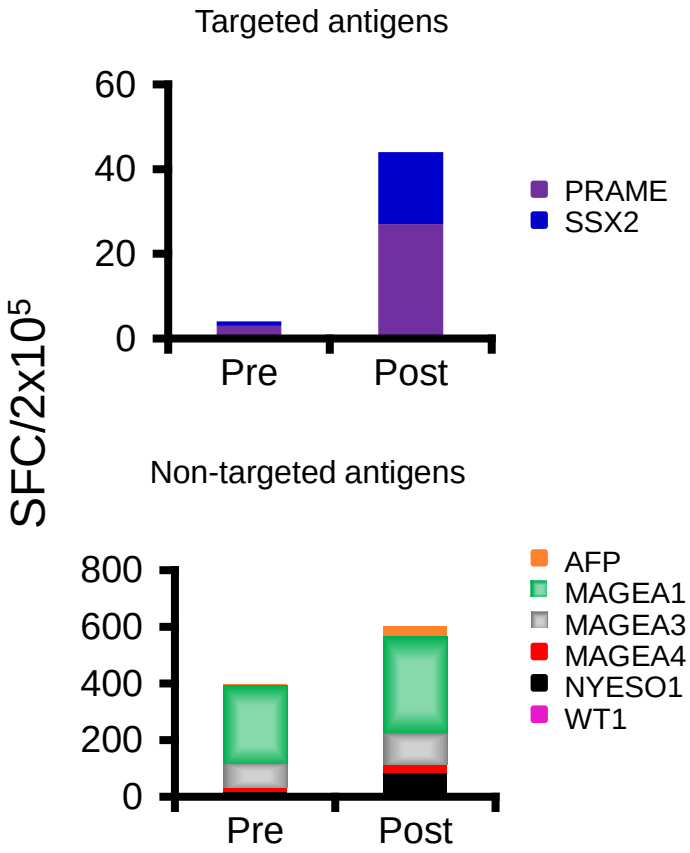
Clinical Response – HL

Pre T cells



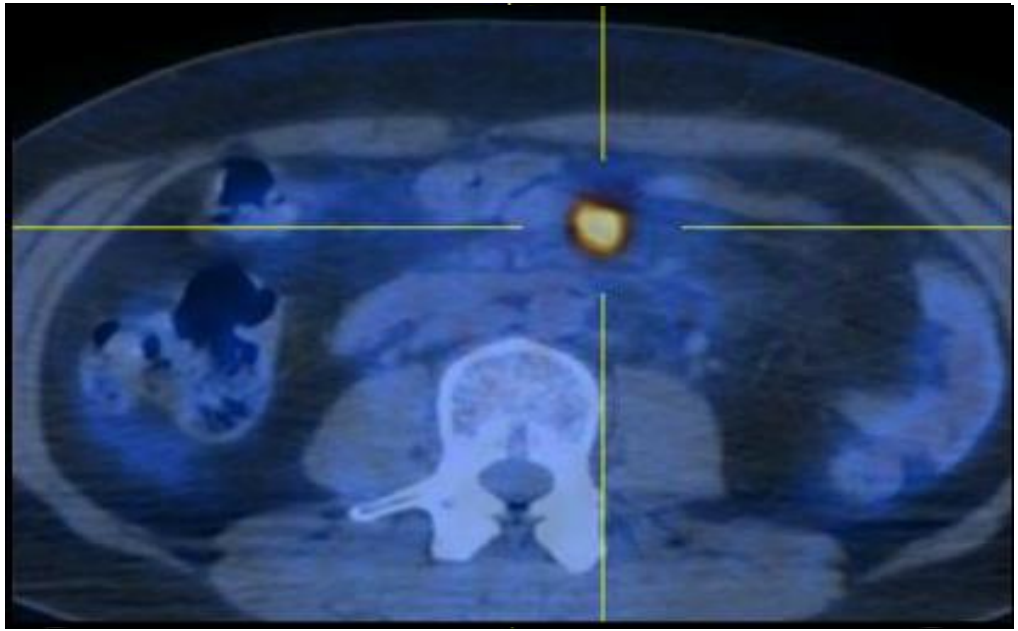
Post T cells

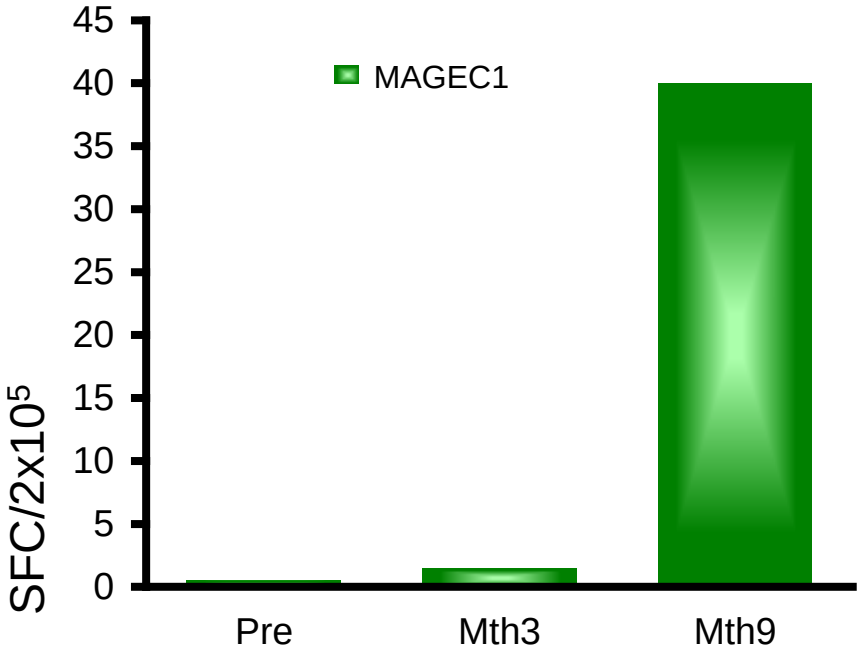




Clinical Response – DLBCL

Mth3 Mth9 Infusion





TACTAL: TAA-specific T cells for Lymphoma

Group A; Adjuvant

16/18 in remission 3m to >42m

Group B; Therapy (No conditioning)

40% - 6/15 CR

27% - 4/15 SD (>5m to >18m)

33%- 5/15 SD- PD

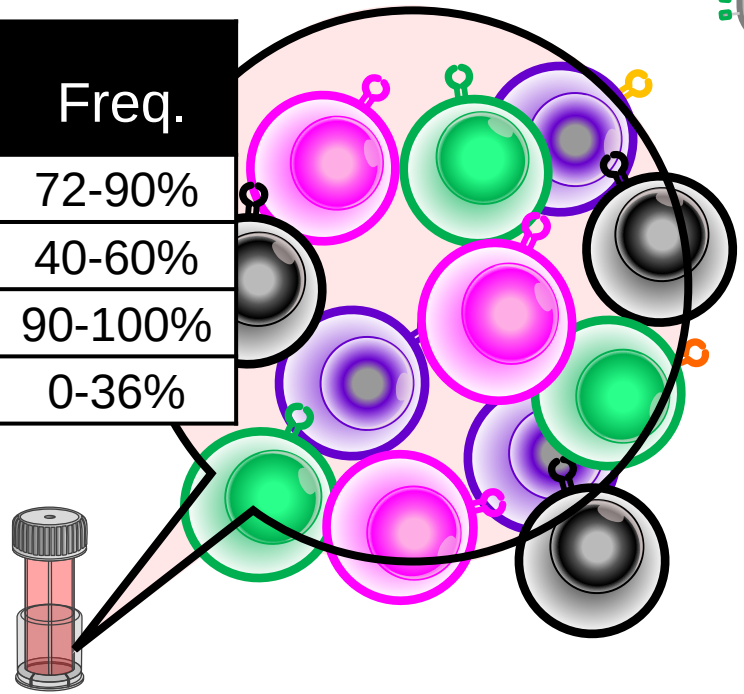
No CRS

Ann Leen

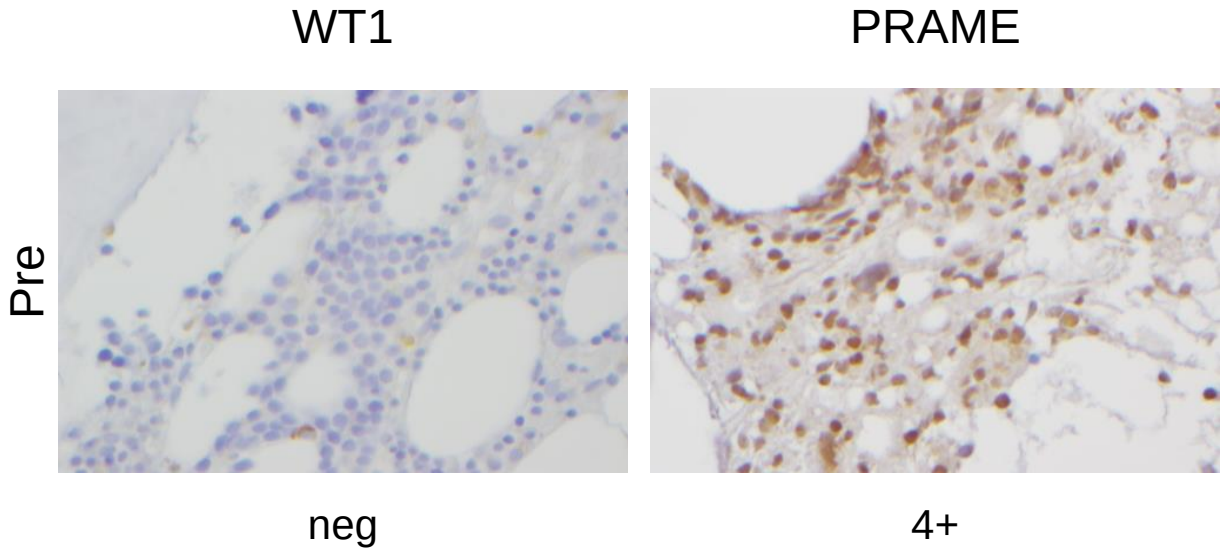
George Carrum

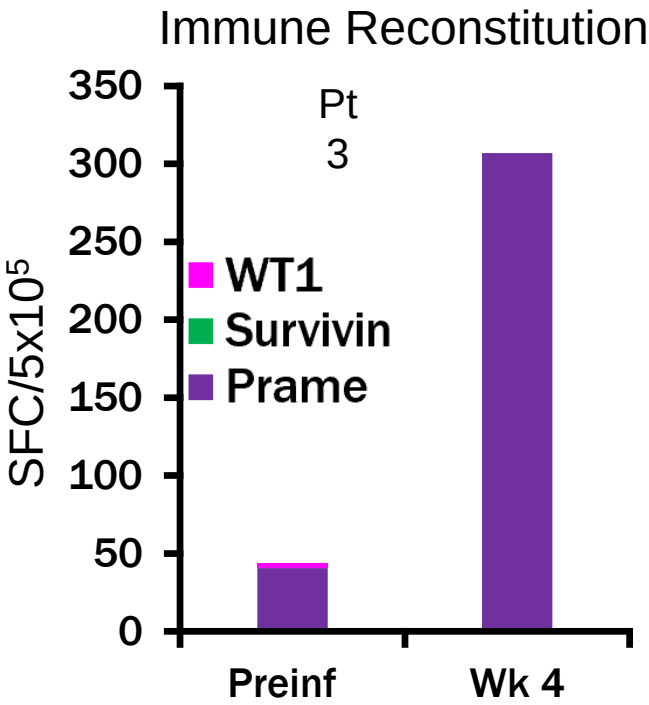
MultiTAA-T cells for AML/MDS and ALL

TAA	Freq.
WT1	72-90%
PRAME	40-60%
Survivin	90-100%
NY-ESO1	0-36%



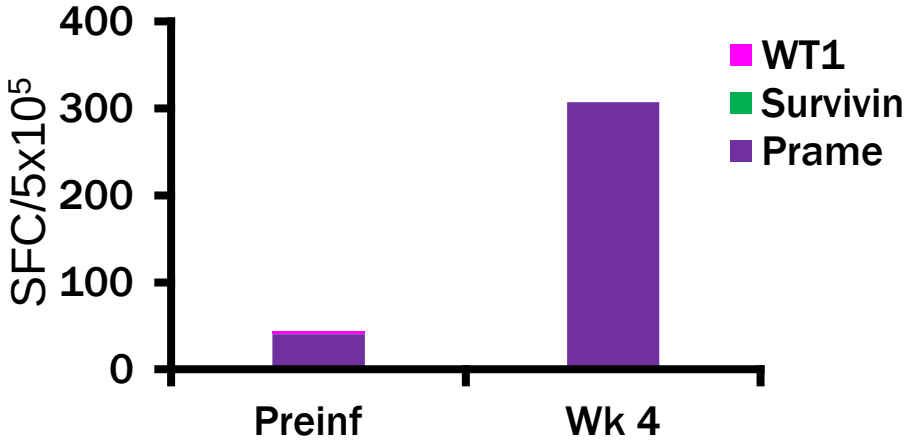
Tumor Antigen Expression And T Cell Expansion



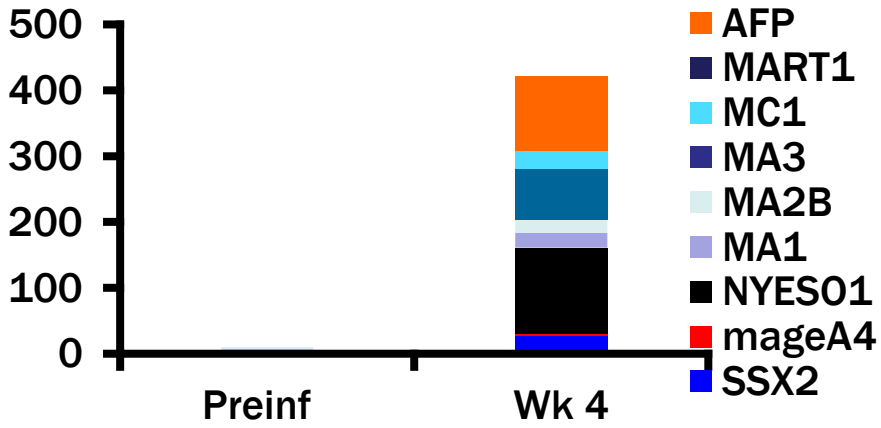


Antigen Spreading

Pt 3 Target Antigens



Antigen spreading



TAA-specific T cells for AML and ALL

Adjuvant

6/7 ALL remained in remission

9/13 AML remain in CR

- 2 isolated CNS relapse- both alive in CR
- 1 marrow relapse
- 1 bone relapse

Therapy of relapsed AML (No conditioning)

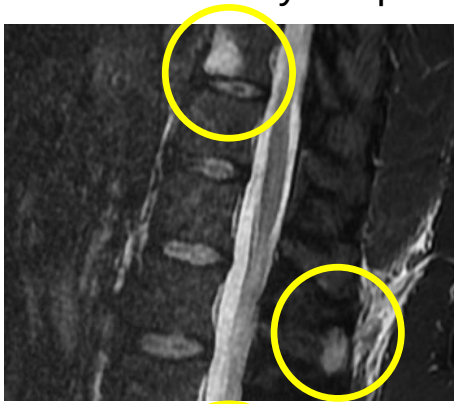
- 2/6 responses

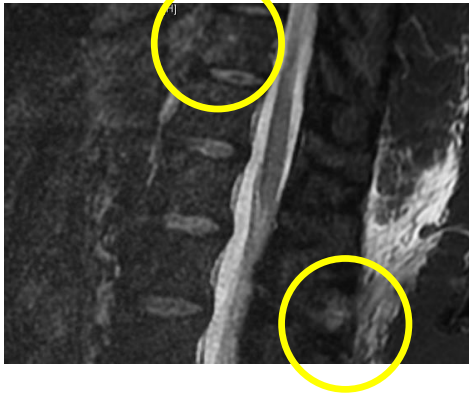
Premal Lulla

Swati Naik

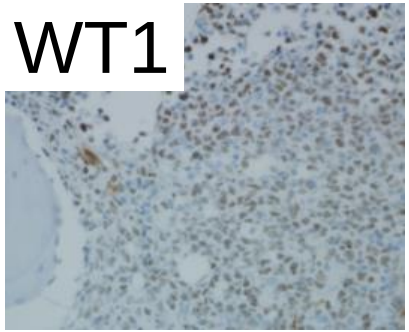
TAA T Cells for Relapse Post HSCT

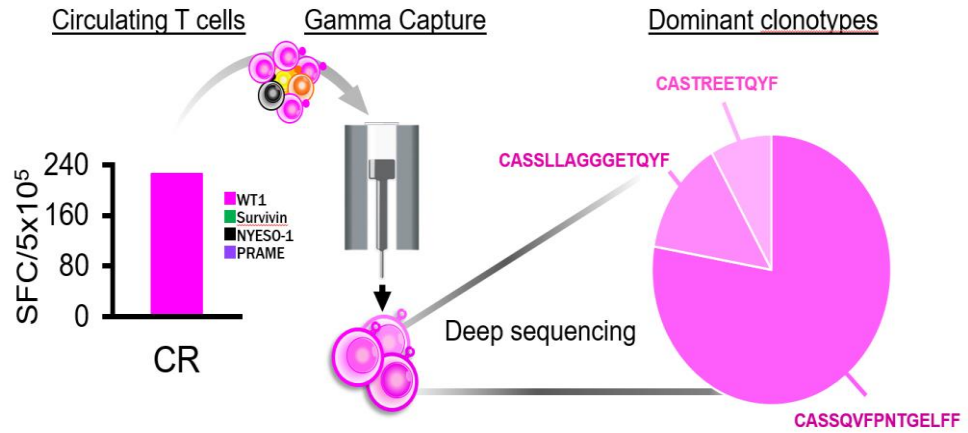
Extramedullary relapse AML





WT1





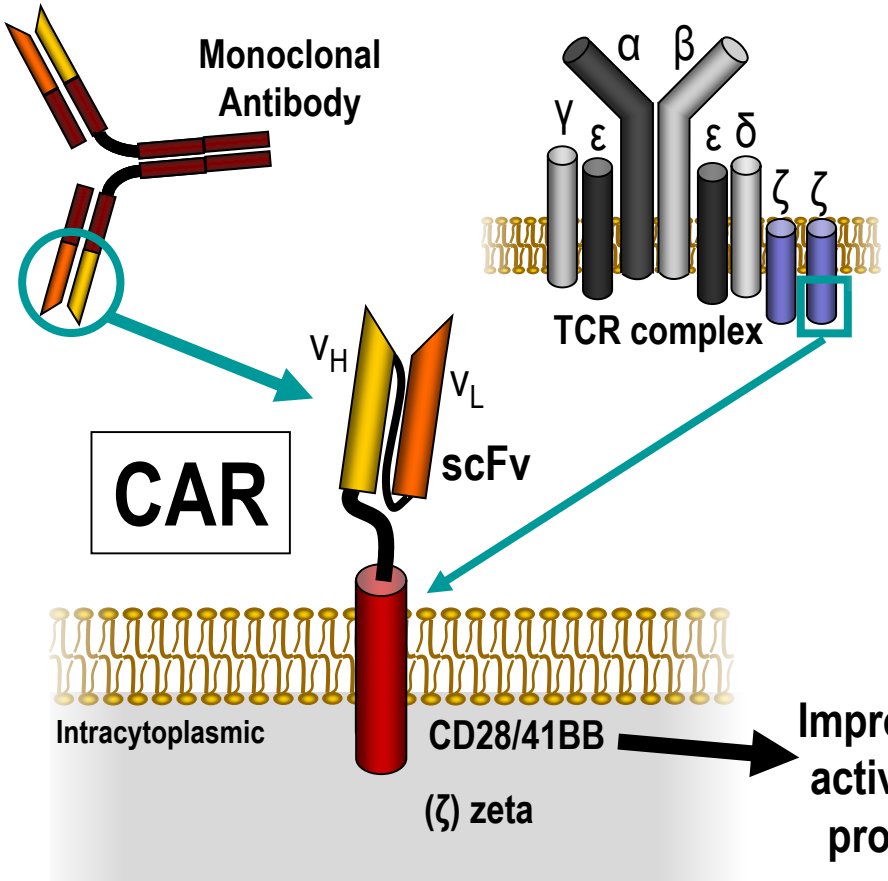
Implication

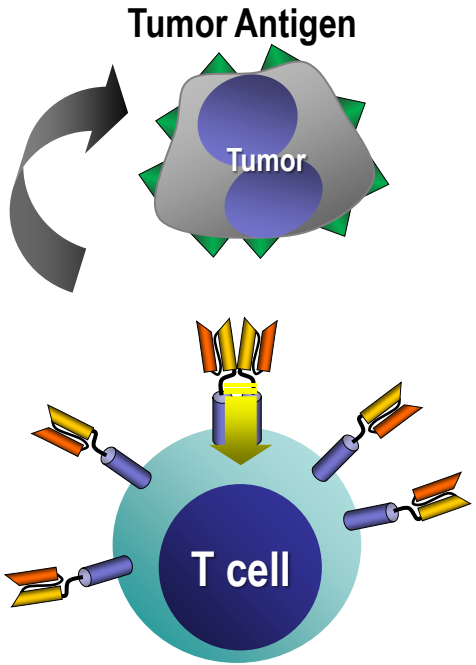
- T cells specific for WT1 have activity in AML
- Extend to neoantigens and AML specific mutations

MultiTAA T Cells - Summary

- Safe to date
- Feasible adjuvant and treatment
- In vivo expansion of tumor-specific T cells
- Antigen spreading
- Potential to extend to neoantigens
- Clinical benefit in lymphoma, myeloma and acute leukemia

Chimeric Antigen Receptors





Gross, Waks & Eshhar, PNAS 1989

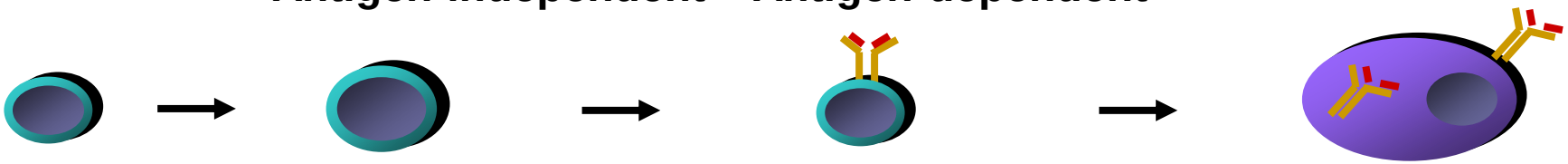
(Ramos & Dotti, Expert Opin Biol Ther 2011)

Advantages of CAR-modified T cells

- Retain most desired properties of T cells
  - Trafficking
  - Expansion/persistence
  - Effector Function
- MHC independent/unrestricted
- Can target carbohydrates and glycolipids or non-processed surface proteins

Selecting B-cell Antigens

Antigen-independent **Antigen-dependent**



HSC → **B lymphocyte precursor** → **Naïve mature B lymphocyte** → **Plasma cell**

CD19	**+**	**+**	**–/+**
CD20	**–**	**+**	**–/+**
CD22	**+**	**+**	**-/+**
CD38	**+**	**+**	**+++**
CD138	**–**	**–**	**+++**
sIg (κ/λ)	**–**	**+ (IgM,IgD)**	**–/+**

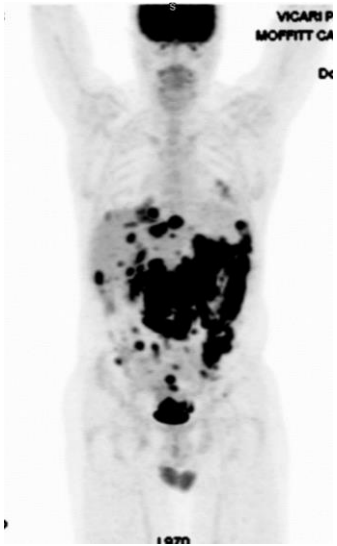
CD19 as a Target

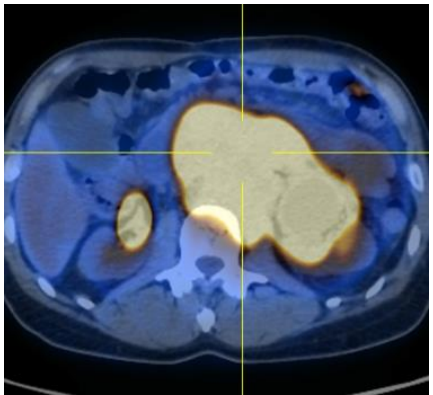
- Present on B lineage cells from the pro-B cell stage to mature B cells
- High expression most B lineage lymphoma
- NOT expressed on hematopoietic stem cells (or other tissues)
  - Should not be myelosuppressive effects
  - Should not be other organ toxicities
- Will cause depletion normal B cells

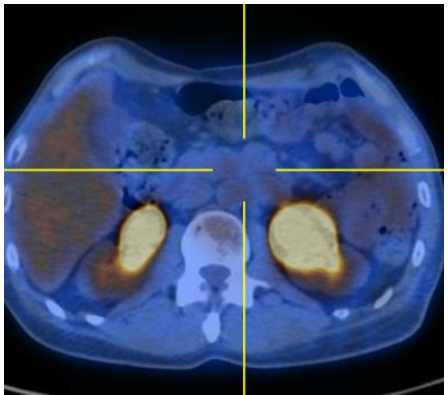
CD19 CAR-T cells for B cell malignancies

- Multiple Centers multiple CAR structures/vectors
- Extensive (>3 logs) expansion
- Persistence can be long-term
- **pre-B ALL** Up to 90% initial CR rate
- ***NH-Lymphoma***: 35% >12mth CR

A







Licensed Products

	Axicabtagene Ciloleucel (Yescarta)	Tisagenleuleucel (Kymriah)
Number of patients	101	93
Objective response	83%	52%
Complete response	58%	40%
Ongoing response	39%	
≥ Grade 3 CRS	11%	22%
≥ Grade 3 neurological events	32%	12%
References	Neelapu et al NEJM 2017 Locke et al Lancet Onc 2019	Schuster et al NEJM 2019

Real World Experience Axicabtagene Ciloleucel

	Zuma 1	17 center consortium real world patients
Number	101	165
% meeting ZUMA1 eligibility	100%	51%
Age, median	58	59
ECOG 0 or 1	100%	84%
ORR/CR	82%/58% (best)	79%/50% (Day 30)
Grade 3 or higher CRS	11%	7%
Grade 3 or higher ICANs	32%	31%

Nastoupil et al ASH 2018

CAR-T Therapy of Hematological Malignancy

- Successes of CAR T cells in Hematological Malignancy;

  CD19 CAR for CD19+ Malignancies

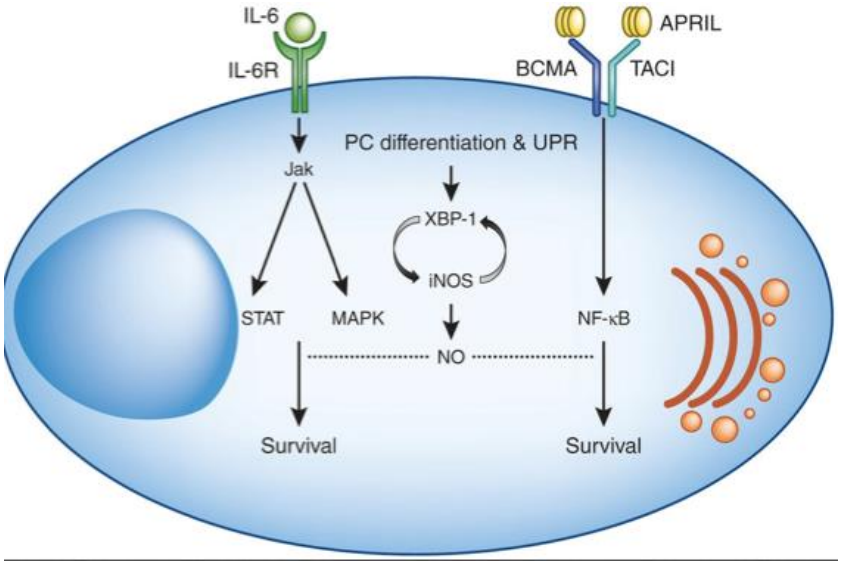
  BCMA CAR for myeloma

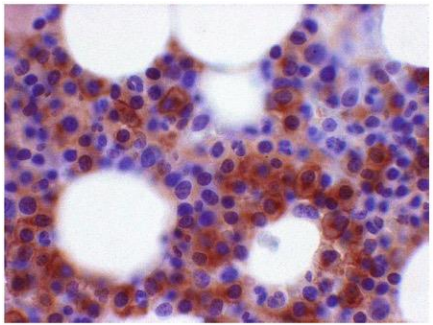
  Others?

BCMA is a Promising Target

B-Cell Maturation Antigen (BCMA) is member of the TNF receptor superfamily

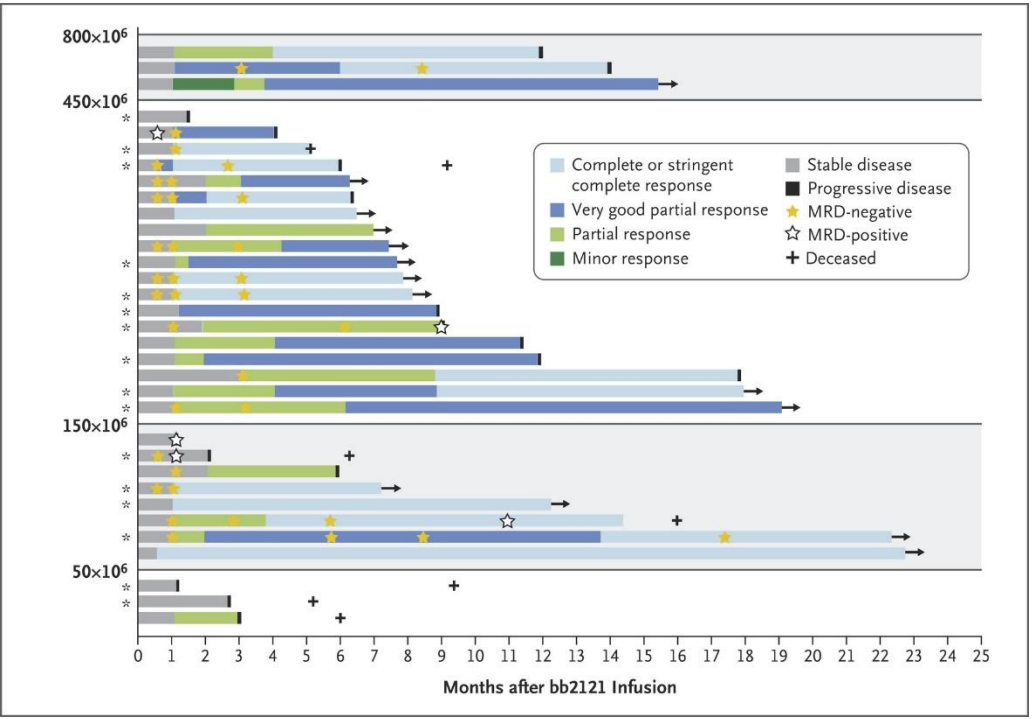
- Expressed nearly universally on multiple myeloma cells
- Expression largely restricted to plasma cells and some mature B cells
- Plays critical role in plasma cell survival

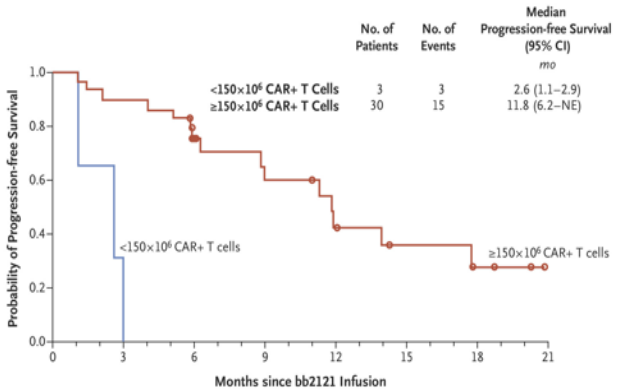




BCMA Expression on myeloma cells
(

Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma



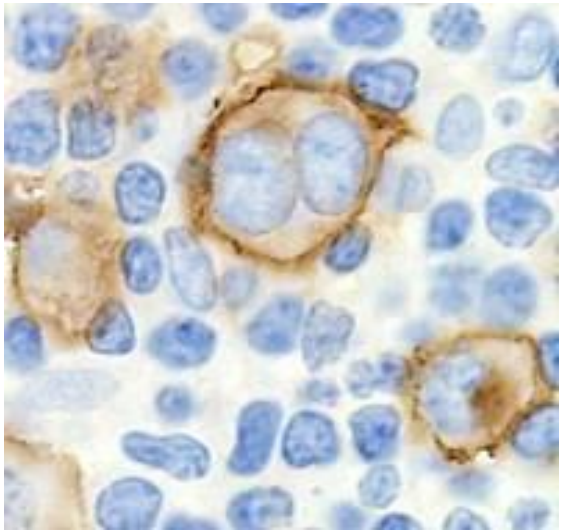


- Objective response rate 85%,
- 45% with complete responses
- Median progression-free survival 11.8 months

Raje et al NEJM 2019

CD30 as a Target

- Expressed by all HRS cells
- Antibody based immunotherapy
  –*Brentuximab vedotin*

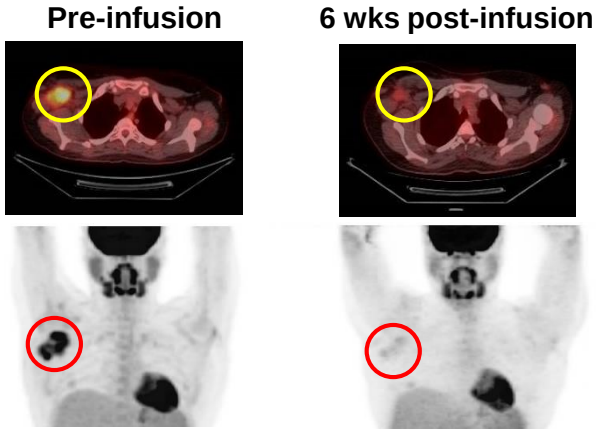


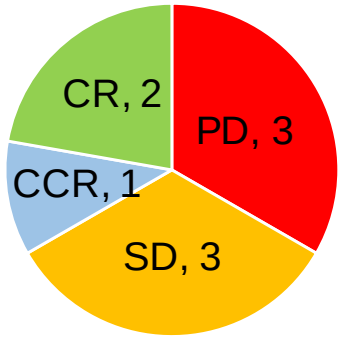
Barbara Savoldo

Carlos Ramos

CD30.CART Trial Summary

- Gender
  - 4 F
  - 5 M
- Diagnoses
  - HL
    - NS (6)
    - MC (1)
  - ALCL
    - ALK^+ (1)
    - ALK^- (1)
- Age
  - Median 30 yrs (range 20-65 yrs)
- Prior treatments
  - Median 5 regimens (range 3-9)
  - Brentuximab vedotin used in 7 patients
  - HDT/ASCT used in 6 patients

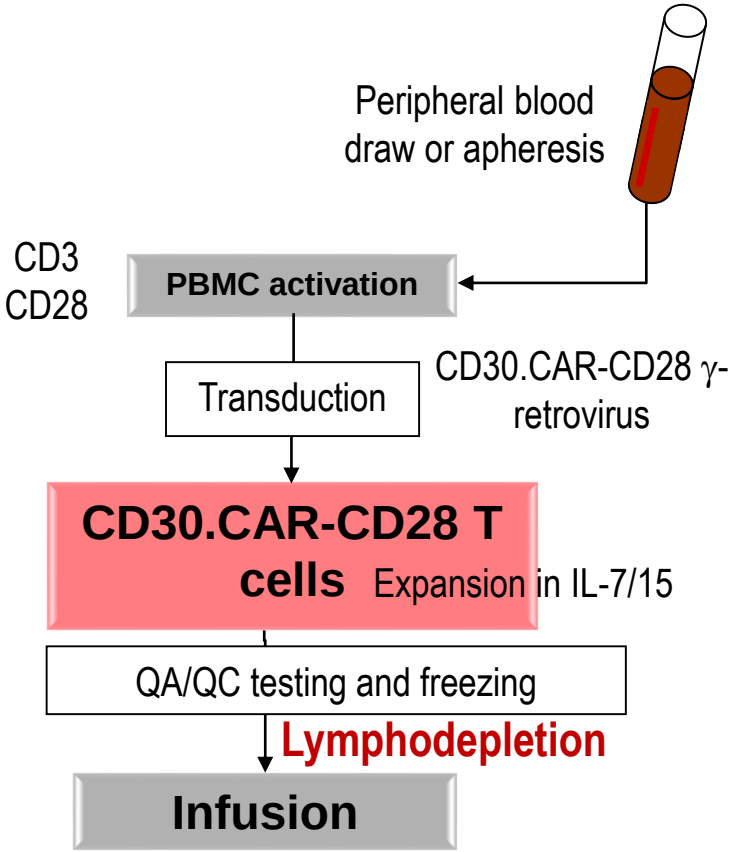




No significant toxicities

Ramos *et al.*, J Clin Invest 2017

RELY-30 Trial (NCT02917083)

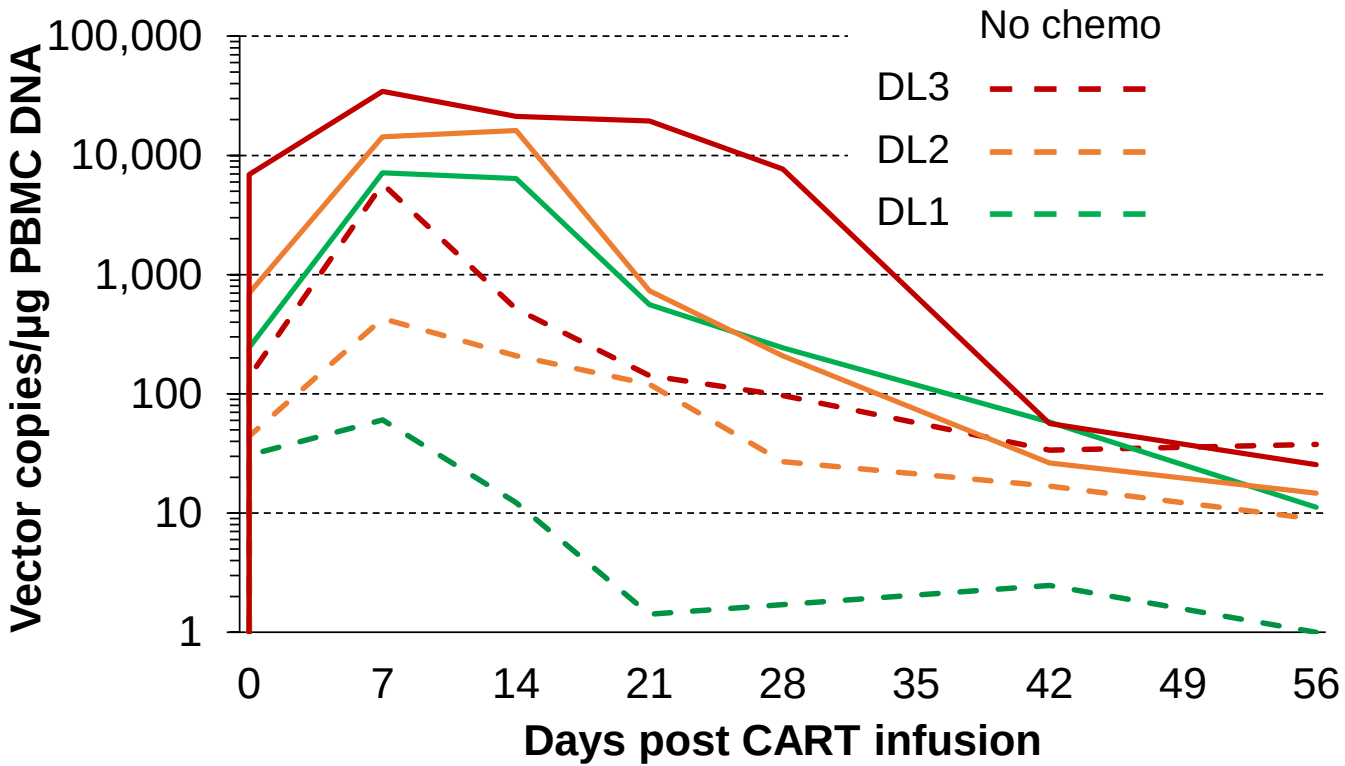


- Phase 1 trial
- $CD30^+$ malignancies
  - Active disease
  - Failure of standard treatment
- Dose escalation by continual reassessment
  - 2×10^7 (DL1), 1×10^8 (DL2), 2×10^8 (DL3) CAR^+ cells/m^2
- Single infusion
- Cyclophosphamide and fludarabine prior to CART infusion
- Primary objective: safety
- Secondary: response per Lugano
  - Initial assessment at week 6

RELY-30 Patients Characteristics

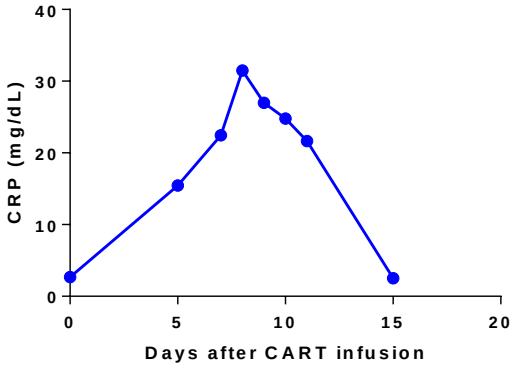
- Gender
  - 6 F
  - 8 M
- Diagnoses
  - HL
    - NS (13)
    - “NOS” (1)
- Age
  - Median 30 yrs (range 18-68 yrs)
- Prior treatments
  - Median 5 regimens (range 2-9)
  - PD-1 inhibitor in 13 patients
  - Brentuximab vedotin in 11 patients
  - HDT/ASCT in 9 patients

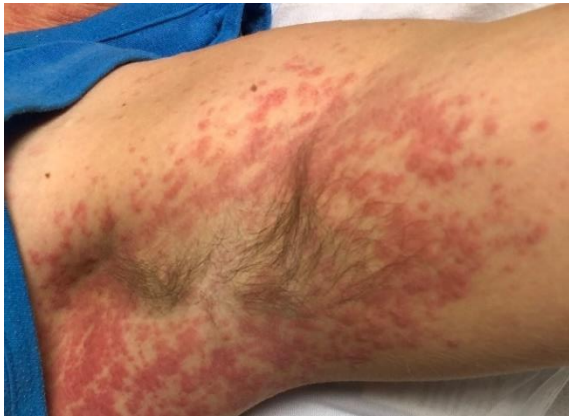
CD30.CART Expansion Is Increased By Lymphodepleting Chemotherapy

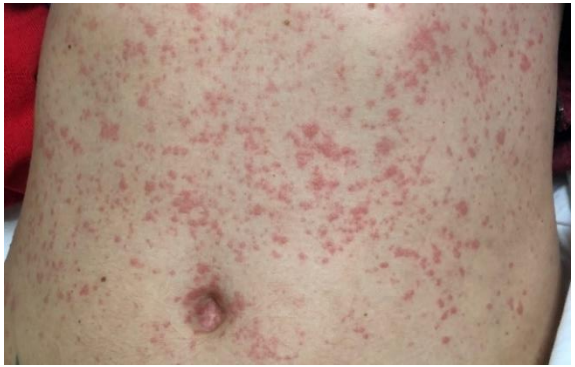


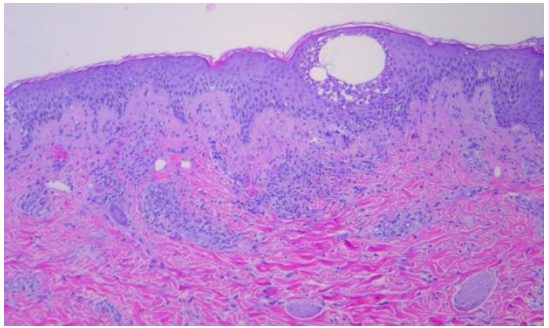
CD30.CART Toxicities (Patient #9)

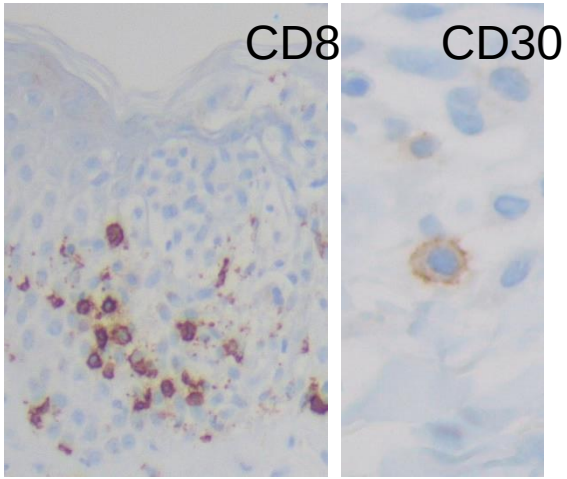
- Mild CRS (grade 1)
  - Supportive care only
- Maculopapular rash
- Transient cytopenias, nausea, alopecia (related to chemo)







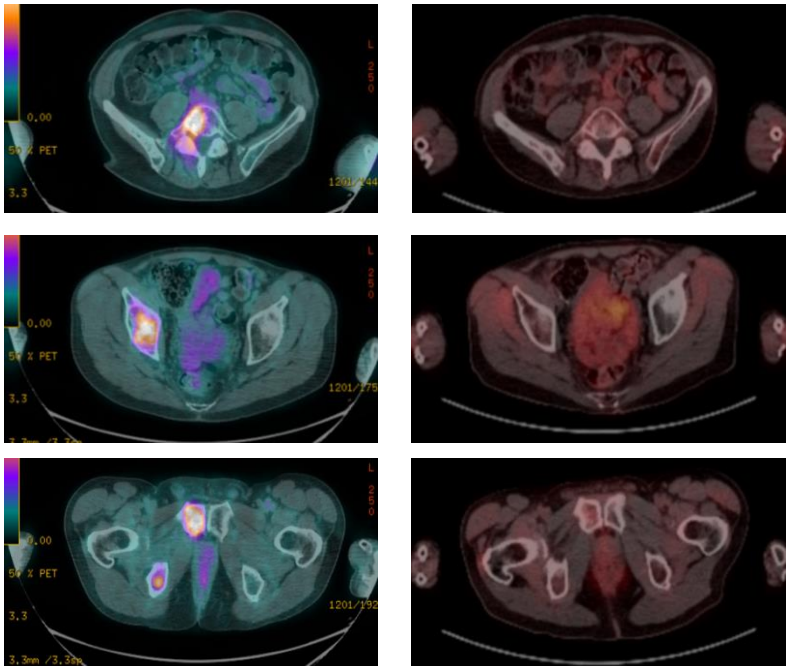




Outcomes: CD30 CAR Post Lymphodepletion

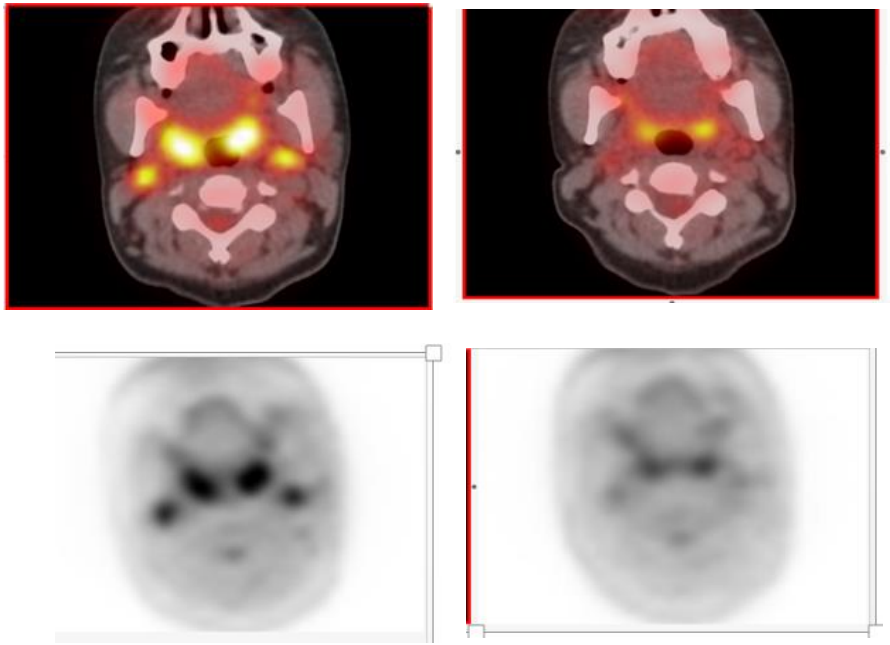
Pre-infusion

6 weeks post infusion

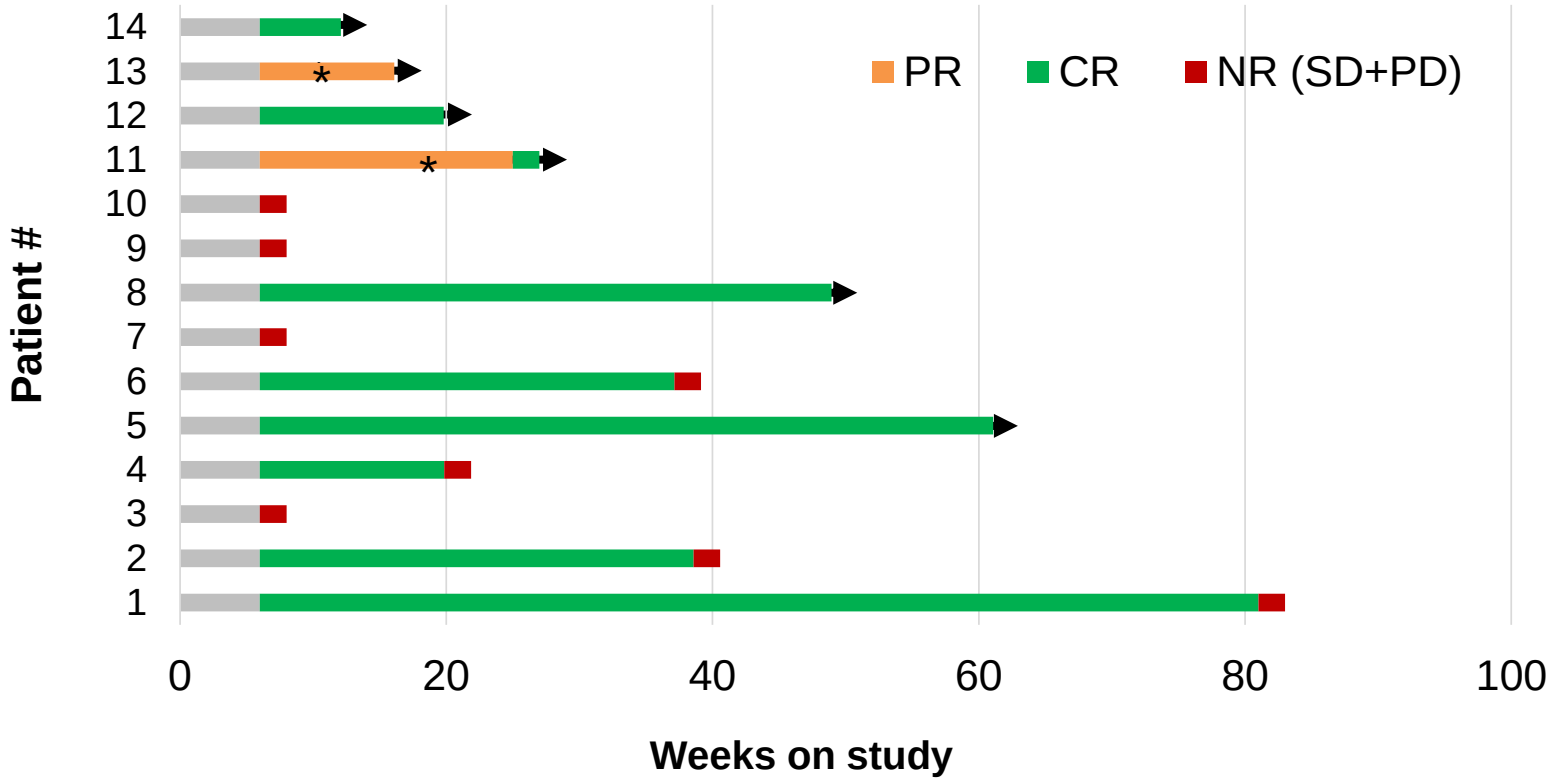


Pre-infusion

6 weeks post infusion



RELY-30 Outcomes



Conclusions

- Adoptive transfer of CD30.CAR-T cells is safe
- Expansion and persistence is dose-dependent
- Responses are improved with lymphodepleting chemotherapy
- Increased expansion may be associated with CRS and limited skin toxicity
- Follow-up is limited: response duration unknown
- Expansion cohorts are planned

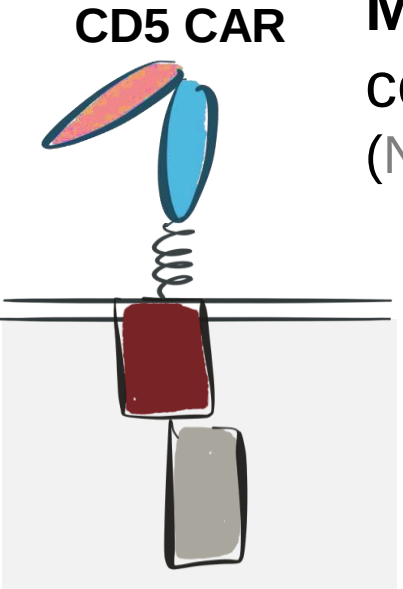
Limitations in Developing CAR-T for T-cell Malignancies

Fratricide of CAR T cells → Impaired expansion

Targeting normal T cells → Immune deficiency

Modification of malignant blasts → Tumor escape

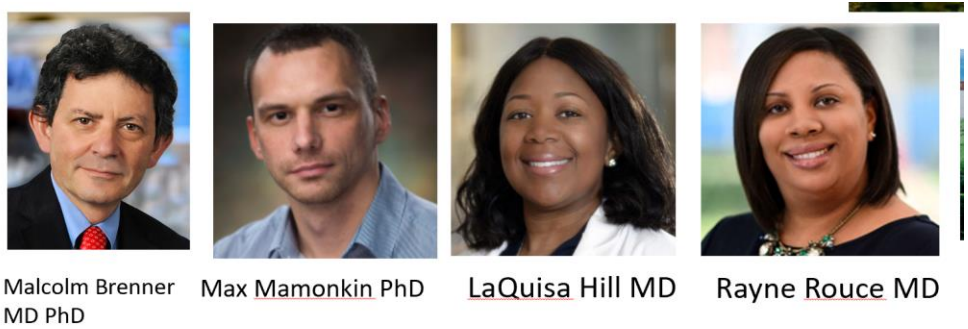
Clinical Study Of CD5 CAR T Cells



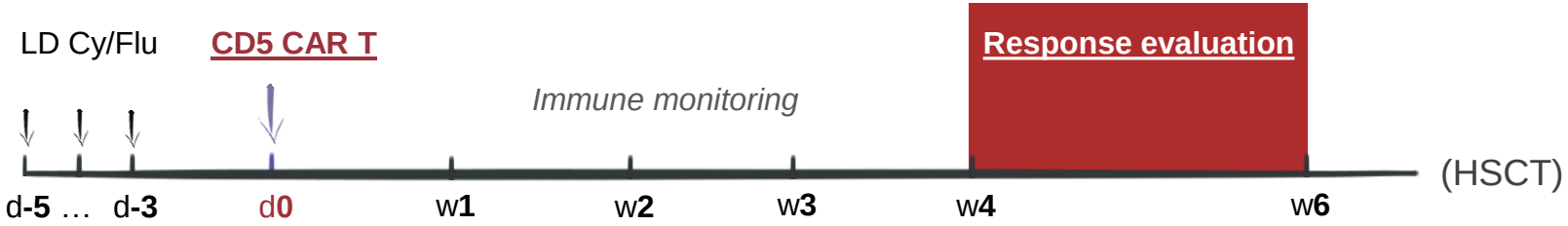
Mamonkin et al
Blood 2015

MAGENTA: Clinical trial of CD28.zeta CD5 CAR T cells in patients with r/r T-ALL or T-NHL (NCT03081910).

- Bridge to allo-transplant for adult and pediatric patients with CD5+ disease
- Single infusion of CAR T cells after Cy/Flu lymphodepletion



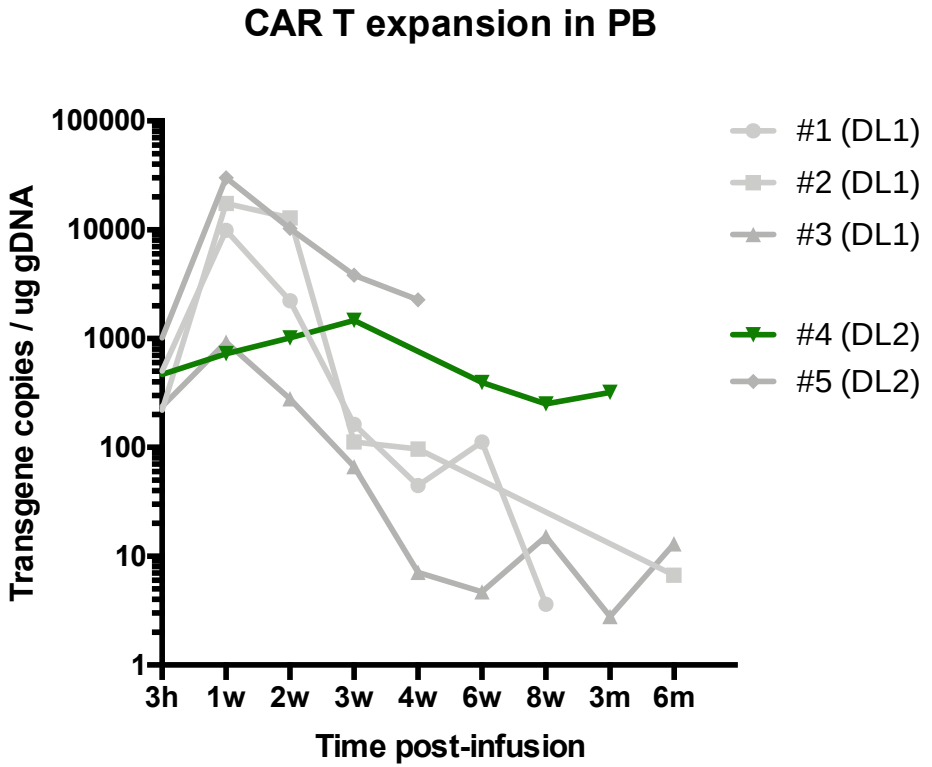
CD5 CAR T cells in T-cell malignancies: a Phase I study (MAGENTA)



ID	Age/Sex	Disease Type	Disease status	Dose Level
1	63 F	CTCL/Sezary	Relapse post-alloSCT	DL**1**: 1x10e7/m2
2	70 M	AITL	Relapse post-autoSCT	DL**1**: 1x10e7/m2
3	39 M	T-ALL	Primary Refractory	DL**1**: 1x10e7/m2
4	63 F	AITL	Relapse post-autoSCT	DL**2**: 5x10e7/m2
5	51 F	T-ALL	Relapse post-alloSCT	DL**2**: 5x10e7/m2
6	67 M	PTCL	Primary Refractory	DL**2**: 5x10e7/m2

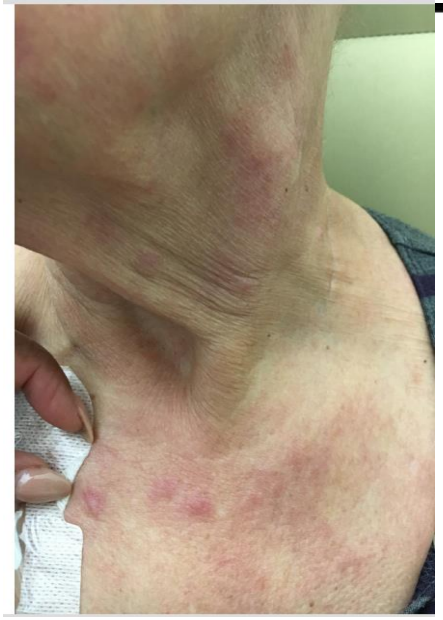
Patient 4: Relapsed Refractory AITL

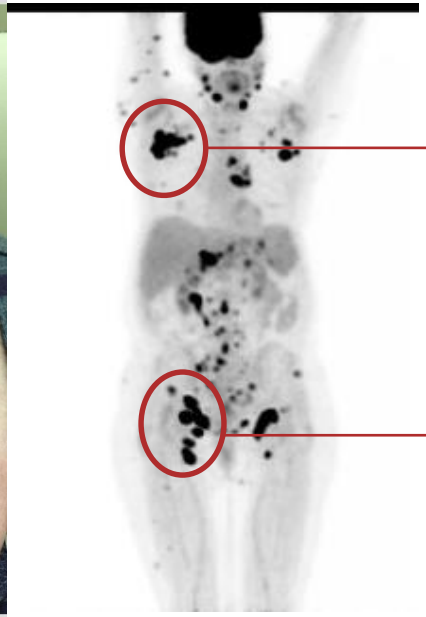
- 63 F; Relapsed chemorefractory AITL
- CHOEP ➡ CR with autoSCT as consolidation
- Relapse ➡ Pembro x 8 ➡ brentuximab x 2 ➡ Romidepsin ➡ ASTS-660 ➡ Pembro x 3 ➡ gemcitabine x 1
- Multiple metabolically active cutaneous, subcutaneous lesions and adenopathies at the time of enrollment



Patient #4: Week 4 Evaluation

Week 4

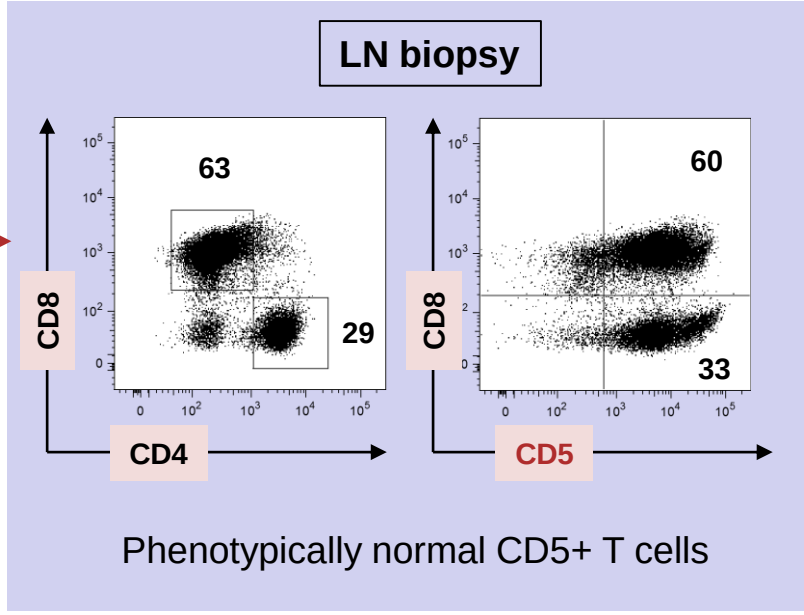




Transgene #

3,108 → *necrotic*

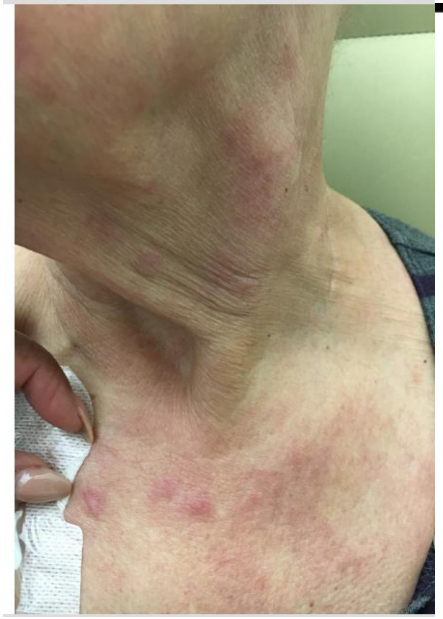
34,445 →

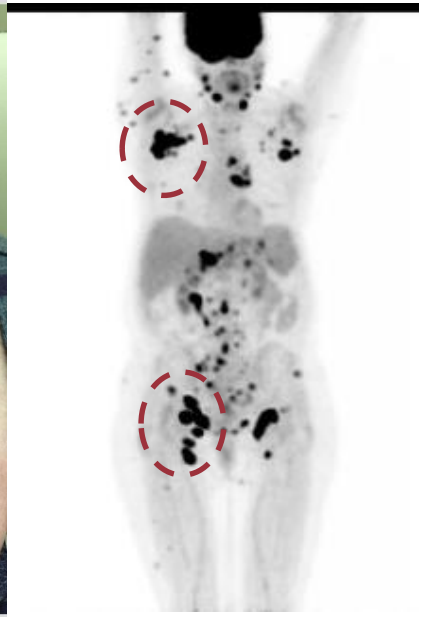


Phenotypically normal CD5+ T cells

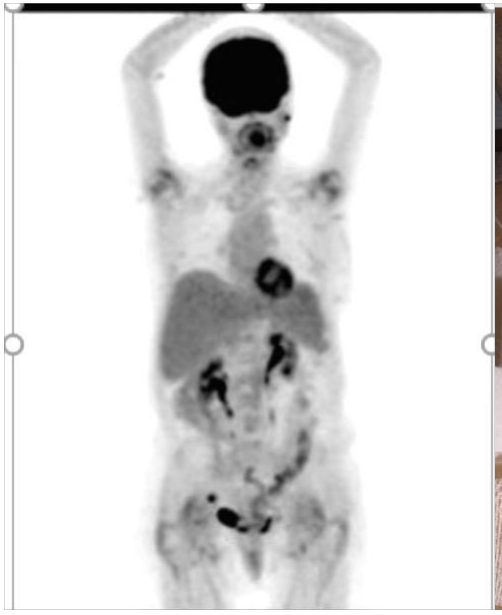
Patient #4: Most PET-active lesions resolved by week 8

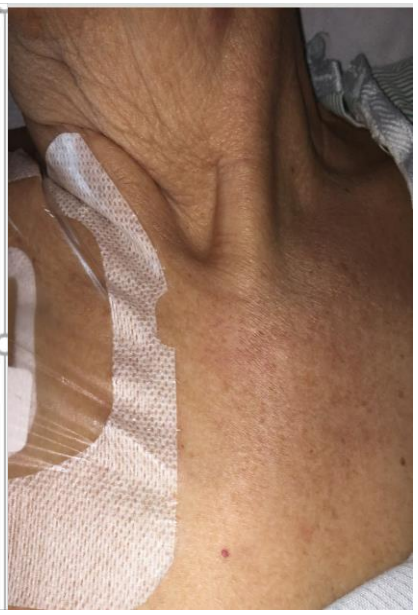
Week 4





Week 8

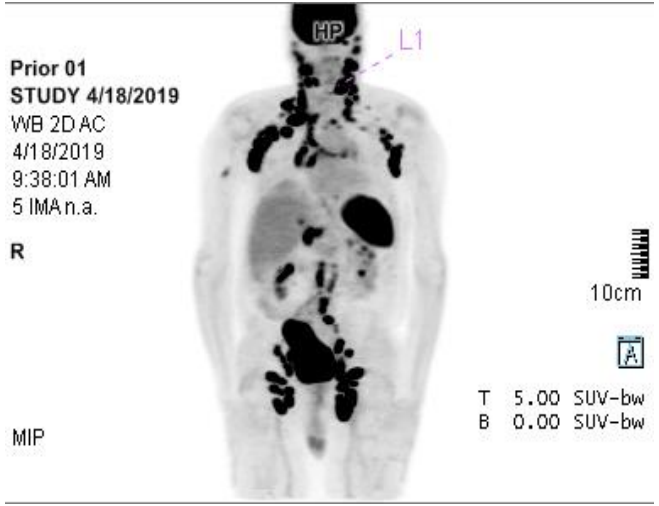




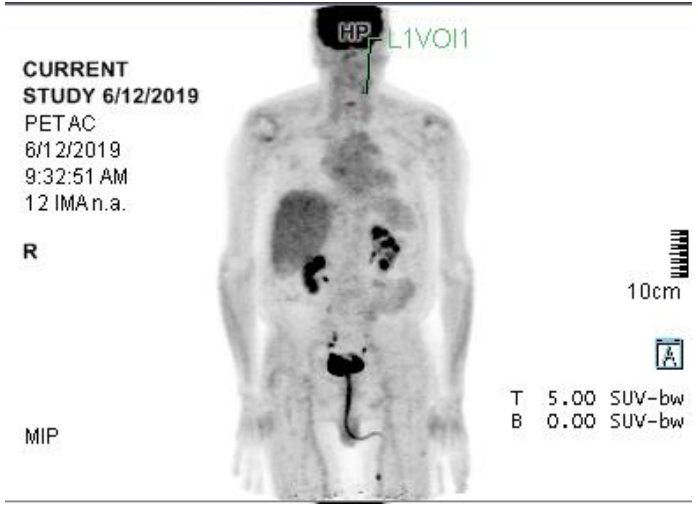
Repeated CD5 CAR T infusion ➡ Allo-HSCT

71M with R/R PTCL

PRE CAR-T infusion

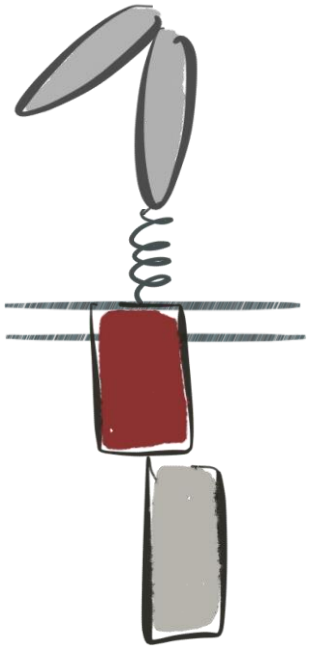


Week 4 post CAR-T infusion



CD5 CAR T cells in T-cell malignancies: a Phase I study (MAGENTA)

CD5 CAR

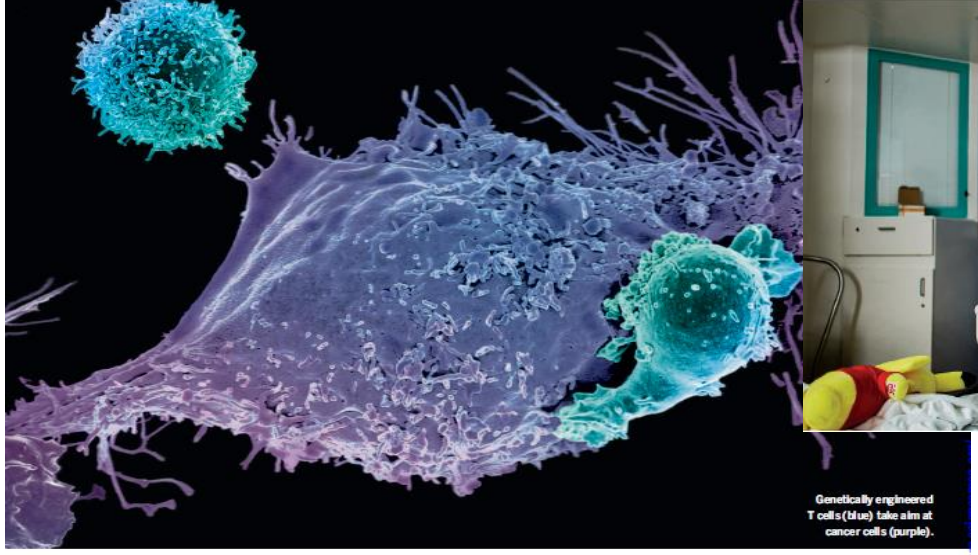


CD28.zeta

- CD5 CAR T cells are safe at current dose levels (1 – 5 x10^7/m^2) so far
- Early evidence of activity in T-cell malignancies
- No prolonged T-cell aplasia observed
- Dose escalation continues
- Adjusting the manufacturing process to further enhance potency

Conclusions

- 2nd generation CD19 CARTs can have remarkable activity against B-cell malignancies
- CARs can successfully travel beyond CD19
  - BCMA, CD5 and CD30
- Extension to myeloid and T cell disease requires strategy to mitigate effects on normal progenitors



Genetically engineered T cells (blue) take aim at cancer cells (purple).

SECOND CHAPTER

T cell therapy has successfully targeted blood cancers. A bigger challenge is to make it work on solid tumors

By **Jennifer Couzin-Frankel**

Last month, Roisin O'Cearbhaill, an Irish oncologist who looks younger than her 37 years, slipped on gloves and a protective gown and stepped through the doorway of a room in her hospital's intensive care unit. Patient No. 1 awaited her.

All other treatments had failed this woman, who is in her early 70s and has ovarian cancer. Now, she was about to be infused with her own T cells, the workhorses of the immune system, which had been removed and genetically engineered to fight her disease.

Like all first-in-human trials, O'Cearbhaill's is small and narrowly focused: She hopes to enroll just 15 women at her home base, Memorial Sloan Kettering Cancer Center in New York City, over the next 18 months, and she's testing mainly whether the treatment is safe. But it's hard not to fantasize about something more dramatic. Genetically engineered T cells have proven almost miraculously effective in some patients with blood cancers, including certain leukemias and lymphomas. Dozens of adults and children near death have been helped, and some remain healthy 4 or 5 years after treatment.

As researchers try to take T cell therapy in blood cancers from proof-of-principle to practical treatment, trials like O'Cearbhaill's present another looming test for the approach: Can engineered T cells also save people with solid tumors spreading through the breasts, lungs, brain, and ovaries? Solid tumors are far more common than blood cancers and, if they metastasize, can be very difficult to halt. Immunotherapy drugs called checkpoint inhibitors are approved or in testing for a number of solid tumors—but even there, the fraction that responds is often modest and response doesn't always last. O'Cearbhaill and colleagues at Sloan Kettering, around the country, and beyond hope this first wave of clinical trials will help chart a path toward success for a strategy that could upend cancer treatment as we know it.

In a sarcoma trial at Texas Children's Hospital, pediatric oncologist Stephen Gottschalk was heartened to see that engineered T cells persisted for up to 6 weeks—considered an achievement in this setting, even though they can hang around for years in people with leukemia.

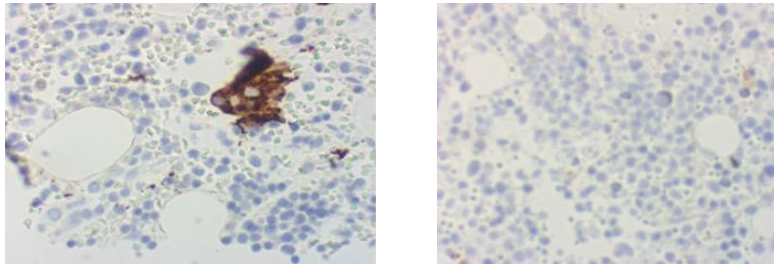
So far, "it hasn't worked very well," Albelda says, sounding gloomy. His team recently finished two trials in patients with mesothelioma, lung cancer, and pancreatic cancer, targeting a protein called mesothelin. The therapy seemed safe but, at best, minimally effective."I think a lot of people are in that same boat," he says.

Published Clinical CART Studies in Solid Tumors

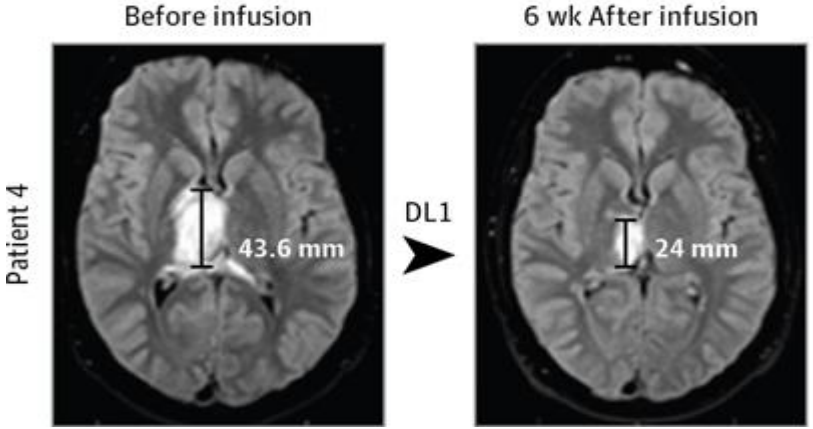
Target	Disease	Outcome
FR	Ovarian Cancer	No activity (Clin Can Res, 2006)
CAIX	Renal Cancer	On target/Off cancer tox (JCO, 2006)
CD171	Neuroblastoma	1/6 PR (Mol Ther, 2007)
GD2	Neuroblastoma	3/11 CR (Nat Med, 2008)
HER2	Colon Ca	1 Death (Mol Ther, 2010)
Mesothelin	Mesothelioma, Pancreas Ca	2/14 with tumor shrinkage (Cancer Imm Res 2014
HER2	Sarcoma	4/17 SD (JCO, 2015)
IL13Ra2	GBM	2/3 transient response (Clin Can Res, 2015) 1 impressive regression (NEJM, 2016)
HER2	GBM	1/17 PR & 7/17 SD (JAMA Onc, 2017)
EGFRvIII	GBM	1/10 SD (STM 2017)

CARs in Solid Tumors: Responses

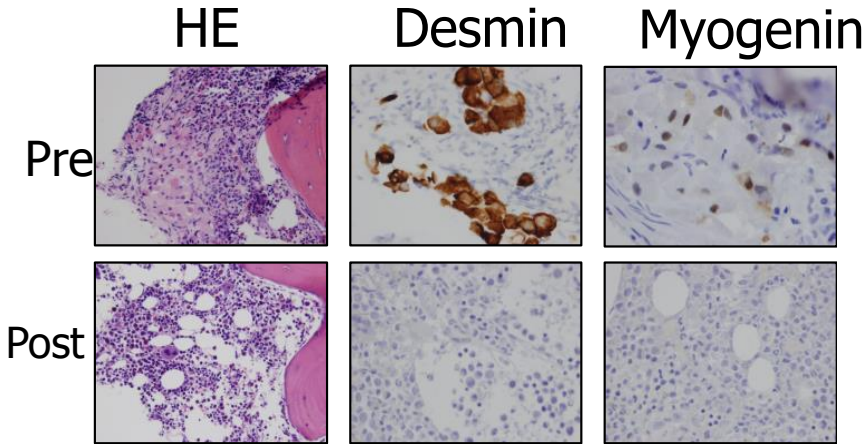
GD2 CARTs in neuroblastoma



Her2Neu CARTs in glioblastoma

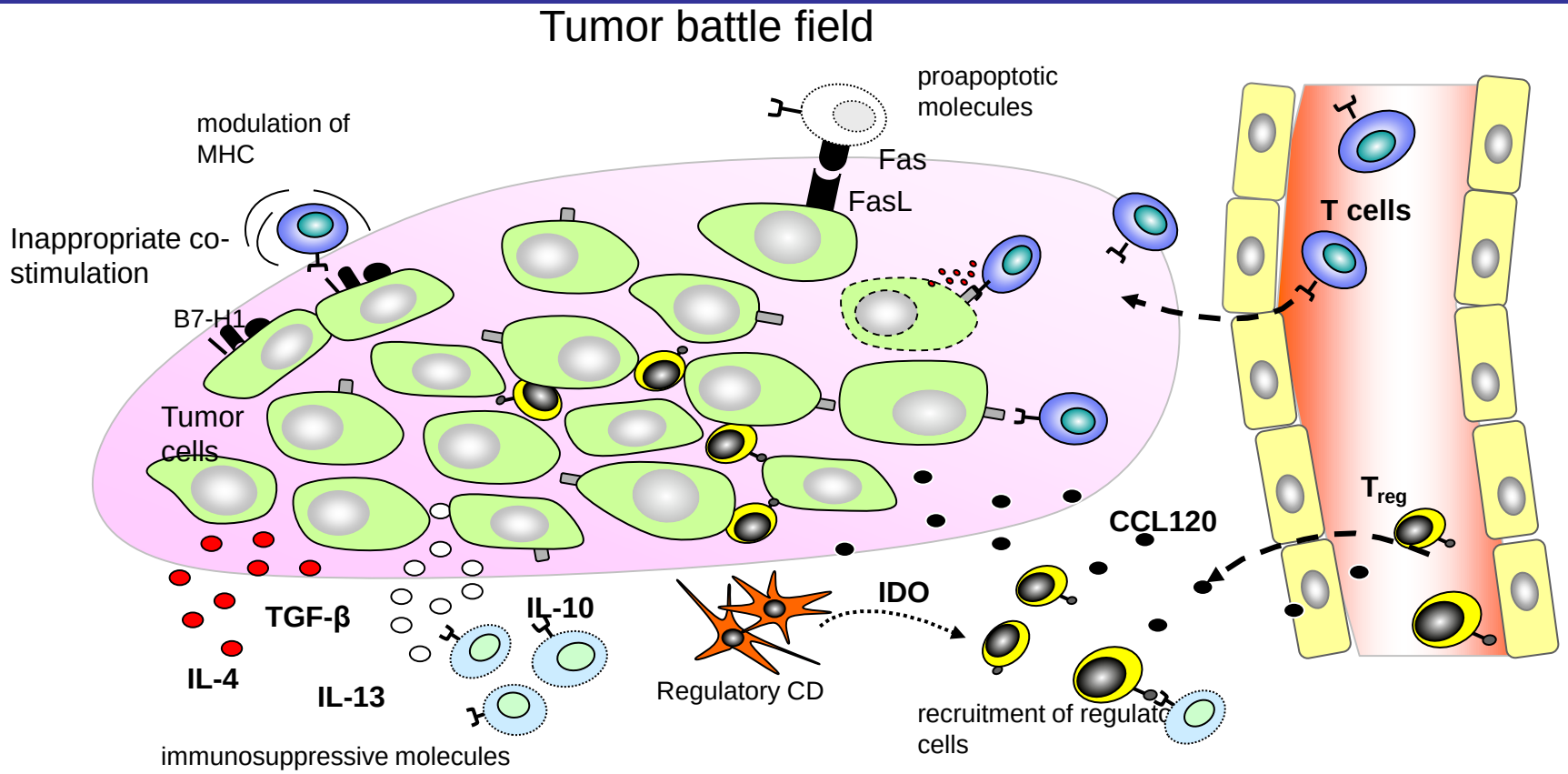


Recurrent/refractory Rhabdomyosarcoma: CR post HER2-CART



Malcolm Brenner, Stephen Gottschalk, Nabil Ahmed, Meena Hegde

Tumor Microenvironment

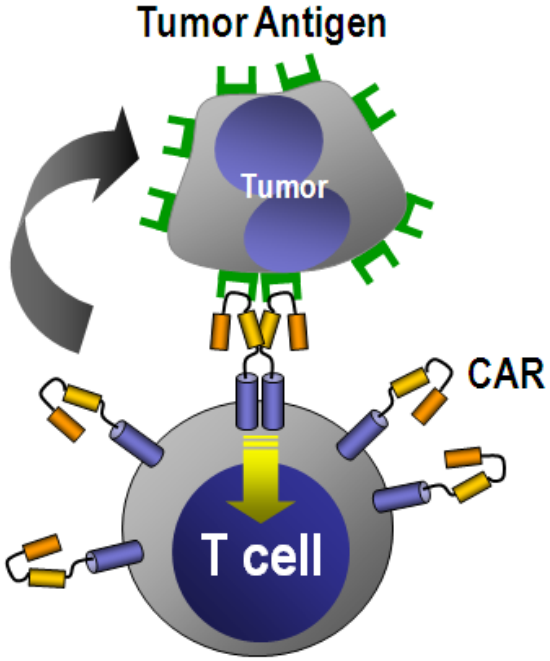


CAR-T Therapy for Solid Tumors

- Need broad response that evolves with tumor and tumor microenvironment
- Need to convert “cold” tumor to “hot” tumor
- Overcome tumor evasion strategies

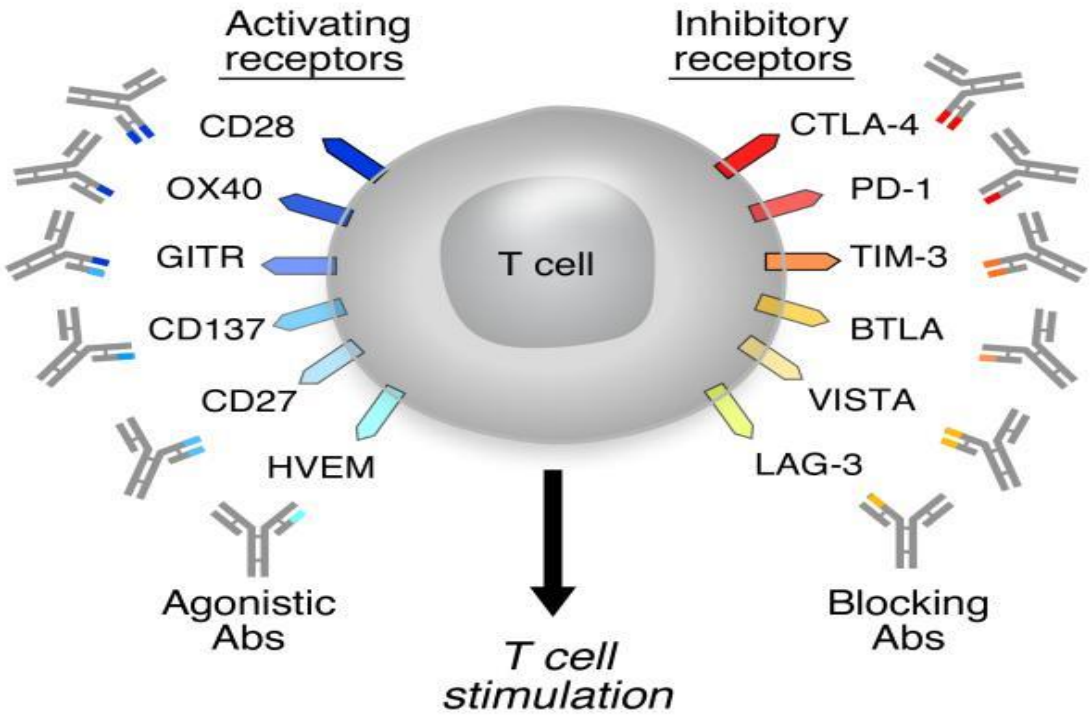
CAR T cells for Treatment of Cancer

Genetic Modifications
iC9 suicide gene
DN TGFßR
cIL7
IL15
Il4/IL7



CAR Targets
GD2
CD19
Her2Neu
Kappa
CD30
CD5
Glypican 3
CLL-1
PSCA
CD7
IL13R
MUC1

Combination Therapies

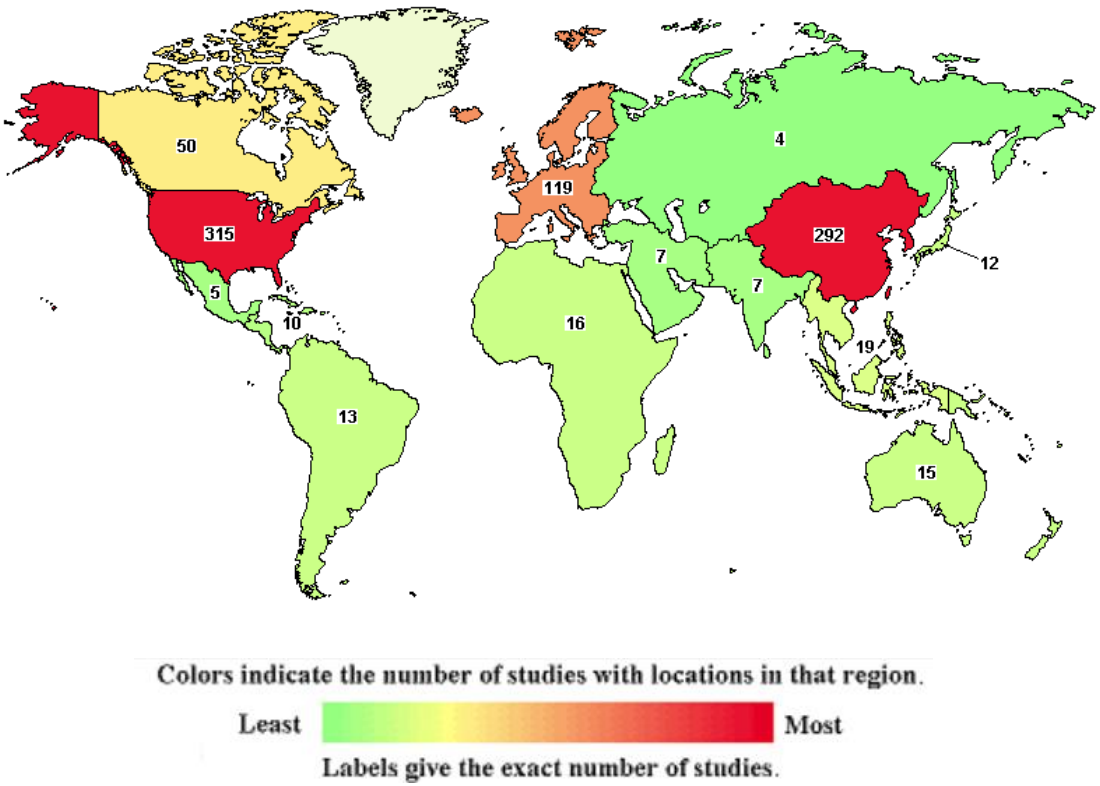


- Combinations
  - Other Immune modulators
  - Oncolytic viruses

Future Directions

- Combination CAR-T cells and
  - checkpoint inhibitors
  - other immunomodulatory agents
  - oncolytic viruses
- Genetic strategies to enhance function and overcome tumor evasion mechanisms
- Targeting multiple antigens

Geographic Distribution CAR studies



CAR-T search on clintrials.gov
827 trials listed as of September 4, 2019

Cell and Gene Therapy 2017

FDA approvals for

- Tisagenleuleucel (Kymiah) - CD19 CAR T cells for pediatric ALL
- Axicabtagene Ciloleucel (Yescarta) CD19 CAR T cells for adult NHL
- Voretigene neparvovec-ryzl (Luxturna) for inherited retinopathy due to RPE65 mutations

Trials that Produced Approvals

ELIANA: Novartis Pediatric ALL Study with Kymriah

- CR rate of 83%
- 75% ongoing responses at 6 months
- 64% in CR at 12 months

ZUMA-1: Kite B-NHL Study with Yescarta

- ORR of 82% with 49% CRs
- 41% ongoing responses at 3 months
- 36% in CR at 6 months

DRUG DEVELOPMENT

Safety concerns blight promising cancer therapy

As the first T-cell treatments for tumours near US approval, researchers race to engineer less-toxic versions.

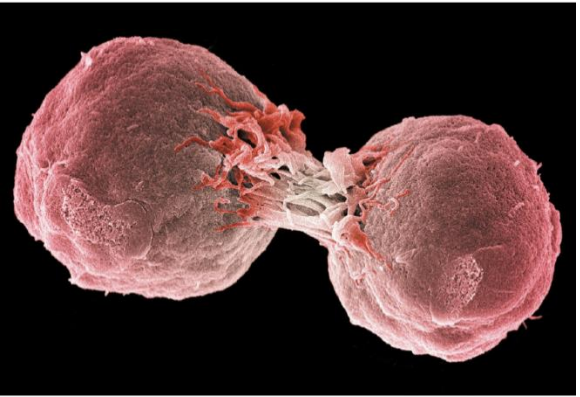
BY HEIDI LEDFORD

A groundbreaking treatment that arms immune cells called T cells to battle cancer is barrelling towards regulators, fuelled by unprecedented clinical success and investor exuberance.

But progress of the therapy, called CAR-T, has been marred by its toxicity; several deaths have been reported in clinical trials. Even as the first company readies its application to the US Food and Drug Administration (FDA) — expected by the end of the year — researchers are hard at work to make the supercharged T cells safer.

Doing so is crucial to expanding the use of the therapy to more people, says Anthony Walker, a managing partner at Alacrita, a consulting firm in London. "Right now it is heroic medicine," he says — a gruelling treatment deployed only in people for whom all else has failed. "Patients are taken sometimes to within an inch of their lives."

Most CAR-T procedures begin by harvesting a patient's white blood cells and sifting out the T cells. Those T cells are engineered to recognize cancer cells, and then infused into the patient, ready to do battle. The approach has shown remarkable success against leukaemias and lymphomas: in one



Adverse Events with CD19 CARs

- Cytokine Release Syndrome (CRS)/ Macrophage Activation Syndrome
- Immune effector cell-associated neurotoxicity syndrome (ICANS)

CRS/ICANS Toxicities by Organ System

Neurologic

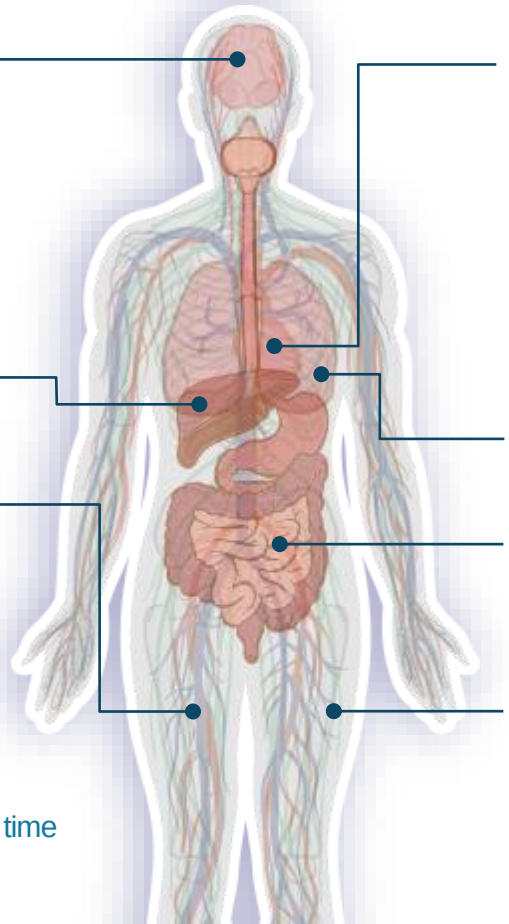
- Headaches
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Tremor
- Dysmetria
- Myoclonus
- Facial Nerve palsy
- Seizures

Hepatic

- Transaminitis
- Hyperbilirubinemia

Hematologic

- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile Neutropenia
- Lymphooenia
- B-Cell Aplasia
- Elevated D-Dimer
- Hypofibrinogenemia
- Dissembled Intravascular Coagulation
- Hemophagocytic Lymphohisticyclosis
- Prolonged Prothrombin time
- Prolonged Activated Partial Thromboplastic time



Cardiovascular

- Tachycardia
- Widened pulse pressure
- Hypotension
- Arrhythmias
- Decreased left ventricular ejection fracture
- Troponinemia
- QY prolongation

Pulmonary

- Tachypnea
- Hypoxia

Gastrointestinal

- Nausea
- Diarrhea
- Emesis

Musculoskeletal

- Myalgias
- Weakness
- Elevated creatine kinase

Constitutional

- Fevers
- Rigors
- Malaise
- Fatigue
- Anorexia
- Aethralgais

Renal

- Acute kidney injury
- Hyponatremia
- Hypokalemia
- Hypophosphatemia
- Tumor lysis syndrome

blood

ELIANA Trial (in B-ALL): CRS

	All Patients with CRS N=49
Time of onset (days)*	3 (1–22)
Duration of CRS (days)*	8 (1–36)
Admitted to ICU**	59%
ICU stay (days)*	8 (1–34)
Anti-cytokine therapy	51%
High dose vasopressors	33%
Invasive ventilation	20%
Dialysis	12%

*median/range

** ICU admission for **all patients** : **46.8% (29/62)**

Grupp, et al. ASH 2016

ZUMA-1 Summary of Adverse Events

Adverse Event, n (%)	Cohort 1 (n=73)	Cohort 2 (n=20)	Total (N=93)
Grade ≥3 adverse event	68 (93)	18 (90)	86 (92)
Grade ≥3 cytokine release syndrome	10 (14)	2 (10)	12 (13)
Grade ≥3 neurologic events (NE)	18 (25)	9 (45)	27 (29)
Fatal events excluding PD 2 of 3 KTE-C19-related	1 (1)	2 (10)	3 (3)

- **CRS and NE were generally reversible**
  - 38% received tocilizumab, 17% received corticosteroids, 17% received both
- **Grade 5 events occurred in 3 patients (3%)**
  - KTE-C19-related: HLH (Cohort 1) and cardiac arrest (Cohort 2) in the setting of CRS
  - KTE-C19-unrelated: pulmonary embolism (Cohort 2)

Neelapu et al ASH 2016, #LBA-6

FDA Approved August 30, 2017

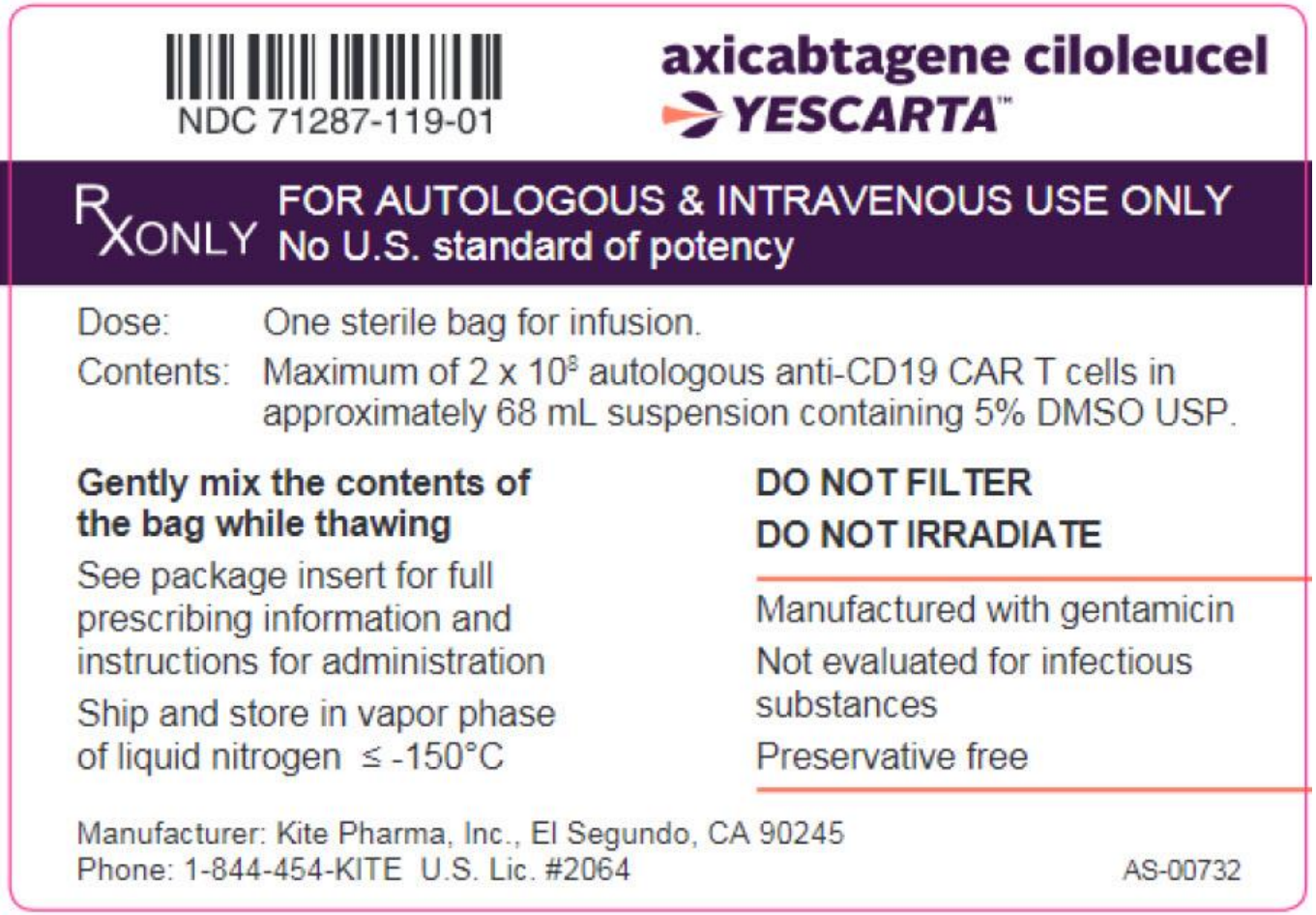
Relapsed/Refractory Pediatric and Young Adult ALL up to age 25 years

$475,000 per product

Risk Evaluation and Mitigation Strategy (REMS) mandated by FDA for CRS/ICANS

- **Dedicated prescribers who are trained in the toxicities**
- **Ensure that hospitals and clinics have immediate access to tocilizumab**

FDA Approved 10-17-2017 $373,000 per product



Adults ≥18 yrs. with Relapsed/Refractory:

- **DLBCL**
- **1^0 Mediastinal LCL**
- **DLBCL arising from Follicular NHL**

REMS program mandated by FDA

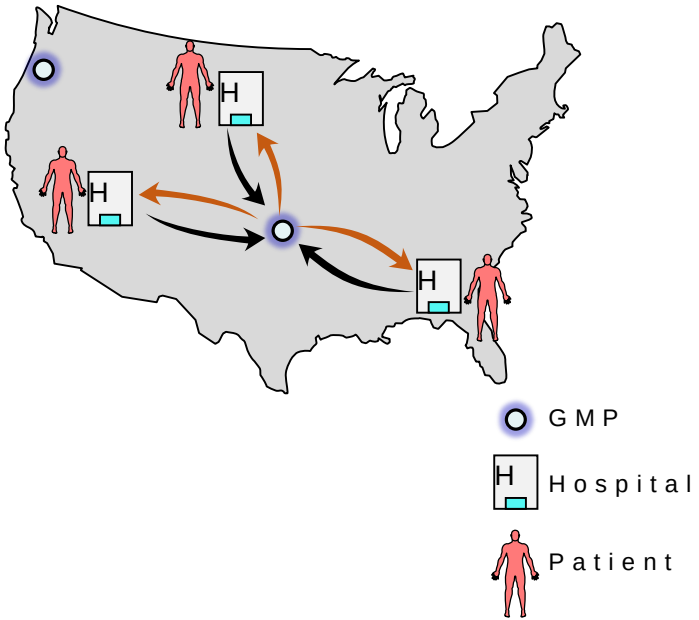
Cell and Gene Therapy 2017

FDA approvals for

- Tisagenleuleucel (Kymiah) - CD19 CAR T cells for pediatric ALL $475,000
- Axicabtagene Ciloleucel (Yescarta) CD19 CAR T cells for adult NHL $373,000
- Voretigene neparvovec-ryzl (Luxturna) for inherited retinopathy due to RPE65 mutations $850,000

Commercial CAR Products

"Living drug" with significant side effects"



Infrastructure to Access Therapy

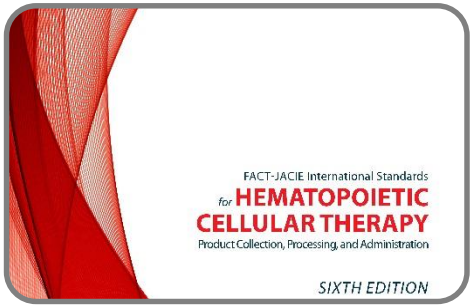
- Apheresis center & tertiary hospital
- Local cell processing facility to assist with handling
- Contract with Pharma company
- Agreement with insurers
- Expertise in handling complications
- REMs trained and approved prescribers

Commercial Products

- Requires lymphodepletion, cell infusion and aftercare
- Long term follow-up
  - Data reporting - CIBMTR cell therapy forms
- FACT Immune Effector Standards define required support
  - Interaction with third party GMP facilities
  - Chain of custody
  - Care of complications

FACT Standards for Immune Effector Cells, First Edition

- Common Standards + Immune Effector Cell-Specific Standards
- Apply to programs *only* performing immune effector cell therapy



FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration, Edition 6.1

- HCT Standards + Immune Effector Cell-Specific Standards
- Apply to transplant units that may or may not administer immune effector cells

HEALTH NEWS JULY 30, 2019 / 10:07 PM / 10 DAYS AGO

Expensive Gilead, Novartis cancer therapies losing patients to experimental treatments

Deena Beasley

6 MIN READ

LOS ANGELES (Reuters) - Unusually high numbers of U.S. lymphoma patients are choosing experimental treatments over expensive cell therapies sold by Gilead Sciences Inc (GILD.O) and Novartis AG (NOVN.S), new data shows, helping explain why sales of the two products have not met rosy expectations.

Vizient analyzed health insurance claims from 58 major U.S. hospitals, including most of the centers authorized to administer CAR-Ts. The consultancy found that medical bills for clinical trial patients, who receive the cell therapies free of charge from the drugmaker, were about 50% percent lower than costs for people treated with Yescarta or Kymriah on a commercial basis.

Medicare Coverage

- August 7, 2019, the Centers for Medicare & Medicaid Services (CMS) issued a final National Coverage Determination (NCD) memorandum for CAR-T therapy
- Administered in health care facilities enrolled in the Risk Evaluation & Mitigation Strategy (REMS) Program
- Coverage for FDA-approved indications
- Will fund 65% cost

Commercial CAR-T Cell Therapy: Current State of the Art

- ≥50% of patients with refractory B cell malignancies showing durable complete responses to CD19-CAR T cell therapy

- Potent therapy, but associated with unique toxicities:
  - Cytokine Release Syndrome (CRS; high fevers, hypotension, hypoxia, multi-organ damage)
  - Immune effector cell-associated neurotoxicity syndrome (aphasia, encephalopathy, seizures)

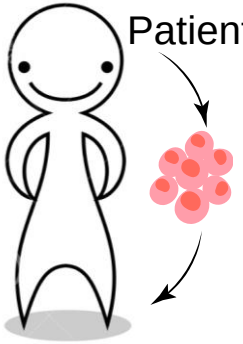
Future Directions: Reduce Toxicity

- Use earlier in course disease
- Earlier treatment with Tociluzumab and steroids
- Evaluation novel strategies

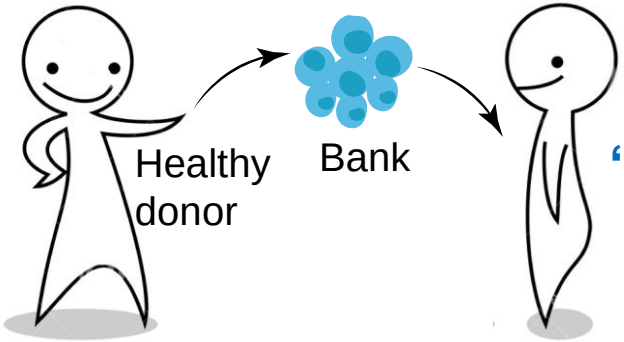
Future Directions: Improve accessibility

- “Off the shelf” Third party cell
  - Gene edited T cell
  - Multivirus specific T cell
  - Non alloreactive Immune cell populations
    - NK cell
    - NK-T cell

Autologous vs Allogeneic CAR-T Cells



Autologous cell product



Allogeneic 'off-the-shelf' (OTS) cell product

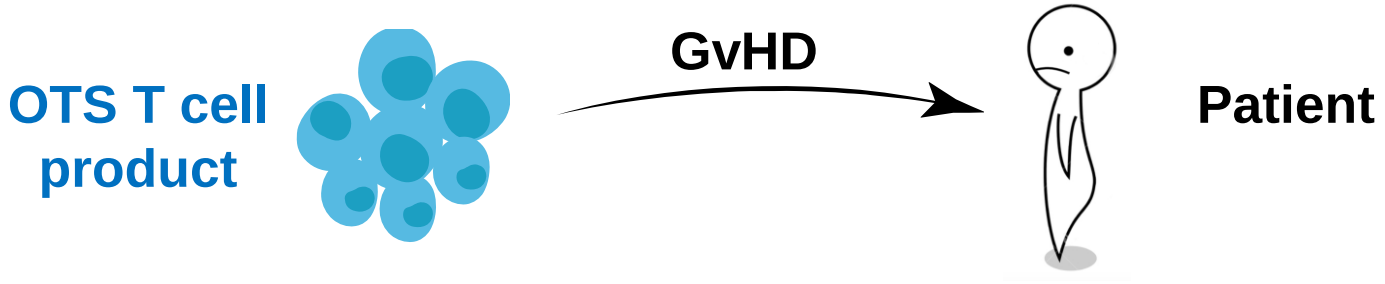
Limitations:

- Patient-specific, variable quality
- Time-consuming
- Expensive

Address limitations of autologous products:

- Predictable functionality
- Readily available
- Less expensive

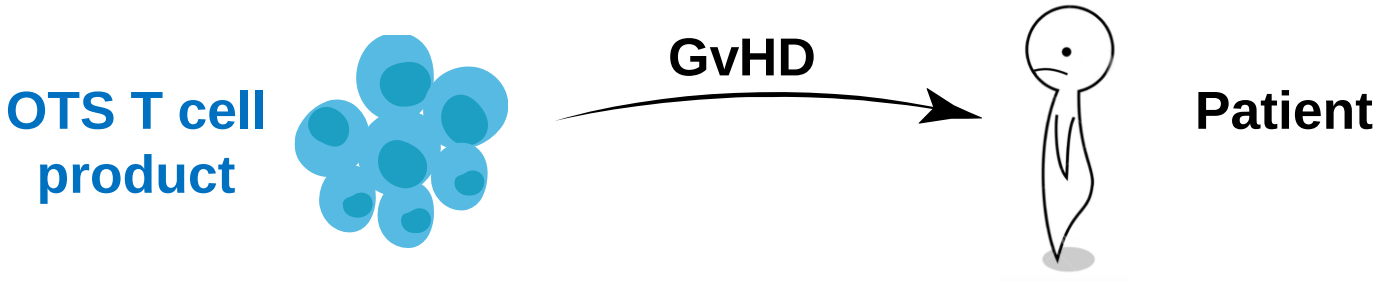
Challenges Using Allogeneic OTS T Cells



- **OTS T cells can attack normal host tissues (GvHD).**

Solutions: Manufacture CAR T cells without endogenous TCR/CD3 complex- but lose TCR functionality

Challenges Using Allogeneic OTS T Cells



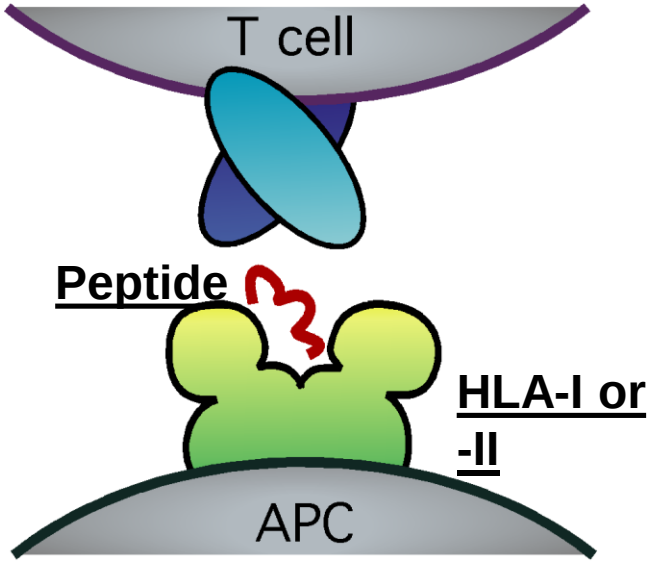
- **OTS T cells can attack normal host tissues (GvHD).**

Solutions: Manufacture CAR T cells without endogenous TCR/CD3 complex

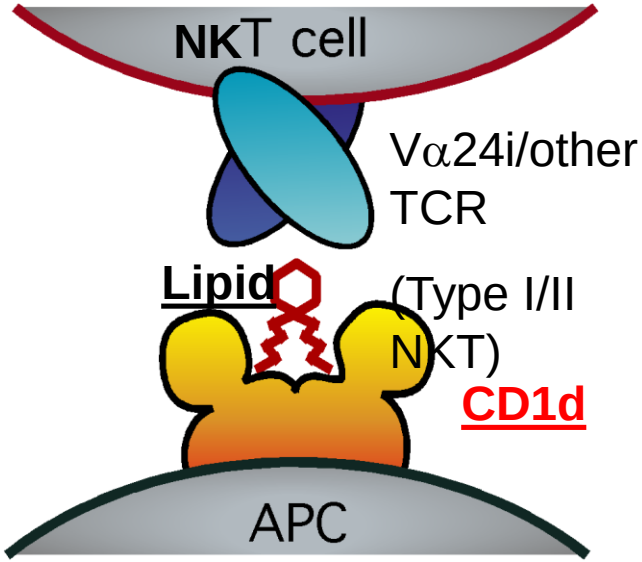
OR

Manufacture banked CART products using ***known*** TCR e.g virus-specific T cells **(Tzannou , Leen et al J.Clin Oncol. 35 [31] I3547-3557; *2017)***

NKT versus T cells



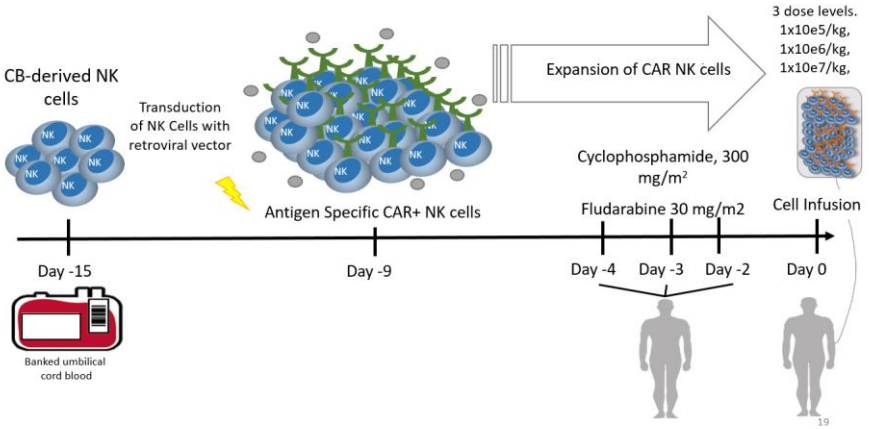
MHC + peptide

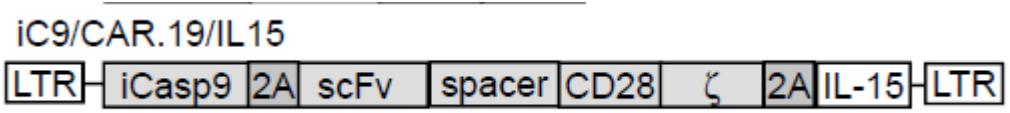


CD1d + glycolipid

Leonid Metelitsa

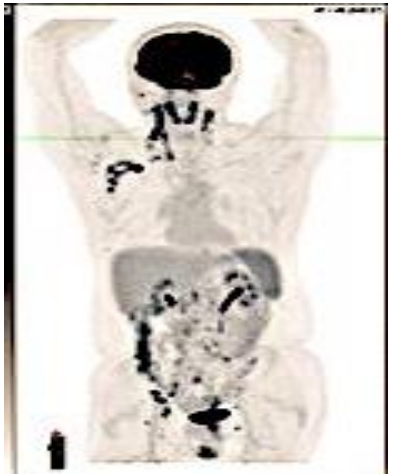
CD19.CAR cord NK Cell Study
PI: Katy Rezvani MD, PhD; MD Anderson Cancer Center



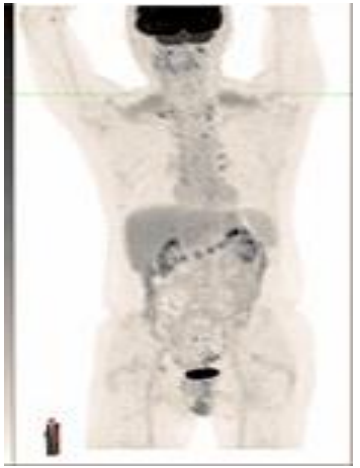


Gianpietro Dotti

Pre-admission



Day 30 post CAR NK



Complete metabolic response

Increasing Accessibility of CAR-T

- Point of care delivery for autologous products
- Off the shelf normal donor products

Reduced cost of goods

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