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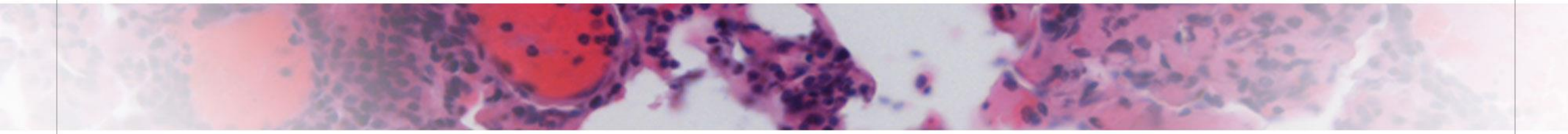

NTLA-5001, a T Cell Product Candidate with CRISPR-Based Targeted Insertion of a High-Avidity, Natural, WT1-Specific TCR, Shows Efficacy in *In Vivo* Models of AML and ALL

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Conflict of Interest Disclosure and Legal Disclaimer

- D. Liu, A. Prodeus, A. Becker, M. Foisey, I. Balwani, I. Dutta, Q. Zhang, M.S. Arredouani, M. McKee, L. Sepp-Lorenzino, and B.C. Schultes are employees of Intellia Therapeutics, Inc.
- F. Ciceri and C. Bonini are consultants for Intellia Therapeutics, Inc.
- C. Bonini received research funding from Intellia Therapeutics, Inc.

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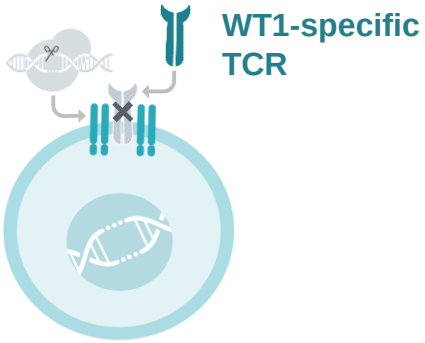
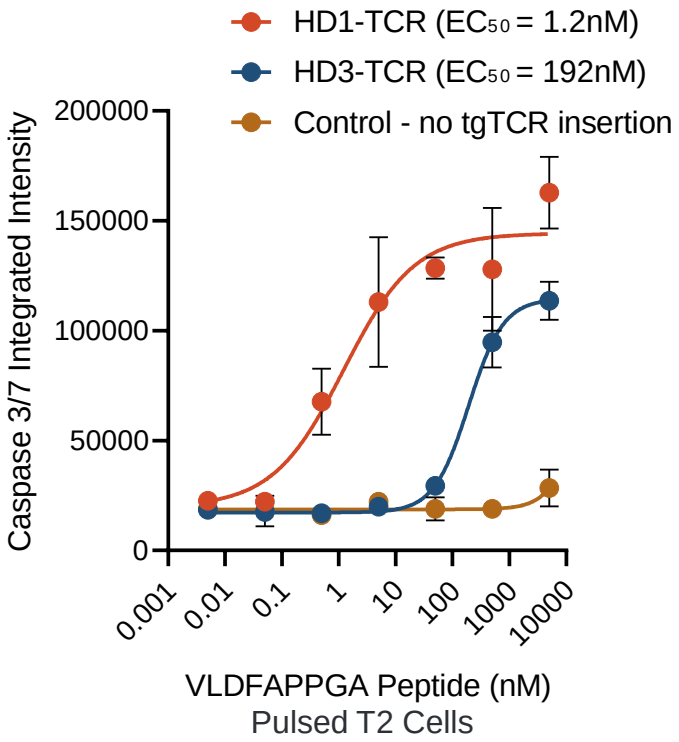
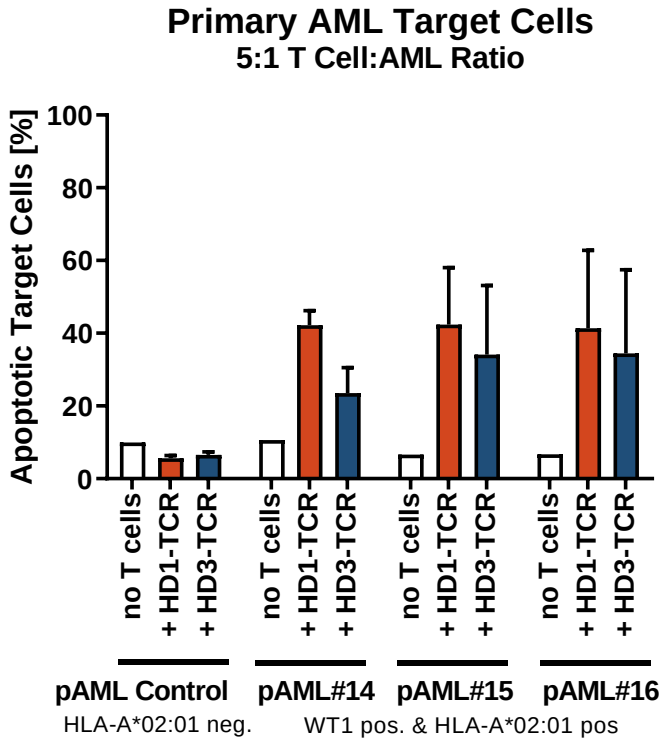
NTLA-5001: Engineered T Cell Product Candidate with Site-Specific Insertion of a High-Avidity, Natural TCR to $WT1_{37-45}$

- Initial clinical indication: **AML**, the most common type of acute leukemia in adults with limited treatment options[1]
- HD1-TCR selected for NTLA-5001 based on high avidity and ability to specifically kill AML blasts







[1] NIH SEER Cancer Stat Facts: Leukemia – Acute Myeloid Leukemia (AML)

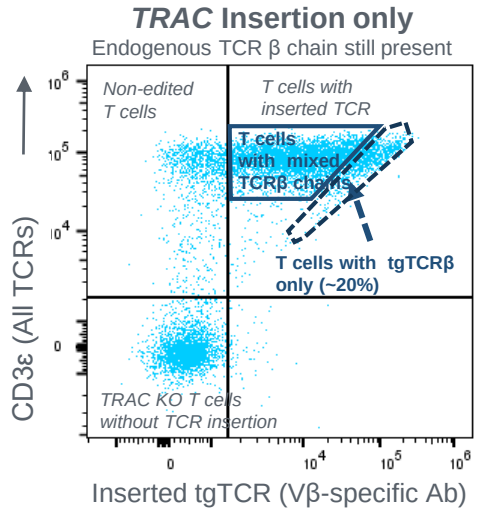
AML: acute myeloid leukemia **TCR**: T cell receptor **WT1**: Wilms' Tumor 1

CRISPR Editing Overcomes Key Challenges in TCR T Cell Engineering

Traditional tgTCR addition

Heterogenous Cell Product

Mixed TCRs
(tgTCR,endogenous and misspaired TCRs)



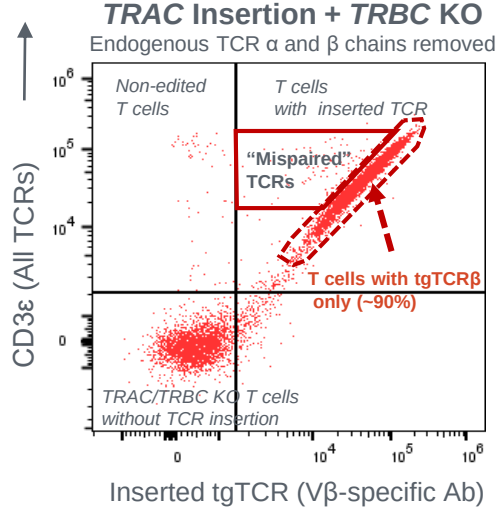
Key Challenges

- Mutagenesis risk from random lentiviral insertion
- Mixed expression of endogenous, tg and mispaired TCRs
- Unpredictable specificities of mispaired TCRs and GvHD risk
- Lower tgTCR expression per T cell leads to reduced efficacy

CRISPR/Cas9 tgTCR replacement

Homogenous Cell Product

tgTCRs only



Our Solution

- Precise replacement of endogenous TCR with tgTCR
- No insertional mutagenesis risk
- Reduced risk of normal tissue reactivity
- High tgTCR expression per T cell leads to higher efficacy

Intellia THERAPEUTICS

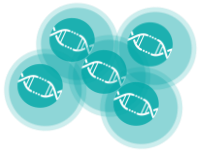
 tgTCR: transgenic therapeutic TCR **KO:** knockout gene edit **GvHD:** graft-versus-host-disease

Proprietary Sequential Editing Process Enables Multiple Edits with High Efficiency and Cell Viability

Cell Engineering Workflow

DAY 0

Thaw



1st Edit

TRBC KO

2nd Edit

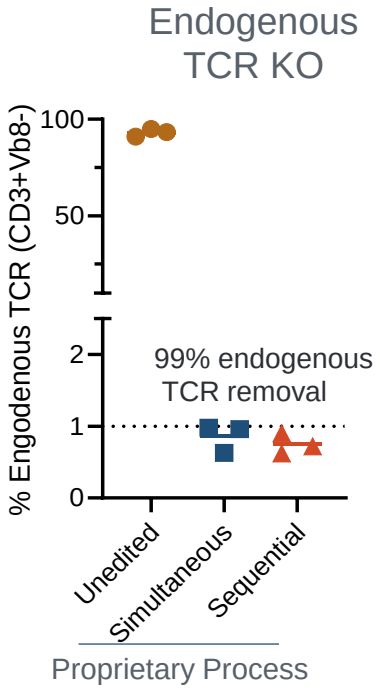
TRAC KO Transgene Insertion

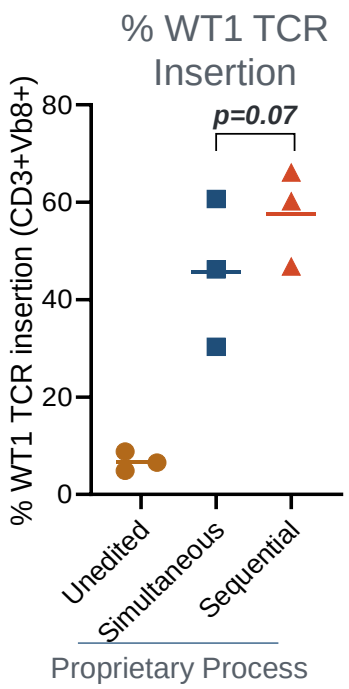
T Cell Expansion

DAY 10

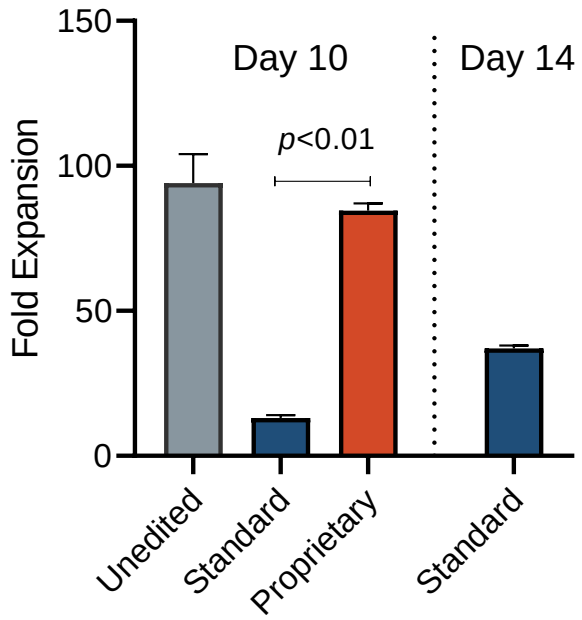
Harvest

T Cell Editing





T Cell Expansion



Proprietary process can overcome limitations of standard electroporation methods:

- **High endogenous TCR KO (~99%) and TCR insertion rates (>50%)**
- **More rapid expansion post-editing (80-200x in 10 days)**

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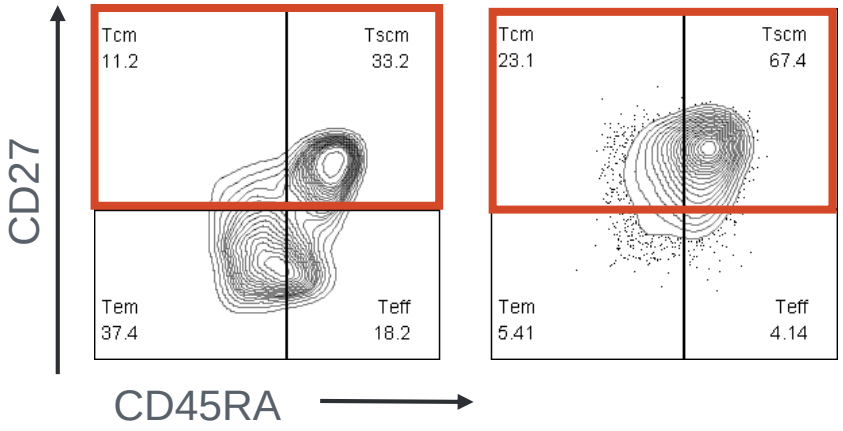
WT1-TCR T Cells Engineered with Proprietary Process Have Enhanced Potency vs. Standard Methods

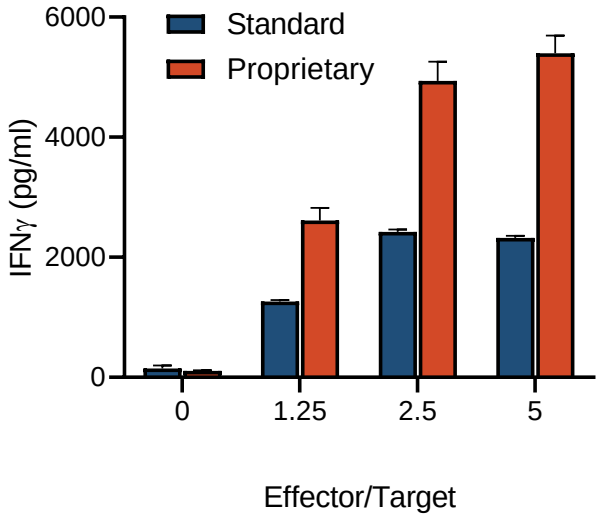
T Cell Memory Phenotype

Standard Process | Proprietary Process



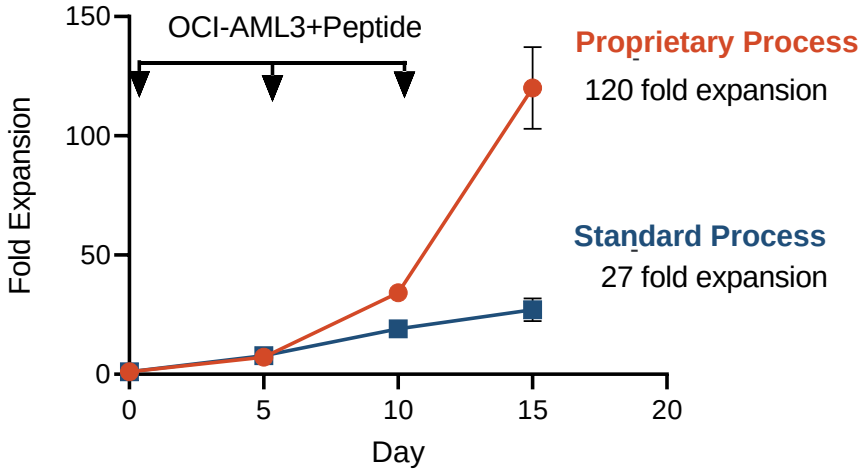
IFN-γ Secretion

K562-HLA-A*02:01+ Cells



Re-stimulation Stress Test

OCI-AML3 pulsed cells



- **~90% of T cells carry desirable central and stem cell memory phenotype**
- **Higher cytokine secretion in response to WT1-presenting tumor cell lines *in vitro***
- **Long-term proliferative capacity in a repeat-stimulation assay with tumor cells *in vitro***

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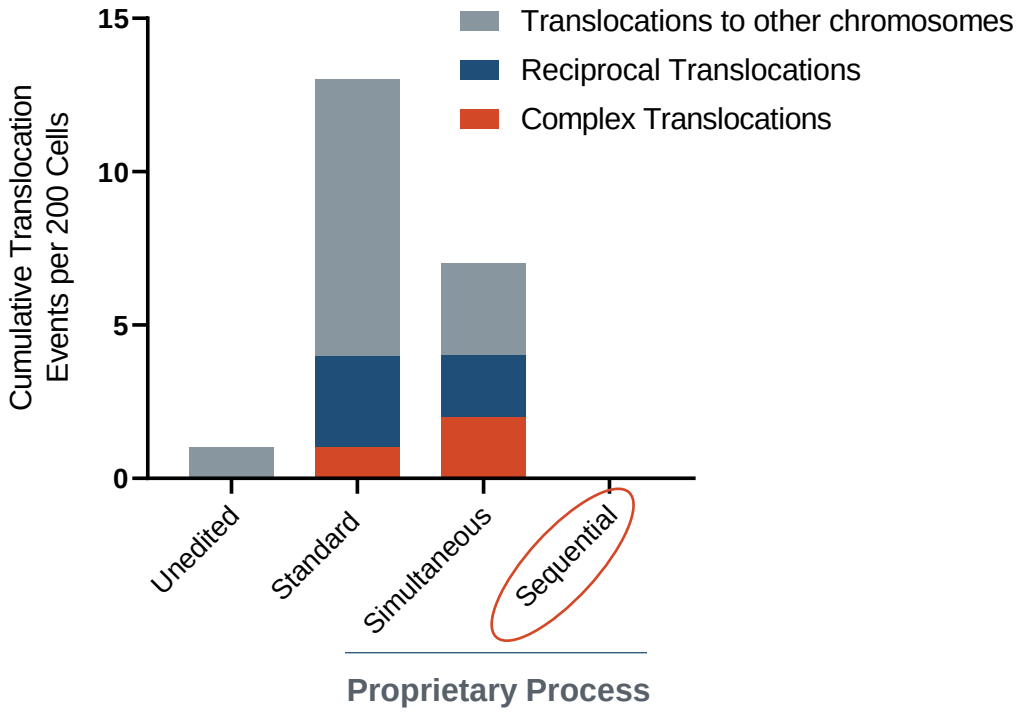
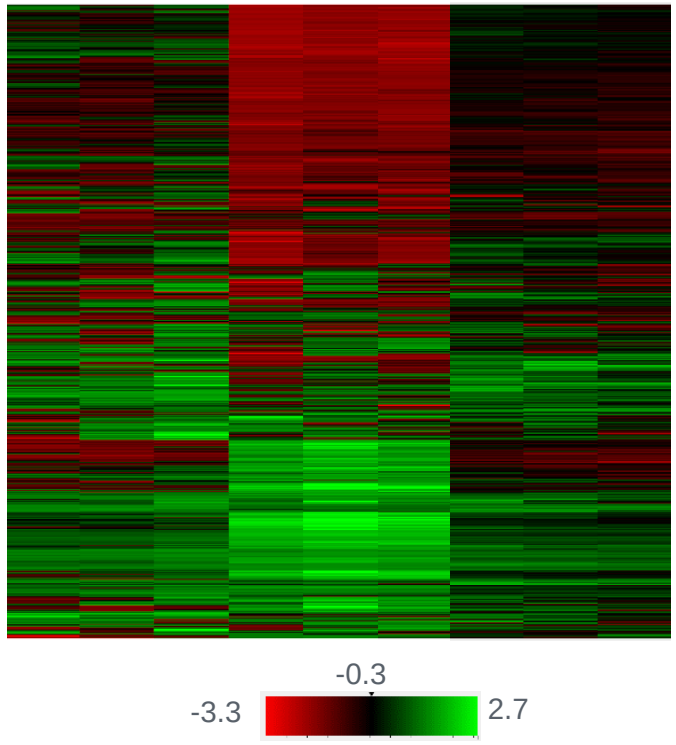
Proprietary Process Minimizes Translocations and Gene Expression Changes vs. Standard Electroporation Process

KromaTiD dGH™ Assay Shows No Detectable Translocations With Sequential Editing



Gene Expression Profiling[1] (780 genes)



Genes Differentially Regulated

6h	Std	Proprietary
P<0.05	195	75
>2 FC & P<0.05	34	4

- **Standard process leads to gene expression changes in pathways of metabolism, memory and exhaustion**
- **Proprietary process results in minimal gene expression changes**

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

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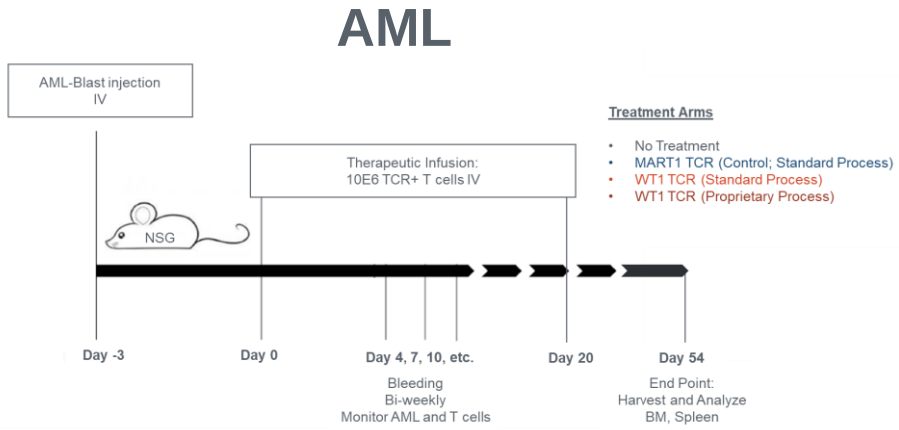
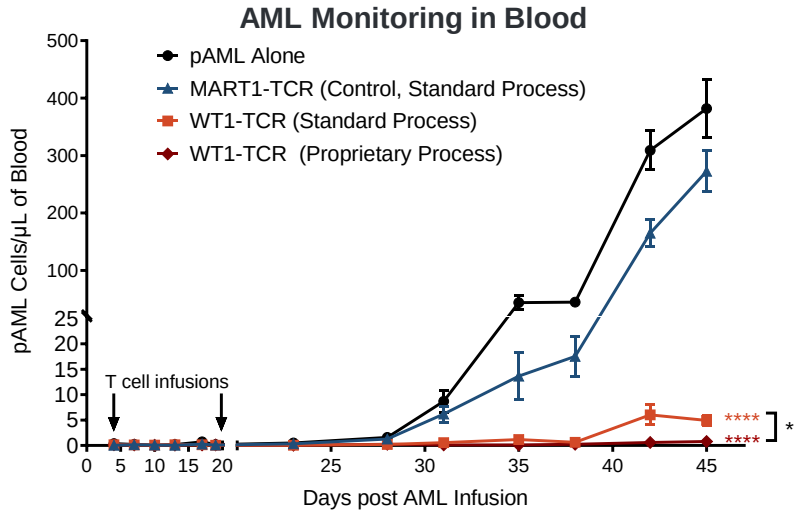
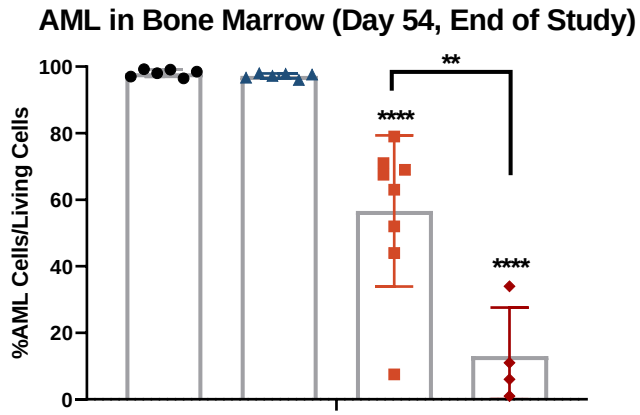
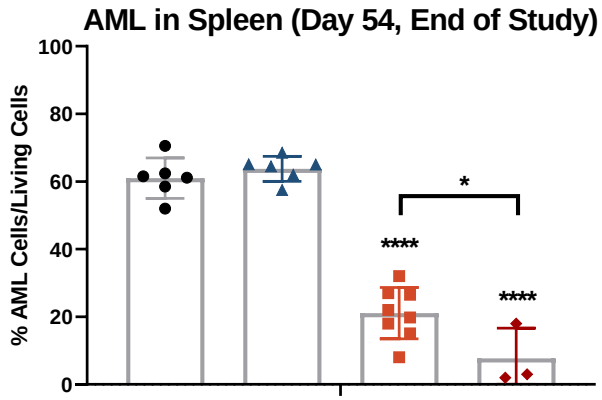
WT1-Specific TCR T Cells Are Efficacious *In Vivo* in Mice; Proprietary Process Enhances Anti-Tumor Activity





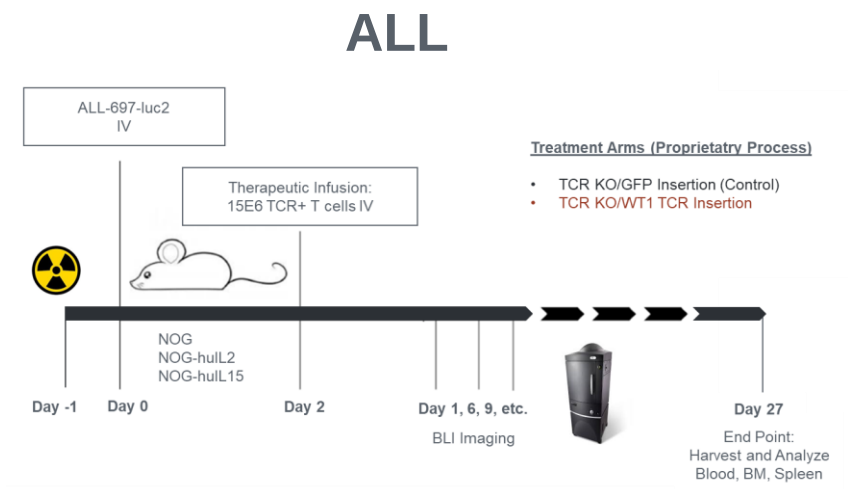
***** p<0.0001, WT1 TCR vs. MART1 Control TCR (2-way ANOVA)*
** or ** p<0.05 or p<0.01, Standard vs. Proprietary Process (2-way ANOVA)*

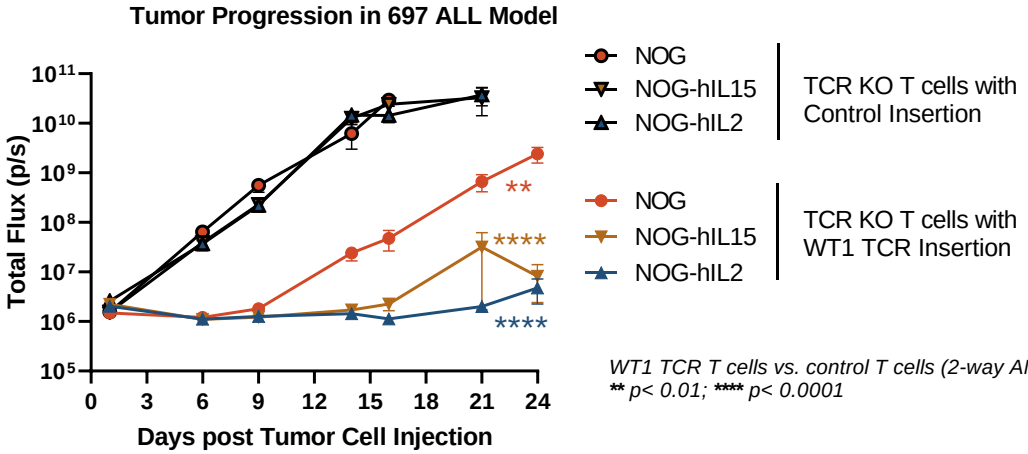




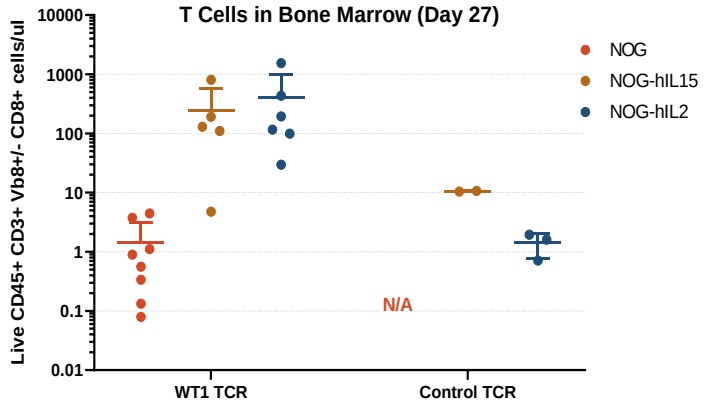
Better tumor control with WT1 T cells manufactured using the proprietary process

WT1-Specific TCR T Cells Are Efficacious *In Vivo* in Mice; Human IL2/IL15 Enhances Anti-Tumor Activity





WT1 TCR T cells vs. control T cells (2-way ANOVA):
*** p< 0.01; **** p< 0.0001*



In NOG mice producing human IL2 or IL15* WT1 T cells

- **Persist longer**
- **Control tumor burden more effectively**

**IL2 or IL15 levels comparable to levels in patients post lymphodepletion*

Conclusions and Next Steps for NTLA-5001

- Proprietary process enables efficient, scalable genome editing
  - ~99% KO efficiency of target genes; 50-70% in locus insertion of tgTCRs
  - Sequential editing with high viability and potential for safer products
  - Faster T cell expansion with favorable T cell memory phenotype leading to potentially reduced vein-to-vein time
  - Enhanced *in vitro* function and *in vivo* anti-tumor efficacy in mouse models
- Intellia is continuing to advance NTLA-5001 toward the clinic in 2021
  - Scale-up for clinical process completed

NTLA-5001: Proposed first-in-human trial evaluating safety and activity in AML

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THERAPEUTICS