



Special Edition: Expanding Intellia's Toolbox with Base Editing

7th Cold Spring Harbor Laboratory (CSHL):
Nucleic Acid Therapies

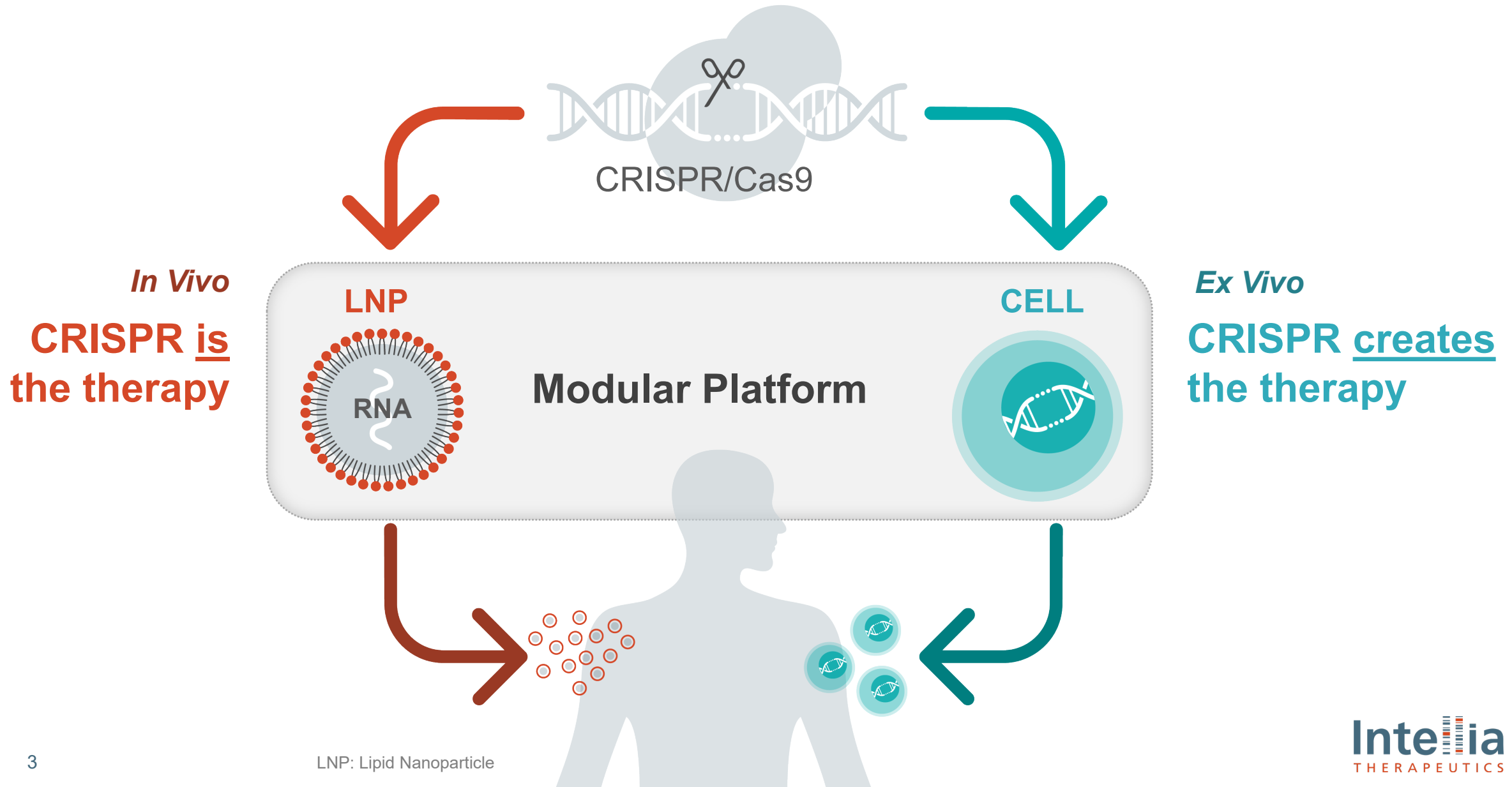
Christian Dombrowski, Ph.D. | March 25, 2021

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Intellia Therapeutics is a Full-Spectrum Genome Editing Company



Ex Vivo

CRISPR creates the therapy

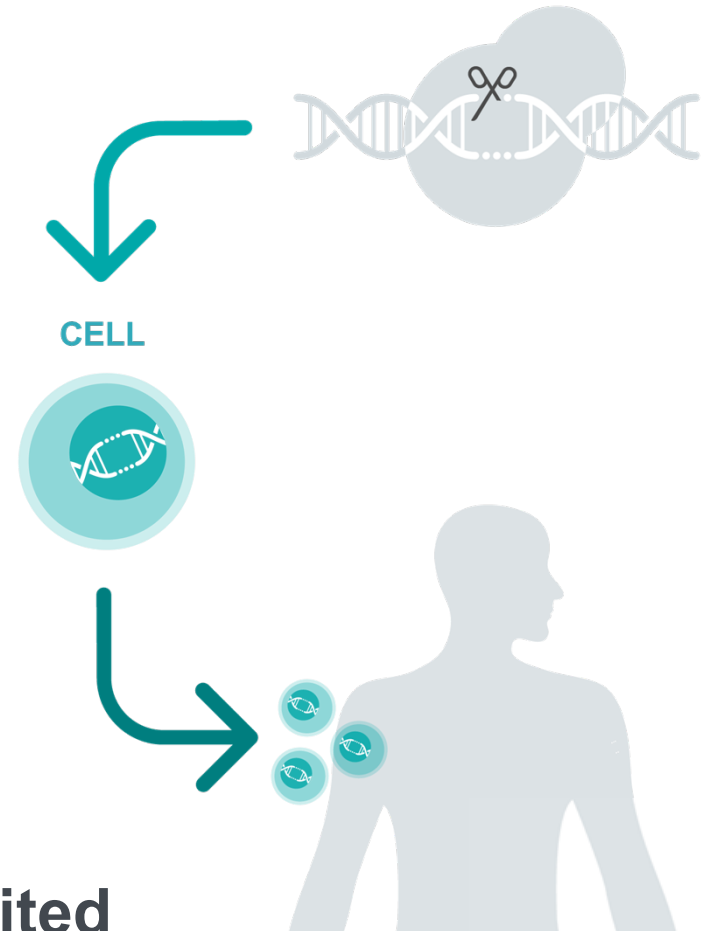
IMMUNO-ONCOLOGY / AUTOIMMUNE DISEASES

Strategic Advantages:

Utilizing proprietary CRISPR engineering platform to create differentiated cell therapies for IO and AI diseases





















Targeting modalities, such as TCR, with broad potential in multiple indications

The possibilities to engineer cells *ex vivo* are limited only by the extent of the editing that we can do



No Single Tool Addresses the Full Spectrum of Possible Edits

Intellia TOOLBOX

	Gene knockout 	Precise insertion 	Exon skipping 	Multiplex knockout 	Mutation repair 
Spy Cas9					
Nme2 Cas9					
Cas9 + Template					

 Applicable  Not Applicable

Electroporation is the Current Gold Standard for Delivery in T cells



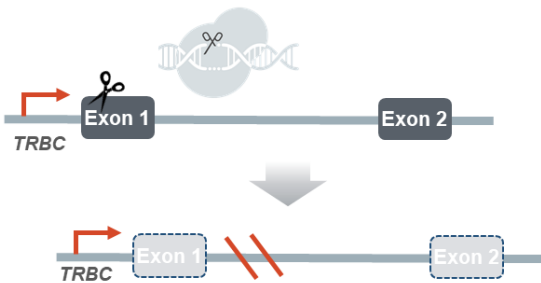
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EP

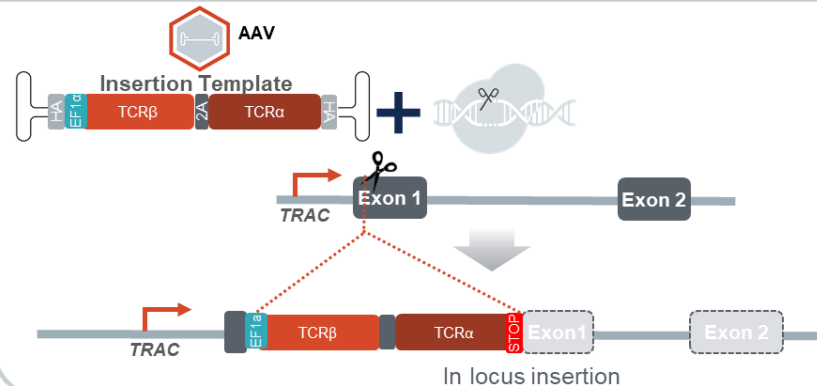


CRISPR/Cas9 for *TRBC1/2* KO



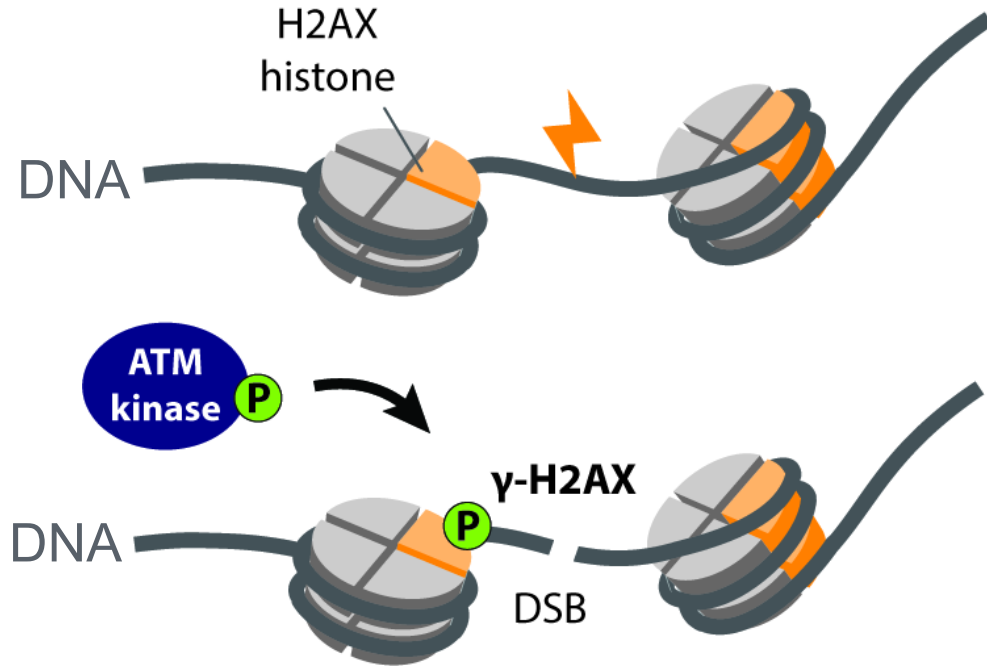
tgTCR: Transgenic TCR

CRISPR/Cas9 for tgTCR insertion in *TRAC* locus

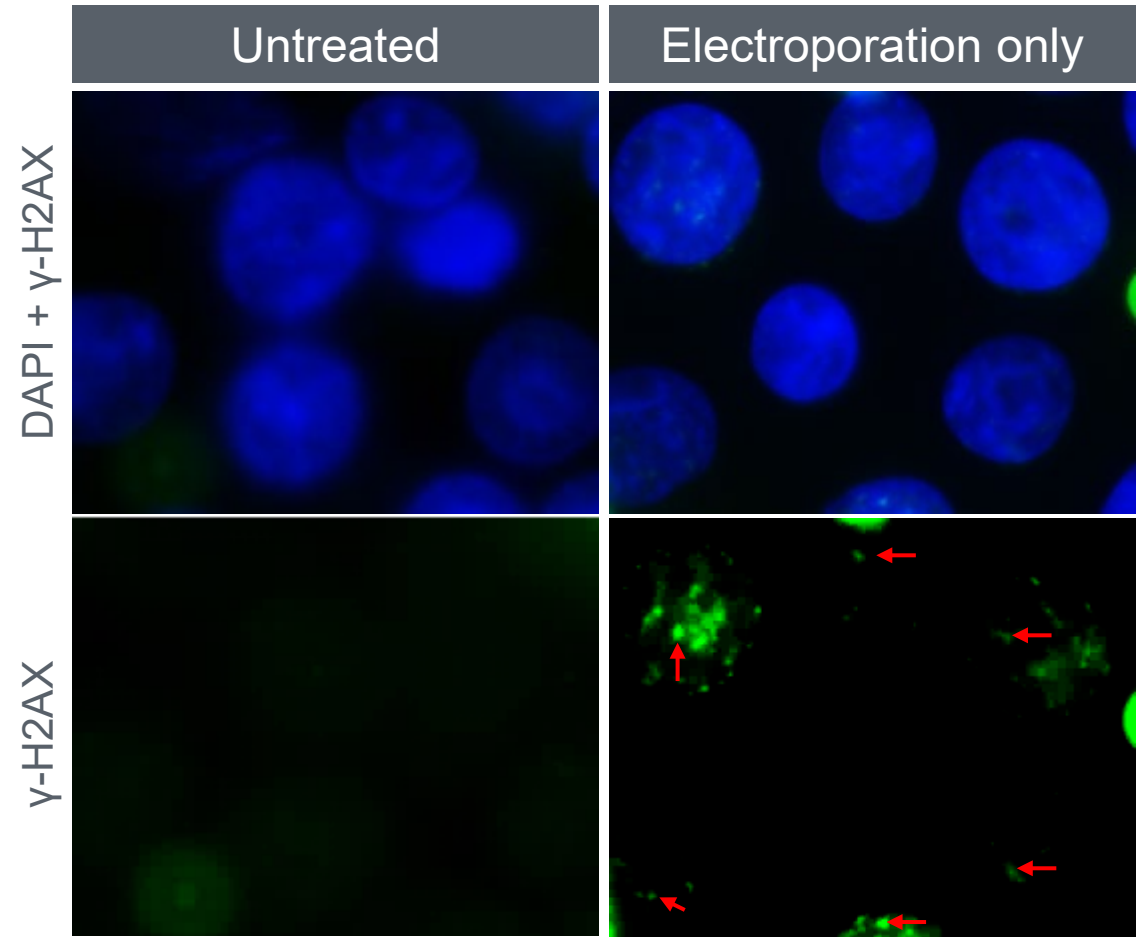


- Scalable
- High efficiency
- Clinically validated
- Preserves activity
- Preserves phenotype

Electroporation Alone Leads to Double Stranded Breaks

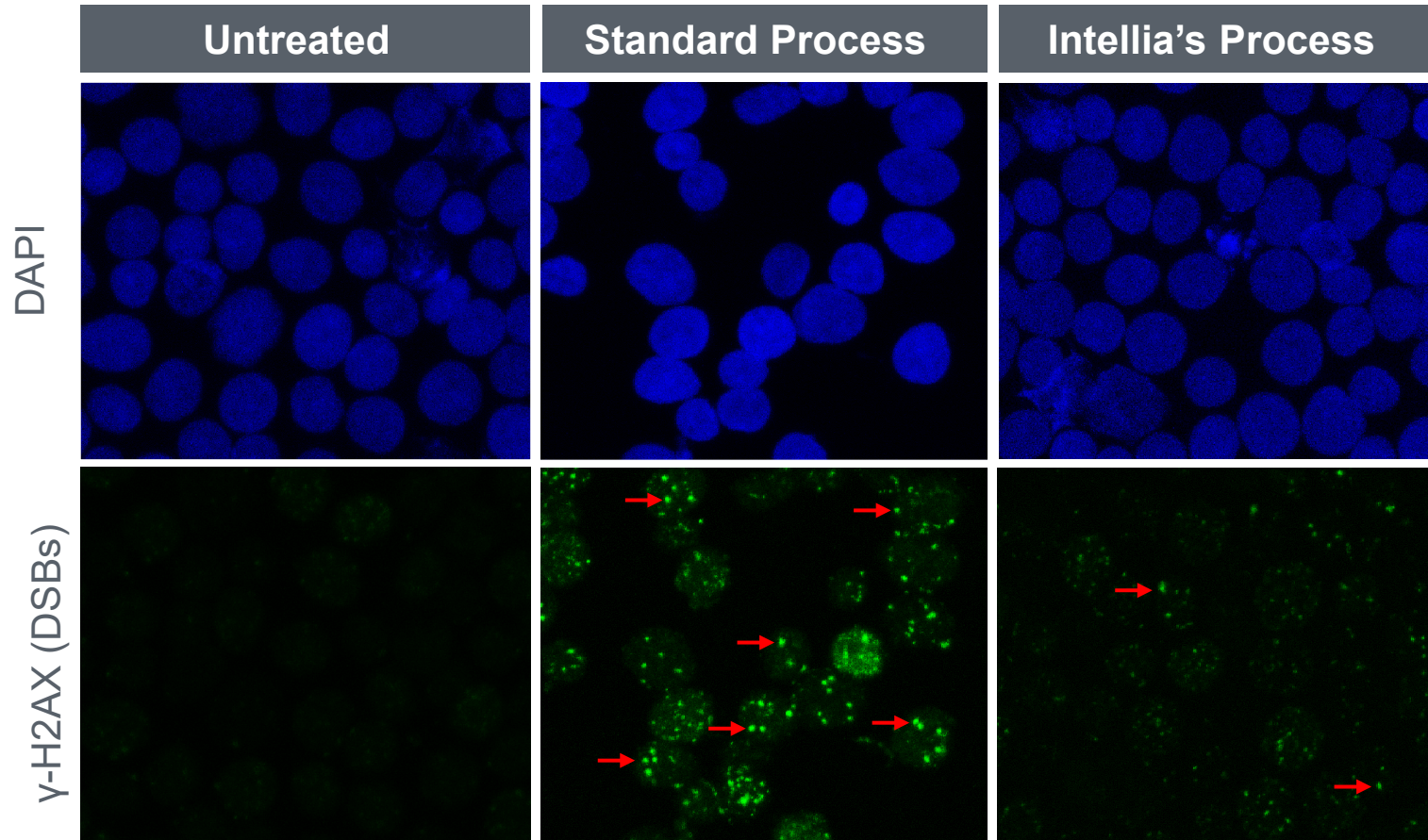


DNA double-stranded breaks (DSBs) lead to phosphorylation of proximal H2AX histones generating γ -H2AX

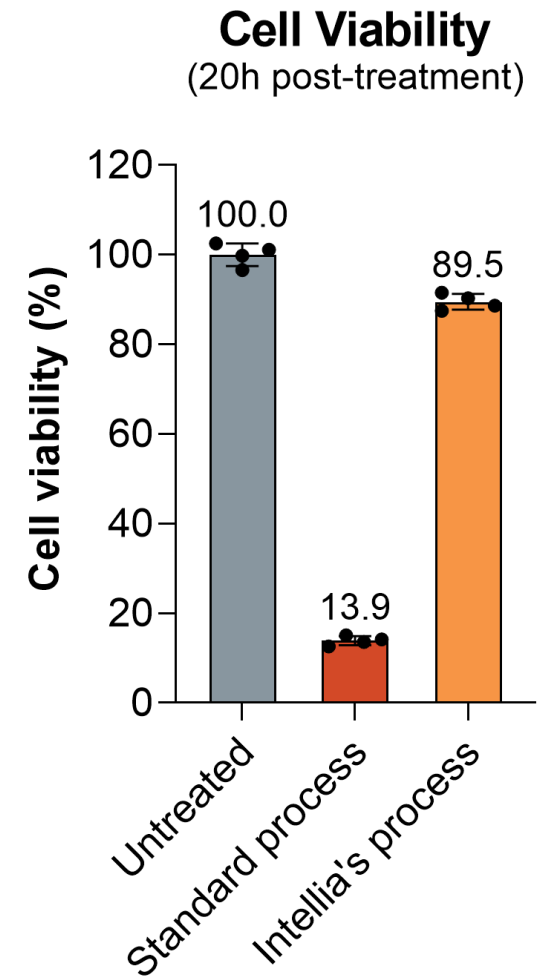


γ -H2AX proximal to double-stranded breaks (→)

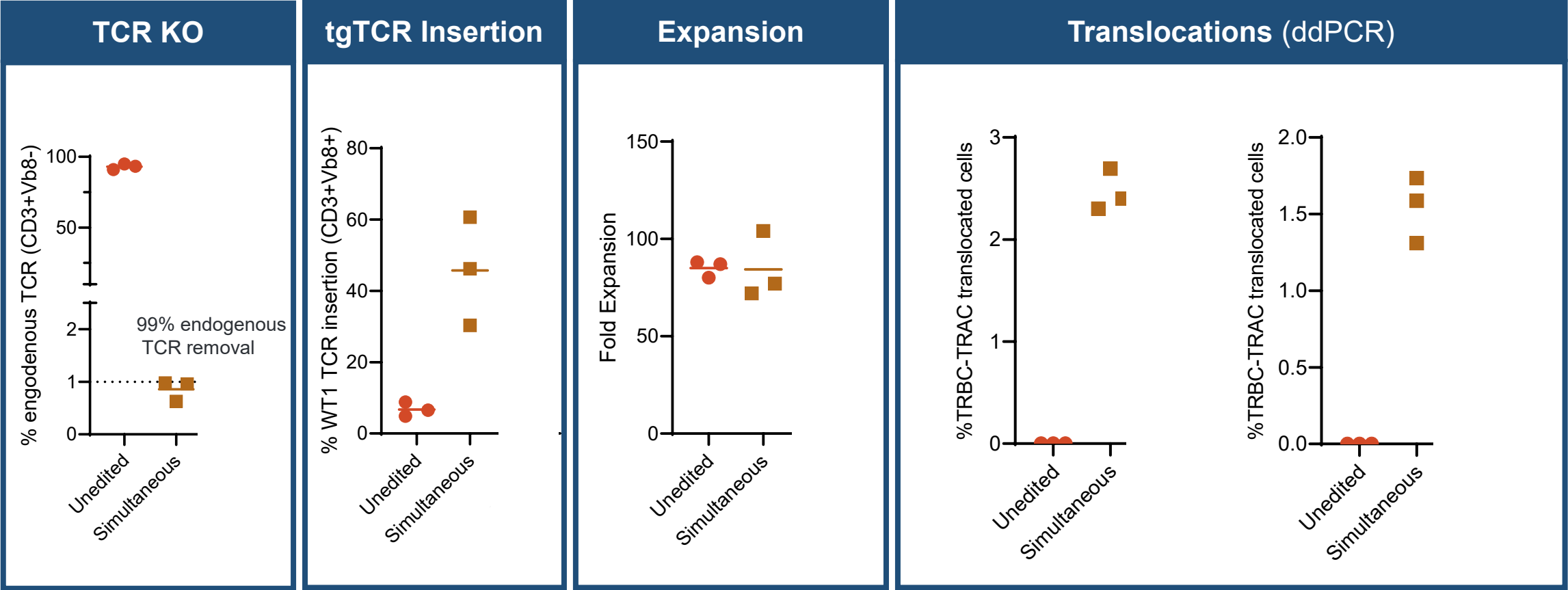
Intellia's Proprietary Process Leads to Fewer Breaks and Better Cell Viability



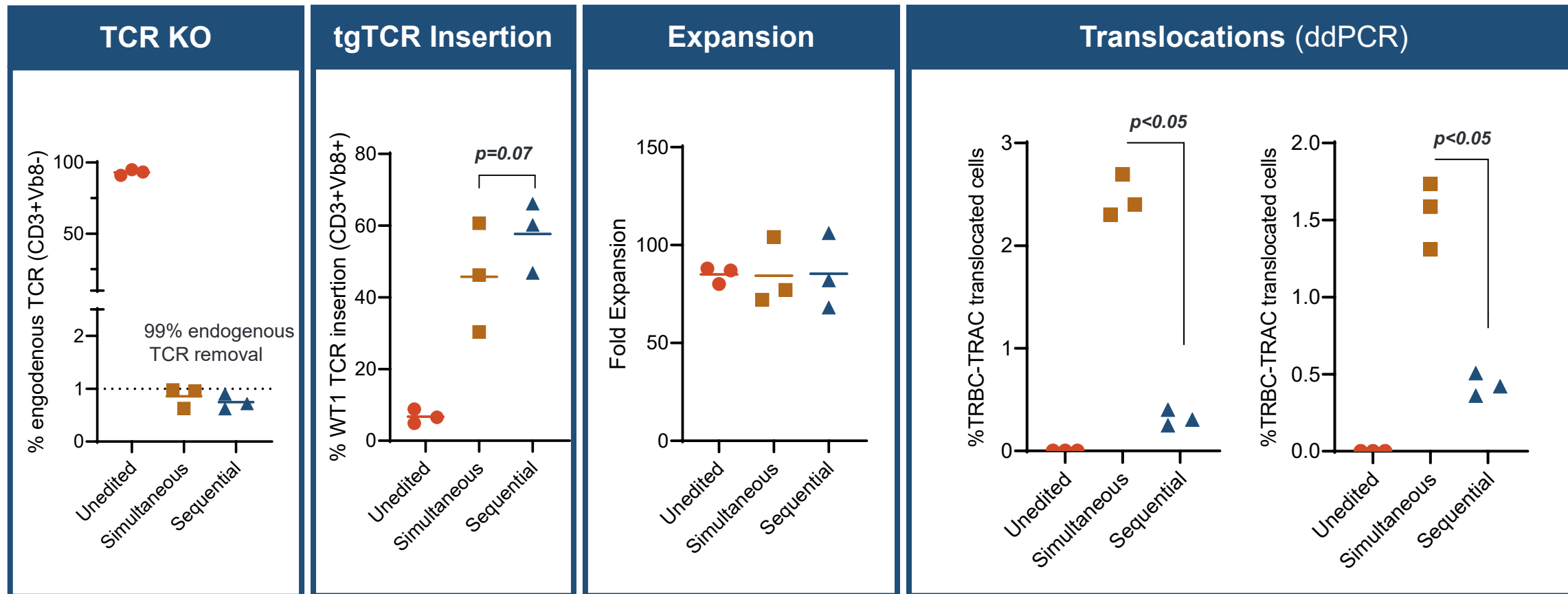
γ-H2AX proximal to double-stranded breaks (→)



Simultaneous Editing Strategy Leads to Translocations



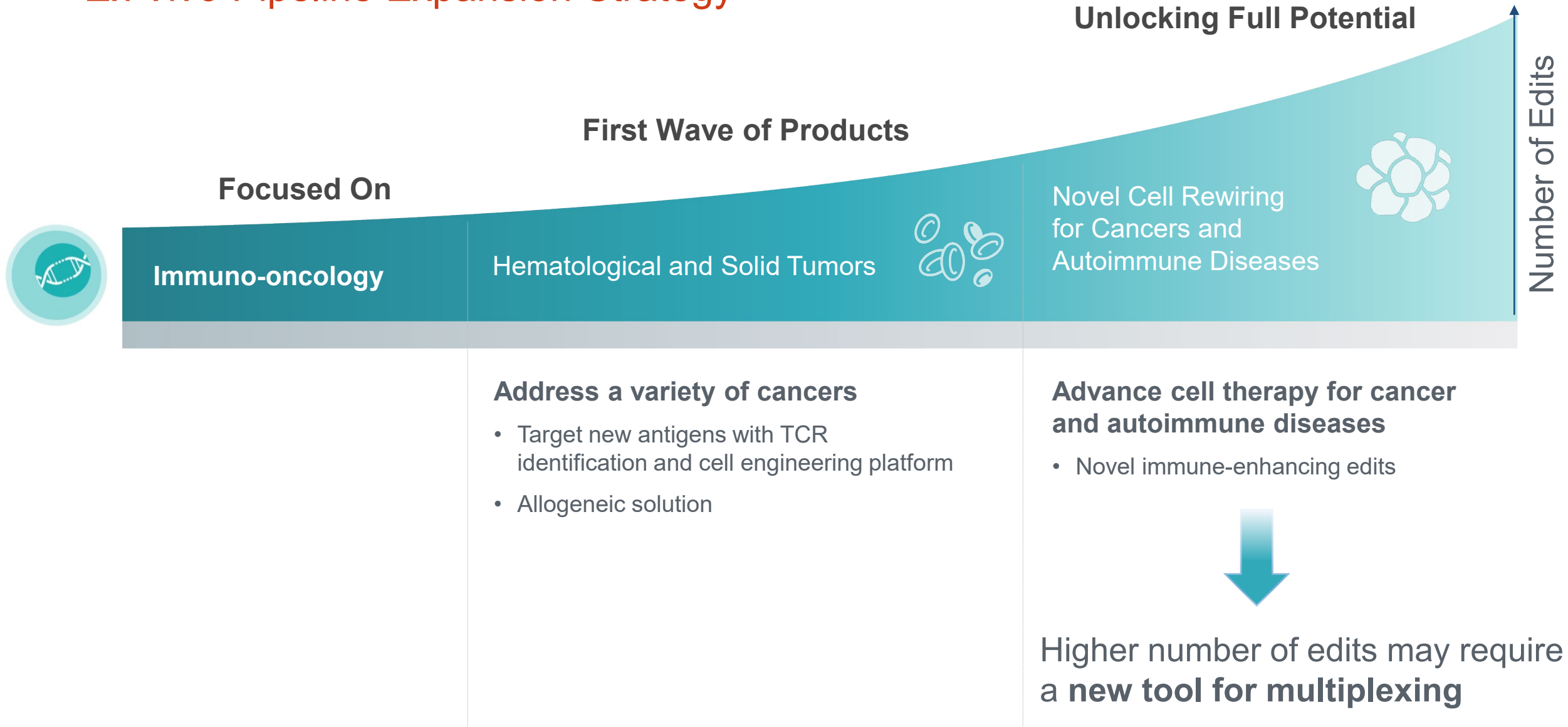
Proprietary Process Allows Sequential Editing and Minimizes Translocations



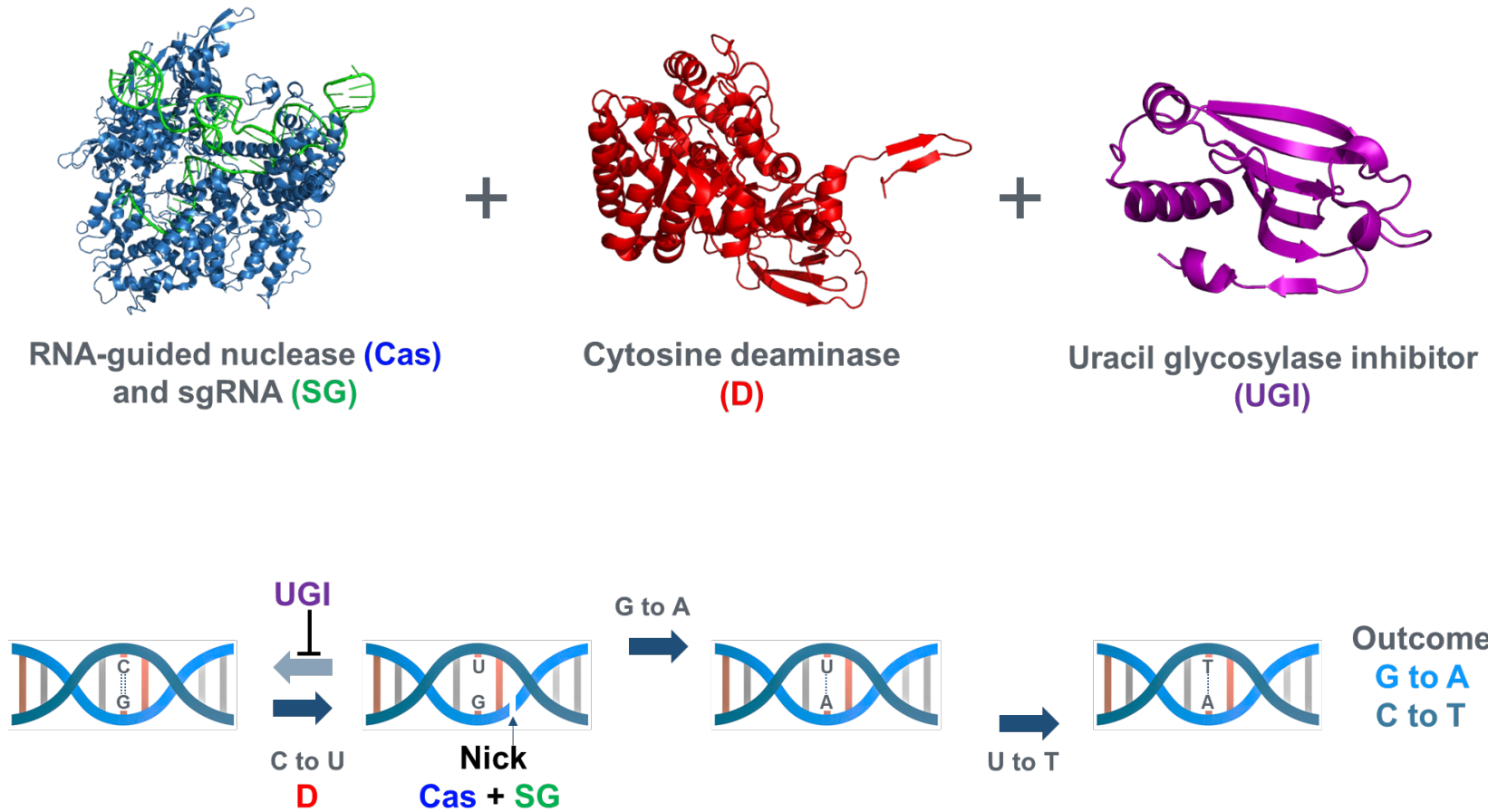
Sequential editing of *TRAC* and *TRBC* results in:

- High endogenous TCR KO (~99%)
- High insertion rates (>50%)
- High cell expansion
- Reduction of *TRAC-TRBC* translocations

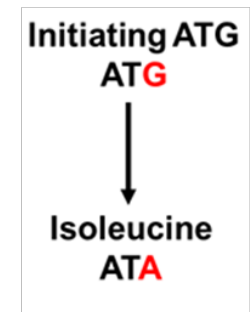
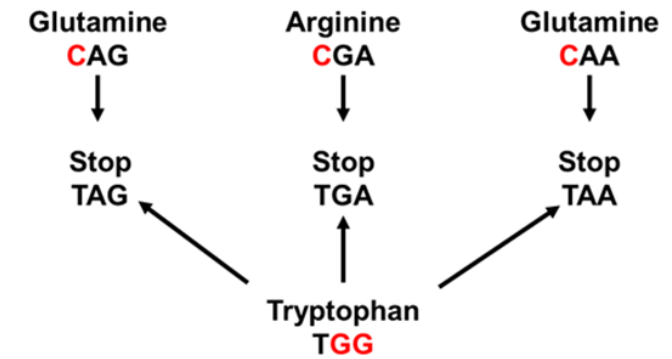
Ex Vivo Pipeline Expansion Strategy



Engineering a Base Editor for Multiplex Knockout

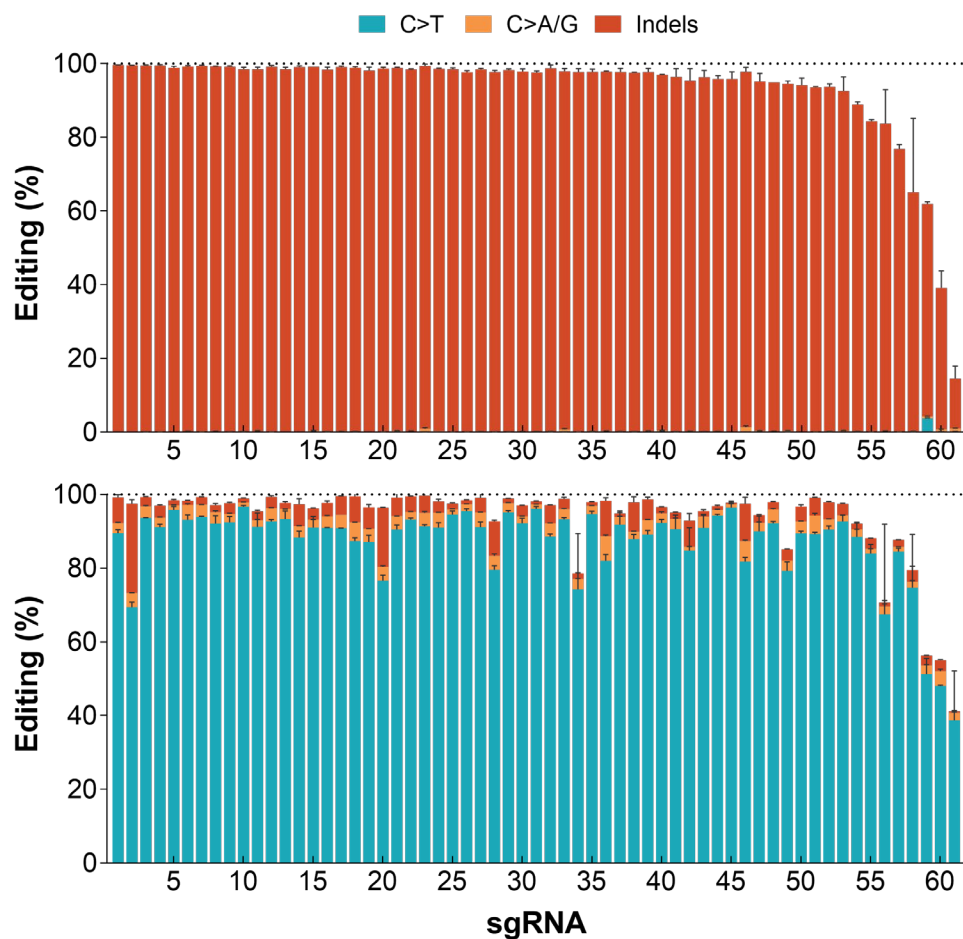


Editing outcomes



Intellia's Base Editor is Equipotent to Cas9 for *Ex Vivo* Editing

Intellia's base editor is highly active
with similar activity to Cas9 cleavase

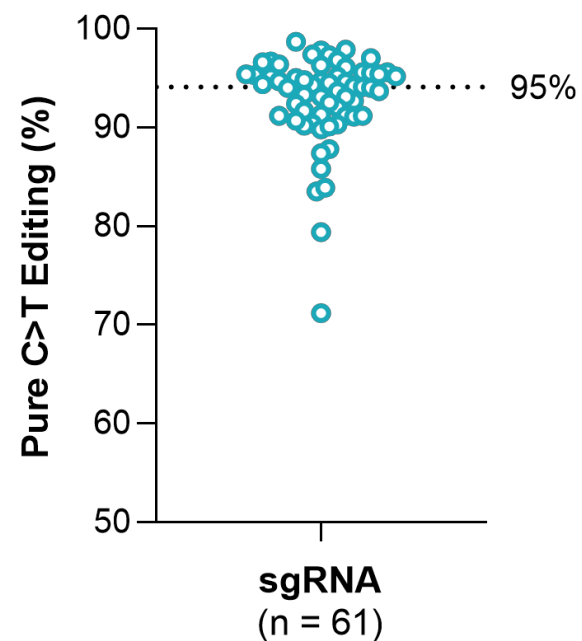


Cas9

Base
Editor






>700 constructs screened for potency
85% of guides gave >90% editing
36% of guides gave >95% C to T purity

Pure C>T edits
(without indels)



Intellia Expands *Ex Vivo* Toolbox to Include Base Editing

Intellia TOOLBOX

	Gene knockout 	Precise insertion 	Exon skipping 	Multiplex knockout 	Mutation repair 
Spy Cas9	●	○	◐	◐	○
Nme2 Cas9	●	○	◐	◐	○
Cas9 + Template	○	●	○	○	●
Cas9 Base Editor	●	○	●	●	◑




























Applicable



Not Applicable

Expanded Toolbox Permits Selection of the Optimal Tool for Each Edit Type

Intellia TOOLBOX

	Gene knockout 	Precise insertion 	Exon skipping 	Multiplex knockout 	Mutation repair 
Spy Cas9					
Nme2 Cas9					
Cas9 + Template					
Cas9 Base Editor					



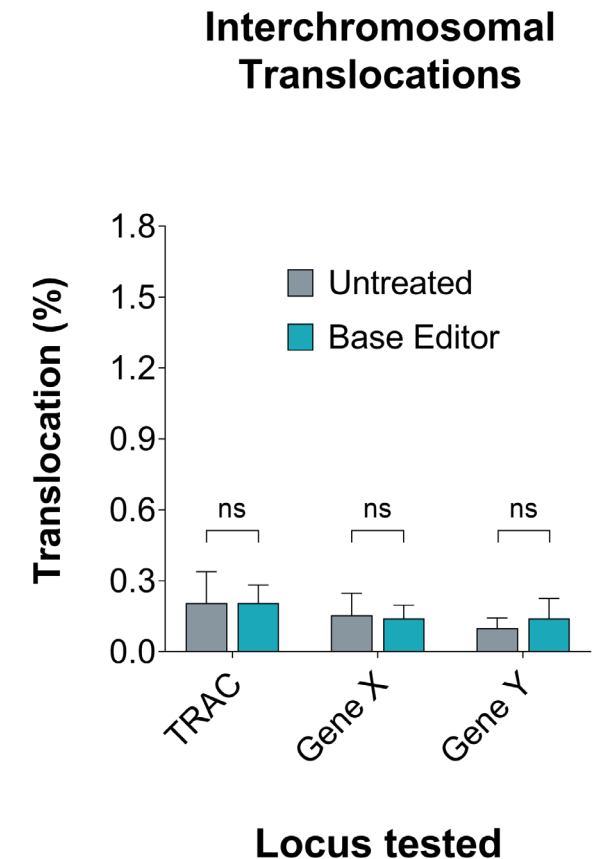
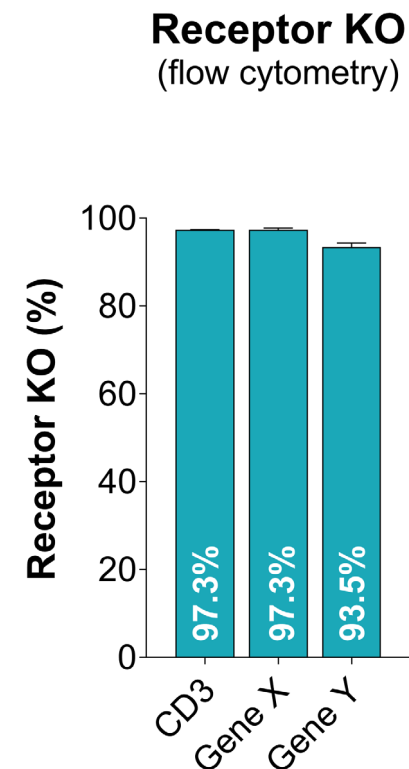
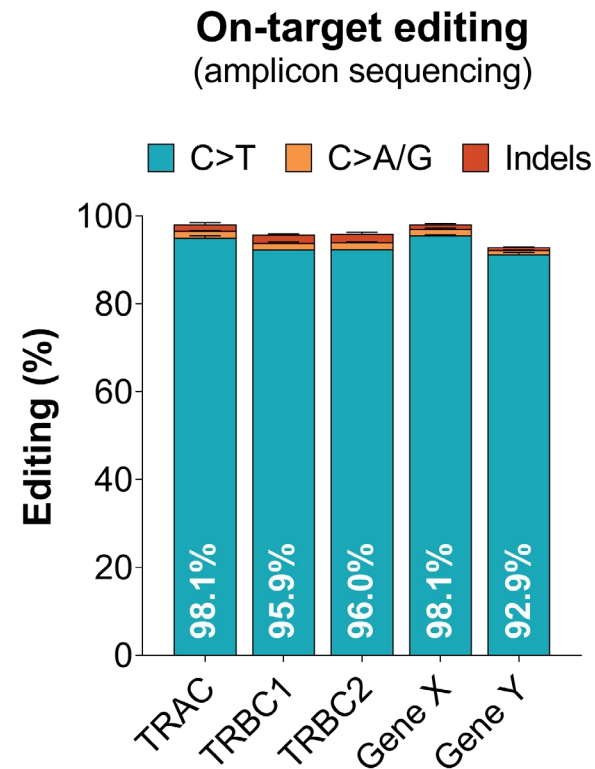
Applicable



Not Applicable

Simultaneous Knockout with Base Editing **Does Not** Lead to Translocations

- 1 Isolate primary T cells
- 2 Deliver base editor + 4 sgRNAs
- 3 Evaluate editing, receptor KO and translocations



Base Editors Potentially Introduce Additional Types of Off-Target Editing

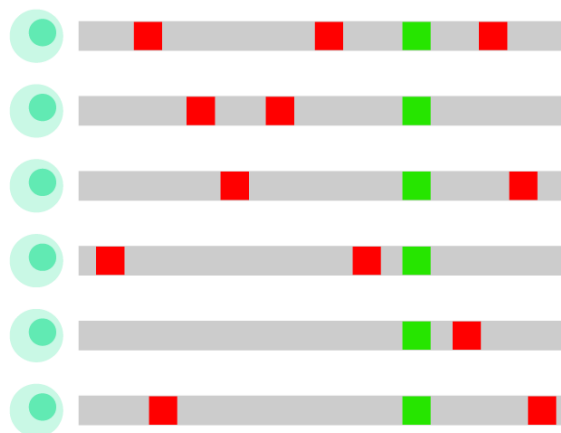
Potential Off-Target	Cas9	Base Editors
sgRNA sequence-dependent off-target editing	<ul style="list-style-type: none">Standard workflow:<ul style="list-style-type: none"><i>In silico</i> and biochemical off-target discoveryNGS targeted off-target validation in clinically relevant cell typesExtensive regulatory precedence	
Stochastic, sgRNA sequence-independent DNA deamination*	None	<ul style="list-style-type: none">Deep whole genome sequencing
Stochastic, sgRNA sequence-independent RNA deamination*	None	<ul style="list-style-type: none">RNA seq

*Challenging to measure; regulatory confidence yet to be established

Measuring sgRNA-Independent Off-Targets is Challenging

Bulk genomic DNA contains
genomes from many different cells

■ C>T on-target
■ C>T off-target



Consensus:



Potential off-targets
may drop-out

Discovery of stochastic deamination off-targets
requires **single-cell whole genome sequencing**



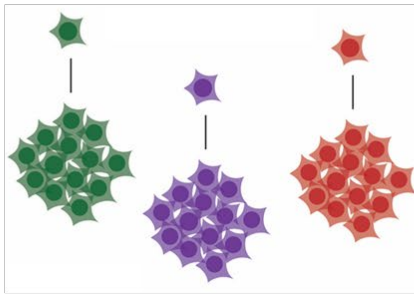
A diploid human cell contains only **6 picograms** of
DNA – not enough for sequencing



Single cell genome amplification is required to
confidently call base changes

Options to Generate Single-Cell Libraries for Whole Genome Sequencing

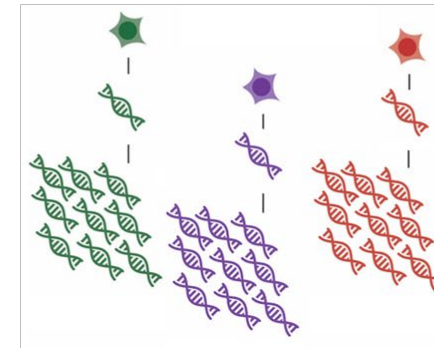
Clonal expansion of single cells



Only possible with immortalized cell lines

- Cell lysis is done after clonal expansion
- Uniform sequencing coverage
- No allelic drop-out
- Repair machinery may differ from primary cells

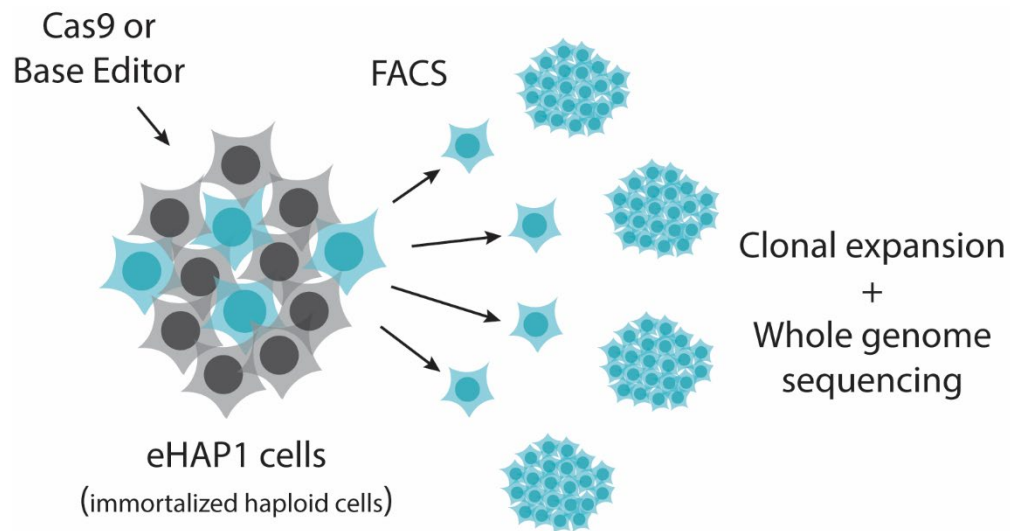
Whole genome amplification (WGA)



Only option for primary cells (so far)

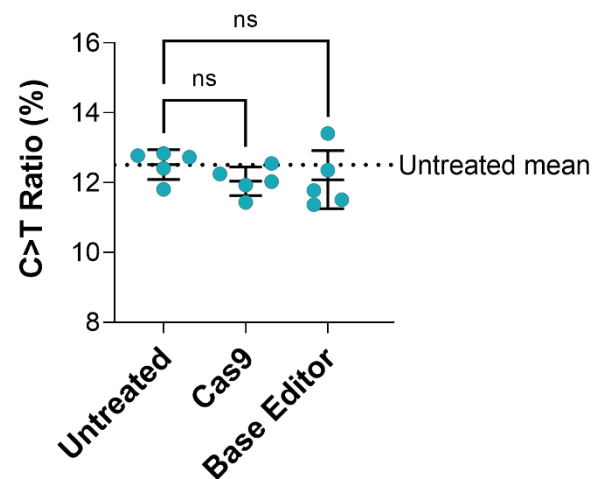
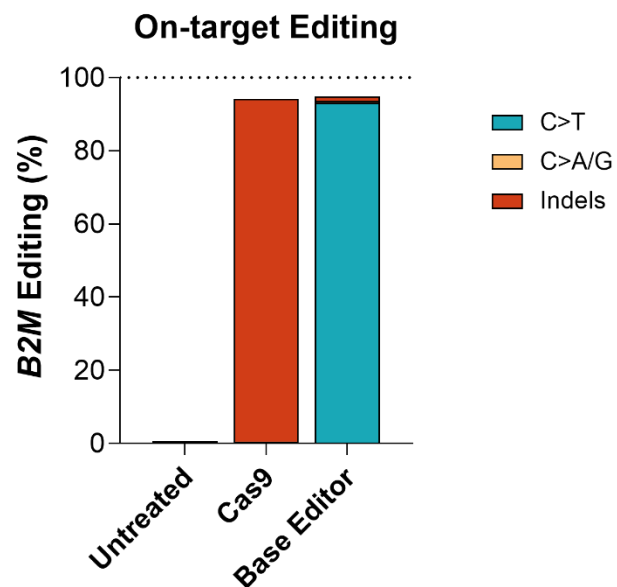
- Single cell lysis can introduce C>T artifacts
- Hexamers can lead to amplification bias
- Alleles can drop-out
- Clinically relevant cell type

Intellia's Base Editor Does Not Lead to Increased C>T Levels in eHAP1 Cells

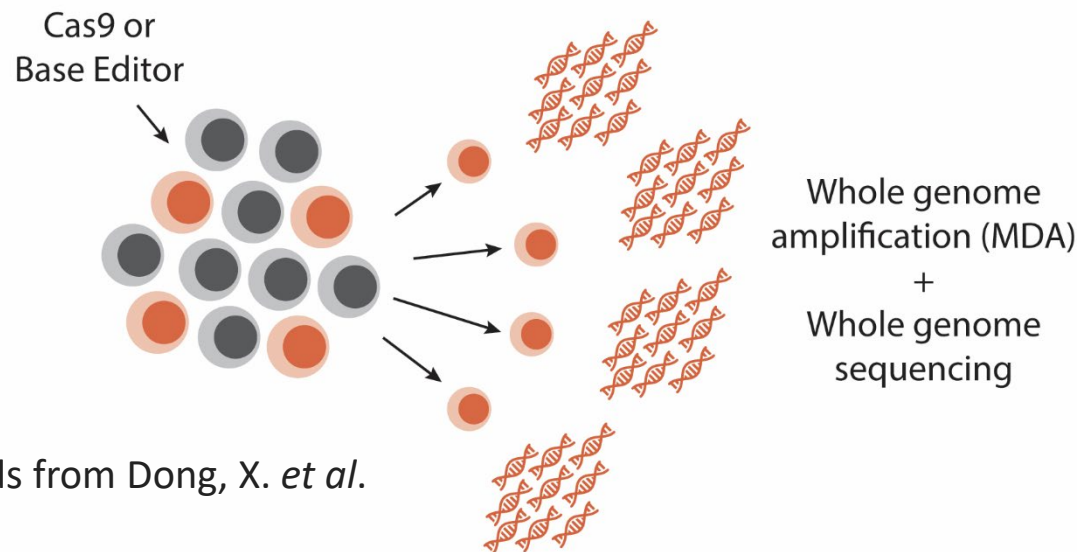


	Untreated					Cas9					Base Editor			
A		10.6	6.2	4.2			11.3	6.1	4.7			10.6	6.0	4.8
G	12.4		12.2	4.8		12.3		11.0	5.1		12.4		11.3	4.9
T	6.5	4.2		10.4		6.2	4.5		10.9		6.3	4.7		10.9
C	11.8	4.1	12.5			11.2	4.5	12.0			11.6	4.4	12.1	
	A	G	T	C		A	G	T	C		A	G	T	C

Alternate base (%)



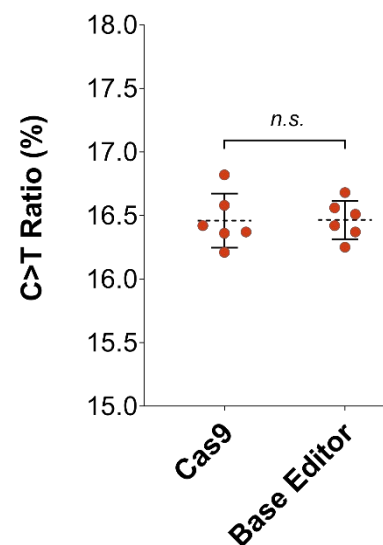
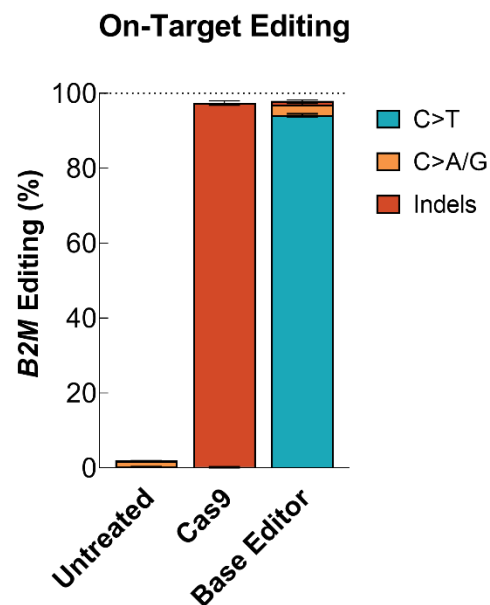
Intellia's Base Editor Does Not Lead to Increased C>T Levels in T Cells



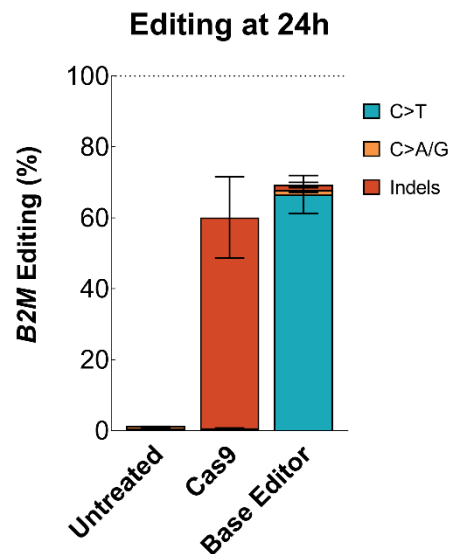
Methods from Dong, X. *et al.*

Dong, X. *et al.* Accurate identification of single-nucleotide variants in whole-genome-amplified single cells. *Nat Methods* 14, 491–493 (2017).

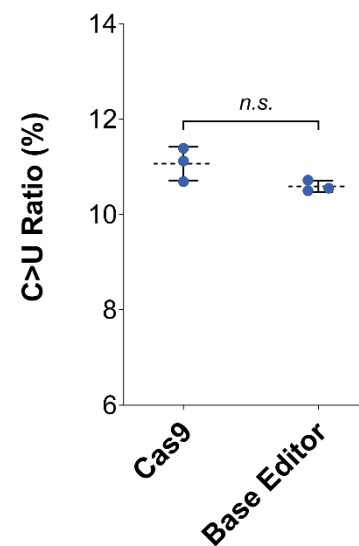
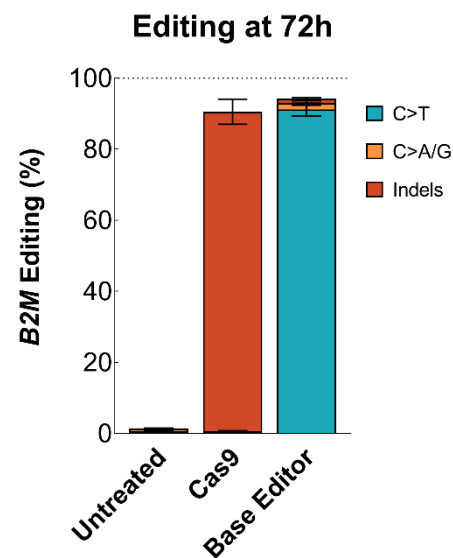
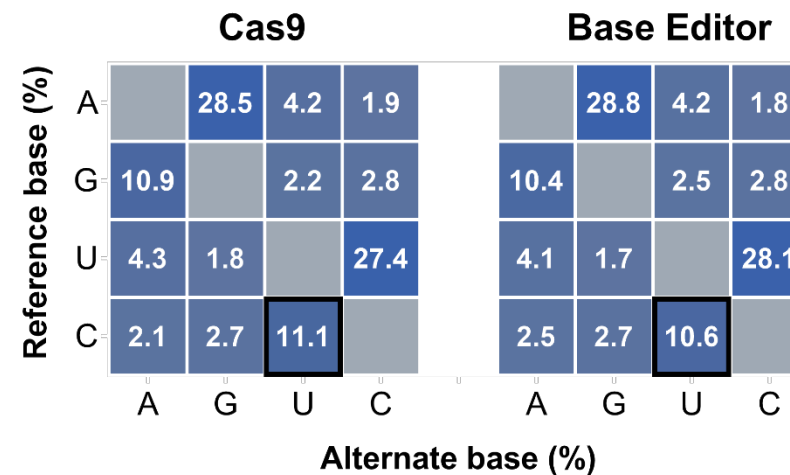
	Cas9					Base Editor			
Reference base (%)	A	G	T	C		A	G	T	C
A		17.2	4.0	4.0			17.1	4.0	4.0
G	16.4		4.2	4.2		16.4		4.2	4.2
T	4.0	4.0		17.2		4.0	4.0		17.2
C	4.2	4.2	16.5			4.2	4.2	16.5	
	A	G	T	C		A	G	T	C
	Alternate base (%)								



Intellia's Base Editor Does Not Lead to Increased C>U Levels in T Cell RNA



RNA-Seq



Key Takeaways

- Intellia has developed a base editor that is equipotent to Cas9 for T cell editing
- Use of Intellia's base editor with its proprietary cell engineering process can knockout several genes simultaneously with >90% efficiency while maintaining translocations at background levels
- The measurable off-target profiles of our base editor and Cas9 cleavase systems are currently comparable
- In T cells, our base editor does not lead to a global increase in C-to-T transition in the genome or C-to-U in the transcriptome
- To fully characterize off-targets unique to the base editing category, assessment should include deeper sequencing methods that are still evolving for the field
- In conclusion, Intellia has developed a base editing approach that has a favorable off-target profile and is compatible with our proprietary T cell engineering process

IT TAKES A VILLAGE



Intellia

THERAPEUTICS