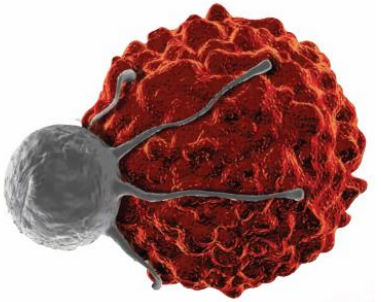
September 4-7 2018, Boston, MA

CAR-TCR Summit



P-MUC1C-101: A Stem Cell Memory CAR-T Therapy for Epithelial-Derived Solid Tumors

Devon J. Shedlock, PhD

VP, Preclinical Development

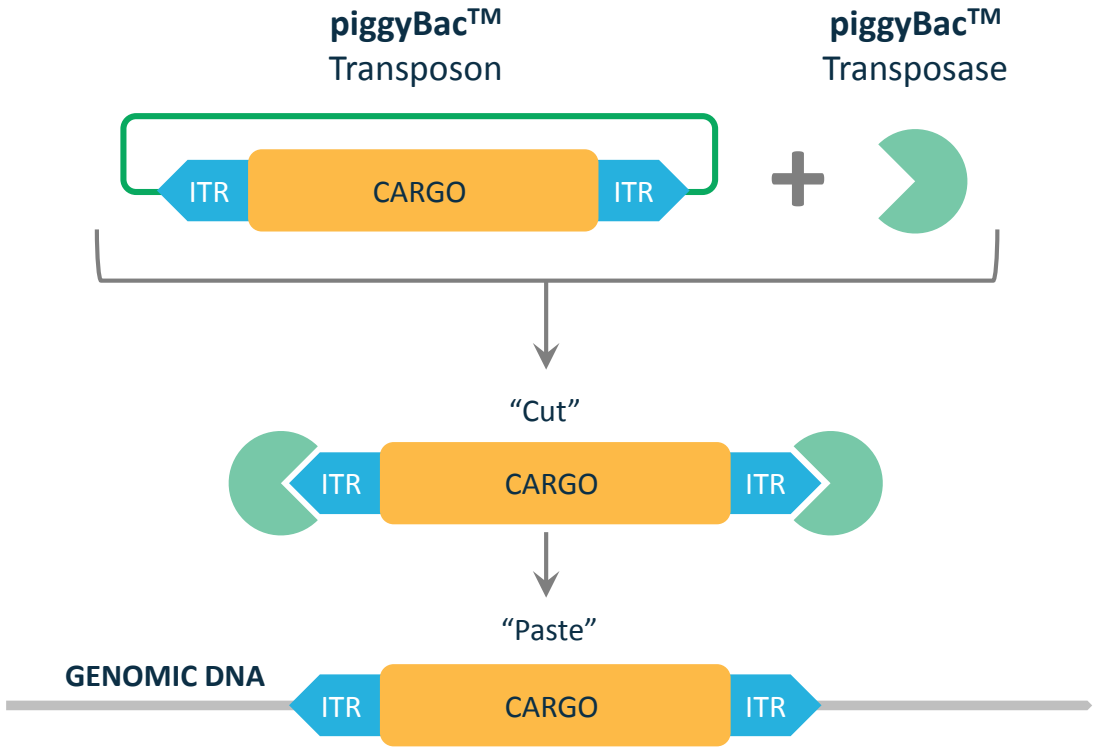
September 5th, 2018

POSEIDA THERAPEUTICS

piggyBac™ Enables Multiple Differentiated CAR-T Product Attributes

piggyBac™ is a superior DNA delivery system for developing CAR-T and other gene therapy products

- **Unprecedented cargo capacity (>30X lentivirus)** – three-in-one transgene and possibility of multiple CAR or TCR molecules
- Creates highly desirable **T Stem Cell Memory (Tscm) Phenotype**
- Non-viral delivery system **– non-oncogenic and non-mutagenic**
- **High insertion efficiency** and **stable transgene expression**
- **Faster** to clinic with **lower cost** than viral methods
- **Substantial IP portfolio** with no dominant or competing IP

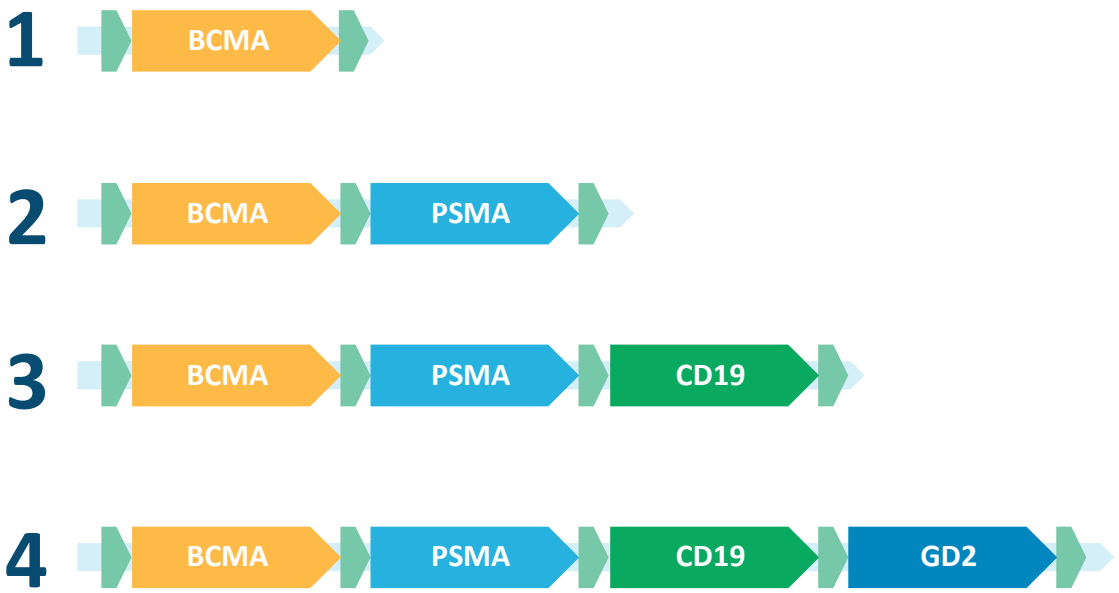


POSEIDA THERAPEUTICS

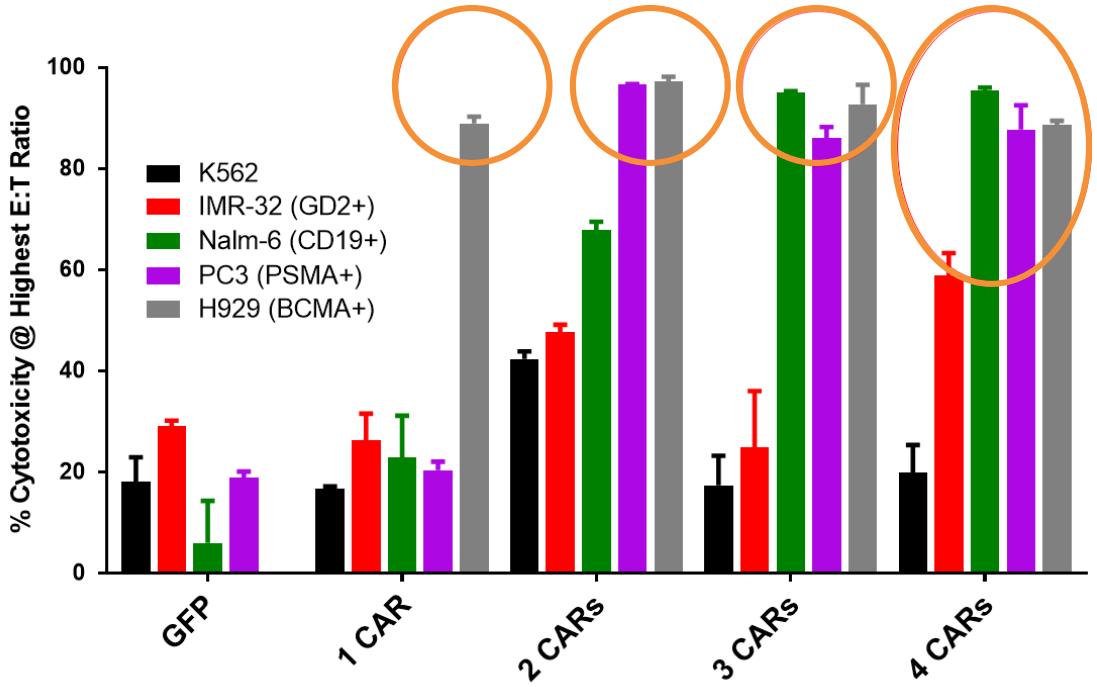
piggyBac™ Unmatched Cargo Capacity Increases Optionality

piggyBac™ effectively delivers multiple full-length CARs in single transposon system

 # Full-length CARs*



Function (Killing)



** Plus selection gene and marker gene*

POSEIDA THERAPEUTICS

Massive piggyBac™ Cargo Capacity Allows for Delivery of Three-In-One Transgene for CAR-T products

1 CAR-T MOLECULE

Superior binding molecule

- Molecule (Centyrin, VH, scFv, etc…) with **high-specificity binding**
- Fully human and **not susceptible to tonic signaling**

2 POSITIVE SELECTION

Drug resistance gene permits positive selection

- **~100% of T-cells** in final product express the CAR molecule
- Predicted to result in **better therapeutic index**

3 SAFETY SWITCH

Incorporates proprietary safety switch

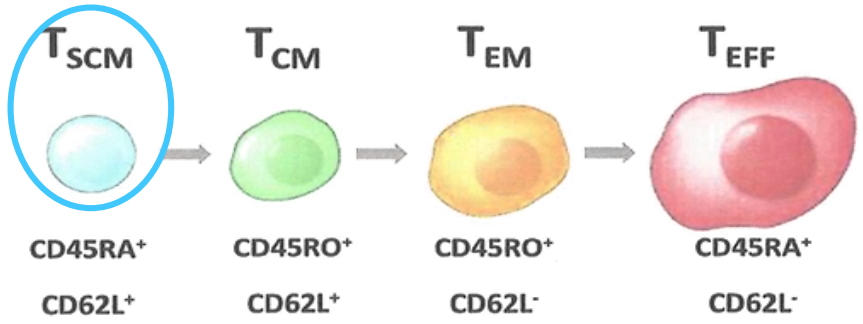
- Rapid, dose-dependent elimination of engineered T-cells if needed
- Management of Cytokine Release Syndrome (CRS) or other AEs

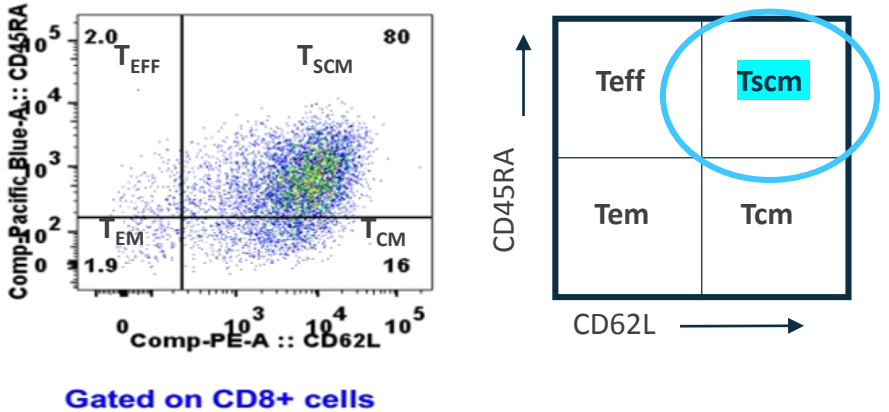
POSEIDA THERAPEUTICS

Poseida CAR-T Products Comprised of Highly Favorable Stem Cell Memory T Cells

Tscm phenotype should increase duration of response and allow for relapse control without re-administration

- Ability to develop product with **high percentage of Tscm** cells is a distinct competitive advantage
- **piggyBac™ preferentially transposes in Tscm cells**
  - **Tscm cells persist and live longer** than effector cells
  - **Tscm cells** can produce potentially unlimited effectors cells
- Tscm-rich product should lead to **better engraftment** and **better duration** of response with the **potential for re-response**
- **Lentivirus-produced products have not achieved high Tscm** *published* percentages ranging from less than 1% to ~14%





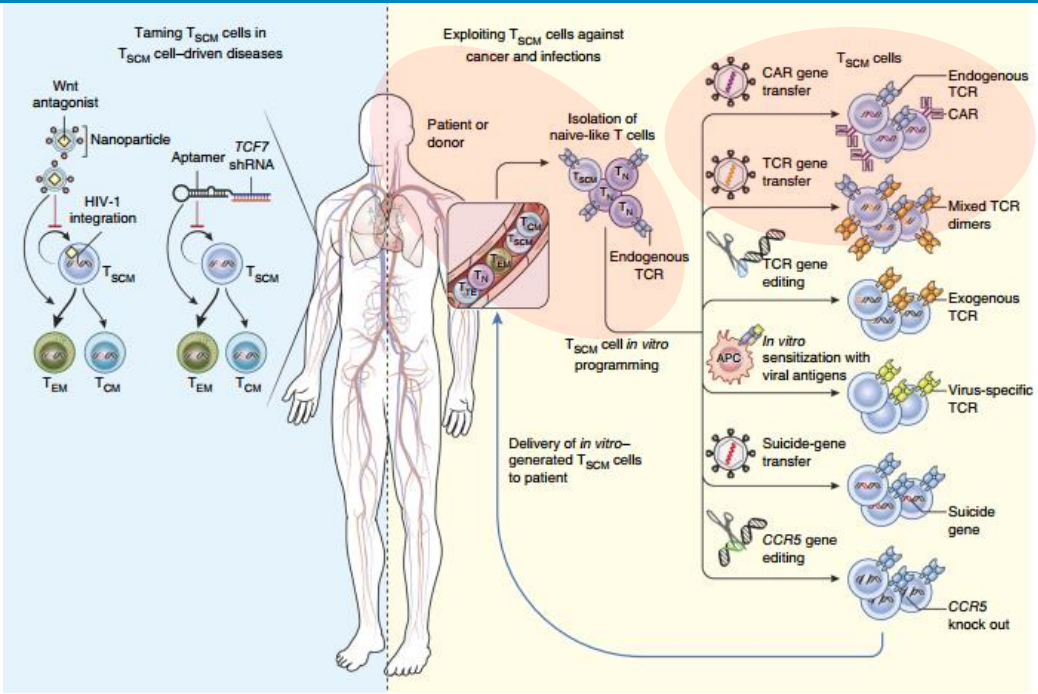
Gated on CD8+ cells

POSEIDA THERAPEUTICS

T_{scm} May Be Key to Potent and Durable Responses

Poseida CAR-T Products Comprised of Highly Favorable Stem Cell Memory T Cells

- **Correlates with clinical response**
  - *Melenhorst J. et al., UPenn (2017) 20th ASGCT*
  - *Basu et al., Adaptimmune (2017) CAR-TCR Summit*
  - *T_{CM}: Larson, Juno (2018) AACR*
- Without prior fractionation of T_N/T_{CM}, Akt inhibitors and shortened process are mostly successful in increasing T_{CM} during viral manufacture
- "The extreme longevity, the robust proliferative potential and the capacity to reconstitute a wide-ranging diversity of the T cell compartment make **the T_{scm} cell type an ideal cell population to employ in adoptive immunotherapy**"



T memory stem cells in health and disease

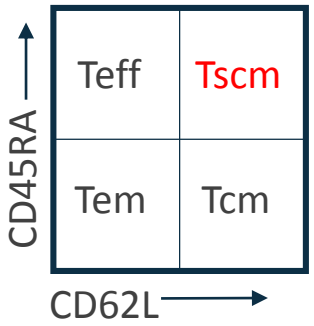
Luca Gattinoni[1], Daniel E Speiser[2], Mathias Lichterfeld[3] & Chiara Bonini[4,5]

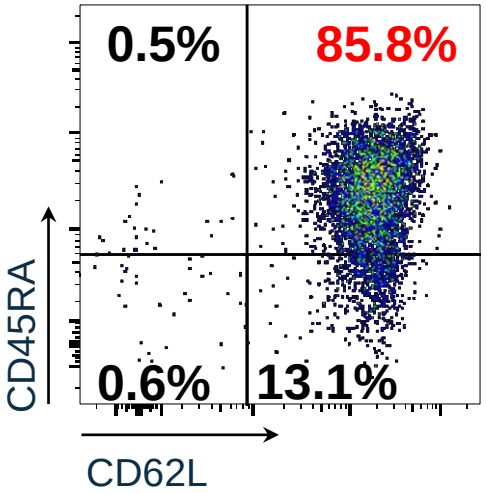
18 VOLUME 23 | NUMBER 1 | JANUARY 2017 NATURE MEDICINE

Gattinoni et al. (2009) Nat Med; Hinrichs et al. (2009) PNAS; Hinrichs et al (2011) Blood; Gattinoni et al. (2011) Nat Med; Lugli et al. (2013) JCI; Klebanoff et al (2016) JCI; Sukumar et al (2016) Cell Met; Sabatino et al. (2016) Blood;

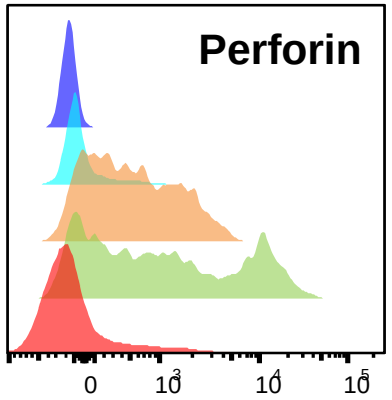
POSEIDA THERAPEUTICS

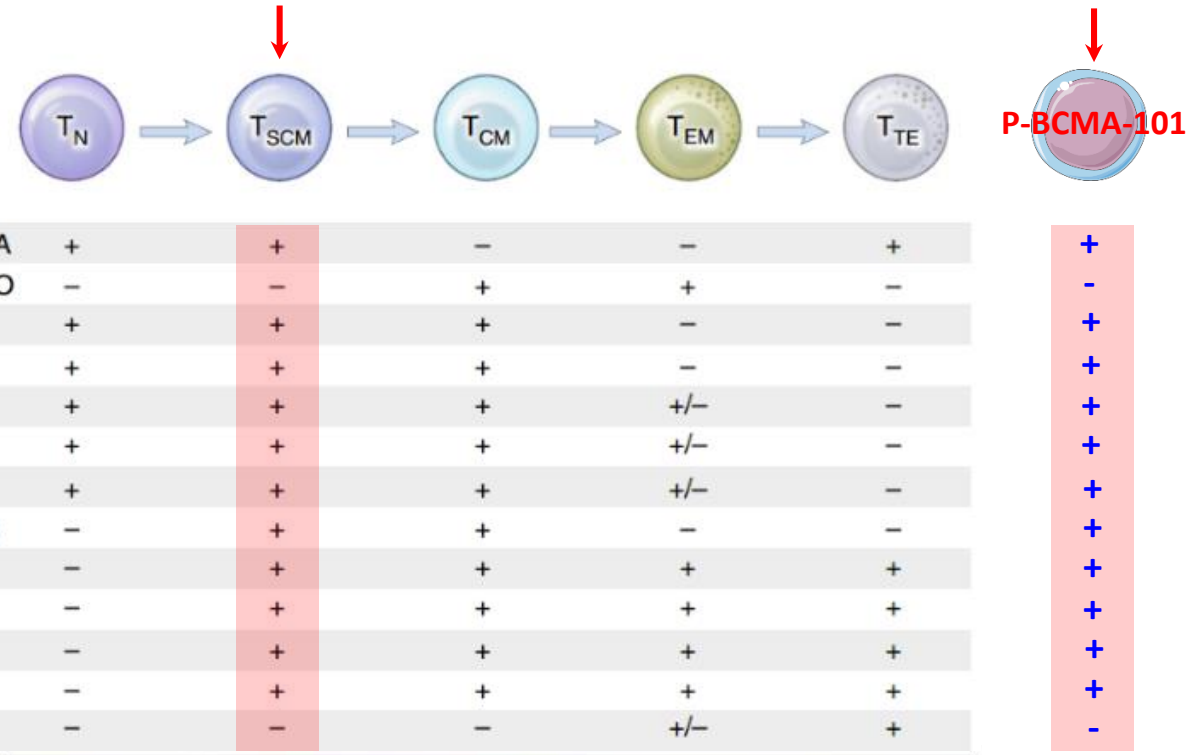
Poseida CAR-T Comprised of Highly Favorable Tscm





Naïve/Tscm
Tcm
Tem
Teff
P-BCMA-101





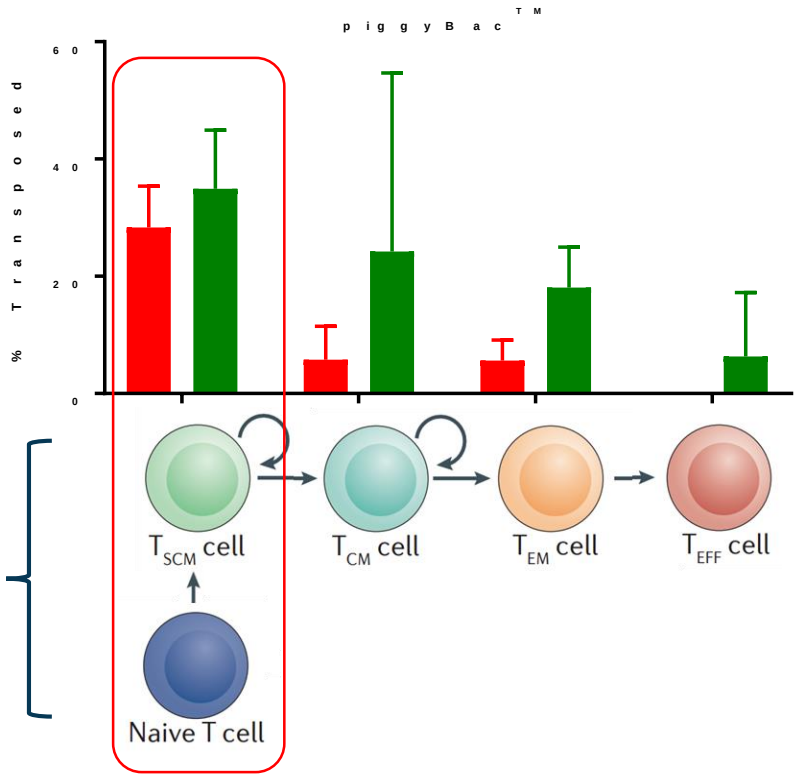
Adapted from Gattinoni *et al.* (2017) *Nat. Med.*

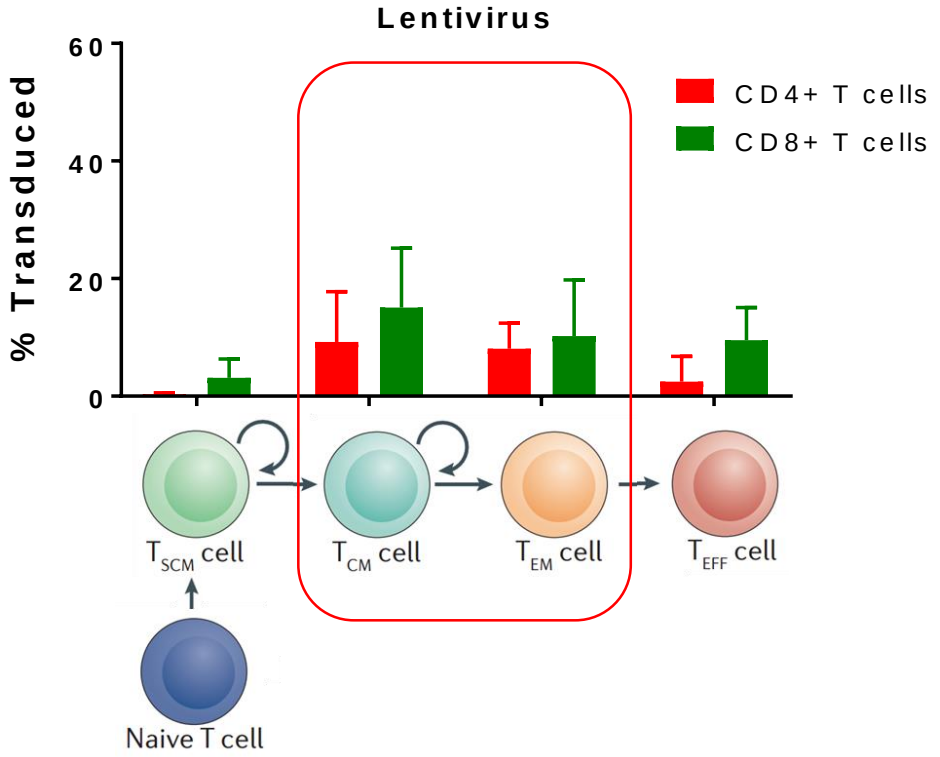
POSEIDA THERAPEUTICS

piggyBac™ and Lentivirus Modify Different T Cell Subsets

piggyBac™ preferentially transposes early Tscm cells, while lentivirus prefers differentiated T cells

We purified donor cells to these T-cell subsets and then performed optimized piggyBac™ or optimized lentivirus manufacturing on each subset





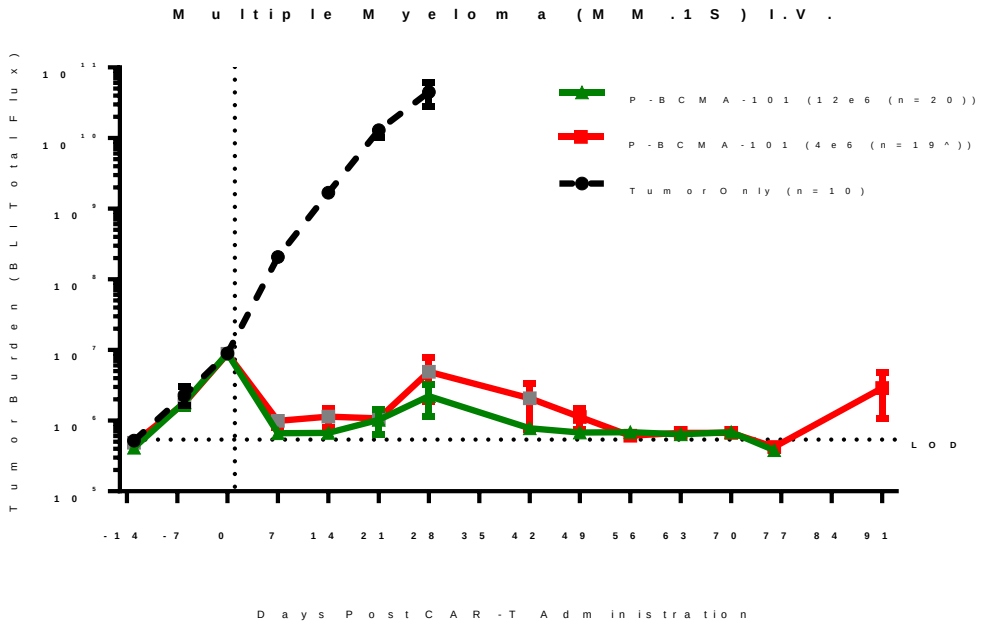
Cell graphics adapted from Henning *et al., Nat. Rev. Immunol.*, 2018

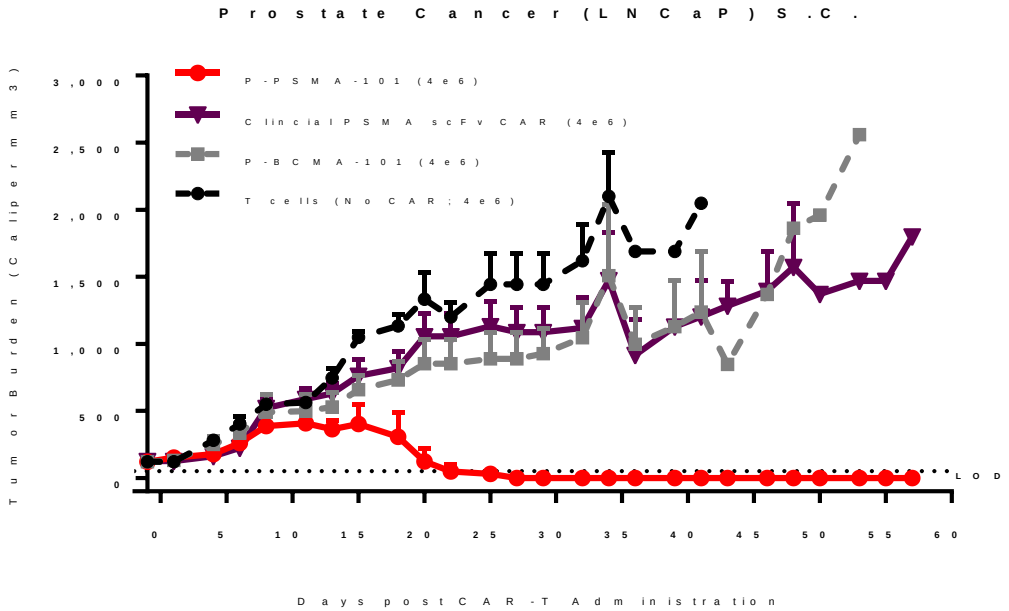
POSEIDA THERAPEUTICS

Poseida CAR-T_{scm} Unprecedented Preclinical Efficacy

P-BCMA-101: Liquid tumor (MM.1S) disseminated IV implantation in NSG mice

P-PSMA-101: Solid tumor (LNCaP) SC implantation in NSG mice





POSEIDA THERAPEUTICS

Poseida P-BCMA-101: Phase I Study Ongoing

- **Design**
  - Single dose, 3+3 dose escalation + selected expansion
  - Adult subjects with relapsed or refractory MM

- **Key Objectives**
  - **Safety**, maximum tolerated dose and/or optimal dose
  - Anti-myeloma **efficacy**
  - Expansion and functional **persistence** of the CARTyrin-T cells

CIRM
CALIFORNIA'S STEM CELL AGENCY

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	P-BCMA-101 Tscm CAR-T Cells in the Treatment of Patients With Multiple Myeloma (MM)	• Multiple Myeloma	• Biological: P-BCMA-101 CAR-T cells	• Colorado Blood Cancer Institute Denver, Colorado, United States • Johns Hopkins University Baltimore, Maryland, United States • University of Pennsylvania Philadelphia, Pennsylvania, United States • (and 2 more...)

NIH U.S. National Library of Medicine
ClinicalTrials.gov

P-MUC1C-101

Autologous CAR-T Therapy for Multiple Solid Tumors

POSEIDA THERAPEUTICS

MUC1 Target Has Broad Pan-Tumor Potential

Mucin-1 (MUC1) is highly expressed in most epithelial-derived cancers

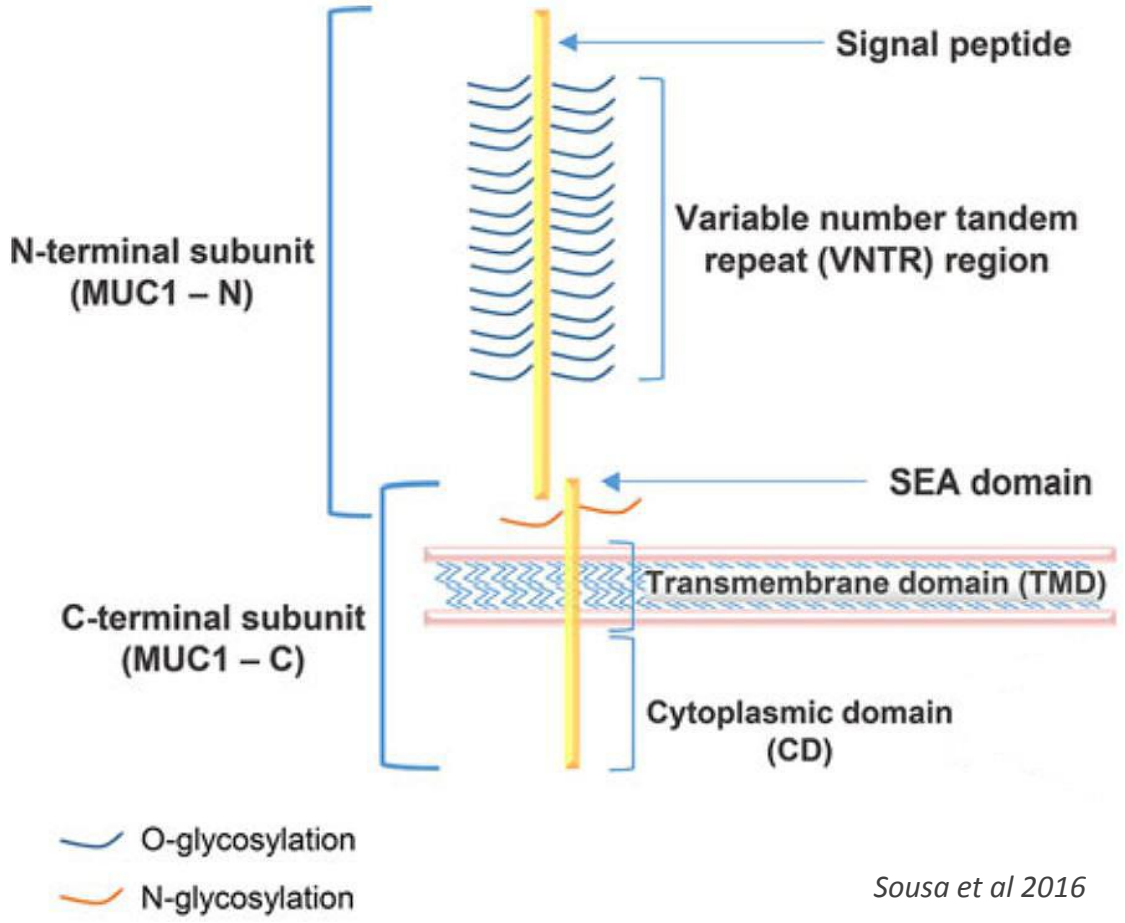
- MUC1 normally expressed on apical surface of epithelium
- Aberrant form of MUC1 is expressed on cancer cells, which is specifically recognized by our binder
- Target for multiple immunotherapies (e.g. cancer vaccines, antibody therapies)

Tumor Type	MUC1 Expression	Number of Tissues	Reference
Breast	91%	1,447	Rakha et al (2005)
NSCLC	99%	231	Merck Serono. Data on file
RCCa	84%	133	Langner et al (2004)
Colorectal	81%	243	Baldus et al (2002)
Ovarian	83%	63	Chauhan et al (2006)
H&N SCCa	82%	29	Croce et al (2001)
Nasopharyngeal	100%	38	Zhong et al (1993)
Gastric	77%	136	Utsunomiya et al (1998)
Prostate	79%	89	DeNardo et al (2005)
Pancreatic	81%	53	Qu et al (2004)
Mesothelioma	75%	20	Saad et al (2005)
Multiple myeloma	59%	125	Cloosen et al (2006)
Esophageal	32%	53	Kijima et al (2001)

Lambrechts et al

MUC1 is a Highly Complex Protein

- Single pass Type I transmembrane protein
  - N-terminal subunit (MUC1-N) and C-terminal subunit (MUC1-C) form stable heterodimeric complex
- Canonical isoform 1 is a 1,255aa protein
  - 42 20aa repeats
- MUC1 is highly polymorphic; various alleles change number of tandem repeats in N'
  - >90 isoforms; many with 20-200 VNTR repeats

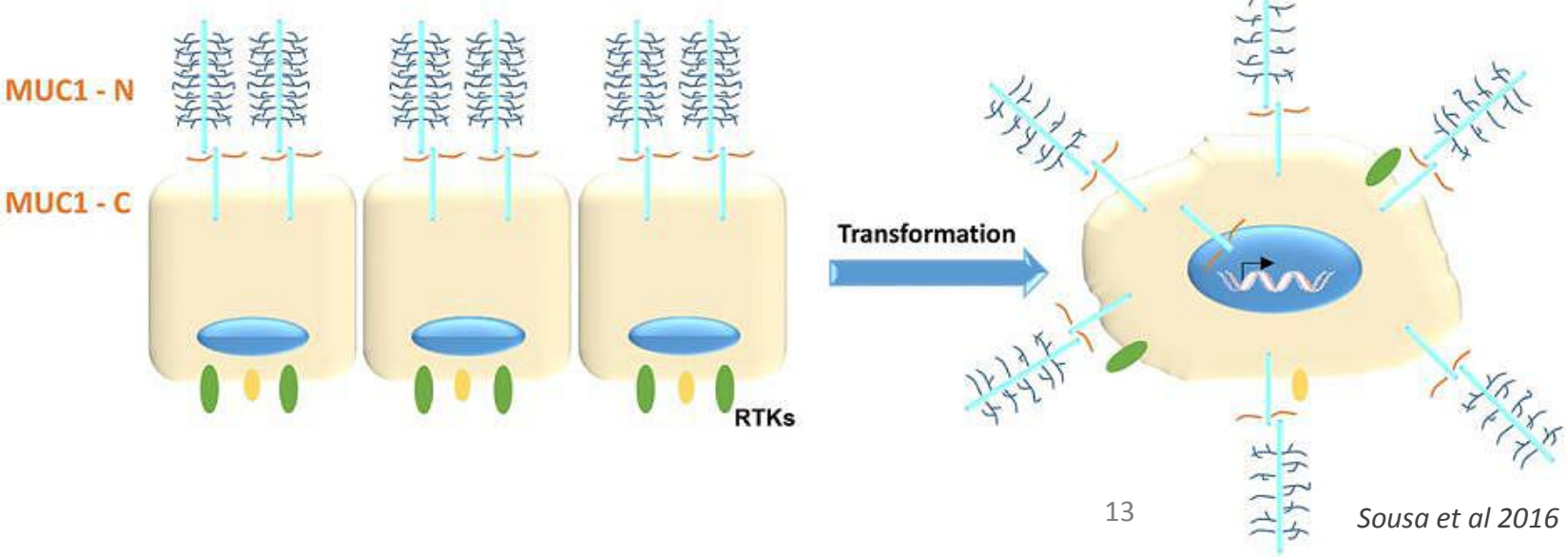


Sousa et al 2016

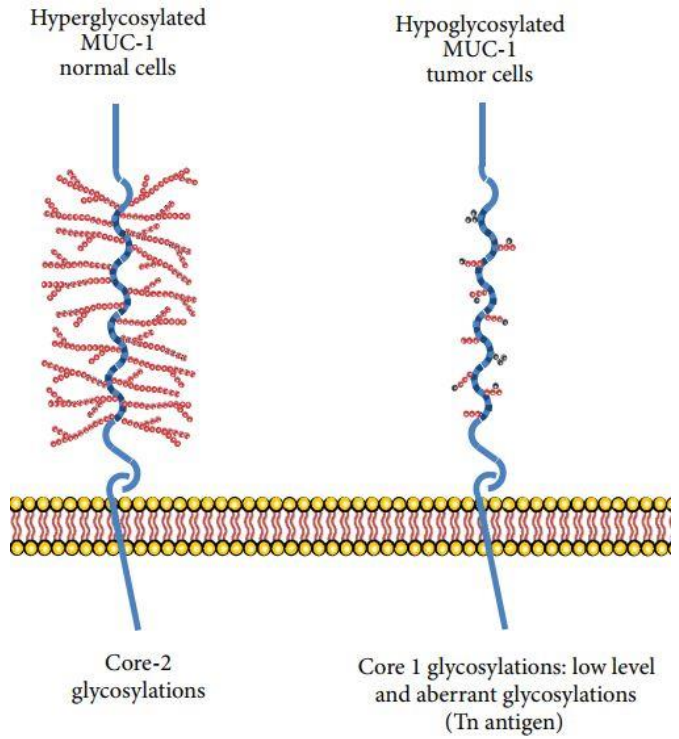
POSEIDA THERAPEUTICS

MUC1 is a Highly Complex Protein

- MUC1 confined to apical surface of normal epithelial cells
  - Hyperglycosylated on normal cells
- Polarity is lost in tumor cells
  - Hypoglycosylated on tumor cells; branches seem highly immunogenic



Sousa et al 2016



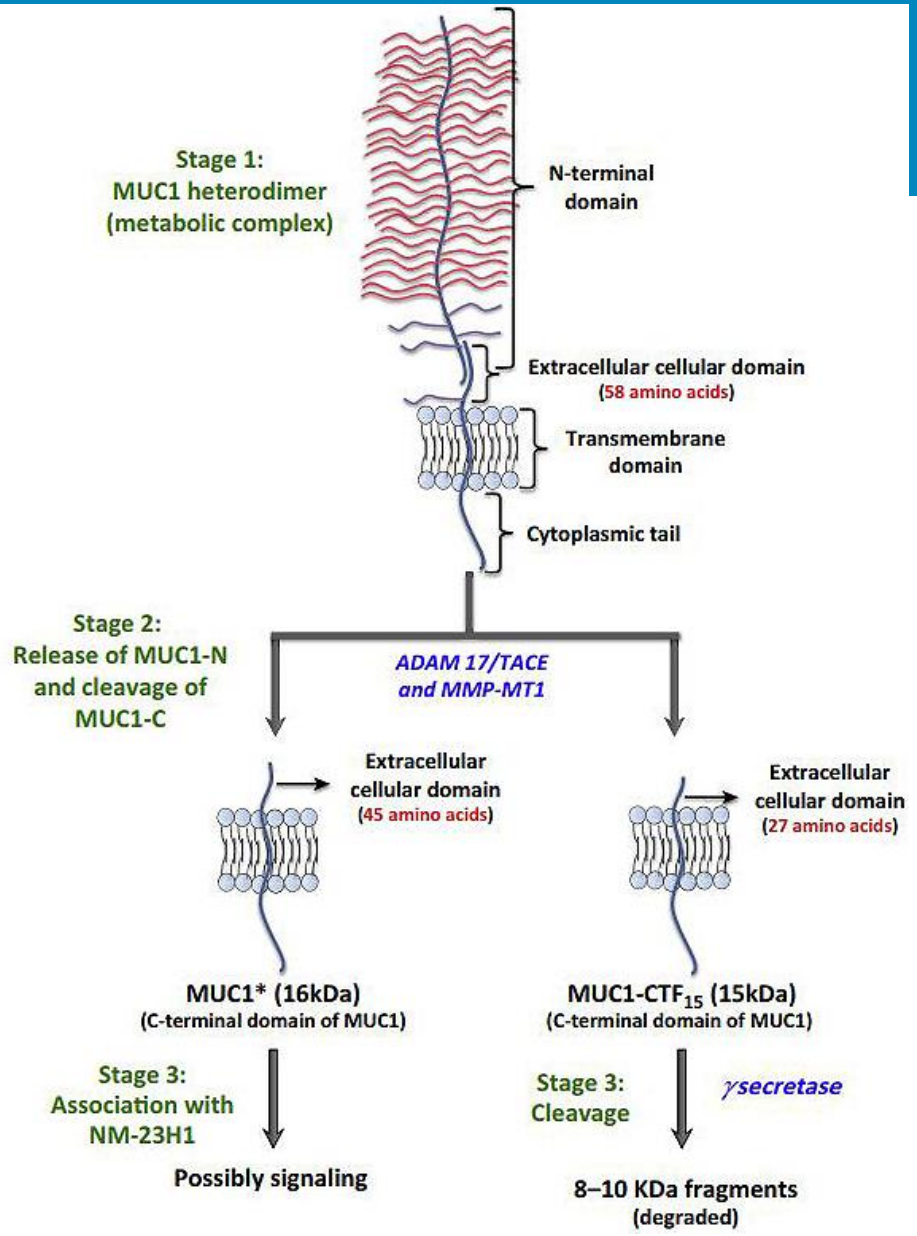
Roulois et al 2013

POSEIDA THERAPEUTICS

MUC1 is a Highly Complex Protein

MUC1 can be cleaved by proteases

- MUC1 remains heterodimeric under normal growth conditions
- ECD is cleaved (ADAM 17/TACE and MMP-MT1) to generate shorter membrane-associated peptide fragments (MUC1-C)
  - MUC1* and MUC1-CTF_{15}
- Cleaved MUC1-N is shed from cell and triggers inflammation
  - Soluble MUC1-N is target for MUC1-N-specific immunotherapies and may limit their efficacy

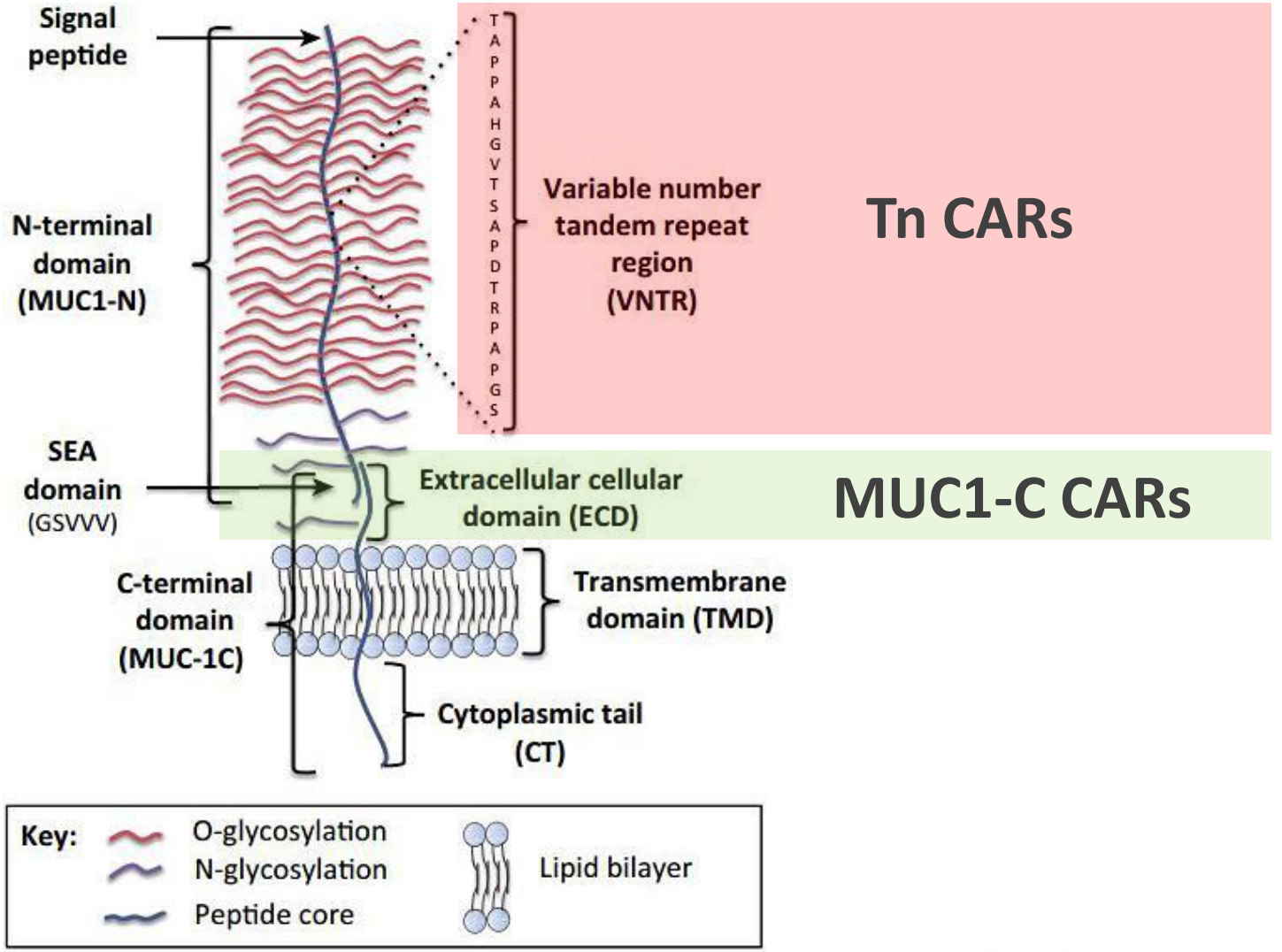


Nath et al 2014

POSEIDA THERAPEUTICS

MUC1 Comprises Various Epitopes for CAR Targeting

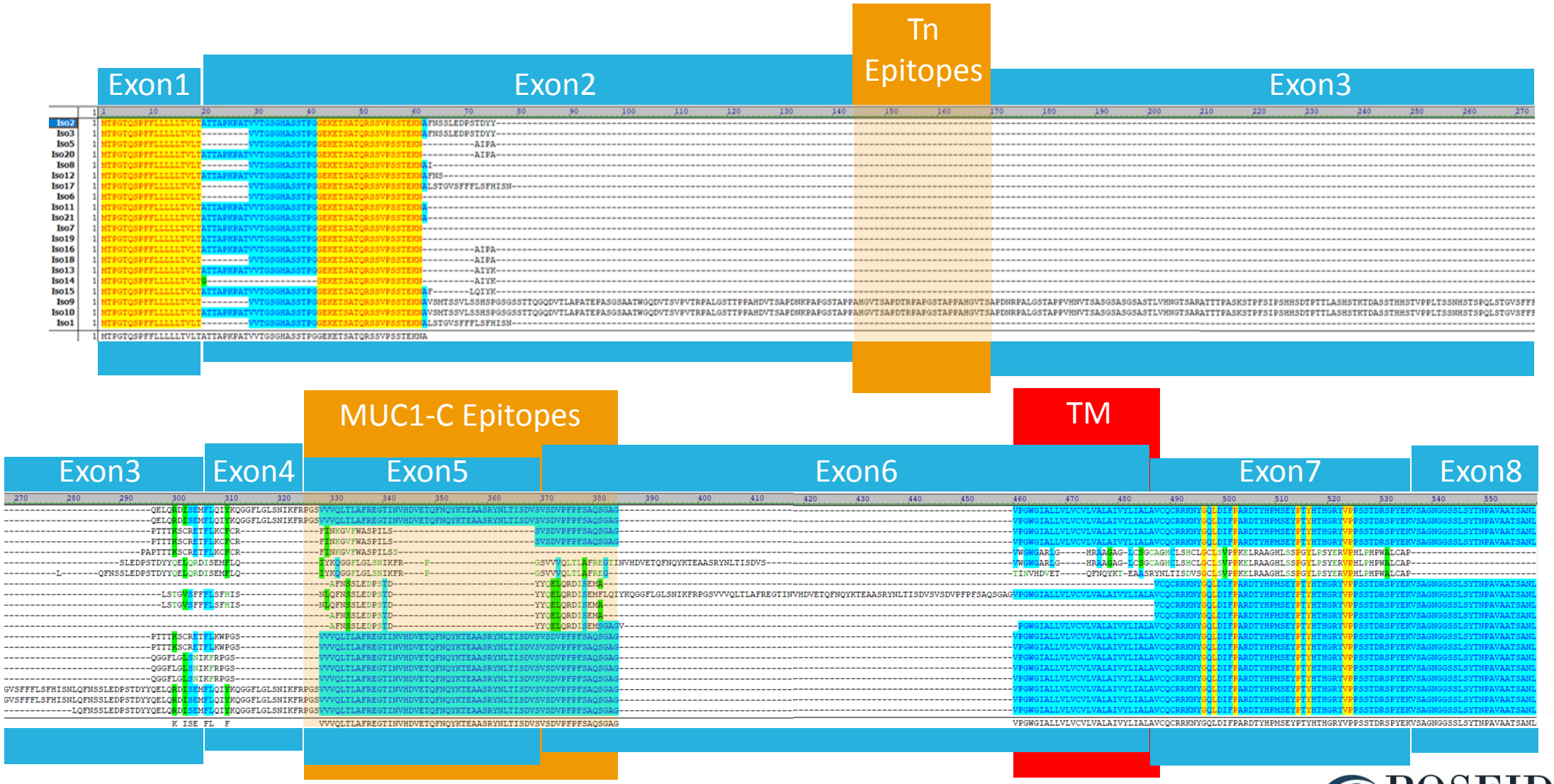
- Hypoglycosylated branches on tumor cells are highly immunogenic
  - Tn-specific binders recognize cancer-associated Tn glycoforms occurring in VNTR (*Posey et al, 2016*)
- MUC1-C specific binders
  - Target epitopes in region proximal to cell membrane
    - May be retained post-cleavage
  - Are difficult to produce and currently more rare



Adapted from Nath et al 2014

POSEIDA THERAPEUTICS

Many MUC1 Isoforms, But Not All Comprise Tn Epitopes



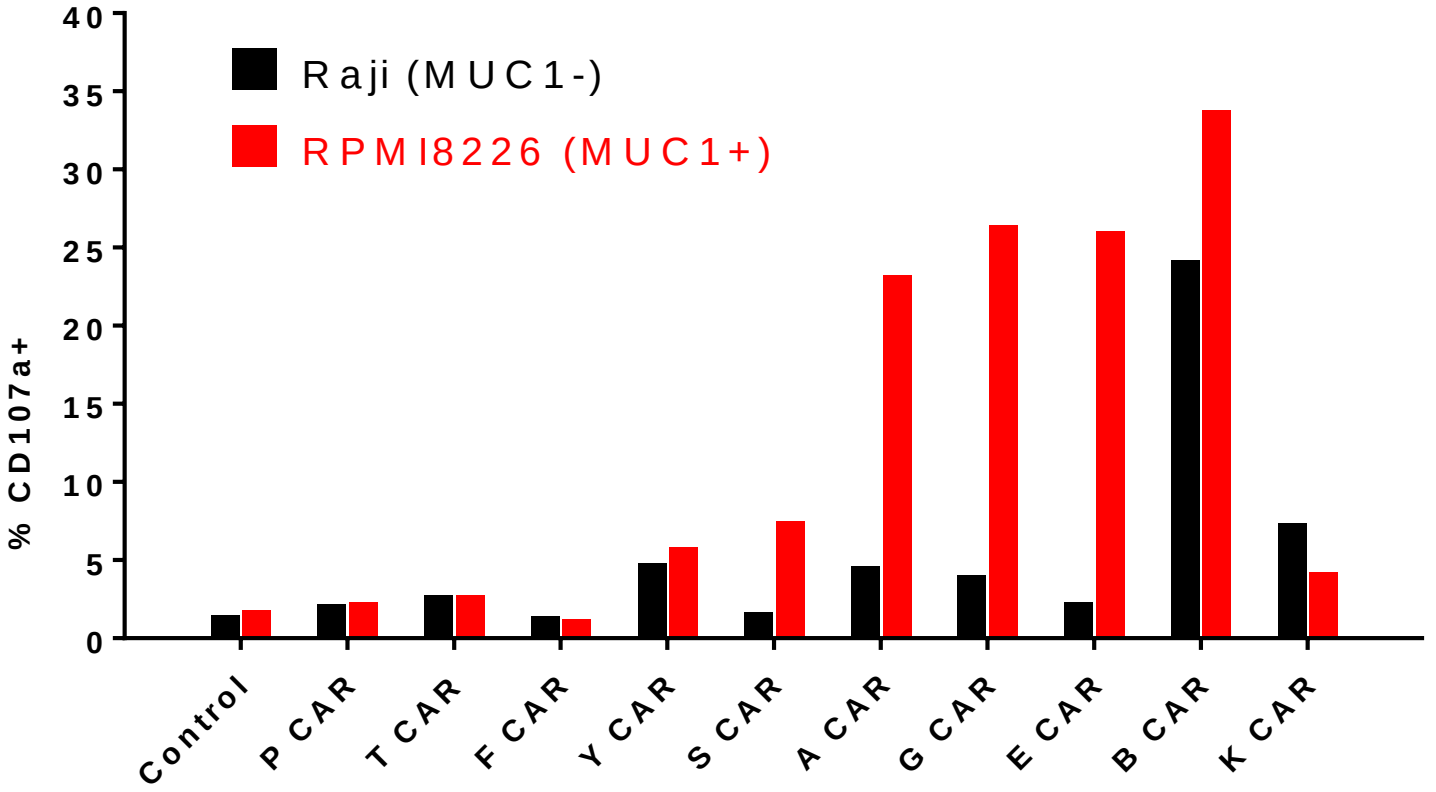
POSEIDA THERAPEUTICS

Screening CARs Recognizing MUC1

Several CAR candidates exhibited antitumor activity against a MUC1^{+} cancer cell line

We constructed multiple MUC1-C CARs and tested:

- mRNA CAR Expression in primary human pan T cells
  - Confirmed surface expression of all
- Evaluated antitumor activity against a MUC1+ cancer cell line
- A few CARs (A,G, and E) expressed MUC1-specific antitumor activity

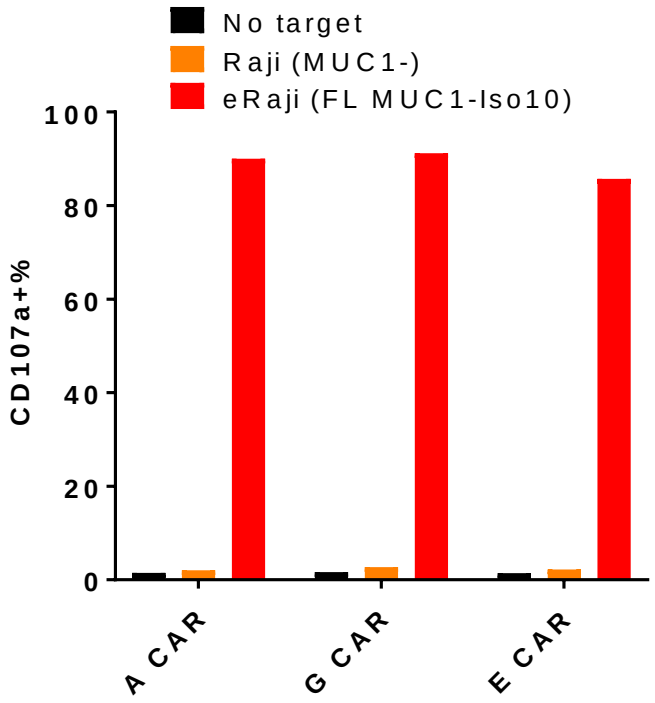


POSEIDA THERAPEUTICS

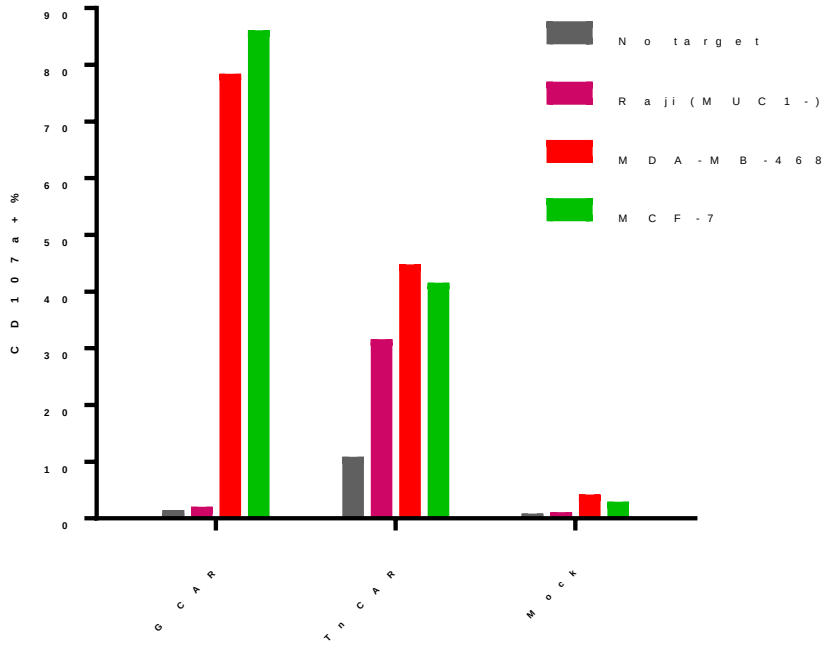
Screening CARs Recognizing MUC1

G MUC1 CAR exhibited strong antitumor activity against multiple MUC1+ cancer cell lines

We assessed mRNA CAR activity against MUC1 (full-length Isoform 10):



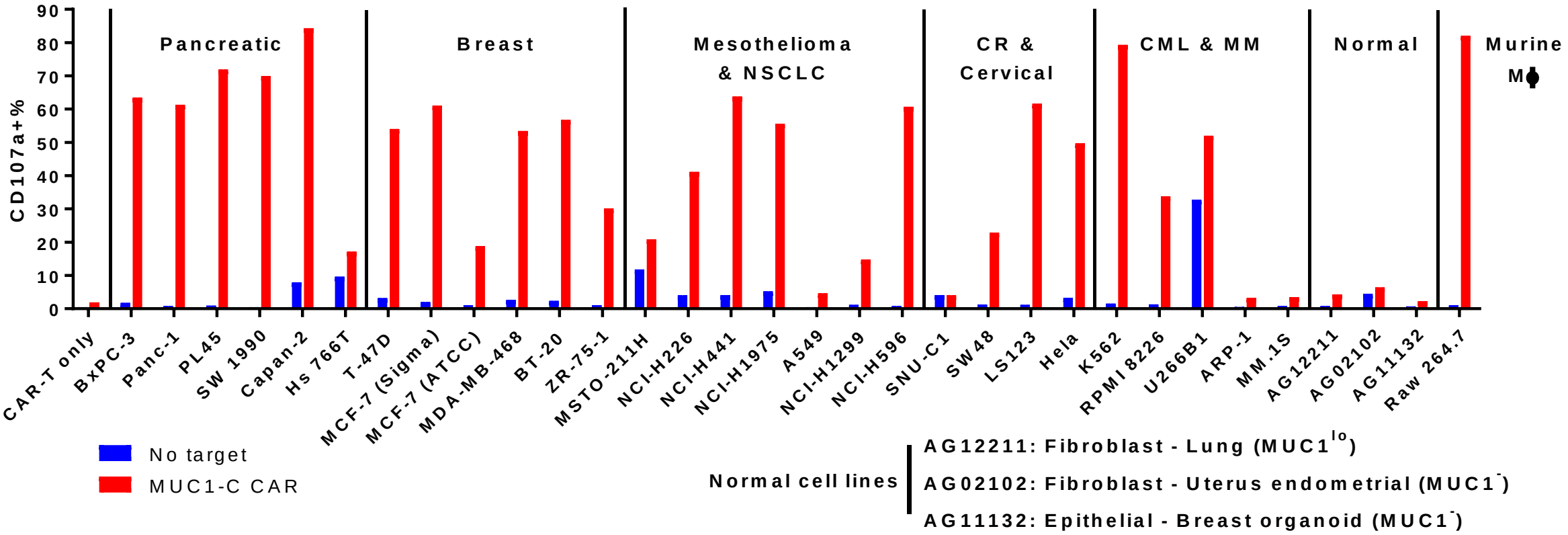
We compared mRNA MUC1 (MUC1-C vs TN) CAR activity against several breast cell lines:



POSEIDA THERAPEUTICS

MUC1 is Expressed on Numerous Cancers with High Unmet Need

Poseida MUC1-C CAR mediates robust anti-tumor activity against multiple tumor lines



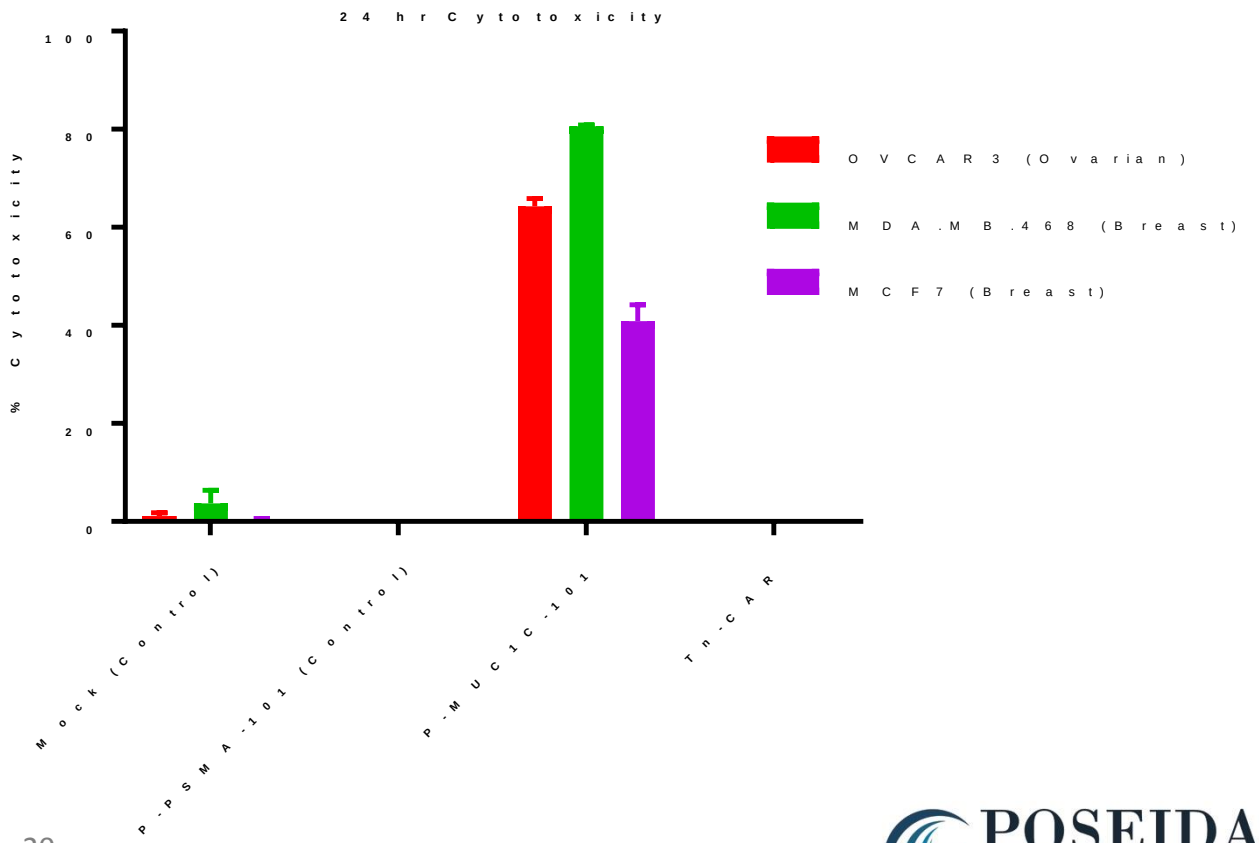
POSEIDA THERAPEUTICS

MUC1 is Expressed on Numerous Cancers with High Unmet Need

Poseida MUC1-C CAR mediates robust anti-tumor activity against multiple tumor lines including ovarian

We assessed P-MUC1C-101 activity against ovarian tumor line (OVCAR3):

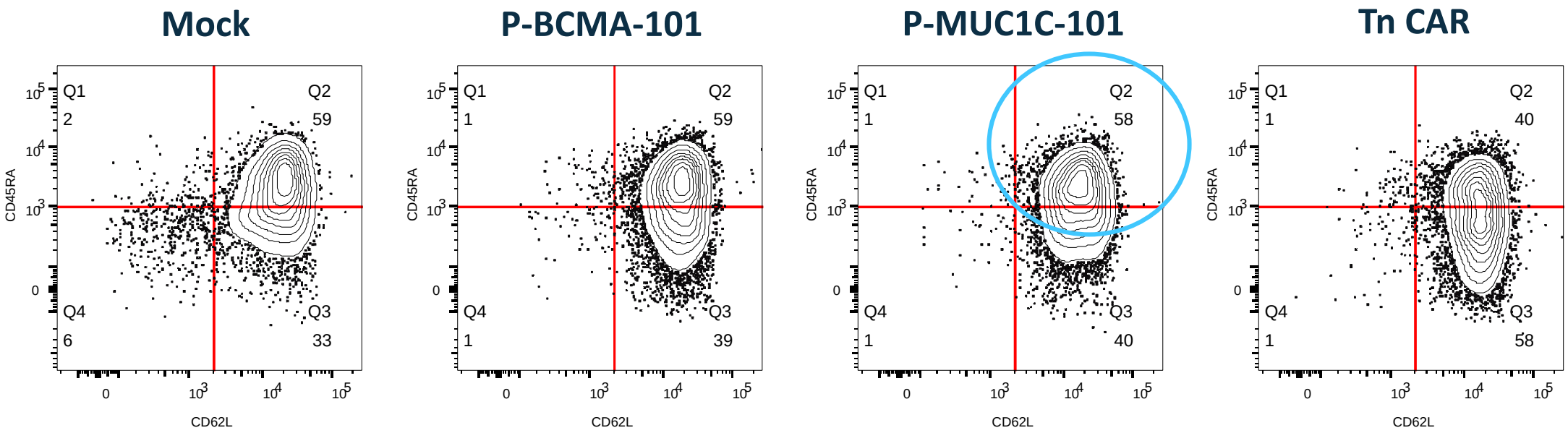
- Strong cytotoxicity
- CAR-Ts also proliferated and secreted IFNg
- Studies evaluating additional ovarian lines underway

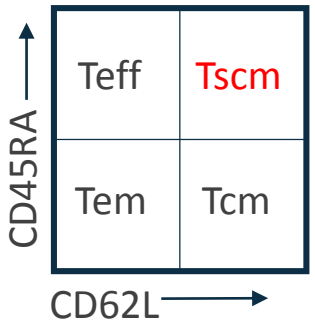


POSEIDA THERAPEUTICS

Poseida piggyBac™ manufacture of P-MUC1C-101

piggyBac™ manufacturing process yields high levels of CAR-T_{scm}

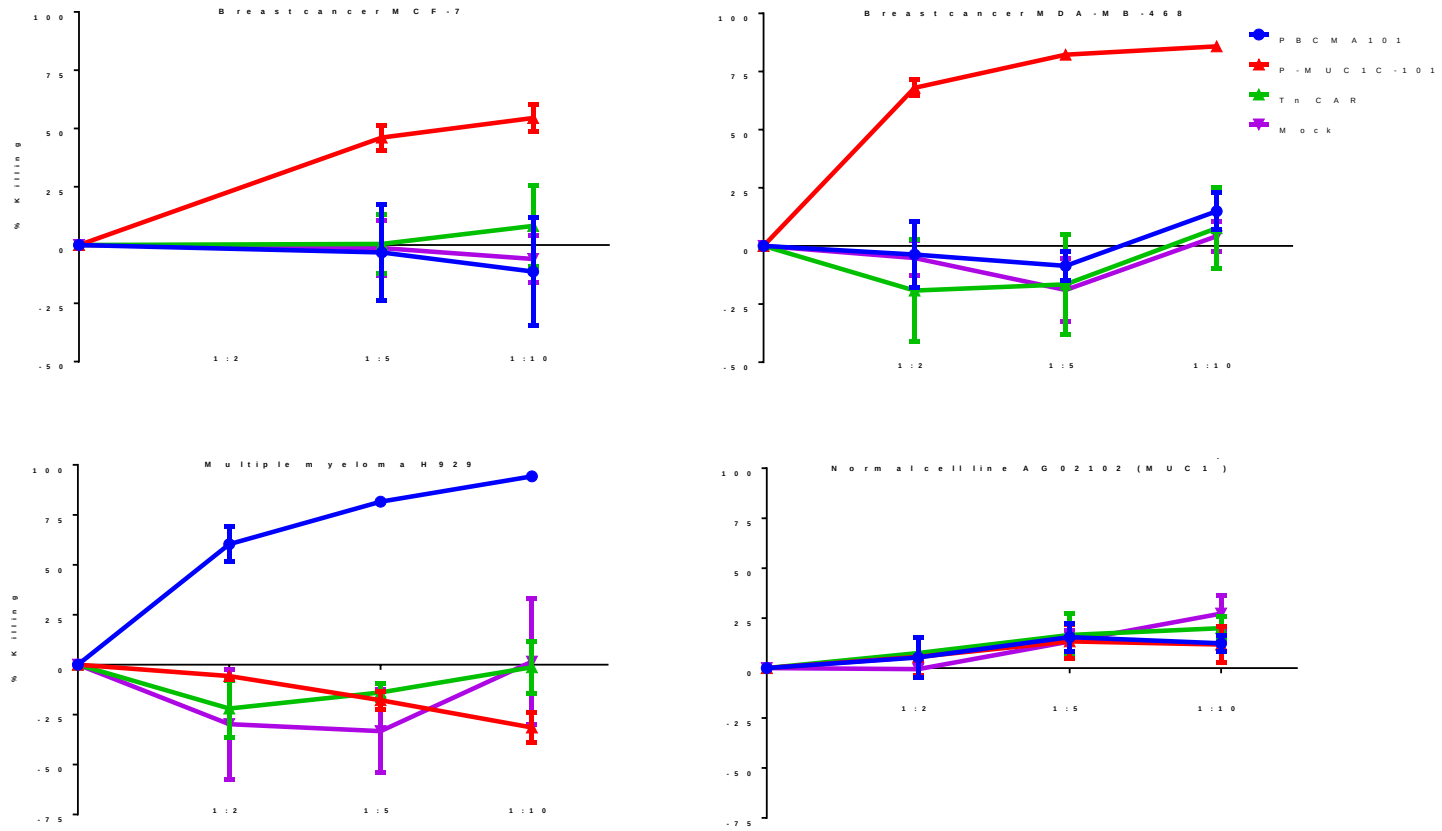




POSEIDA THERAPEUTICS

Evaluation of P-MUC1C-101 *in vitro*

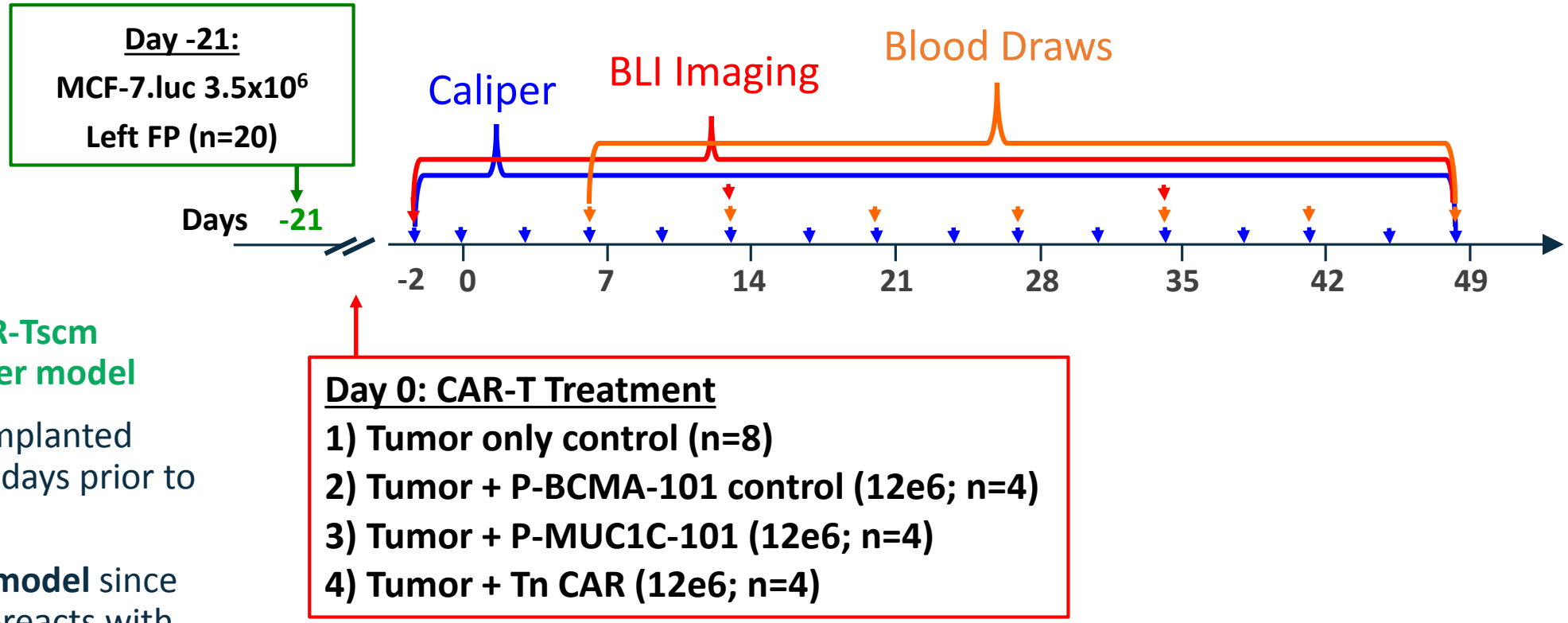
Robust *in vitro* Tumor Killing by MUC1-C CAR-T_{scm}



POSEIDA THERAPEUTICS

Evaluation of P-MUC1C-101 *in vivo*

MUC1 CAR-T_{scm} were evaluated in MCF-7 breast cancer orthotopic tumor model



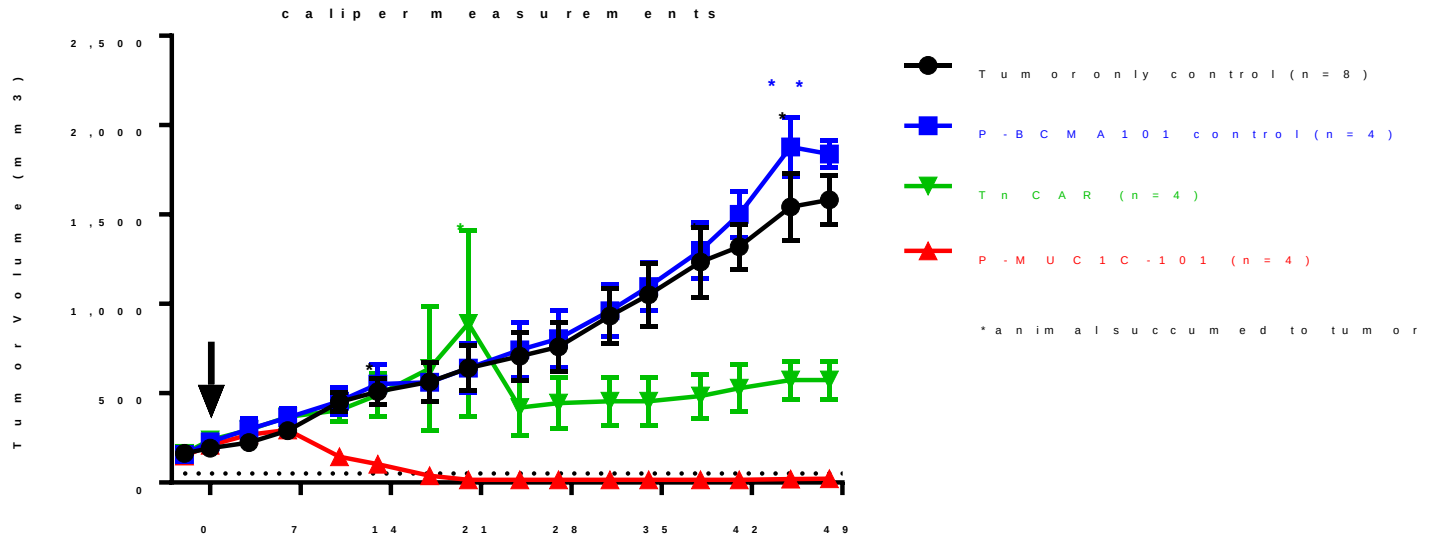
Efficacy of MUC1 CAR-Tscm (12e6) in breast cancer model

- MCF-7.luc tumor implanted into left fat pad 21 days prior to CAR-T treatment
- Also **serves as tox model** since P-MUC1-101 cross-reacts with murine MUC1

POSEIDA THERAPEUTICS

Potent *in vivo* Efficacy of P-MUC1C-101

Tumor elimination in 100% of animals at standard dose in human breast cancer xenograft model



POSEIDA THERAPEUTICS

Summary: Developing MUC1 CAR-T to Address Multiple Indications

Discovery program with compelling preclinical data and multiple development options

- P-MUC1C-101 demonstrated **robust antitumor activity against multiple tumor types**
- P-MUC1C-101 T_{scm} mediated rapid, sustained tumor regression and **completely eliminated established tumors** in an MCF-7 based orthotopic mouse model
- Compelling **data suggesting molecule is binding tumor-specific MUC1**
- Preclinical data portends **broad product potential**

Acknowledgments

Eric Ostertag, M.D., Ph.D, CEO
Mark J. Gergen, J.D., CBO & CFO
Matthew Spear, M.D., CMO

Devon J Shedlock, Ph.D., VP of Preclinical Development

Immuno-Oncology
Jenessa Smith, Ph.D.
Xinxin Wang, Ph.D.*
Burton Barnett, Ph.D.
Stacey Cranert, Ph.D.
Christopher Martin, Ph.D.
Elvira Khialeeva, Ph.D.
Srinivas Rengarajan, M.S.
Yenning Tan, M.S.
Rebecca Codde

POSEIDA THERAPEUTICS