POSEIDA THERAPEUTICS

Optimizing Allogeneic Cell Therapy Manufacturing Processes

8th Annual CAR-TCR Summit

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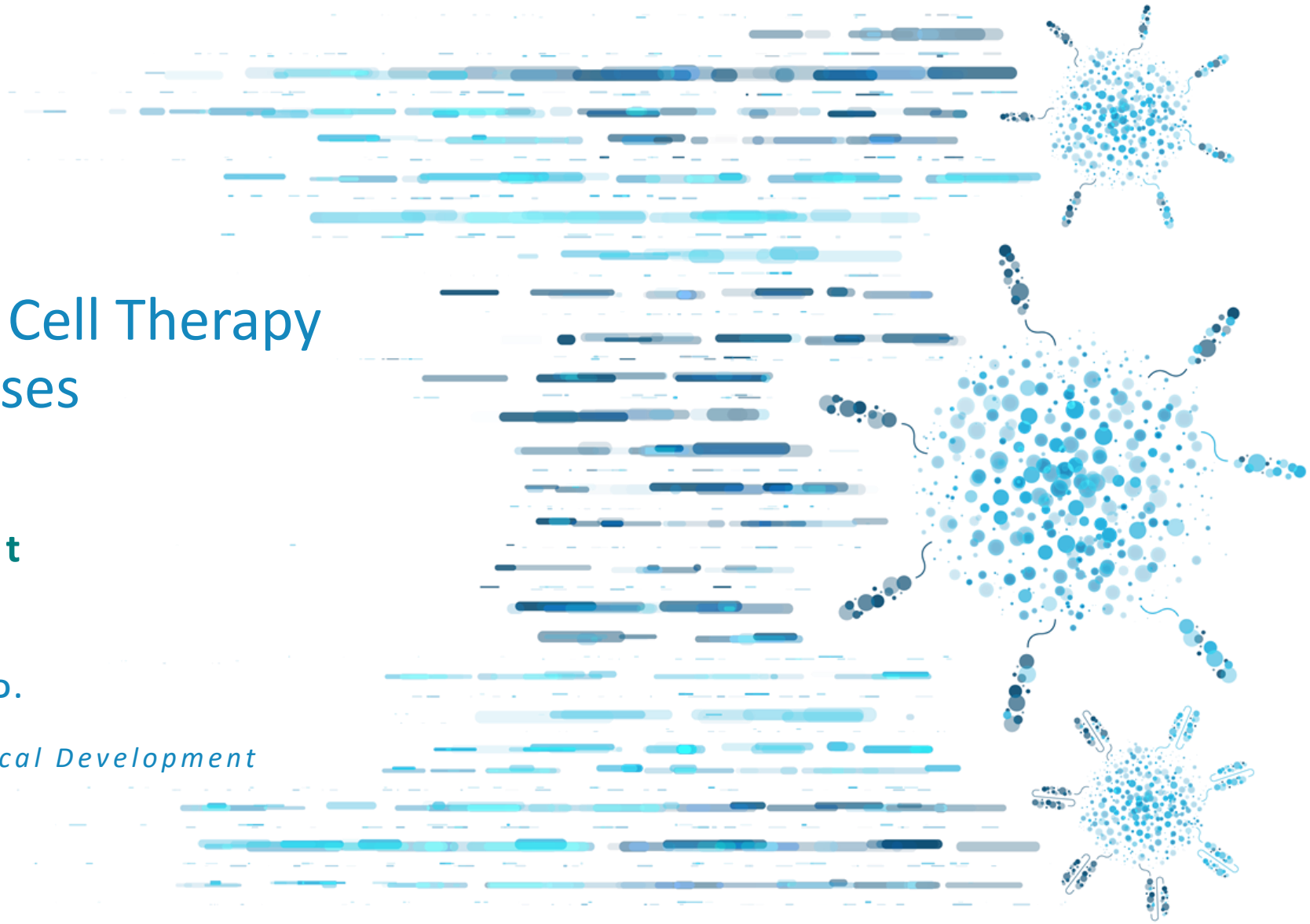

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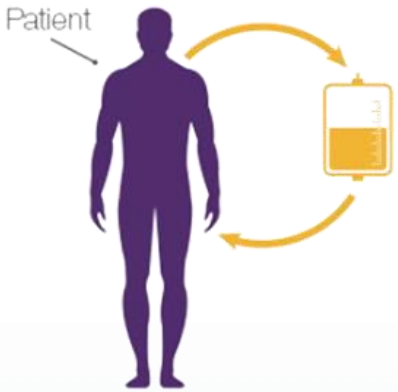
Challenges for Off-the-Shelf, Allogeneic CAR αβ T Cell Therapy

- Recently, industry has increasingly focused on the manufacture and advancement of allogeneic cell therapies
  - Off-the-shelf availability
  - Significantly lower manufacturing cost per dose
- However, there are several challenges with the manufacturing of allogeneic cell therapies

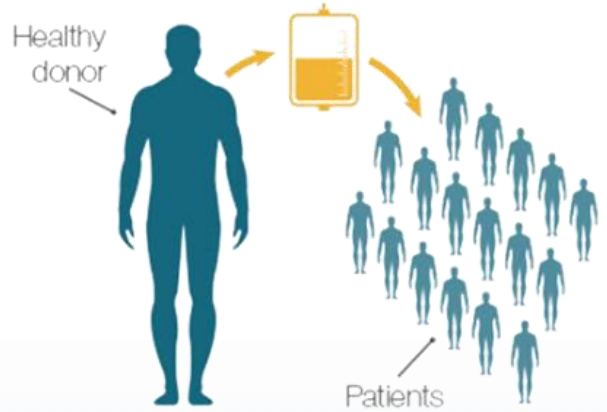
Challenges:

- Complicated logistics
- Significant lot to lot variability
- Expensive

Autologous
Cell Therapy



Allogeneic
Cell Therapy



Challenges:

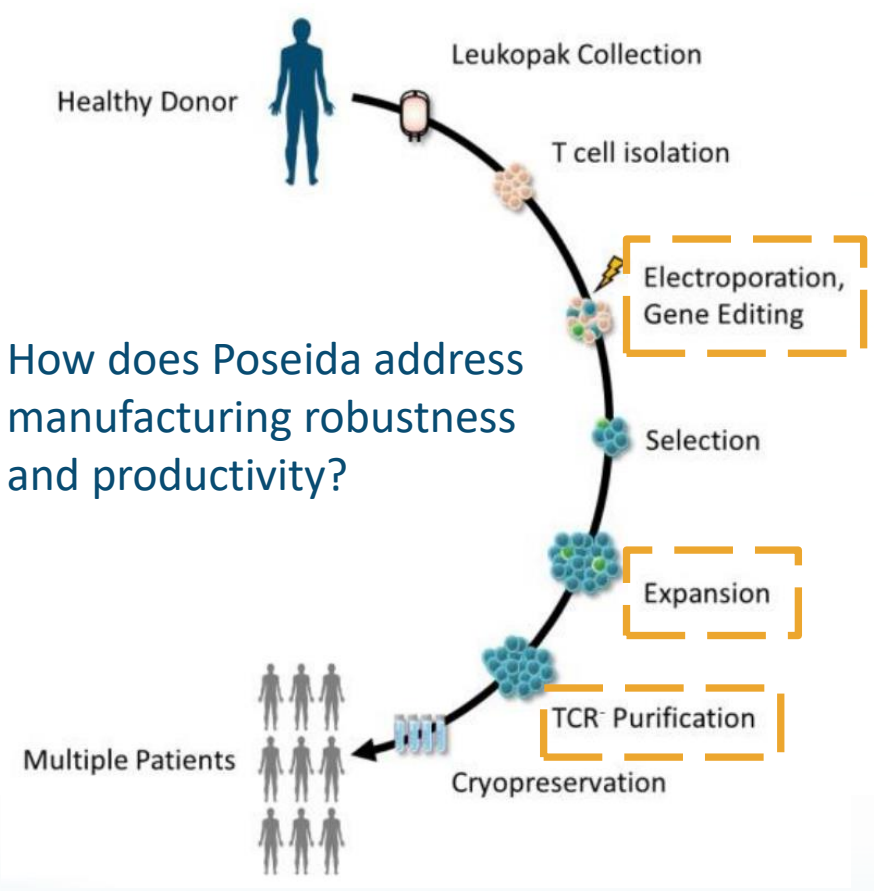
- Risk of GvHD
- Decreased persistence

Poseida Manufacturing Facility

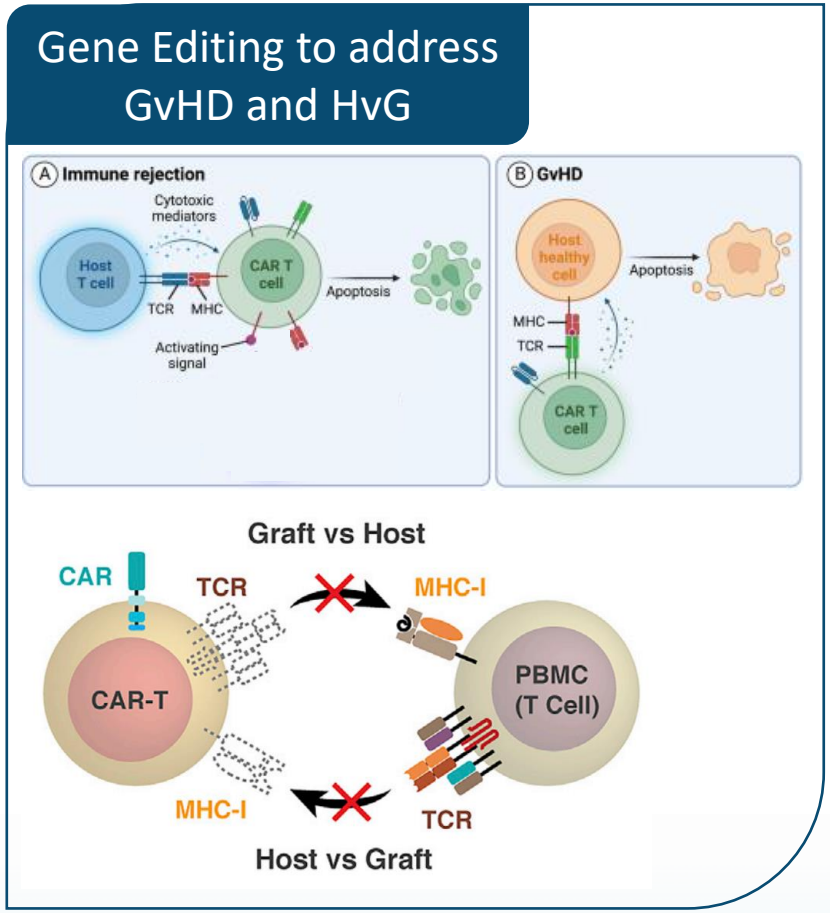
Facility Highlights			
Manufacturing Area	**Process Support**	**Laboratory Spaces**	**Office Space**
• GMP manufacturing suite • Flexible manufacturing suite for pre-IND through IND-enabling activities • Dedicated area for materials transfer into cleanrooms	• Final product storage and distribution • GMP storage for raw materials and consumables with quarantined and released dedicated areas	• QC Analytical lab to support product specific in-process and release testing assays • QC Micro lab to support environmental monitoring program activities	• Main lobby entrance • Large conference room • Huddle rooms • Open seating concept • Work center team area

Gene Editing to Mitigate GvHD and HvG

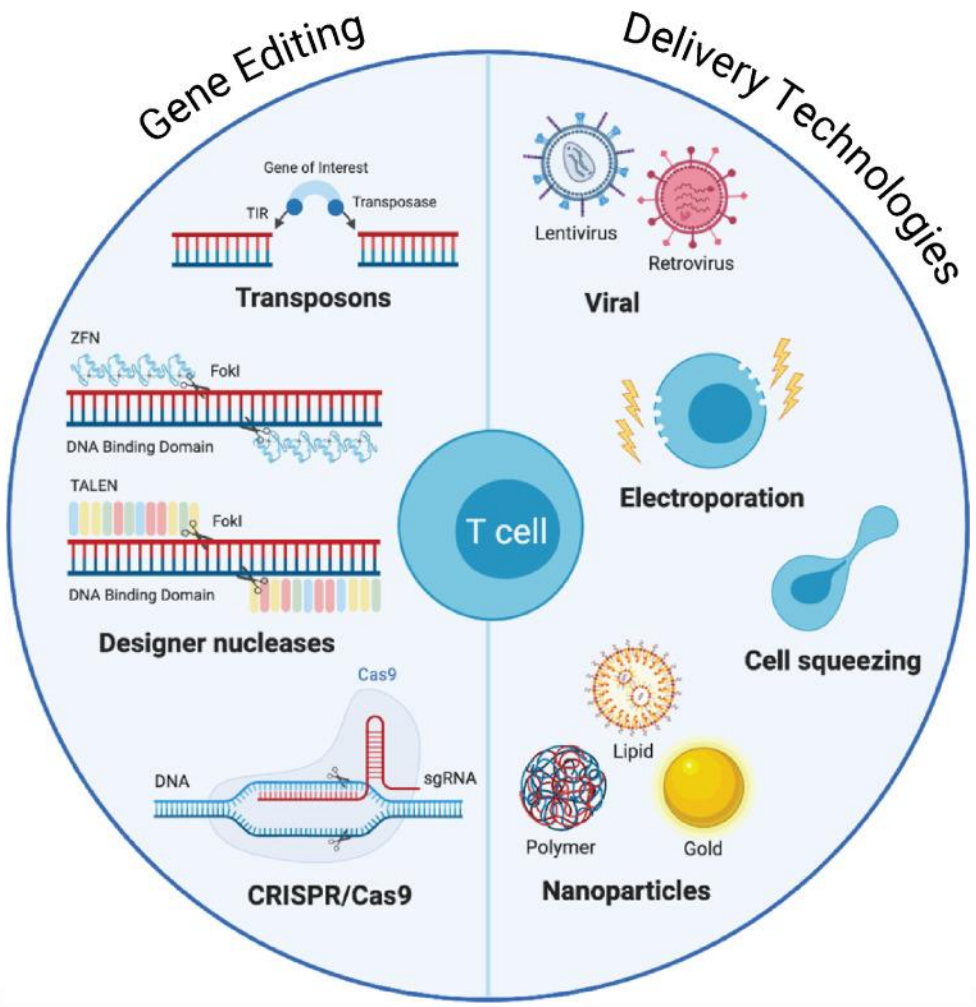
- Poseida utilizes Cas-CLOVER™ gene editing technology to knock out endogenous T cell receptor and MHC class I molecules to address GvHD and HvG



Poseida Internal Process Development

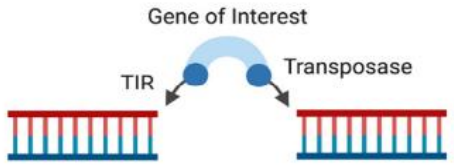


Gene Editing and Delivery Technologies



**Reference: Atsavapranee, E., et al., Billingsley, M. Mitchel, M., Delivery Technologies for T cell gene editing: Applications in cancer immunotherapy; EBioMedicine, 67 (2021), 1-12*

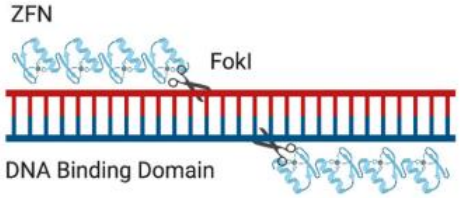
Transposons



- Low genotoxicity
- Cost-effective
- Less toxic than viral transduction
- Suitable for co-delivery of multiple genes

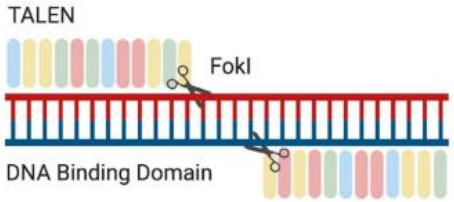
- Inefficient plasmid delivery into human cells
- Not suitable for gene disruption or replacement

Zinc finger nucleases (ZFN)



- Specific editing with few off-target effects
- Efficient delivery due to their small size

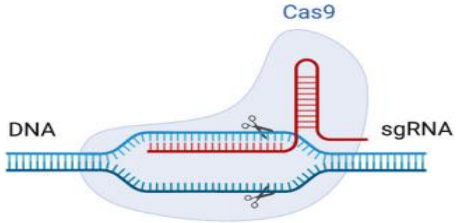
- Substantial protein engineering required for different gene targets



- Specific editing with few off-target effects
- More simple design than ZFN

- Inefficient delivery due to their large size
- Substantial protein engineering required for different gene targets

Clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9



- Minimal alteration to reach new targets
- Efficient and scalable manufacturing
- Suitable for a variety of delivery platforms

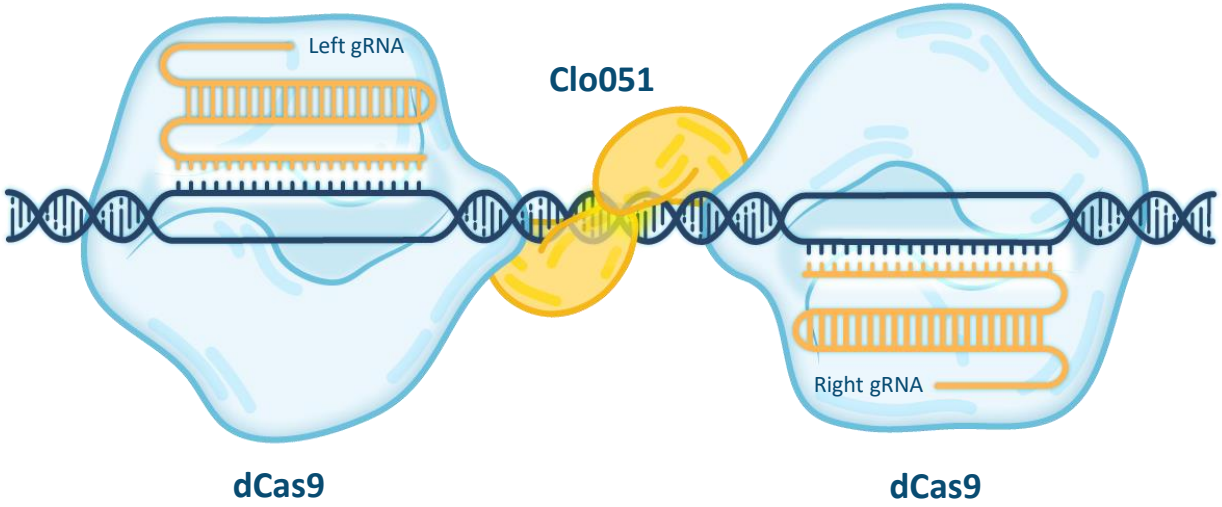
- Less specific editing than ZFN and TALEN
- Risks of off-target mutagenesis and immunogenicity
- Inefficient *in vivo* delivery

Introduction to Poseida's Gene Editing Platforms

Editing T_{SCM} population

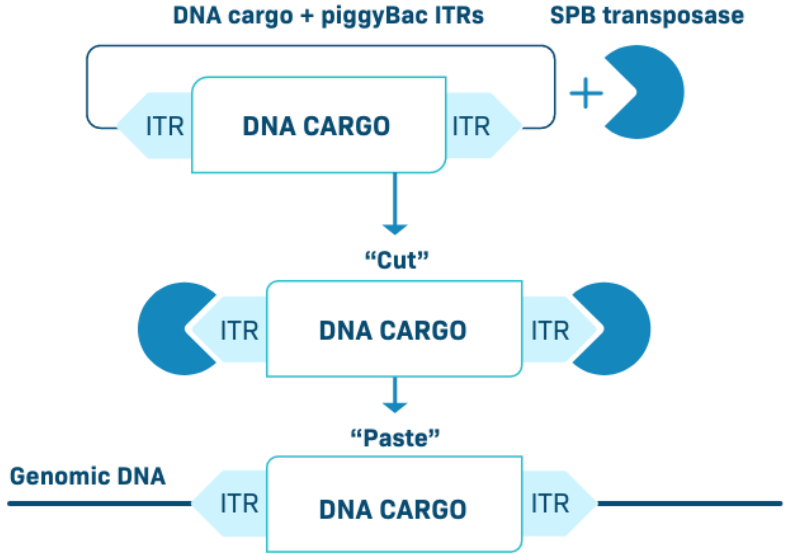
Gene Editing and Gene Insertion

Cas-CLOVER™: High-fidelity Gene Editing Technology



- Extensively vetted for Off-Target effects in peer-reviewed publication[1]
- Key ability to efficiently edit single or multiple genes
- Fully non-viral approach for in vivo gene editing
- Diverse toolbox of variants for expanded targeting (e.g. PAM diversity)

Insertion: piggyBac®



- Low to No Off-Target cutting
- Ease of use/design
- Multiplexing ability
- High specificity
- Lower potential costs
- Greater Knock-in rate than Cas9

Reference: Madison et al., Molecular Therapy – Nucleic Acids, 2022. (https://www.sciencedirect.com/science/article/pii/S216225312200155X)

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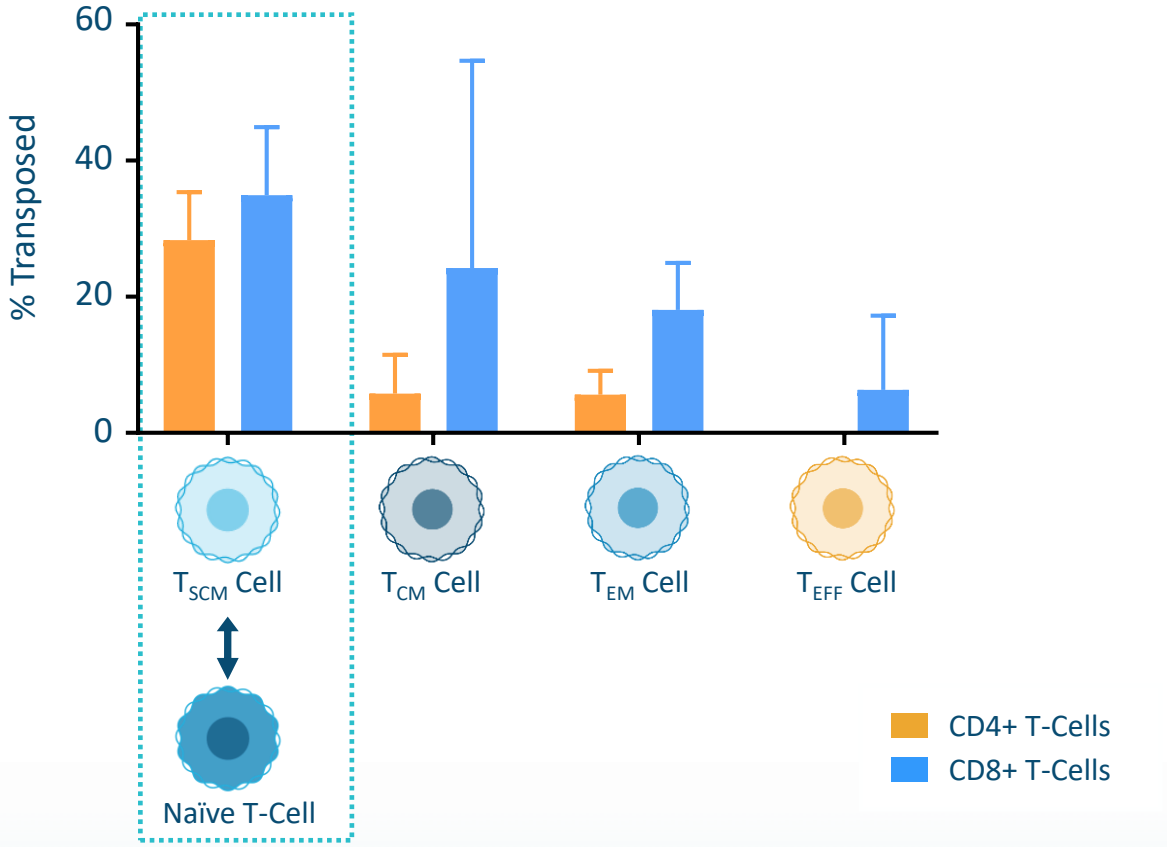
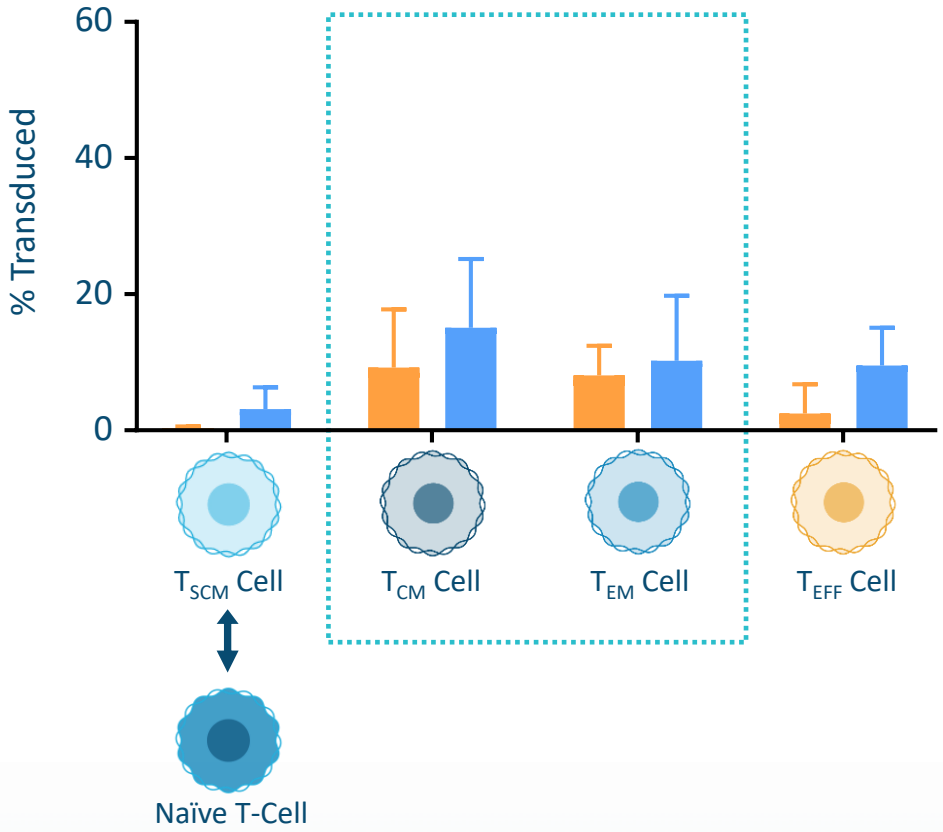
Poseida's piggyBac® Preferentially Transposes T_{SCM} Cell and Naïve Precursors

Precursor cells correlate with better clinical responses, including better duration of response

piggyBac transposes more progenitor T-Cells



Lentivirus transduces fewer T_{SCM} cells and more differentiated T-Cells



Booster in Action: Increased Expansion and High CAR-T_{SCM}

Preclinical and clinical products exhibit favorable expansion and phenotype

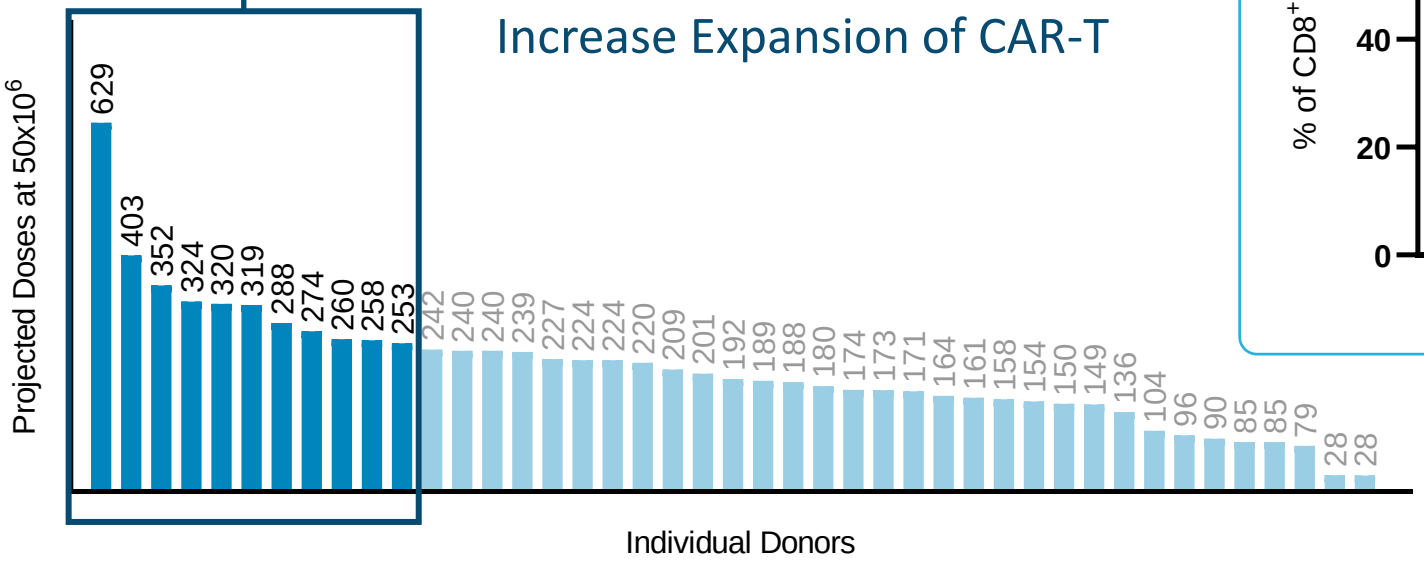
Top Quartile Donors **Yield >250 Doses**

>40 healthy donors screened

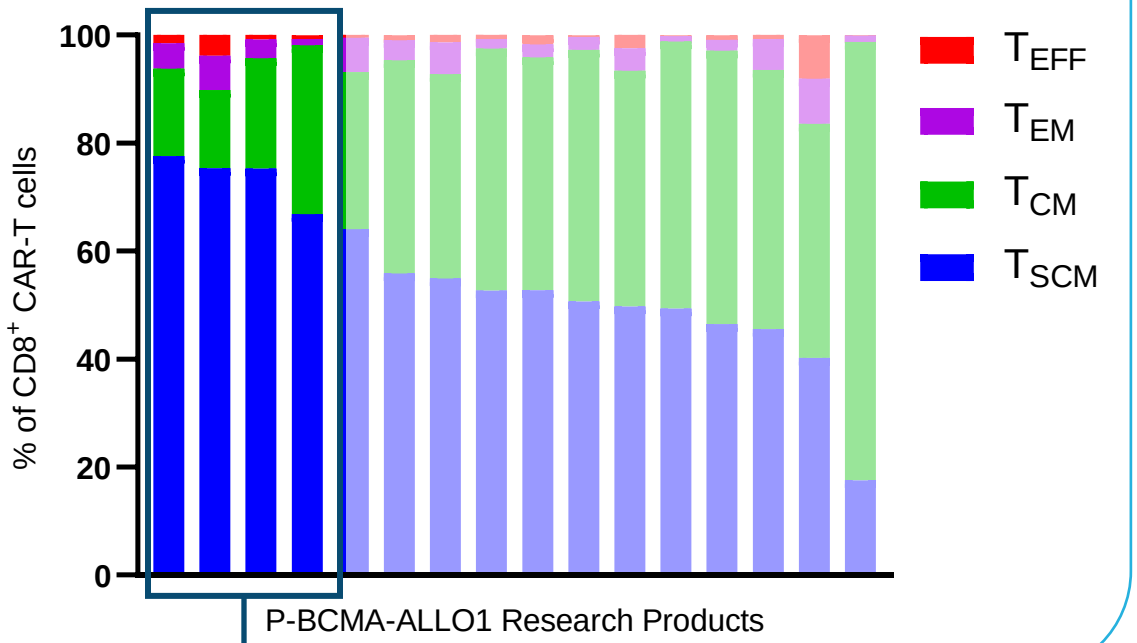
>90% success in small scale production

Clinical manufacturing getting optimized to meet the projected dose

Increase Expansion of CAR-T



Preserve High % of CAR-T_{SCM} Cells

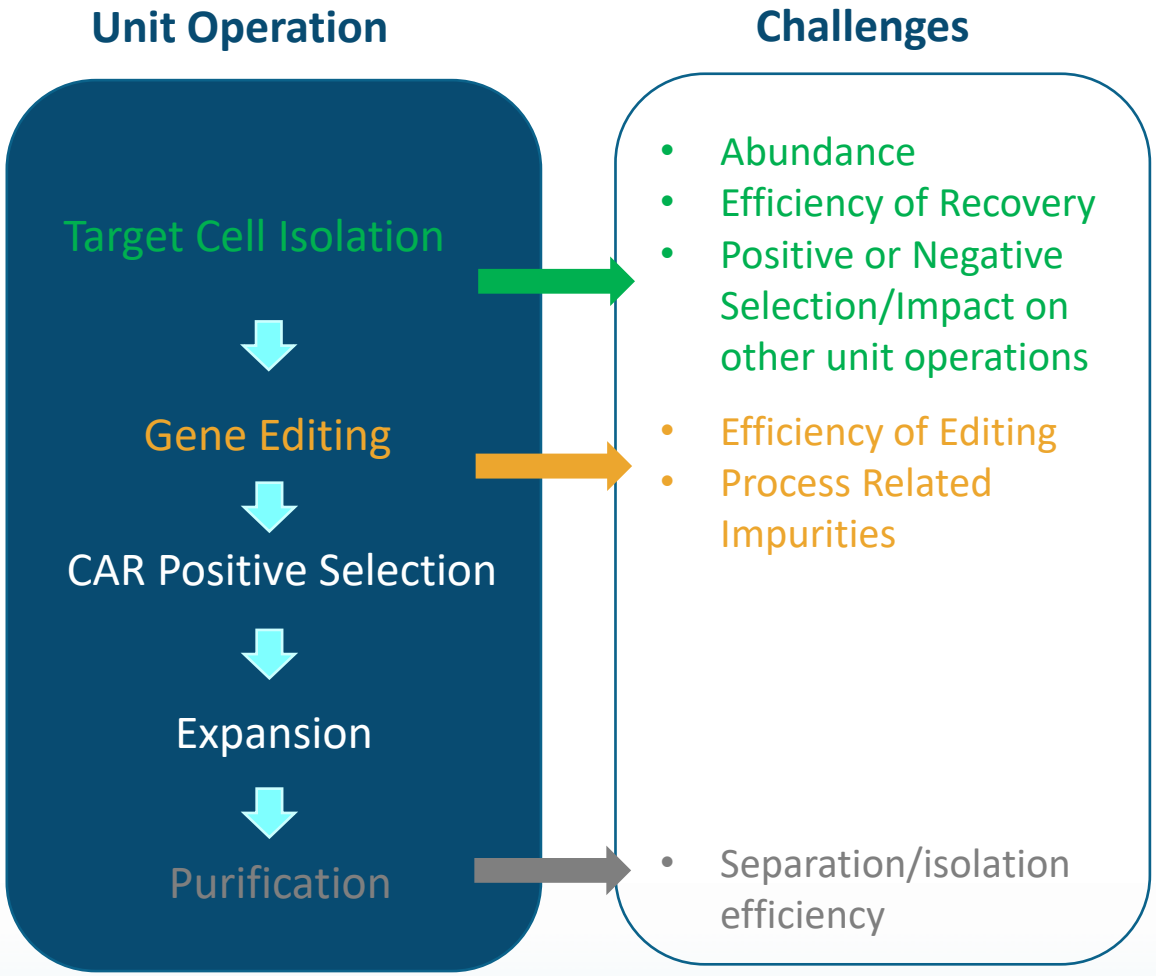


Top Quartile Products are **74% T_{SCM} and 94% T_{SCM} + T_{CM}**

Impact of Gene Editing Efficiency on Purity and Recovery of Target Cells

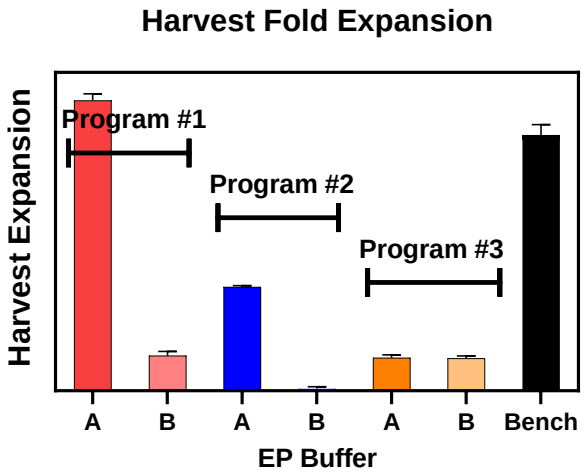
Introduced challenges with gene editing choices and their impact on the product recovery and quality

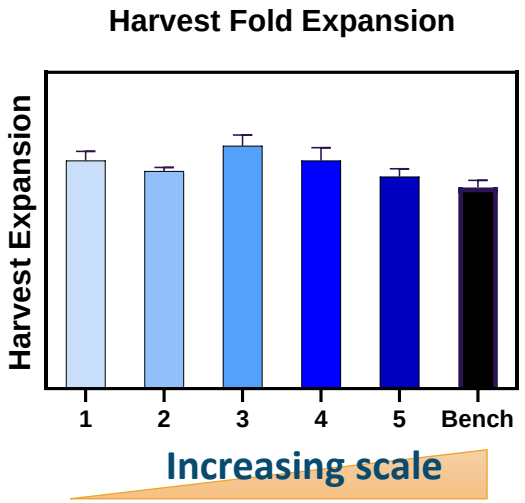
- The editing tools can introduce residual impurities (*e.g.* plasmids, Nucleic acids, Viral vectors)
- Genotoxicity/Fidelity of editing
  - Replication Competent Viruses
  - Off target editing
- Editing Efficiency (unedited cells)
  - Expansion of unedited (**TCR^{+} and CAR^{-}**)
  - Impact of Electroporation on Cell recovery, health and expansion

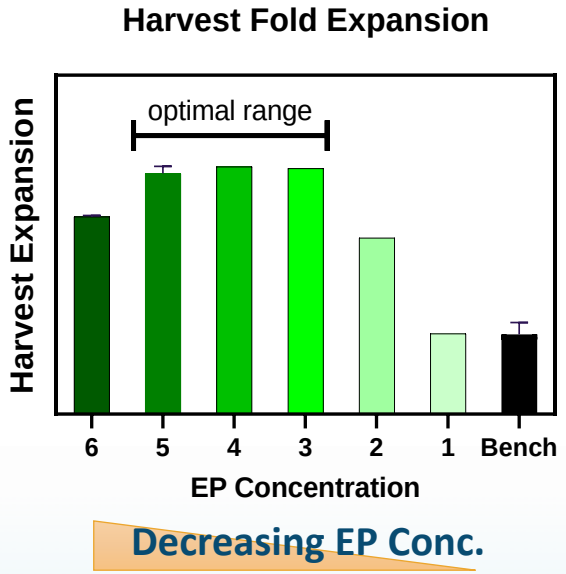


Gene Editing Optimization

- Part 1: Determine EP Program and Equipment
- Part 2: Determine EP Buffer
- Part 3: Confirm Scalability
- Part 4: Determine EP Cell Range
- Part 5: Determine Optimal Nucleic Acid Range







Remaining Challenge:

Variable TCRαβ knock out efficiency has been observed after gene editing

Final Product Specifications for TCR/CD3+ Cells < 3%
What unit operation in the process will ensure meeting the tight specification?

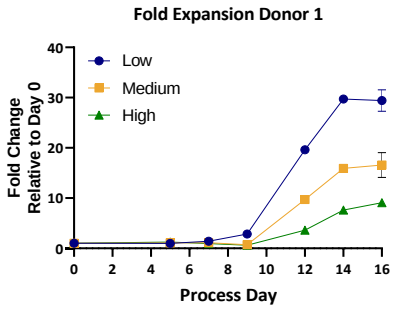
Cell Expansion (Productivity per Batch)
Preservation of Phenotypes

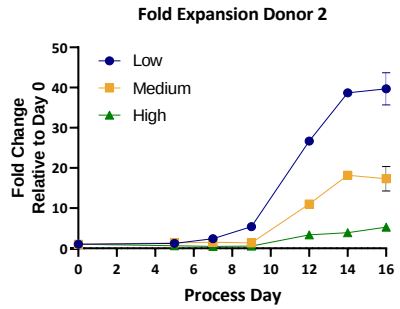
Scale Up/Out and Seeding Density Optimization

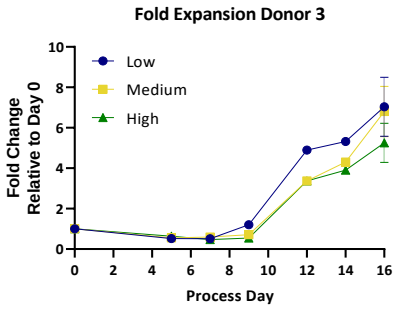
GRex6M = 10cm^2

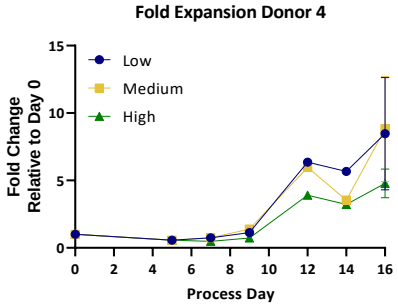
GRex100M = 100cm^2

GRex500M = 500cm^2

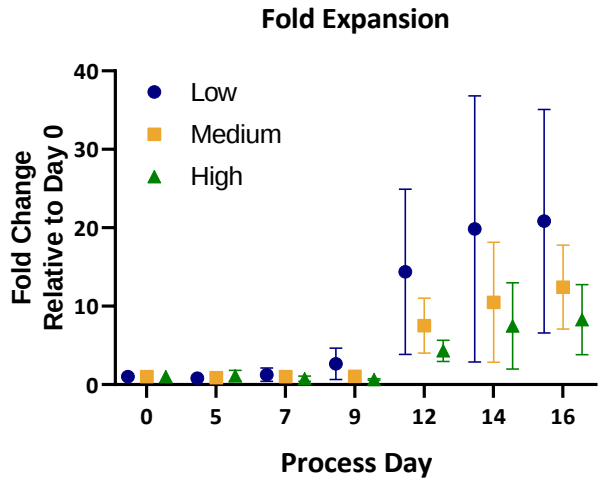








- Seeding density per surface area is the scaling factor
- A range of seeding density was explored and recommended to result in best productivity per surface area/manufacturing batch
- Seeding density can be used as a parameter to optimize cell growth/fold expansion



- ***Highest fold expansion achieved with lowest seeding density in Poseida's process***
- **The scale out along with scale up resulted in a three-fold increase in the final product cells compared to historical benchmark (*e.g.* vendor recommended seeding densities)**
- **No cytokine additives are used throughout the process in order to preserve phenotyping**
- **At least a couple hundred doses can be manufactured from single donor**
- **All improvements were achieved while preserving the stemness of the final product**

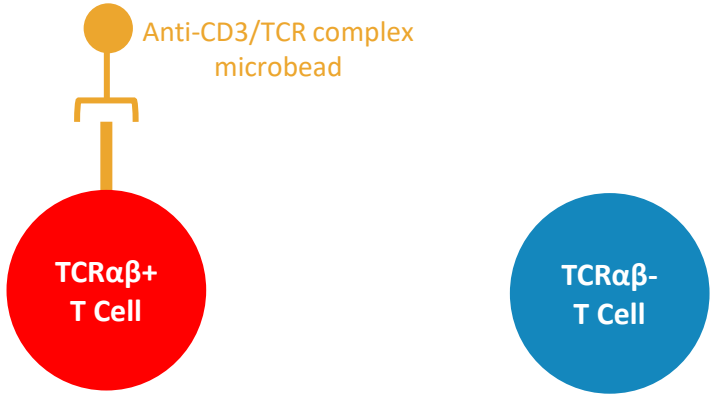
TCR+ Depletion Cell Expansion

TCRαβ+ Depletion Process Overview

- Initial depletion process resulted in **low purity** and **low product recovery**
- Manufacturer recommendations were initially utilized; however, significant development work has been required to identify critical process parameters and optimize the process to maximize purity and recovery

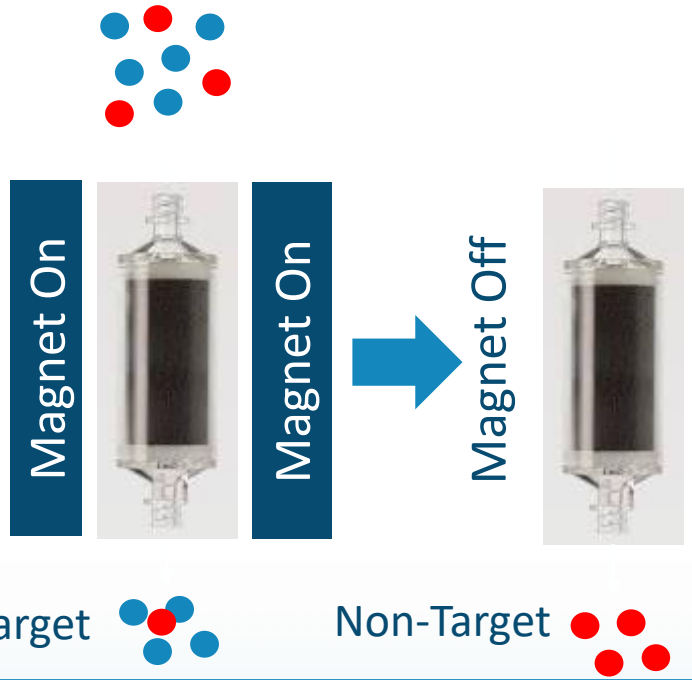
Labeling

- Reagent: cell ratio
- Reagent concentration
- Incubation times
- Labeling saturation, binding isotherm



Depletion Cycles

- Residence time
- Column cell loading
- Column washing

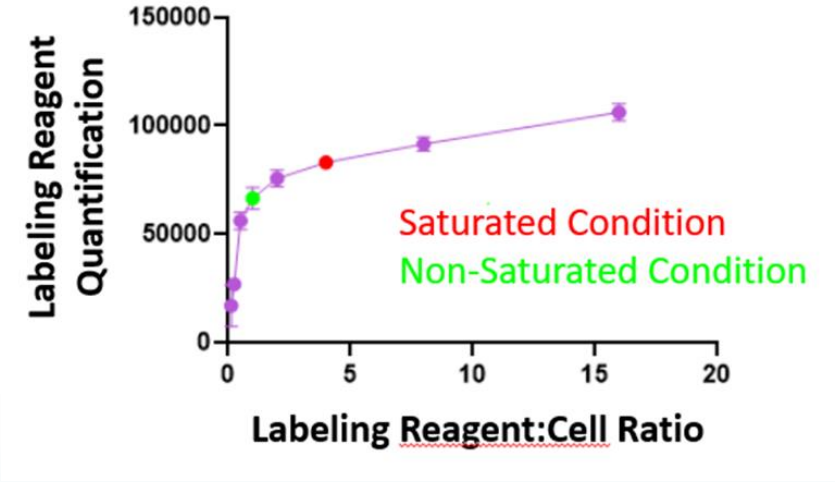


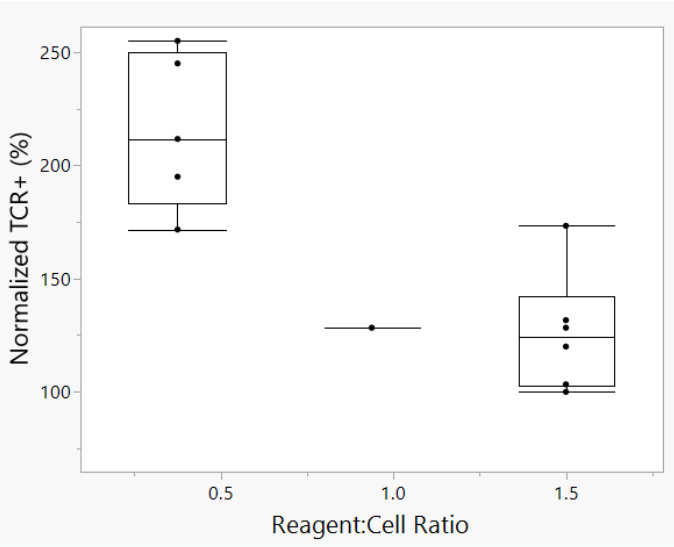
Sensitive Depletion

- Product recovery
- Carryover

Impact of Labeling Reagent: Cell Ratio on Purity

- Labeling saturation studies were performed to identify **optimal bead: cell ratio**
- Decreased depletion performance at non saturating labeling conditions was confirmed
- Reagent lot to lot variability, reagent stability, reagent concentrations and other factors are not well understood and can influence final product purity
  - The concentration of the magnetic beads are not known which introduces a challenge on controlling the bead/cell ratio
  - TCR measurement on the depletion day is not currently performed in manufacturing set up

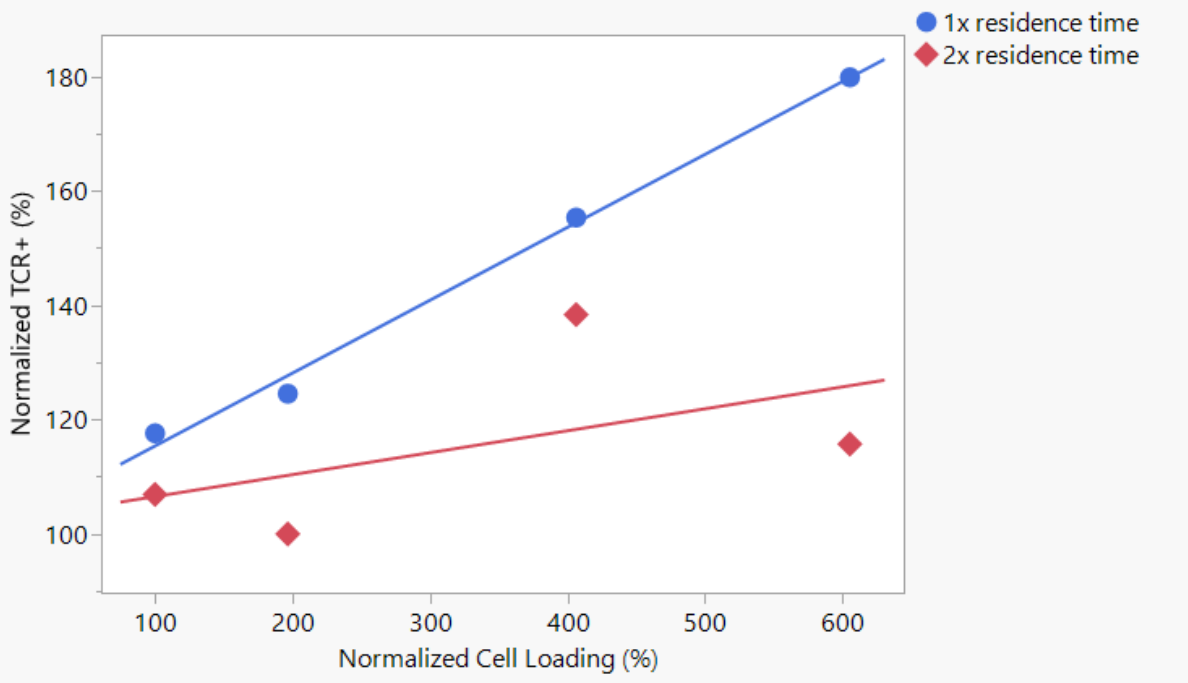




Normalized to the minimum TCR of these data set

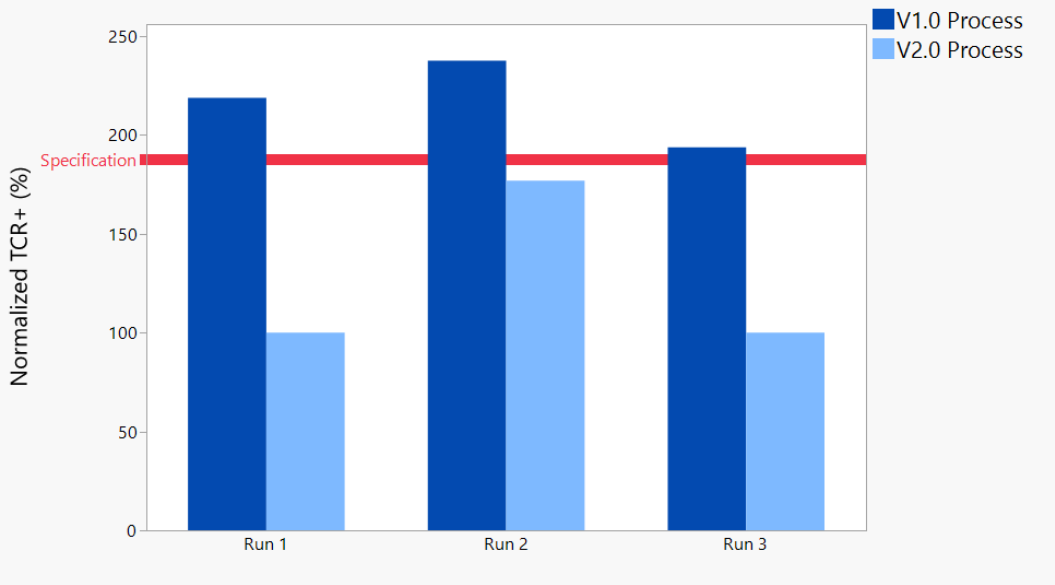
Impact of TCRαβ+ Column Capacity and Residence Time On Purity

- Depletion parameters such as **TCRαβ+ column loading capacity** and **column residence time** are critical process parameters for efficient depletion performance
- Depletion scale down model and offline labeling model have been used to perform optimization studies to identify acceptable operating ranges



Control Strategy for Final Depletion

- Controlled Labeling with increased ratio of beads to cell (based on total cells) and other parameters *(e.g.* incubation time) improved the depletion performance
  - In process measurement of TCR prior to depletion day for optimal labeling is in progress
- Controlled and limit the number of TCR positive loaded to Prodigy
- Operating flowrate/residence time can make an impact on the TCR+ clearance



Significant changes in final product purity across depletion cycles have been observed

Conclusions

- Poseida utilizes a unique and proprietary gene editing tool and technologies which have the potential for significant benefits over other common available technologies
  - Cost
  - Speed of manufacturing
  - Safety
  - Fidelity
  - Favorable Phenotyping
- Many process variables and parameters can have significant impact on product attributes and yield; little information is available from manufacturers so optimization by the company is required
- Poseida has a continuous productivity improvement mindset that has already led to improvements in multiple areas; for example nucleic acid delivery, cell seeding density, downstream purification
  - Gene editing performance and critical parameters for EP in combination with the equipment of choice
  - Process Scale up and out were performed in Grex flasks with optimized seeding density to increase process productivity
  - Critical parameters and their impact on depletion performance has been studied:
    - Labeling, flowrate, TCR^+ loading, etc.
    - Alternative technologies for cell separation

Acknowledgements

- Immuno-Oncology/Research team
- Early Process Development
- Manufacturing and Sciences Technology Teams
- Manufacturing team

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Q&A

A New Class of Cell & Gene Therapies with the Capacity to Cure