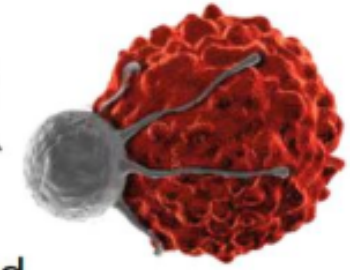
CAR-TCR Summit
Engineering a Cancer-Free World



September 10-13, 2019
Boston, MA, USA

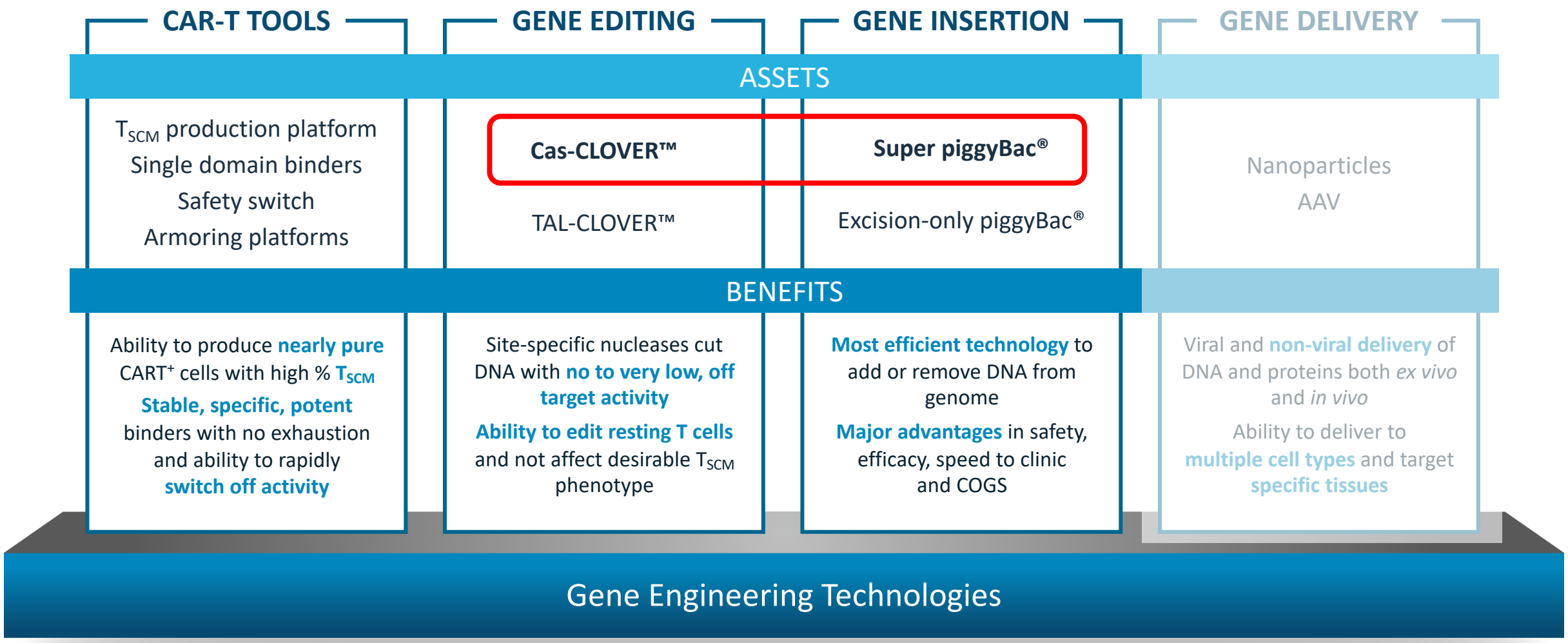
Nonviral piggyBac® and Cas-CLOVER™ Genetic Engineering Technologies for Development of Stem Cell Memory (T_{SCM}) CAR-Ts

Devon J. Shedlock, PhD
VP, Preclinical Development

September 13th, 2019

POSEIDA THERAPEUTICS

Poseida Platform of Superior Gene Engineering Technologies



POSEIDA THERAPEUTICS

Overcoming The Challenges in CAR-T with Poseida Technologies

OUR TECHNOLOGY

piggyBac®
DNA Modification System

Early memory T-cells

Very large cargo capacity

Cas-CLOVER
Genome Editing Tool

Potential to enable allogeneic products

MAJOR ATTRIBUTES

High % of Desirable T_{SCM}

Cargo Capacity

Precise Gene Editing

POTENTIAL TO OVERCOME CAR-T CHALLENGES

Activity / Durability

- Solid and Hematologic Tumors
- Relapse control
- Longer duration of response

Tolerability

- More gradual killing: less toxicity
- Positive selection: ↑ therapeutic index
- Safety switch and non-oncogenic

Scalability / Cost

- Efficient pipeline expansion
- Little / no off target cutting
- Cost / timeline benefits vs. viral

POSEIDA THERAPEUTICS

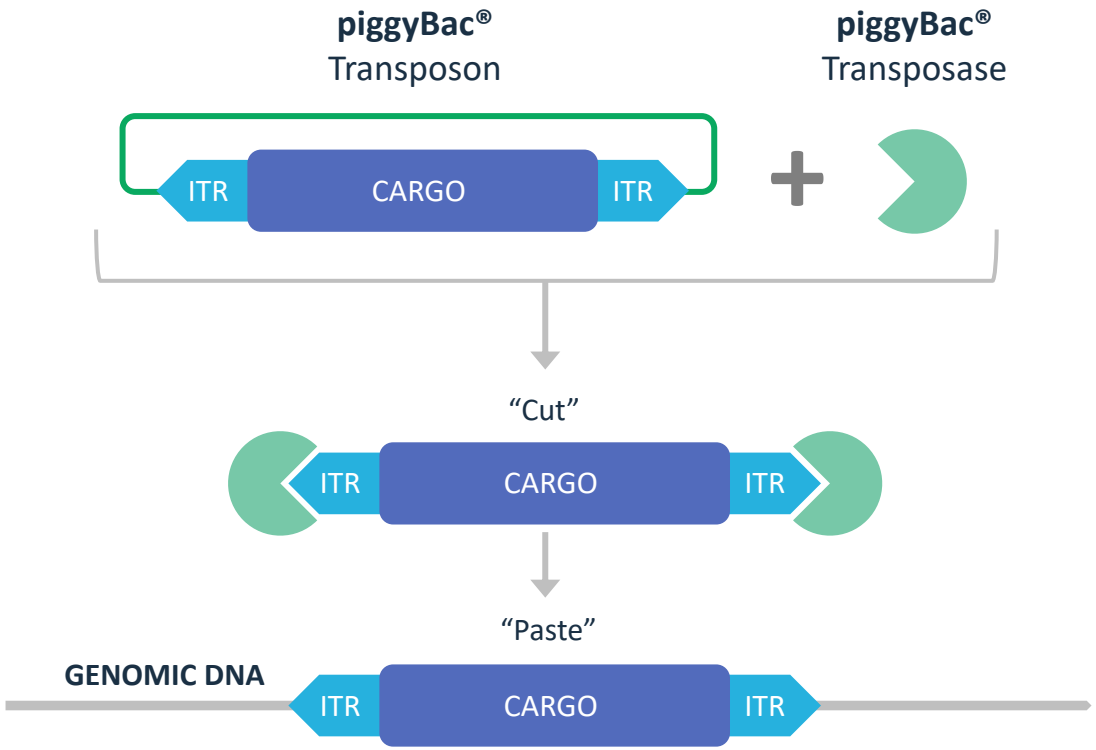
PiggyBac® DNA Modification System for CAR-T_{SCM} manufacture

POSEIDA THERAPEUTICS

PiggyBac® DNA Modification System

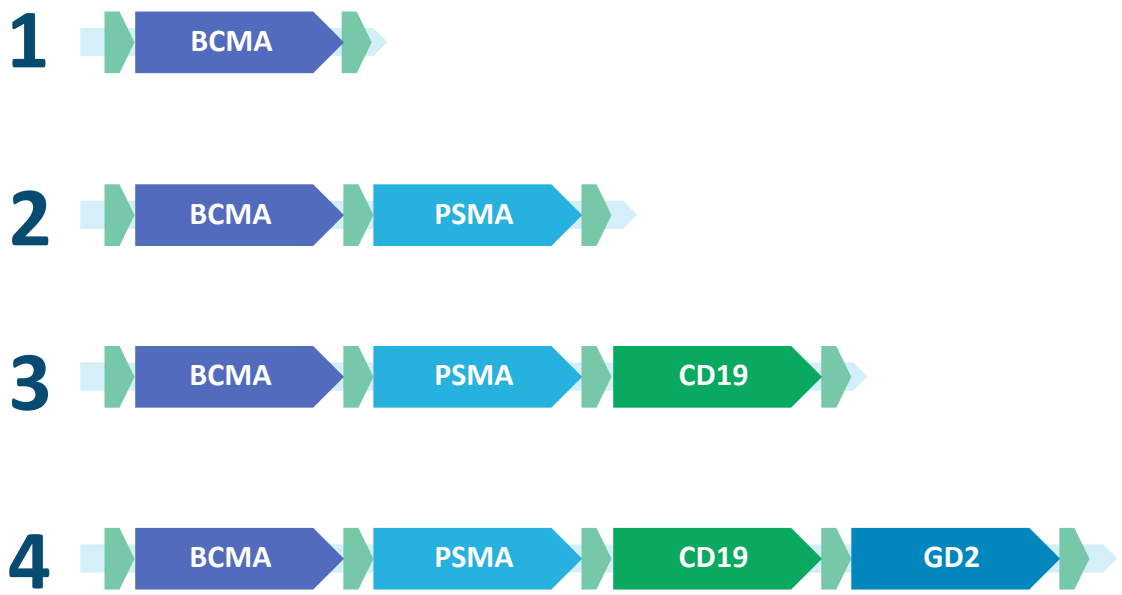
An Ideal DNA Delivery System for Developing CAR-T and Other Gene Therapy Products

- Cargo is cloned into piggyBac® (PB) transposon pDNA vector
- Co-transfect PB transposon pDNA along with hyperactive PB transposase enzyme (pDNA, mRNA, or protein)
- Transposase recognizes transposon ITRs, cuts transgene out of plasmid and integrates stably into genome
  - Cut and paste mechanism
  - Targets TTAA sites and prefers open chromatin

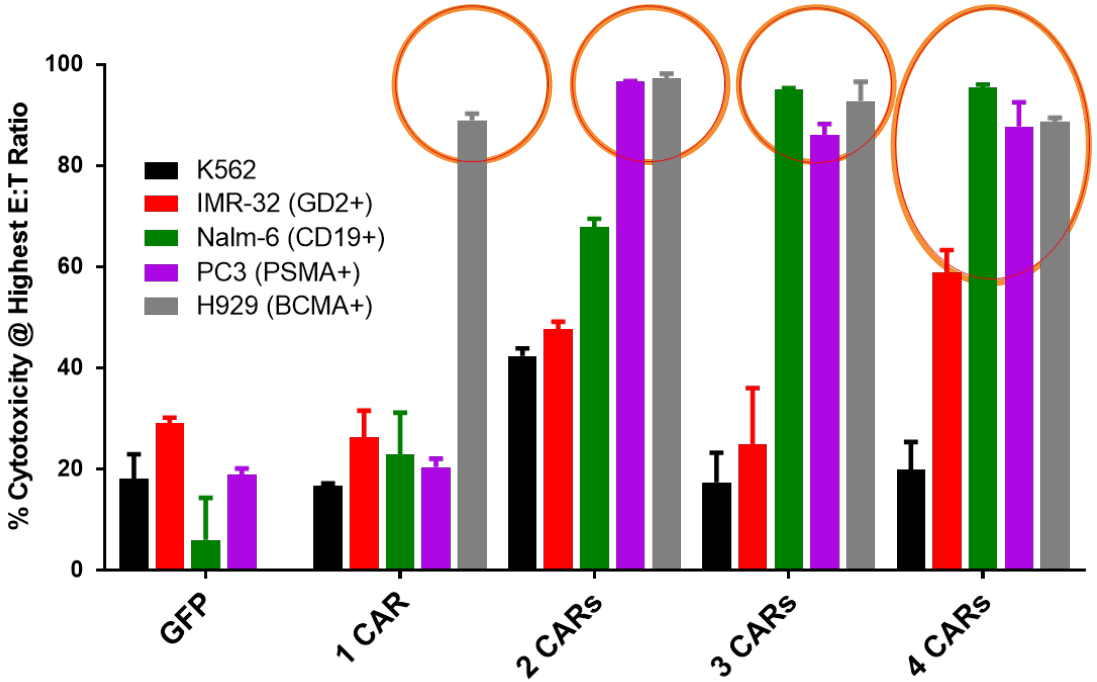


PiggyBac's® Massive Cargo Capacity Allows Delivery of Multiple Fully Functional CAR Molecules to Every Cell

 # Full-length CARs*



Function (Killing)

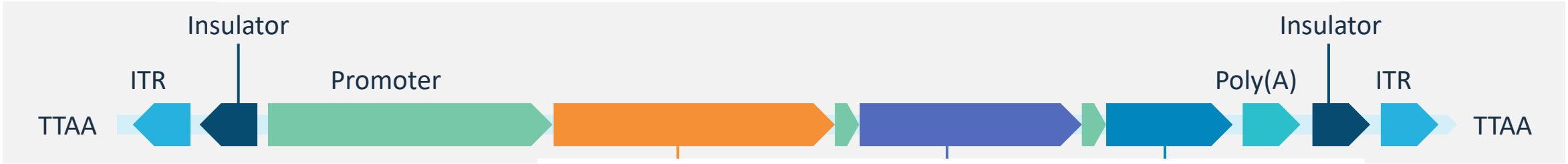


**Single plasmid system encoding 1-4 CARs including EGFP and selection genes*

POSEIDA THERAPEUTICS

PiggyBac® Cargo Capacity Allows for Desirable Product Attributes

Designed To Have Desirable Product Attributes



INCORPORATES PROPRIETARY SAFETY SWITCH

- Rapid, dose-dependent **elimination** of engineered T- cells as needed
- Potential **management of** Cytokine Release Syndrome (**CRS**) or other AEs

DIFFERENTIATED BINDING CAR-T MOLECULE

- Centyrin™ or VH molecule with **high-specificity binding**
- Fully human with no **tonic signaling observed to date**

DRUG RESISTANCE GENE PERMITS POSITIVE SELECTION

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

POSEIDA THERAPEUTICS

Not All T-Cells are Equal: The Importance of Stem Cell Memory Cells

LESS DIFFERENTIATED

MORE DIFFERENTIATED

Stem Cell Memory	Central Memory	Effector Memory	Effector T-Cell
T_{SCM} Cell	T_{CM} Cell	T_{EM} Cell	T_{EFF} Cell

- Self renewing
- Long lived
- Multipotent

THE POTENTIAL BENEFITS

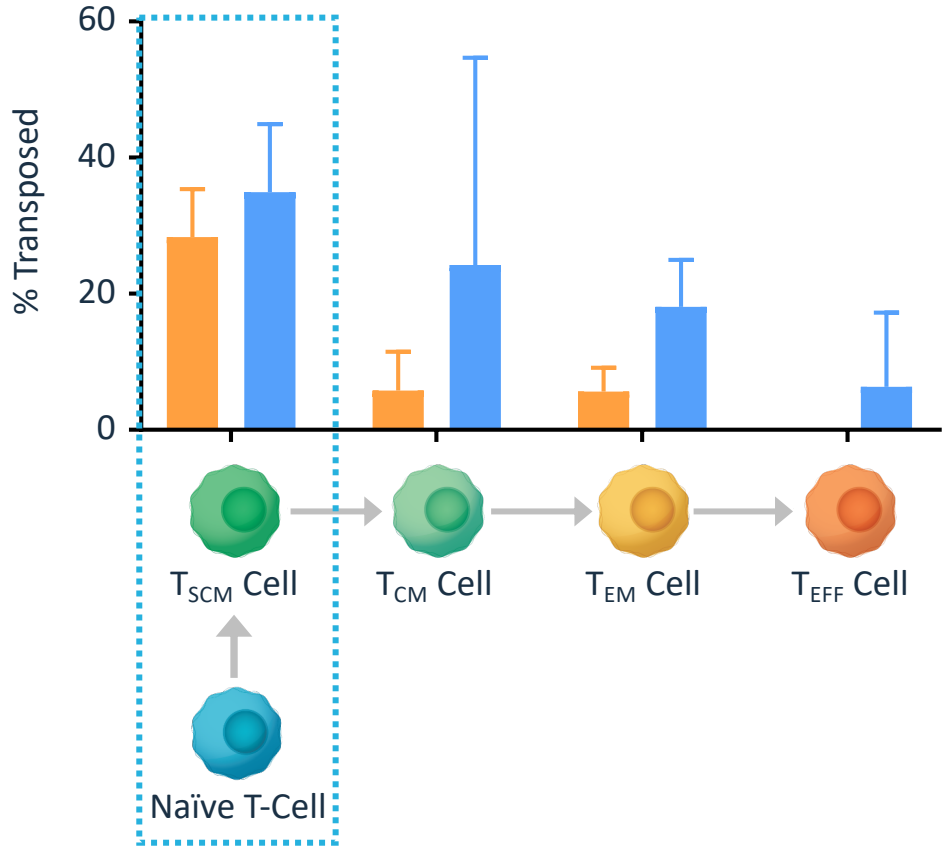
Products with High % of T_{SCM} Cells:

- More gradual tumor killing with less toxicity
- Better duration of response and potential for re-response
- Key to CAR-T success in solid tumors

POSEIDA THERAPEUTICS

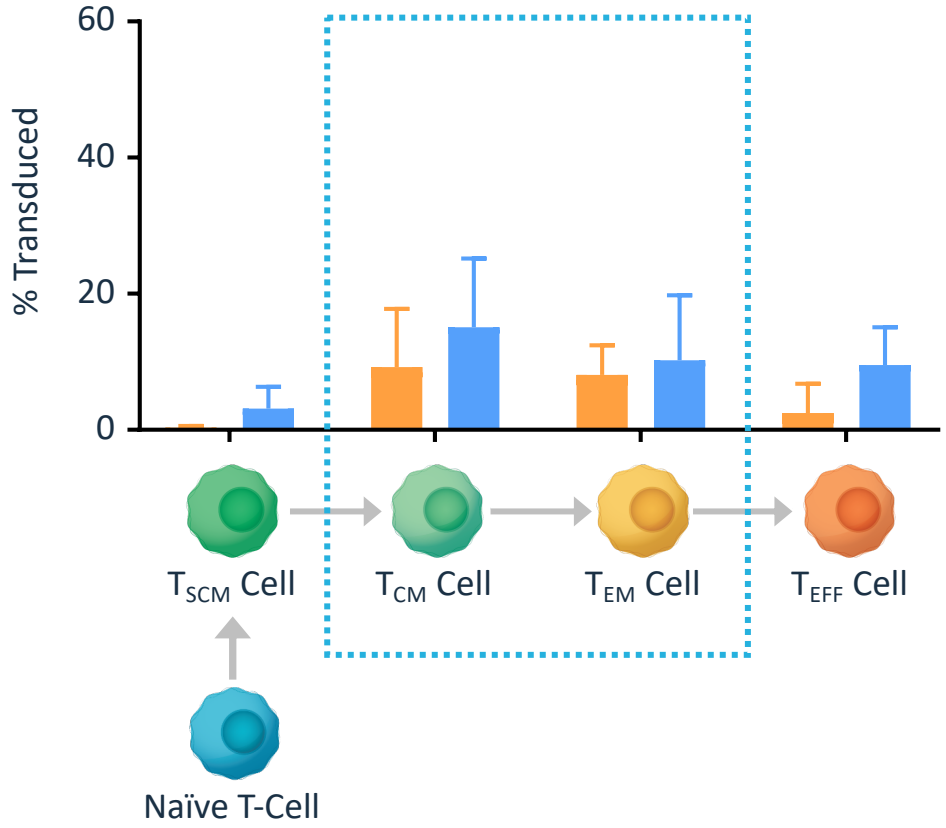
PiggyBac® Preferentially Transposes T_{SCM} Cells

piggyBac®



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

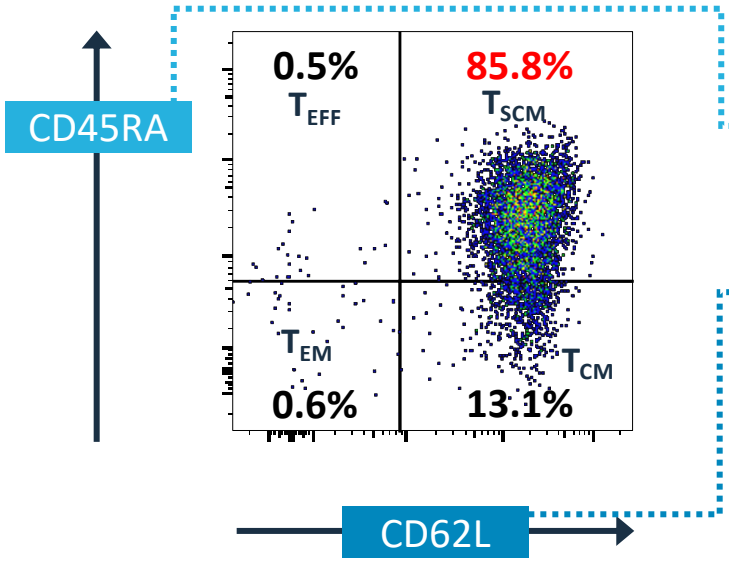
Lentivirus

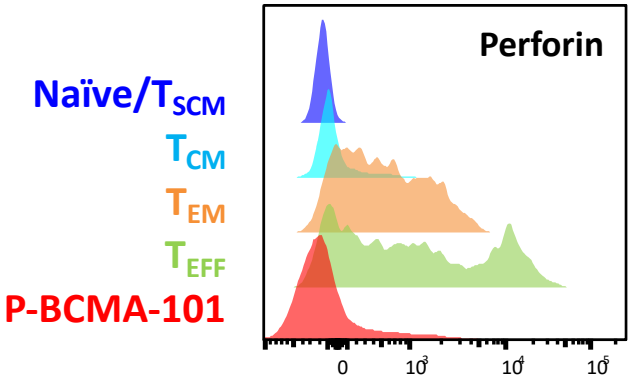


Percentage transposed (% GFP+) data are displayed for CD4+ T cells (CD3+CD4+CD8-) or CD8+ T cells (CD3+CD4+CD8+) within the final cell product

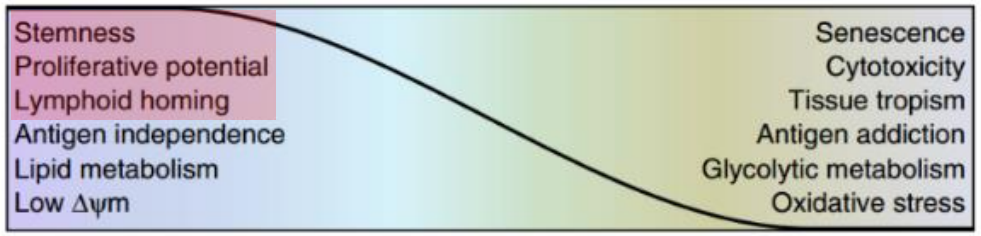
POSEIDA THERAPEUTICS

Poseida CAR-T Stem Cell Memory T_{SCM} Phenotype





	T_N	T_{SCM}	T_{CM}	T_{EM}	T_{TE}	P-BCMA-101
CD45RA	+	+	-	-	+	+
CD45RO	-	-	+	+	-	-
CCR7	+	+	+	-	-	+
CD62L	+	+	+	-	-	+
CD28	+	+	+	+/-	-	+
CD27	+	+	+	+/-	-	+
IL-7Rα	+	+	+	+/-	-	+
CXCR3	-	+	+	-	-	+
CD95	-	+	+	+	+	+
CD11a	-	+	+	+	+	+
IL-2Rβ	-	+	+	+	+	+
CD58	-	+	+	+	+	+
CD57	-	-	-	+/-	+	-



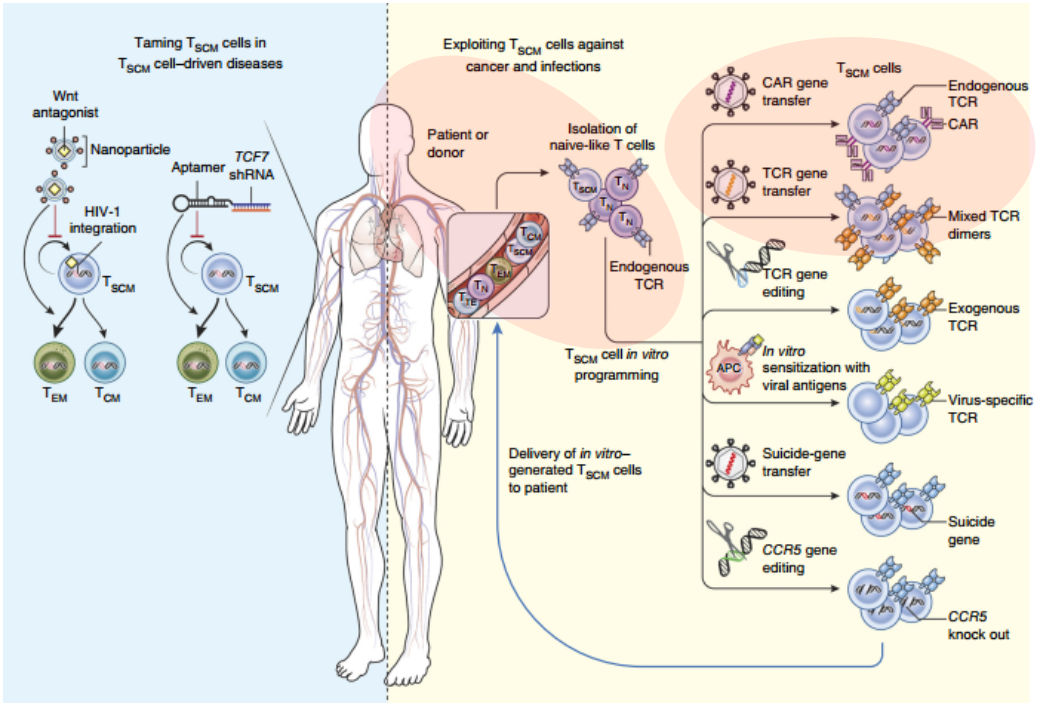
Adapted from Gattinoni et al. (2017) Nat. Med.

POSEIDA THERAPEUTICS

T_{SCM} May Be Key to Safe, Potent and Durable Responses

- "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**"

- **Correlates with CAR-T clinical response**
  - *Melenhorst J. et al., **UPenn** (2017) 20th ASGCT*
  - *Basu et al., **Adaptimmune** (2017) CAR-TCR Summit*
  - *T_{CM}: Larson, **Juno** (2018) AACR*
  - *Bot A., et al., **Kite** (2018) SITC*
  - *T_{SCM} TIL: Beatty M., **Moffitt** (2018) SITC*
  - *T_{CM}: Fraietta J. et al., **UPenn** (2018) TET2 Disruption, PMID: 29849141*
  - *Spear M. et al., **Poseida** (2019) CAR-TCR Summit*



T memory stem cells in health and disease

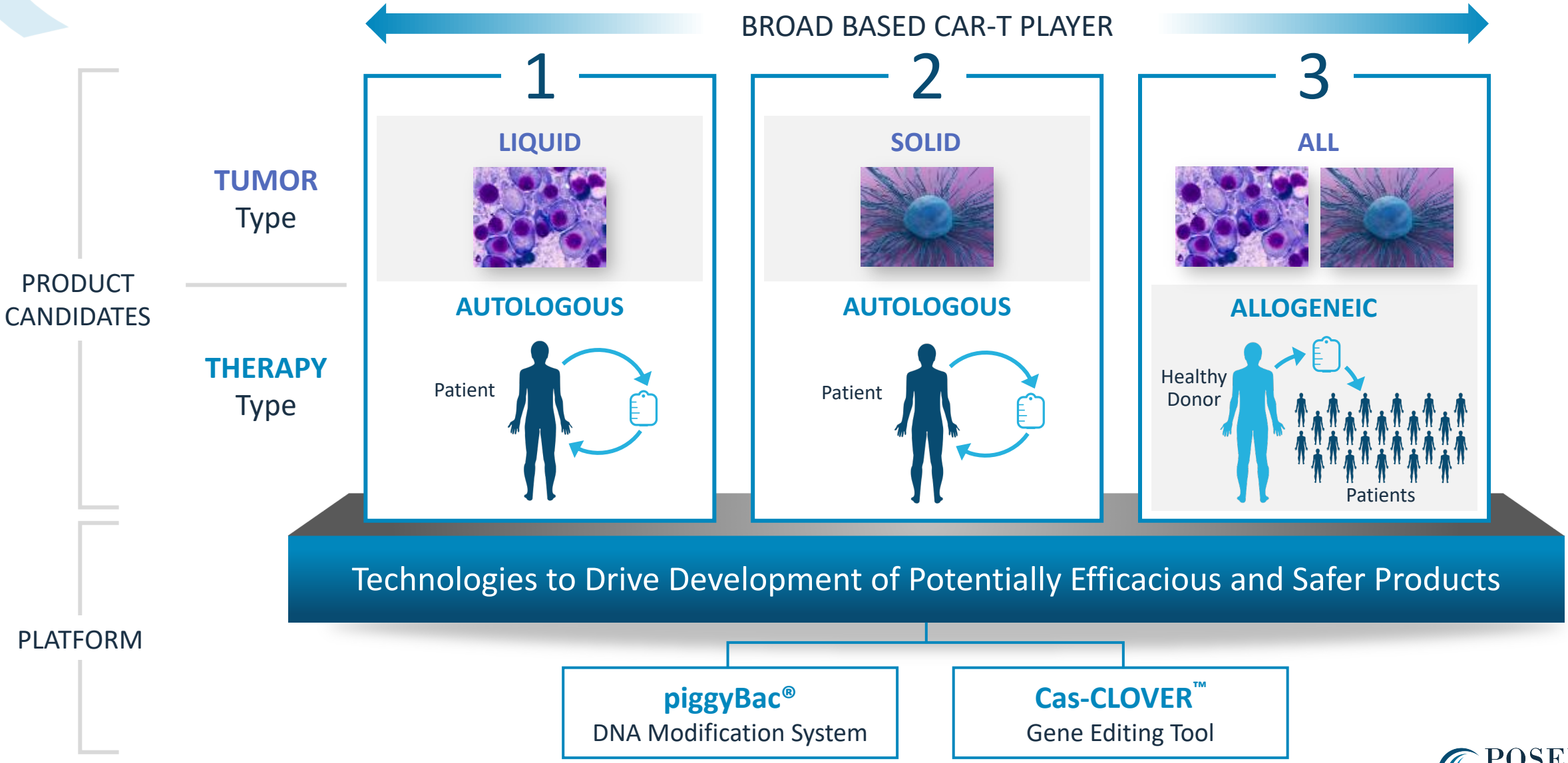
Luca Gattinoni[1], Daniel E Speiser[2], Mathias Lichterfeld[3] & Chiara Bonini[4,5]

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;

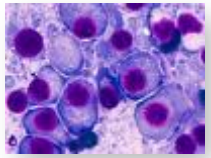
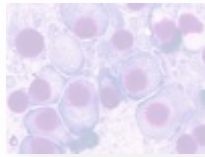
POSEIDA THERAPEUTICS

The Three Pillars of CAR-T



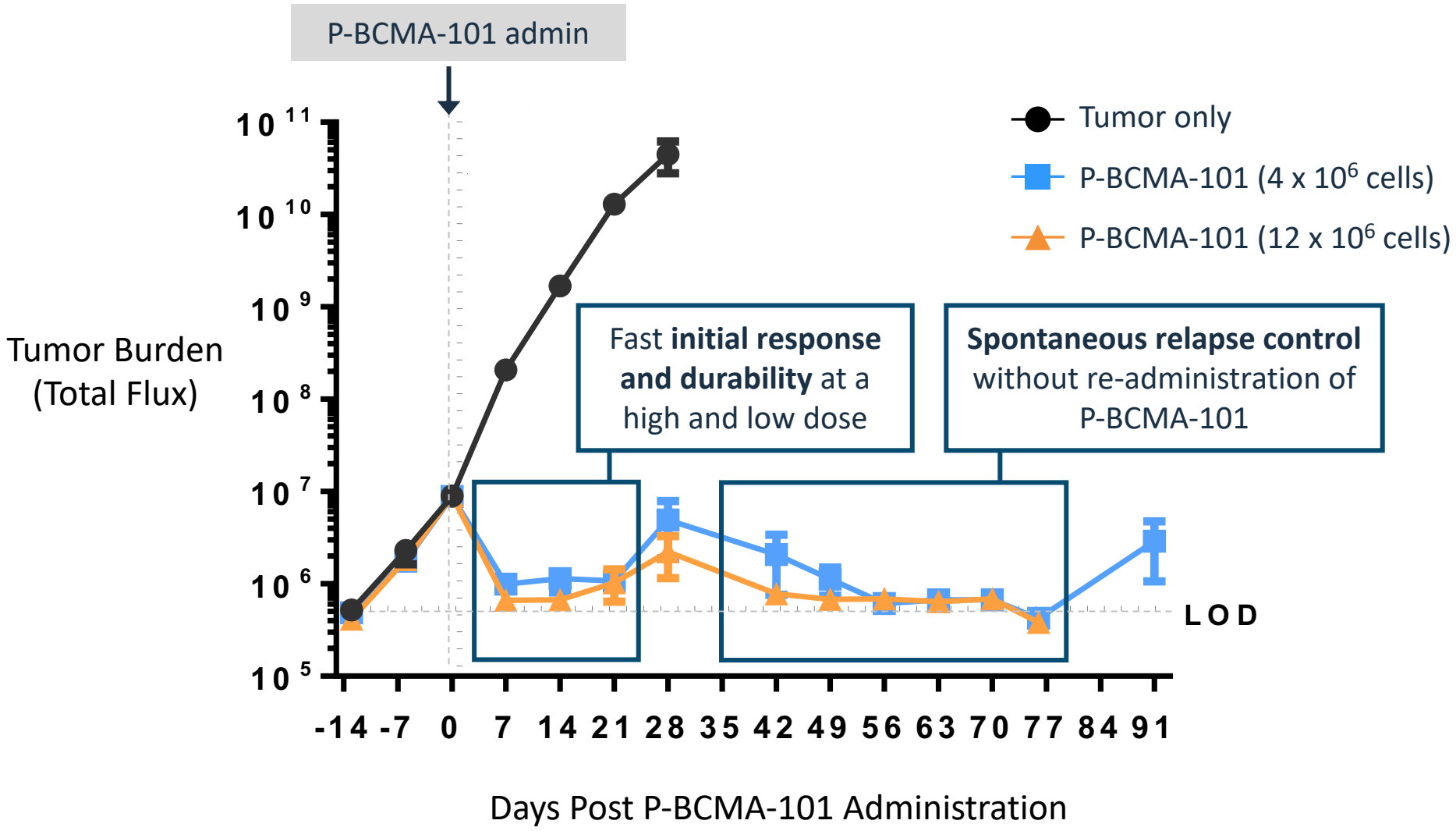
POSEIDA THERAPEUTICS

Our Lead Product Candidate: P-BCMA-101 for Relapsed/Refractory Multiple Myeloma

	1	2	3
	Liquid	Solid	Liquid
TUMOR TYPE			
THERAPY TYPE	Autologous	Autologous	Allogeneic
INITIAL INDICATION	Multiple Myeloma	Prostate Cancer / Other Solid Tumors	Multiple Myeloma
PRODUCT CANDIDATES	P-BCMA-101	P-PSMA-101 / P-MUC1C-101	P-BCMA-ALLO1
ESTIMATED MARKET OPPORTUNITY	Big	Bigger	Biggest

POSEIDA THERAPEUTICS

P-BCMA-101 Eliminated Tumors in Aggressive MM Cancer Model



POSEIDA THERAPEUTICS

Phase 1/2 Clinical Trial in R/R Myeloma: P-BCMA-101-001

Phase 1 Trial Design

- Open Label, 3+3 Design, Single Ascending Dose Study
- 30 mg/m^2 fludarabine + 300 mg/m^2 cyclophosphamide x 3d lymphodepletion regimen
- P-BCMA-101 administered intravenously as a single dose
  - Allowance for 2nd dose and retreatment after other CAR-Ts
  - Outpatient administration allowed
- Up to 80 subjects

Phase 2 Trial Design

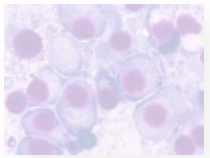
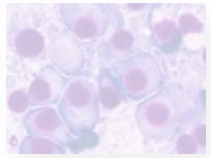
- Same schema as Phase 1
- P-BCMA-101 administered intravenously at 6-15 x 10^6 cells/kg
- 100 subjects

Clinical Sites / Investigators

- Colorado Blood Cancer Institute- Tara Gregory, M.D.
- Hackensack University Medical Center- David Siegel, M.D.
- Johns Hopkins- Syed Abbas Ali, M.D.
- Karmanos Cancer Institute- Abhinav Deol, M.D.
- MD Anderson Cancer Center- Krina Patel, M.D.
- Swedish Cancer Institute- William Bensinger, M.D.
- Tennessee Oncology- Jesus G. Berdeja, M.D.
- UC San Diego Moores Cancer Center- Caitlin Costello, M.D.
- UC San Francisco- Nina Shah, M.D.
- University of Chicago- Andrzej Jakubowiak, M.D.
- University of Kansas Cancer Center- Siddhartha Ganguly, M.D.
- University of Maryland- Aaron Rapoport, M.D.
- University of Pennsylvania- Adam Cohen, M.D.

15

Our Approach to CAR-T in Solid Tumors

	1	2	3
TUMOR TYPE	Liquid	Solid	Liquid
			
THERAPY TYPE	Autologous	Autologous	Allogeneic
INITIAL INDICATION	Multiple Myeloma	Prostate Cancer	Other Solid Tumors	Multiple Myeloma
PRODUCT CANDIDATES	P-BCMA-101	P-PSMA-101	P-MUC1C-101	P-BCMA-ALLO1
ESTIMATED MARKET OPPORTUNITY	Big	Bigger		Biggest

POSEIDA THERAPEUTICS

High % of T_{SCM} Cells: Unlocking Potential of CAR-T to Successfully Treat Solid Tumor Indications

Conventional Experience and Perception

- **Poor CAR-T responses in solid tumors** to date
- **Rare instances with complete response** (CR) have occurred (GBM, HCC) only after **multiple administrations**
- CAR-T can cause CRs in solid tumors, but **numerous waves of more differentiated cells are required**

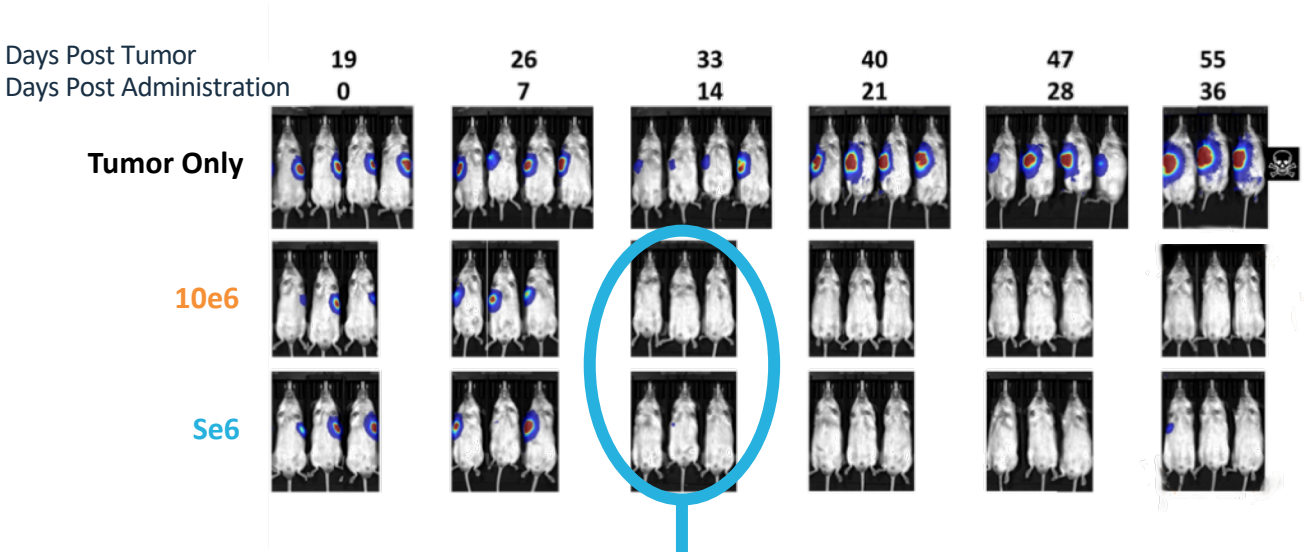
Our Approach

Our product candidates are comprised of a high percentage of **T_{SCM} cells**, which we believe hold the potential to engraft, self renew and **create wave after wave of more differentiated effector cells with one administration**

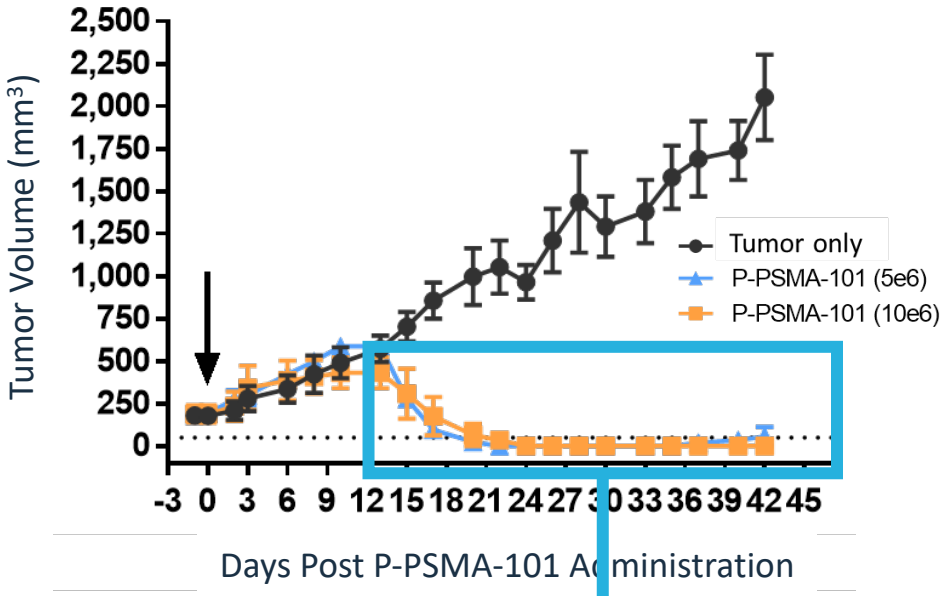
P-PSMA-101 Observed Potent *In Vivo* Activity

EFFICACY OF P-PSMA-101 IN PROSTATE CANCER MODEL (LNCaP.luc)

Imaging



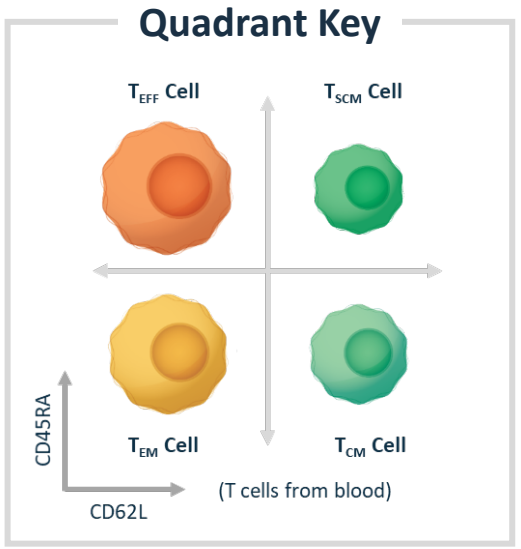
Caliper Measurement

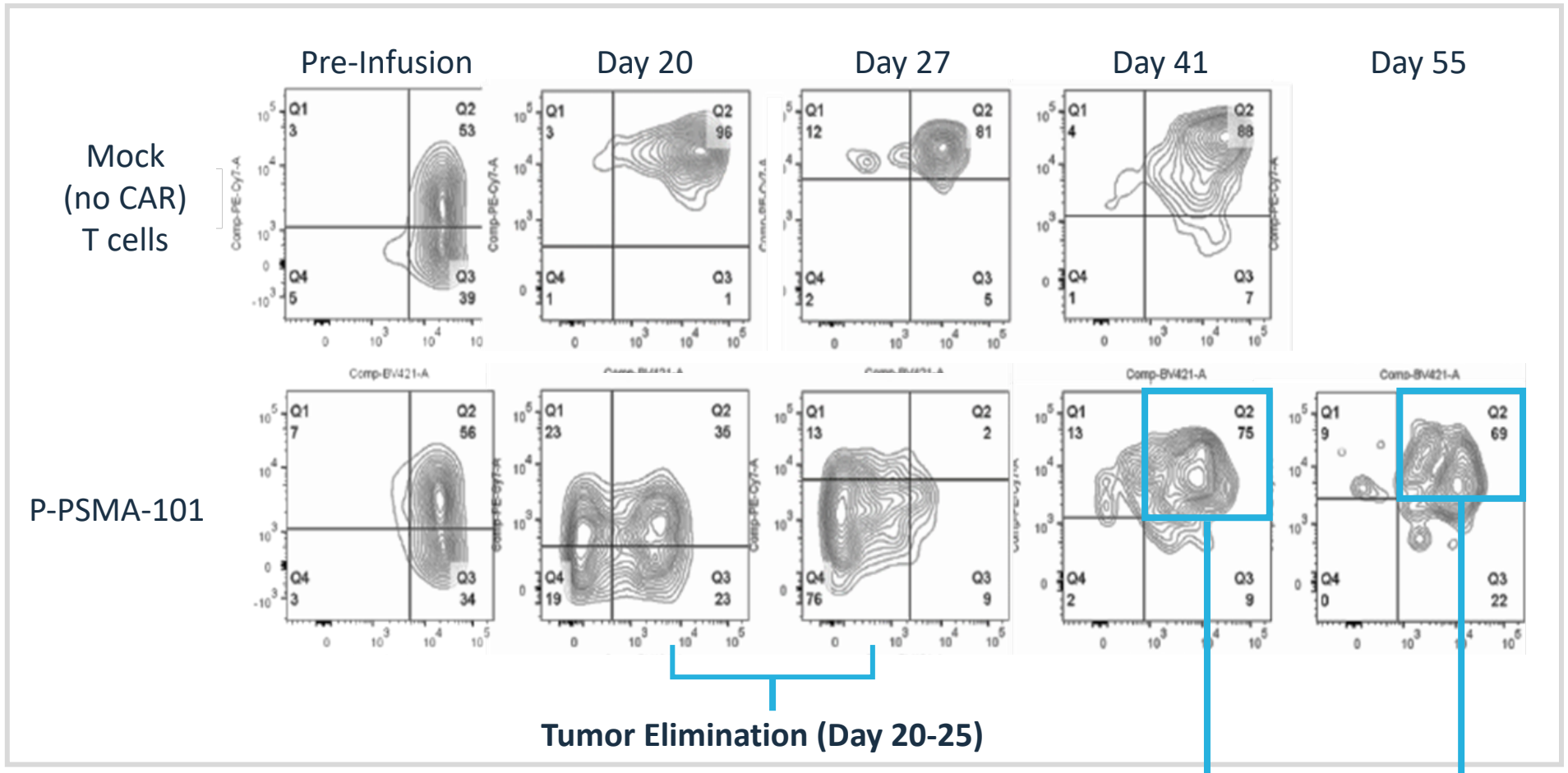


Tumor Elimination in 100% of Animals at Standard and Low Doses After ~ 2 Weeks

POSEIDA THERAPEUTICS

P-PSMA-101 Data Suggest Persistence of T_{SCM} Cells

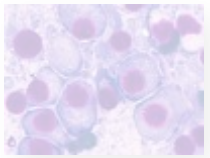
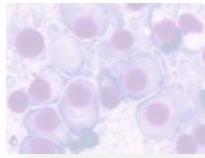




P-PSMA-101 T_{SCM} Cells Persisted After Solid Tumor Elimination

POSEIDA THERAPEUTICS

Our Approach to CAR-T in Solid Tumors

	1	2	3
TUMOR TYPE	Liquid 	Solid 	Liquid 
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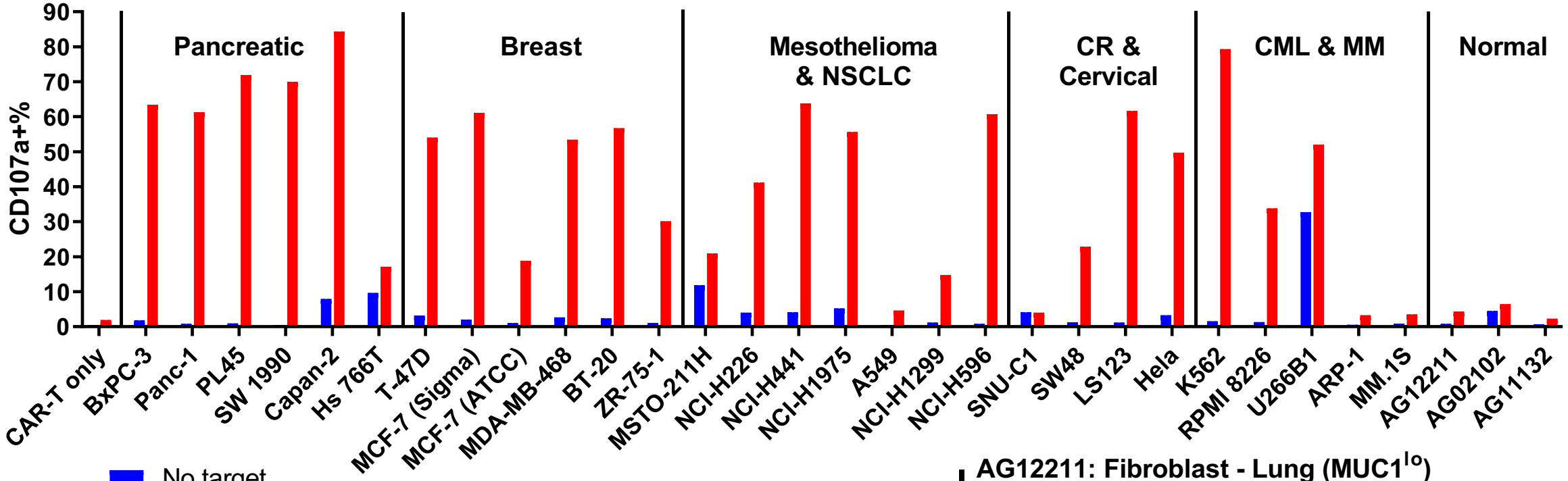
INITIAL INDICATION	Multiple Myeloma	Prostate Cancer	Other Solid Tumors	Multiple Myeloma
PRODUCT CANDIDATES	P-BCMA-101	P-PSMA-101	P-MUC1C-101	P-BCMA-ALLO1
ESTIMATED MARKET OPPORTUNITY	Big	Bigger		Biggest

POSEIDA THERAPEUTICS

P-MUC1C-101: Killed Cancer Cells, Not Normal Epithelial Cells

Broad reactivity of P-MUC1C-101 against multiple primary tumor cells



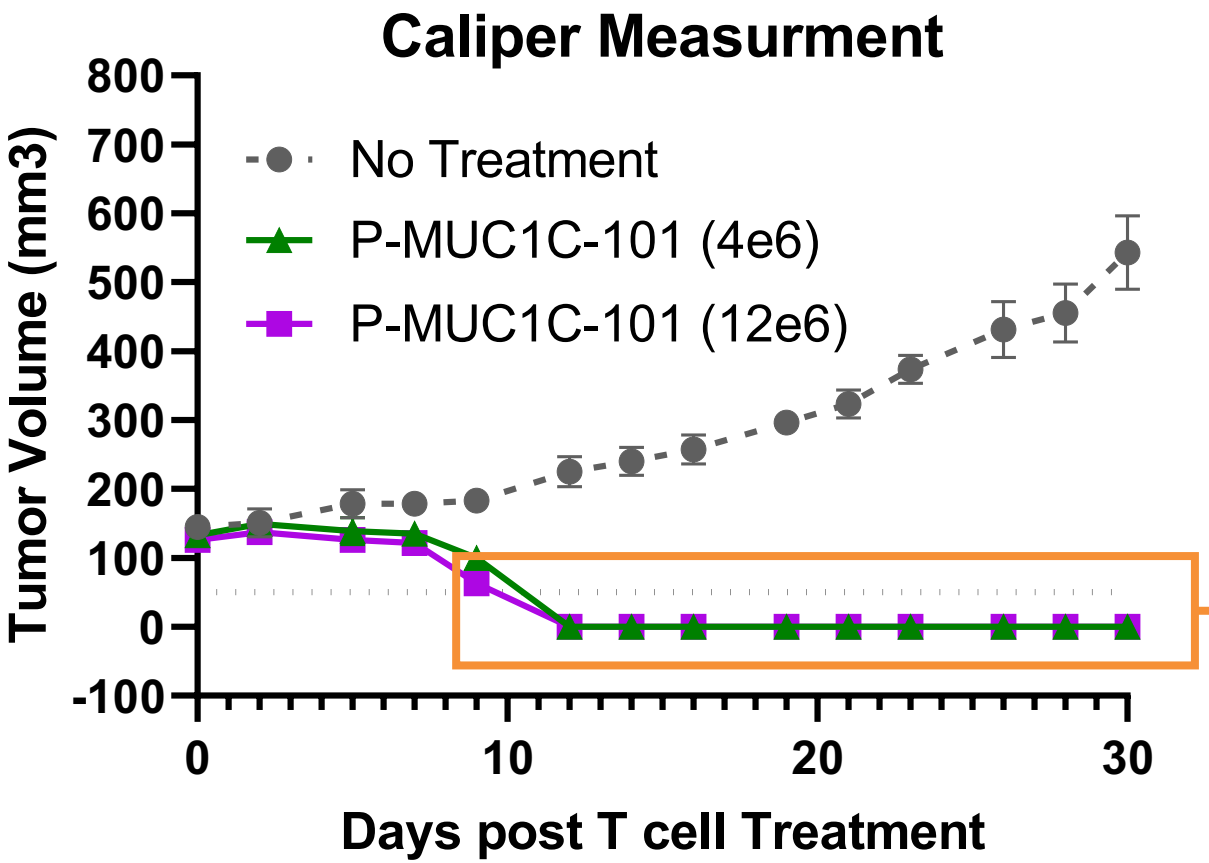
Normal cell lines

- **AG12211: Fibroblast - Lung (MUC1^{lo})**
- **AG02102: Fibroblast - Uterus endometrial (MUC1^{-})**
- **AG11132: Epithelial - Breast organoid (MUC1^{-})**

POSEIDA THERAPEUTICS

P-MUC1C-101: Showed Potent In Vivo Activity Against Triple-Negative Breast Cancer (TNBC)

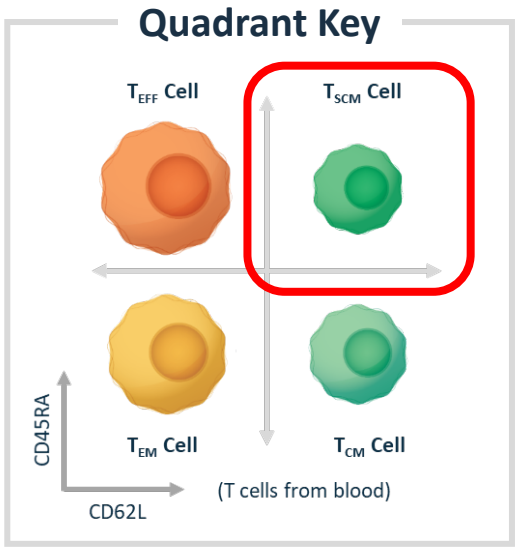
EFFICACY OF P-MUC1C-101 IN BREAST CANCER MODEL (MDA.MB.468)

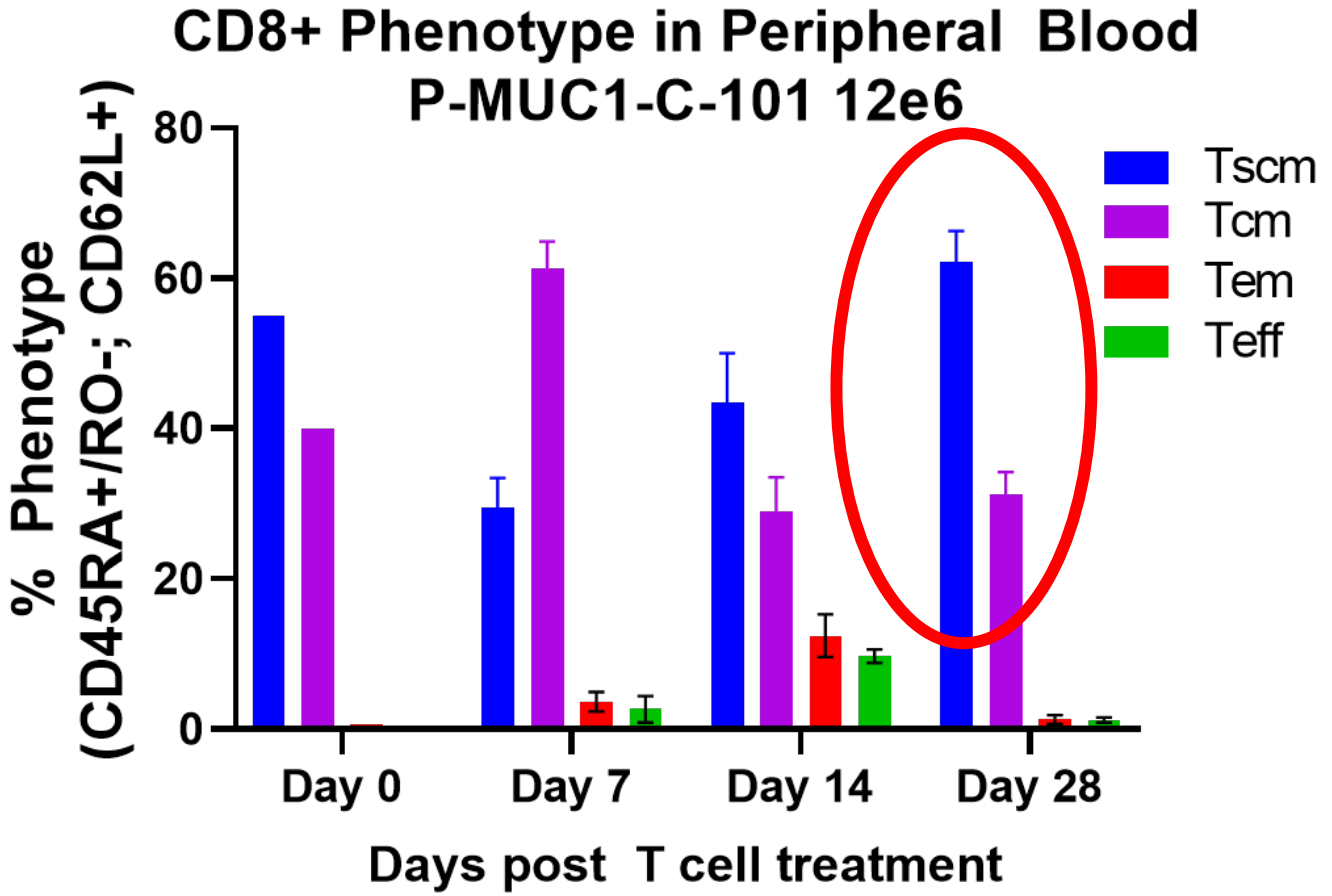


Tumor Elimination Observed at Standard and Low Dose in Very Aggressive Human Triple-Negative Breast Cancer Xenograft Model

POSEIDA THERAPEUTICS

After Tumor Elimination, a Population of P-MUC1C-101 T_{SCM} Persists





POSEIDA THERAPEUTICS

Cas-CLOVER™ Gene Editing for manufacture of Allo CAR-T_{SCM}

POSEIDA THERAPEUTICS

Cas-CLOVER™: Proprietary Gene Editing Platform

The Best of Both Worlds

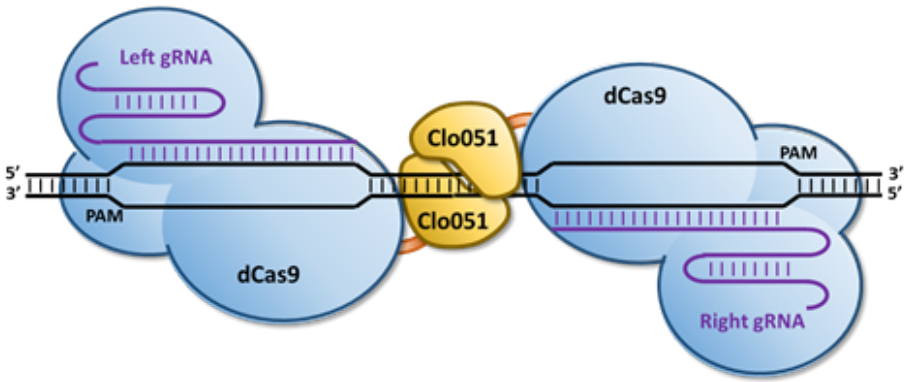
CRISPR/ Cas9

- Ease of use/design
- Low cost
- Multiplexing ability

TALEN/ ZFN

- Specificity

Cas-CLOVER™ Gene Editing System



Additional Potential Benefits

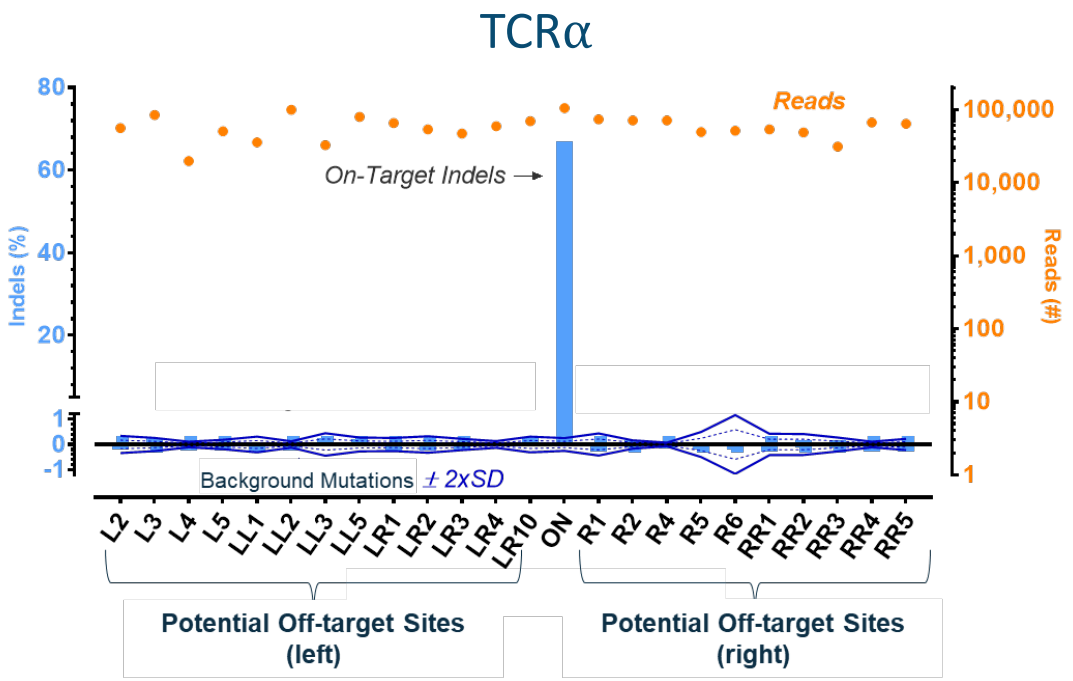
- Highly efficient editing of resting T-cells → high % of T_{SCM} cells
- No to low off-target mutations

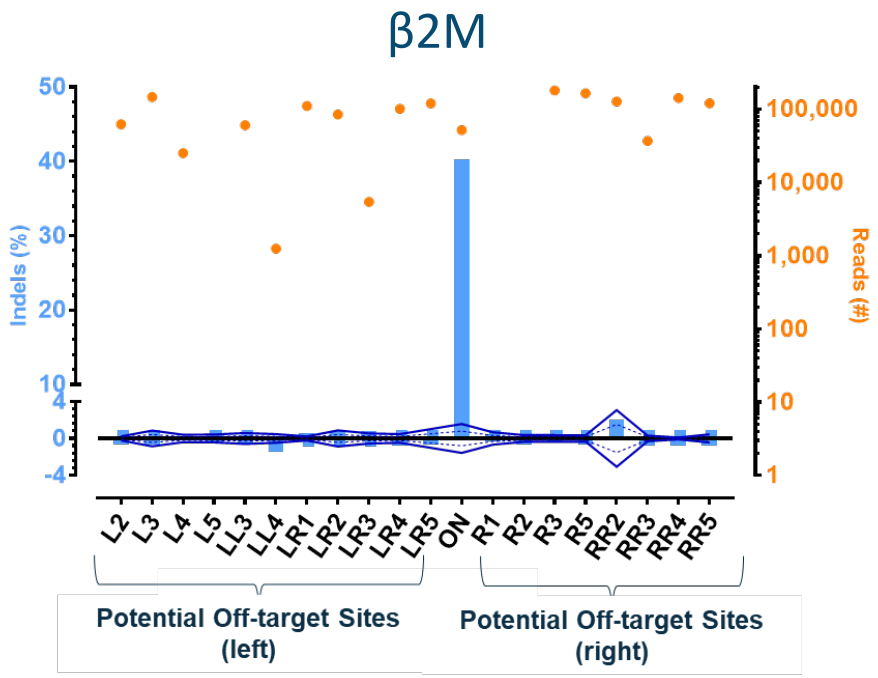
Wholly-Owned with Global Rights and Full Freedom To Operate

POSEIDA THERAPEUTICS

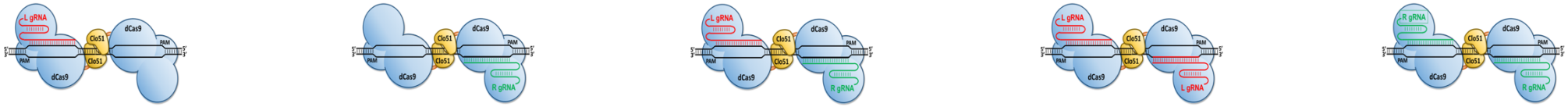
Cas-CLOVER™ Is Highly Precise with No Off-Target Cutting

Data from Millions of Sequence Reads Demonstrate that CAS-CLOVER™ Does Not Cause Off Target Cutting





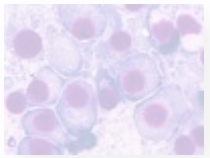
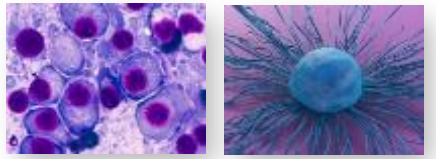
KBIOBOX



gRNA	L	R	LR	LL	RR

POSEIDA THERAPEUTICS

Our Approach to CAR-T in Solid Tumors

	1	2	3
TUMOR TYPE	Liquid 	Solid	Liquid 
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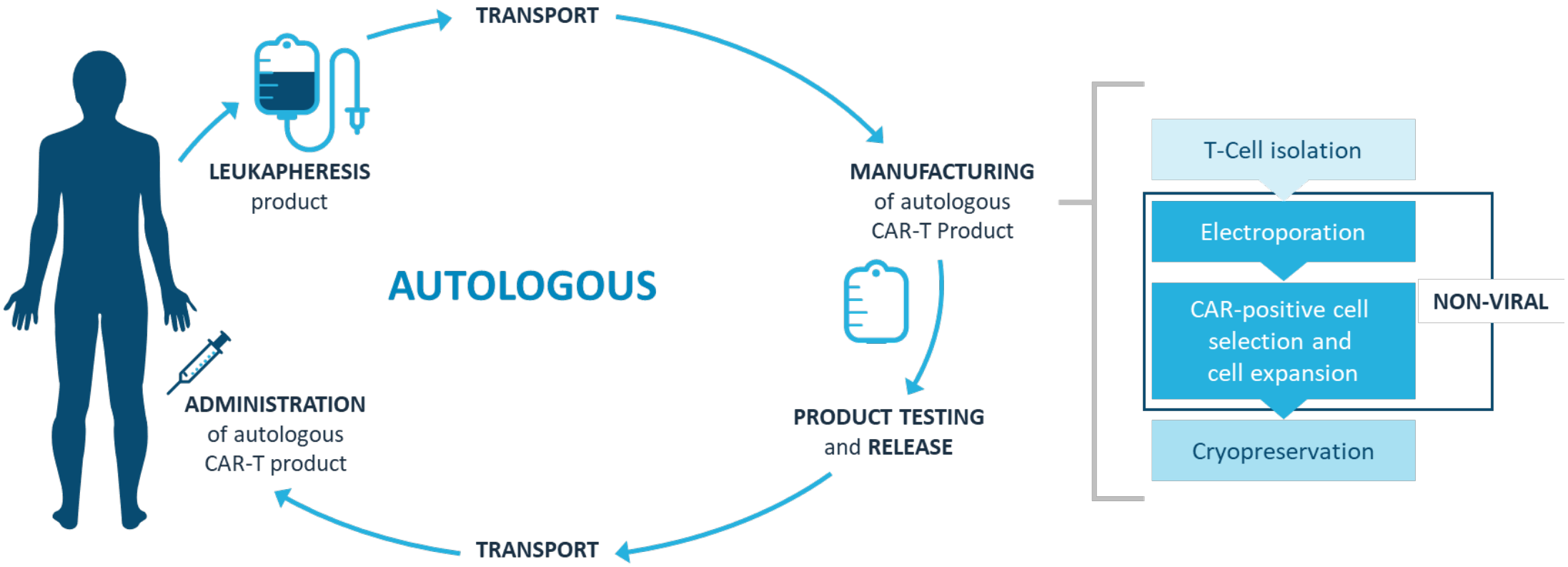
ESTIMATED MARKET OPPORTUNITY	Big	Bigger	Biggest

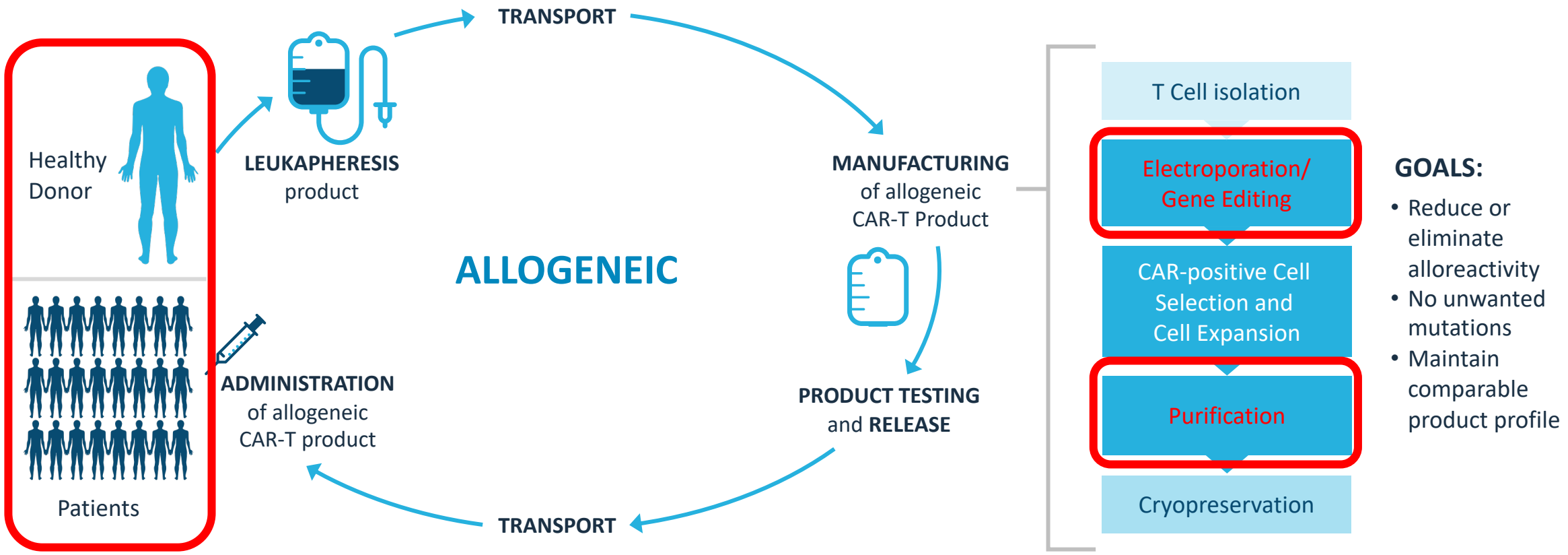
POSEIDA THERAPEUTICS

P-BCMA-ALLO1 Manufacturing Strategy Leverages Existing Processes and Experience



POSEIDA THERAPEUTICS

P-BCMA-ALLO1 Manufacturing Strategy Leverages Existing Processes and Experience



GOALS:

- Reduce or eliminate alloreactivity
- No unwanted mutations
- Maintain comparable product profile

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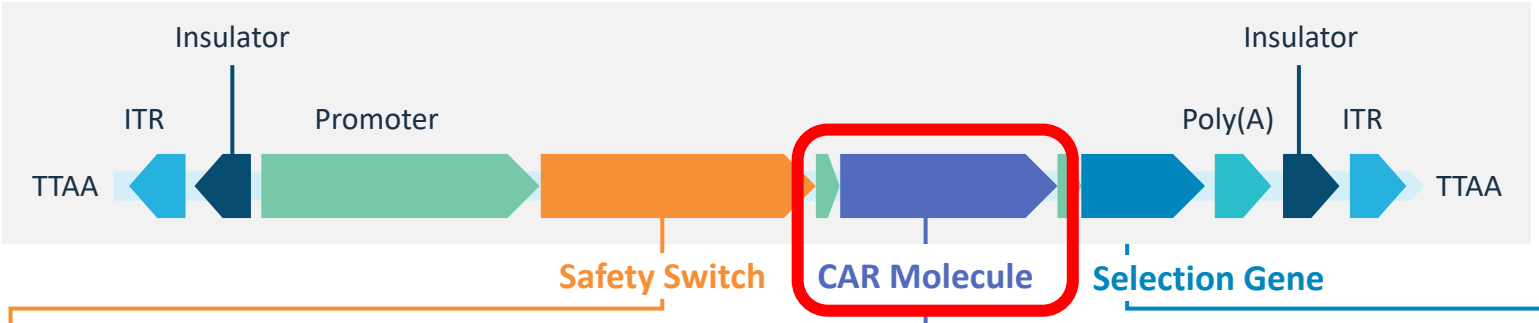
P-BMCA-ALLO1 Transgene Similar to Autologous Products

Designed To Have Desirable Product Attributes



INCORPORATES PROPRIETARY SAFETY SWITCH

- Rapid, dose-dependent **elimination** of engineered T- cells as needed
- Potential **management of** Cytokine Release Syndrome (**CRS**) or other AEs

DIFFERENTIATED BINDING CAR-T MOLECULE

- VH molecule with **high-specificity binding**
- Fully human with no **tonic signaling observed to date**

DRUG RESISTANCE GENE PERMITS POSITIVE SELECTION

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

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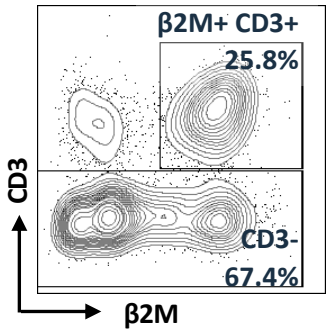
Creating a Potentially Fully Allogeneic Product Candidate

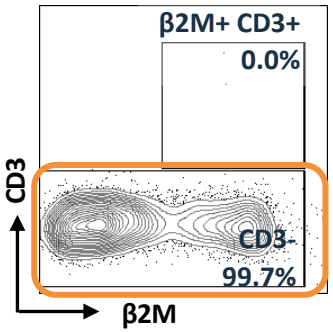
Efficient Editing of Resting T Cells

T Cell Receptor Knock Out (TCR KO) = P-BMCA-ALLO1

NON-PURIFIED



PURIFIED



TCR KO 67.4%

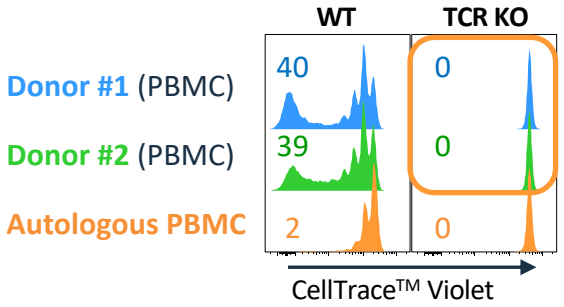
Allogeneic CAR-T 99.7%

Single, multiplexed gene editing step & purification → ~100% pure TCR KO cells

Alloreactivity Eliminated

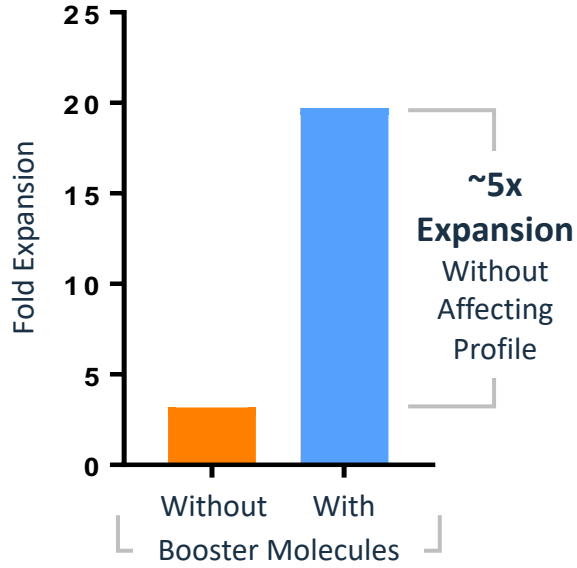
Proliferation (12 Days)

GRAFT VS HOST



"Booster Molecules" to Drive Scale

Allogeneic CAR-T Cell Expansion



Potential to treat 100s - 1,000s of patients from single manufacturing run

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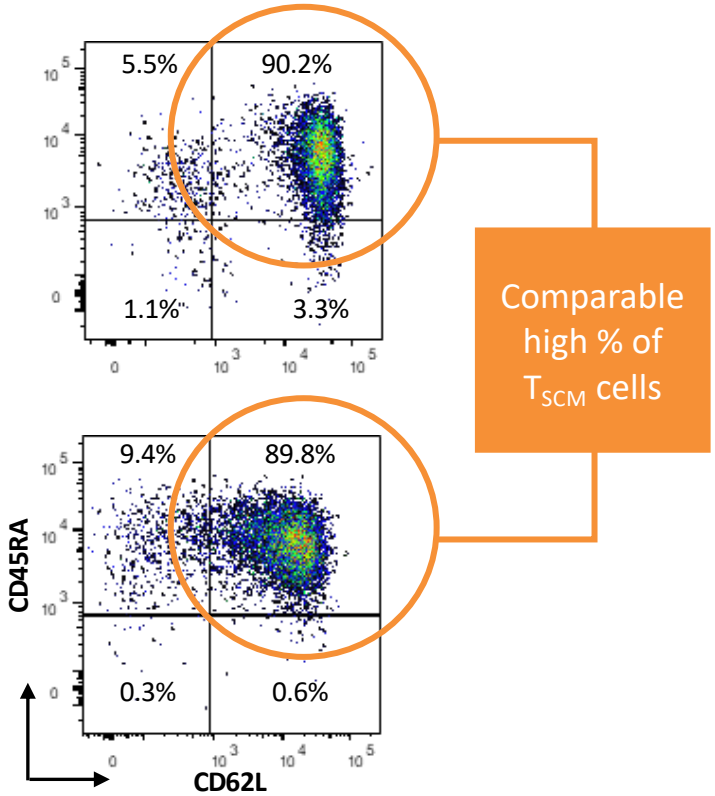
Comparable T_{SCM} Cells and Potency Observed in Autologous vs Allogeneic Versions

T_{SCM} Cells

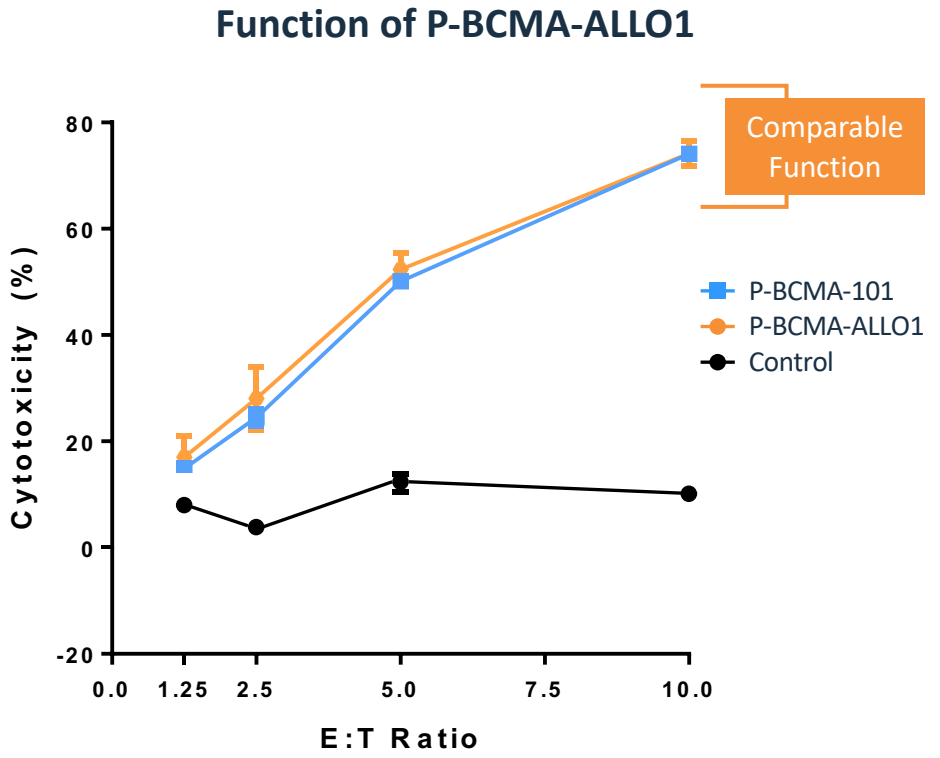
AUTOLOGOUS
(P-BCMA-101)

ALLOGENEIC
(P-BCMA-ALLO1)



Comparable high % of T_{SCM} cells

Specificity Of Killing Target Cells



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Acknowledgements

P-BCMA-101 Patients

Poseida Therapeutics, Inc.

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Clinical Biomarkers

Clinical Operations

Gene Therapy

Gene Engineering

Nanotechnology

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(California Institute for Regenerative Medicine)

MDACC

P-BCMA-101-001 Investigators

TeneoBio

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