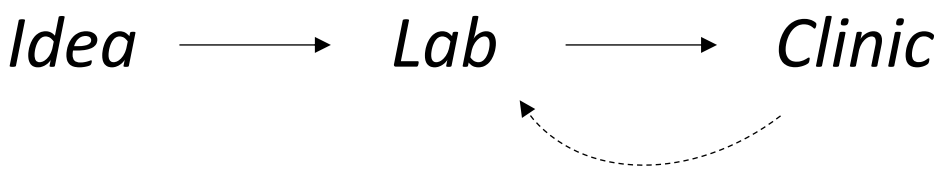
Adoptive cell therapy of cancer



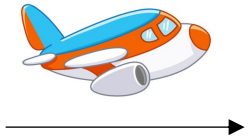
Max Mamonkin, PhD

Center for Cell and Gene Therapy
Baylor College of Medicine

CENTER FOR CELL & GENE THERAPY

CV stuff

Novosibirsk State University
Novosibirsk, Russia



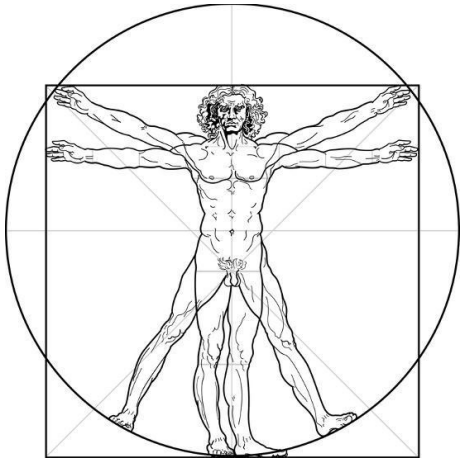
Baylor College of Medicine
Houston, TX USA

- 2001-2006: BS/MS in Biology

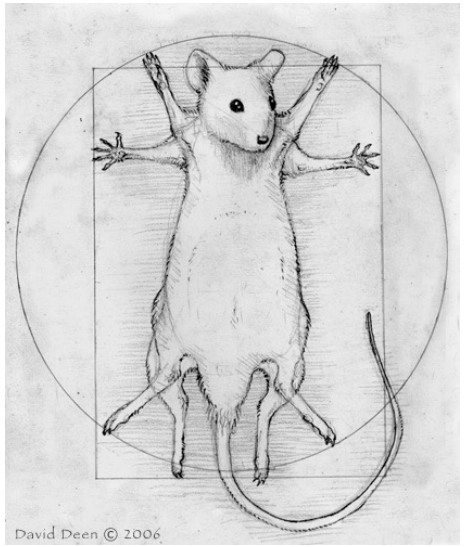
- 2007-2013: Graduate School in Immunology
- 2013-2016: Postdoc (CAGT with M. Brenner)
- 2016-2018: Instructor (CAGT)
- 2018-present: Asst Professor (CAGT)

Graduate School: learn the Basic (the hard way)

- I learned (some) immunology!
- Thesis project: CD8 T-cell differentiation in response to infection
- Back to the drawing board in Year 4
- Took 6 years to complete

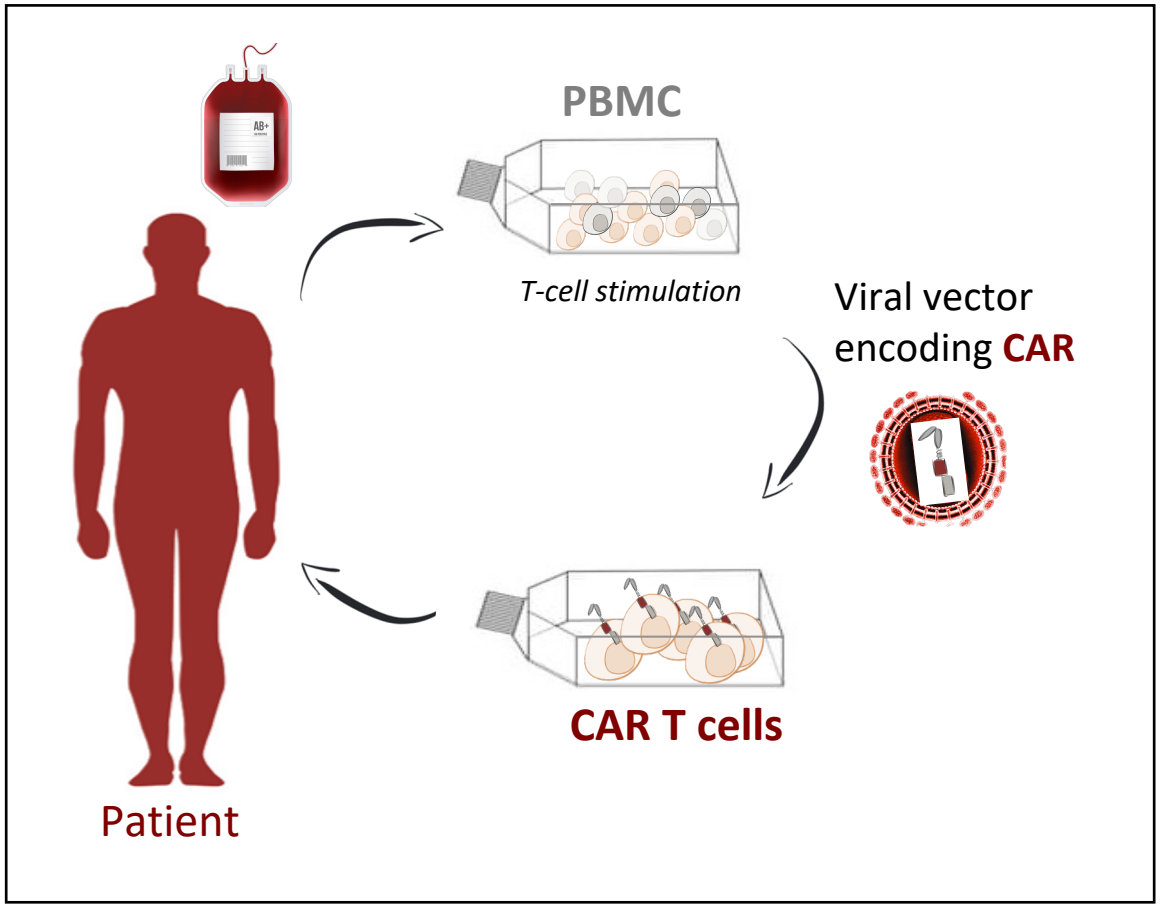


Vs.

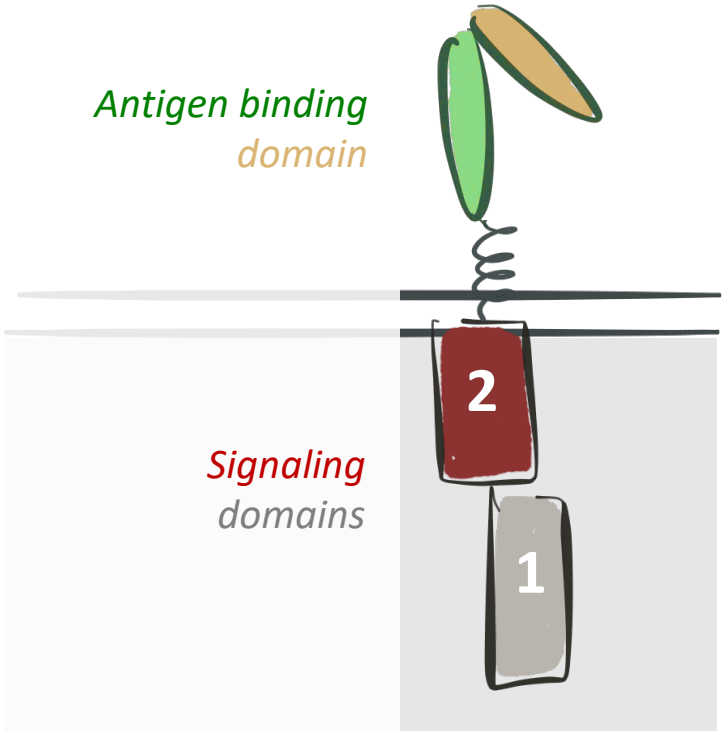


Postdoc: found in Translation

Adoptive cell therapy of cancer



Chimeric antigen receptor (CAR)



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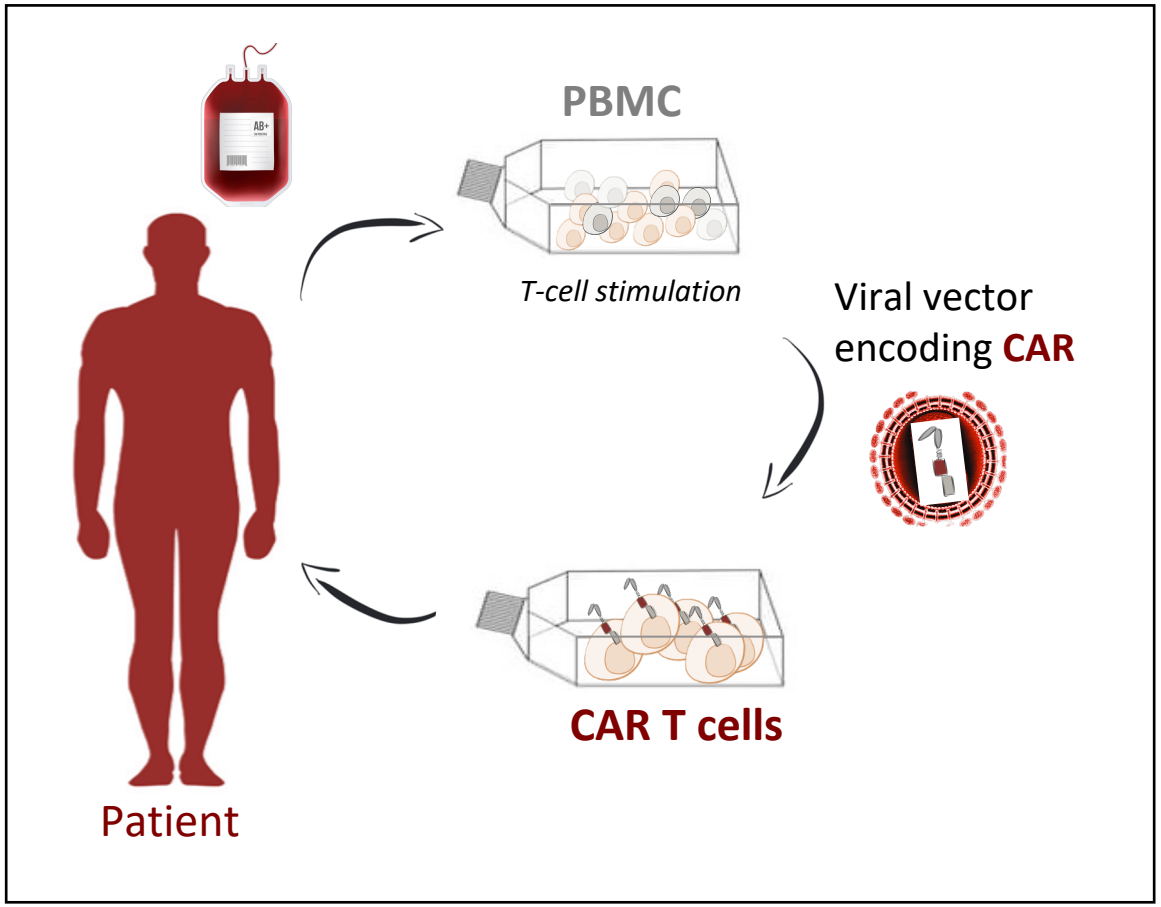
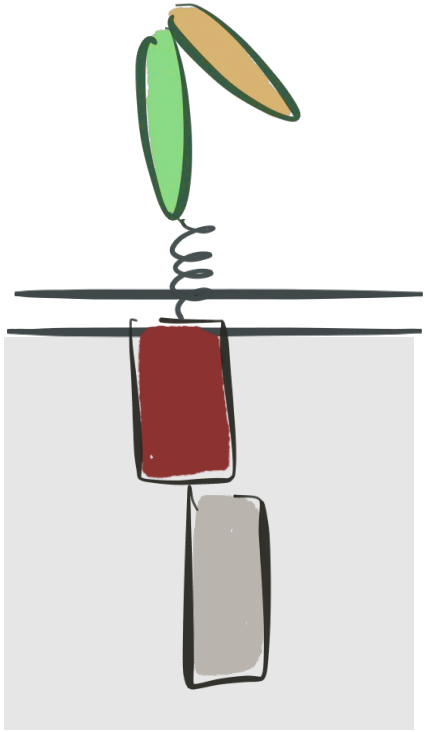
Adoptive cell therapy of cancer



- **CD19 CAR-T cells**: a poster child of clinical success
- Five FDA-approved CAR-T products in the last 2 years (all in B-cell malignancies)

T versus T



- **Developing CAR T-cells for T-cell malignancies is difficult!**
- Most surface antigens we can “safely” target are also present on normal T-cells (including CAR T-cells).
- Two main problems:
  1) Self-elimination of CAR T-cells (fratricide)
  2) Potential T-cell aplasia -> immunodeficiency

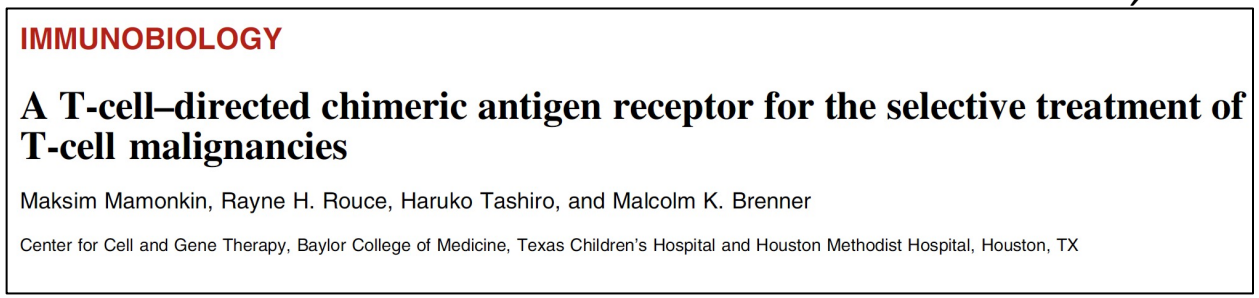
CAR T-cells targeting a T-cell antigen?

- **Observation**: CD5 is a great target in T-cell malignancies. CD5 is also highly expressed in all T-cells.
- **Hypothesis**: CD5 CAR expressing T-cells will kill each other.

- **Outcome**: CD5 CAR T-cells expanded well and killed all CD5+ tumor lines we could find.

- **Mechanism**: CAR expression promotes rapid degradation and loss of detectable CD5.
  CD5 CAR T-cells become invisible to each other while still killing CD5+ tumors.

Blood, 2015



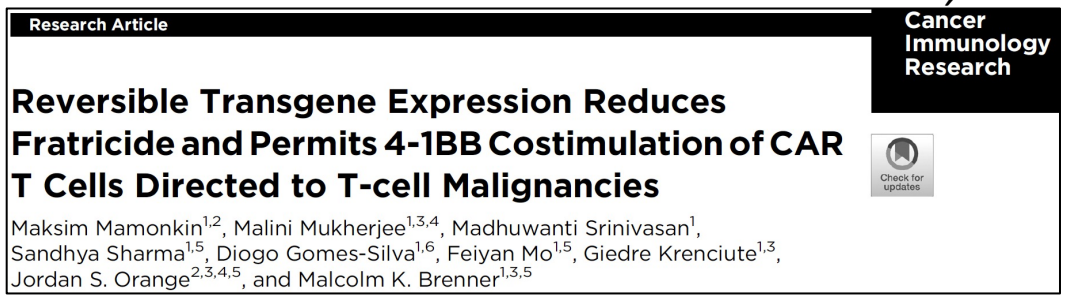
IMMUNOBIOLOGY

A T-cell–directed chimeric antigen receptor for the selective treatment of T-cell malignancies

Maksim Mamonkin, Rayne H. Rouce, Haruko Tashiro, and Malcolm K. Brenner

Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children's Hospital and Houston Methodist Hospital, Houston, TX

Cancer Immunol Res, 2017



Research Article

Cancer Immunology Research

Reversible Transgene Expression Reduces Fratricide and Permits 4-1BB Costimulation of CAR T Cells Directed to T-cell Malignancies

Maksim Mamonkin[1,2], Malini Mukherjee[1,3,4], Madhuwanti Srinivasan[1], Sandhya Sharma[1,5], Diogo Gomes-Silva[1,6], Feiyan Mo[1,5], Giedre Krenciute[1,3], Jordan S. Orange[2,3,4,5], and Malcolm K. Brenner[1,3,5]

Pathway to clinical translation

Research lab

cGMP manufacturing

→

cGMP manufacturing

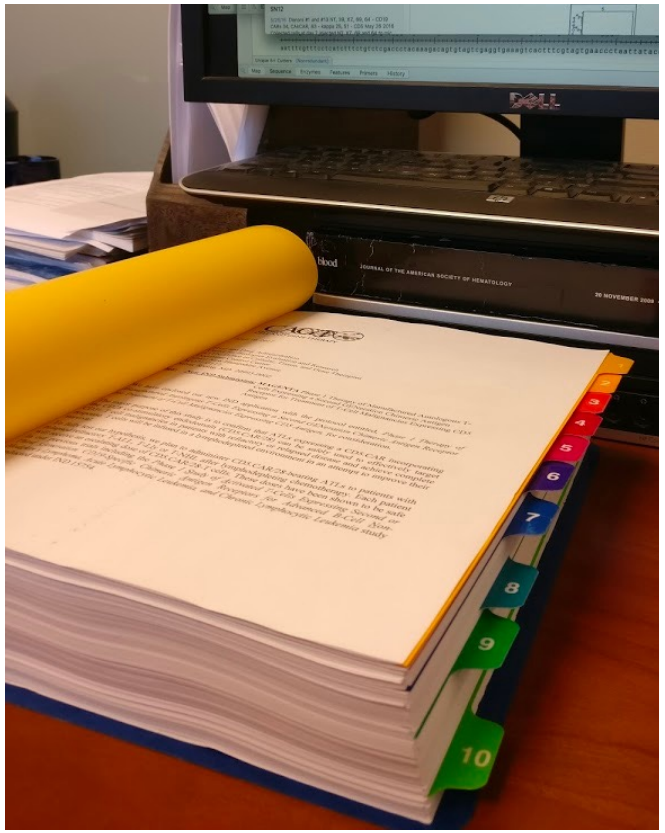
Translating CAR T-cell studies from bench to bedside requires multiple steps:

- Finalize CAR structure/design. Any subsequent modification will require developing new IND and reagents
- Develop robust cGMP SOP/manufacturing protocols compatible with available reagents and equipment
- Produce clinical-grade retroviral vector and perform necessary release tests
- Develop clinical protocol, write IND (CMC, Pharm+Tox etc). Be ready to headbutt with FDA for months.
- Perform validation runs, finalize and document SOPs, release tests, train personnel.
- Somehow obtain $$$ to do all of the above.

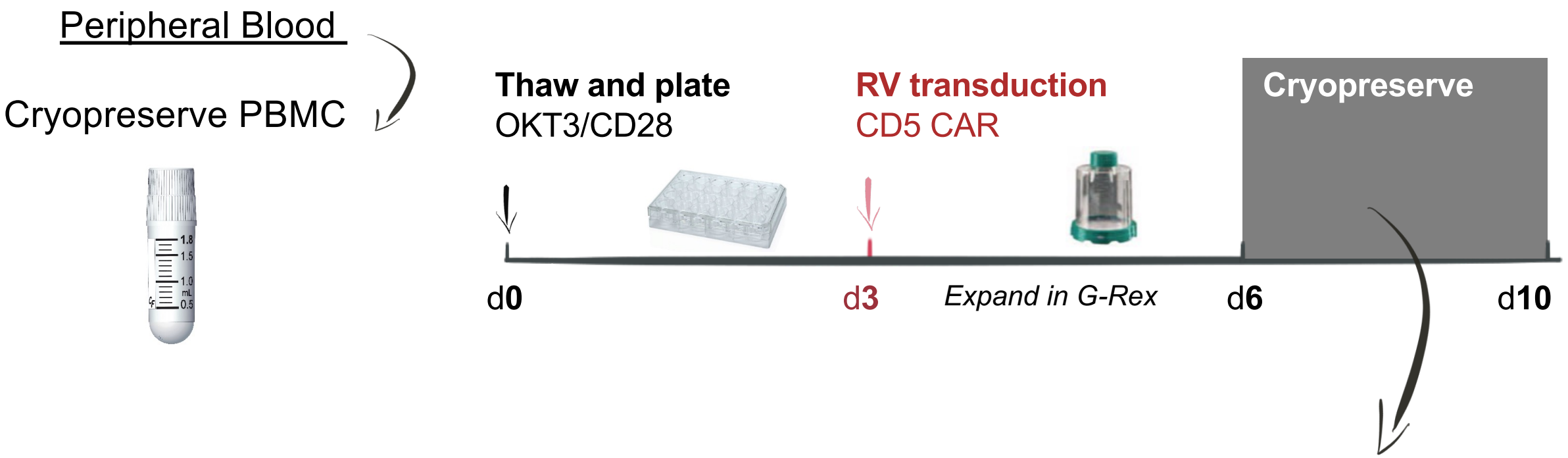
Time line to clinical translation

- **2015** – Initial report published in Blood. Patent filed.
- **2016** – ASH Scholar Award to optimize CD5 CAR-T for clinical evaluation
- **2017** – Follow up mechanistic/optimization studies published in CIR
- **2017** – Developed cGMP manufacturing and clinical protocols. Produced clinical-grade CD5 CAR viral vector
- **2017** – NIH SPORE Award to fund Phase I clinical trial. IND submitted and approved by FDA.
- **2018** – Clinical trial of autologous CD5 CAR T-cells initiated at BCM (Clinical PI: Rouce, Hill, Heslop, Brenner)
- **2020** – Patent application granted.

CD5CAR-T Phase I: IND Application



GMP manufacturing of CD5 CAR T cells



- 44 CAR T-cell lines manufactured
- Release criteria met in 42/44 (95%)
- 20 patients infused

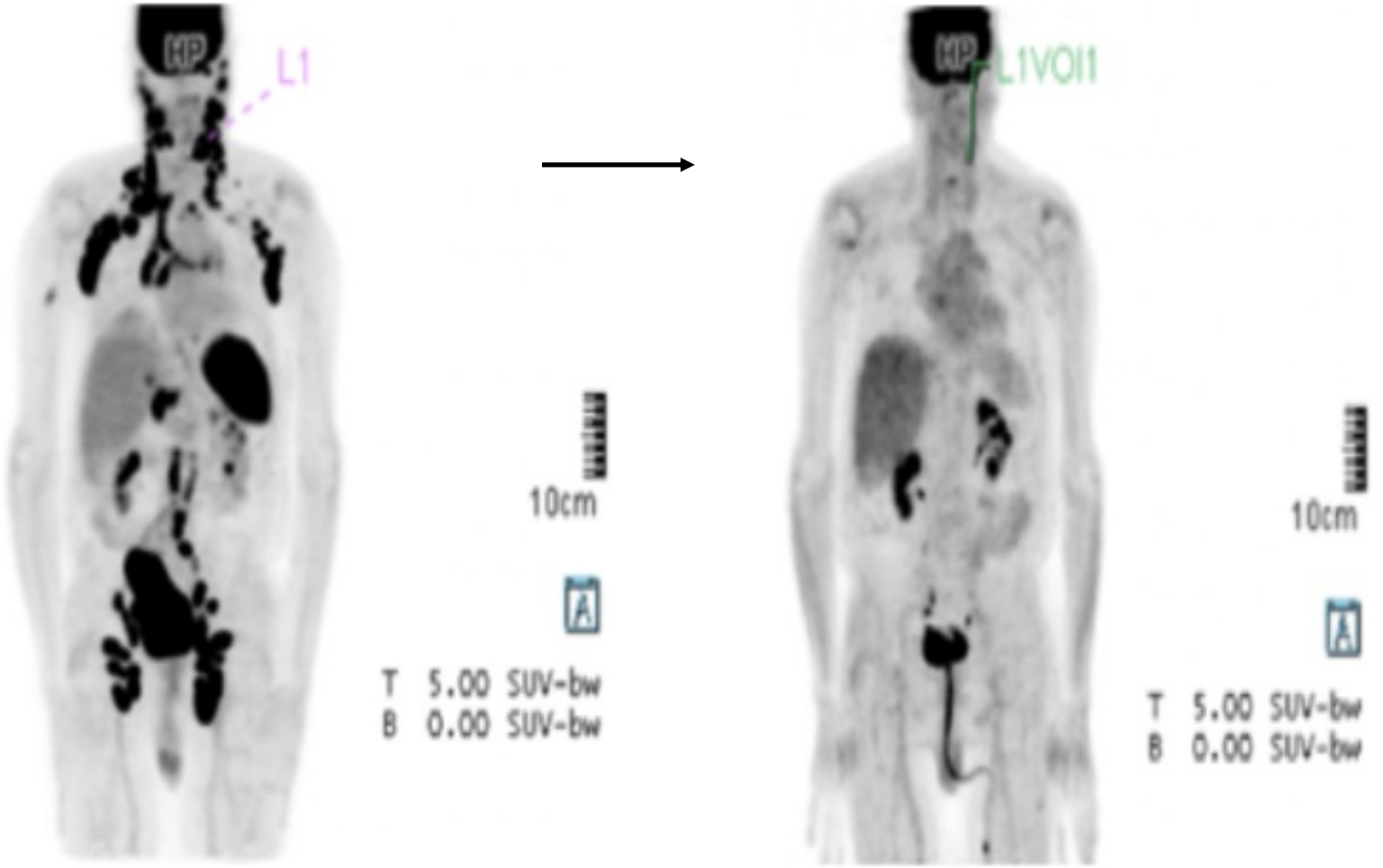
Release testing

- Cytotoxicity
- Standard QC
- Residual malignant blasts by FC

PTCL: CD5 CAR T-cells eradicate disseminated lymphoma

71 yo
relapsed PTCL

Pre-CAR T → **CR @4 weeks post CAR-T**

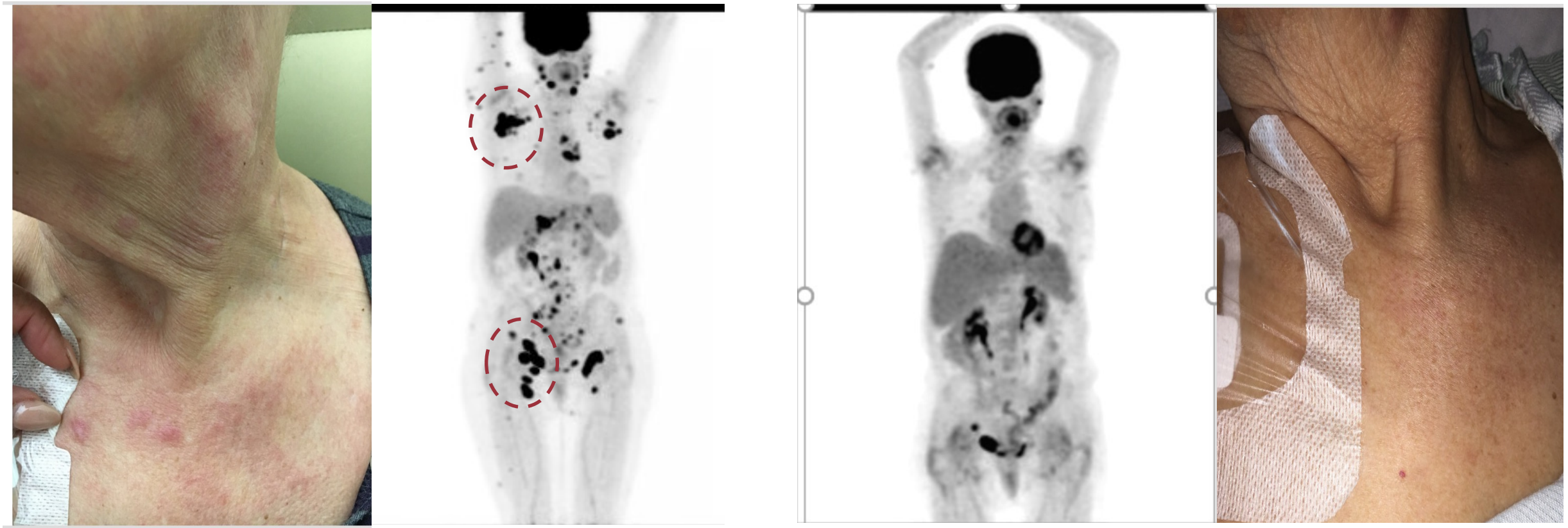


LaQuisa Hill, MD

AITL: PET-active lesions resolved by week 8

Week 4

Week 8

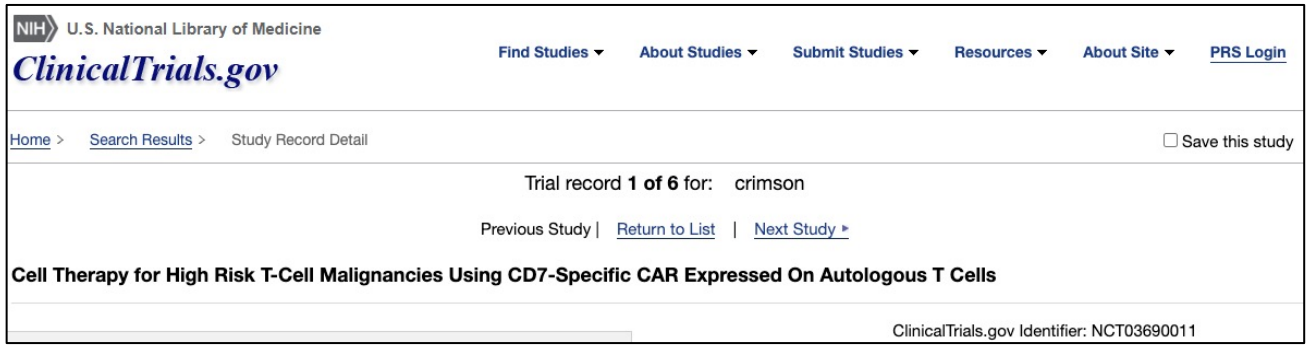


- CD5 CAR T-cells induced **complete remissions** in 7 patients + partial response in one patient.

LaQuisa Hill, MD

Work in progress

- Continuous improvement of CD5 CAR T-cell manufacturing, sourcing T-cells from healthy donors
- Recent manufacturing changes resulted in dramatic gains in clinical activity
- Developed CD7 CAR T-cells for T-cell malignancies and AML (*Gomes-Silva et al. Blood 2017 and Mol Ther 2018*). **Clinical trial opened in 2021**.



- Engineering “off-the-shelf” CAR T-cell platforms that resist host immune rejection (*Mo et al., Nat Biotechnol 2021*). Clinical translation currently underway.
- Commercialization of clinically validated therapies.

Thoughts

- Find great mentors and the right environment for yourself.
- Build your team carefully. Support them any way you can.
- It takes a village to develop and translate therapies. Be patient, respectful, and resourceful.
- **Don’t be afraid to challenge dogmas**
- Failure is not an option, it is a must. Be ready to fail and don’t take it personally
- Make sure your science is bulletproof before taking it to patients.

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CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

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ASH Scholar Award

Gloria Levin Fund

Patients and their families