



Enhanced tgTCR T Cell Product Attributes Through Process Improvement of CRISPR/Cas9 Engineering

23rd Annual Meeting of the American Society
of Gene and Cell Therapy

Aaron Prodeus, Ph.D. | May 12, 2020

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CRISPR/Cas9 Genome Editing Can Power Next-Generation T Cell Therapies



To unlock the full potential of T cell therapies, we need to enable multiple edits with high efficiency and cell viability but low translocations

Today's Presentation



Intellia's proprietary process shows promise to engineer safe and potent CRISPR/Cas9-based T cell therapies with multiple genome edits

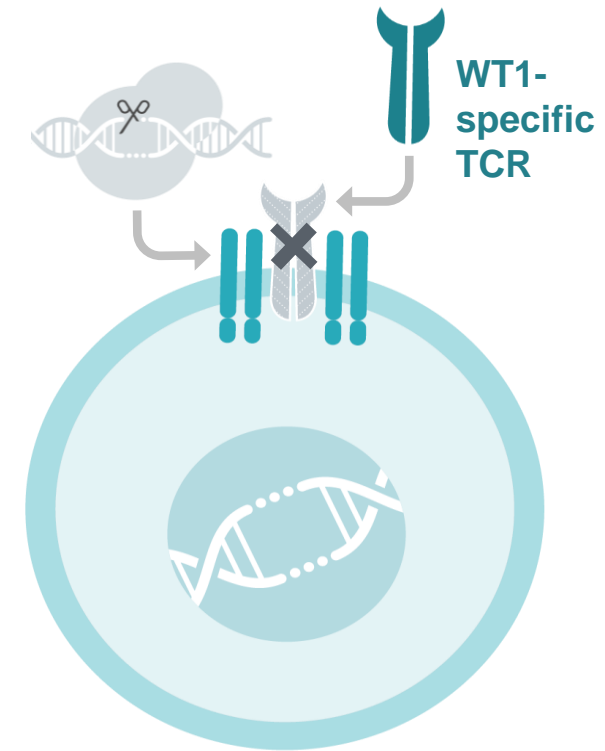
Our Goal: Engineer TCR-T Cell Therapies While Preserving Normal Cell Physiology

CRISPR-Based Gene Engineering

- Overcomes key challenges of traditional TCR approaches
- Enables **precise** gene KO and insertion
- **Replaces** endogenous with therapeutic TCR^{1,2}:
 - Enhances TCR expression and function
 - Reduces mispairing and GvHD risk
 - Improves cell drug quality and potency

NTLA-5001 for the Treatment of AML

- Lead engineered cell therapy **development candidate**
- **WT1** (Wilms' Tumor 1) targeting TCR-T cell therapy:
 - High avidity $\alpha\beta$ -TCR
 - In locus insertion (*TRAC*)
 - *TRBC* KO

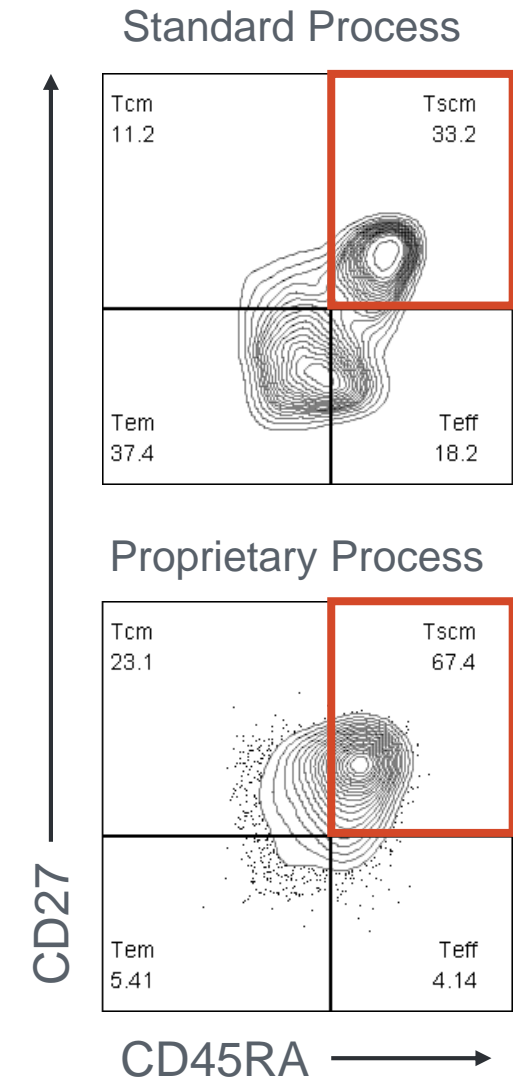
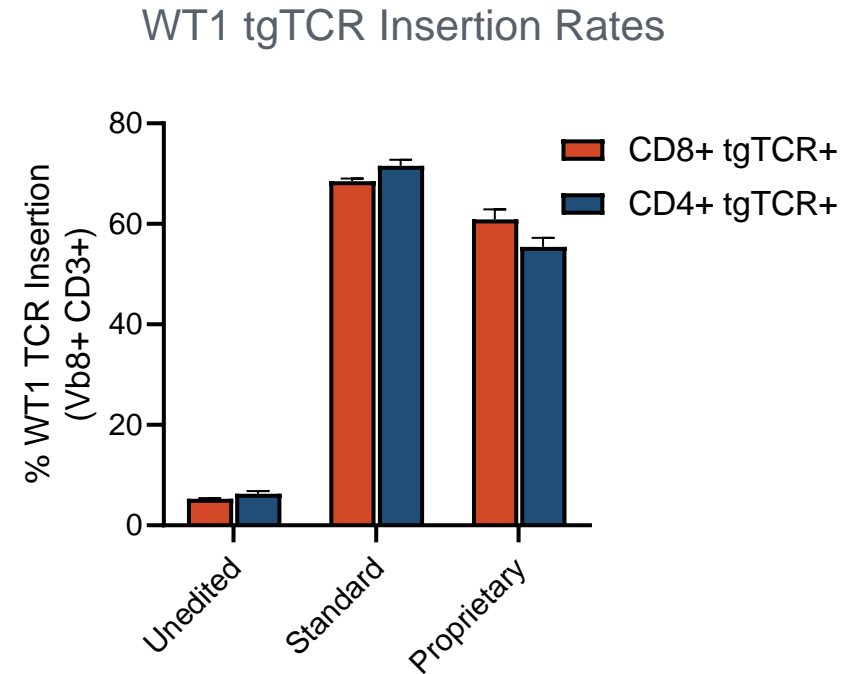
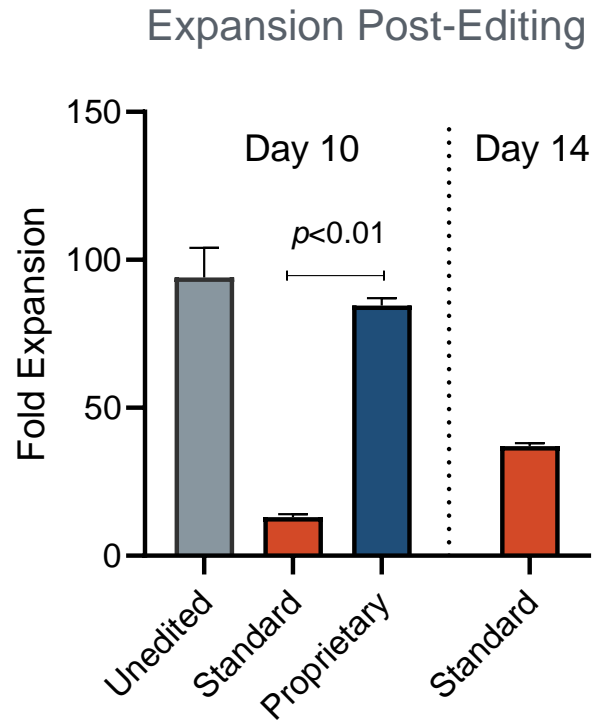


PRECISE • POTENT • PERSISTENT

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Proprietary Process Yields High Editing Rates
While Maintaining Normal T Cell Physiology

Improved T Cell Expansion and Memory Phenotype with Proprietary Process

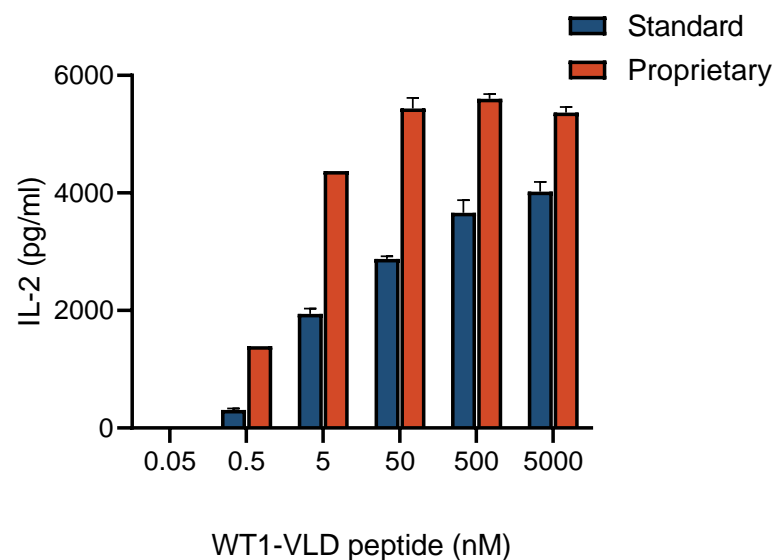


Proprietary process yields:

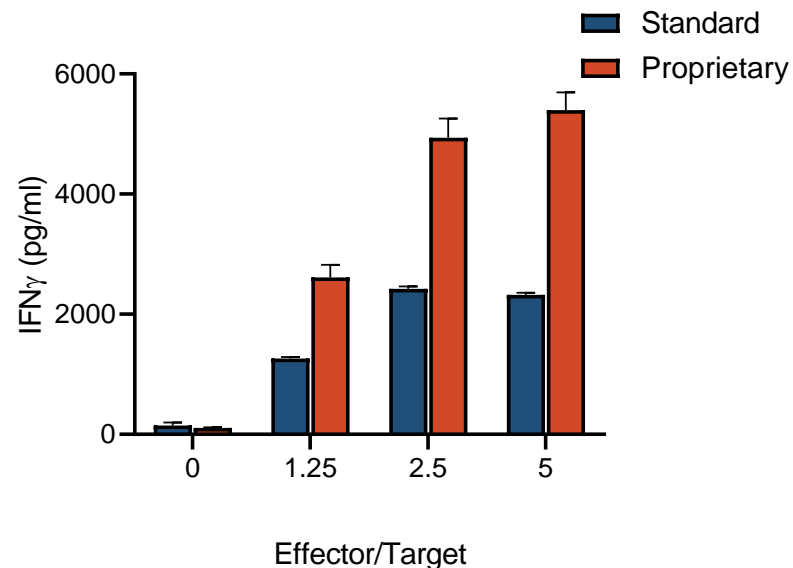
- More rapid expansion post-editing
- Favorable CD45RA⁺CD27⁺ memory phenotype
- Comparable editing rates

WT1 TCR-T Cells Engineered with Proprietary Process Have Enhanced Potency

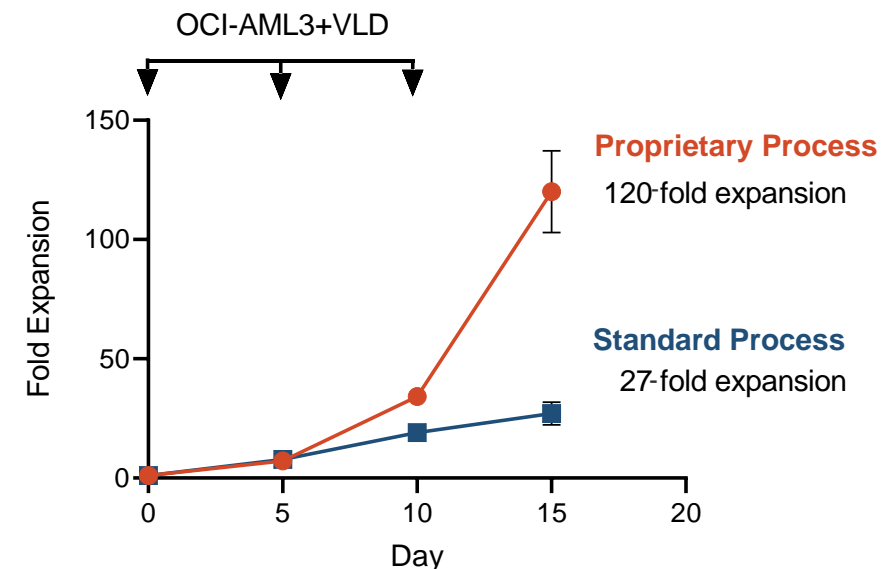
IL-2 Secretion: WT1-VLD
Peptide Pulsed OCI-AML3



IFN- γ Secretion:
K562-HLA-A*02:01+ Cells



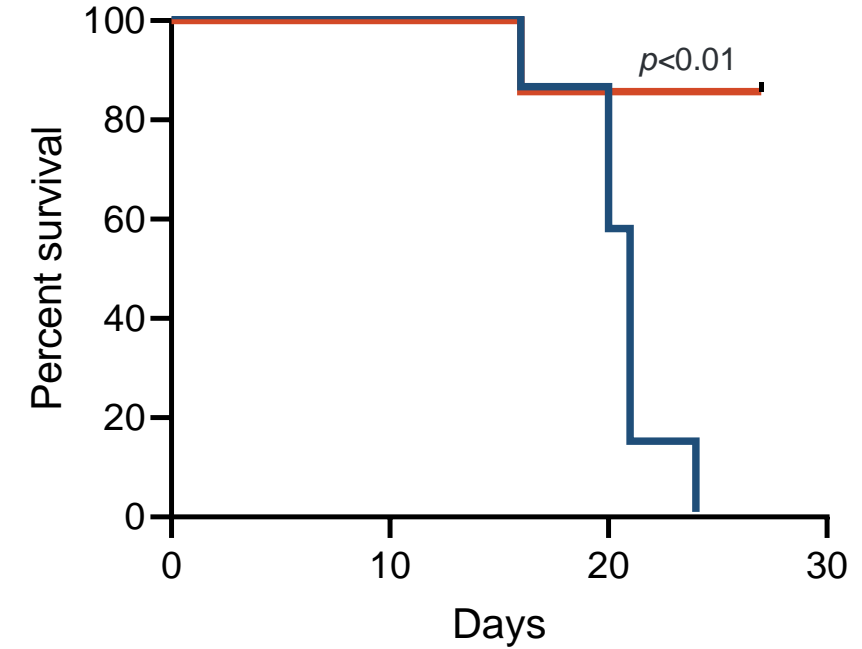
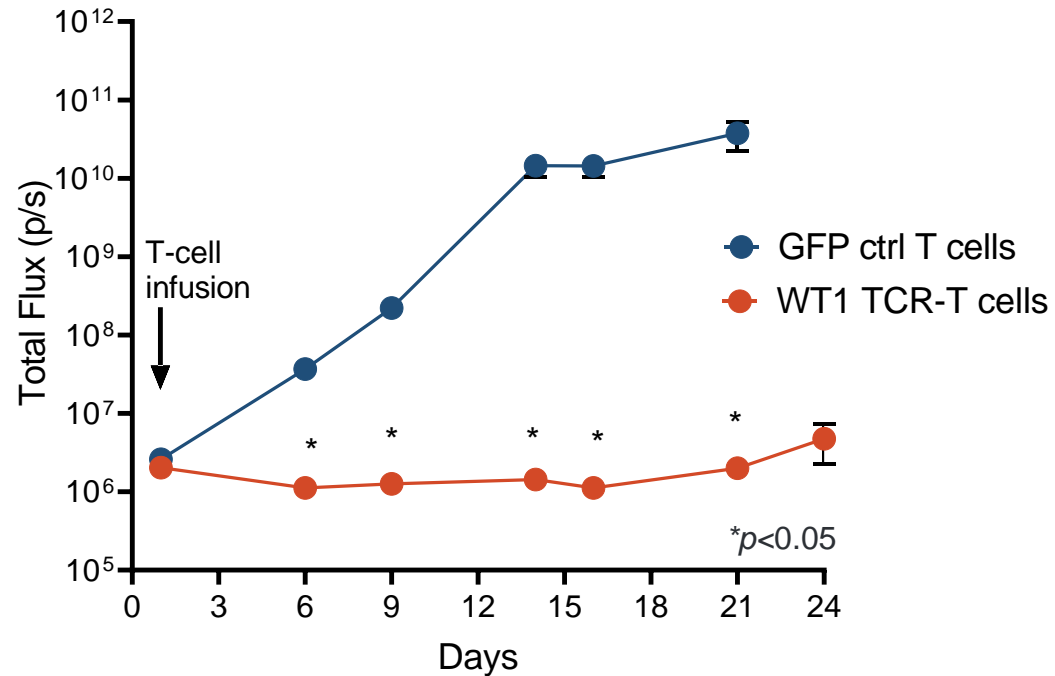
Re-stimulation Stress Test:
OCI-AML3 pulsed cells



WT1 TCR-T cells engineered with proprietary process:

- Secrete more cytokines in response to WT1-presenting tumor cell lines
- Have long-term proliferative capacity in a repeat-stimulation assay with tumor cells

WT1 TCR-T Cells Generated Using Proprietary Method Suppress Tumor Growth and Prolong Survival in a Disseminated Leukemia Model

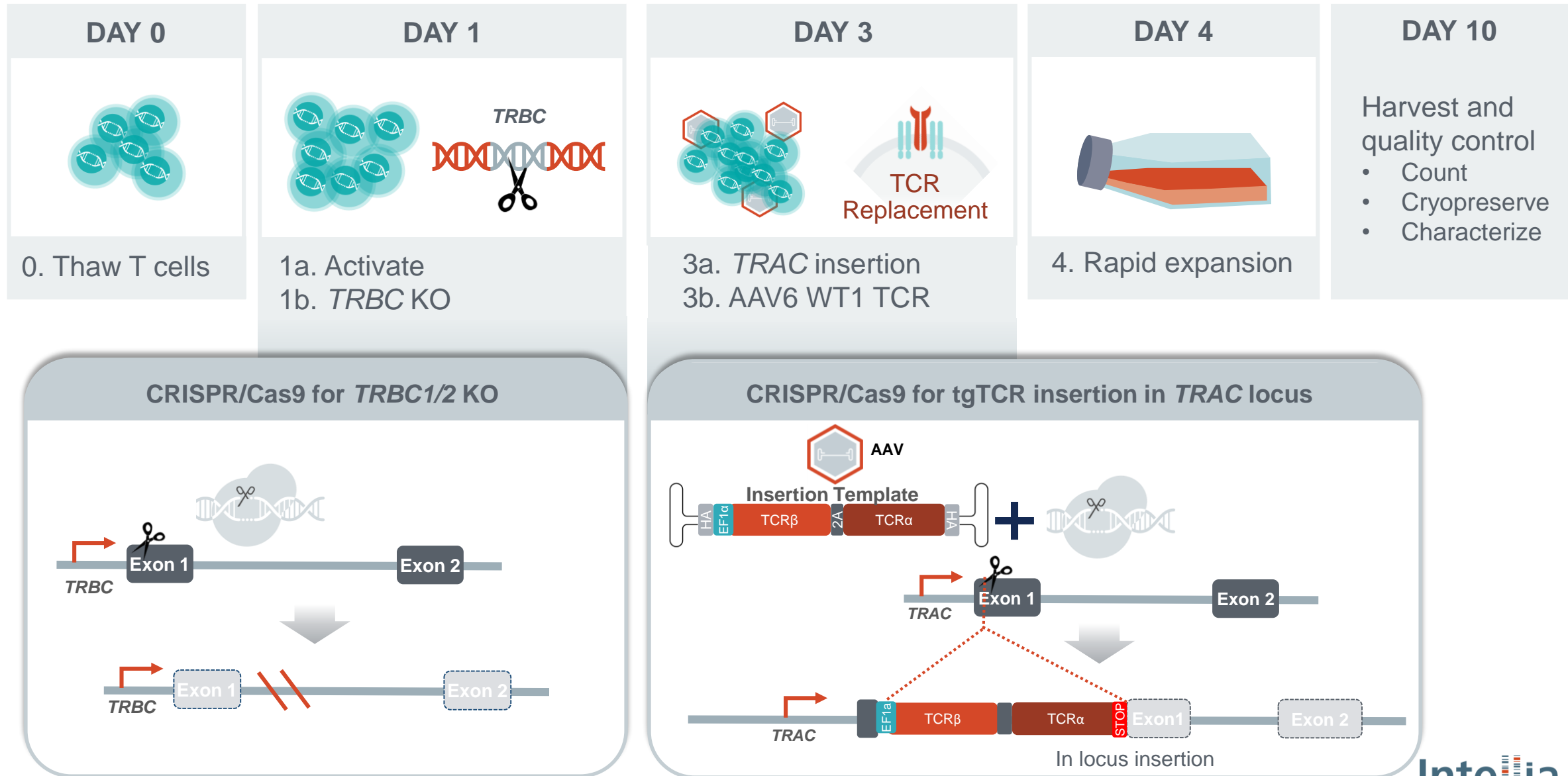


697 ALL cell line expresses endogenous levels of WT1 and is HLA-A*02:01⁺

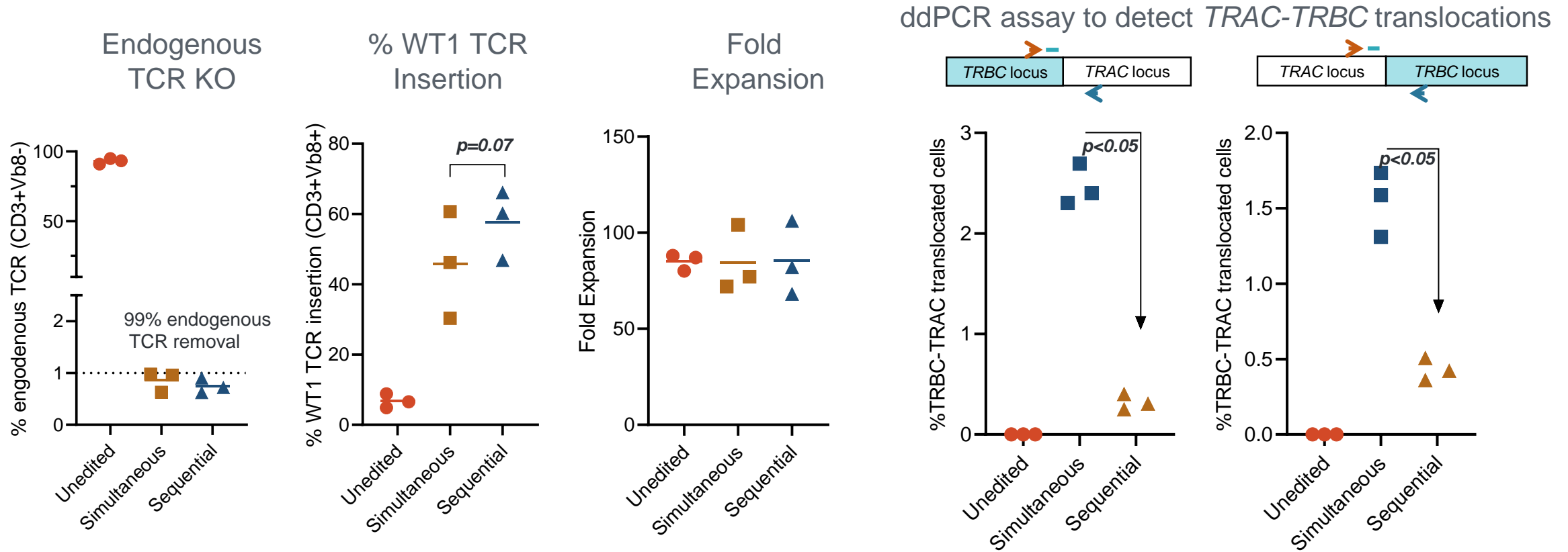
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Proprietary Process Enables Sequential
Editing to Reduce Translocation Rates

Improved Expansion Post-Editing Enables Sequential Editing of *TRBC* and *TRAC*



Proprietary Process Enables Sequential Editing Strategies to Reduce Translocations

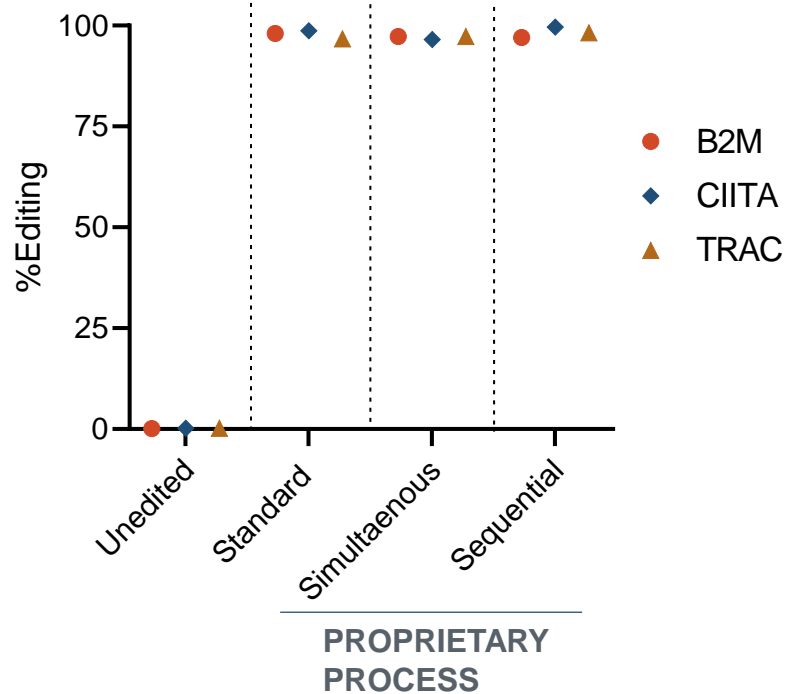


Sequential editing of *TRAC* and *TRBC* results in:

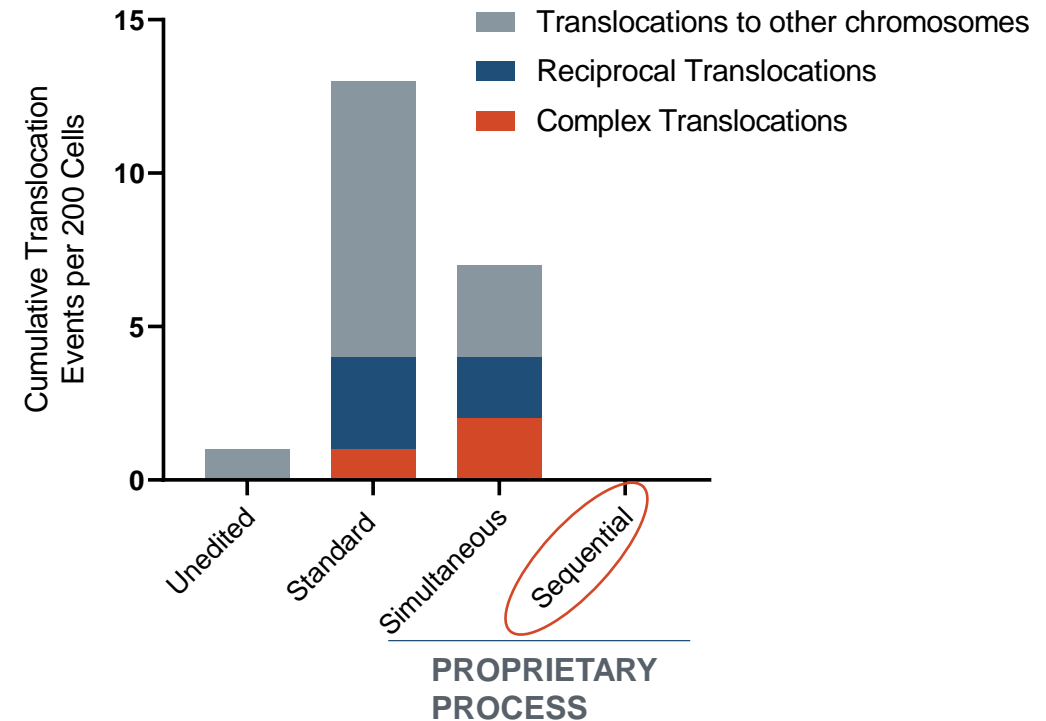
- High cell expansion
- High endogenous TCR KO (~99%)
- High insertion rates (>50%)
- 4- to 8-fold reduction in *TRAC-TRBC* translocations

Proprietary Process Enables Multiple Sequential Edits With Minimal Translocations

>97% Editing Across Three Genes



KromaTiD dGH™ Assay Shows
Reduced Translocation Rates With Sequential Editing



Efficient sequential editing strategy supports development of:

- TCR-T cell therapies like NTLA-5001 that require multiple edits
- Advanced cell therapies that require even more edits, such as allogeneic T cells

Key Takeaways

Proprietary process enables efficient, scalable genome editing of T cells with high viability

- High KO efficiency of target genes (>98%)
- 50-70% in locus insertion of tgTCRs
- Faster and higher T cell expansion for reduced vein-to-vein times
- Improved T cell memory phenotype and increased T cell functionality

Intellia's T cell engineering platform powered by proprietary process unlocks full potential of CRISPR/Cas9

- Supports development of NTLA-5001, with IND or IND-equivalent planned for 1H 2021
- Potential for safer T cell product developed utilizing sequential editing, with minimized chromosomal translocations
- Future potential development of allogeneic TCR and CAR-T cells requiring multiple KOs and insertions
- Lays the groundwork for T cell candidates engineered to overcome immune suppression in solid tumors

Acknowledgements



Intellia's Cell Therapy Team
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THERAPEUTICS