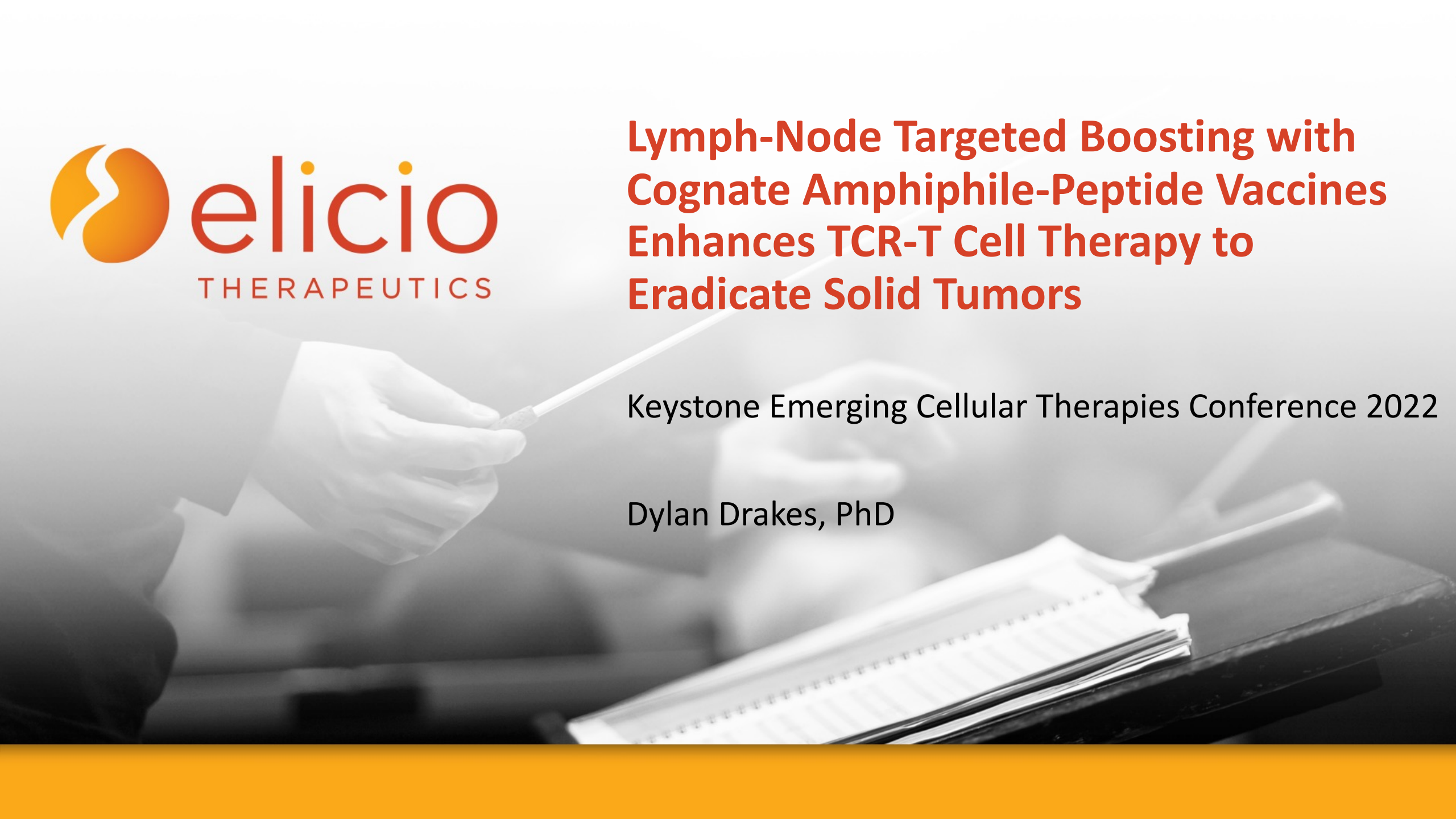
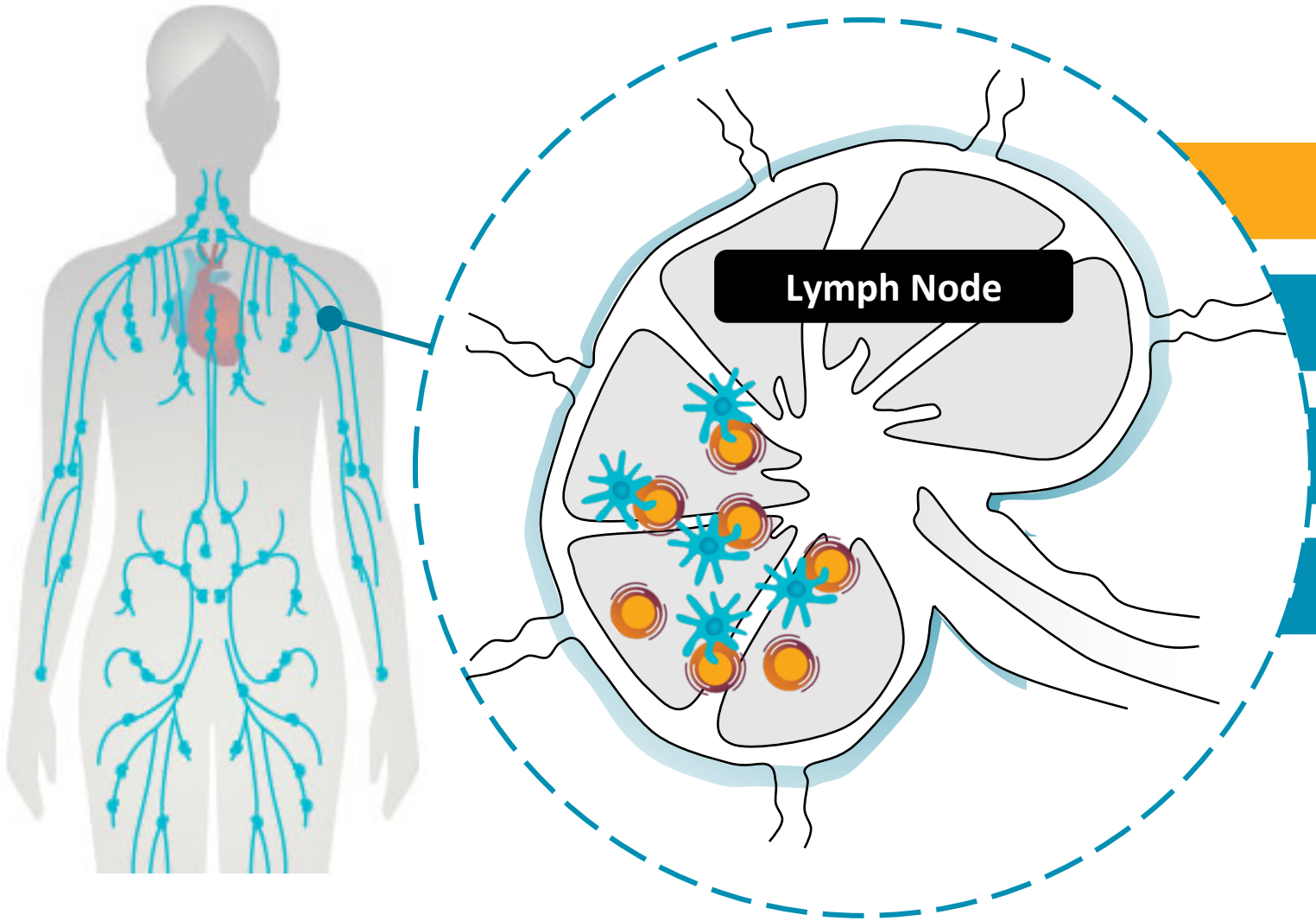


Lymph-Node Targeted Boosting with Cognate Amphiphile-Peptide Vaccines Enhances TCR-T Cell Therapy to Eradicate Solid Tumors

Keystone Emerging Cellular Therapies Conference 2022

Dylan Drakes, PhD

Lymph Nodes are Where the Immune Response is Orchestrated



The Immune "School House"

Numerous Immune Cells

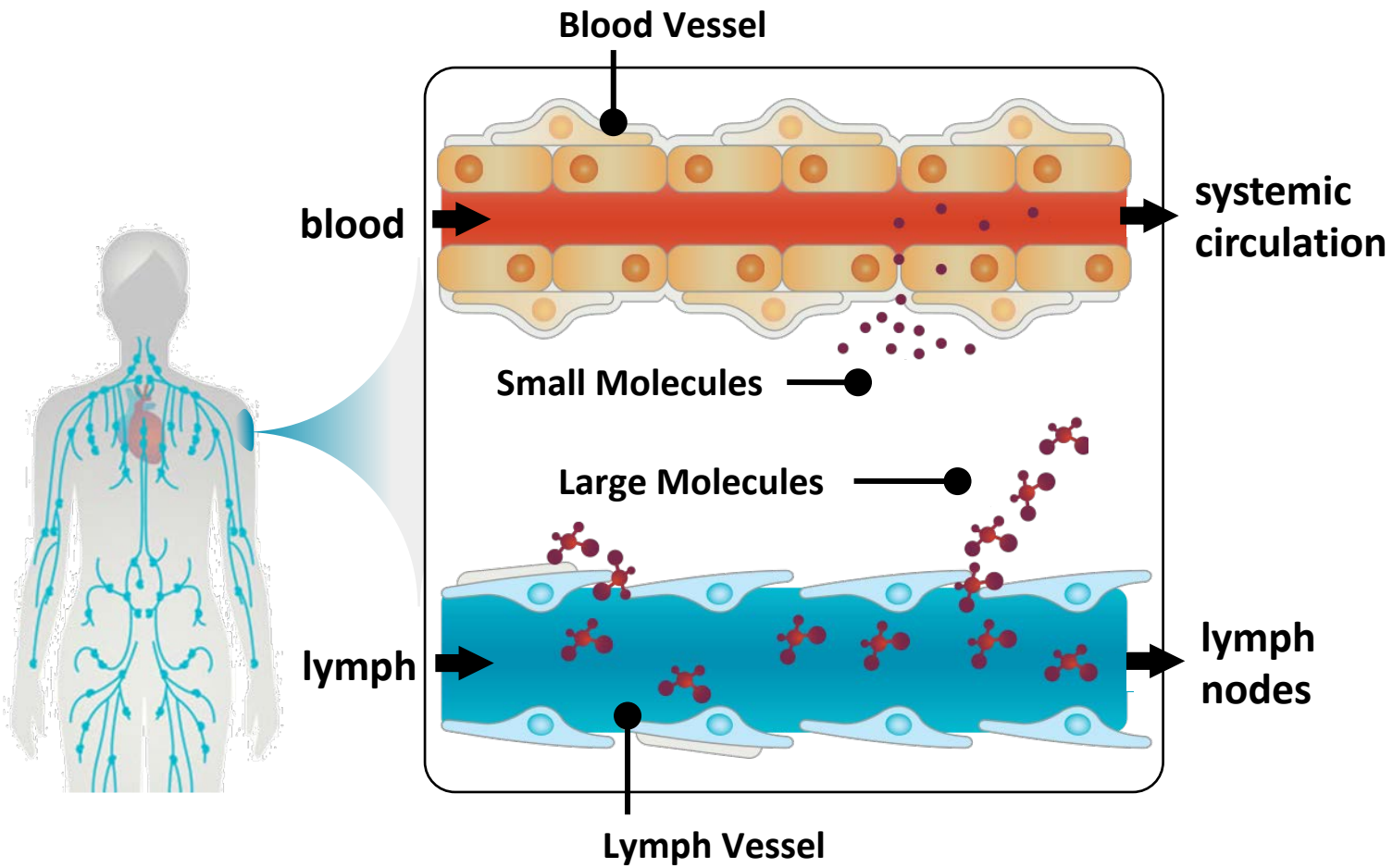
Response Coordination

APC : T Cell Interaction

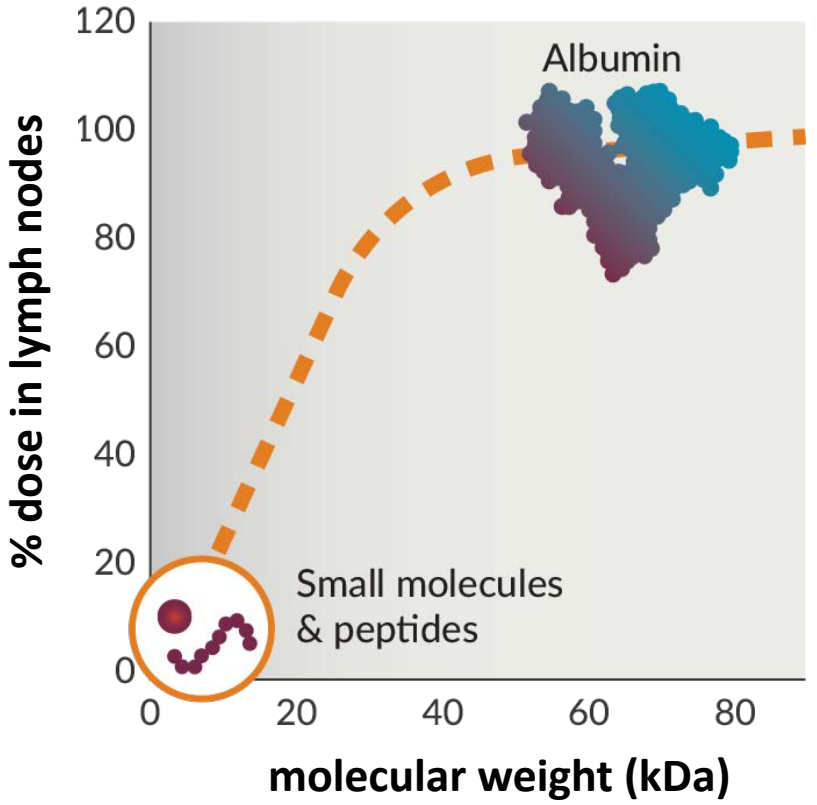
- **Expansion**
- **Persistence**
- **Anti-tumor Activity**

Albumin is the Ideal Carrier to Transport Immuno-therapies and Vaccines into Lymph Nodes

Tissue Injection Site



Molecular Size Drives Lymphatic Targeting

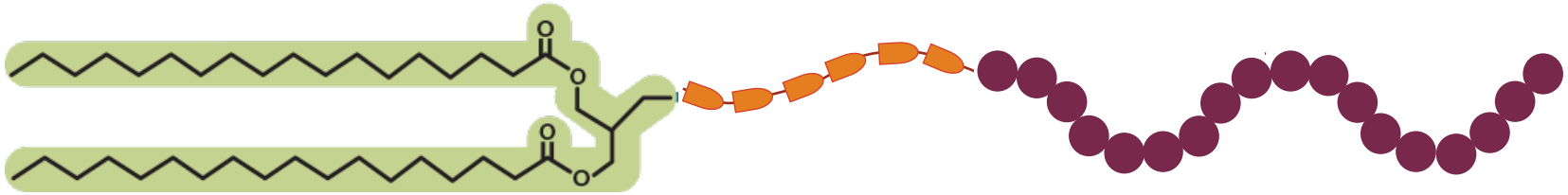


How can Lymph Node Targeting Improve Cognate Peptide Vaccination to Enhance TCR-T Cell Therapy Against Solid Tumors?

The AMP Platform - Designing a Lymph Node Targeted Booster for TCR-T Cell Therapy

(1) AMP-Peptide
Peptide Antigen

- Cognate peptide target for cancer antigen-specific TCR
- AMP modification gives >10-fold improved lymph node targeting



AMP Modification: Albumin Binding Lipid for Lymph Node Targeting

PEG Linker

Peptide: Cognate TCR Epitope

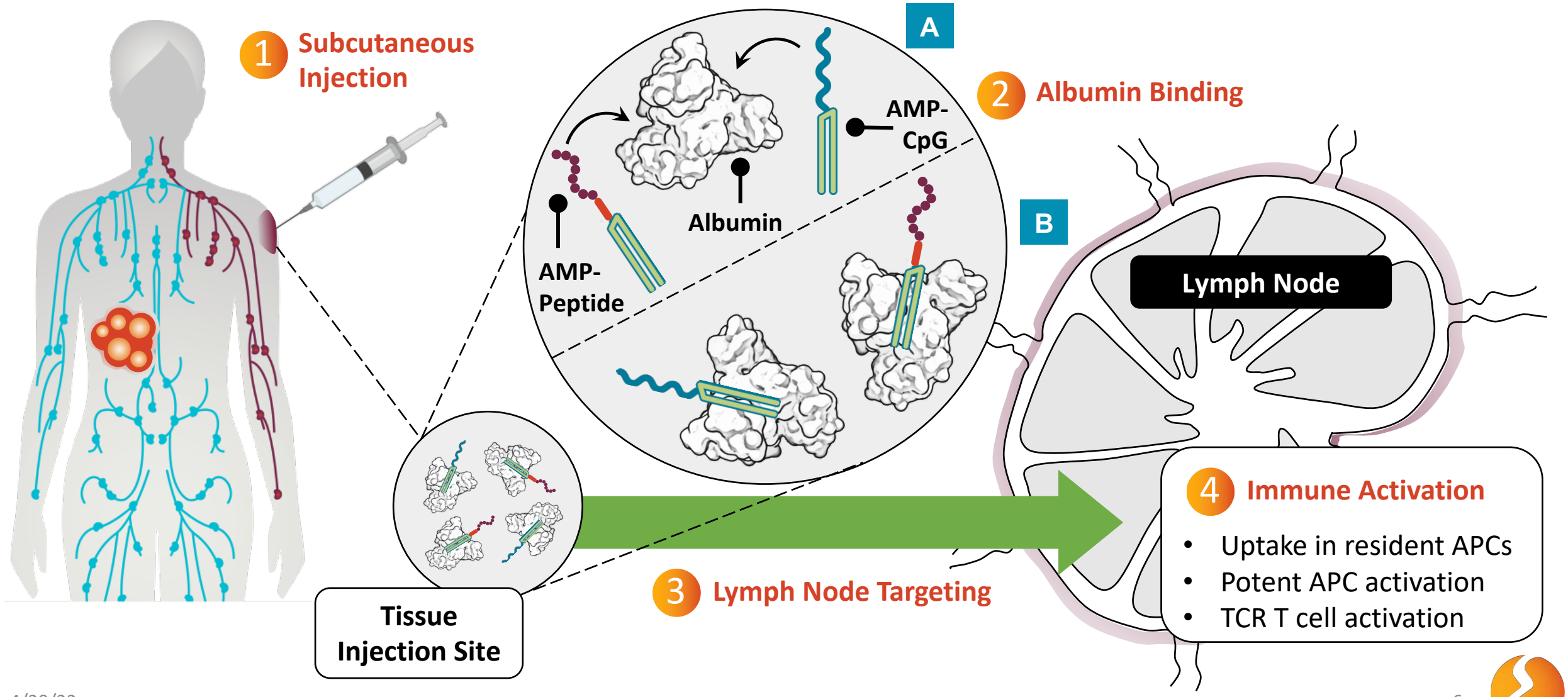
(2) AMP-CpG
Adjuvant

- Potent TLR-9 immuno-activator
- AMP modification gives >10-fold improved lymph node targeting

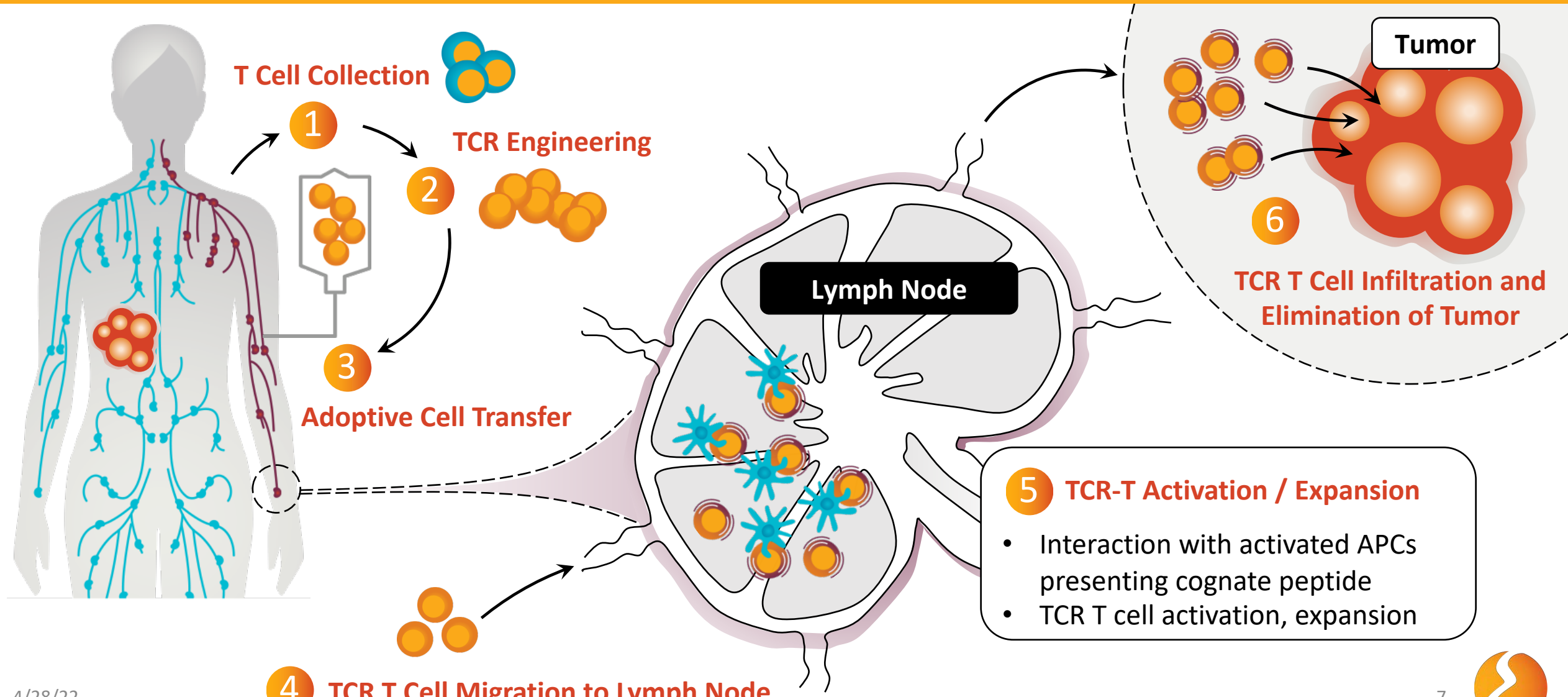
AMP Modification: Albumin Binding Lipid for Lymph Node Targeting

CpG DNA: TLR-9 Agonist

Designing a Lymph Node Targeted Booster for TCR-T Cell Therapy

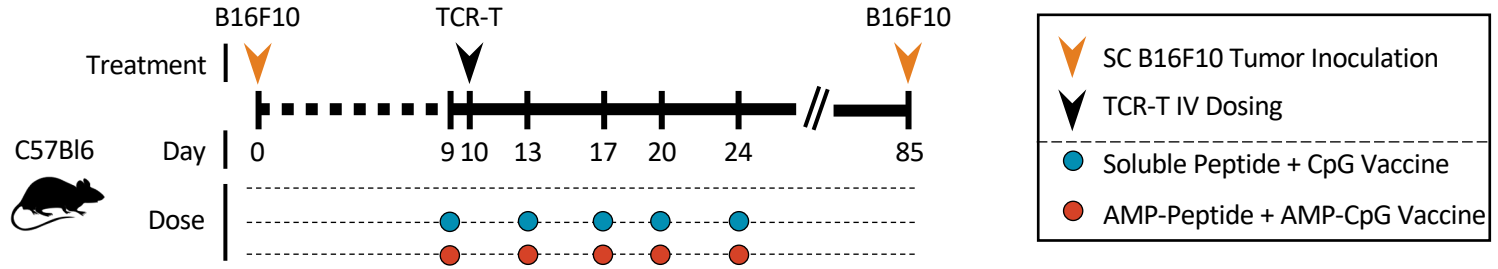


Designing a Lymph Node Targeted Booster for TCR-T Cell Therapy



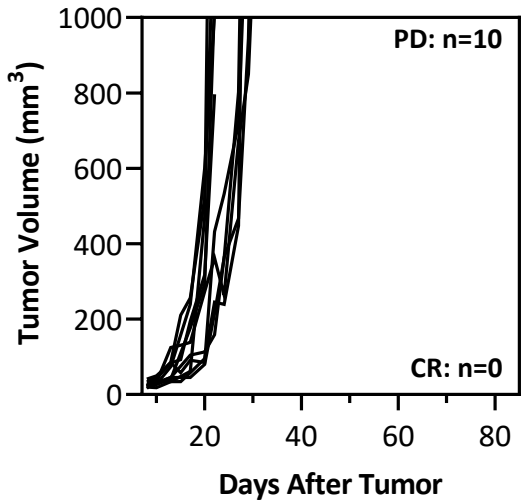
AMP-Boosting Potently Enhances TCR-T Therapy to Eliminate Established Solid Tumors

Experimental Schema:

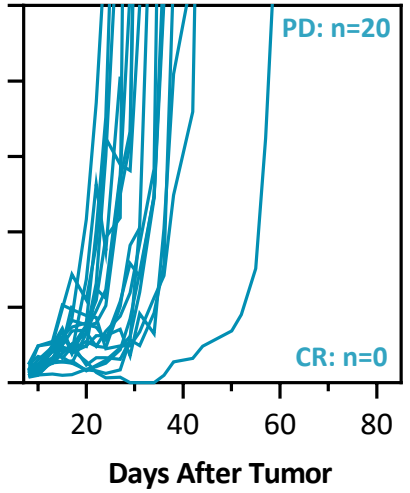


Anti-tumor Therapeutic Efficacy

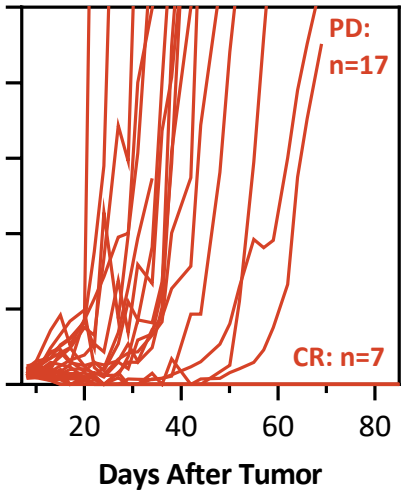
TCR-T Cell Therapy



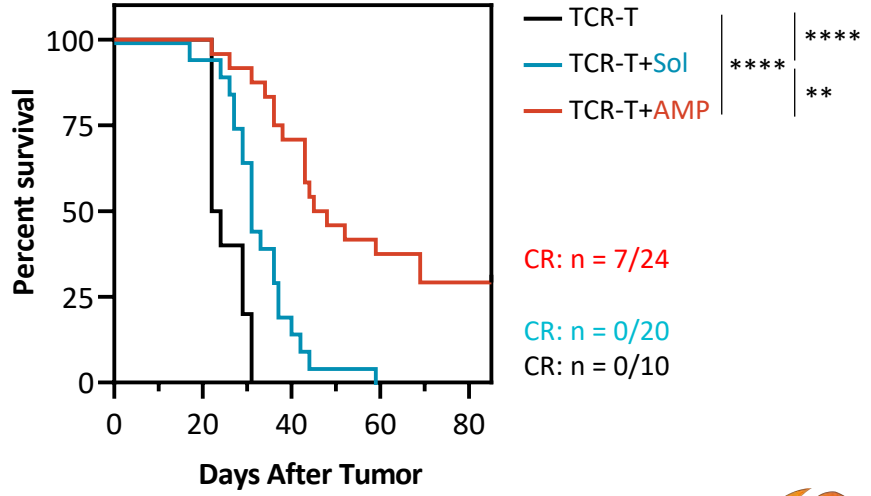
TCR-T Cell Therapy
+ Soluble CpG/Peptide



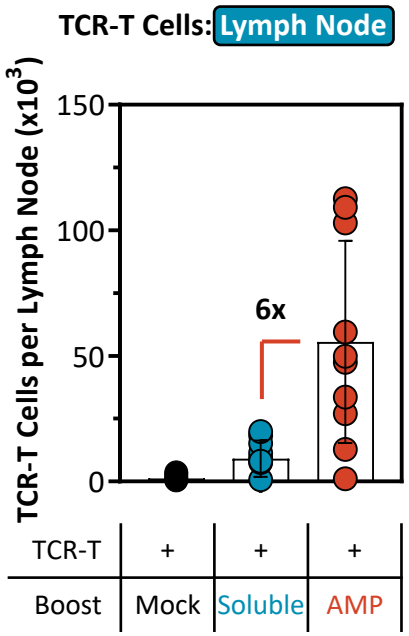
TCR-T Cell Therapy
+ AMP CpG/Peptide

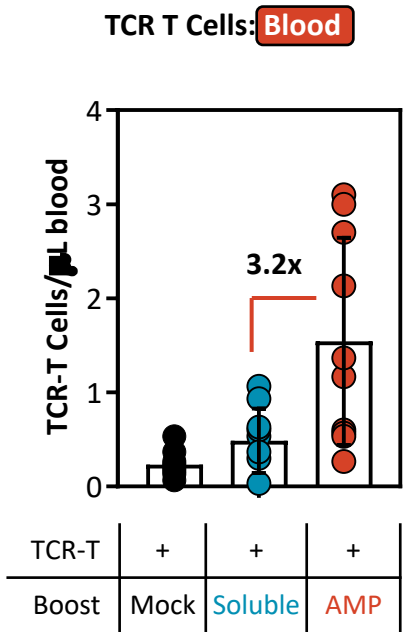


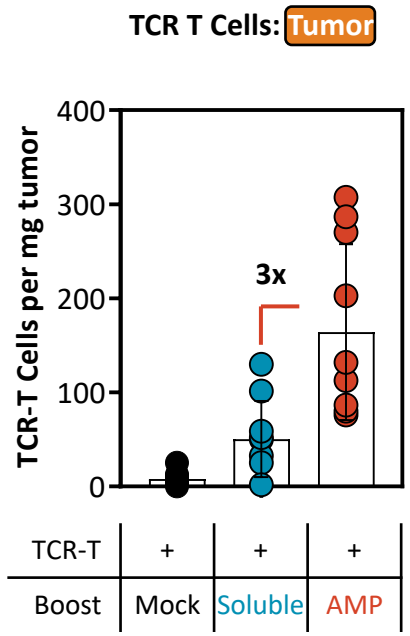
Overall Survival

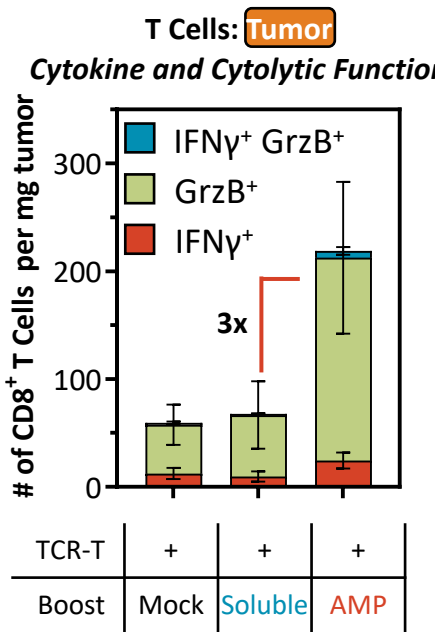


AMP-Boosting Enhances TCR-T Expansion and Function in Lymph Nodes and Solid Tumors









Tumor Microenvironment

- Increased T cell **activation**
- Enhanced **cytokine production**
- Enhanced T cell **proliferation**
- Improved **cytotoxic function**

AMP-vaccination **primes and expands** TCR-T cells in lymph node

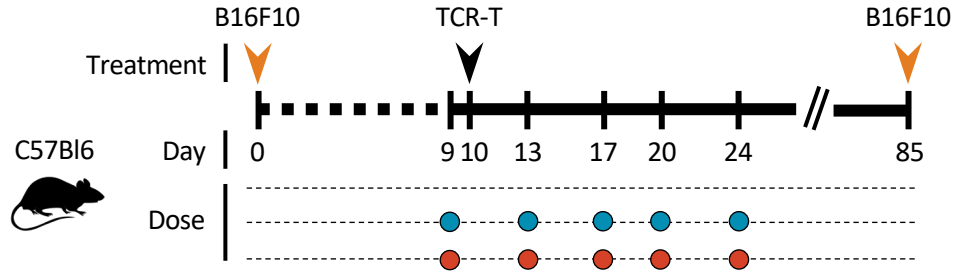
TCR-T cells circulate and **target** peripheral tumor sites

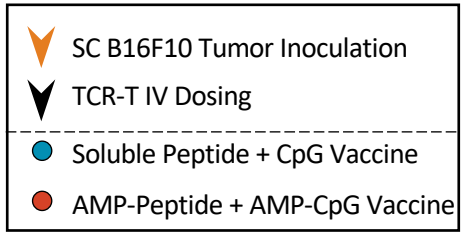
Leading to greater **tumor infiltration**

For significantly improved T cell **function** in the tumor

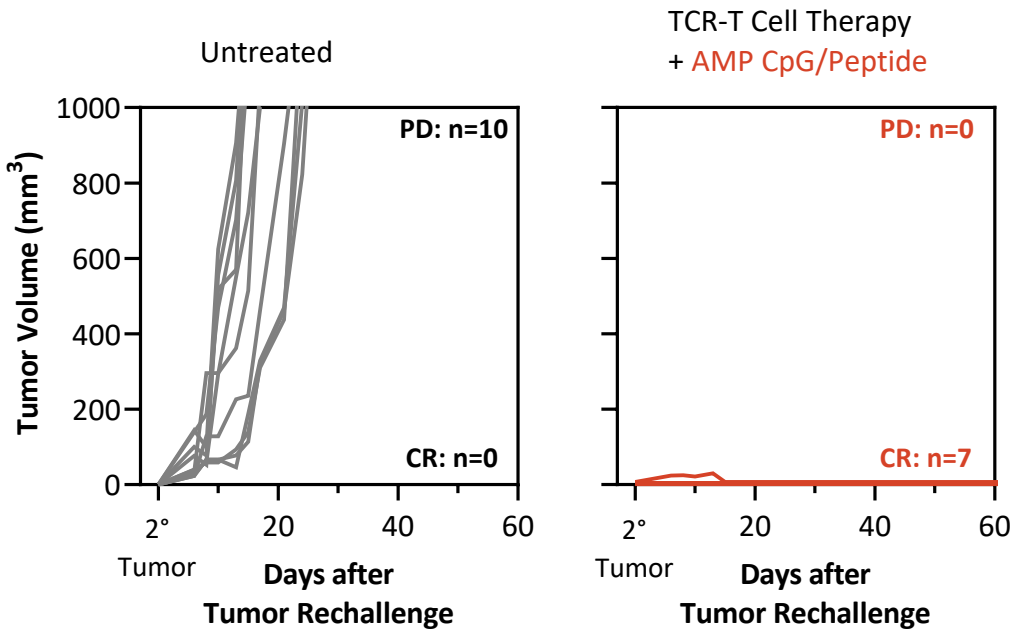
AMP-Boosting Promotes Complete Durable Protection Against Solid Tumor Recurrence

Experimental Schema:

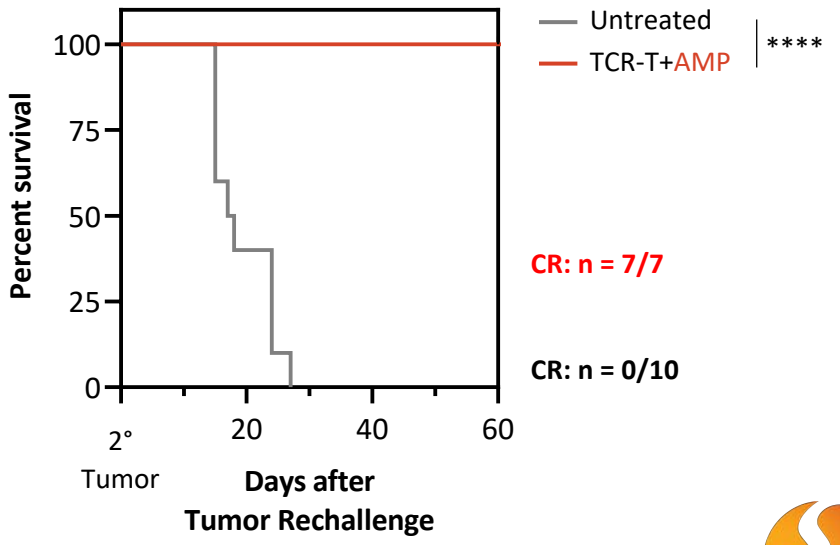




Protection Against Tumor Recurrence



Overall Survival



AMP-Boosting of TCR-T Cell Therapy for Solid Tumors

Enhance Anti-Tumor Activity

- AMP-boosted TCR-T cells eradicate established tumors in a syngeneic mouse model
- Protection against secondary tumor challenge

Promote TCR-T Cell Persistence and Fitness

- AMP-vaccination activates and expands TCR-T cells within lymph nodes
- Activated TCR-T cells circulate and target peripheral sites

Increase TCR-T Cell Tumor Infiltration

- TCR-T cells traffic to and infiltrate tumors
- Infiltrating TCR-T cells resist TME inhibition and remain proliferative and cytotoxic

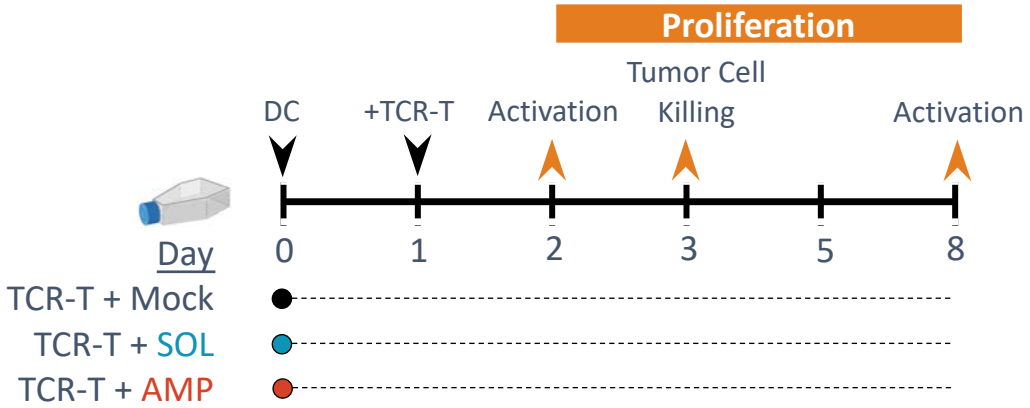
Induce Endogenous Anti-Tumor Response

- Induce endogenous T cells specific for tumor associated antigens
- Protection from secondary challenge after depletion of adoptively transferred T cells.

Can AMP-Peptides Enhance the Functional Characteristics of NY-ESO-1 Specific TCR-T Cells?

Amphiphile Boosting of NY-ESO-1 Specific TCR-T Cells

NY-ESO-1; HLA A*02:01



Experimental Strategy:

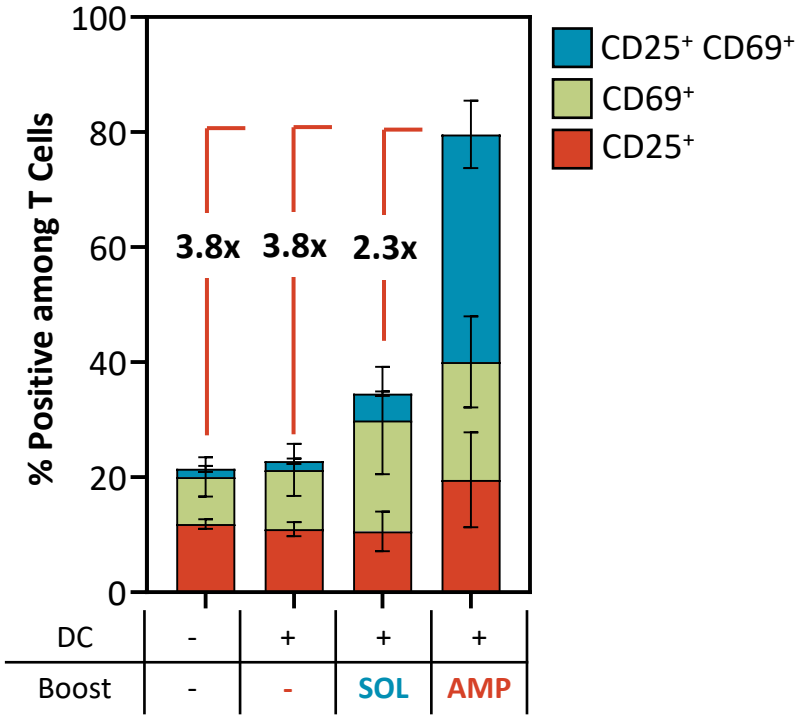
1. HLA-matched human T cells are transduced with NY-ESO-1-specific TCRs
2. Autologous human DCs are pulsed with AMP/SOL-peptides
3. T-cells co-cultured with AMP-peptide-pulsed DCs overnight
4. T cells assessed for activation (CD25/CD69), proliferation, cytokine production, and target tumor cell killing

Evaluating AMP-peptide activity on human NY-ESO-1-specific T cells, in the context of human DC and tumor cells

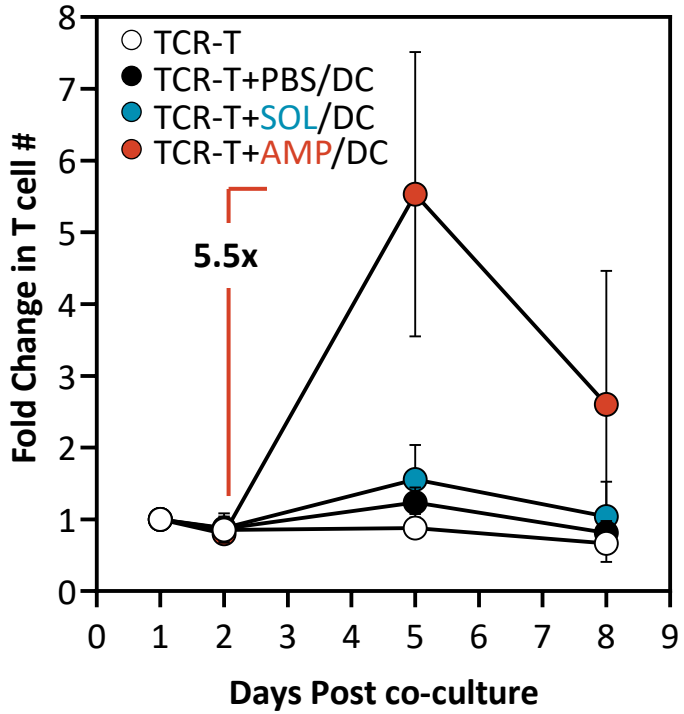
AMP-Vaccination Enhances Functional Characteristics of Human TCR-T Cells While Soluble Comparators are Not Active

NY-ESO-1; HLA A*02:01

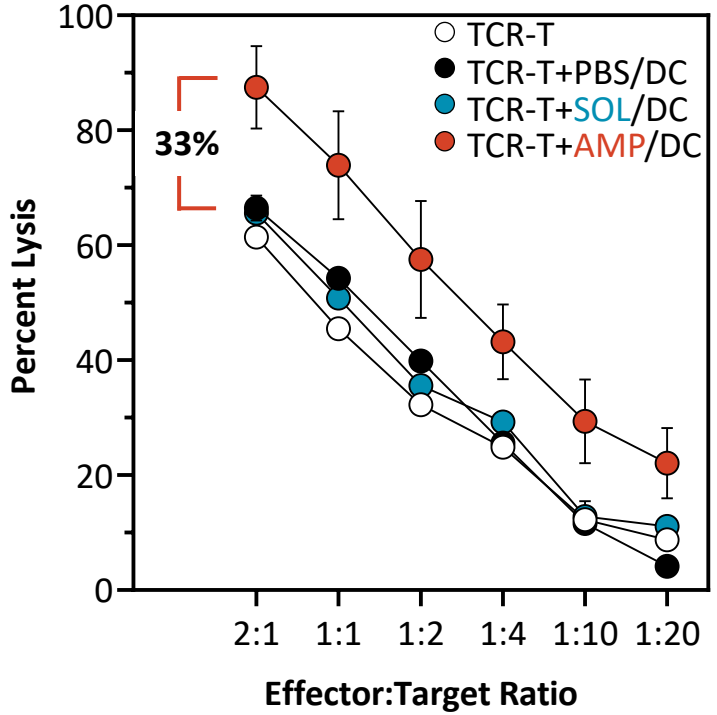
TCR-T Activation



TCR-T Proliferation



TCR-T Tumor Killing



AMP-peptides activate human NY-ESO-1-specific TCR-T cells to promote anti-tumor cell effector function

AMP-Boosting of TCR-T Cell Therapy for Solid Tumors

Syngeneic Murine Tumor Model

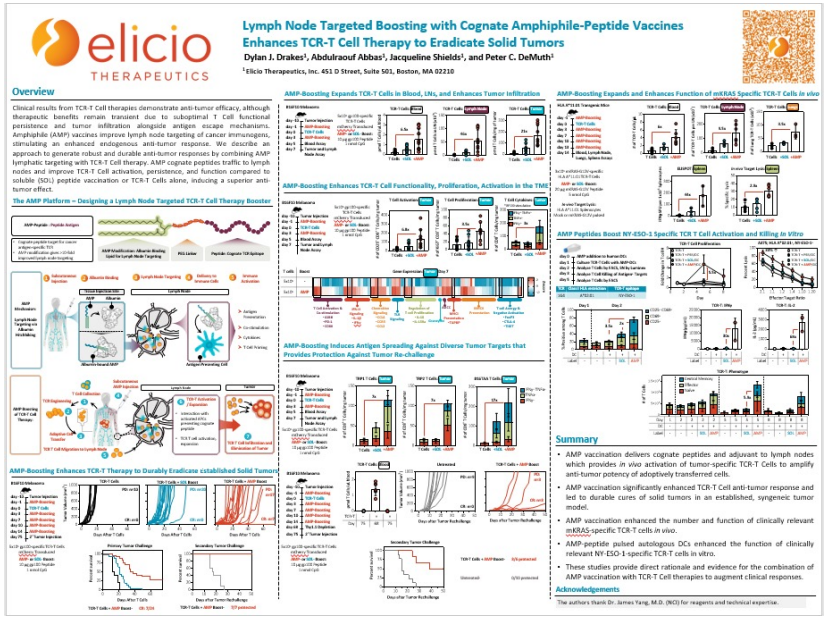
- Increased TCR-T Cell Expansion
- Enhanced TCR-T Cell Lymph Node Activation
- Improved Solid Tumor Infiltration
- Solid Tumor Elimination
- Durable Protection Against Recurrence

Clinically Relevant Human Model System

- Drove TCR-T Cell Proliferation
- Enhanced TCR-T Cell Activation
- Increased Production of Pro-inflammatory Cytokines
- Enhanced TCR-T Cell Cytotoxic Function

Peter DeMuth PhD, Abdul Abbas MS, Jackie Shields MS

Visit us at Poster #2029 during Poster Session #2 Tonight!



Liu, Irvine, et al. **Nature** 2014
Steinbuck, DeMuth, et al. **Science Advances** 2021
Martin, Irvine, et al. **Biomaterials** 2021