Bill, living with transthyretin amyloidosis, and his wife, Maura

Lipid nanoparticles (LNPs) as a superior CRISPR/Cas9 delivery modality for highly efficient multiplex gene editing of T cells for adoptive cell therapy

Aaron Prodeus, PhD

European Society of Gene and Cell Therapy Annual Congress

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Intellia THERAPEUTICS

Disclosure: Employee of Intellia Therapeutics, Inc

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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 gene edits with high efficiency and cell viability but low translocations

1

LNPs readily deliver CRISPR/Cas9 to T cells

2

Improved method vs. standard electroporation methods

3

Multiplex sequential edits for safe and effective T cell therapies

Intellia's proprietary LNP CRISPR/Cas9 delivery technology empowers safe and potent T cell therapies with multiple genome edits

LNP: Lipid Nanoparticle

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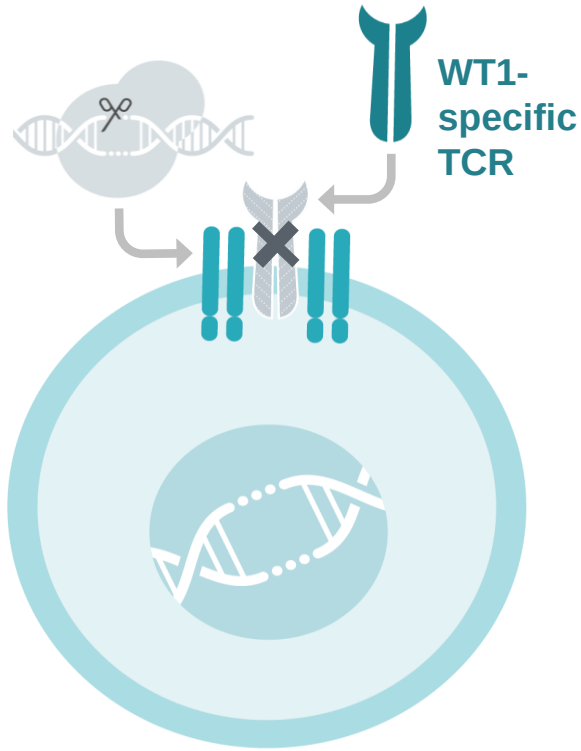
Our Goal: Engineer T Cell Therapies While Preserving Normal Cell Physiology

CRISPR-Based Gene Engineering

- **Precise** gene knockout (KO) and insertion
- **Site-specific insertion: TCR or CAR transgenes**
  - Homogeneous targeted insertion and expression
  - Improved cell drug quality and potency

LNP-based T cell transfection of CRISPR/Cas9

- Improved method for engineering autologous and allogeneic cell therapies
- **Modular** platform for sequential multiplex genome editing with minimal translocation rates
- **Scalable:** manufacturing process suitable for clinical development of autologous and allogeneic therapies



PRECISE • POTENT • PERSISTENT

TCR: T Cell Receptor **KO:** Knockout

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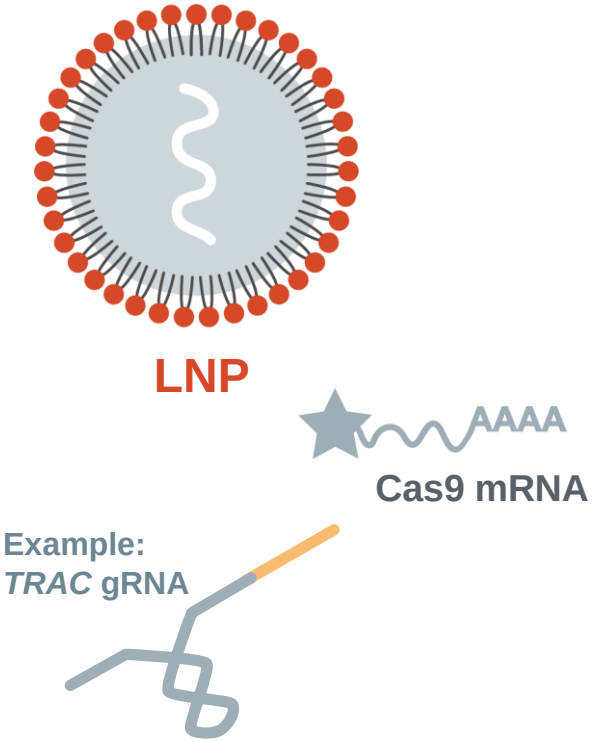
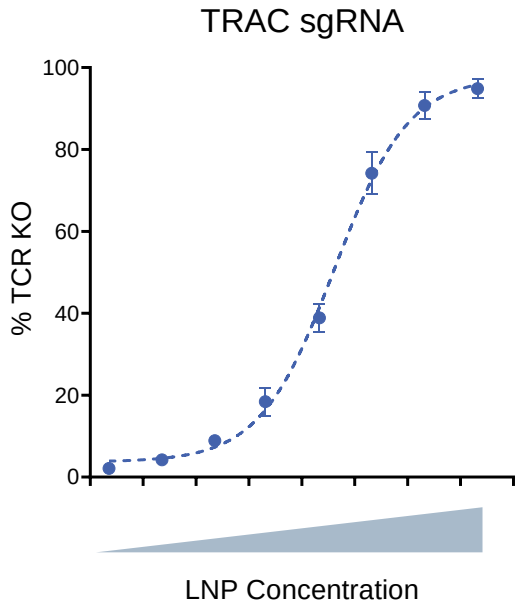
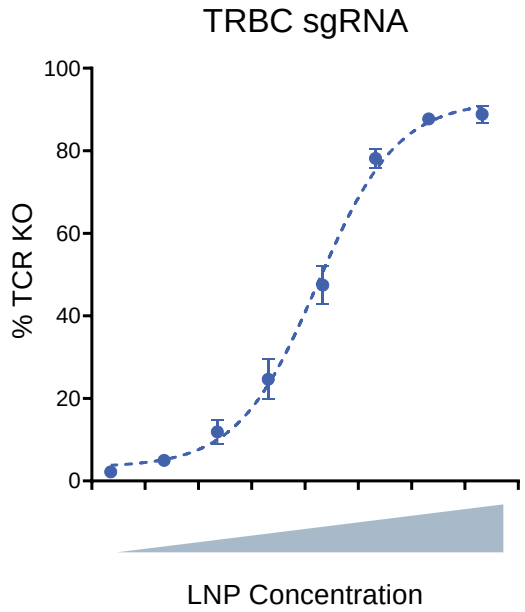
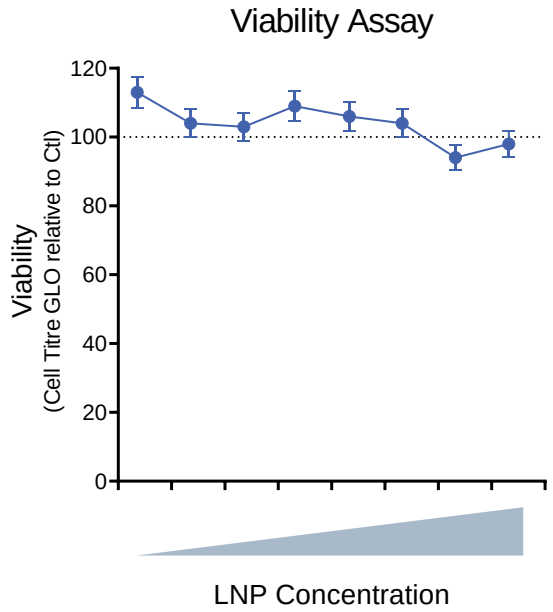
LNPs are an improved delivery system for CRISPR/Cas9 T cell engineering

Dose-dependent Knockout of TRAC and TRBC by LNP Transfection of CRISPR/Cas9 in Primary Human T Cells









- **LNP formulation designed for *ex vivo* delivery to T cells**
- **High KO rates without negative impact on T cell viability**

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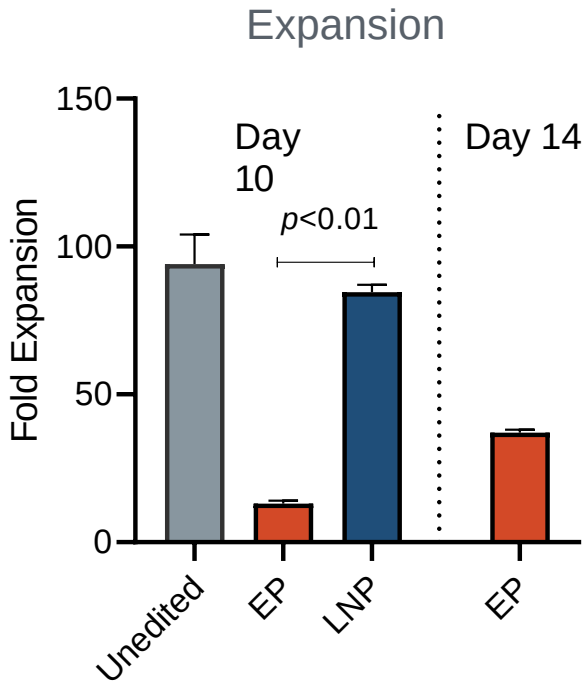
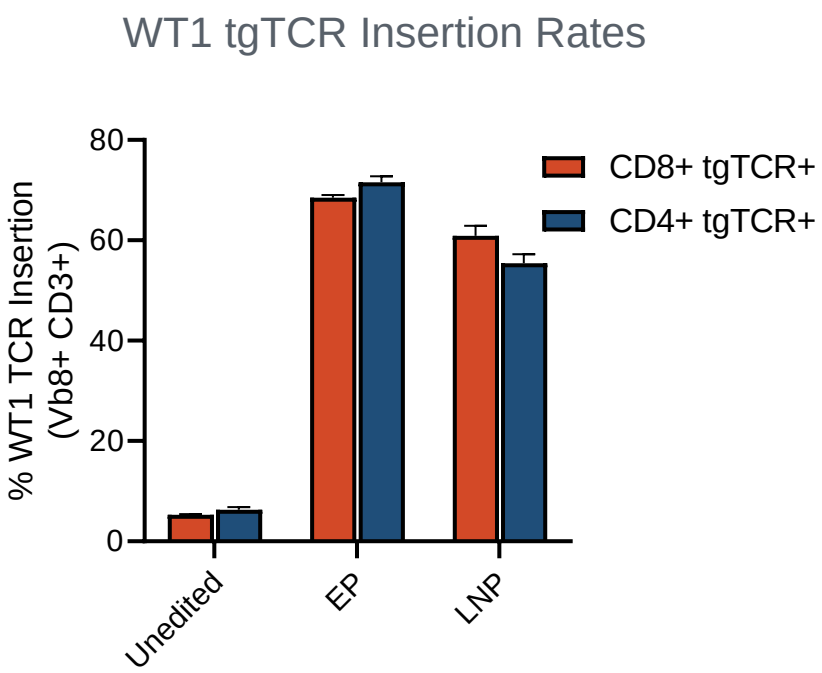
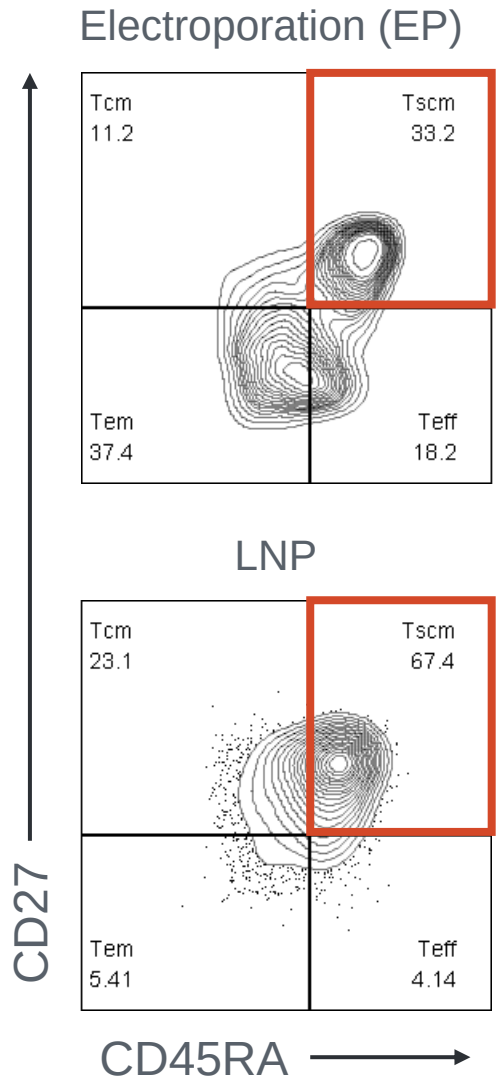
Improved Expansion and Memory Phenotype of WT1 TCR-T cells using LNPs

- T cells engineered with WT1 antigen specific TCR insertion in *TRAC locus*, combined with *TRBC* KO







$LNP_{[CRISPR/Cas9]}$ delivery results in:

- **More rapid expansion post-editing**
- **Favorable $CD45RA^{+}CD27^{+}$ memory phenotype**
- **Comparable editing rates**

EP was performed following manufacturer's protocol with standard conditions

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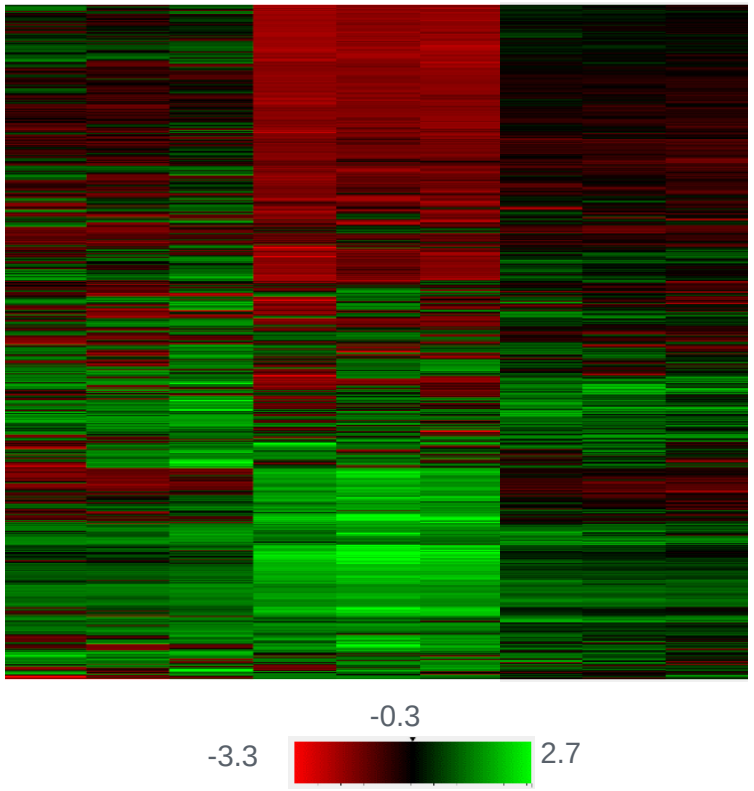
LNP [CRISPR/Cas9] Transfection Minimizes Gene Expression Aberrations vs. Electroporation

Gene Expression Profiling[1]
(780 genes)



[1]NanoString nCounter® CAR-T characterization panel;
EP: Electroporation

Genes Differentially Regulated

6h	EP	LNP
P<0.05	195	75
>2 FC & P<0.05	34	4

- **LNP [CRISPR/Cas9] transfection showed minimal gene expression changes**
- **Electroporation results in global transcriptome aberrations in key pathways such as metabolism, memory and exhaustion**

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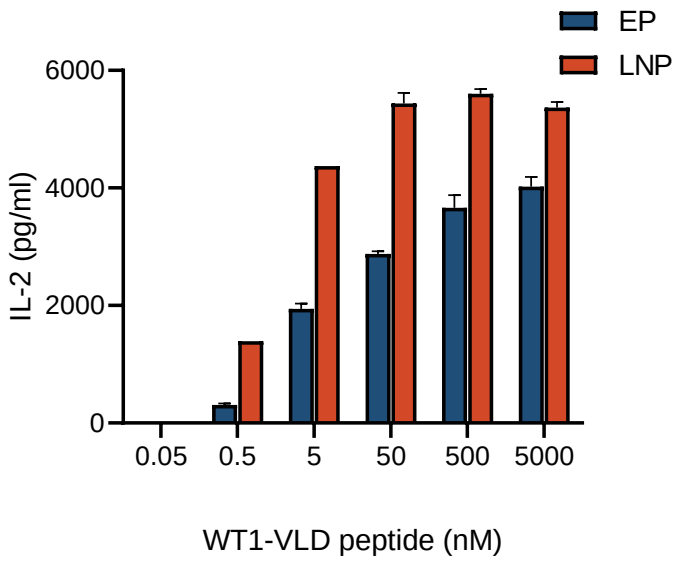
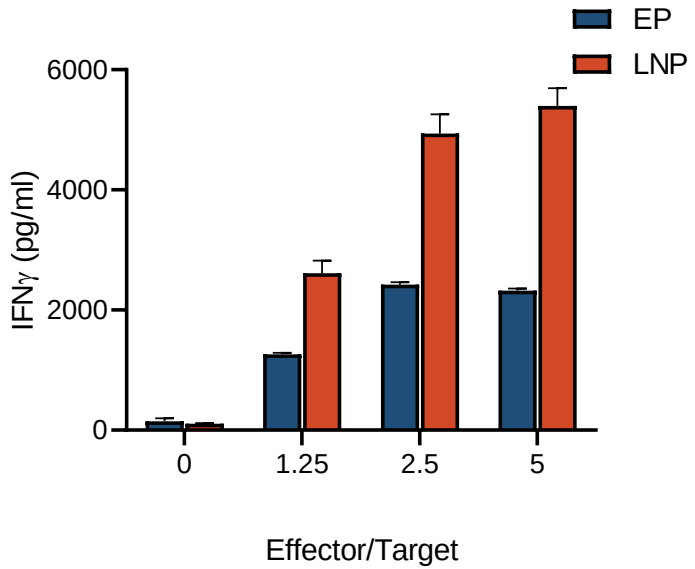
WT1 TCR-T Cells Engineered with LNP$_{[CRISPR/Cas9]}$ Method Have Enhanced Potency

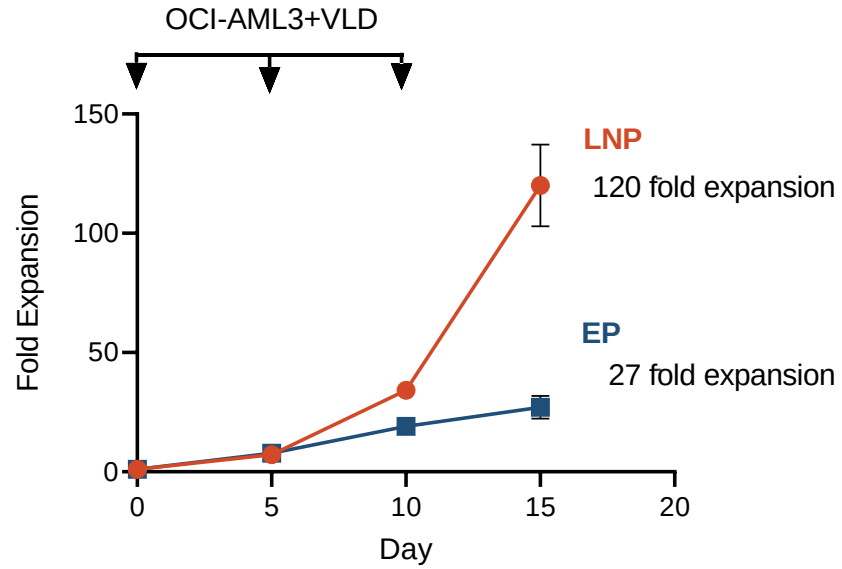
IL-2 Secretion: WT1-VLD Peptide Pulsed OCI-AML3



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



Re-stimulation Stress Test: OCI-AML3 pulsed cells



WT1 TCR-T cells engineered with LNP $_{[CRISPR/Cas9]}$ delivery:

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

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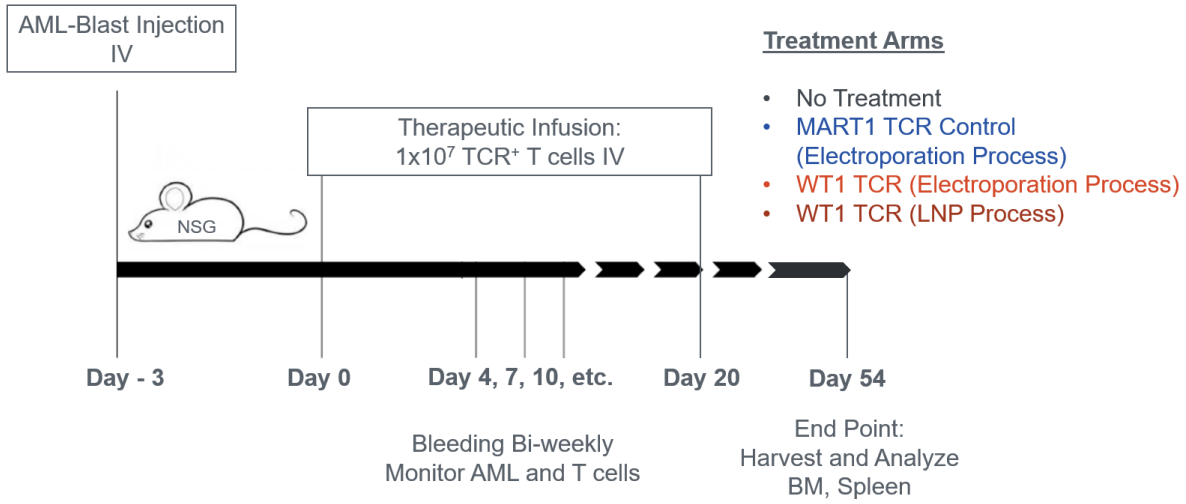
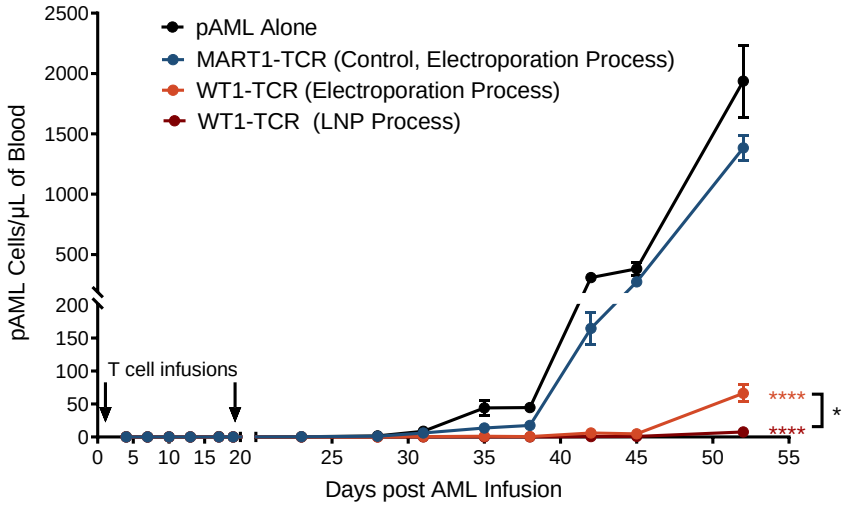
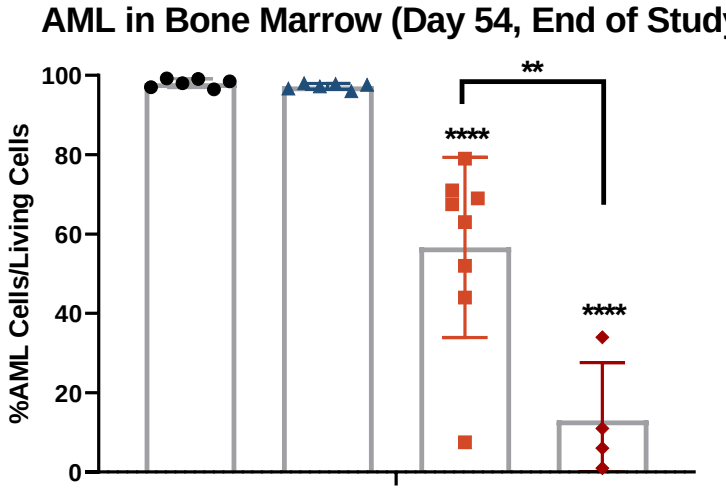
WT1-Specific TCR T Cells Are Efficacious *In Vivo* in Mice; $LNP_{[CRISPR/Cas9]}$ engineered T Cells Possess Enhanced Anti-Tumor Activity

AML-PDX Model







Better tumor control with WT1 T cells manufactured with $LNP_{[CRISPR/Cas9]}$ delivery vs. electroporation

***** p<0.0001, WT1 TCR vs. MART1 Control TCR (2-way ANOVA)*
** or ** p<0.05 or p<0.01, EP vs. LNP Process (2-way ANOVA)*

OSPEDALE SAN RAFFAELE

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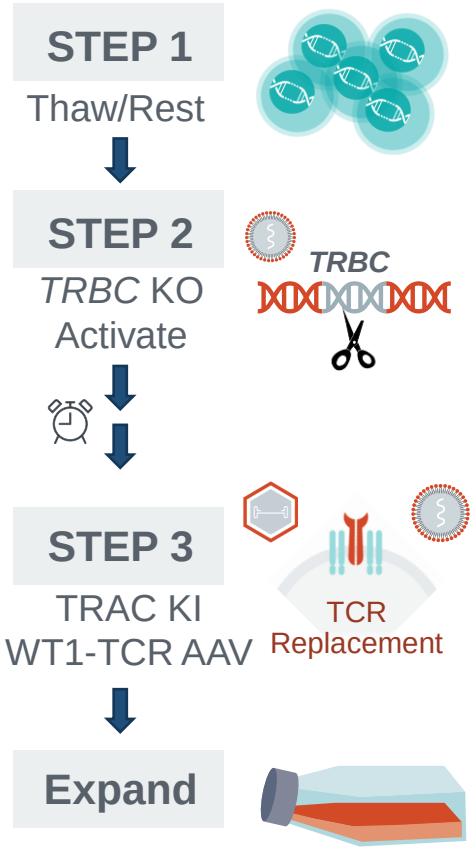
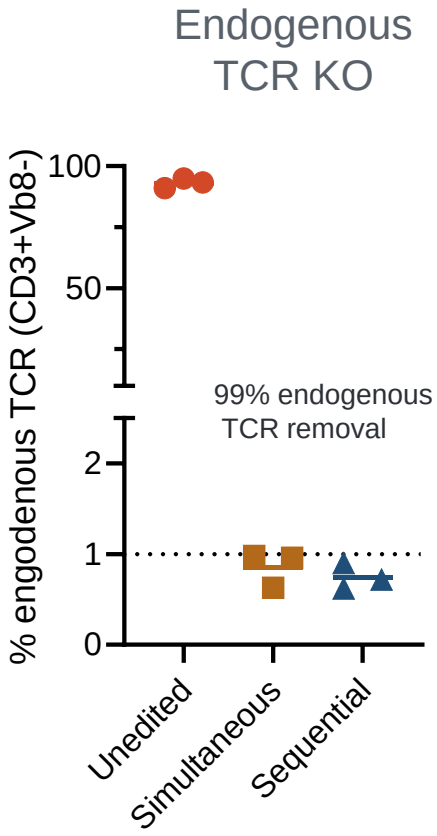
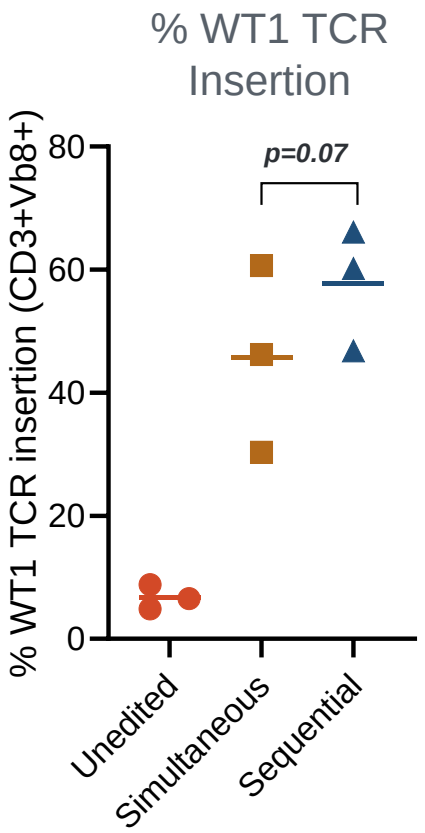
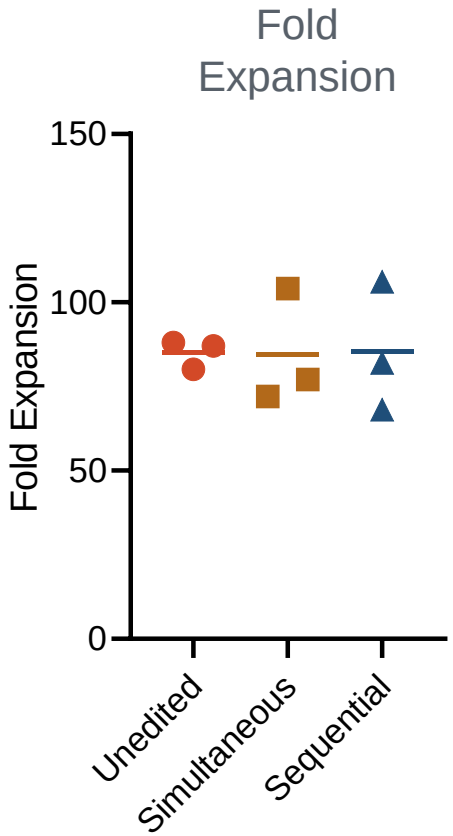
Sequential Editing of Target Genes Reduced Translocations Without Impacting Expansion Rates









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

- **High endogenous TCR KO (~99%) & insertion rates (~50%)**
- **High cell expansion**

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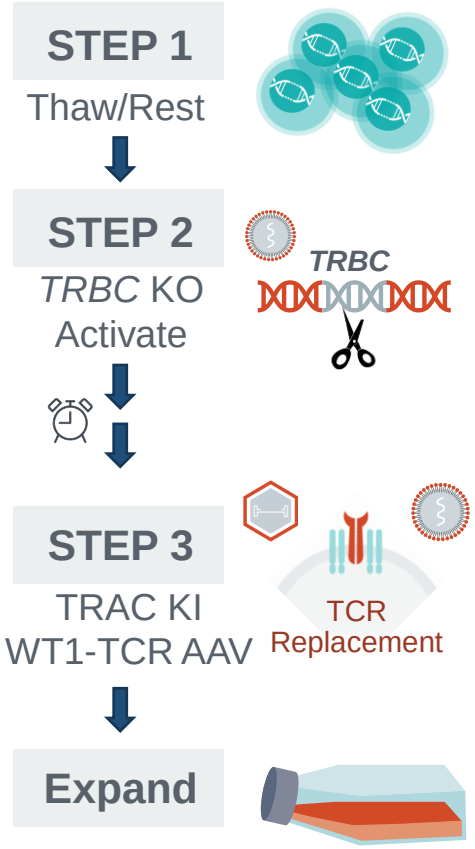
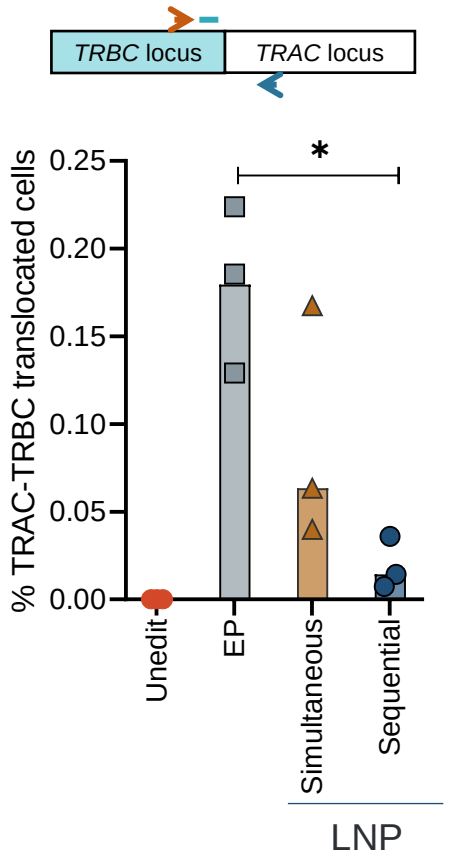
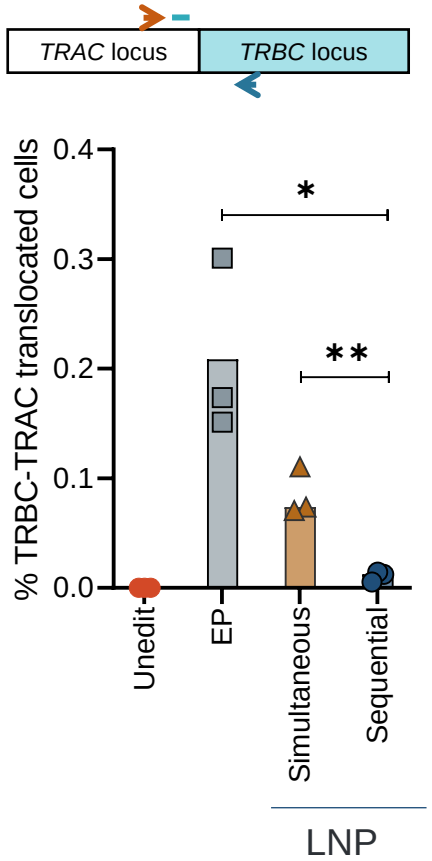
Sequential Editing of Target Genes Reduced Translocations Without Impacting Expansion Rates



ddPCR assay to detect *TRAC-TRBC* translocations





Sequential LNP [CRISPR/Cas9] editing results in a significant reduction in *TRAC-TRBC* translocations

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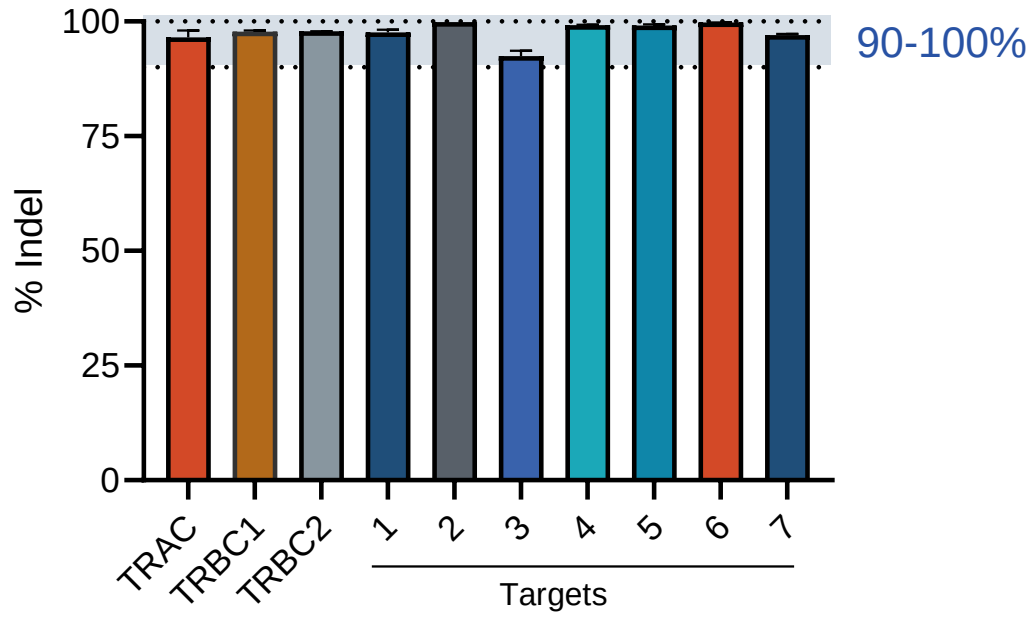
Modular Processes for Allogeneic TCR and CAR-T cell therapies

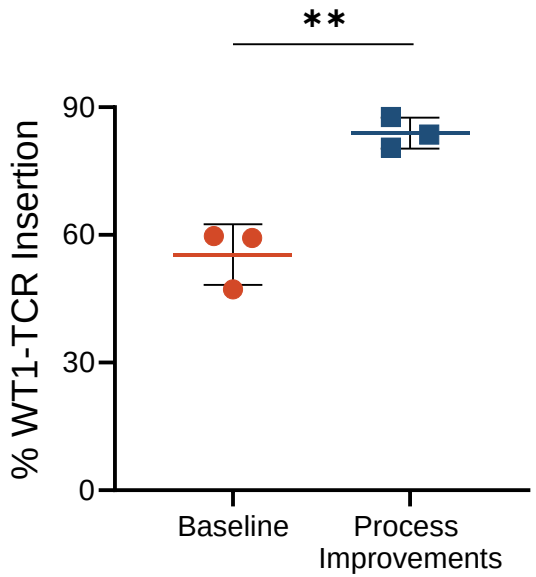
Building a Modular Platform for Next-Generation T Cell Therapies

- Allogeneic and solid tumor T cell therapies will require edits of numerous targets

90+% editing achieved via LNP delivery across numerous targets



Process Improvements to Enhance Site-Specific Insertion Efficiency



High insertion has been reproduced across several TCRs, CARs, and other transgenes

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Multiplex CRISPR/Cas9 T Cell Editing: 4 KO Edits with a tgTCR Insertion

STEP 1
Thaw

STEP 2
HLA-Class II KO
Activate

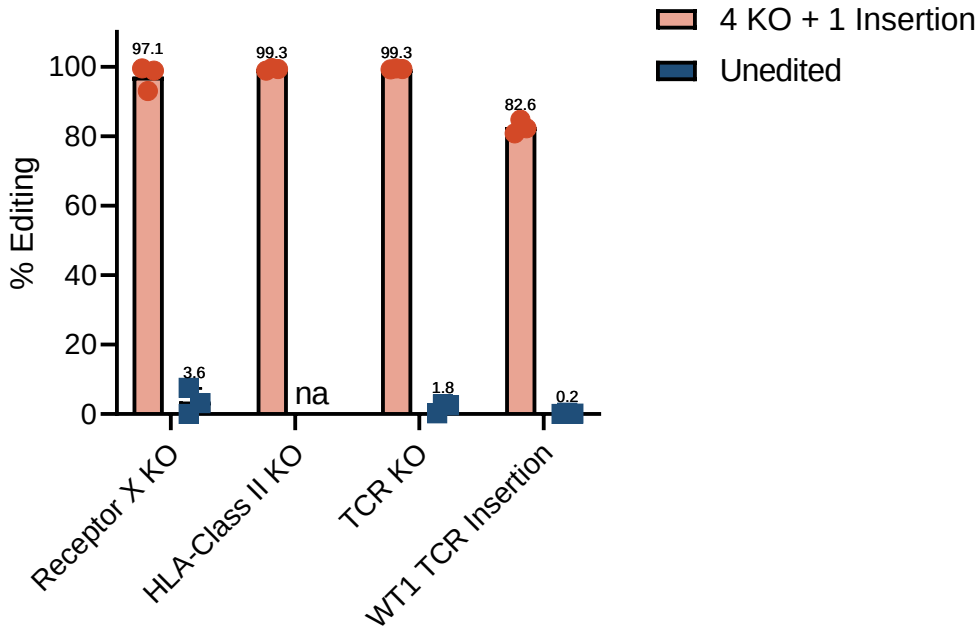
STEP 3
Receptor X KO

STEP 4
TRAC KI
WT1-TCR AAV

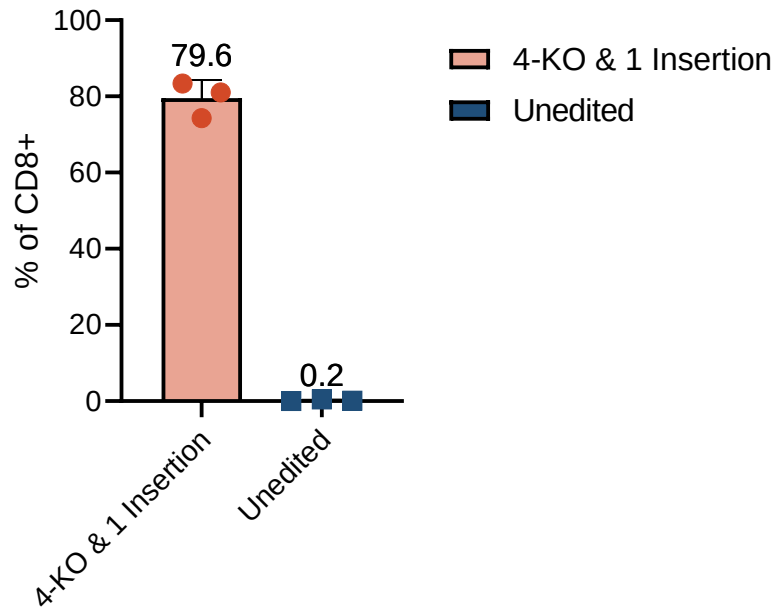
TCR Replacement

STEP 5
TRBC KO

% Editing Across Loci



% Fully Edited T Cells



- **Highly efficient editing across all targets while retaining high viability & expansion**
- **Yield of ~80% fully-edited T cells will support allo-T cell therapy candidates**
- **For more information on Intellia's allogeneic platform see Dr. Yong Zhang's presentation: Session 2c (OR18) Oct. 20th 10:45 CEST**

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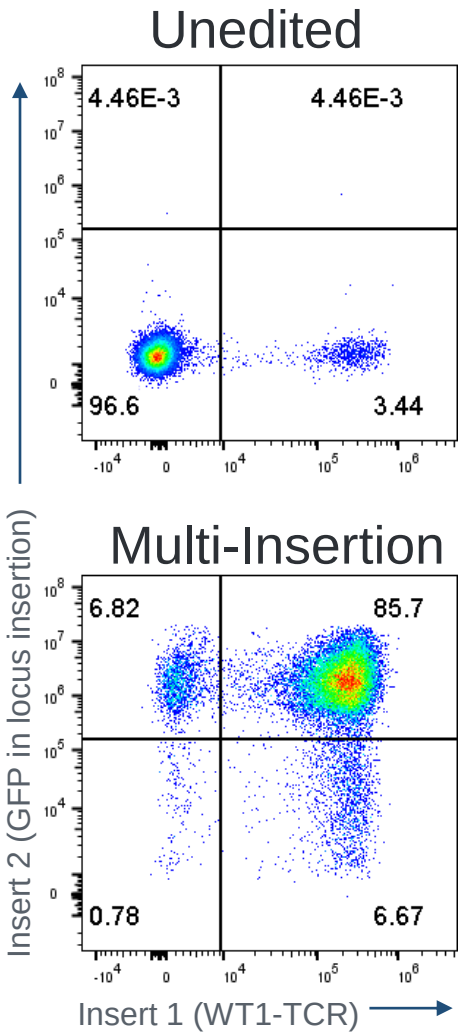
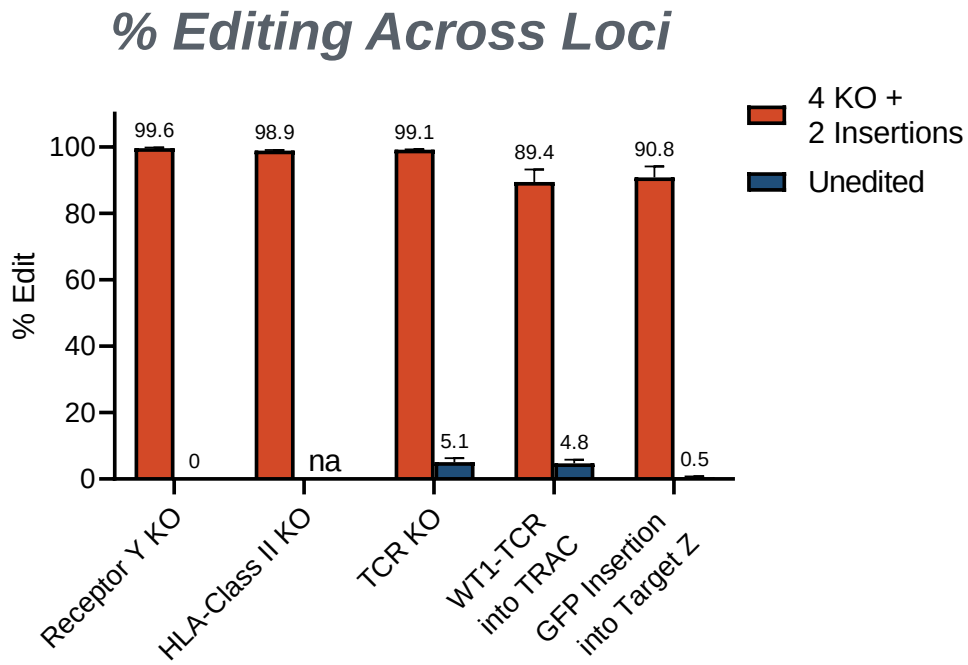
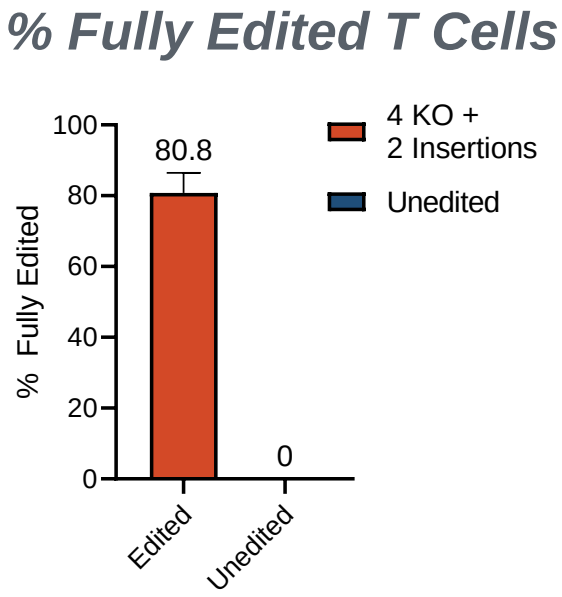
Multiplex CRISPR/Cas9 T Cell Editing: 4 KO Edits with 2 Insertions

Dual site-specific insertion strategy enables co-expression of CAR/TCR construct and immune enhancing transgene







- **>80% of cells have insertion of both the TCR and GFP transgene as well as complete editing of 4 other KO targets**
- **Cells retained high viability**
- **Modular platform for insertion of T cell supporting transgenes**

Key Takeaways

1. LNPs represent a superior CRISPR/Cas9 delivery system for *ex vivo* T cell editing

- Improvements on cell viability and expansion vs. standard electroporation methods
- Improved phenotype and potency of WT1 TCR-T cells
- Sequential editing with LNP transfections minimizes translocations
- NTLA-5001: First-in-human clinical study with LNP-edited CRISPR/Cas9 T cells expected to begin screening in 2021 (NCT05066165)

2. Modular cell engineering platform for highly multiplex editing of T cells

- High editing across numerous targets
- Process improvements led to 80-90+% CAR and TCR insertion rates
- Efficient sequential multiplex editing of up to 5 genes including multiple insertion and KOs

Robust and modular platform technology enables allogeneic and solid tumor candidates with highly multiplex gene edits

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