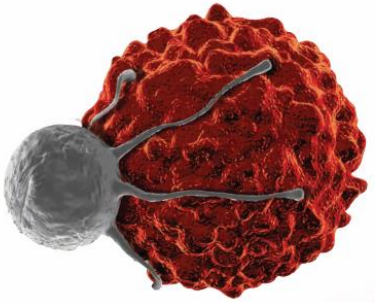
September 4-7 2018, Boston, MA

CAR-TCR Summit



Manufacture of Allogeneic "Universal Donor" CAR-T Therapies using piggyBac™ and Cas-CLOVER™

Burton Barnett, PhD

Research Scientist

September 5th, 2018

POSEIDA THERAPEUTICS

P-BCMA-ALLO1

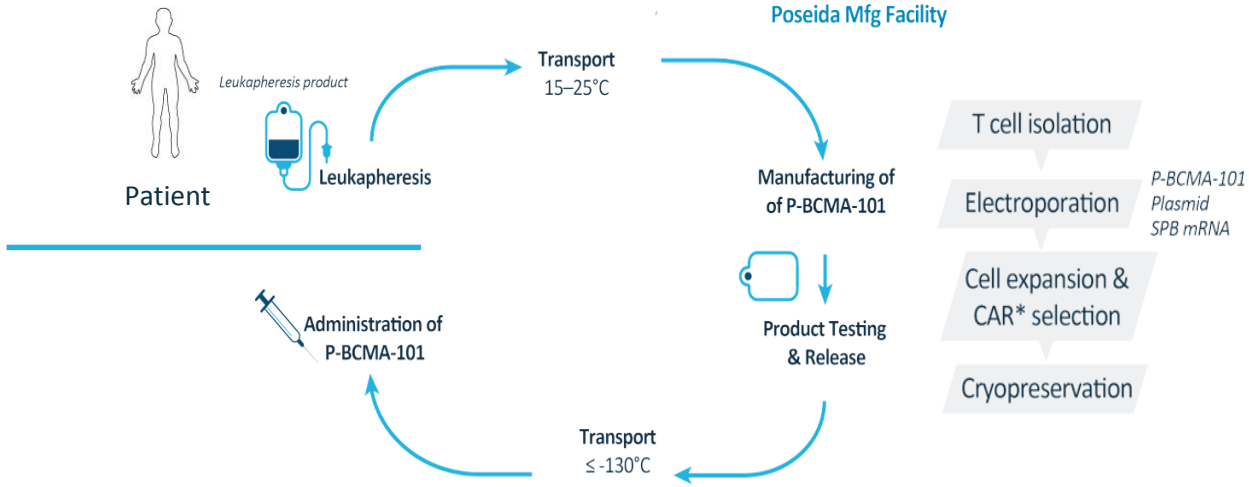
Allogeneic CAR-T Therapy for Multiple Myeloma

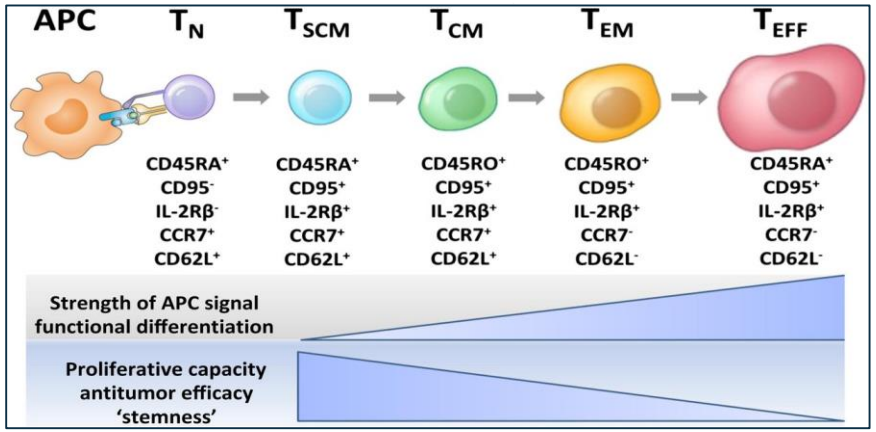
POSEIDA THERAPEUTICS

P-BCMA-101 is a young CAR T cell product

P-BCMA-101 is largely comprised of young memory T cells due to unique manufacturing characteristics

- The ability of piggyBac™ to modify resting T cells and
- A simple bead-free, cytokine-free manufacturing process
- Result in a young memory T cell phenotype
  - Advantages include
    - Improved therapeutic index
    - Potential for long-term *in vivo* durability



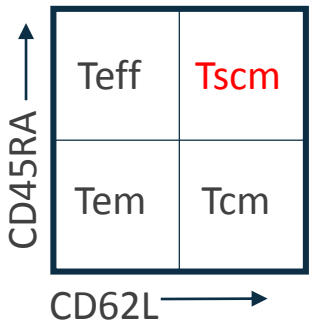


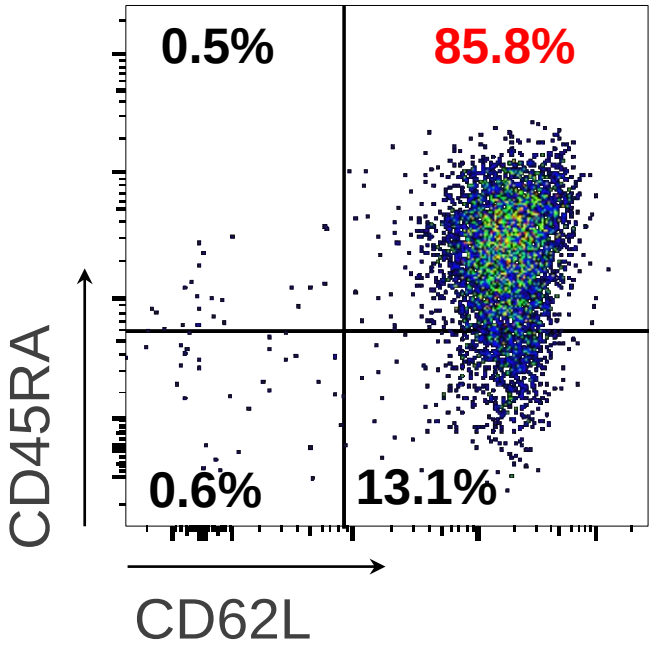
From Restifo, Blood 2014

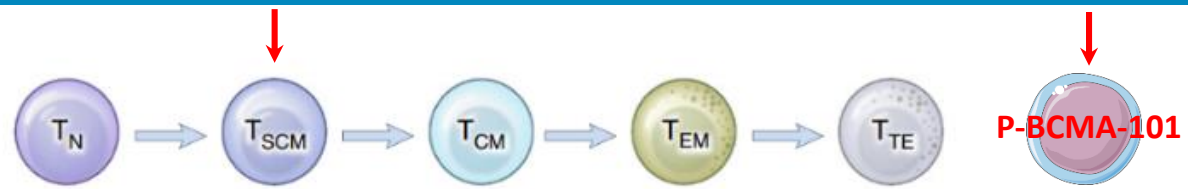
POSEIDA THERAPEUTICS

Memory phenotype of P-BCMA-101 cells

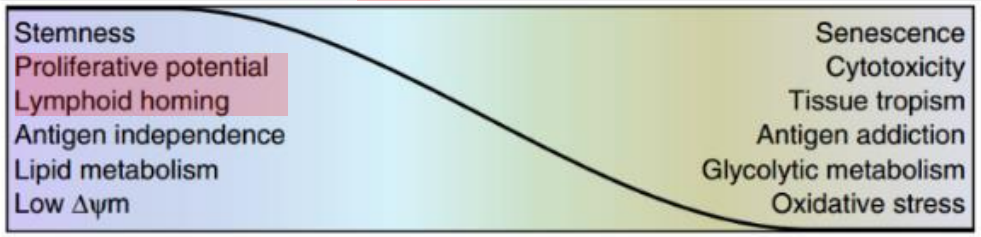
P-BMCA-101 cells exhibit extensive phenotypic markers characteristic of Tscm and Tcm cells







→	CD45RA	+	+	–	–	+	+
	CD45RO	–	–	+	+	–	-
	CCR7	+	+	+	–	–	+
→	CD62L	+	+	+	–	–	+
	CD28	+	+	+	+/–	–	+
	CD27	+	+	+	+/–	–	+
	IL-7Rα	+	+	+	+/–	–	+
	CXCR3	–	+	+	–	–	+
	CD95	–	+	+	+	+	+
	CD11a	–	+	+	+	+	+
	IL-2Rβ	–	+	+	+	+	+
	CD58	–	+	+	+	+	+
	CD57	–	–	–	+/–	+	-



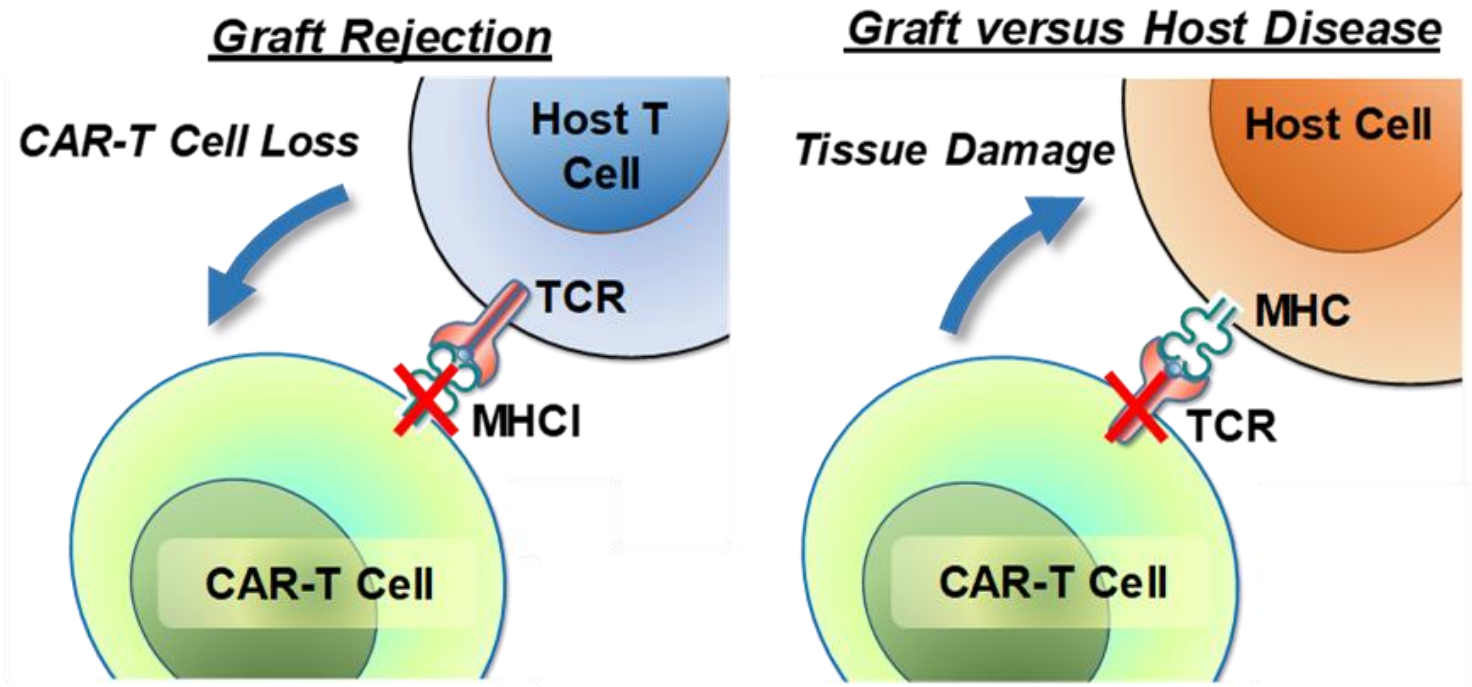
Adapted from Gattinoni *et al.* (2017) *Nat. Med.*

POSEIDA THERAPEUTICS

Universal CAR-Ts Require Precise Gene Editing of Several Targets

Allogeneic targets during adoptive T cell transfer: TCR and MHCI

- TCR on CAR-Ts mediates GvH (alloreactive TCRs target patient MHC)
- MHCI (b2M) on CAR-Ts mediates HvG (recipient alloreactive T cells)

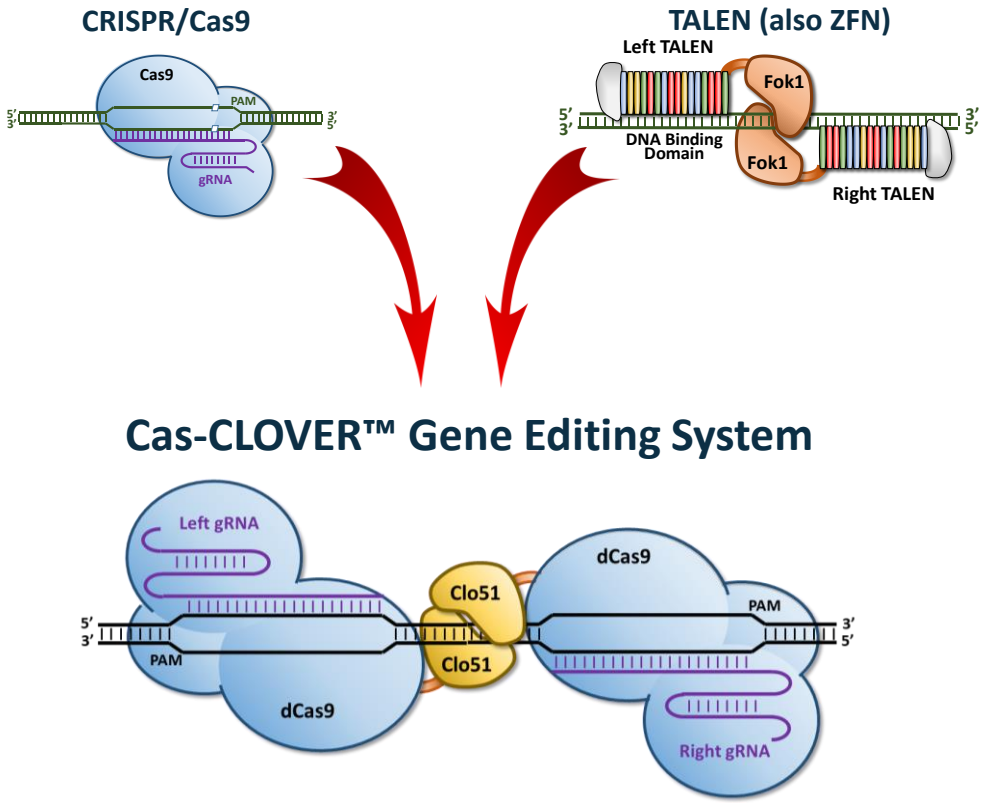


POSEIDA THERAPEUTICS

P-BCMA-ALLO1 Uses Cas-CLOVER™ to Reduce or Eliminate Alloreactivity

Cas-CLOVER™ is a high-fidelity genome editing tool enabling allogeneic approach

- Cas-CLOVER™ is **a next generation editing system** that overcomes many known challenges with CRISPR
- Dimeric system with **no off target cutting** detected despite significant testing
- **Highly efficient** and able to edit **resting T-cells, which allows for maintenance of Tscm phenotype**
- Ability to **multiplex** (e.g. create double knockouts)
- Easy to design and manufacture and **low cost**
- **Proprietary IP** outside of CRISPR disputes

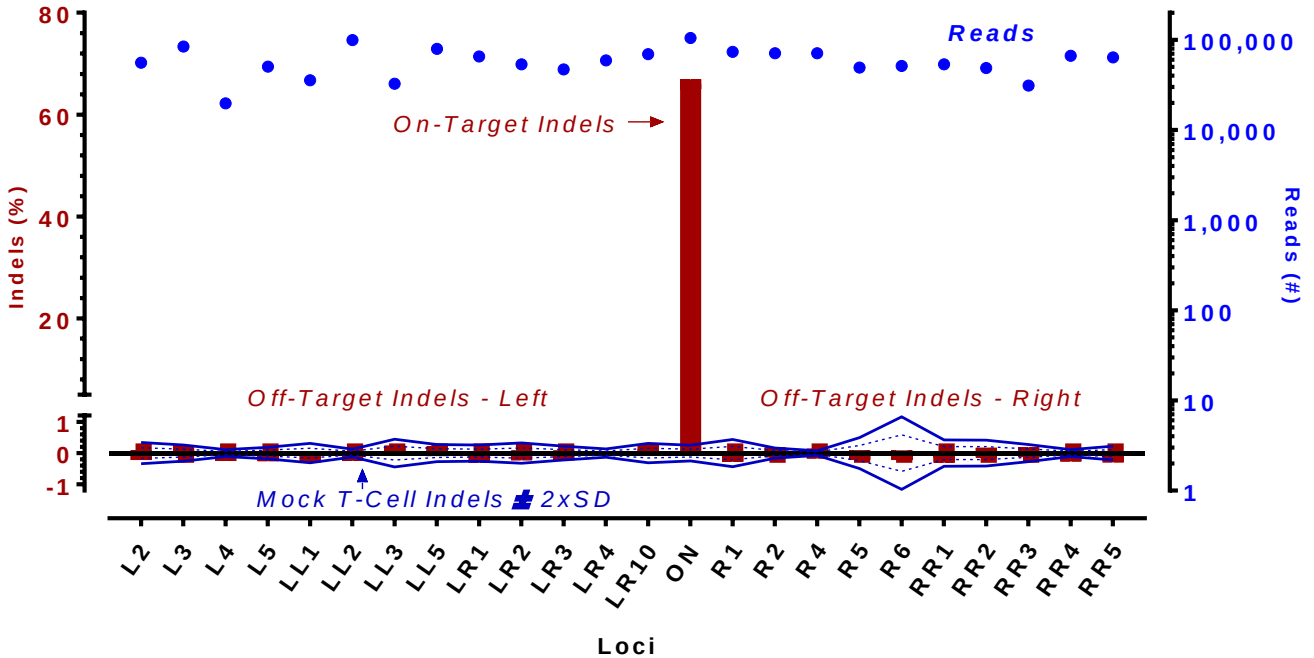


POSEIDA THERAPEUTICS

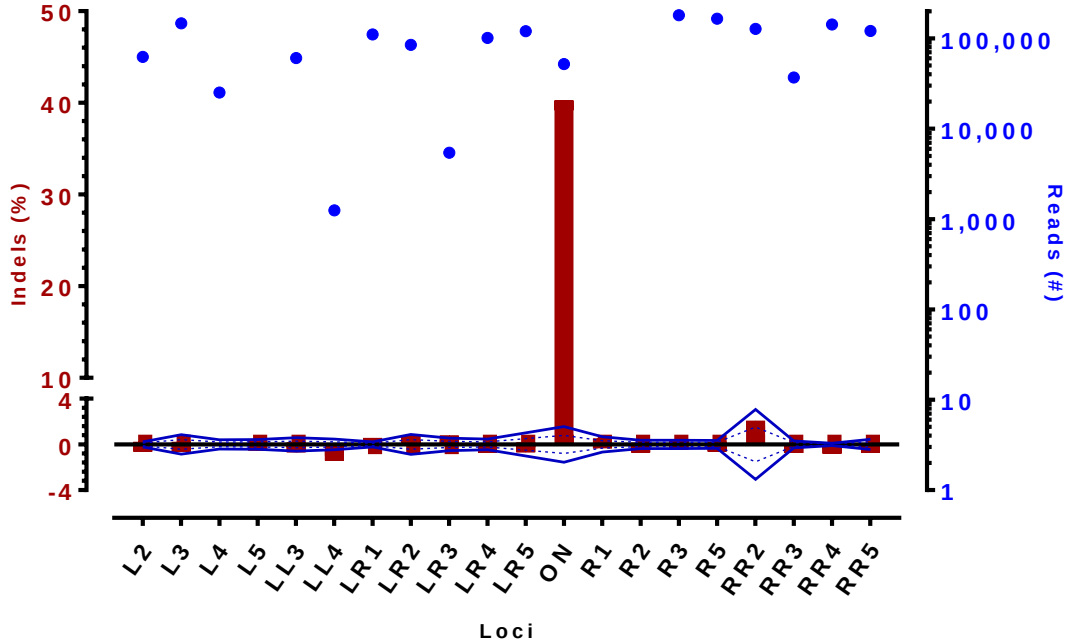
Cas-CLOVER™ Is Highly Precise With No Off-Target Cutting

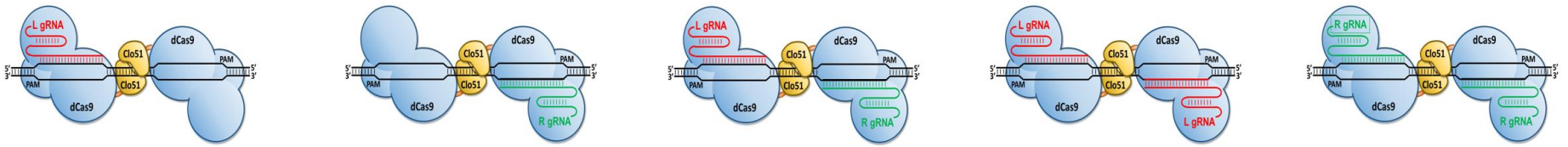
Data from millions of sequence reads demonstrates that Cas-CLOVER™ does not cause off target cutting

TCRα



β_2M





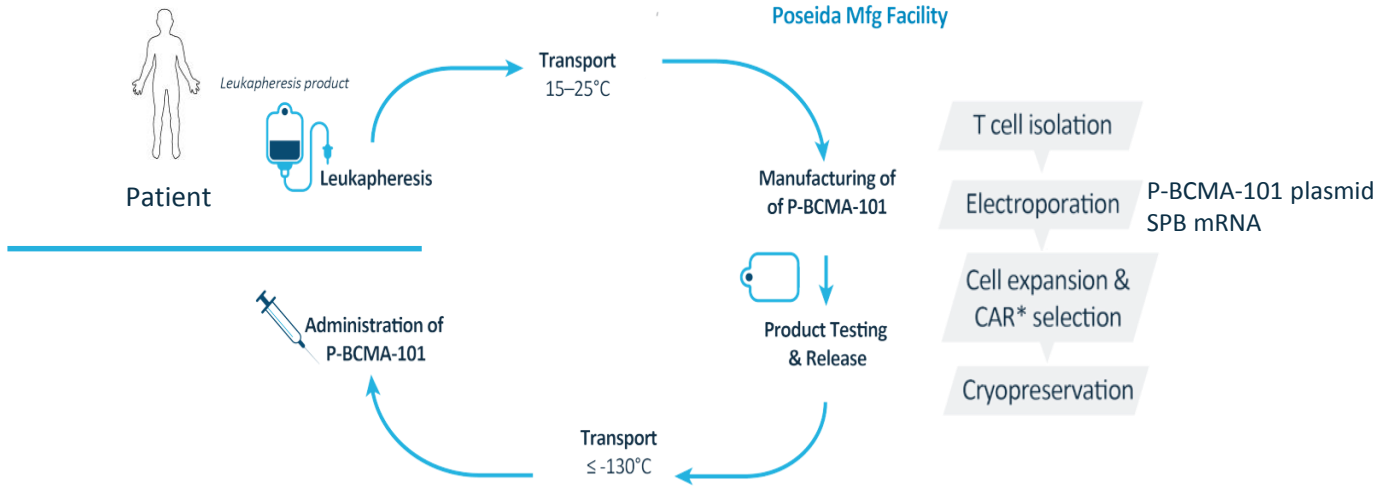
gRNA	L	R	LR	LL	RR

KBIOBOX

POSEIDA THERAPEUTICS

P-BCMA-ALLO1: Allogeneic “Universal Donor” CAR-T

Poseida’s allogeneic approach leverages much of our existing processes and experience



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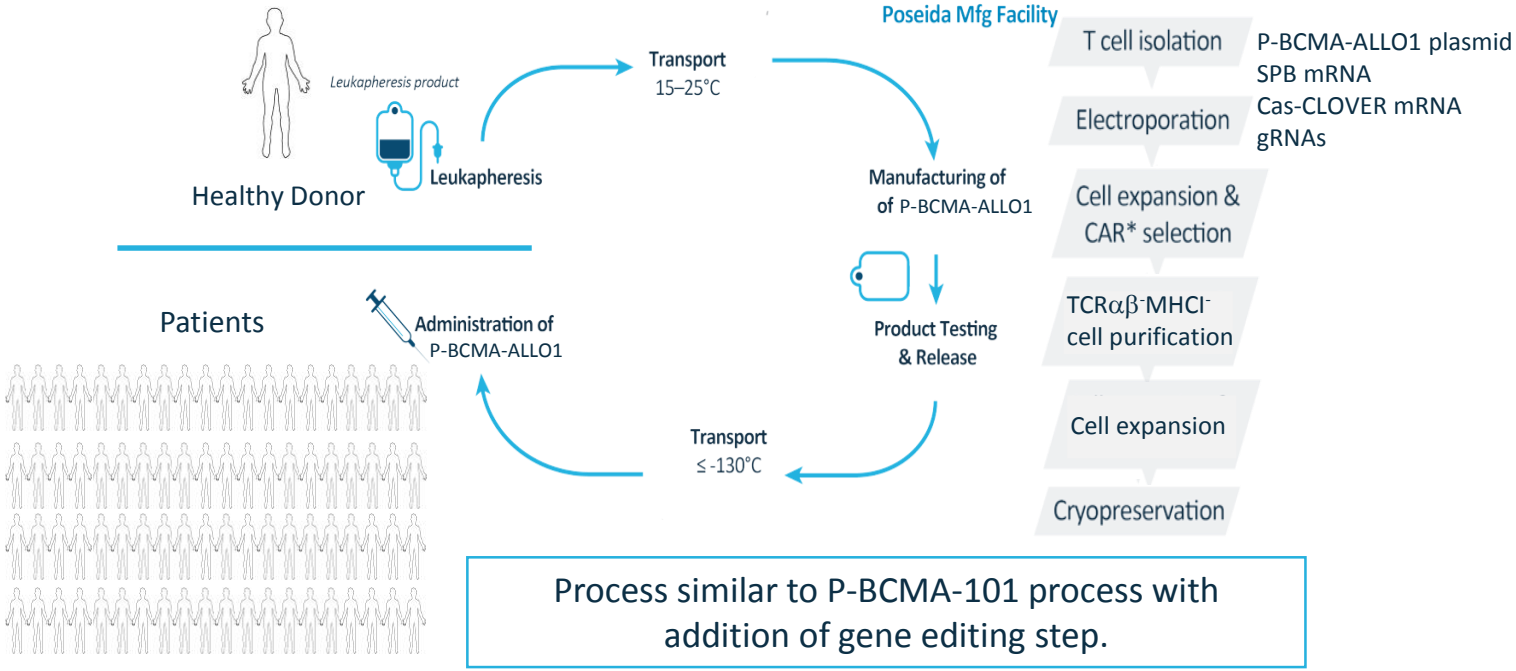


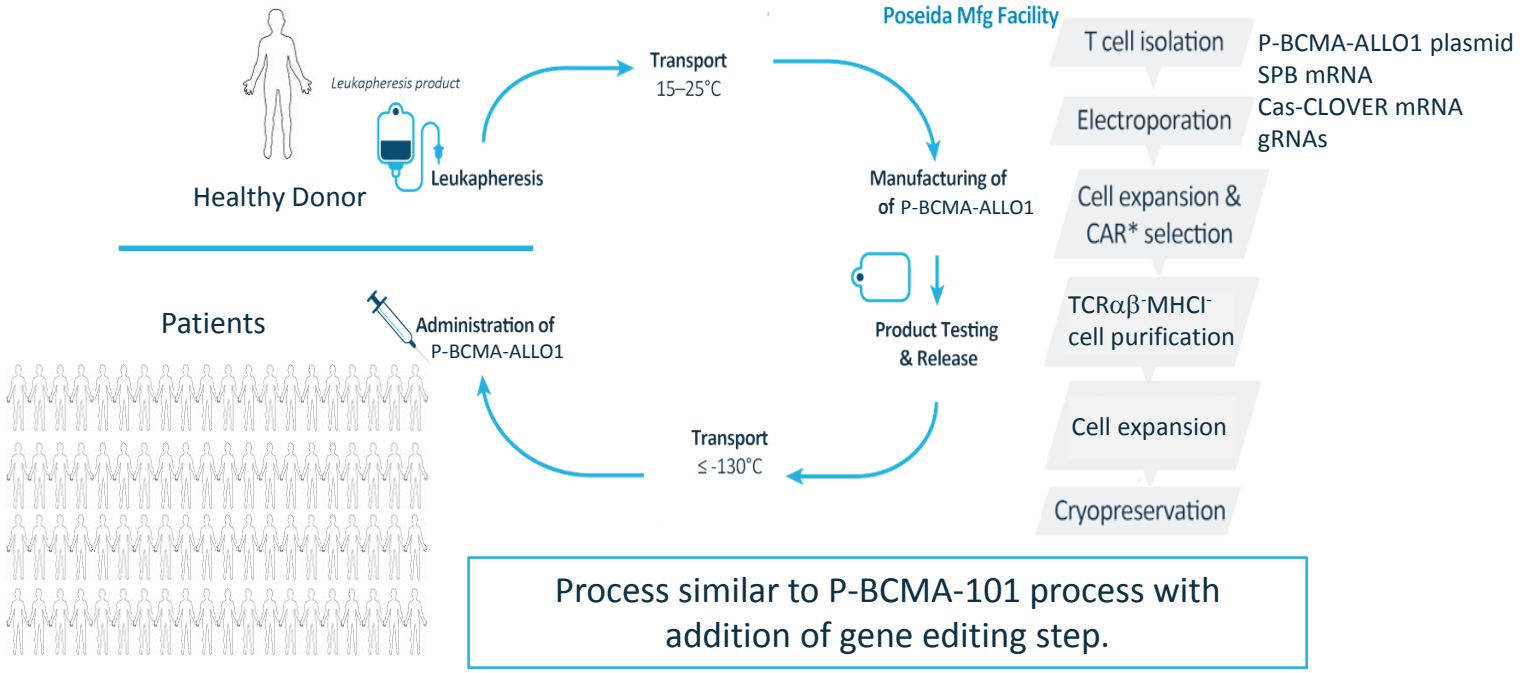
Process similar to P-BCMA-101 process with addition of gene editing step.

POSEIDA THERAPEUTICS

P-BCMA-ALLO1: Allogeneic "Universal Donor" CAR-T

Poseida's allogeneic approach leverages much of our existing processes and experience

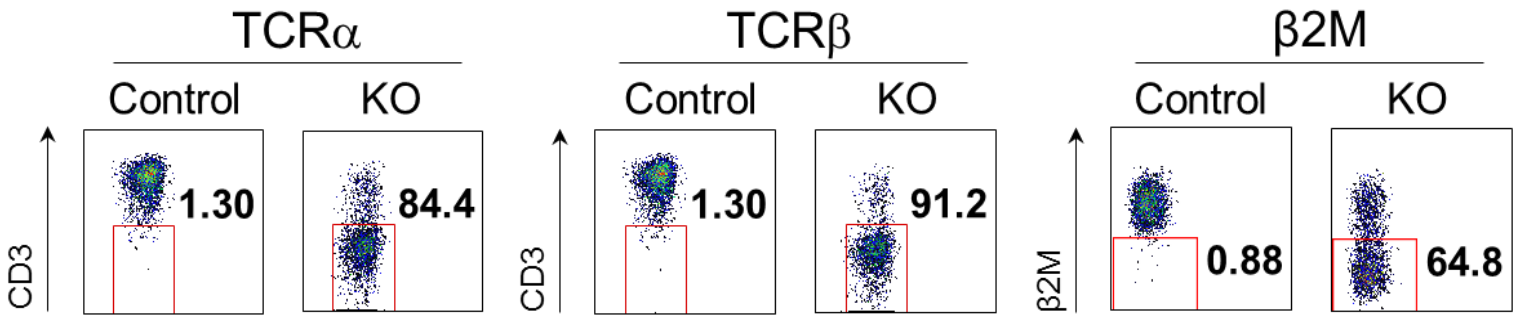
- Gene editing to **eliminate alloreactivity**
- Allows **for defined donor source cells** with desirable manufacturing and efficacy characteristics
- **Drastically reduces cost** per patient

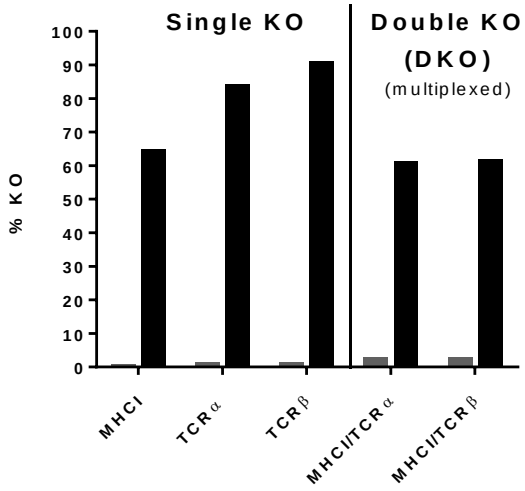


POSEIDA THERAPEUTICS

Cas-CLOVER™ Enables High-Frequency Gene Editing in Resting T Cells

Multiplexed gene editing can efficiently create homozygous double knockout cells





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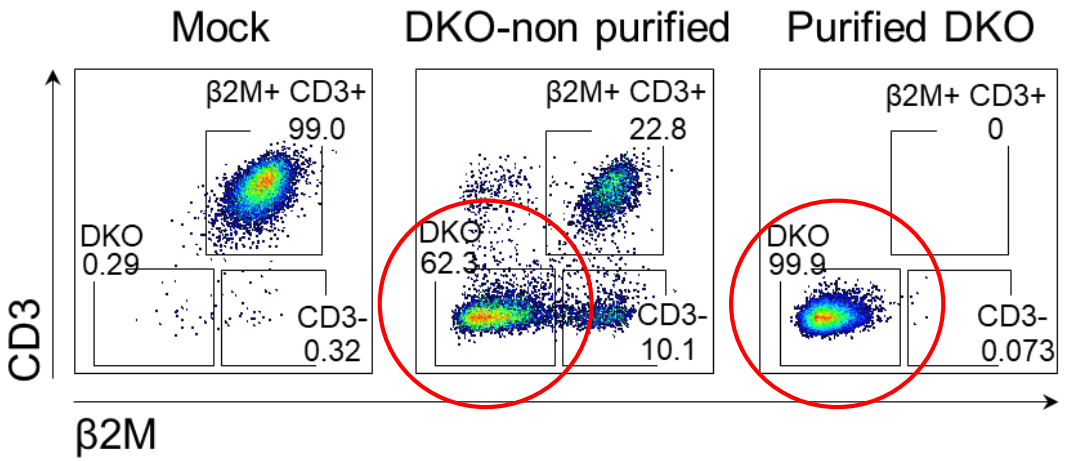


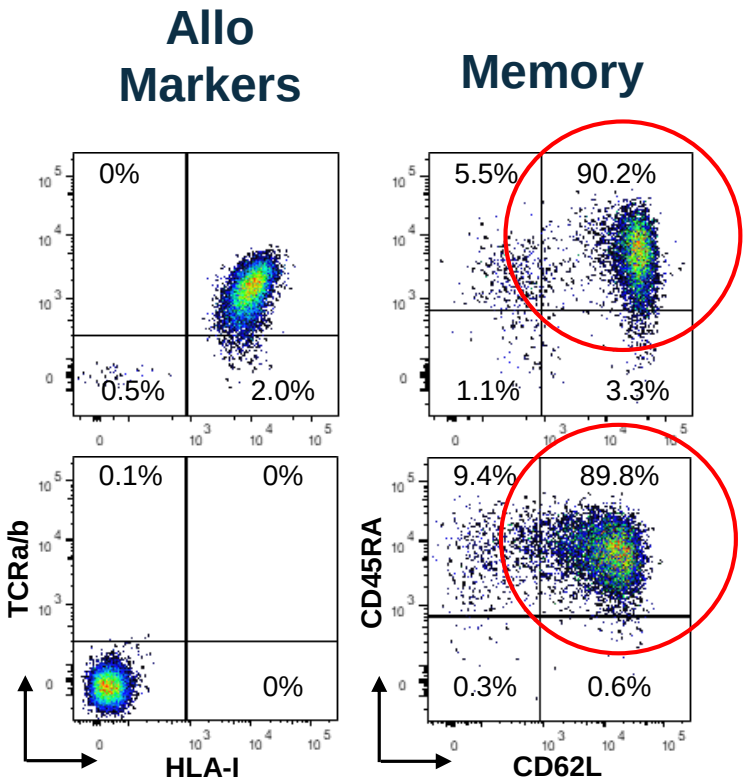
POSEIDA THERAPEUTICS

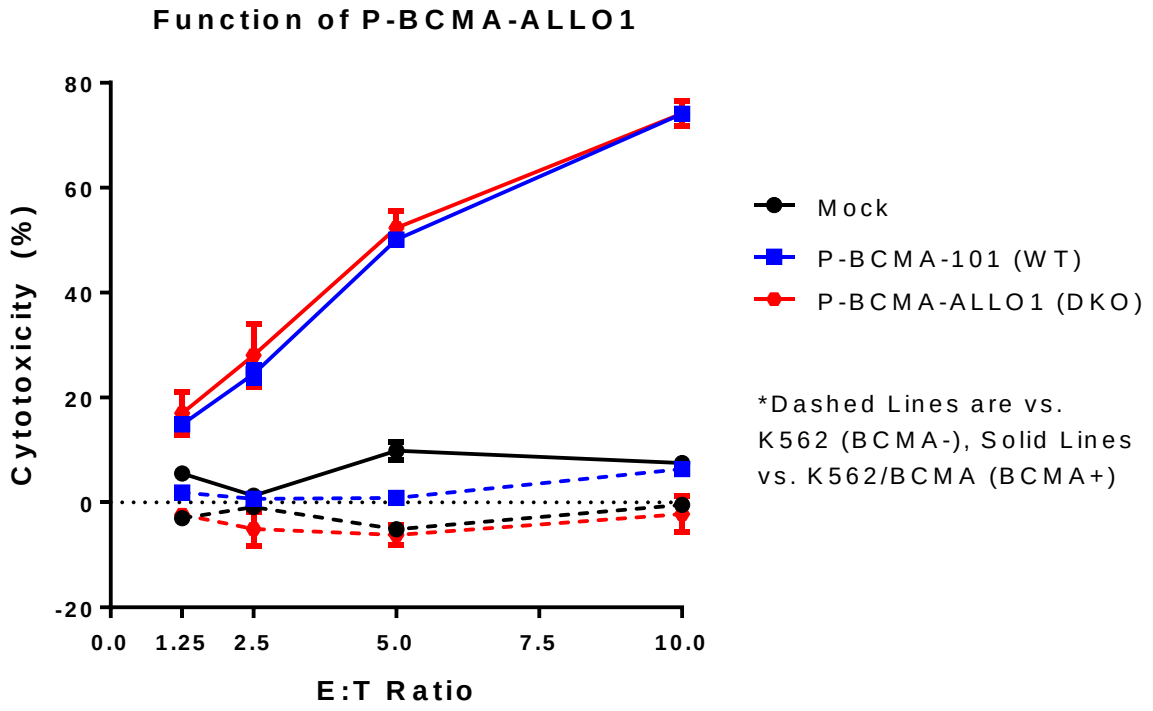
P-BCMA-ALLO1 CAR-T Cells Maintain Tscm Phenotype and are Potent

Ability to perform gene editing in resting T cells allows for maintenance of Tscm phenotype and killing ability

P-BCMA-101 (WT)

P-BCMA-ALLO1 (DKO)





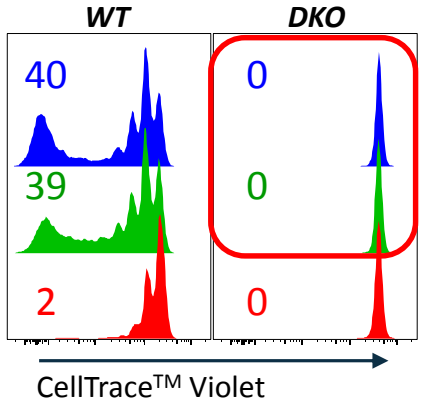
POSEIDA THERAPEUTICS

P-BCMA-ALLO1 Demonstrates Reduced or Eliminated Alloreactivity

Multiple preclinical experiments demonstrate the ability to reduce or eliminate both GvH and HvD

Proliferation
(12 days)

Graft vs Host
(irradiated PBMC)

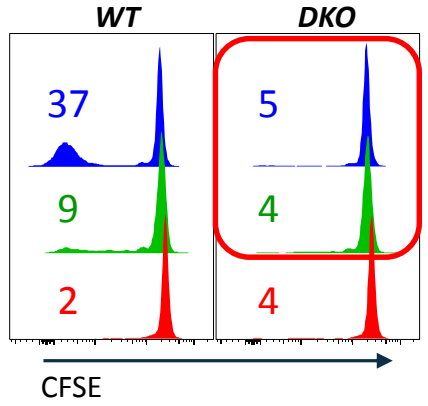


Donor #1 PBMC

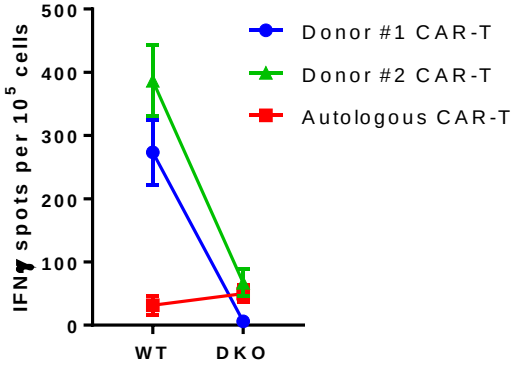
Donor #2 PBMC

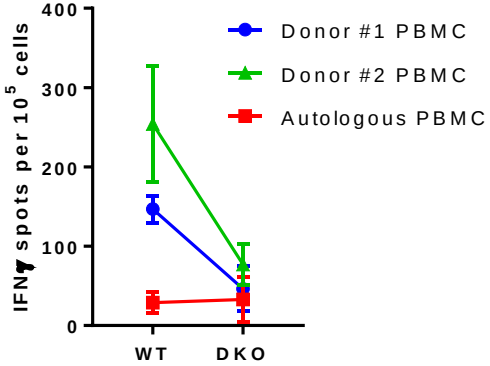
Autologous PBMC

Host vs Graft
(irradiated CAR T)



ELISPOT
(20 hrs)





POSEIDA THERAPEUTICS

Improving allogeneic CAR T cell functionality

How will the absence of surface TCR affect efficacy of P-BCMA-ALLO1?

- Published reports are conflicting on the requirement for TCR expression in memory T cell maintenance
- Data suggests that TCR KO CAR-T cells may have functional disadvantages under some conditions
  - Without mitigation this could potentially bode poorly for post-infusion proliferation and durability
- We designed ‘Booster Molecules’ to potentially address these issues
  - These can be transiently expressed or encoded in PiggyBac™

POSEIDA THERAPEUTICS

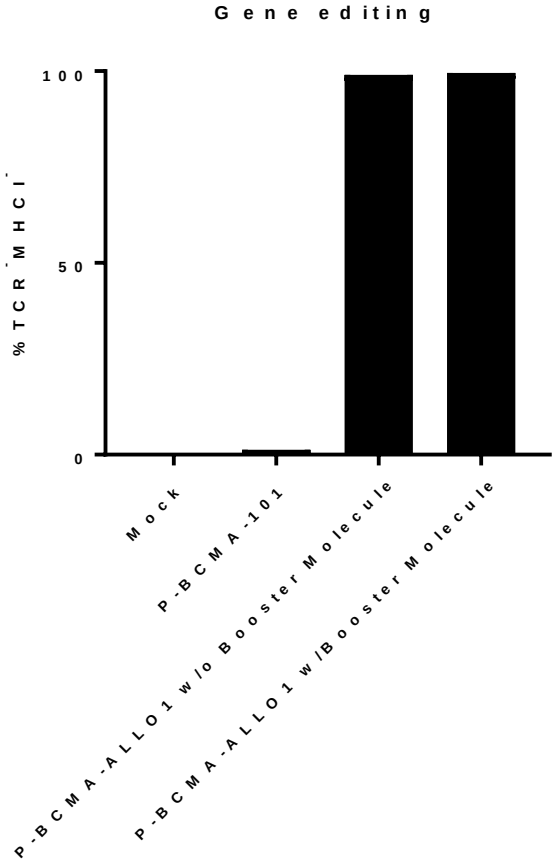
P-BCMA-ALLO1 with Booster Molecule

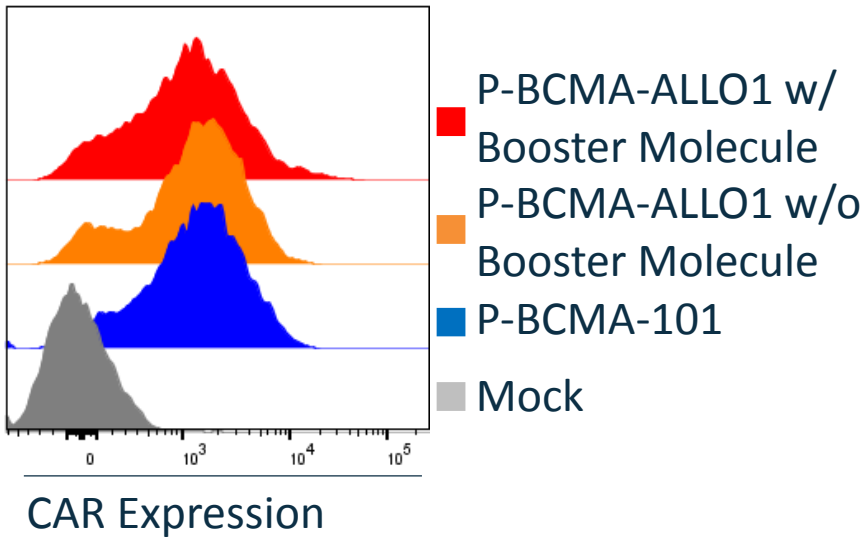
What is the effect of the Booster Molecule on P-BCMA-ALLO1?

- How is the phenotype of the cells impacted?
- Do the cells retain antigen-specific functionality?
- Can sufficient doses be generated to significantly lower cost?

P-BCMA-ALLO1 Modification

The final efficacy of gene editing and insertion





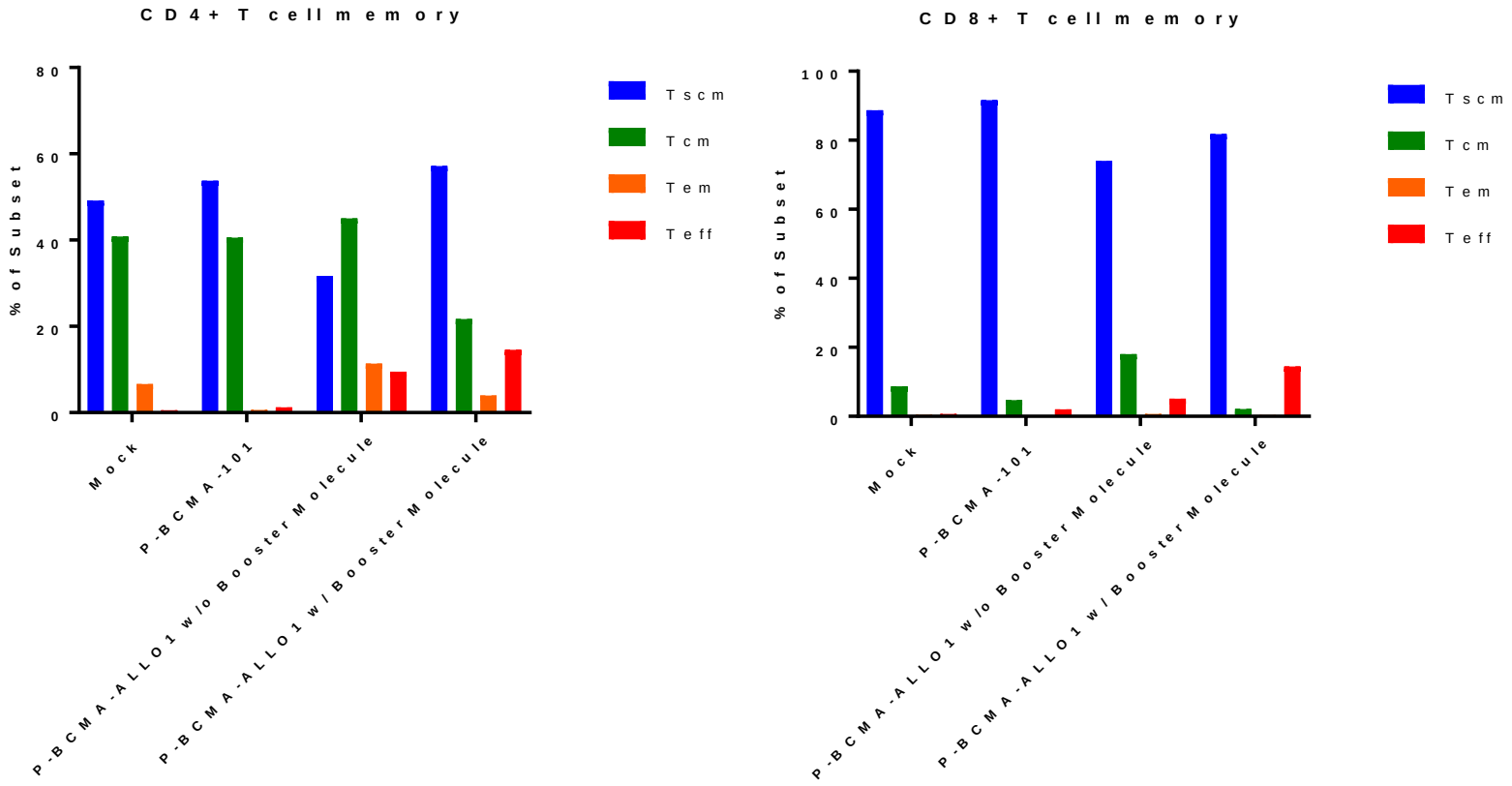
- P-BCMA-ALLO1 cells with or without the Booster Molecule
  - Express comparable levels of BCMA-specific CAR to P-BCMA-101 cells
  - Lack MHCI and TCR expression

POSEIDA THERAPEUTICS

P-BCMA-ALLO1 Phenotype

The memory phenotype of P-BCMA-ALLO1 cells

Tscm: $CD45RA^{+}CD45RO^{-}CD62L^{+}$
Tcm: $CD45RA^{-}CD45RO^{+}CD62L^{+}$
Tem: $CD45RA^{-}CD45RO^{+}CD62L^{-}$
Teff: $CD45RA^{+}CD45RO^{-}CD62L^{-}$

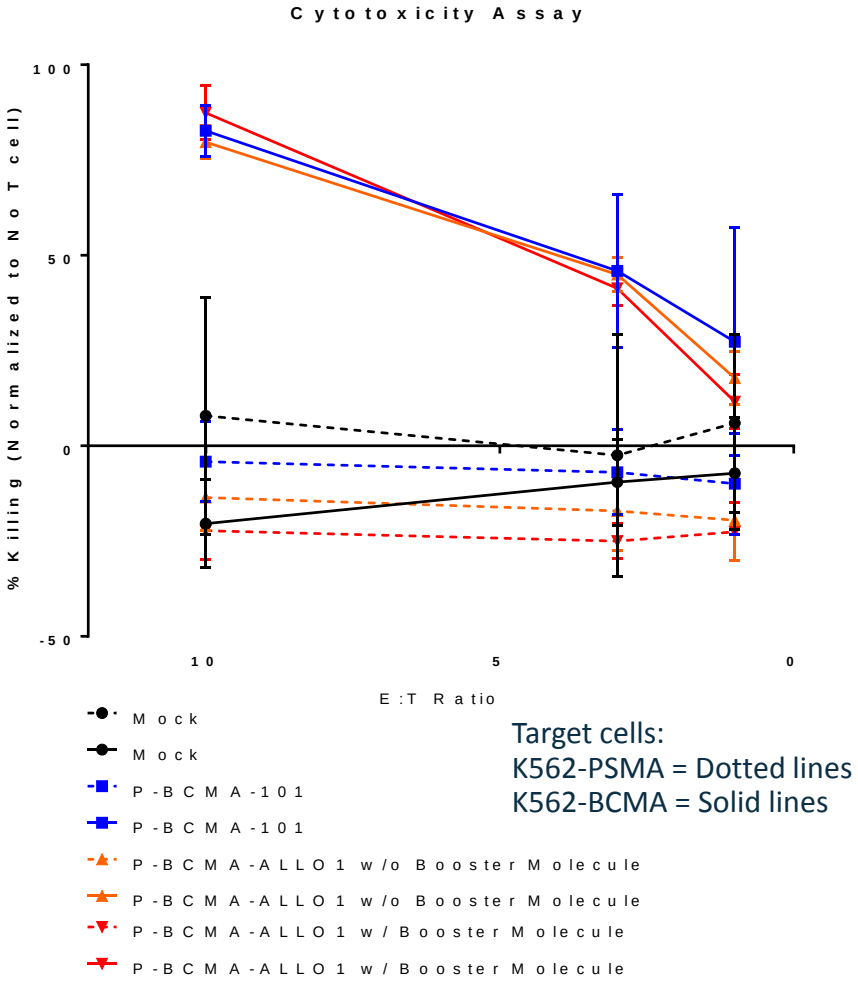


- P-BCMA-ALLO1 cells retain a young memory phenotype, similar to P-BCMA-101

POSEIDA THERAPEUTICS

P-BCMA-ALLO1 Functionality

BCMA-specific functionality measured by 48 hour in vitro killing assay, cytokine production, and 5 day proliferation assay



Target cells:
K562-PSMA = Dotted lines
K562-BCMA = Solid lines

- P-BCMA-ALLO1 cells exhibit comparable antigen-specific functionality to P-BCMA-101
  - Potent *in vitro* killing of BCMA^{+} target cells by P-BCMA-101 and P-BCMA-ALLO1 cells with and without the Booster Molecule

POSEIDA THERAPEUTICS

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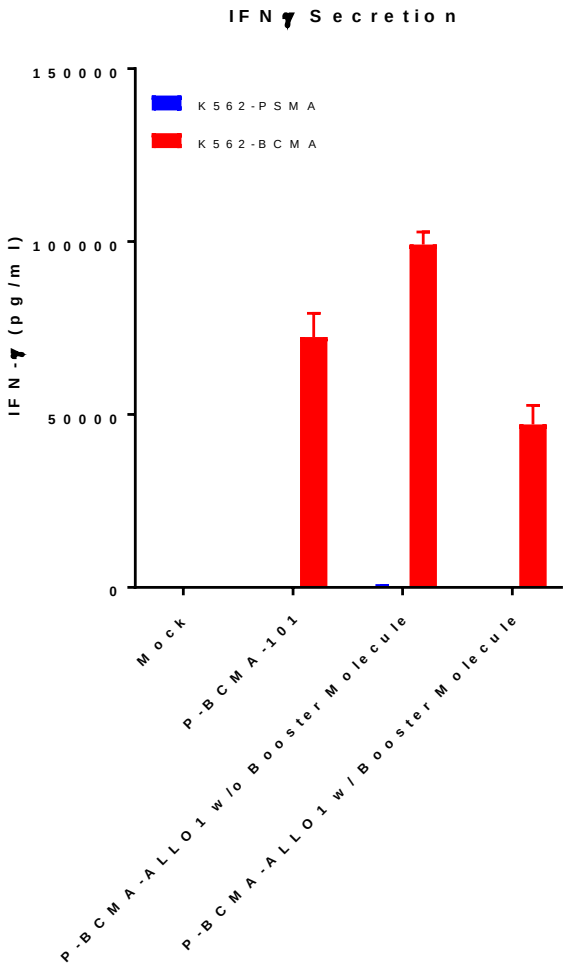

- P-BCMA-ALLO1 cells exhibit comparable antigen-specific functionality to P-BCMA-101
  - Potent *in vitro* killing of BCMA$^+$ target cells by P-BCMA-101 and P-BCMA-ALLO1 cells with and without the Booster Molecule
  - All BCMA-specific CAR-T cells secrete IFNγ in response to BCMA$^+$ target cells, but not in response to an irrelevant antigen

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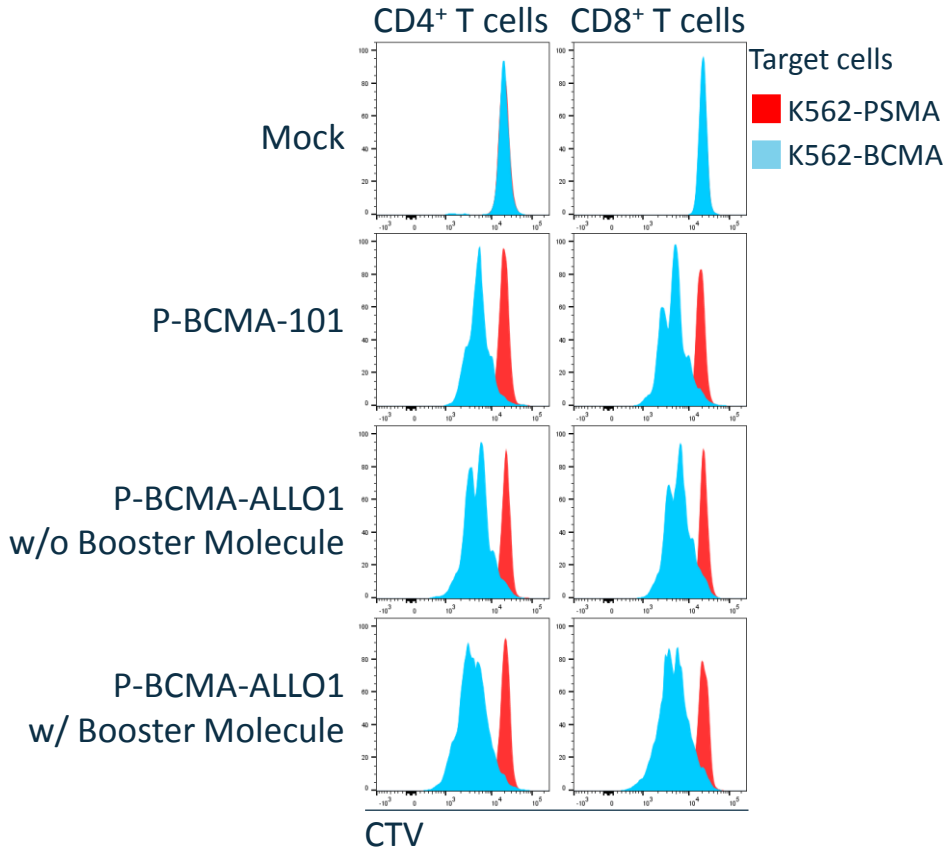

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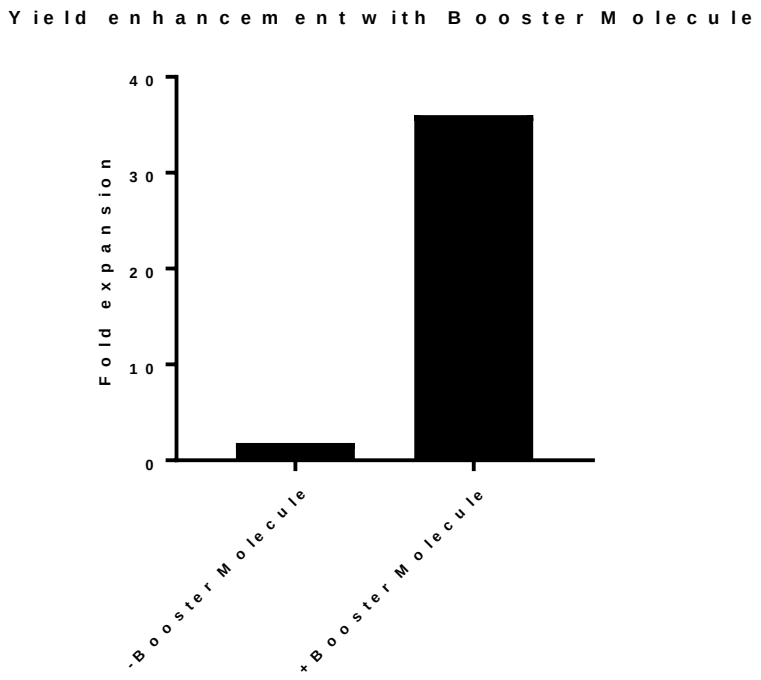
  - All BCMA-specific CAR-T cells secrete IFNγ in response to BCMA$^+$ target cells, but not in response to an irrelevant antigen
  - CD4$^+$ and CD8$^+$ T cells from P-BCMA-101 and P-BCMA-ALLO1 cells with and without the Booster Molecule proliferate *in vitro* in response to BCMA$^+$ targets

POSEIDA THERAPEUTICS

P-BCMA-ALLO1 Production

P-BCMA-ALLO1 cells can be manufactured to treat numerous patients from a single donor

- Much greater expansion is seen in the presence of the booster molecule
- Suggests that the booster molecule may make up for any deficiencies due to the absence of the TCR
- Current manufacturing plan will dramatically reduce the cost of cellular therapy



POSEIDA THERAPEUTICS

P-BMCA-ALLO1: First Product in Allogeneic CAR-T

Recent concerns with CRISPR gene editing represent opportunity for Poseida's next-gen technology

- The non-viral piggyBac™-based manufacturing process of P-BCMA-101 generates a young memory phenotype
  - This provides potential advantages in improved therapeutic index and *in vivo* durability

POSEIDA THERAPEUTICS

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- Cas-CLOVER™ can precisely and efficiently edit resting naïve T cells
  - Nucleic acid components can be easily added to the P-BCMA-101 manufacturing process
  - Editing resting naïve T cells results in a younger memory phenotype in the final product
  - Minimal changes to the manufacturing process result in similar functionality to P-BCMA-101

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- Introduction of the Booster Molecule mitigates potential disadvantages of allogenicity
  - Knocking out the TCR may put allogeneic CAR T cells at a proliferative disadvantage *in vivo*
  - Adding the Booster Molecule mitigates this disadvantage without impairing the phenotype or functionality of the cells

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  - Knocking out the TCR may put allogeneic CAR T cells at a proliferative disadvantage *in vivo*
  - Adding the Booster Molecule mitigates this disadvantage without impairing the phenotype or functionality of the cells
- The data suggest our platforms provide a product with the advantages of autologous CAR T cells and the potential to treat numerous patients

Acknowledgments

Poseida Therapeutics, Inc.

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

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

Immuno-Oncology
Burton Barnett, Ph.D.
Jenessa Smith, Ph.D.
Christopher Martin, Ph.D.
Stacey Cranert, Ph.D.
Srinivas Rengarajan, M.S.
Yening Tan, M.S.
Rebecca Codde, B.S.

To learn about our program targeting a universal tumor antigen:
Dr. Devon Shedlock, 6:25PM, Discovery

Join us for further discussion at a panel session:
Thursday 9/6/2018 2:35PM, CAR-TCR Manufacturing Track

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