Penn Medicine

Chimeric Antigen Receptor T Cell Therapies for Advanced Prostate Cancer

Clinical Trials (and Tribulations)

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ABRAMSON CANCER CENTER

NASPCC Symposium **06/24/2021**

Division of Hematology/Oncology

OBJECTIVES

- REVIEW CURRENT MECHANISMS AND RATIONALE FOR RE-DIRECTED T CELL THERAPIES FOR ADVANCED PROSTATE CANCER
- DESCRIBE AN EARLY EXPERIENCE WITH CAR-T THERAPY FOR ADVANCED PROSTATE CANCER
- DISCUSS CHALLENGES AND FUTURE APPROACHES FOR PROSTATE CANCER CAR-T THERAPY


THE
CANCER
IMMUNOTHERAPY
REVOLUTION
A PATIENT'S GUIDE TO

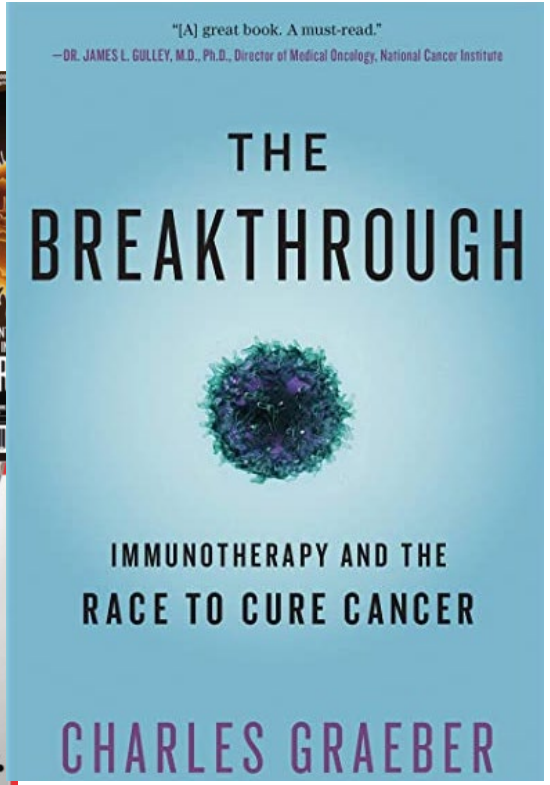
COVER STORY
The
Immunotherapy
Revolution
ALSO IN THIS ISSUE
SPRING 2017


Science
Breakthrough of the Year
Cancer
Immunotherapy
T cells on the attack


nature
IMMUNE-CHECKPOINT
BLOCKADE
CANCER

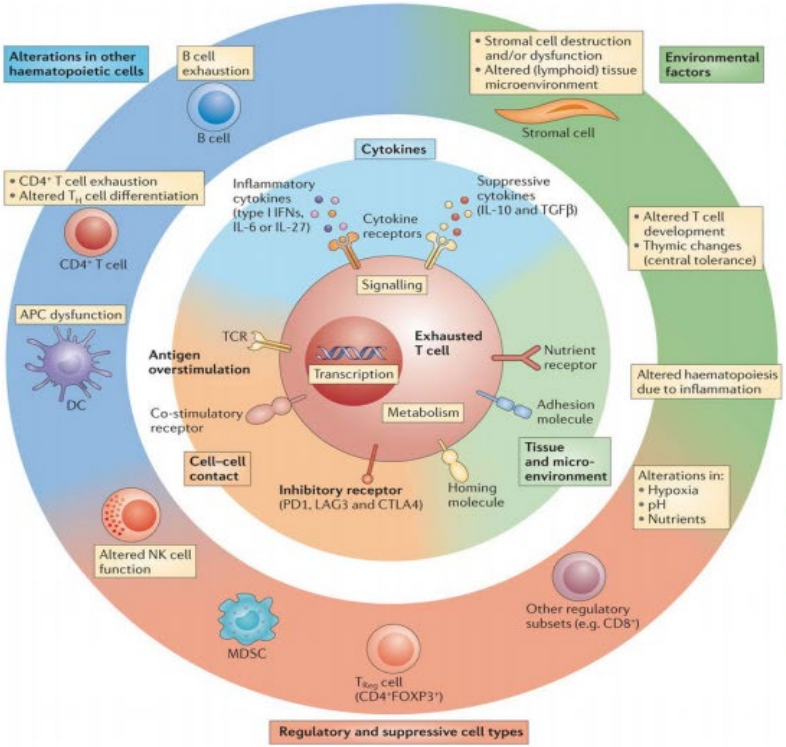

Science
Cancer Immunology and
Immunotherapy


TIME
What if your immune system could be taught to kill cancer?
Inside the brutally selective, hugely expensive, lifesaving trials of immunotherapy.


"[A] great book. A must-read."
—DR. JAMES L. GULLEY, M.D., Ph.D., Director of Medical Oncology, National Cancer Institute
THE
BREAKTHROUGH
IMMUNOTHERAPY AND THE
RACE TO CURE CANCER
CHARLES GRAEBER

Complexity of Immune Oncology Targets in Advanced Cancer

Other checkpoints:
PD-1/PD-L1
CTLA-4
Ox40
LAG-3
Tim3.....



Other Targets:
Inflammation
Innate Immunity
Metabolism
Regulatory Cells

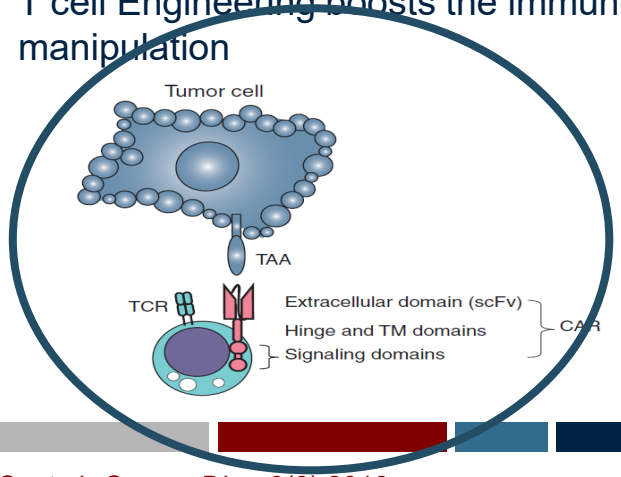
Combinations
Radiation
Chemo
Vaccines
Immune+Immune

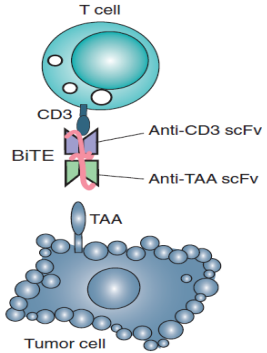
Engineered T-Cell Therapy: CARs, BiTEs, TCRs, and more

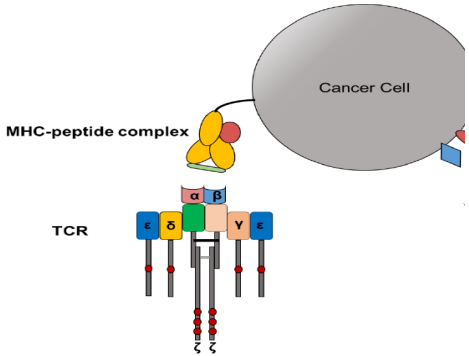
- Immunotherapy aims to induce anti-tumor response by “active” or “passive” means:
  - Augmenting immune surveillance and cytotoxicity
  - Reducing immune suppression

- Native tumor-specific T cell repertoire is generally limited and low affinity (central tolerance)

- T cell Engineering boosts the immune system’s natural recognition abilities through genetic manipulation

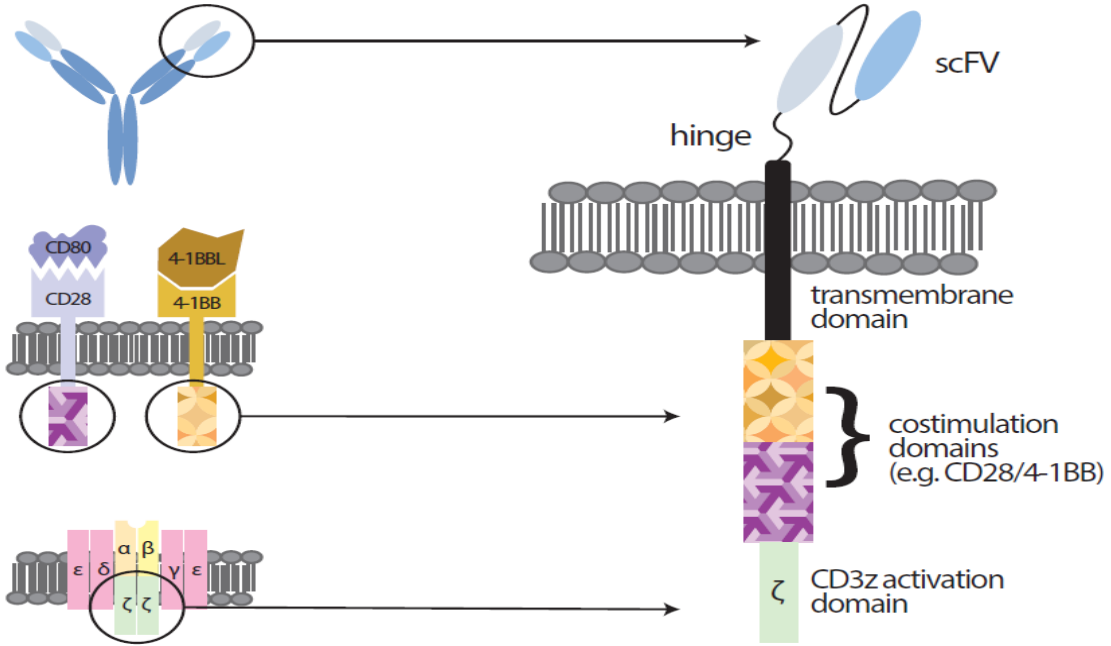






Slaney C, et al. *Cancer Disc.* 8(8) 2018.
Chen, L, et al. *Immunol Lett.* 2019

Chimeric antigen receptor Structure



Extracellular Domain:
- Target recognition
- scVf of a monoclonal antibody

Hinge Region:
- Spacer providing flexibiity

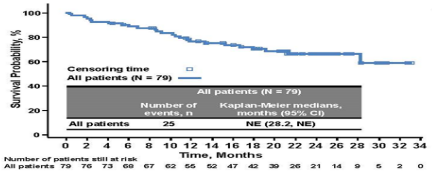
Costimulatory Domain(s):
- Enhancing cytotoxicity
- Derived from CD28, 4-1BB

Activation Domain:
- Initiating cytotoxicity
- Cytoplasmic motif from CD3z

Pantuck M. et al. *Cancer Treat Res Comm.* 17 (2018)

High Response Rates in Refractory Acute Lymphoblastic Leukemia

Median Overall Survival Not Reached



- Overall survival rates among all infused patients
  - 12-month: 76% (95% CI, 65–85)
  - 18-month: 70% (95% CI, 58–79)
  - 24-month: 66% (95% CI, 54–76)

Note: All patients infused with tisagenlecleucel were included. Time is relative to infusion

Grupp SA, et al. *Blood*. 2018;132: Abstract 895.

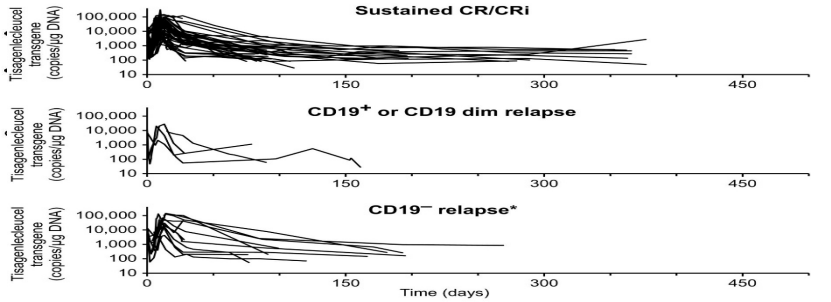
CART cells for ALL: phase I/II trials:

Maude, Grupp	*NEJM* 2018	**82% CR 3 months**
Park	*NEJM* 2018	**83% CR 3 months**

Characteristics of Remission and Relapse

- Relapses tended to occur early (within the first year)
- The majority of relapses were CD19-negative:

CD19-Negative	CD19-Positive	Unknown CD19 Status
14/19 (73.7% of relapses)	3/19 (15.8% of relapses)	2/19 (10.5% of relapses)



*Three of 12 patients were classified as CD19$^{+/-}$ relapse.

Durable remission associated with T cell Intrinsic Factors:

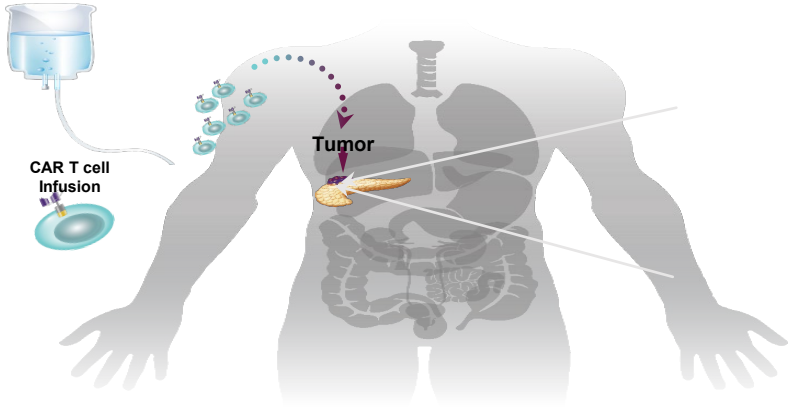
- **Increased peak expansion of CAR T cells and long persistence**
- **Cell products demonstrating greater proliferative capacity *ex vivo***
- **Phenotypic signatures of early memory differentiation (versus terminal differentiation/exhaustion in Non-Responders)**

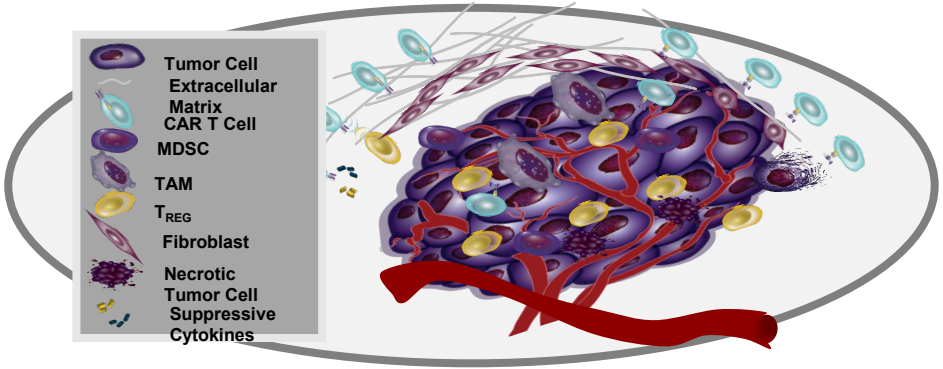
Fraietta, J.A., et al., *Nat. Med*. 2018; 24: 563-571

Challenges for CAR T Cell Therapy in Solid Tumors

- In experience to date, clinically meaningful responses are rarely observed.

- Anti-tumor potency limited by:
  - Lack of substantial expansion and/or survival of CAR T cells
  - Tumor Microenvironment (Immunosuppressive, Physical Barriers)
  - Antigen Loss / Heterogeneity
  - On-Target / Off-Tumor Toxicity

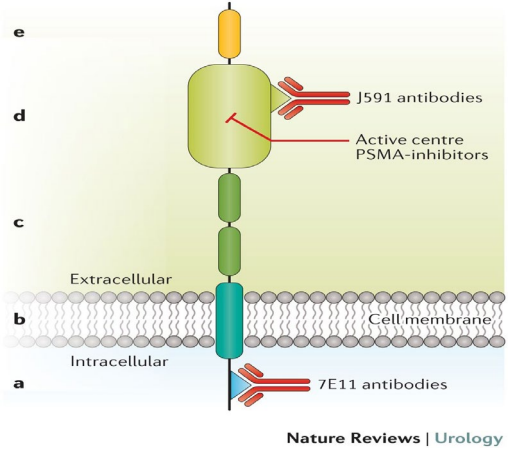


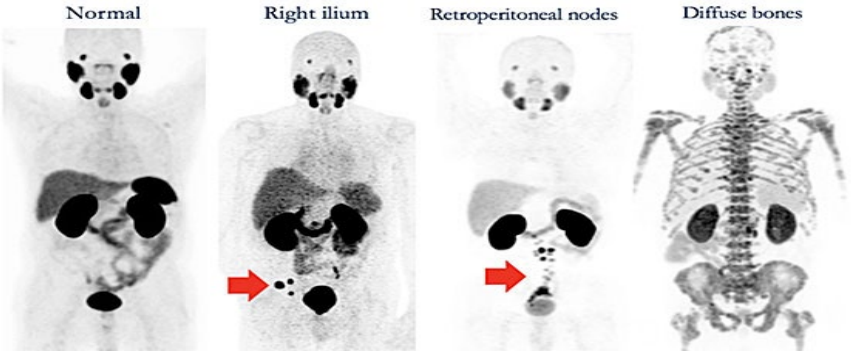


Long, KB. et al., *Front Immunol.* 9:2740. (2018)

Prostate Specific Membrane Antigen (PSMA)

- Membrane glycoprotein – evaluated as a tumor-associated antigen for >30 years
- Highly expressed in both normal prostate and PCa tissue
- High PSMA expression associated with PCa progression and castration-resistance
  - Expression increases with tumor grade





Ristau BT, et al. Urol Oncol 2013.
Rajasekaran A, et al. Cell Physio 2005.

Target Antigen: PSMA vs CD-19

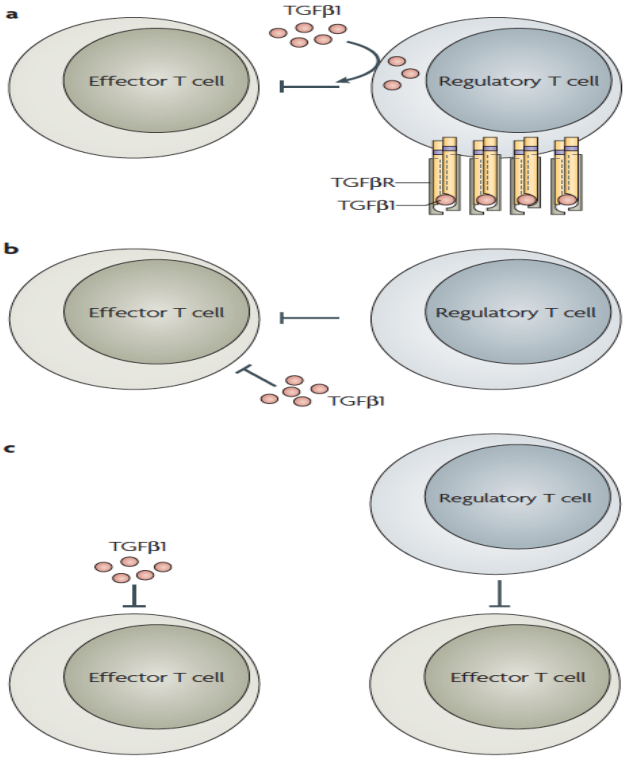
	PSMA	CD-19
High / Universal Tumor Expression	✓	✓
Limited Normal Tissue Expression	Low level Salivary, Renal, Intestinal	Normal B cells
Functional Role in Tumor / Indispensable	?? Folate metabolism	✓
Antigen-related toxicity concerns	?? Sialotoxicity, ? other	Hypogammaglobulinemia

Ristau BT, et al. Urol Oncol 2013.
Rajasekaran A, et al. Cell Physio 2005.

Transforming Growth Factor β (TGFβ)

- Contributes to immunosuppressive microenvironment encountered by re-directed T cells upon tumor infiltration
  - Negative feedback of T cell proliferation
  - Limits T cell-mediated autoimmunity

- Co-expression of dominant negative TGFβRII can enhance anti-tumor immunity



Rubtsov Y, et al. Nature Reviews 2007.
Bendle G, et al. J Immunol 2013.

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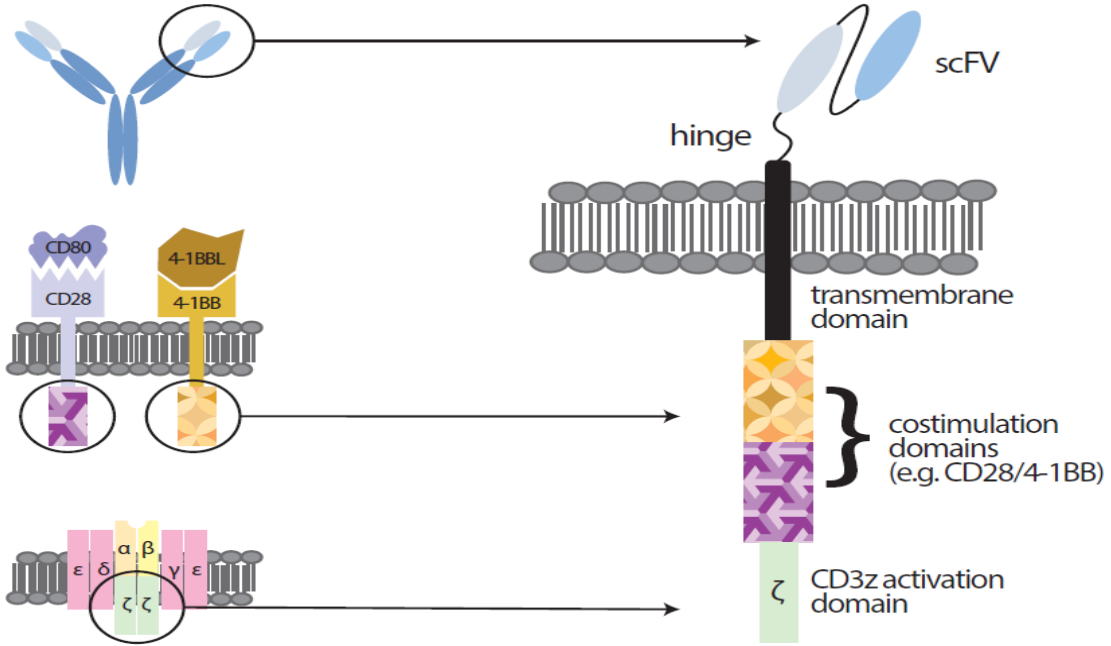

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Pantuck M. et al. *Cancer Treat Res Comm.* 17 (2018)

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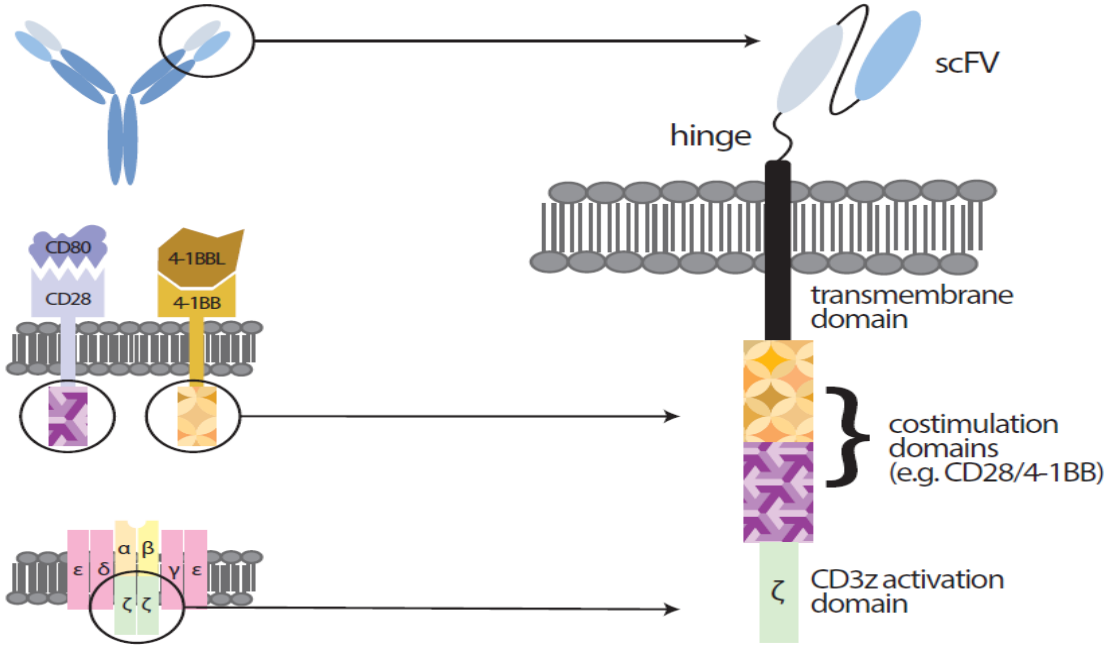


Lentiviral vector gene transfer

Extracellular Domain:
- J591 scFv for PSMA target Ag

Hinge Region:
- Spacer providing flexibiity

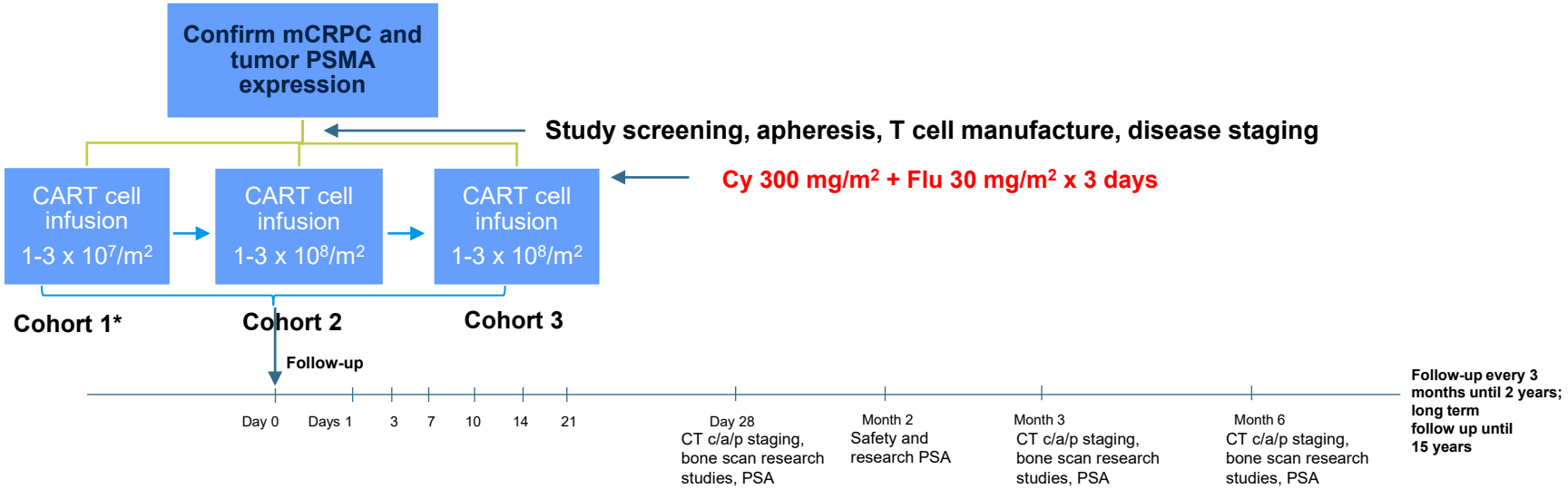
Costimulatory Domain(s):
- 4-1BB

Activation Domain:
- CD3z

"Armoring" with co-expression of a dominant negative TGFβ receptor (TGFβRdn) to enhance antitumor immunity

Pantuck M. et al. *Cancer Treat Res Comm.* 17 (2018)

Study Schema



*** Enrollment follows in succession from Cohort 1 to Cohort 3**

ClinicalTrials.gov Identifier: NCT03089203. PI: N. Haas.

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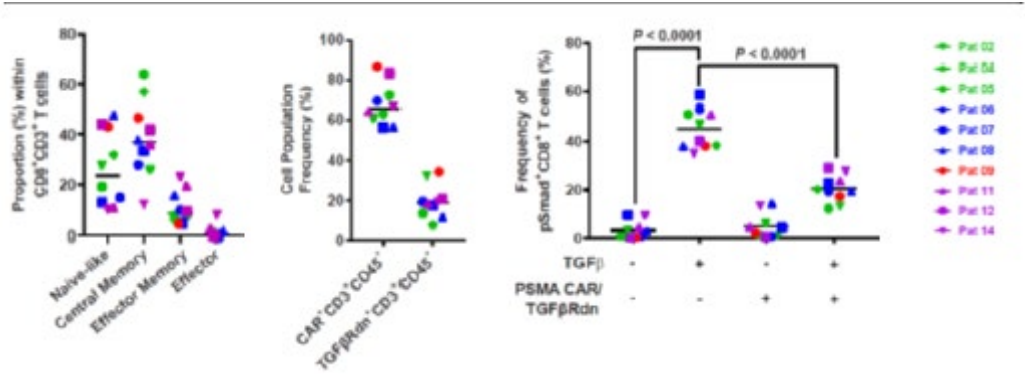
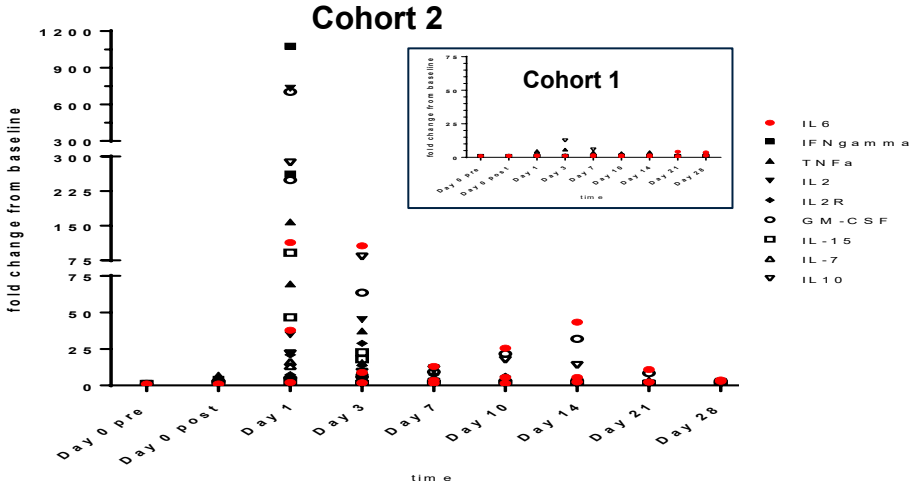
Clinical Apheresis & Pre-Infusion Product Analysis



- T cell Differentiation Phenotype in Apheresis Product showed donor variability **(left)**
- Frequencies of expanded patient CD3+CD45+ T cells in Infusion Product expressing anti-PSMA CAR (median 65%) and TGFbRDN (median 19%) **(center)**
- Expression of TGFbRDN on manufactured PSMA-targeted CAR-T cells potently inhibited TGFb signaling through Smad2/3 phosphorylation **(right)**

Summary of Initial Cohorts (without LD chemotherapy)

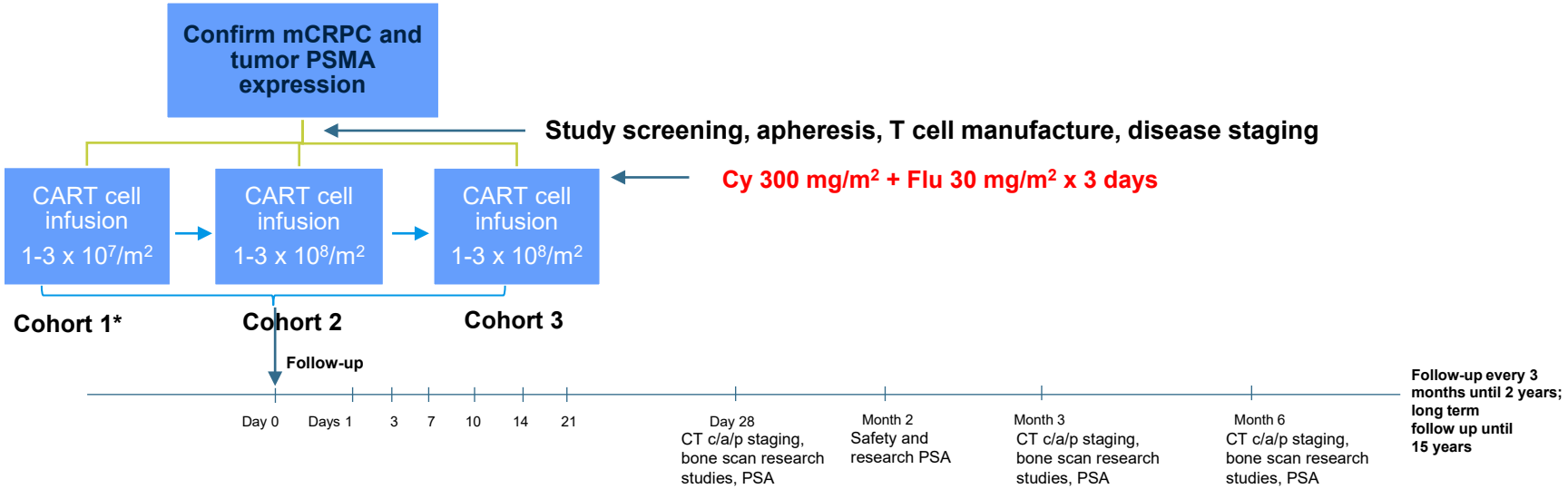
- No evidence of CAR T cell activity in Cohort 1
  - No related Adverse Events
  - Little cytokine activity (Figure Inset)
- Evidence of anti-tumor CAR T cell activity in Cohort 2
  - Grade 3 CRS within hours of CAR T cell infusion
  - Adverse events were reversible
  - Robust cytokine activity in patients with Gr3 CRS



Conclusions:

- **CART-PSMA-TGFβRDN cells are safe at $3x10^8/m^2$ CAR+ cells without conditioning chemotherapy.**
- **There is a dose dependent relationship with cytokine detection.**

Study Schema



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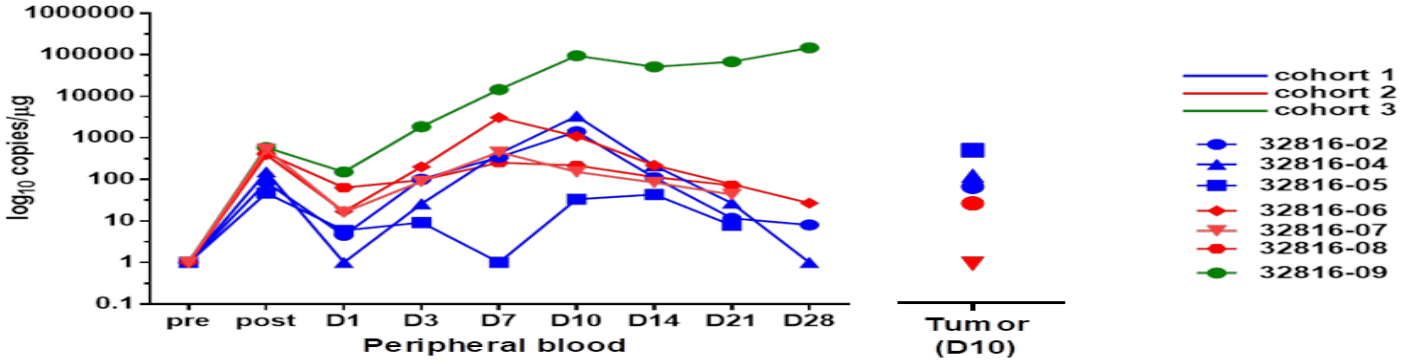
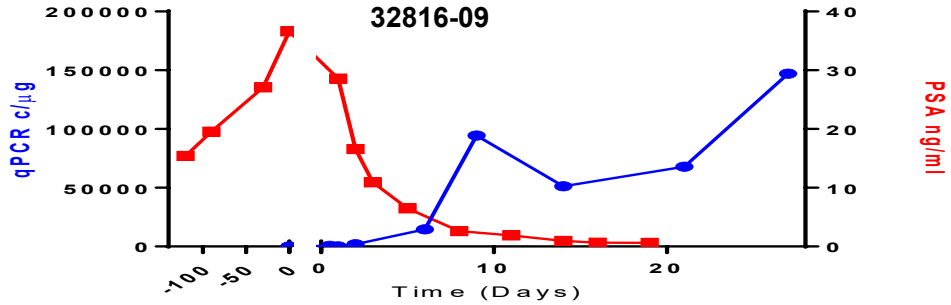
Dose- and LD Chemo-Dependent CAR T Cell Expansion in Peripheral Blood



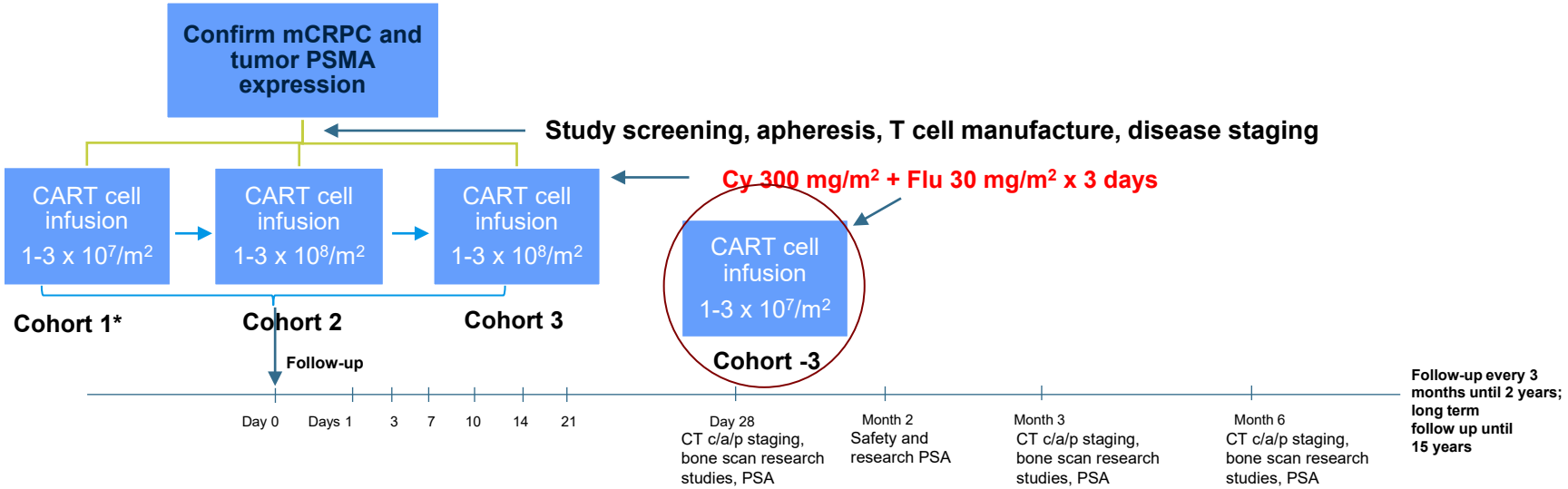


Correlation between CART-PSMA-TGFβRDN expansion and PSA reduction

Grade 5 Toxicity

How to optimize therapeutic index?

Study Schema



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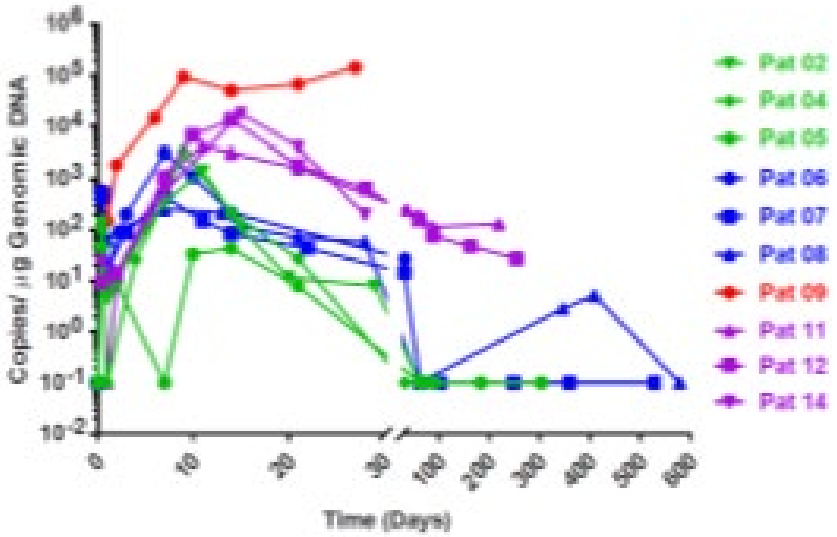
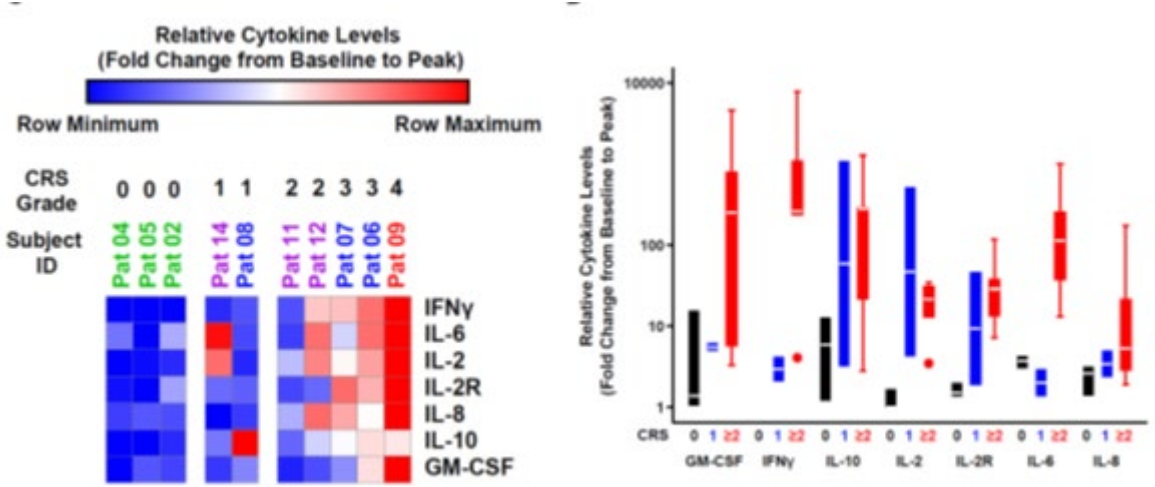
CART-PSMA-TGFβRDN Cell Engraftment (qPCR in peripheral blood)



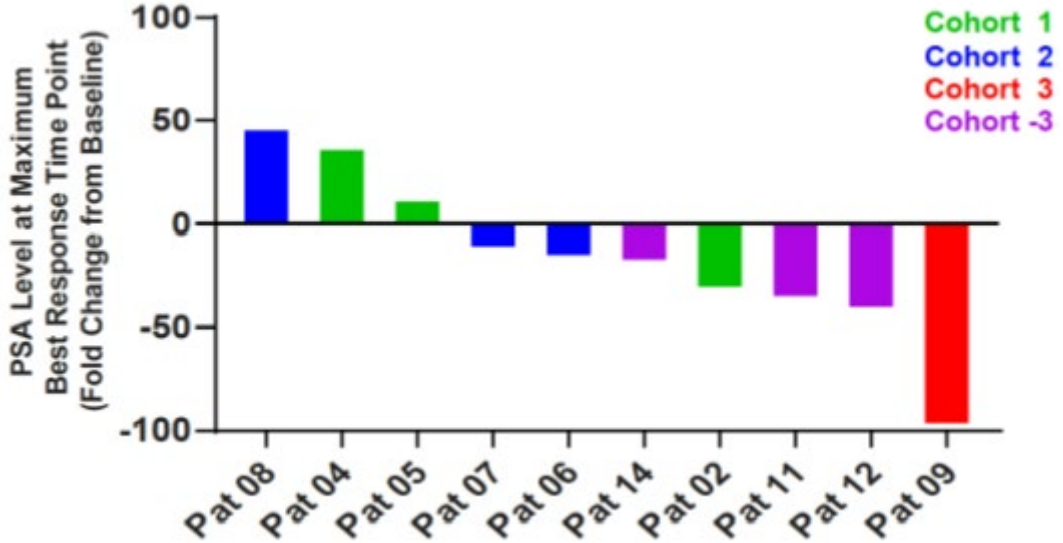
CAR-T peak expansion increased with dose-escalation and incorporation of Cy / Flu LD chemotherapy

Peak Fold-Change in Pro-Inflammatory Cytokine Production



- Higher grade CRS was associated with a greater magnitude of fold change in pro-inflammatory analytes post-infusion.

Preliminary Evidence for Dose-Dependent and LD-Chemo Dependent Anti-Tumor Response



CART-PSMA-TGFβRDN-02: A Phase 1 Open-Label Multi-Center Study of PSMA Targeted Genetically Modified Chimeric Antigen Receptor T-cells in Patients with Metastatic Castration Resistant Prostate Cancer

Current Study Schema

- Completed cohort
- No dosing occurred in cohort
- Cohort to be initiated

Cohort 5
5-7 x 10^8 TDN cells
Single infusion

Cohort 5a

Biotech

Tmunity stops solid tumor CAR-T trial after 2 patients die

Process 2

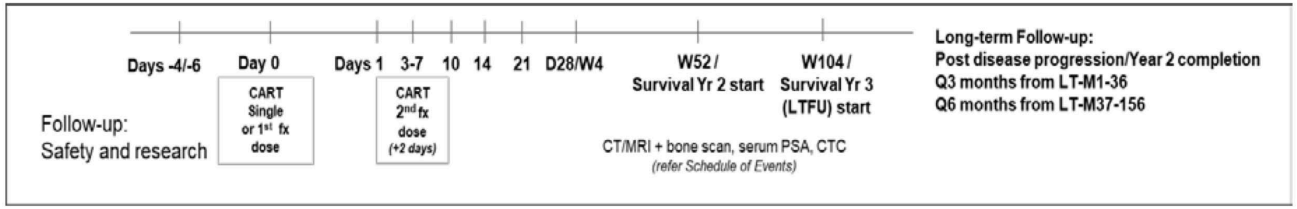
Process =2

Cohort 2
5-7 x 10^7 TDN cells
Single infusion

Cohort 3a
7-10 x 10^7 TDN cells
Single infusion
N=3-6
Process 2

Cohort 1
1-3 x 10^7 TDN cells
Single infusion
N=2
Process 1

Use of prophylactic anakinra in applicable cohorts



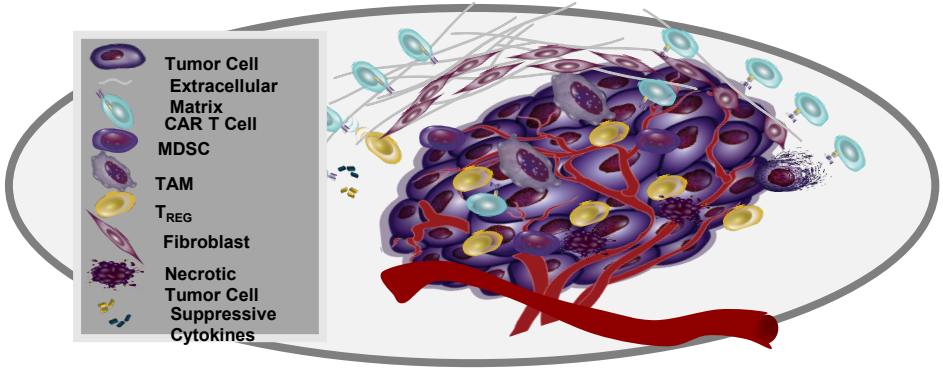
Lymphodepleting Chemotherapy (D-6 to D-4)
- Cyclophosphamide 300 mg/m2 x3-days
- Fludarabine 30 mg/m2 x3-days

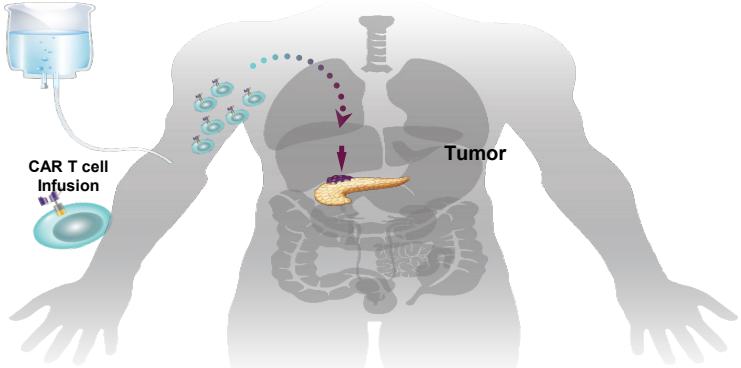
TMUNITY

Ongoing Trials for Metastatic Prostate Cancer

Trial	Target	Sponsor	NCT Identifier
Phase 1 Study of CART-PSMA-TGFβRDN in Patients With Metastatic Castration Resistant Prostate Cancer	PSMA	Tmunity Therapeutics	NCT04227275
Phase 1/2 Study of PSCA-Targeted CAR-T Cells (BPX-601) in Subjects With Selected Advanced Solid Tumors	PSCA	Bellicum Pharmaceuticals	NCT02744287
P-PSMA-101 CAR-T Cells in the Treatment of Subjects With Metastatic Castration-Resistant Prostate Cancer (mCRPC)	PSMA	Poseida Therapeutics	NCT04249947
PSCA-CAR T Cells in Treating Patients With PSCA+ Metastatic Castration Resistant Prostate Cancer	PSCA	City of Hope	NCT03873805

Challenges for CAR T Cell Therapy in Solid Tumors





Scientific Challenges:

CAR Expansion/Survival

Tumor Microenvironment

Antigen Heterogeneity/Loss

On-Target / Off-Tumor Effects

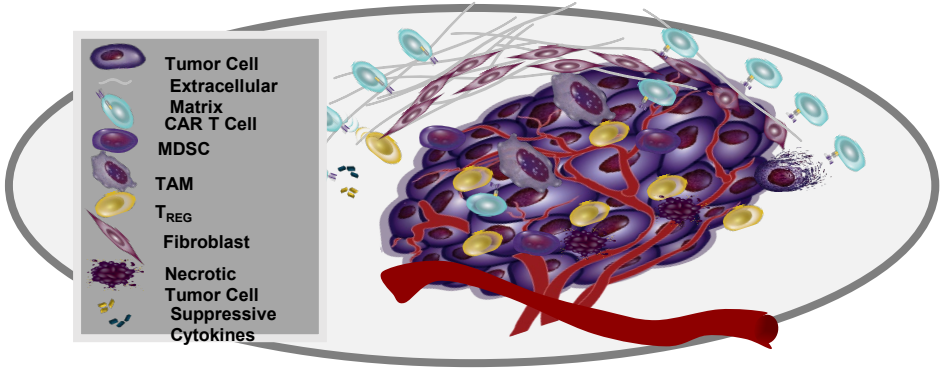
Clinical Challenges:

Patient Selection

Safety / Toxicity

Therapeutic Window

Challenges for CAR T Cell Therapy in Solid Tumors



Scientific Challenges:

CAR Expansion/Survival

Tumor Microenvironment

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On-Target / Off-Tumor Effects

Tumor Microenvironment

"Armoring" strategies – IL-12, IL-18, CD40L

Dominant-Negative Receptors (dnTGFβRII, PD1)

PD1 / CD28 "switch" receptors

Combination Treatment Strategies (low dose RT)

CAR Persistence / "Exhaustion"

Serial dosing strategies

Novel inducible co-activation switches

Immune checkpoint inhibitor adjuvants

CRISPR-Cas9 editing (PD1 / LAG3)

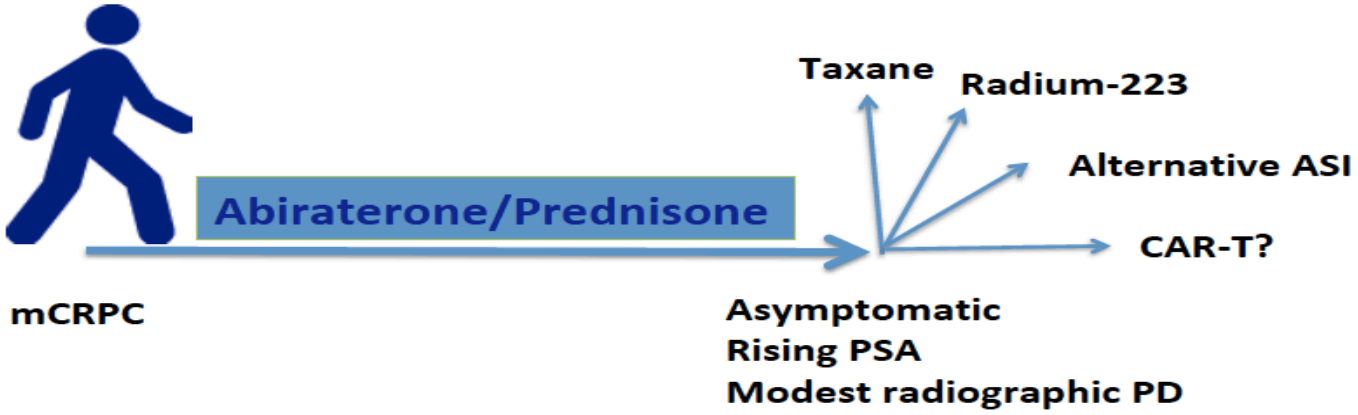
Antigen Selection / Targeting

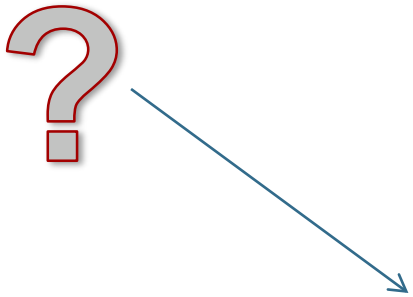
Combination TAA scFvs

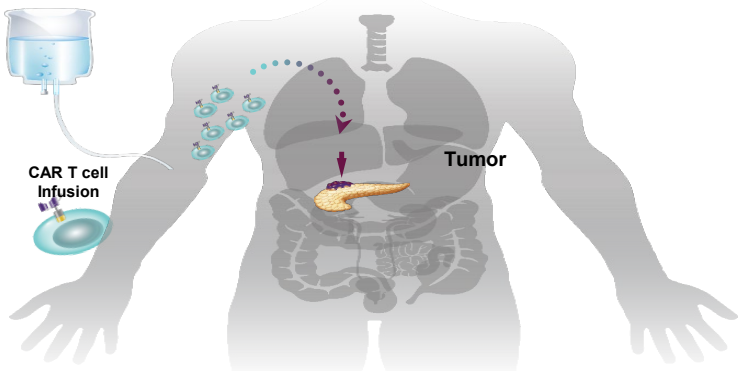
Conditional activation switches

Antigen spread

Challenges for CAR T Cell Therapy in Solid Tumors







Clinical Challenges:

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Safety / Toxicity

Therapeutic Window

Conclusions:

- Adoptive Cell Therapy with CAR-Modified T Cells is a transformative treatment for refractory cancers
- Multiple Tumor and Host factors will influence efficacy for prostate cancer CAR therapy
  - T cell potency / persistence
  - Antigen Heterogeneity
  - Tumor Microenvironment
  - Off-tumor Effects
- Rational combination / multifunctional approaches are needed
- Enhanced toxicity mitigation strategies remain critical for optimal Risk : Benefit (first in human trials)


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