Intellia is Leading the Genome Editing Revolution

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

Intellia THERAPEUTICS

Corporate Overview

MAY 2022

Intellia Therapeutics' Legal Disclaimer

This presentation contains "forward-looking statements" of Intellia Therapeutics, Inc. ("Intellia", "we" or "our") within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements include, but are not limited to, express or implied statements regarding Intellia's beliefs and expectations regarding: the safety, efficacy and advancement of our clinical programs for NTLA-2001 for the treatment of transthyretin amyloidosis, NTLA-2002 for the treatment of hereditary angioedema, and NTLA-5001 for the treatment of acute myeloid leukemia pursuant to its clinical trial applications ("CTA") and IND submissions, including the expected timing of data releases, regulatory filings, and the initiation and completion of clinical trials; the advancement of development candidates including NTLA-3001 for the treatment of alpha-1 antitrypsin deficiency (AATD)-associated lung disease, NTLA-2003 for AATD-associated liver disease, and NTLA-6001 for CD30+ lymphomas; the ability to generate data to initiate clinical trials and the timing of CTA and IND submissions; the expansion of its CRISPR/Cas9 technology and related technologies, including manufacturing and delivery technologies, to advance additional development candidates; the ability to maintain and expand our related intellectual property portfolio, and avoid or acquire rights to valid intellectual property of third parties; the ability to demonstrate our platform's modularity and replicate or apply results achieved in preclinical studies, including those in our NTLA-2001, NTLA-5001, and NTLA-2002 programs, in any future studies, including human clinical trials; its expectations of Rewrite Therapeutics, Inc.'s ("Rewrite") DNA writing to advance additional novel platform capabilities; the ability to optimize the impact of our collaborations on our development programs, including, but not limited to, our collaboration with Regeneron Pharmaceuticals, Inc. ("Regeneron"), including our co-development programs for hemophilia A and hemophilia B, with AvenCell Therapeutics, Inc. ("AvenCell") for the development of universal CAR-T cell therapies, with SparingVision SAS ("SparingVision") for the development of ophthalmic therapies, with Kyverna Therapeutics, Inc. ("Kyverna") for the development of KYV-201, and with ONK Therapeutics Ltd. ("ONK") for the development of engineered NK cell therapies; and the potential timing and receipt of future milestones and royalties, or profits, as applicable, based on our license, collaboration and, if applicable, co-development agreements with Regeneron, Novartis Institutes for Biomedical Research, Avencell, SparingVision, Kyverna, and ONK; the timing of regulatory filings and clinical trial execution, including dosing of patients, regarding our development programs; the potential commercial opportunities, including value and market, for our product candidates; our use of capital and other financial results during 2022; and our ability to fund operations beyond the next 24 months.

Any forward-looking statements in this presentation are based on management's current expectations and beliefs of future events, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: risks related to our ability to protect and maintain our intellectual property position; risks related to valid third party intellectual property; risks related to our relationship with third parties, including our licensors and licensees; risks related to the ability of our licensors to protect and maintain their intellectual property position; uncertainties related to regulatory agencies' evaluation of regulatory filings and other information related to our product candidates; uncertainties related to the authorization, initiation and conduct of studies and other development requirements for our product candidates; risks related to the development and/or commercialization of any of Intellia's or its collaborators' product candidates, including that they may not be successfully developed and commercialized; risks related to the results of preclinical or clinical studies, including that they may not be positive or predictive of future results; risks related to the Rewrite acquisition, including that it may not result in novel platform capabilities; risks related to Intellia's reliance on collaborations, including that its collaborations with Regeneron, AvenCell, SparingVision, Kyverna, ONK or its other collaborations will not continue or will not be successful. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause Intellia's actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in Intellia's most recent Annual Report on Form 10-K as well as discussions of potential risks, uncertainties, and other important factors in Intellia's other filings with the Securities and Exchange Commission ("SEC"). All information in this presentation is as of the date of the release, and Intellia undertakes no duty to update this information unless required by law.

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Intellia is Leading the Genome Editing Revolution

Transforming lives of people with severe diseases by developing curative genome editing treatments

Unsurpassed Genome Editing Pipeline

Leaders of the Field

First company to demonstrate initial safety and efficacy of *in vivo* genome editing in a clinical study

Setting the Standard

Extensive characterization for potent and highly specific editing

Full-Spectrum Strategy

Robust R&D engine to develop *in vivo* and *ex vivo* therapies for diseases with high unmet need

Intellia THERAPEUTICS

World-class Genome Editing Toolbox

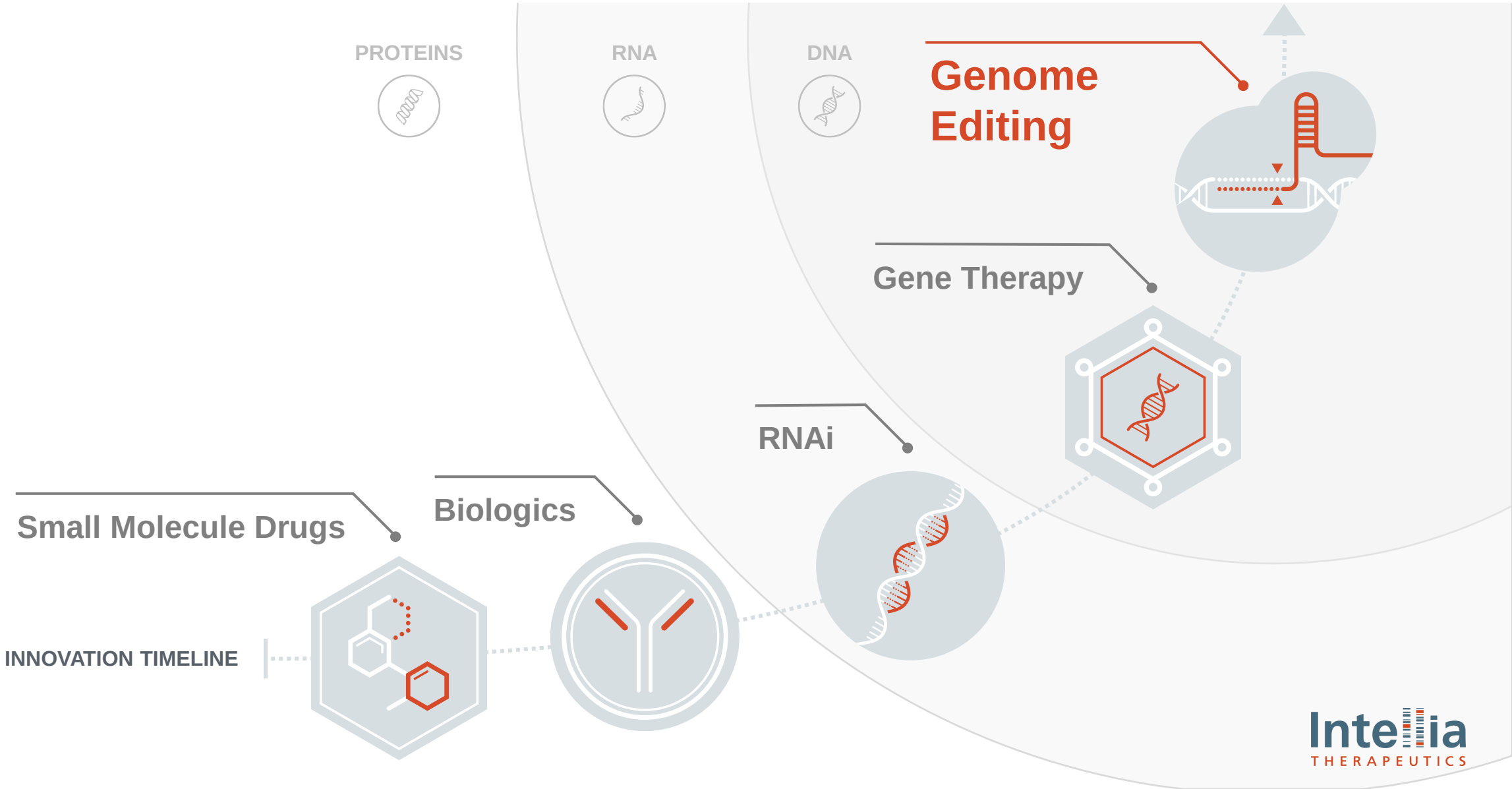
Applying Novel Tools

Building an array of editing tools and delivery modalities for therapeutic application

Modular Solutions

Focused on building differentiated technology with broad applicability that can be applied to future candidates

Therapeutic Strategies to Treat Life-Threatening Diseases Have Advanced Over Time



Power of CRISPR:
Nobel-Prize Winning Genome Editing Technology

Precise and modular approach for editing the genome

Potential for life-long effect following one-time treatment

Locates a genetic sequence to make a permanent change

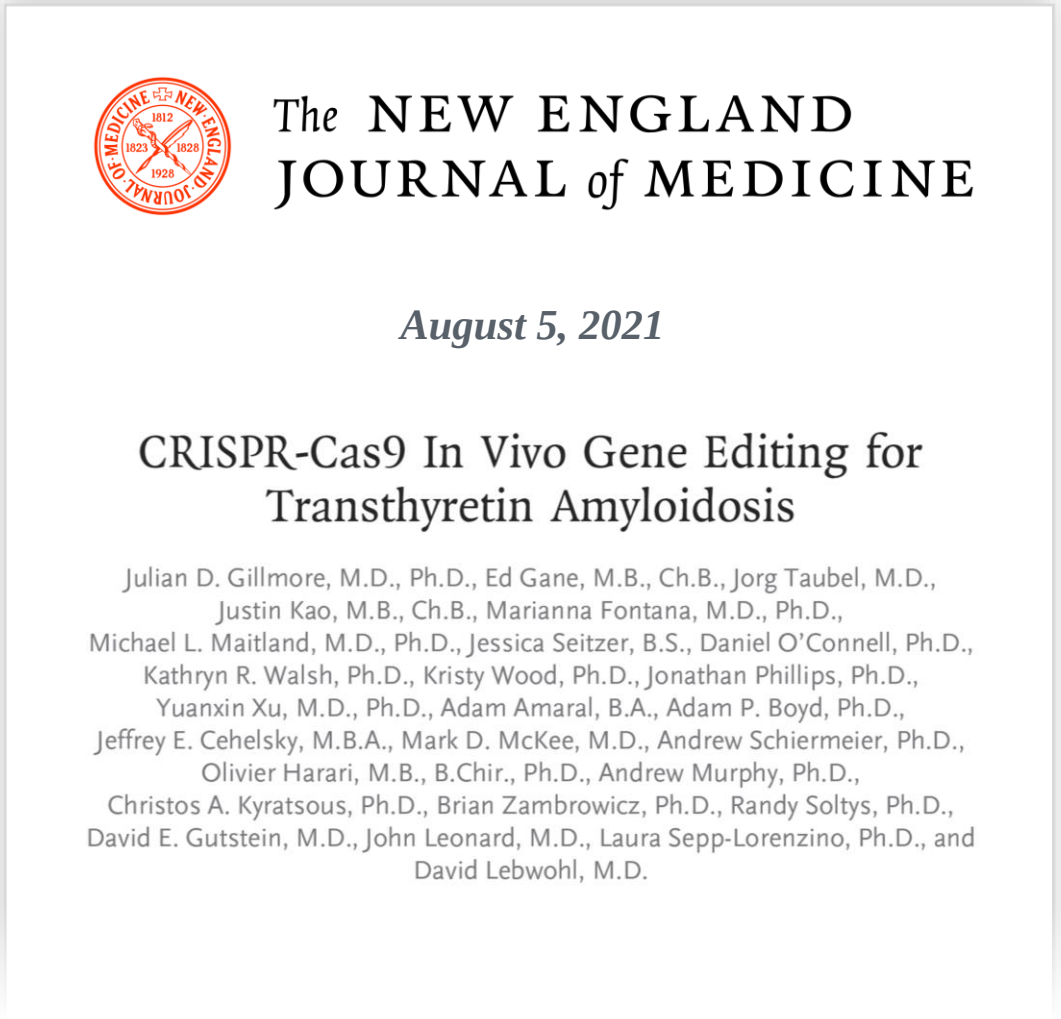
Overcomes key limitations of gene and RNAi therapies

High level of specificity to make one or multiple edits

Provides foundational capabilities for derivative tools

Intellia THERAPEUTICS

In Vivo Leader: First to Demonstrate Systemic CRISPR Gene Editing in Humans



The NEW ENGLAND JOURNAL of MEDICINE

August 5, 2021

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., Ph.D., Adam Amaral, B.A., Adam P. Boyd, Ph.D., Jeffrey E. Cehelsky, M.B.A., Mark D. McKee, M.D., Andrew Schiermeier, Ph.D., Olivier Harari, M.B., B.Chir., Ph.D., Andrew Murphy, Ph.D., Christos A. Kyratsous, Ph.D., Brian Zambrowicz, Ph.D., Randy Soltys, Ph.D., David E. Gutstein, M.D., John Leonard, M.D., Laura Sepp-Lorenzino, Ph.D., and David Lebwohl, M.D.

Science JOURNALS AAAS — *"CRISPR injected into the blood treats a genetic disease for the first time"*

FT FINANCIAL TIMES — *"CRISPR gene-editing 'revolution' treats internal organ for first time"*

USA TODAY — *"'It's a wow': New CRISPR gene-editing success holds promise for treating many genetic diseases with a single dose"*

nature — *"Landmark CRISPR trial shows promise against deadly disease"*

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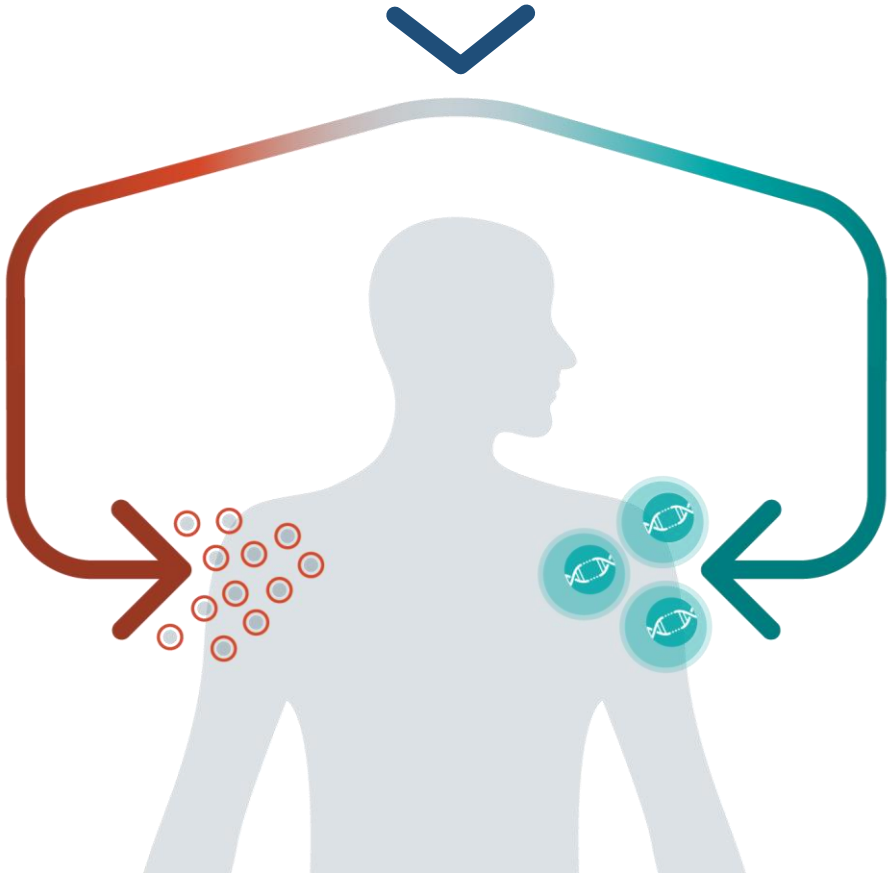
Building a Full-Spectrum Genome Editing Company

CRISPR-based Modular Platform

EMPLOY NOVEL EDITING AND DELIVERY TOOLS



In Vivo

CRISPR *is* the therapy

FIX THE TARGET GENE

Genetic diseases

Ex Vivo

CRISPR *creates* the therapy

REWIRE & REDIRECT CELLS

Immuno-oncology

Autoimmune diseases

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2022 and Beyond: Key Expected Milestones

In Vivo	
NTLA-2001 **ATTR**	○ Report additional interim data from ATTRv-PN arm of Phase 1 study in June 2022 ○ Present interim data from ATTR-CM of Phase 1 study in 2H 2022 ○ Complete enrollment of Phase 1 study for both ATTRv-PN and ATTR-CM subjects in 2022
NTLA-2002 **HAE**	○ Present interim data from Phase 1/2 study in 2H 2022
NTLA-3001 **AATD**	○ Plan to file an IND or IND-equivalent in 2023
Ex Vivo	
NTLA-5001 **AML**	○ Continue to enroll patients in Phase 1/2a study in 2022
Platform Innovation	
Research and Platform Advancements	✓ Nominated NTLA-6001, an allo-CAR-T cell therapy for CD30+ lymphomas ✓ Nominated NTLA-2003, an *in vivo* knockout candidate for AATD-associated liver disease ○ Advance at least one additional *in vivo* development candidate by end of 2022 ○ Advance additional novel platform capabilities in 2022[1]

[1] Intellia acquired Rewrite Therapeutics in February 2022

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In Vivo Development Pipeline Fueled by Robust Research Engine

PROGRAM	APPROACH	Research	IND-Enabling	Early-Stage Clinical	Late-Stage Clinical	PARTNER
***In Vivo:* CRISPR is the therapy**						
NTLA-2001: Transthyretin Amyloidosis	Knockout					LEAD Intellia* THERAPEUTICS REGENERON
NTLA-2002: Hereditary Angioedema	Knockout					Intellia THERAPEUTICS
NTLA-2003: AATD-Liver Disease	Knockout					Intellia THERAPEUTICS
NTLA-3001: AATD-Lung Disease	Insertion					Intellia THERAPEUTICS
Hemophilia B	Insertion					Intellia THERAPEUTICS LEAD REGENERON*
Hemophilia A	Insertion					Intellia THERAPEUTICS LEAD REGENERON*
Research Programs	Knockout, Insertion, Consecutive Edits					Intellia THERAPEUTICS
Research Programs	Various					Intellia THERAPEUTICS REGENERON** SPARINGVISION

*Lead development and commercial party **Rights to certain *in vivo* targets

AATD: Alpha-1 Antitrypsin Deficiency

Intellia THERAPEUTICS

Ex Vivo Development Pipeline Fueled by Robust Research Engine

PROGRAM	APPROACH	Research	IND-Enabling	Early-Stage Clinical	Late-Stage Clinical	PARTNER
***Ex Vivo:* CRISPR creates the therapy**						
OTQ923 / HIX763: Sickle Cell Disease	HSC					Intellia*** THERAPEUTICS, NOVARTIS
NTLA-5001: Acute Myeloid Leukemia	WT1-TCR					Intellia THERAPEUTICS
NTLA-6001: CD30+ Lymphomas	Allo CAR-T					Intellia THERAPEUTICS
Solid Tumors	WT1-TCR					Intellia THERAPEUTICS
Allo Undisclosed	Undisclosed					Intellia THERAPEUTICS
Research Programs	Allo Universal CAR-T					Intellia THERAPEUTICS, AVENCELL
Other Novartis Programs	CAR-T, HSC, OSC	Undisclosed				Intellia*** THERAPEUTICS, NOVARTIS

***Milestones & royalties only

CAR-T: Chimeric Antigen Receptor T Cells **HSC:** Hematopoietic Stem Cells **OSC:** Ocular Stem Cells **TCR:** T Cell Receptor

Intellia THERAPEUTICS

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In Vivo

CRISPR is the therapy

GENETIC DISEASES

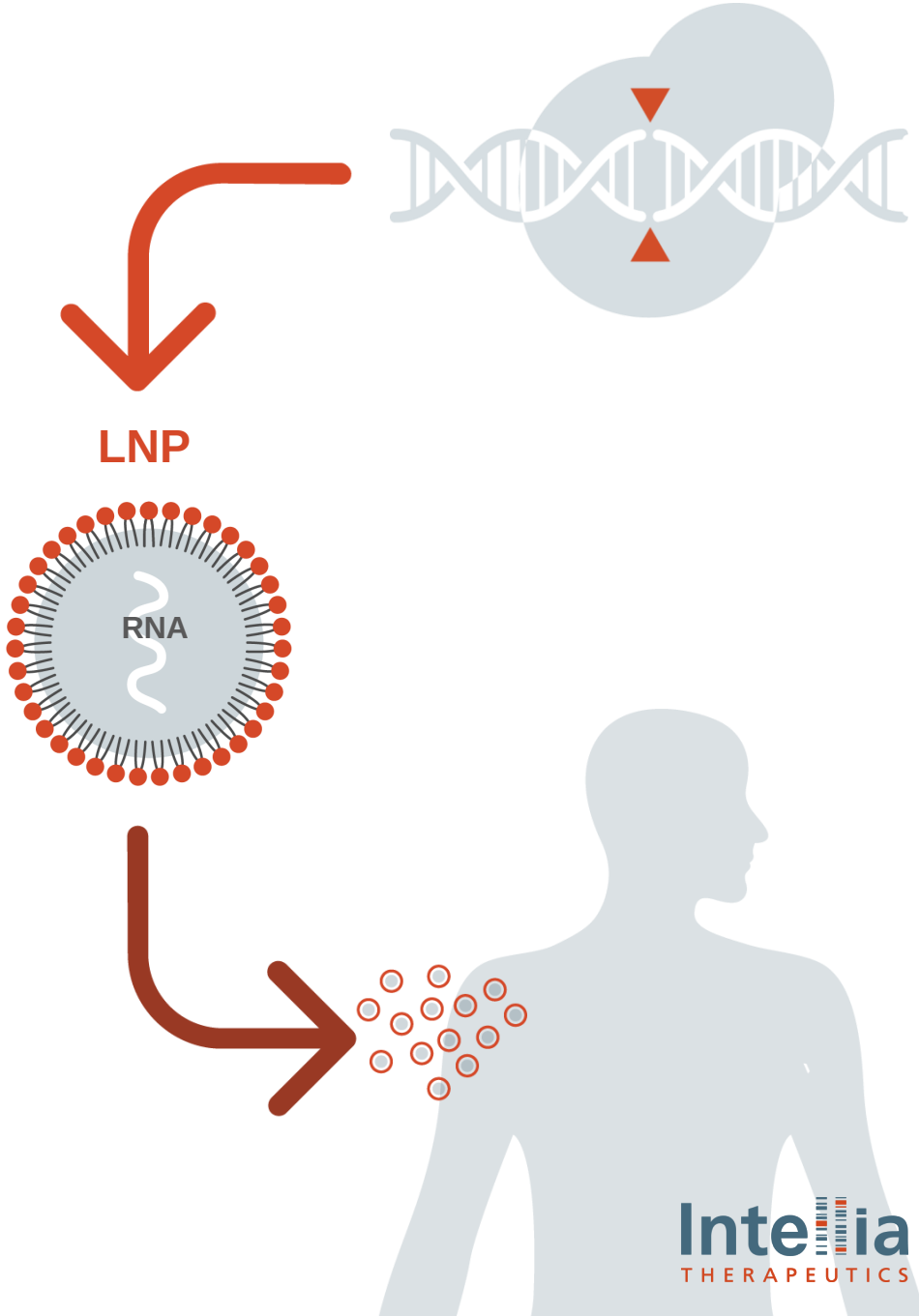
Strategic Advantages:

Potential curative therapy from single dose

Systemic non-viral delivery of CRISPR/Cas9 provides transient expression and potential safety advantages

Permanent gain of function with targeted gene insertion

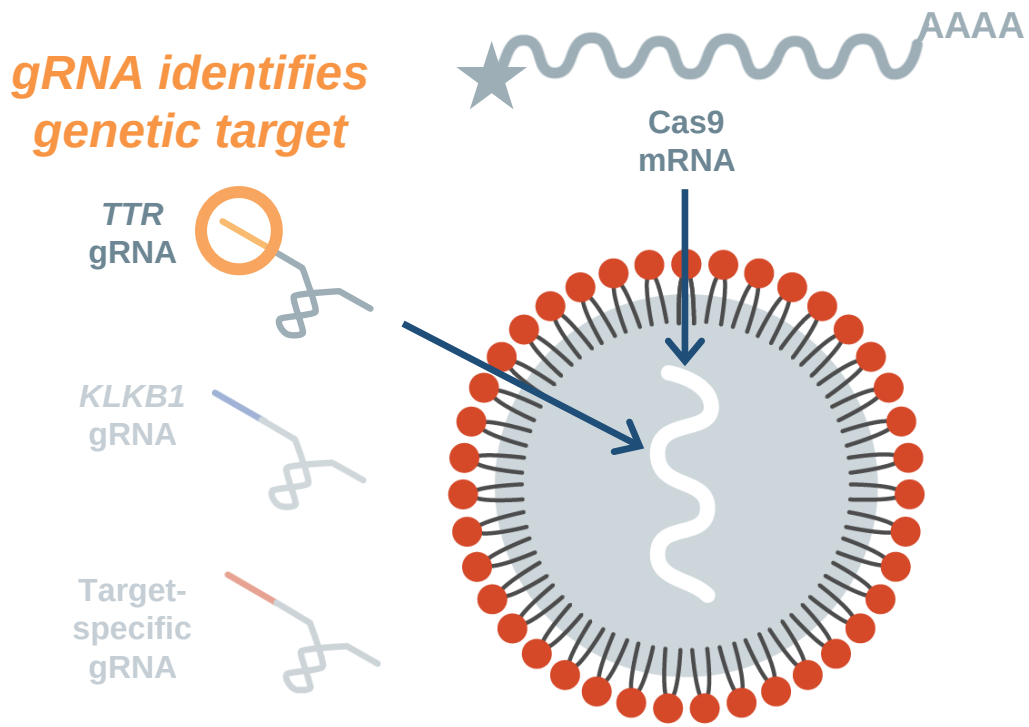
Capable of delivering to multiple tissue types for various therapeutic applications



LNP: Lipid Nanoparticle

Modular Delivery Platform Enables Rapid and Reproducible Path to Clinical Development

LNP Delivery System:



Key Advantages of LNP Delivery

- Clinically-proven delivery to liver
- Large cargo capacity
- Transient expression
- Biodegradable
- Low immunogenicity
- Well-tolerated
- Redosing capability
- Scalable synthetic manufacturing
- Tunable to other tissues

gRNA: Guide RNA

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NTLA-2001 for Transthyretin (ATTR) Amyloidosis

- Caused by accumulation of misfolded transthyretin (TTR) protein, which affects nerves, heart, kidneys and eyes
- Chronic dosing is required with current treatments

50K

ATTRv patients worldwide[1]

~200-500K

ATTRwt patients worldwide[2]

OUR APPROACH

Knock out *TTR* gene with a single dose

- Reduce wild-type and mutant TTR protein
- Aims to address polyneuropathy and cardiomyopathy

KEY ADVANTAGES

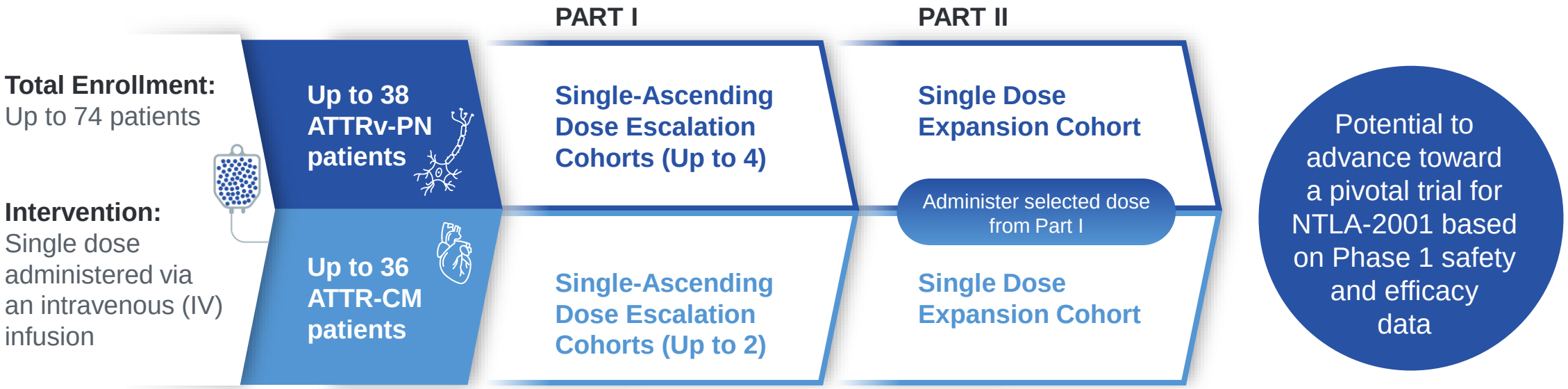
- Potential to halt and reverse disease
- Potential “one-and-done” treatment
- Expect lifelong, stable TTR reduction

[1]*Ann Med*. 2015; 47(8): 625–638. [2] Compiled from various sources **ATTRv**: Hereditary ATTR **ATTRwt**: Wild-Type ATTR

REGENERON Intellia THERAPEUTICS

NTLA-2001 Expanded Phase 1 Study

Two-part, open-label, multi-center study in adults with hereditary ATTR with polyneuropathy (ATTRv-PN) or ATTR amyloidosis with cardiomyopathy (ATTR-CM)



PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of:

- *Neurologic function in subjects with ATTRv-PN*
- *Cardiac disease in subjects with ATTR-CM*

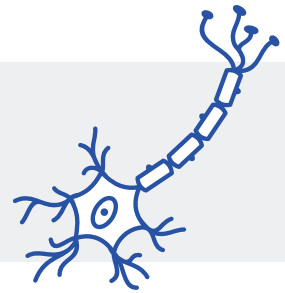
Clinicaltrials.gov ID: NCT04601051

PK: Pharmacokinetics **PD:** Pharmacodynamics

REGENERON Intellia THERAPEUTICS

NTLA-2001 Phase 1 Study: Polyneuropathy Arm

Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN)



Intervention:
Single dose administered via an intravenous (IV) infusion

PART I – DOSING COMPLETE
Single-Ascending Dose

- 1.0 mg/kg (n=6)
- 0.7 mg/kg (n=3)
- 0.3 mg/kg (n=3)
- 0.1 mg/kg (n=3)

PART II – INITIATE IN Q1 2022
Single Dose Expansion Cohort

N = 8 subjects
Administer 80 mg fixed dose

PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of neurologic function

- *Neuropathic impairment endpoints include NIS (Part 1 and 2) and mNIS+7 (Part 2 only)*

Clinicaltrials.gov ID: NCT04601051

NIS: Neuropathy Impairment Score **mNIS+7:** modified NIS+7 **PK:** Pharmacokinetics **PD:** Pharmacodynamics

REGENERON Intellia THERAPEUTICS

NTLA-2001 Phase 1 Study: Cardiomyopathy Arm

Hereditary transthyretin amyloidosis with cardiomyopathy (ATTRv-CM) or wild-type cardiomyopathy (ATTRwt-CM), NYHA Class I - III

Intervention:
Single dose administered via an intravenous (IV) infusion

PART I
Single-Ascending Dose

- 1.0 mg/kg
- 0.7 mg/kg

PART II
Single Dose Expansion Cohort

N = 12 subjects

Administer dose derived from Part I data

PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of cardiac disease

- *Cardiac imaging, biomarkers, cardiopulmonary exercise test, 6MWT*

Clinicaltrials.gov ID: NCT04601051

NYHA: New York Heart Association **PK:** Pharmacokinetics **PD:** Pharmacodynamics **6MWT**: 6 Minute Walk Test

REGENERON Intellia THERAPEUTICS

Interim Clinical Trial Results from Ongoing Phase 1 Study of NTLA-2001 in ATTRv-PN Patients

Data disclosed on February 28, 2022

First-in-human evidence of deep, consistent, and durable TTR reductions following *in vivo* CRISPR-based gene editing

Single systemic administration of NTLA-2001 resulted in deep reductions in serum TTR

93% mean reduction at 1.0 mg/kg by Day 28

6 out of 6 patients at 1.0 mg/kg achieved >80% reductions in TTR

- **Durable reductions in serum TTR observed over follow-up period**
  - **Consistent with animal data supporting potential lifelong TTR suppression**
- **Generally well tolerated: predominately mild adverse events**
- **A fixed dose of 80 mg has been selected for evaluation in Part II pending regulatory feedback**

These data further support and extend early findings from this pioneering trial demonstrating the promise of CRISPR-based *in vivo* gene editing in humans

Data disclosed on February 28, 2022
This slide includes data for investigational products not yet approved by regulatory authorities

REGENERON Intellia THERAPEUTICS

NTLA-2001 was generally well tolerated across all dose levels

- **Across all dose levels, the most frequent adverse events* were headache, infusion-related reactions, back pain, rash†, and nausea**
  - Majority of adverse events were mild in severity with 73% (n=11) of patients reporting a maximal adverse event severity of Grade 1
  - All patients received a complete study dose of NTLA-2001
  - All infusion-related reactions were considered mild, resolving without clinical sequelae
- **A single related Grade 3 event (SAE) of vomiting was reported at the 1.0 mg/kg dose in a patient with underlying gastroparesis**
  - 1.0 mg/kg dose level expanded per protocol to 6 patients to further characterize safety and PD
- **No clinically significant laboratory findings observed**
  - Transient Grade 1 liver enzyme elevations observed
- **Maximally tolerated dose was not reached**

Median follow-up for all subjects is 6 months
* Related and unrelated events in more than 2 patients
† Date of onset D6–D145; all mild in severity
PD, pharmacodynamics; SAE, serious adverse event
Data disclosed on February 28, 2022
This slide includes data for investigational products not yet approved by regulatory authorities

REGENERON Intellia THERAPEUTICS

Majority of adverse events were mild in severity

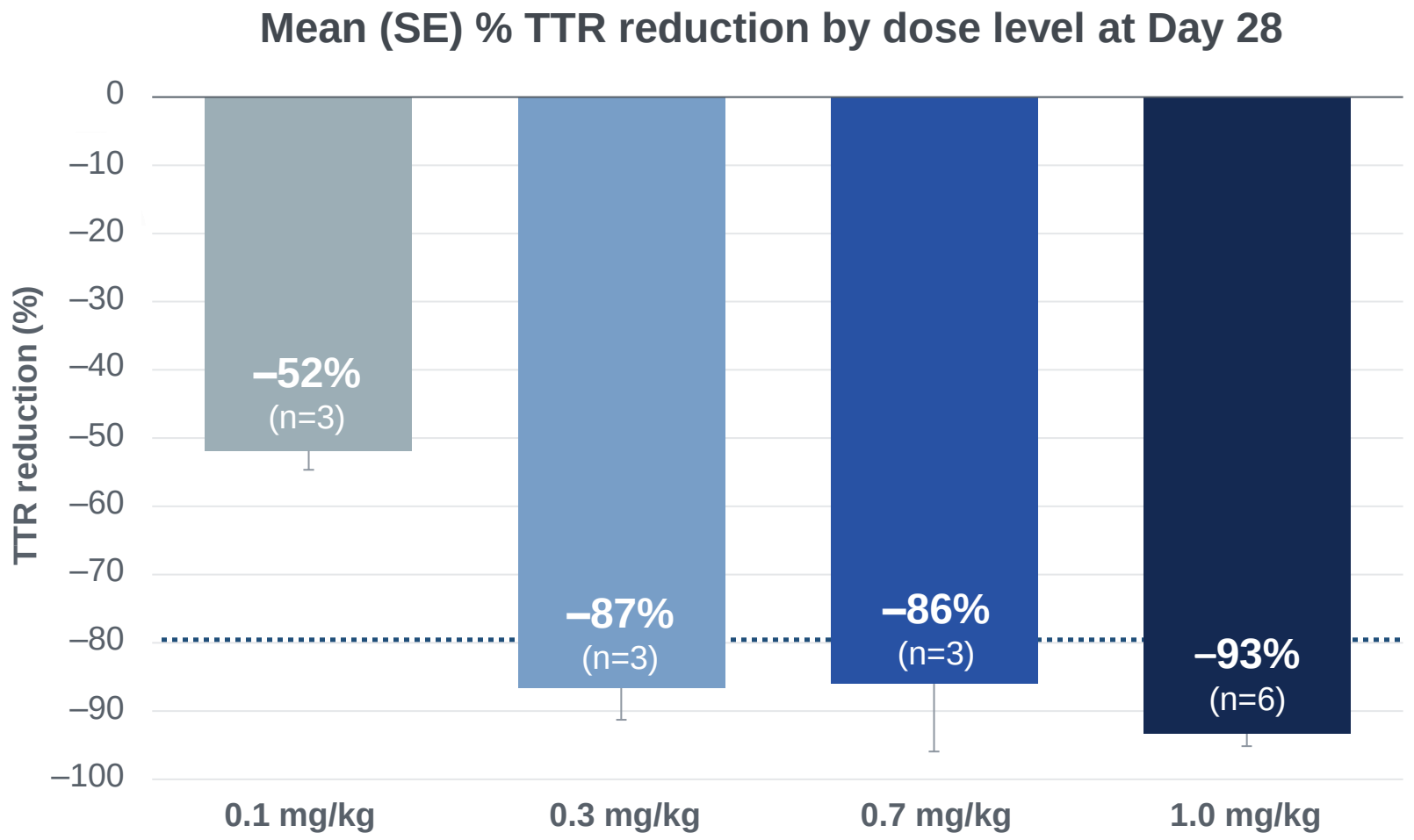
	0.1 mg/kg n=3			0.3 mg/kg n=3			0.7 mg/kg n=3			1 mg/kg n=6			All n=15		
Parameter	**Gr. 1**	**Gr. 2**	**Gr. 3**	**Gr. 1**	**Gr. 2**	**Gr. 3**	**Gr. 1**	**Gr. 2**	**Gr. 3**	**Gr. 1**	**Gr. 2**	**Gr. 3**	**Gr. 1**	**Gr. 2**	**Gr. 3**
Patients with at least one TEAE	3	–	–	3	–	–	2	–	1*	3	2	1†	11	2	2
Headache	2	–	–	–	–	–	2	–	–	3	–	–	7	–	–
Infusion-related reaction	1	–	–	–	–	–	2	–	–	4	–	–	7	–	–
Back pain	1	–	–	–	–	–	2	1	–	1	–	–	4	1	–
Rash	1	–	–	–	–	–	–	–	–	3	–	–	4	–	–
Nausea	1	–	–	–	–	–	1	–	–	1	–	–	3	–	–

Adverse events reported in more than 2 patients
Patients counted once per row, per dose level, as highest grade reported
* Unrelated Grade 3 (SAE) of COVID-19 pneumonia
† Related Grade 3 (SAE) of vomiting in a patient with concomitant medical history of gastroparesis

Gr., Grade; SAE, serious adverse events; TEAE, treatment-emergent adverse event
Data disclosed on February 28, 2022
This slide includes data for investigational products not yet approved by regulatory authorities

REGENERON Intellia THERAPEUTICS

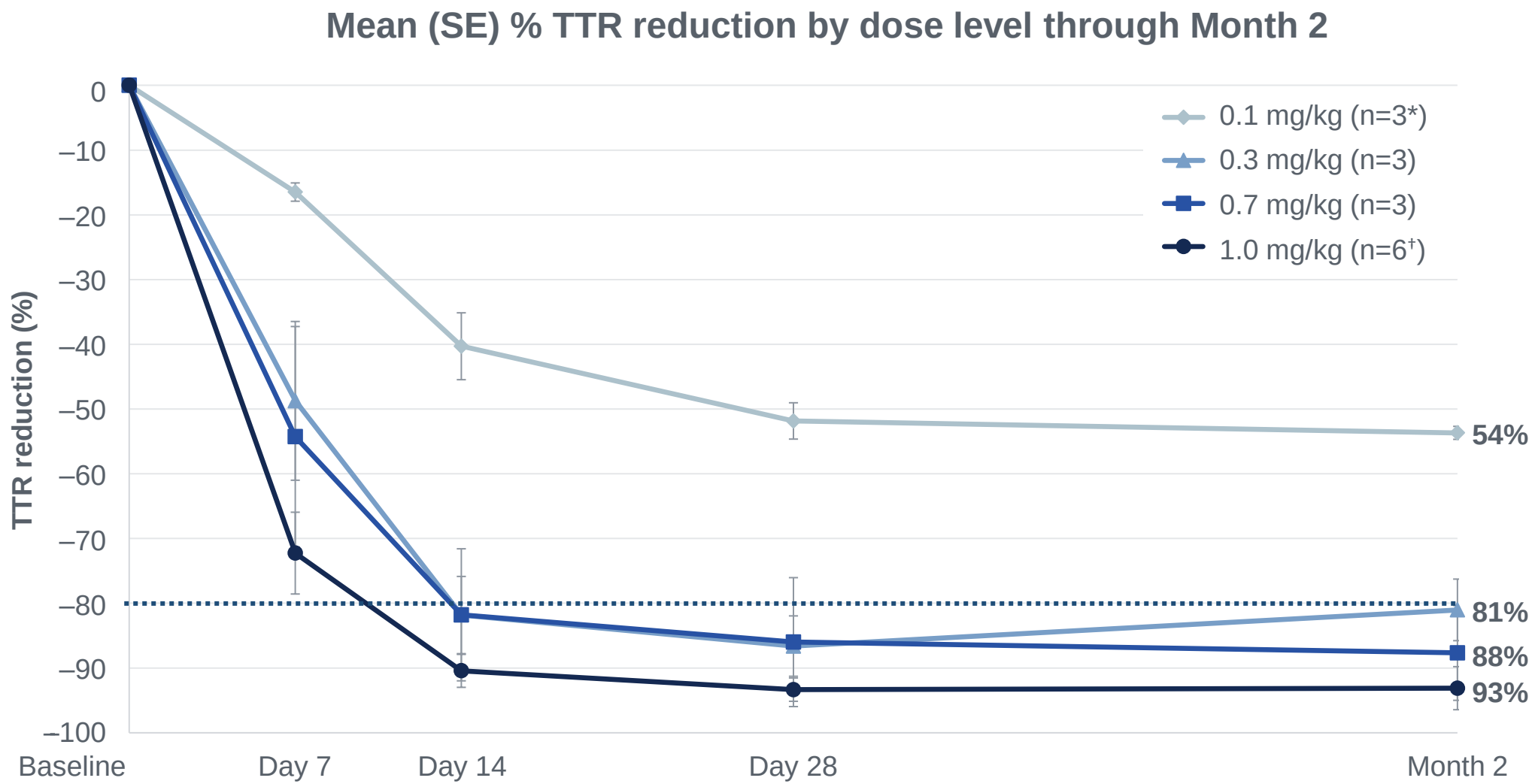
Dose-dependent reductions in serum TTR, reaching a mean reduction of 93% at 1.0 mg/kg



Dashed line represents the targeted minimum reduction
SE, standard error; TTR, transthyretin
Data disclosed on February 28, 2022
This slide includes data for investigational products not yet approved by regulatory authorities

REGENERON Intellia THERAPEUTICS

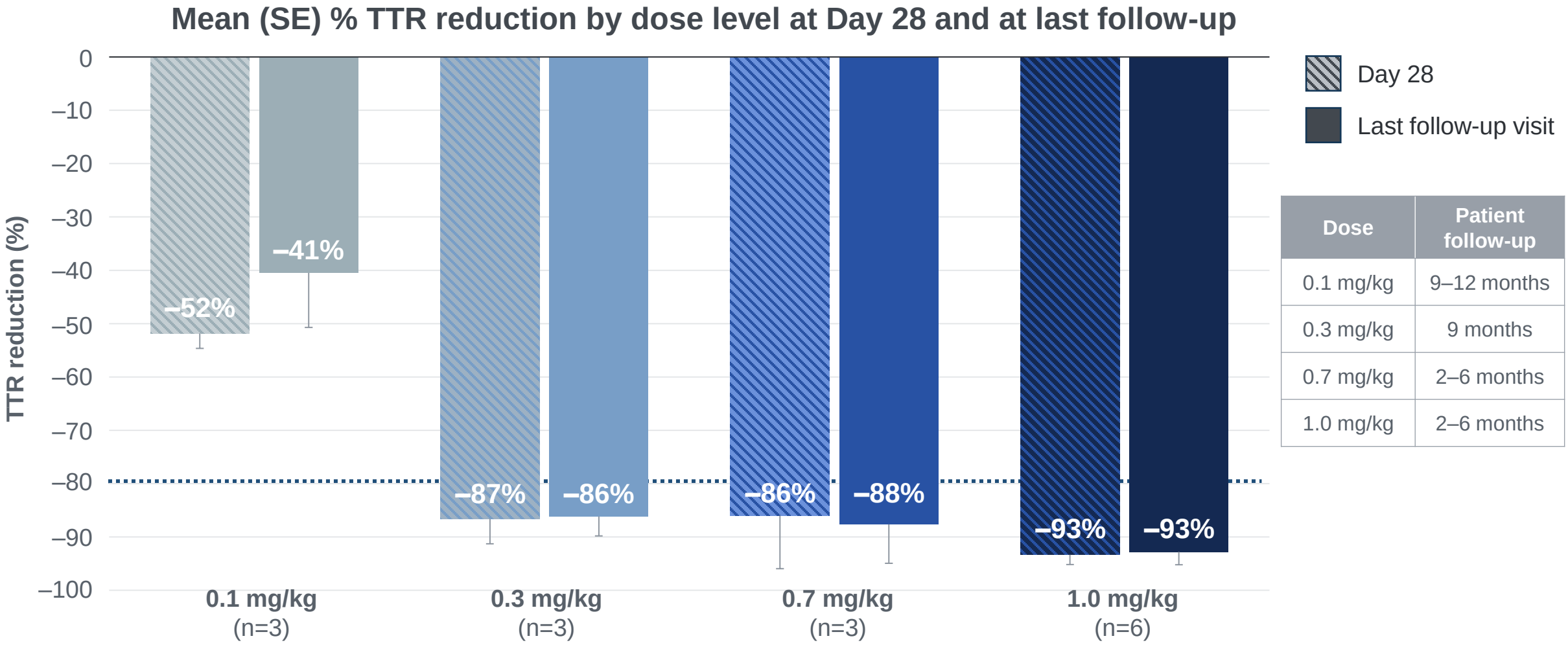
Rapid reductions in serum TTR, achieving nadir by Day 28



* n=2 at Month 2; † n=5 at Month 2
Dashed line represents the targeted minimum reduction
SE, standard error; TTR, transthyretin
Data disclosed on February 28, 2022
This slide includes data for investigational products not yet approved by regulatory authorities

REGENERON Intellia THERAPEUTICS

Durable reductions in serum TTR were observed over the follow-up period



Dose	Patient follow-up
0.1 mg/kg	9–12 months
0.3 mg/kg	9 months
0.7 mg/kg	2–6 months
1.0 mg/kg	2–6 months

Mean % reduction at last follow-up calculated using TTR value from last available follow-up visit for each patient per dose level
Dashed line represents the targeted minimum reduction
SE, standard error; TTR, transthyretin
Data disclosed on February 28, 2022
This slide includes data for investigational products not yet approved by regulatory authorities

REGENERON Intellia THERAPEUTICS

Growing Confidence in NTLA-2001 as Potential Treatment for ATTR Amyloidosis

Key Insights from Ongoing Phase 1 Study	Supported by Interim Data
Generally well-tolerated at all dose levels	✓
Dose-response relationship with deep reductions at higher doses	✓
Consistent reductions in serum TTR across ATTRv-PN patients	✓
Durable response following a single dose	✓

93% mean serum TTR reduction demonstrated at 1.0 mg/kg by Day 28 (n=6)

NTLA-2001 is an investigational product. Safety and efficacy have not been established by any health authority.

REGENERON Intellia THERAPEUTICS

NTLA-2002 for Hereditary Angioedema (HAE)

- Genetic disease characterized by recurring, severe and unpredictable swelling in various parts of the body
- Chronic dosing is required with current treatments

~7-14 days

Average frequency of attacks for untreated patients[1]

~1 in 50,000

HAE patients worldwide[1]

OUR APPROACH

Knock out *KLKB1* gene with a single dose

- Reduce kallikrein activity to prevent attacks

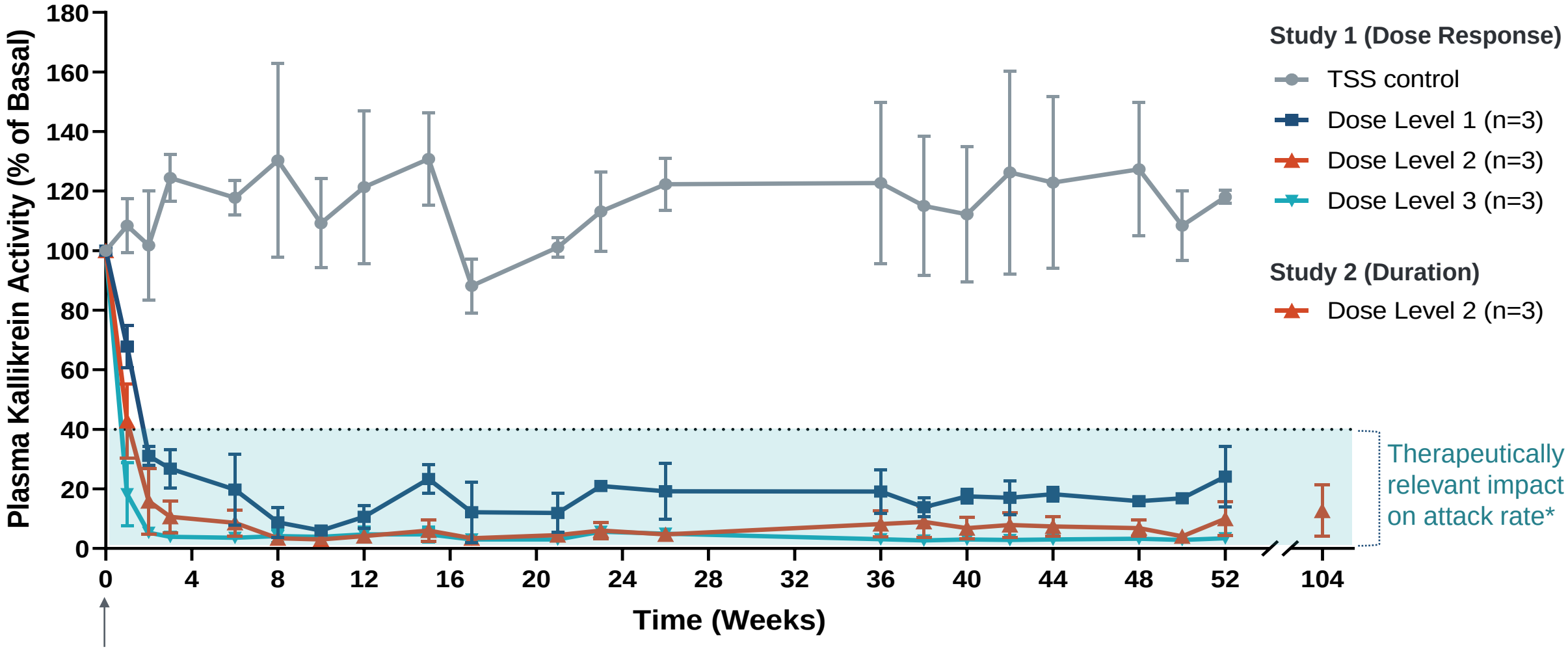
KEY ADVANTAGES

- Potential “one-and-done” treatment
- Expect extensive and continuous reduction in kallikrein activity
  - Intended to minimize the risk of breakthrough attacks
- Potential to eliminate significant treatment burden

[1]Zuraw BL. Hereditary angioedema. *N Engl J Med*. 2008;359:1027-1036

Intellia THERAPEUTICS

Achieved Sustained Therapeutically Relevant Kallikrein Activity Reduction After a Single Dose in NHPs



*Banerji et al., NEJM, 2017

Intellia THERAPEUTICS

NTLA-2002 Phase 1/2 Trial Design

International, multi-center study to assess safety, tolerability, PK, PD and effect of NTLA-2002 on attacks in adults with Type I or Type II HAE

Total Enrollment:

Up to 55 patients, age 18 and older

Intervention:
Single dose administered via an intravenous (IV) infusion

PHASE 1
Open-Label, Single-Ascending Dose

3 dose-escalation cohorts*

PHASE 2
Expansion study to confirm recommended dose

Randomized

- Dose 1 (N=10)
- Dose 2** (N=10)
- Placebo Arm (N=5)

KEY ENDPOINTS

- Evaluate safety and tolerability
- Change in plasma kallikrein protein and activity levels
- Change in attack rates (Phase 2)

Clinicaltrials.gov ID: NCT05120830

PK: Pharmacokinetics **PD:** Pharmacodynamics

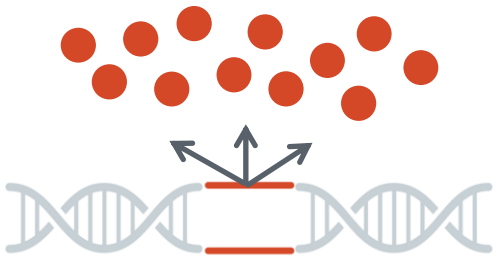
*3 to 6 subjects per cohort; up to 2 additional cohorts, if necessary **Optional cohort

Intellia THERAPEUTICS

Beyond Gene Inactivation, Intellia is Also Advancing Targeted Insertion Programs

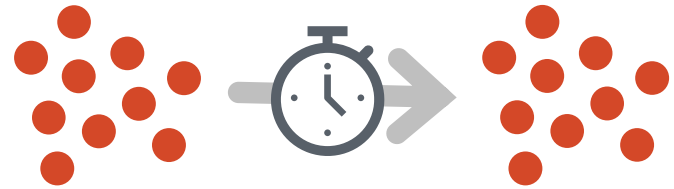
CRISPR-Enabled Targeted Insertion Approach Offers Significant Advantages Over Alternate Gene Therapy Approaches

High Levels of Protein Expression



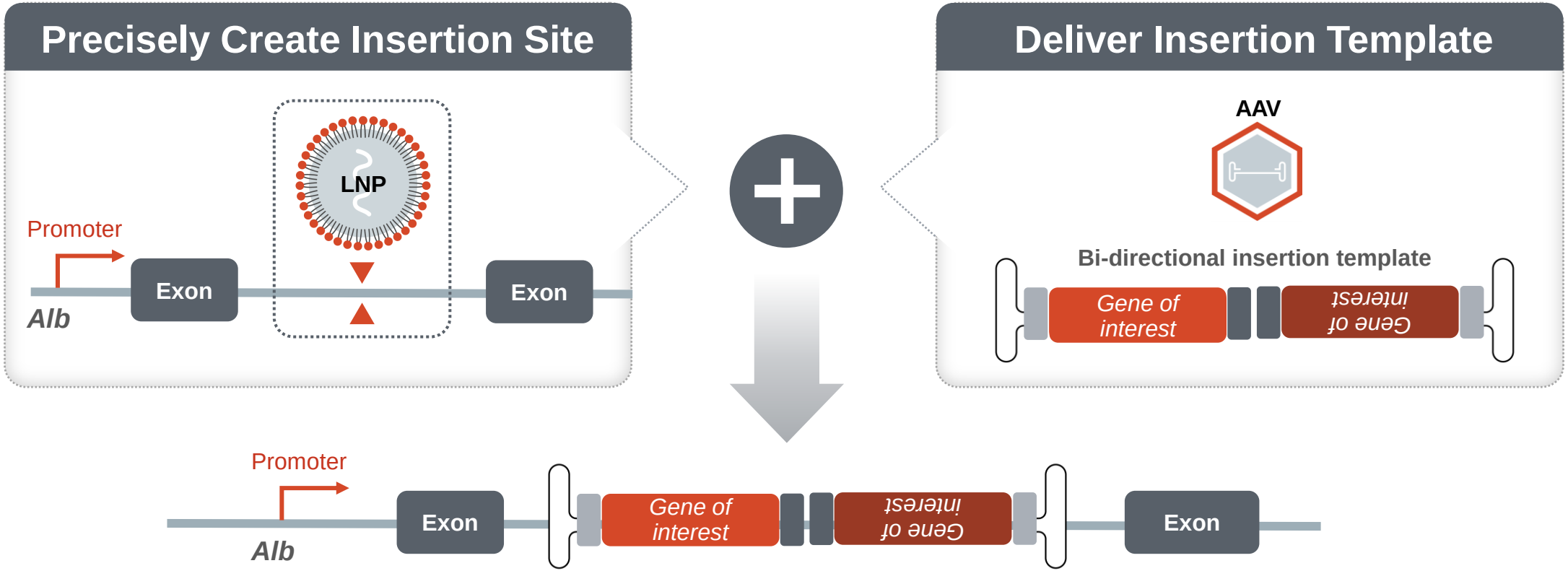
Potential to Revolutionize Gene Replacement

Durable Protein Expression



Intellia THERAPEUTICS

Insertion Technology Enables Production of High Levels of Therapeutic Protein



Targeted, stable gene insertion in the albumin locus

Intellia THERAPEUTICS

NTLA-3001 and NTLA-2003
for Alpha-1 Antitrypsin Deficiency (AATD)

Genetic disorder leading to progressive lung and/or liver disease[1]

AATD patients*

> 60K in the U.S.[2]

~250K globally[3]

OUR APPROACH

NTLA-3001: Targeted insertion of a functional *SERPINA1* gene

- Continuous expression of functional A1AT protein at normal levels
- Address AATD-associated lung disease

NTLA-2003: Knockout mutant *SERPINA1* gene

- Reduce and prevent accumulation of mutant A1AT protein
- Address AATD-associated liver disease

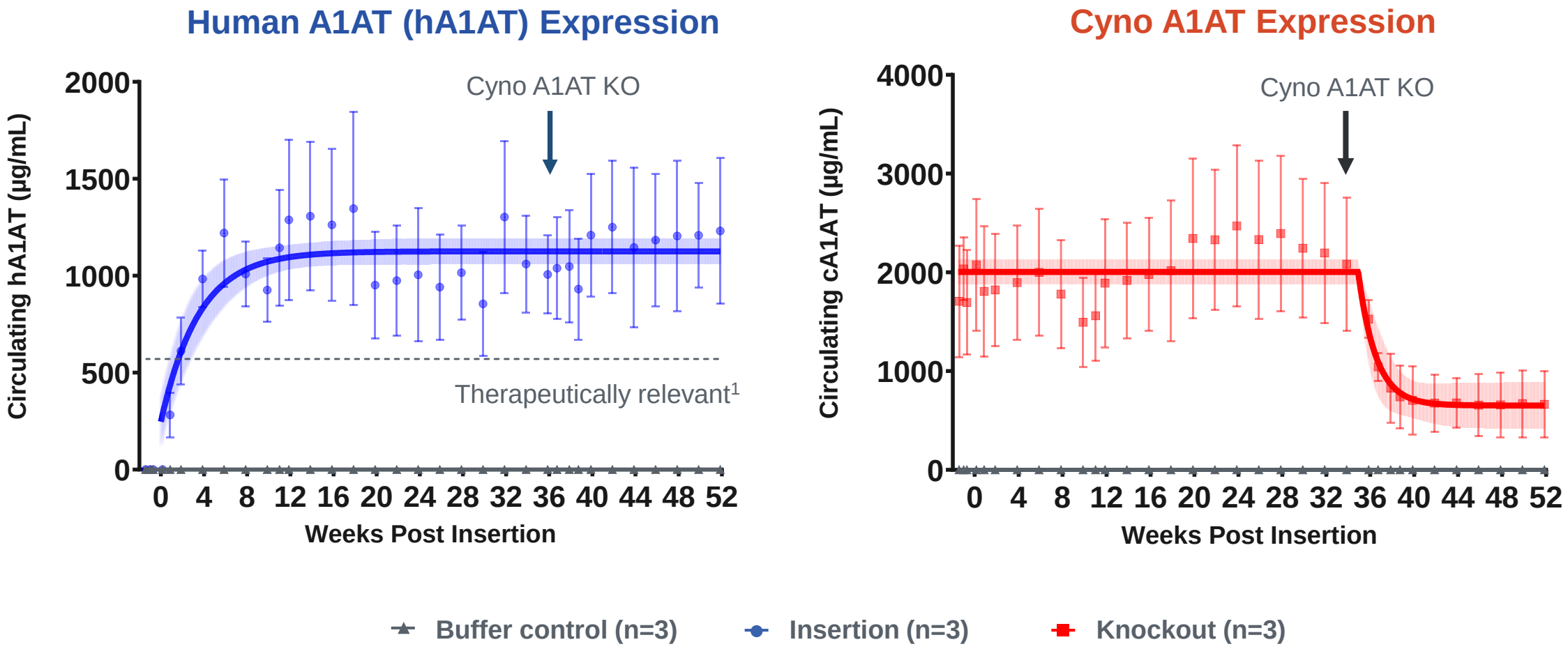
KEY ADVANTAGES

- Each candidate is designed as a single-dose treatment
- **NTLA-3001**: Aims to achieve normal human levels of A1AT protein and halt progression of lung disease
- **NTLA-2003**: Aims to halt the progression of liver disease and eliminate the need for liver transplant in severe cases

[1]https://www.genome.gov/Genetic-Disorders/Alpha-1-Antitrypsin-Deficiency
[2]Brantly M. *Clin Chem*. 2006; 52:2180-2181
[3]Blanco et al. *Int J Chron Obstruct Pulmon Dis*. 2017; 12:561-569
*In severe AATD patients defined as individuals with Pi*ZZ genotype

Intellia THERAPEUTICS

Durable Production of Physiologic Levels of hA1AT and Removal of Mutant Gene Maintained Through One Year in NHP



[1]Stoller & Aboussouan The Lancet, 2005

Intellia THERAPEUTICS

Clinical Validation of LNP Delivery Platform Supports *In Vivo* Pipeline Acceleration

Address diseases with genetically defined targets in the liver

- ☑ Remove a toxic protein via knockout
- ❑ Restore a functional protein via insertion

ATTR, HAE, AATD, Hem B
Hem A, PH, Undisclosed Indications

Enable access to treat diseases across multiple tissue types

Bone Marrow, CNS, Other Tissues

CNS: Central Nervous System **Hem A and B**: Hemophilia A and B **PH:** Primary Hyperoxaluria

Intellia THERAPEUTICS

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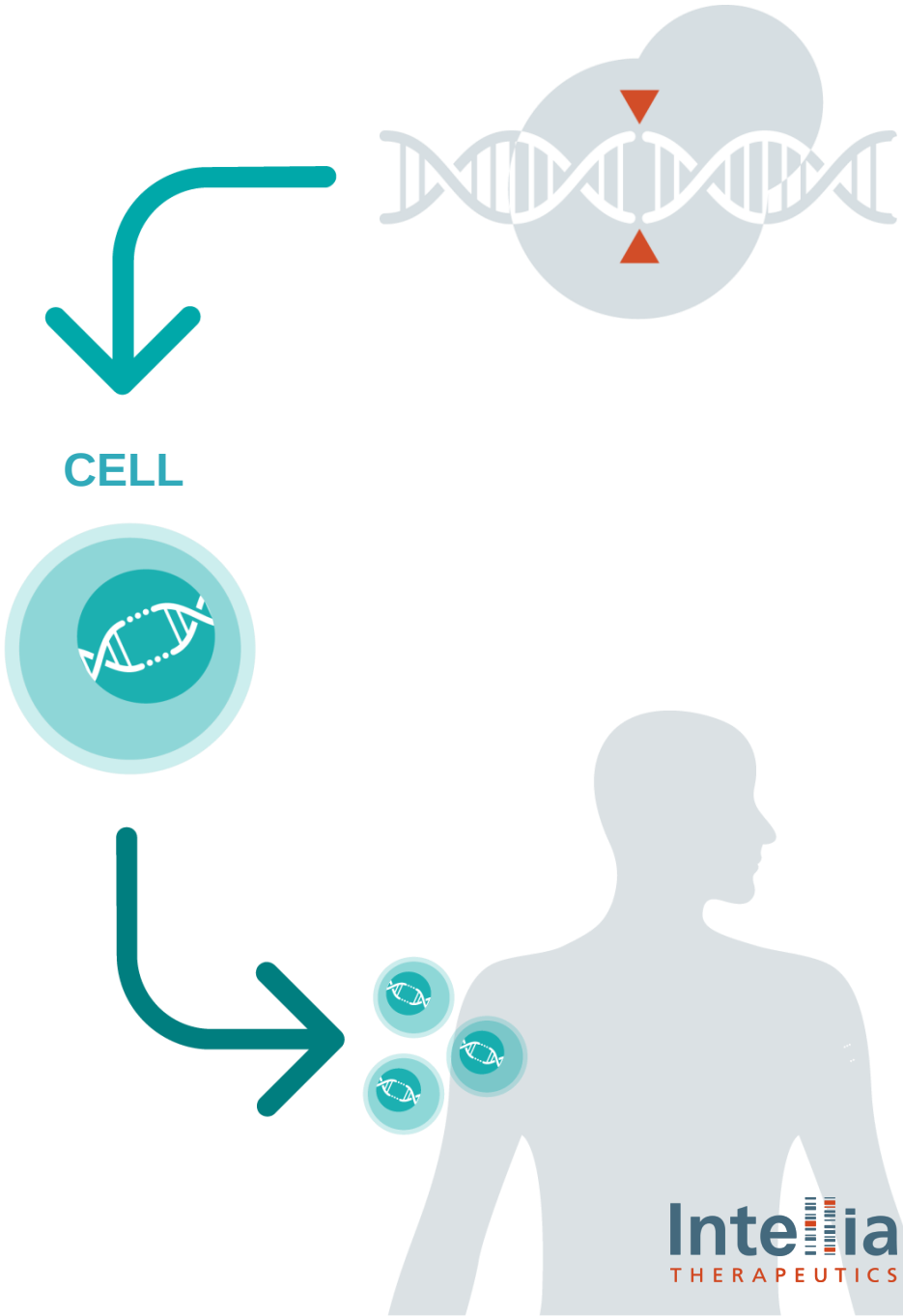
Ex Vivo

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

Focused on reproducing natural cell physiology for potential improvements to safety and efficacy in immuno-oncology

Proprietary Engineering Platform to Power Next-Generation Engineered Cell Therapies

LNP-BASED CELL ENGINEERING PLATFORM

Highly efficient sequential editing | Optimal cell performance | Scalable manufacturing process

ENABLES VERSATILE SOLUTIONS BY "MIXING AND MATCHING" INCLUDING:

Cell Type

HSCs, T cells

NK cells, Macrophages

Targeting Modality

TCRs

CAR-Ts, Universal CARs

Rewiring Instructions

Immune-enhancing edits

Novel targets

NK: Natural Killer **TCR:** T Cell Receptor

Intellia THERAPEUTICS

Differentiated Approach to Cell Therapy Genome Engineering

		Intellia THERAPEUTICS	Other Approaches	
Gene Editing Approach	Delivery	**Lipid Nanoparticle**	Electroporation	Electroporation
	Editing Mode	**Sequential**	Simultaneous	Simultaneous
	Knockout (KO)	**Cleavase or Base Editor**	Cleavase	Base Editor
	Insertion	**CRISPR insertion**	Lenti/Retroviruses	Lenti/Retroviruses
Key Questions From Preclinical Data	Minimize random DSB?	✓	✗	✗
	Minimize random insertion?	✓	✗	✗
	Minimize genotoxicity risk?	✓	✗	✗

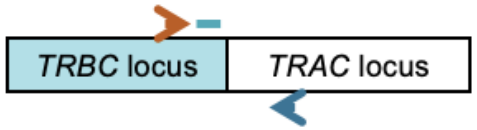
Intellia THERAPEUTICS **LNP-based, sequential process** + **Precise CRISPR KOs & insertion(s)** = **Quality cell product**

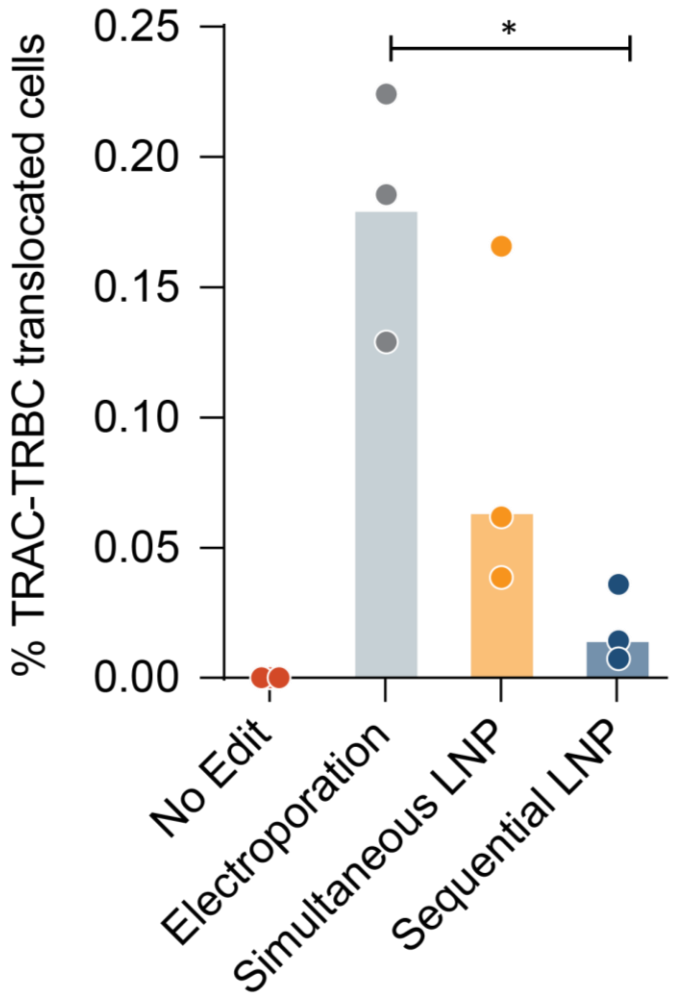
Slide based on preclinical data disclosed by Intellia. Intellia's cell product to be further explored in additional preclinical and clinical studies.

Intellia THERAPEUTICS

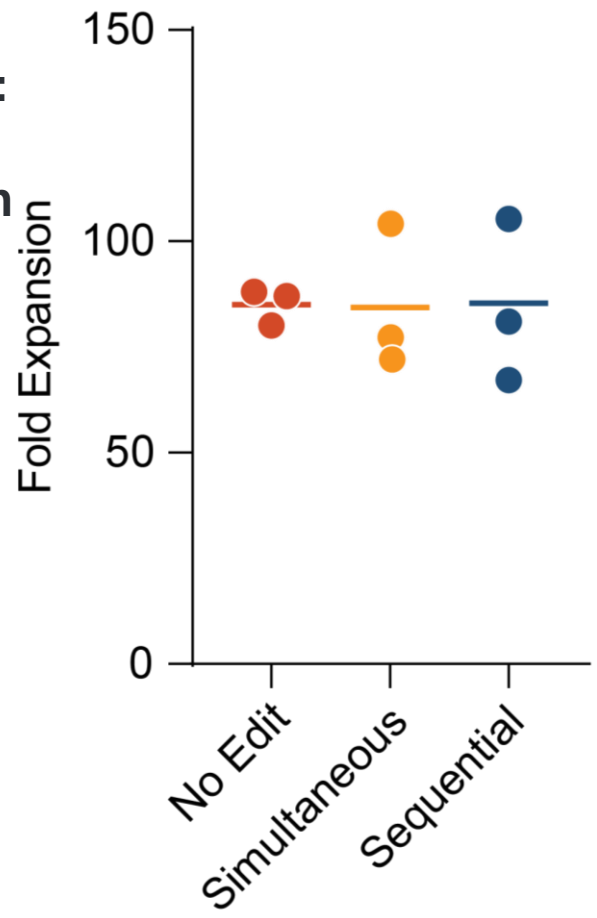
Sequential Editing with LNP Approach Minimizes Translocations While Retaining Robust Cell Viability and Expansion

ddPCR assay to detect *TRAC-TRBC* translocations





LNP Approach: Cell Expansion at D10



Intellia THERAPEUTICS

NTLA-5001 for Acute Myeloid Leukemia (AML)

Most common acute leukemia in adults[1]

~20K

New cases in the U.S. in 2021[1]

> 40K

New cases in the 7 Major Markets in 2020[2]

< 30%

5-year overall survival[1]

OUR APPROACH

Engineer TCR-T cells directed against Wilms' Tumor Type 1 (WT1) to specifically kill AML blasts

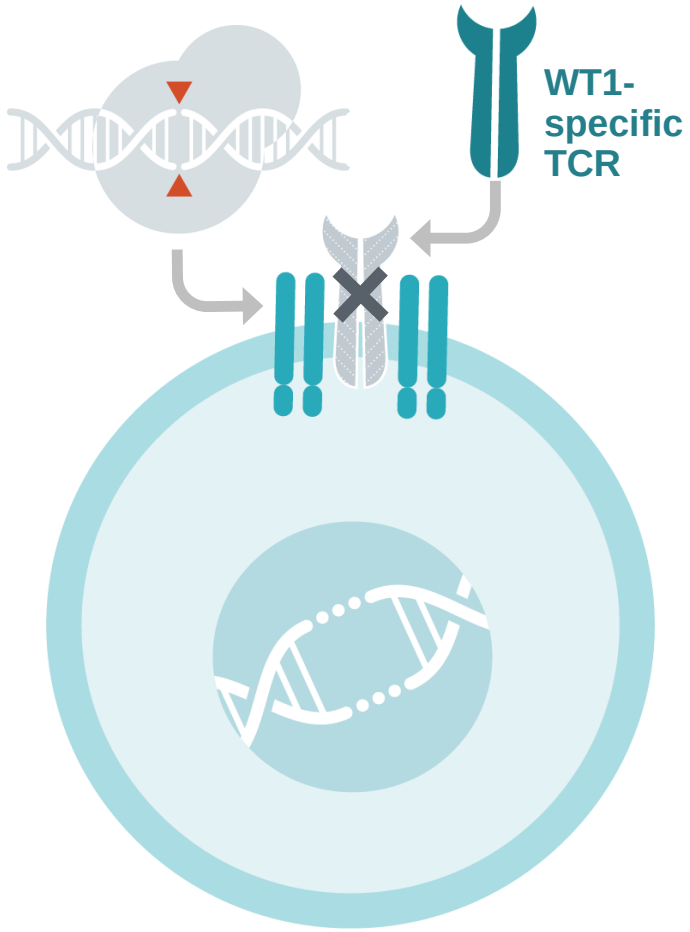
KEY ADVANTAGES

- Potential to address all mutational subtypes of AML
- Low WT1 expression in normal tissues for improved safety
- TCR sourced from healthy donor T cells intended to minimize immune toxicity

[1]NIH SEER Cancer Stat Facts: Leukemia – Acute Myeloid Leukemia (AML)
[2]GlobalData EpiCast Report: Acute Myeloid Leukemia June 2021, 7MM: Seven Major Markets (includes U.S.)

Intellia THERAPEUTICS

NTLA-5001: Potential Best-in-Class Engineered T Cell Therapy For AML



Inserts a **natural, high-avidity TCR** to replace native TCR for upgraded safety profile

- Activates both cytotoxic and helper T cells

Specifically **targets Wilms' Tumor 1 (WT1)**, an antigen overexpressed in >90% of AML blasts[1]

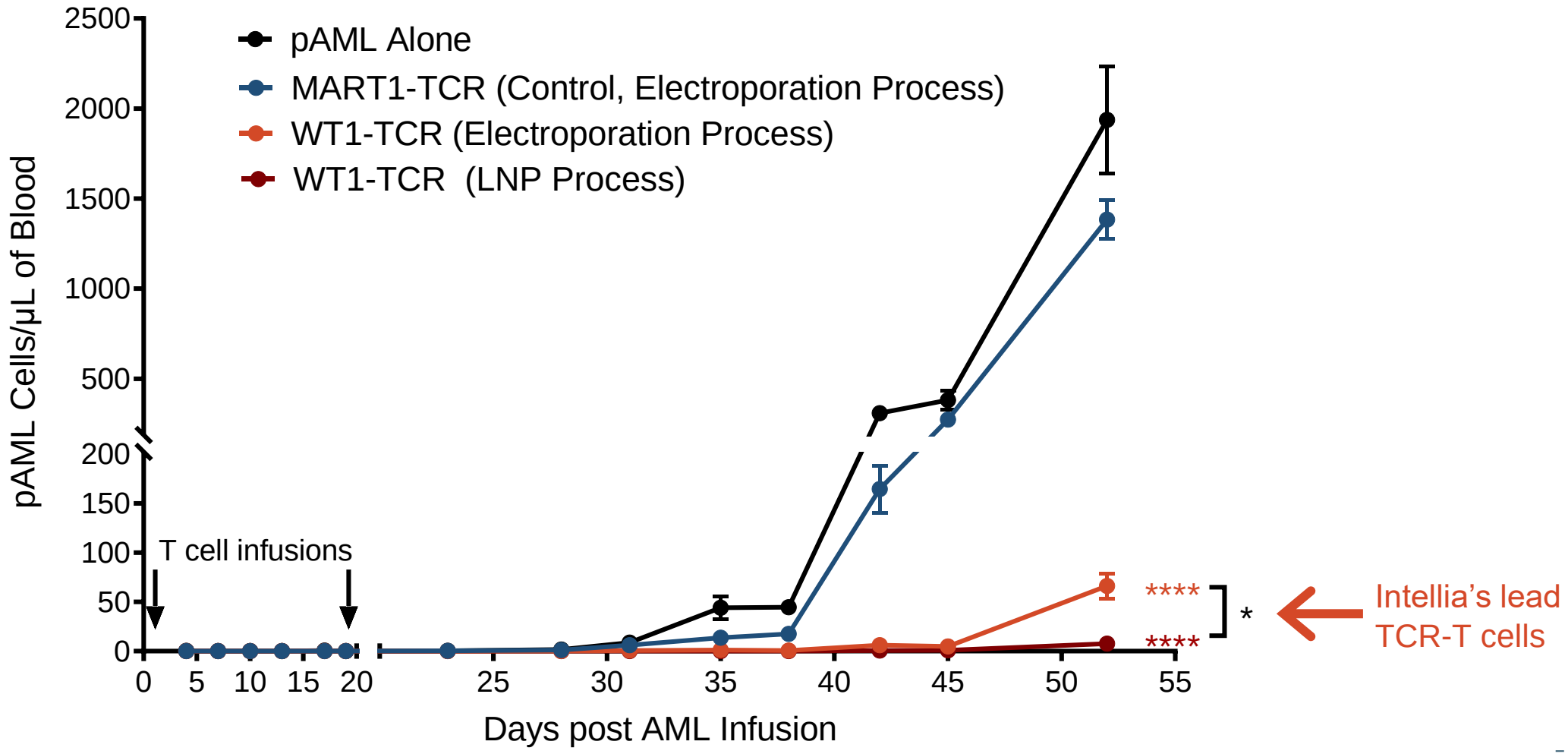
- Recognizes an epitope (VLD[2]) presented broadly by AML blasts with the HLA-A*02:01 allele[3]

Modified by **proprietary cell engineering** technology for optimized cell health and function

[1]Cilloni et al., *J Clin Oncol*, 2009
[2]VLD is the $WT1_{(37-45)}$ epitope VLDFAPPGA
[3]Refer to http://www.allelefrequencies.net for HLA frequency data
In collaboration with IRCCS Ospedale San Raffaele

Intellia THERAPEUTICS

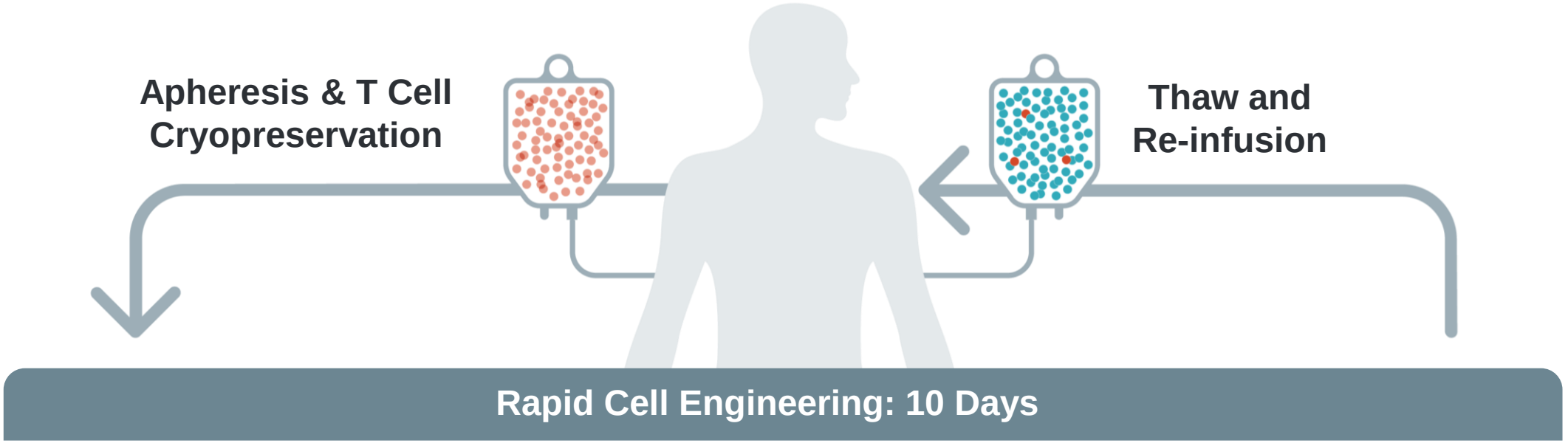
NTLA-5001: Robust Anti-Tumor Efficacy Observed Against Patient-Derived AML Blasts in Mouse Model



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

Intellia THERAPEUTICS

NTLA-5001: Uniform Expression of Therapeutic TCR for Potent Tumor Targeting



Sequential KO of TRAC and TRBC

THAW T cells

ACTIVATE T cells

REMOVE endogenous TCR

INSERT WT1 TCR in locus

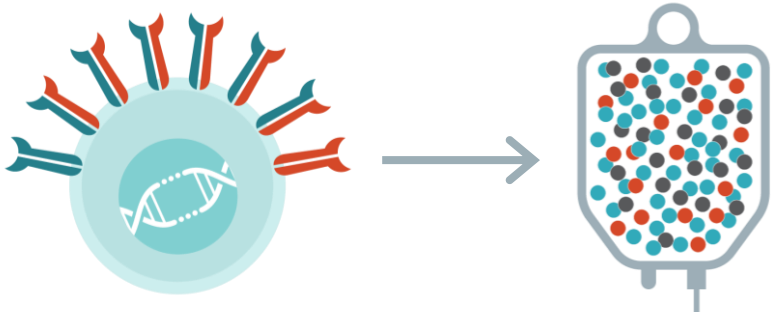
EXPAND rapidly

HARVEST and **FREEZE**

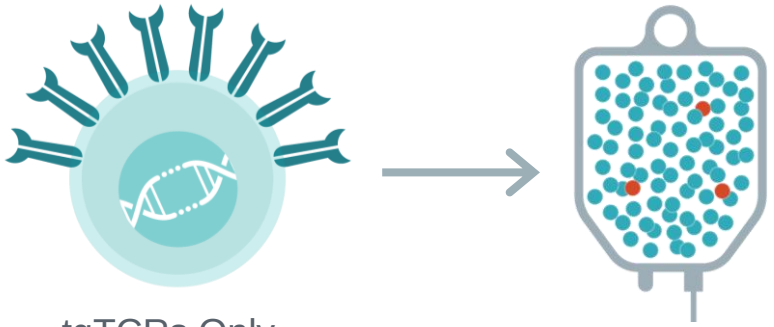
Intellia THERAPEUTICS

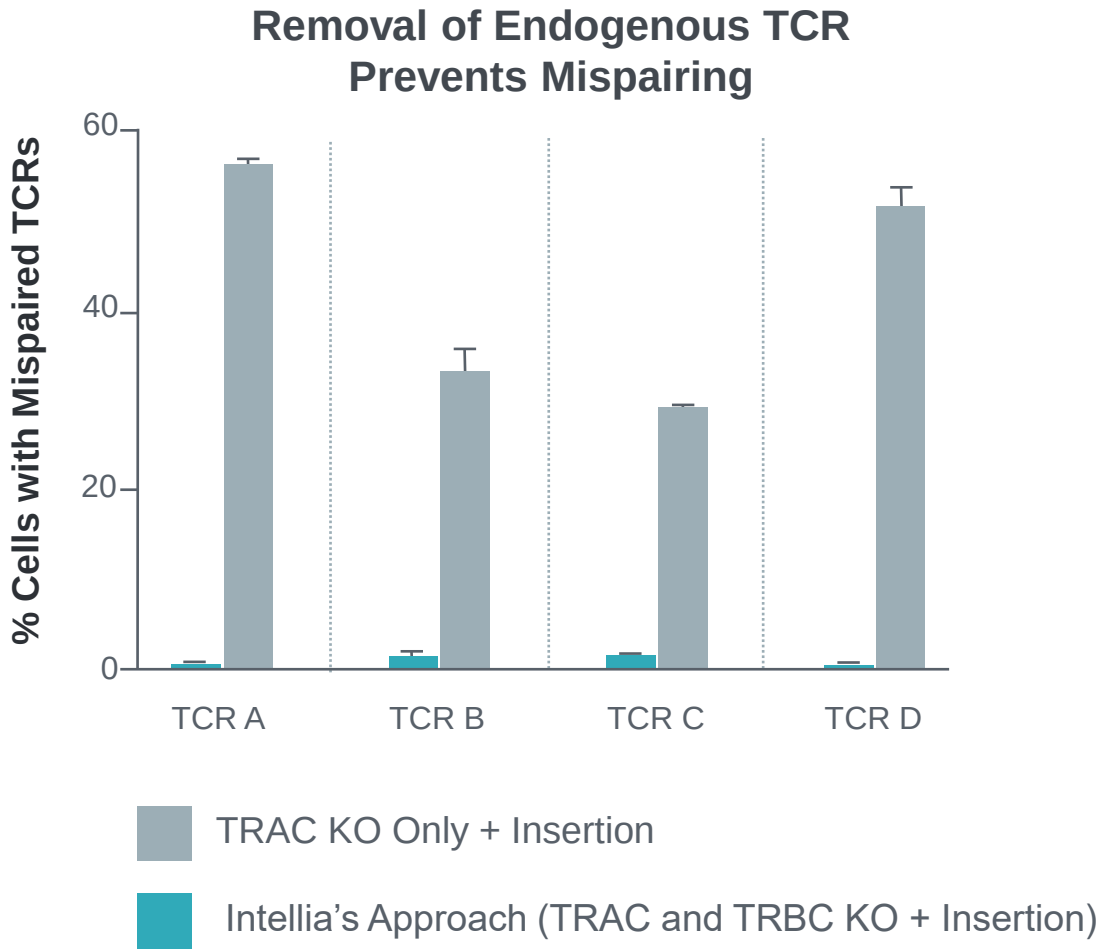
CRISPR Engineering Overcomes Key Challenges of Traditional TCR Approaches

Traditional tgTCR Addition



CRISPR/Cas9 tgTCR Replacement





tgTCR: Transgenic Therapeutic TCR

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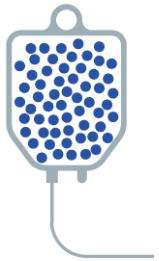
NTLA-5001 Phase 1/2a Trial Design

Open-label, multi-center study of NTLA-5001, a WT1-directed TCR immunotherapy, in adults with AML

Total Enrollment:
Up to 54 patients,
age ≥18 years

Key Inclusion Criteria:

- Relapsed/refractory AML after one or more therapies
- Post transplant patients are eligible
- HLA-A*02:01 positive



Intervention:
Single dose administered via intravenous (IV) infusion

PHASE 1
Dose Escalation

Two-ascending arms: Up to 3 cohorts*

- **ARM 1:** Lower Disease Burden
- **ARM 2:** Higher Disease Burden

PHASE 2
Expansion Cohorts

To confirm recommended dose from each arm of Phase 1

- Dose 1 (N=9)
- Dose 2 (N=9)

KEY ENDPOINTS

- Evaluate safety and tolerability
- Characterize cell kinetics of NTLA-5001
- Determine anti-tumor activity

*3-6 subjects per cohort Clinicaltrials.gov ID: NCT05066165

Lower disease burden: Patients with less than 5% blasts in bone marrow
Higher disease burden: Patients with relapsed/refractory disease with greater than or equal to 5% blasts in bone marrow

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Ex Vivo Pipeline Expansion Strategy

Immuno-oncology

First Wave of Programs

Hematological and Solid Tumors

Address a variety of cancers

- Target new antigens with TCR identification and cell engineering platform
- Allogeneic solution

AML, Undisclosed Indications

Unlock Full Potential

Novel Cell Rewiring for Cancers and Autoimmune Diseases

Advance cell therapy for cancer and autoimmune diseases

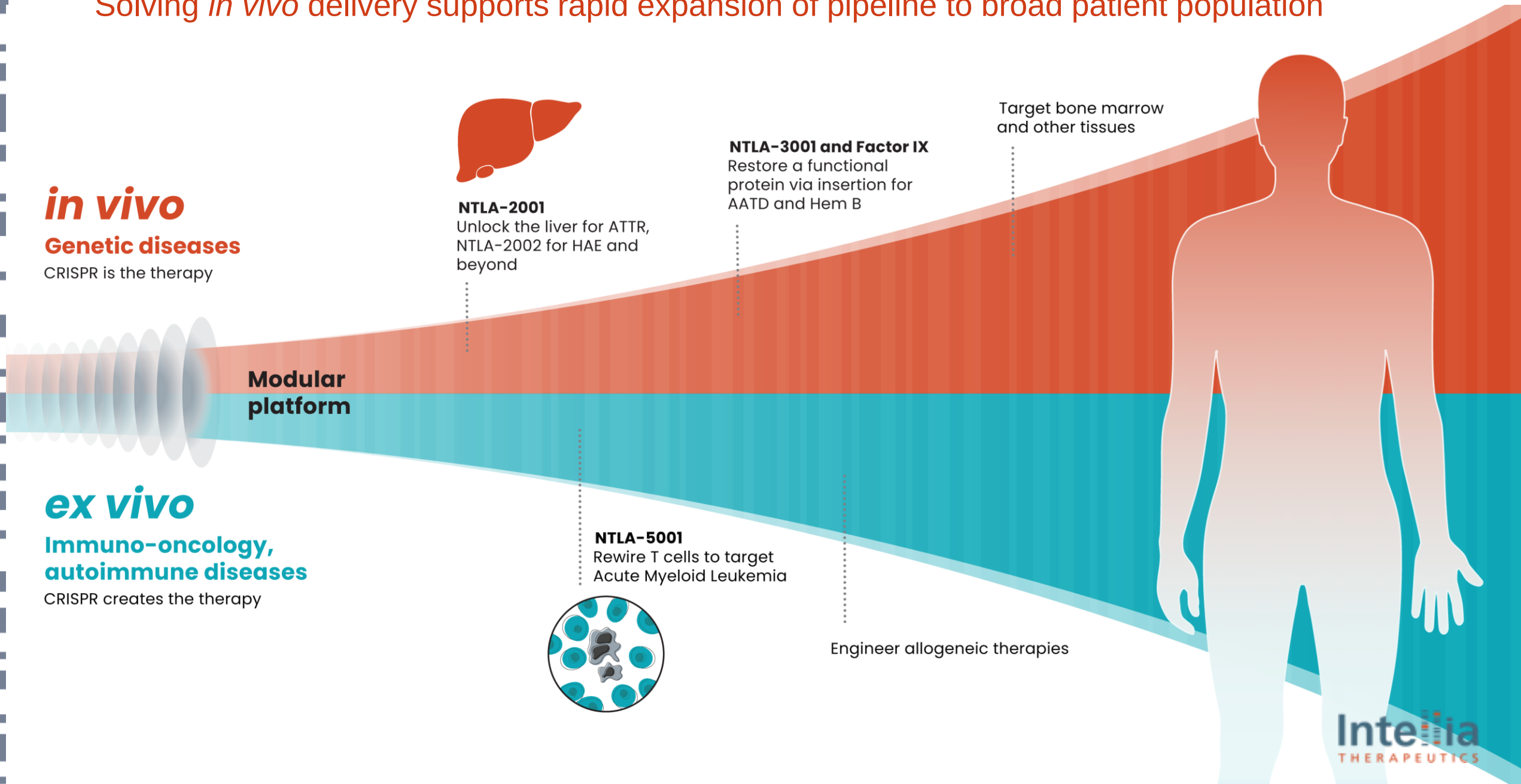
- Novel immune-enhancing edits

Prioritize diseases with significant unmet need

Intellia THERAPEUTICS

Unlocking the Full Potential of CRISPR

Solving *in vivo* delivery supports rapid expansion of pipeline to broad patient population



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LNP-Based Editing of T Cells

Intellia’s Allogeneic Solution

Intellia’s Proprietary Base Editor

Platform: Identifying Potent and Highly Specific Guide RNAs

Strategic Collaborations

Intellia’s Genome Editing Toolbox

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World-Class Genome Editing Platform Allows for Unsurpassed Capabilities

Proprietary CRISPR-based Modular Platform

Editing Tools

CRISPR/Cas9
Spy, HiFi Spy, Nme2

C>T base editor

DNA writer

Delivery Tools

LNPs

AAVs

Additional modalities

ENABLES SELECTING THE BEST TOOLS FOR EACH THERAPEUTIC APPLICATION:

Applies to *in vivo* or *ex vivo* application

Capable of achieving any editing strategy

- Precise knockout and targeted insertions
- Multiplicity of edits
- Single nucleotide modifications

Intellia THERAPEUTICS

Persistence of *In Vivo* Edits

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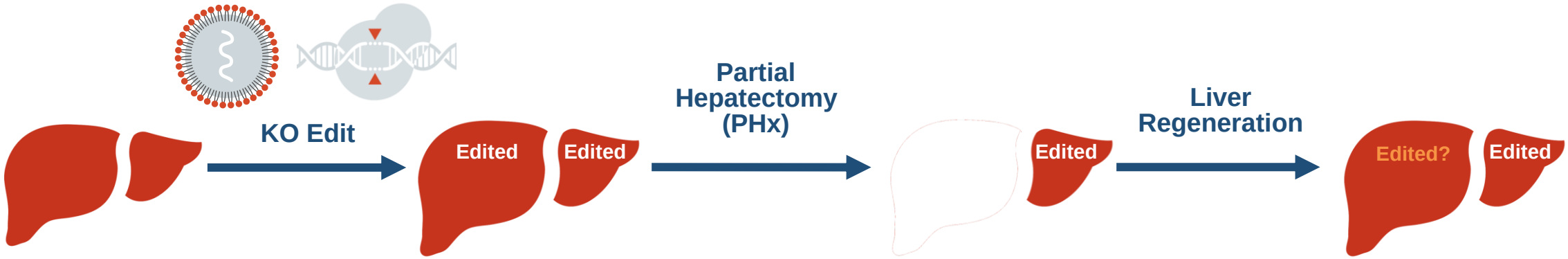
Partial Hepatectomy Model for Investigating Persistence of Knockout Genome Editing

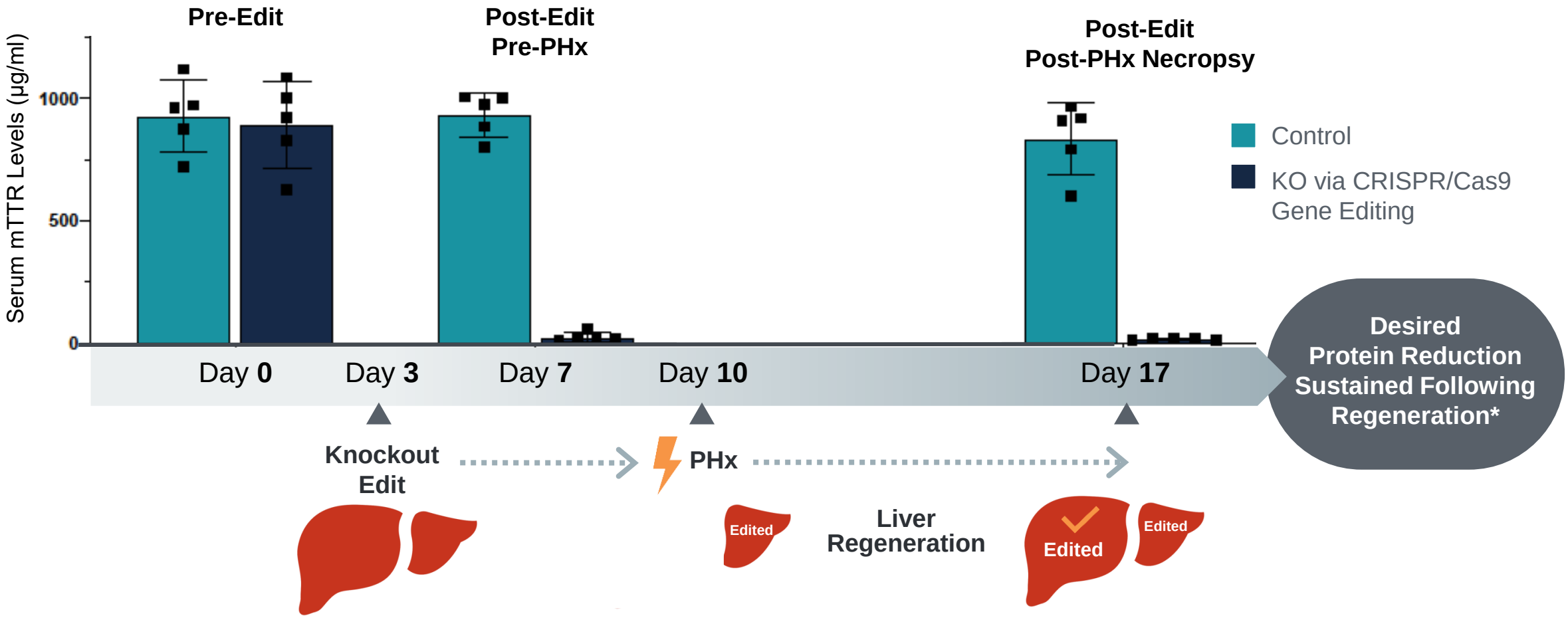


NHP studies demonstrate sustained KO editing and target TTR protein reduction carried through regular cell turnover for 12 months

Key Question: Can editing be carried through tissue regeneration following partial hepatectomy and accelerated cell division?

REGENERON Intellia THERAPEUTICS

Protein Reduction Remains Unchanged Following Murine Liver Regeneration

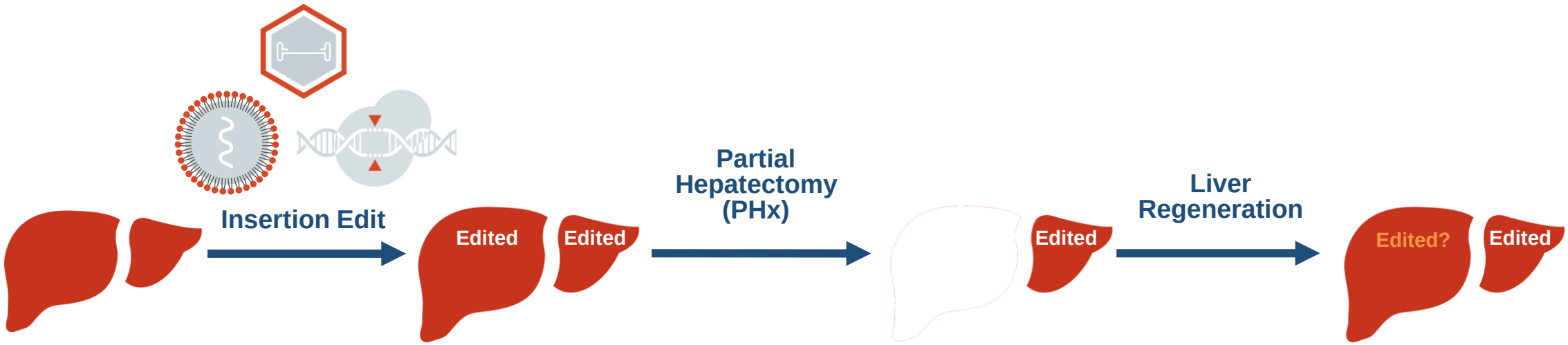


***TTR* gene editing rate similarly remains unchanged post-PHx by NGS analysis**[1]

PHx: Partial Hepatectomy
*Similar results obtained for control and LNP when sham surgery was performed
[1]Next generation sequencing (NGS) analysis to evaluate the frequency of insertion and deletion events (edits).

REGENERON Intellia THERAPEUTICS

Partial Hepatectomy Model for Investigating Persistence of Insertion Genome Editing



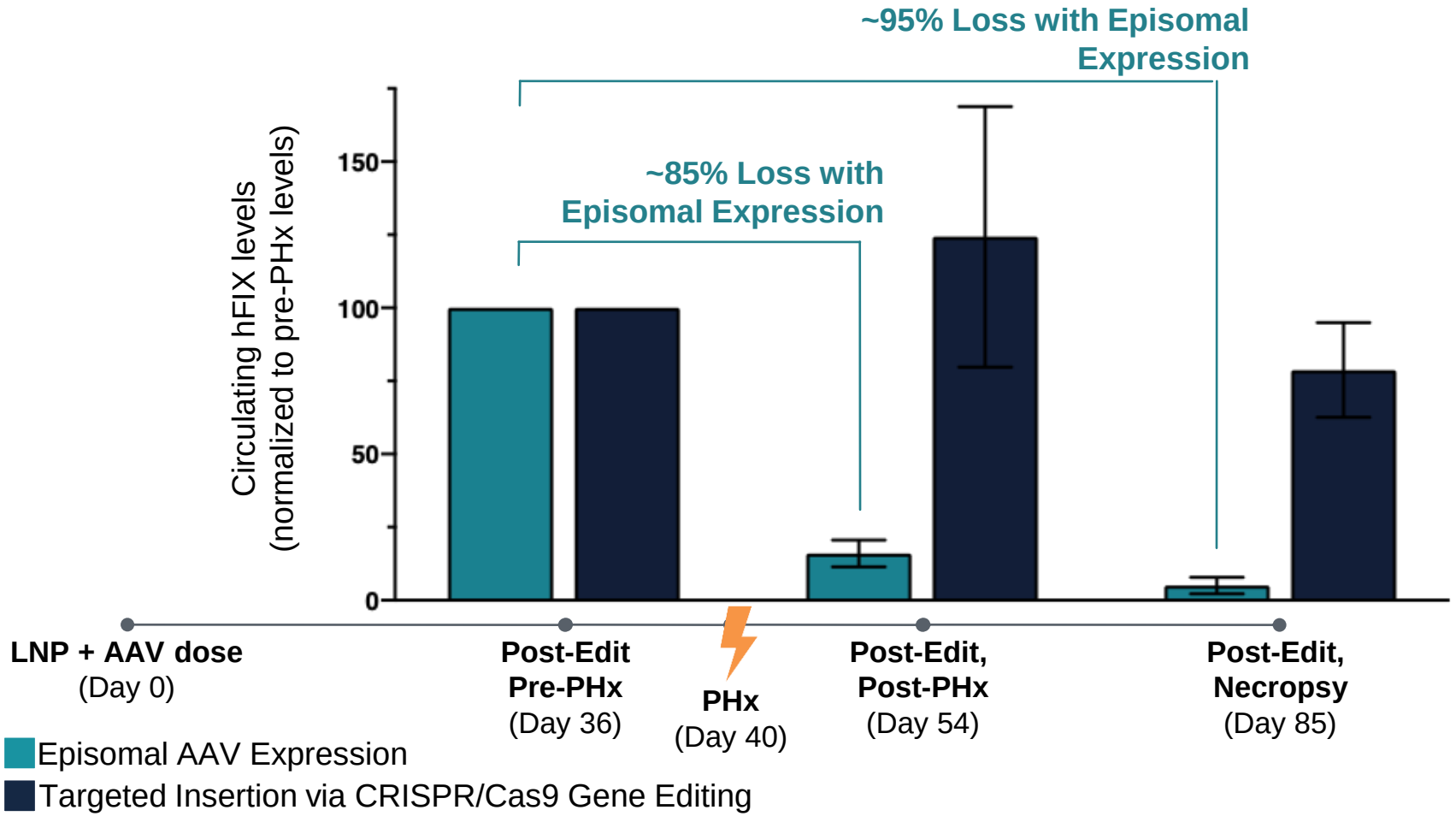
Rodent studies show sustained FIX insertion editing through 12 months, demonstrating that editing is carried through normal cell turnover

Key Question: Can insertion editing be carried through tissue regeneration following partial hepatectomy?

REGENERON Intellia THERAPEUTICS

Persistent Protein Levels Post-PHx from Targeted Gene Insertion in Murine Model, in Comparison to Significant Loss of Protein Expression with Gene Therapy

Correlating editing rate similarly remains unchanged post-PHx by NGS analysis[1]



[1]Next generation sequencing (NGS) analysis to evaluate the frequency of insertion and deletion events (edits).

REGENERON Intellia THERAPEUTICS

In Vivo Editing of Hematopoietic Stem Cells

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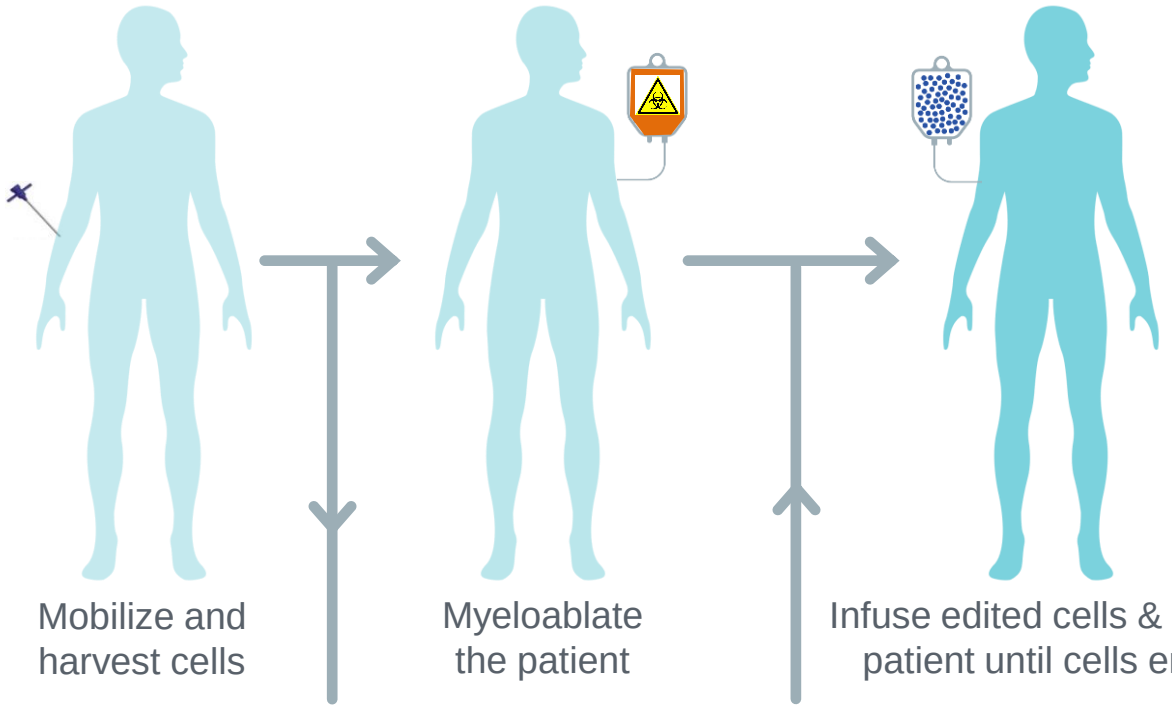
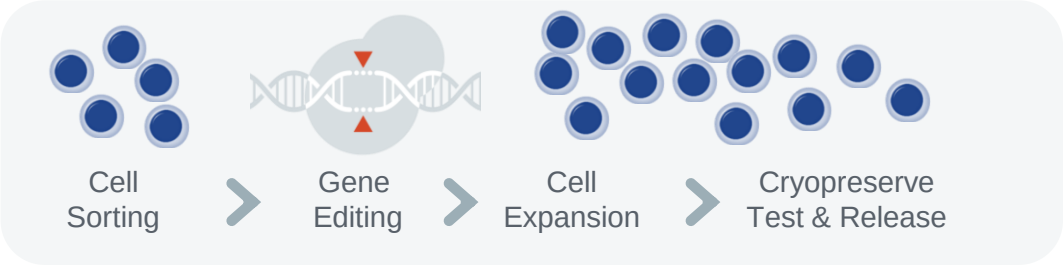
Ex vivo SCD gene editing still has significant limitations

Complex cell manufacturing process





Conditioning regimen toxicity

- Immunosuppression for > 1 month, predisposing to infection
- Risk of malignancy from chemotherapy drugs, especially leukemia
- Risk of infertility

Implications

- *Ex vivo* gene editing will be limited to highly selected SCD patients with severe disease
- Treatment complexity will limit access for patients in resource-poor settings

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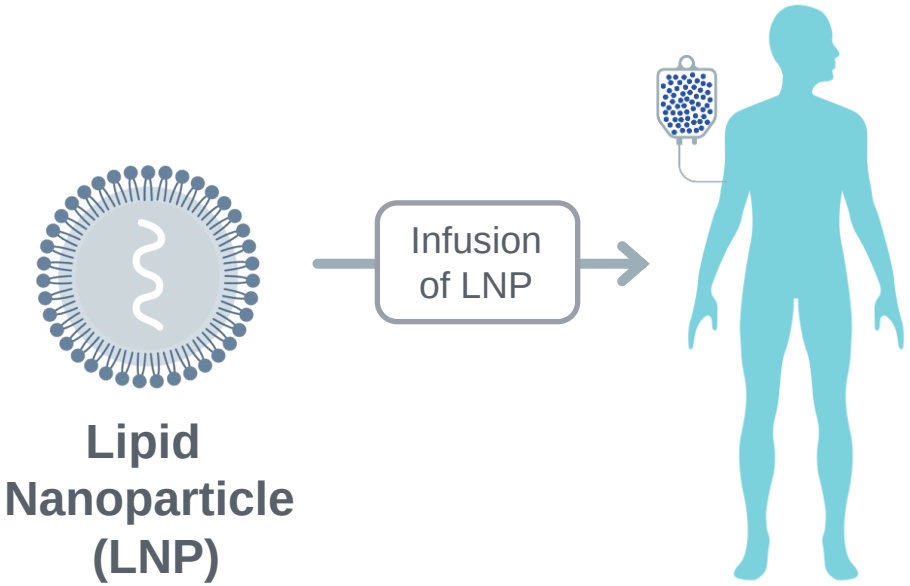
In vivo non-viral SCD gene editing could overcome these limitations

Simplified process



Potential improved safety and accessibility

- Avoids myeloablation and associated risks of immunosuppression, malignancy and infertility
  - Approach could become mainstream therapy for SCD
- Avoids need for complex cell manufacturing or extensive supportive care post-treatment
  - Treatment simplicity could expand access to patients in resource-poor settings

Desired features of *in vivo* approach

- Provides clinically meaningful, durable HSC editing
- Allows for multidosing to reach therapeutic target
- Preserves regenerative potential of edited cells
- Translatable to human HSC population

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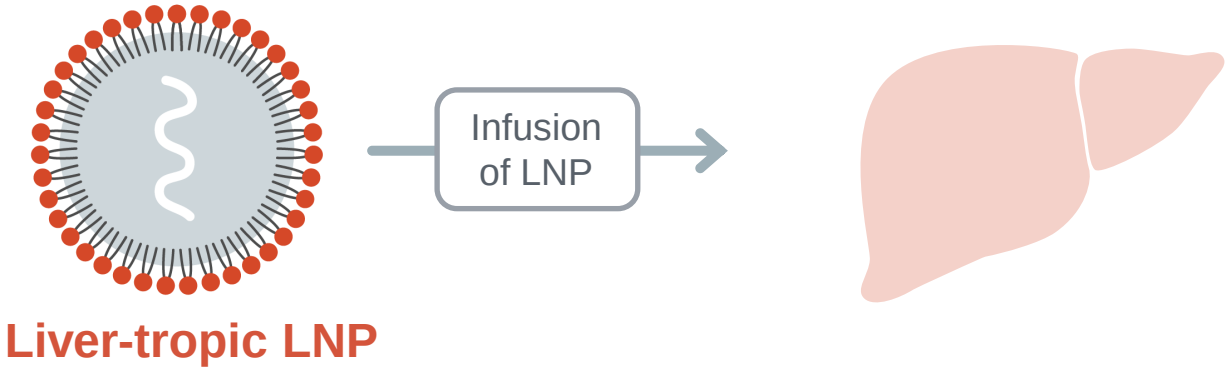
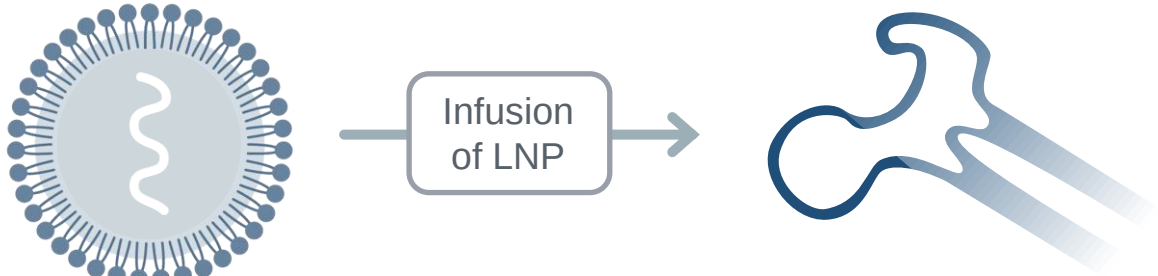
Editing HSCs *in vivo* requires LNPs with bone marrow tropism

- LNPs designed, formulated and tested *in vivo* to identify compositions with enhanced delivery to bone marrow and HSCs



Liver-tropic LNP



Bone marrow-tropic LNP

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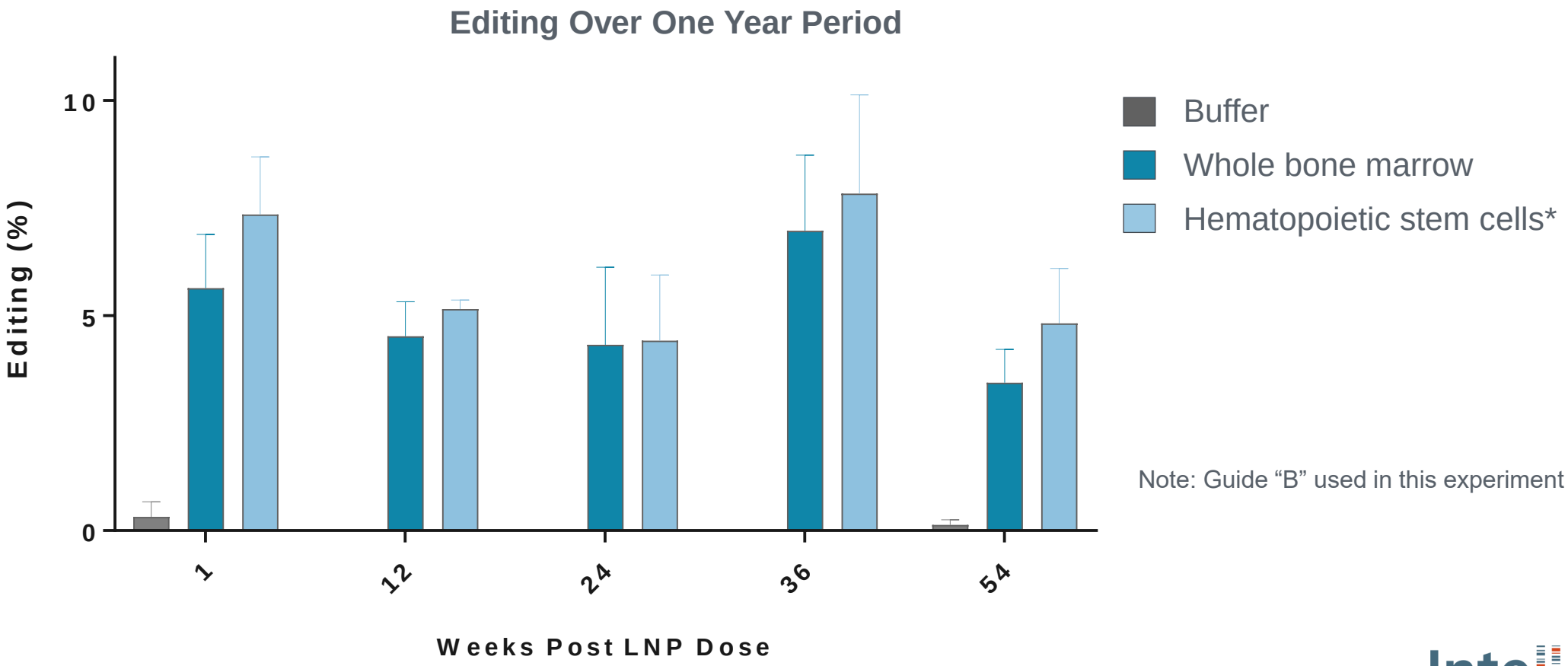
Editing of mouse bone marrow and HSCs is durable through at least one year

- Editing was similar across all time points assessed, in both whole bone marrow and HSCs populations
- Results highlight the potential for a single-course, long-lasting therapy



Note: Guide “B” used in this experiment

* Lin^{-}Sca-1^{+}c-Kit^{+}CD34^{-}Flk2^{-} cell population

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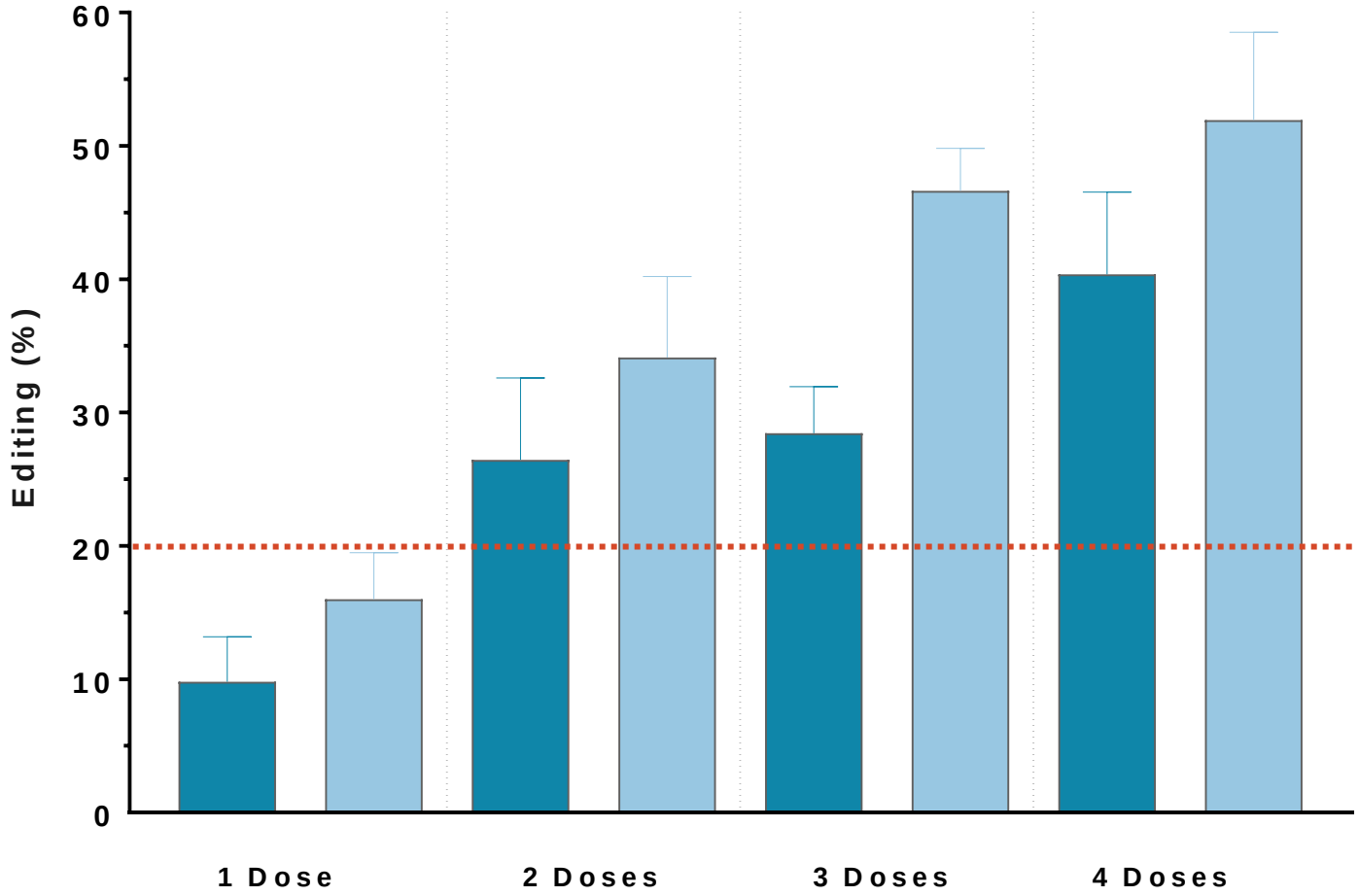
Editing of mouse bone marrow and HSCs increases with multidosing

- Non-immunogenic LNP delivery platform may enable stepwise “treat-to-target” approach



Whole bone marrow

Hematopoietic stem cells**

Level predicted to be curative for SCD*

Note: Guide “B” used in this experiment

Blood. 2017;130(17):1946-1948.

**Lin$^-$Sca-1$^+$c-Kit$^+$CD34$^-$Flk2$^-$ cell population

LNP-Based Editing of T Cells

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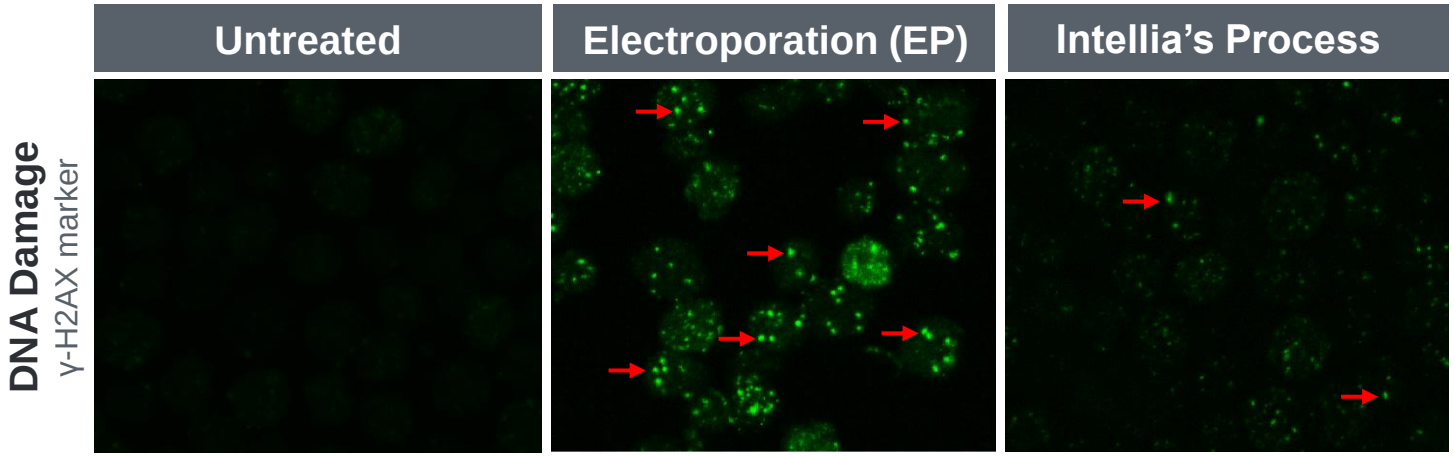
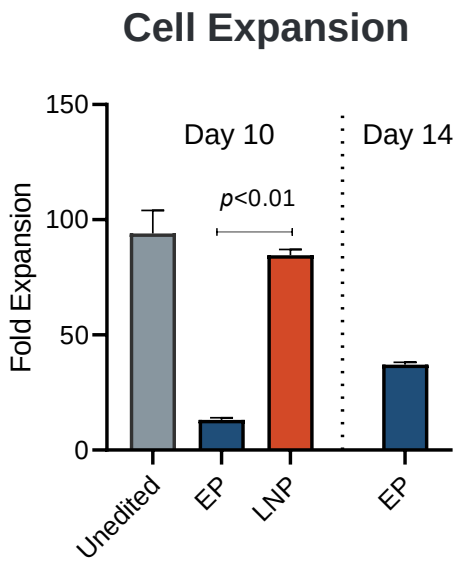
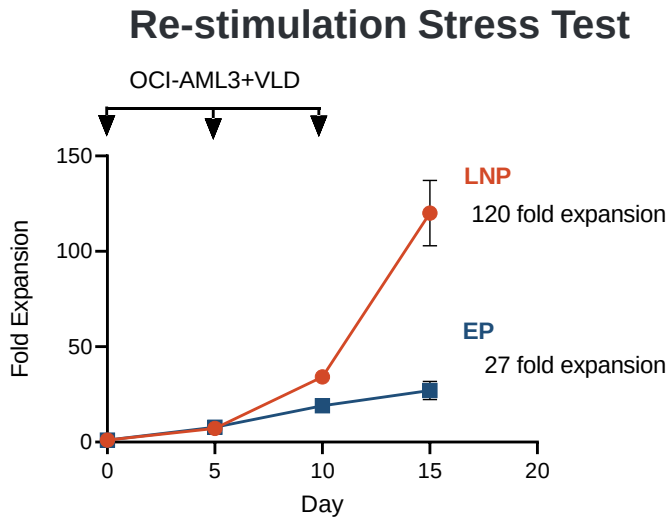
LNP-Based Cell Engineering Technology Optimizes Cell Health and Function







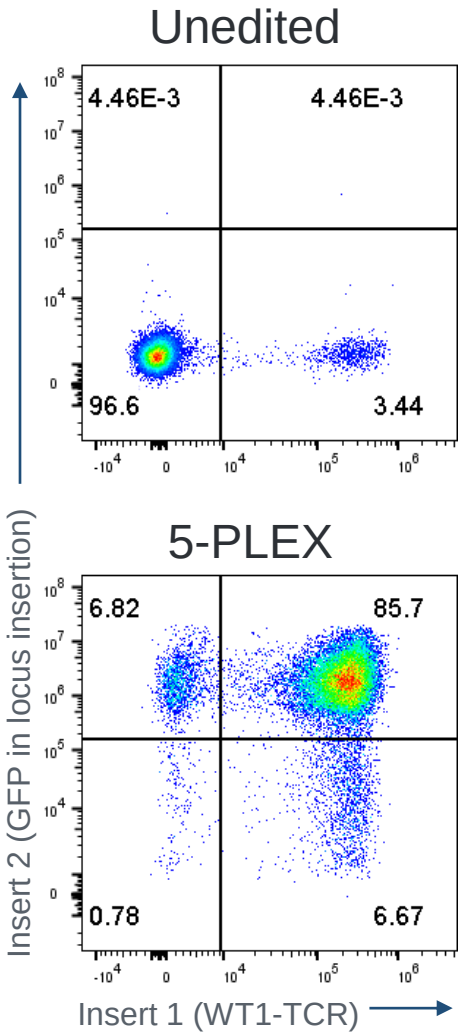
LNP approach to editing T cells

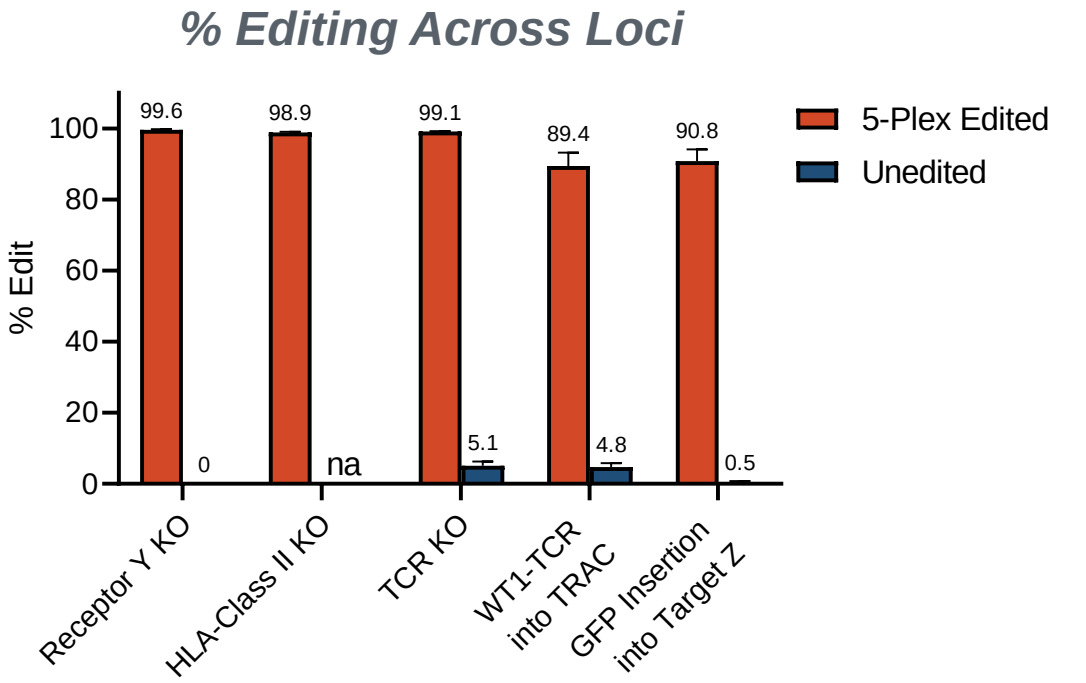
- Enables sequential editing
- Reduces safety risks from unwanted breaks caused by EP
- Produces cells with high expansion and performance

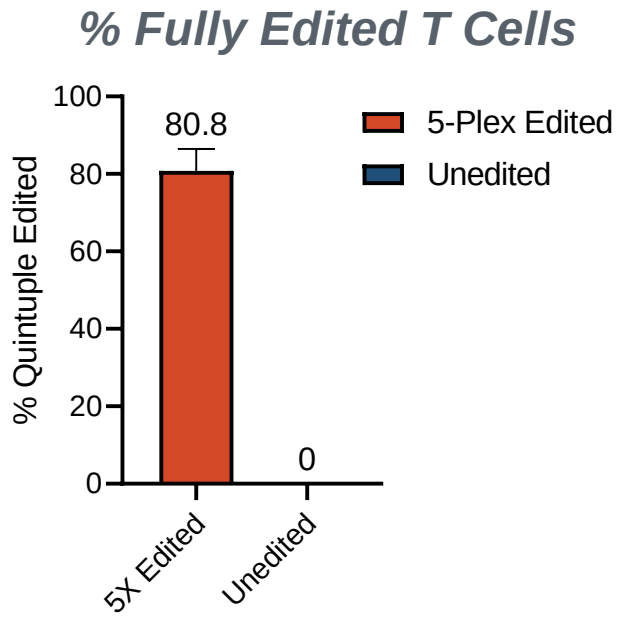
Intellia THERAPEUTICS

Multiplex CRISPR/Cas9 T Cell Editing: 5 Sequential 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**
- **Cells retained high viability and complete editing of 3 other KO targets**
- **Modular platform for insertion of T cell supporting transgenes**

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Intellia’s Allogeneic Solution

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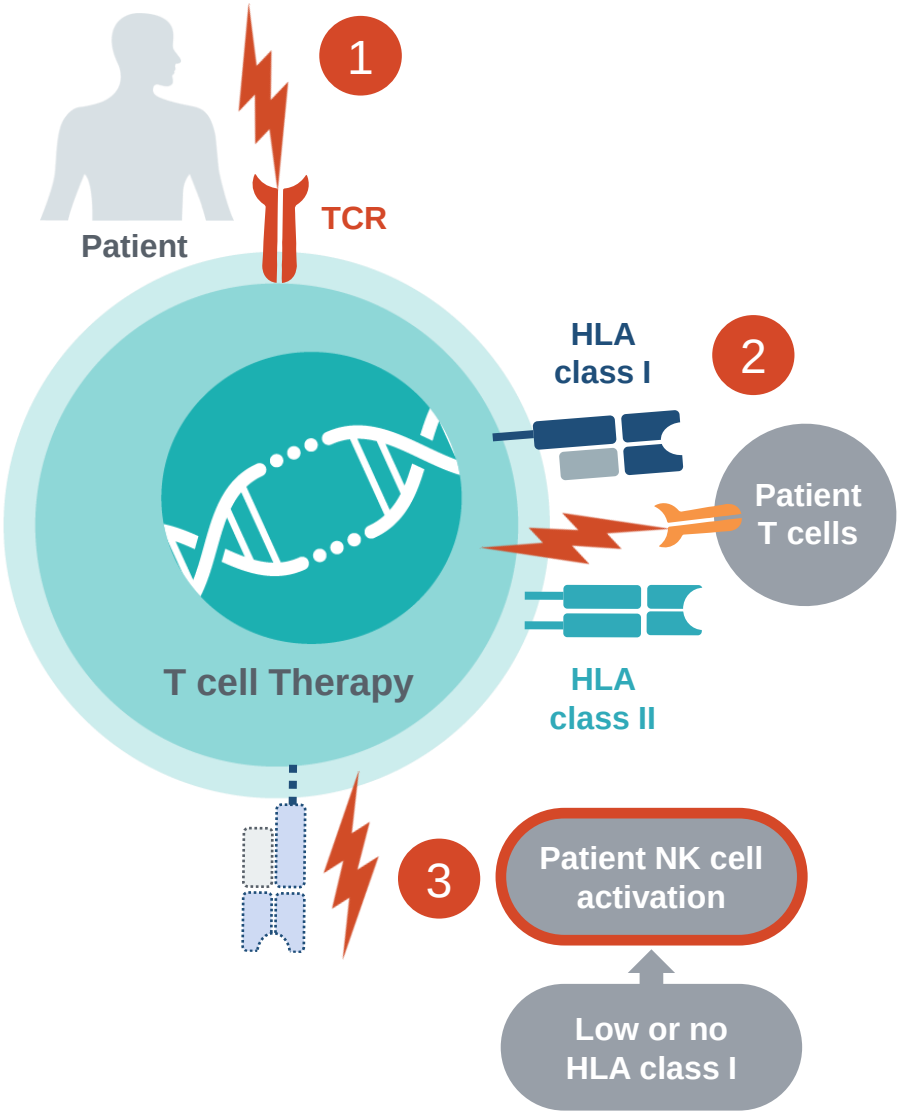
Three Immune Concerns Must Be Addressed by Allogeneic Cell Therapies



1 Graft versus host disease (GvHD)

T cell receptor (TCR) from allogeneic T cells recognizes and kills recipient (host) cells.

Largely solved with knockout (KO) of endogenous TCR

2 Rejection via host T cells

Human Leukocyte Antigen (HLA) molecules must match between donor and recipient to prevent rejection from:

- Host CD8 (HLA class I) T cells
- Host CD4 (HLA class II) T cells

3 Rejection via host natural killer (NK) cells

NK cells will attack cells that lack HLA-I expression or have low HLA-I

No validated solution yet

HLA-I / II: Human leukocyte antigen class I / II

Intellia THERAPEUTICS

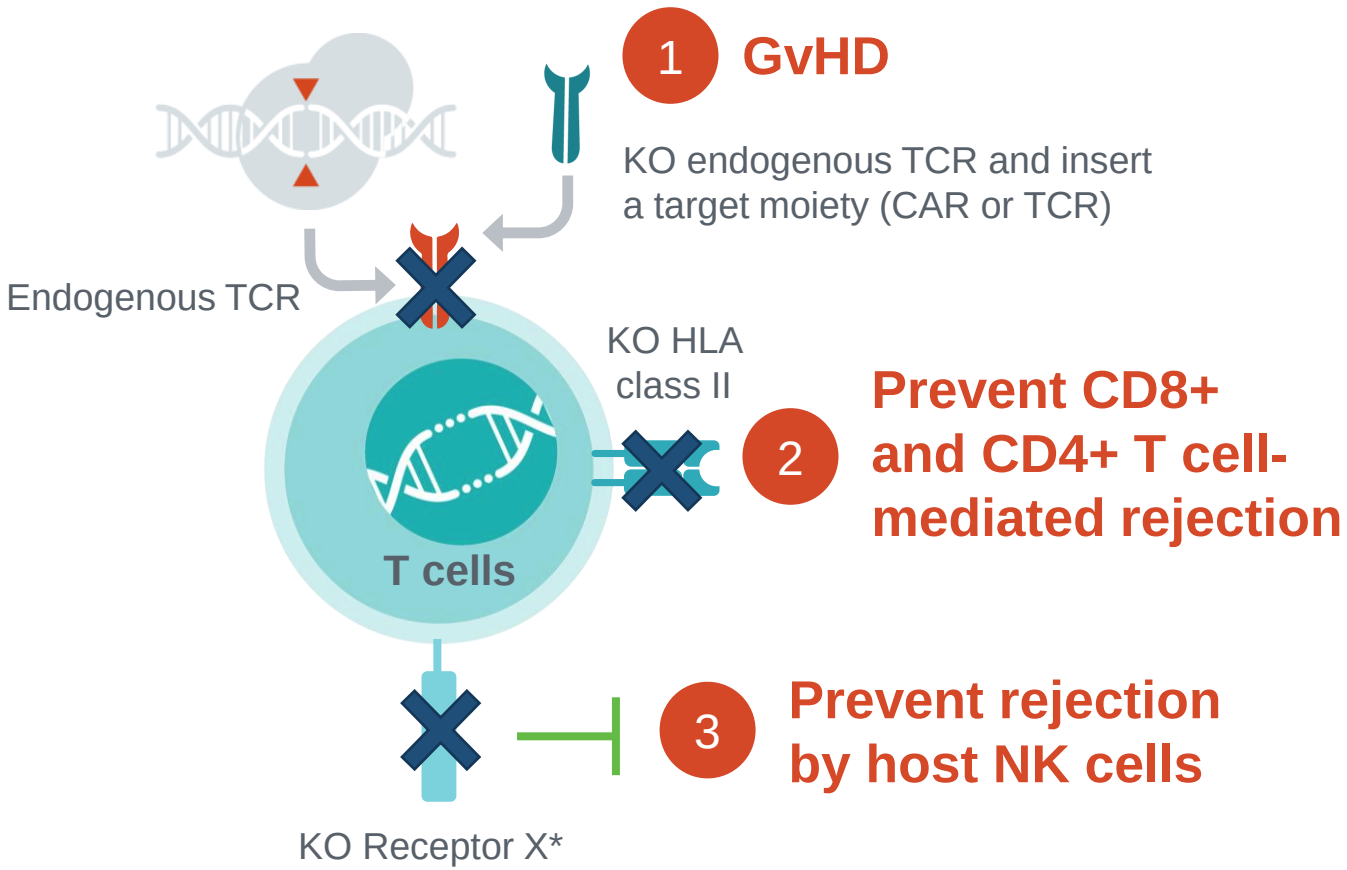
Immune Concerns Unaddressed by Current Allogeneic Solutions

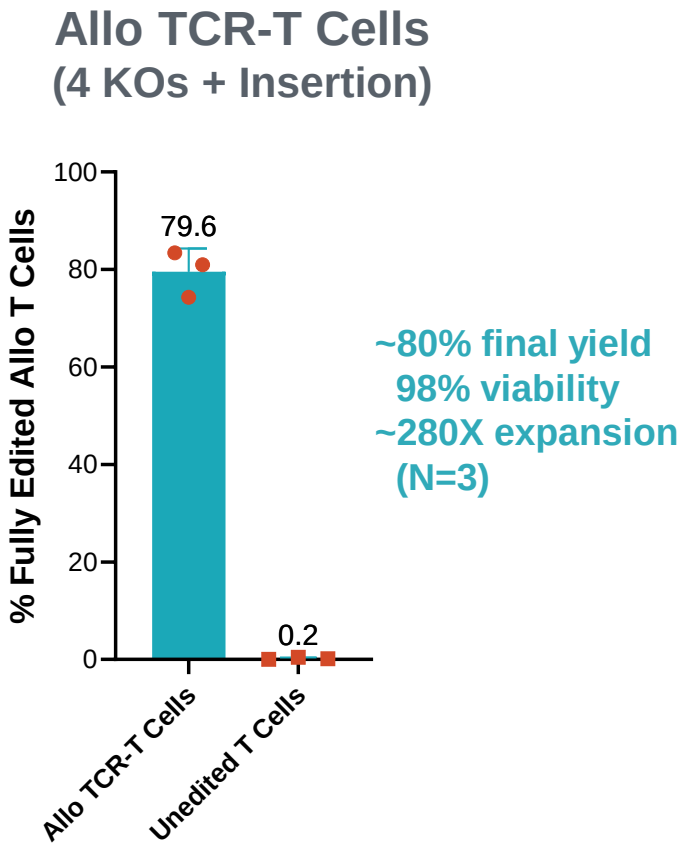
Approach	Employ intense lymphodepletion regimen	Knockout (KO) HLA-I (B2M)	KO HLA-I & express NK inhibitor (HLA-E)	**Intellia's Approach** KO HLA-II & Receptor X*
Avoid rejection of cell therapy by host CD8 T cells	✓	✓	✓	✓
Avoid rejection of cell therapy by host CD4 T cells	✓	✗	✗	✓
Avoid rejection of cell therapy by host NK cells	✓	✗	✗	✓
Avoid profound immunosuppression	✗	✓	✓	✓

*Receptor X: Undisclosed target
B2M: Beta-2-microglobulin
HLA-E: Human leukocyte antigen class E
Slide based on preclinical data disclosed by Intellia. Intellia's cell product to be further explored in additional preclinical and clinical studies.

Intellia THERAPEUTICS

Intellia's Differentiated Allogeneic Approach Aims to Address Immune Requirements



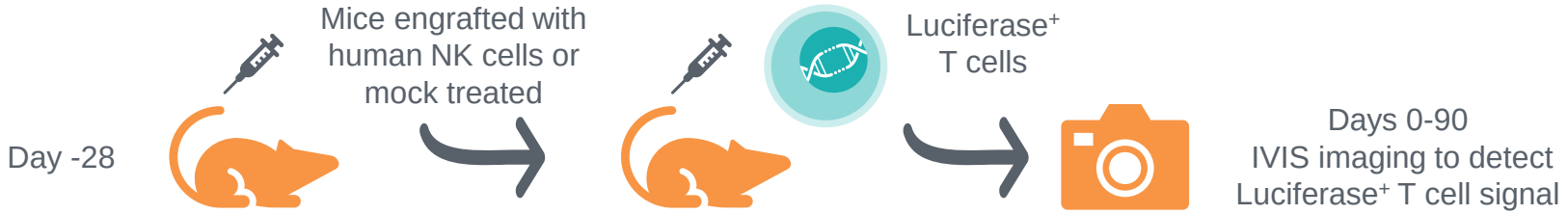


Applicable to CAR and TCR • **Solve for host NK and T cell rejection** • **Avoid long-term immunosuppression**

*Receptor X: Undisclosed target

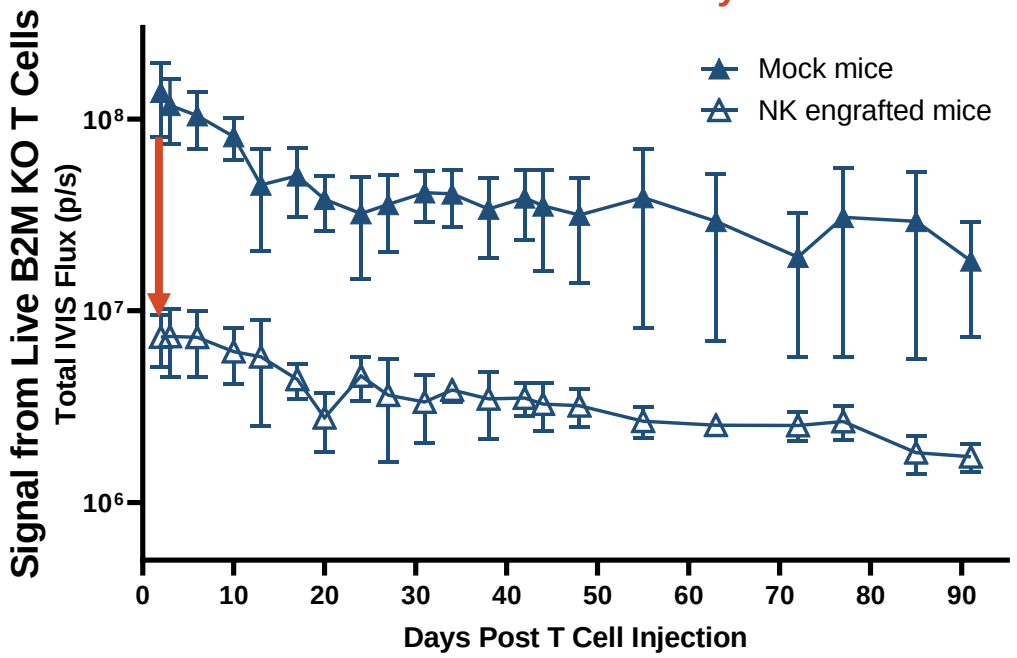
Intellia THERAPEUTICS

Allo TCR-T Cells Resist NK Cell Killing for at Least 90 Days *In Vivo*



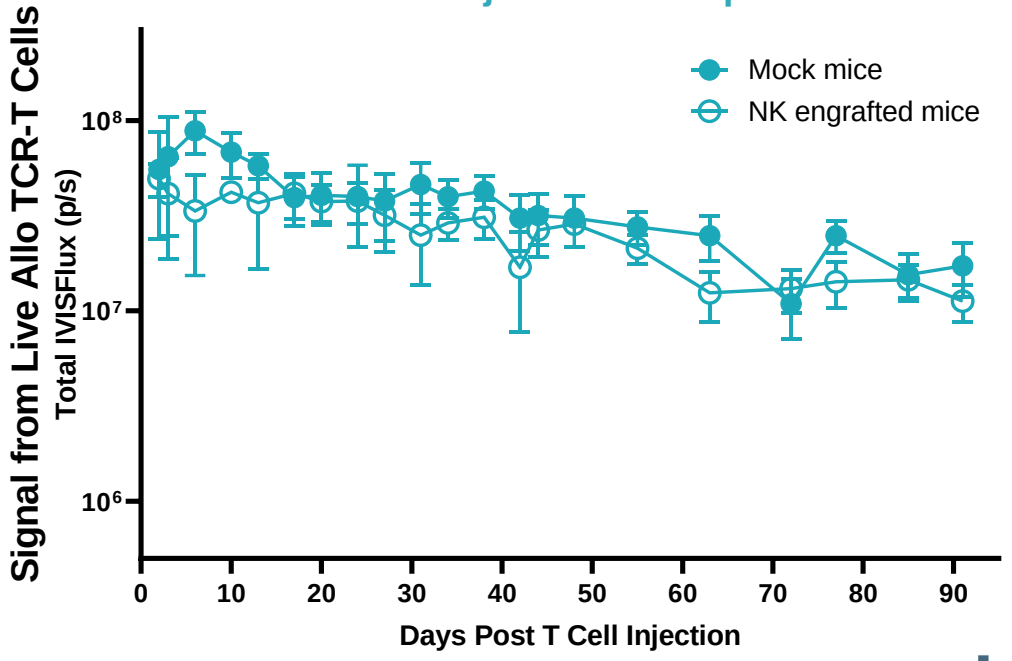
B2M Knockout T cells

>90% B2M KO T cells killed by NKs within 24h



Allo TCR-T Cells

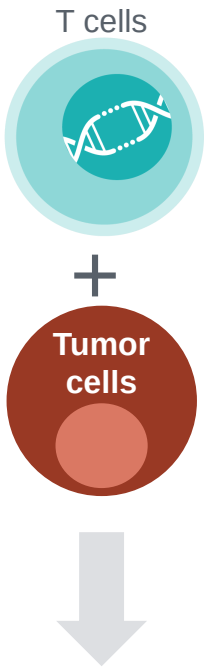
Minimal Allo T cell rejection in the presence of NK cells



Intellia THERAPEUTICS

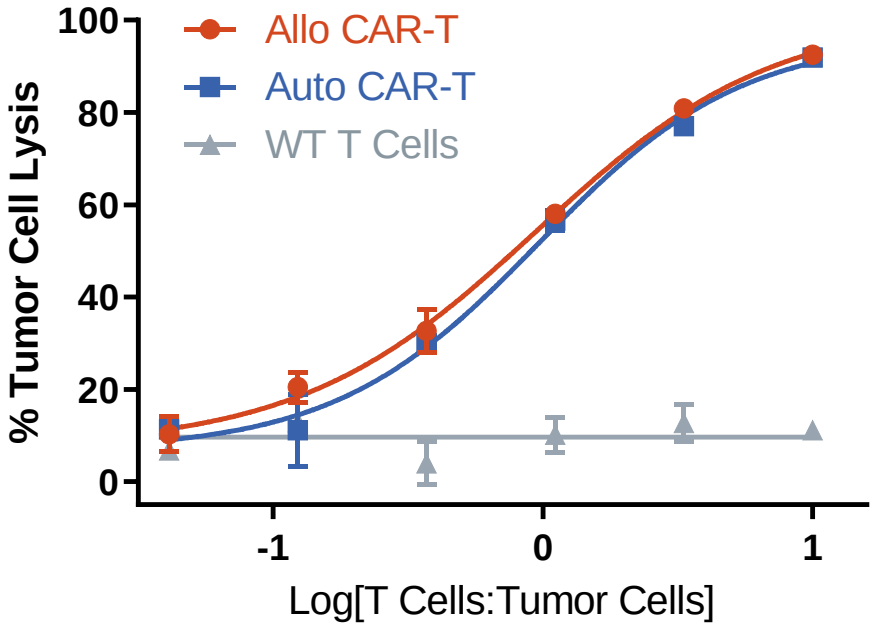
Allo T Cells Have Comparable Tumor Cell Killing Activity to Autologous T Cells

***In vitro* T cell cytotoxicity assay**

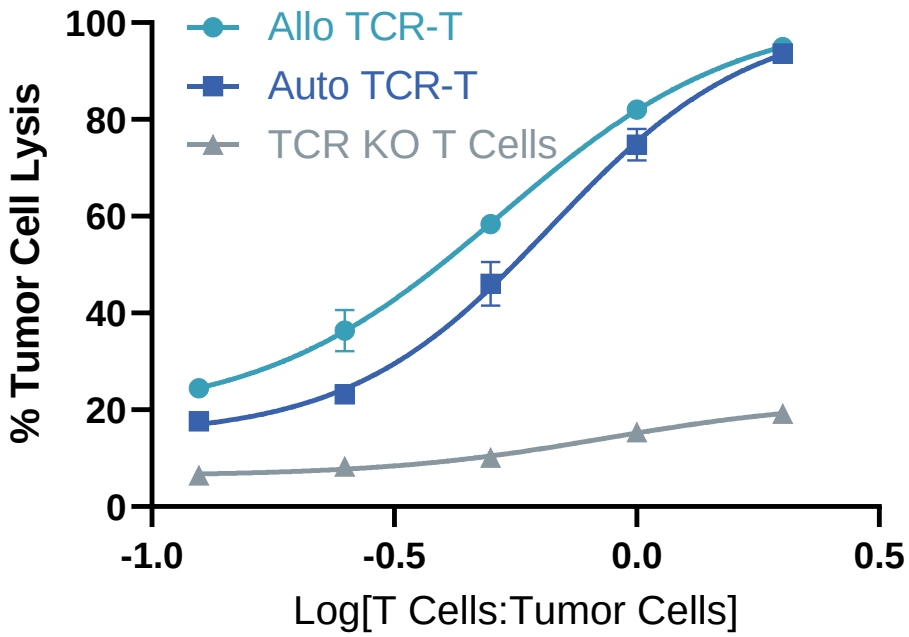


Readout: Tumor cell lysis

Allo CAR-T Cells



Allo TCR-T Cells



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Intellia’s Proprietary Base Editor

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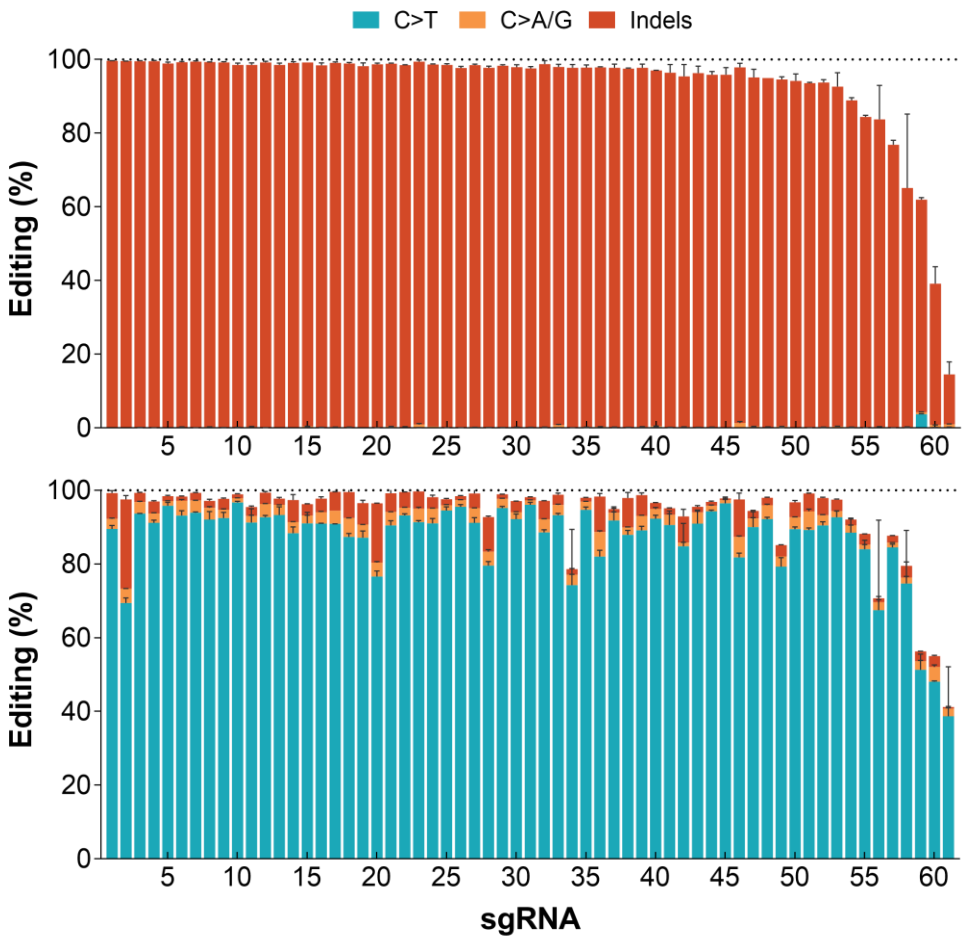
Intellia's Base Editor is Equipotent to Cas9 for *Ex Vivo* Editing

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



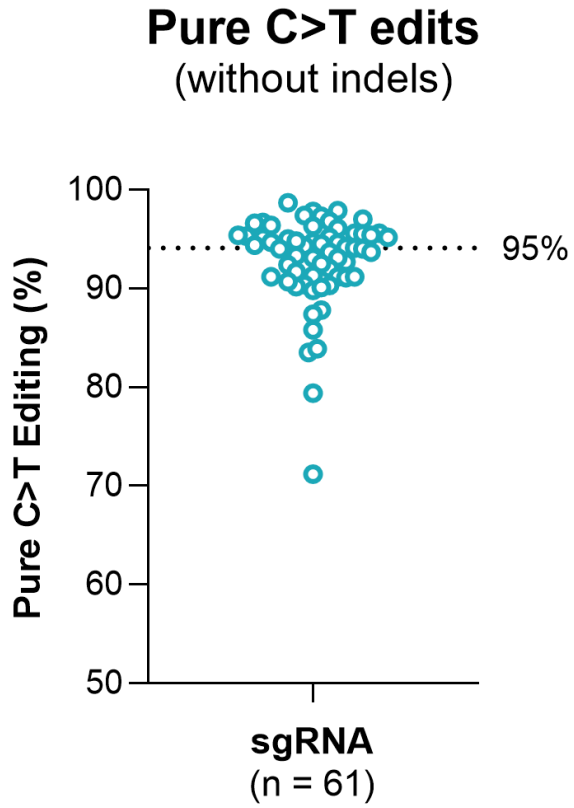
Cas9

Base Editor

>700 constructs screened for potency

85% of guides gave >90% editing

36% of guides gave >95% C to T purity



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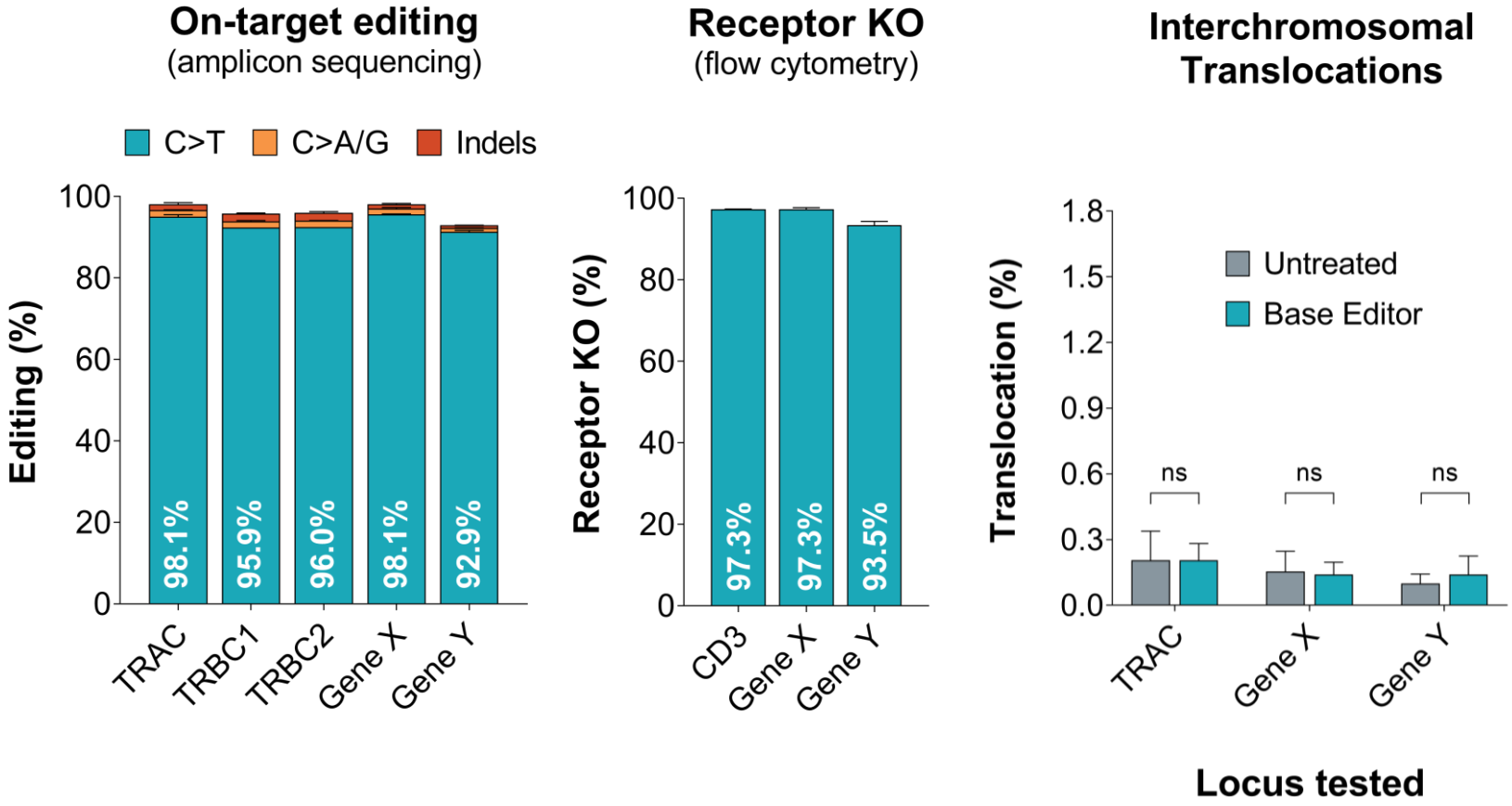
Simultaneous Knockout with Base Editing **Does Not** Lead to Translocations

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



Intellia THERAPEUTICS

Platform: Identifying Potent and Highly Specific Guide RNAs

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Comprehensive gRNA Specificity Assessment: Off-Target Workflow

1: Discovery of Potential Off-Target Edits

Computational prediction

+

SITE-Seq Genomic DNA digest

+

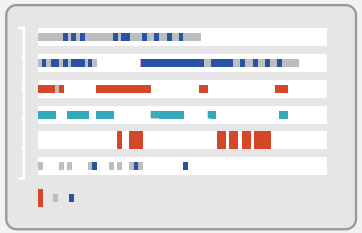
GUIDE-seq Cell-based DNA repair

Aggregate **ALL** potential off-target genomic loci

2: Validation of Off-Target Edits in Cells

Multiplex panel for NGS

Targeted Amp-Seq NGS follow-up



Ex Vivo

- Cell drug product

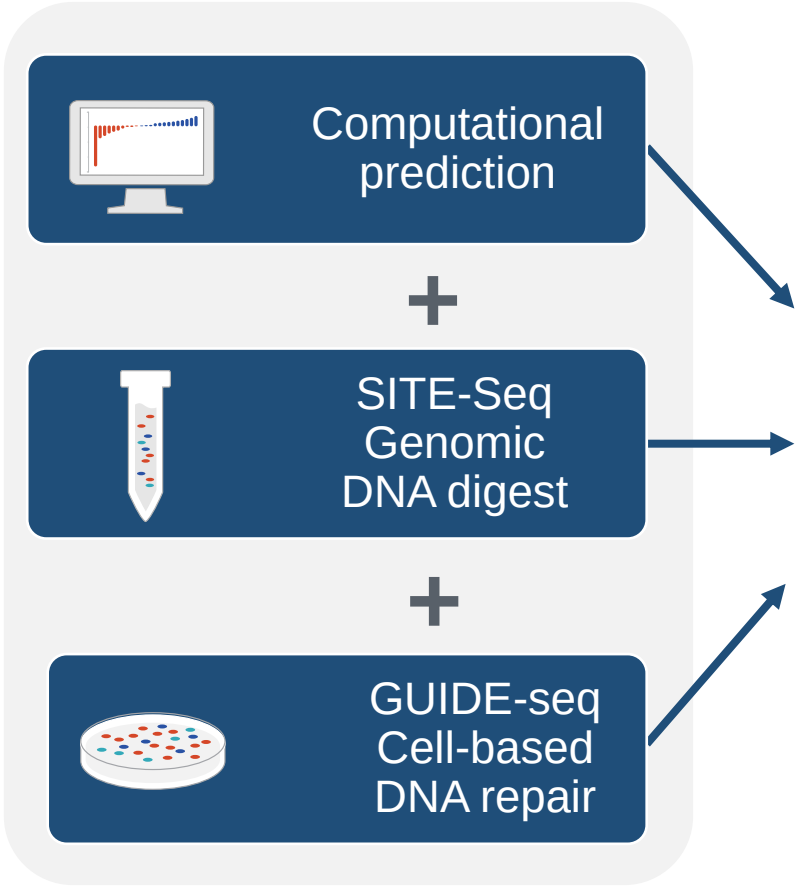
In Vivo

- Edit cells *in vitro* using drug product formulation
- Therapeutically relevant human primary cell type(s) (2 donors)
- Dose range to exceed projected therapeutic exposure (≥10X)

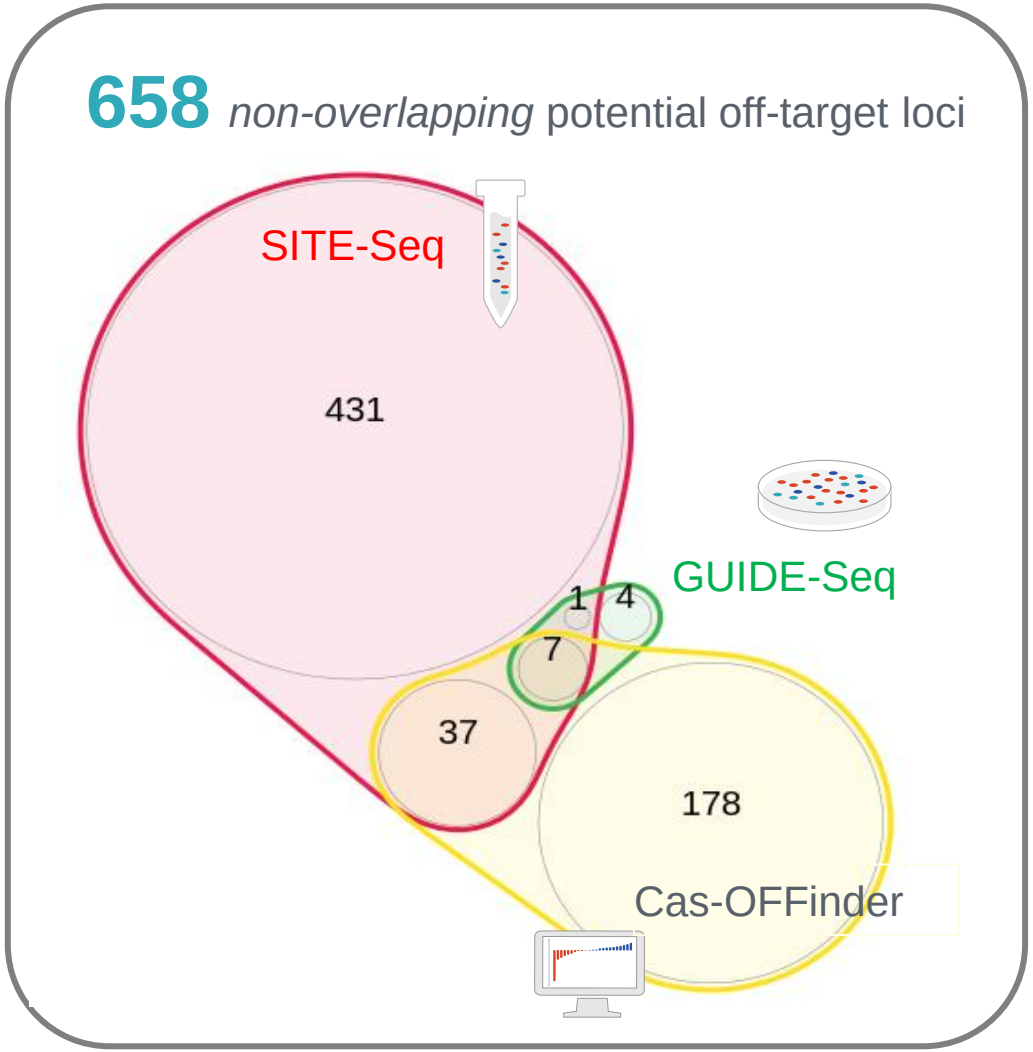
Intellia THERAPEUTICS

Limited Overlap in Discovered Off-Target Loci by Three Leading Methods

1: Discovery of Potential Off-Target Edits



Aggregate **ALL** potential off-target genomic loci



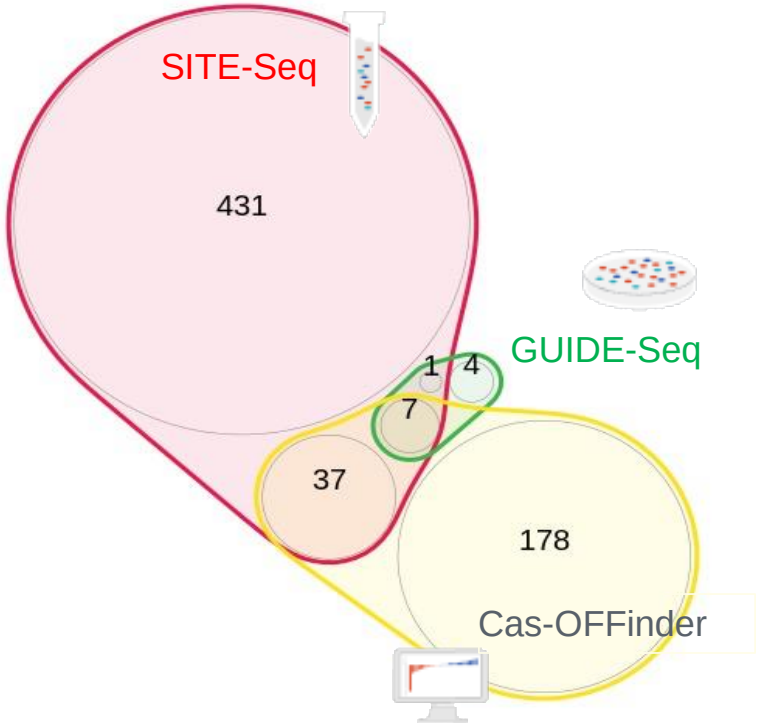
Data above is a representative example

Intellia THERAPEUTICS

Off-Target Workflow In Practice: Representative Example

1: Discovery of Potential Off-Target Edits

658 *non-overlapping* potential off-target loci



2: Validation of Off-Target Edits in Cells

Multiplex panel for NGS

↓

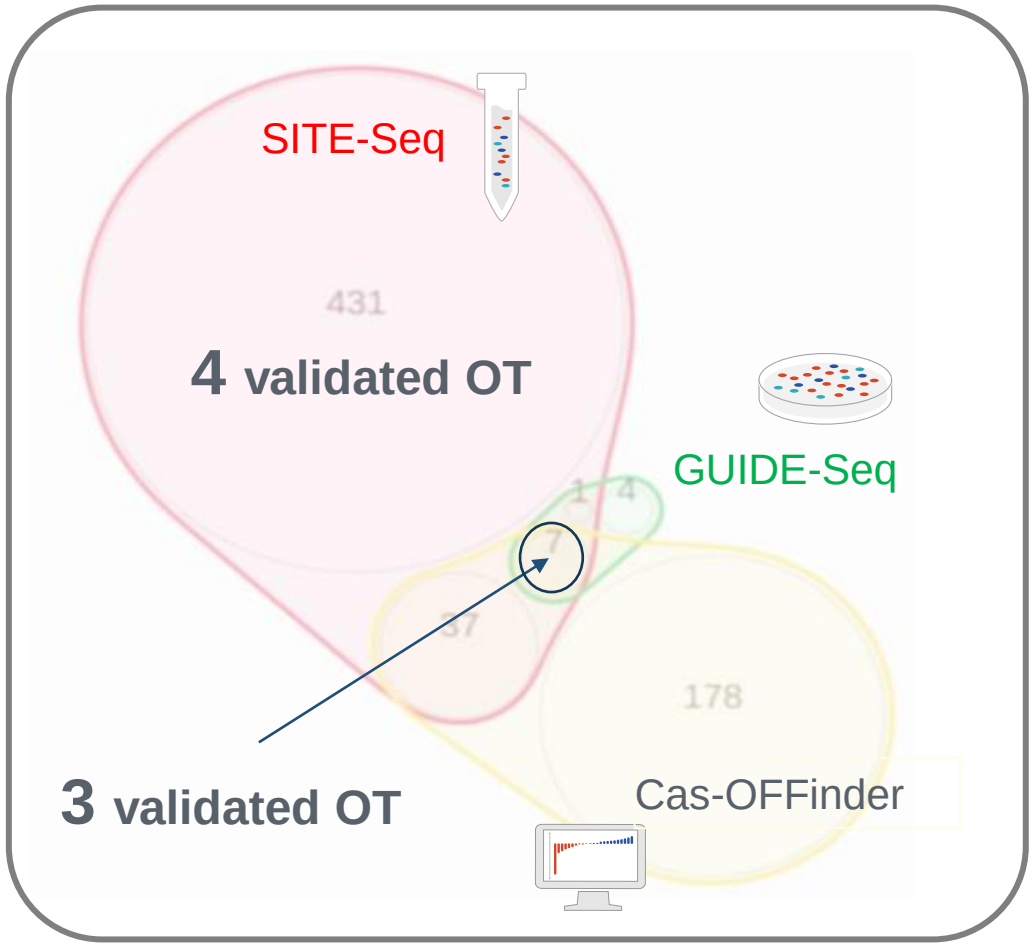
Targeted Amp-Seq NGS follow-up

In Vivo Programs

- Dose responses using drug product formulation
- Therapeutically relevant human primary cell type(s) (2 donors)
- Dose range to exceed projected therapeutic exposure (≥10X)
- Validation: off-target indels detected in edited cells

Data above is a representative example

Validation of Off-Target Editing in Primary Human Hepatocytes at Supersaturating LNP CRISPR Concentrations to Maximize Sensitivity



658 potential off-target loci

7 validated off-target (OT) loci

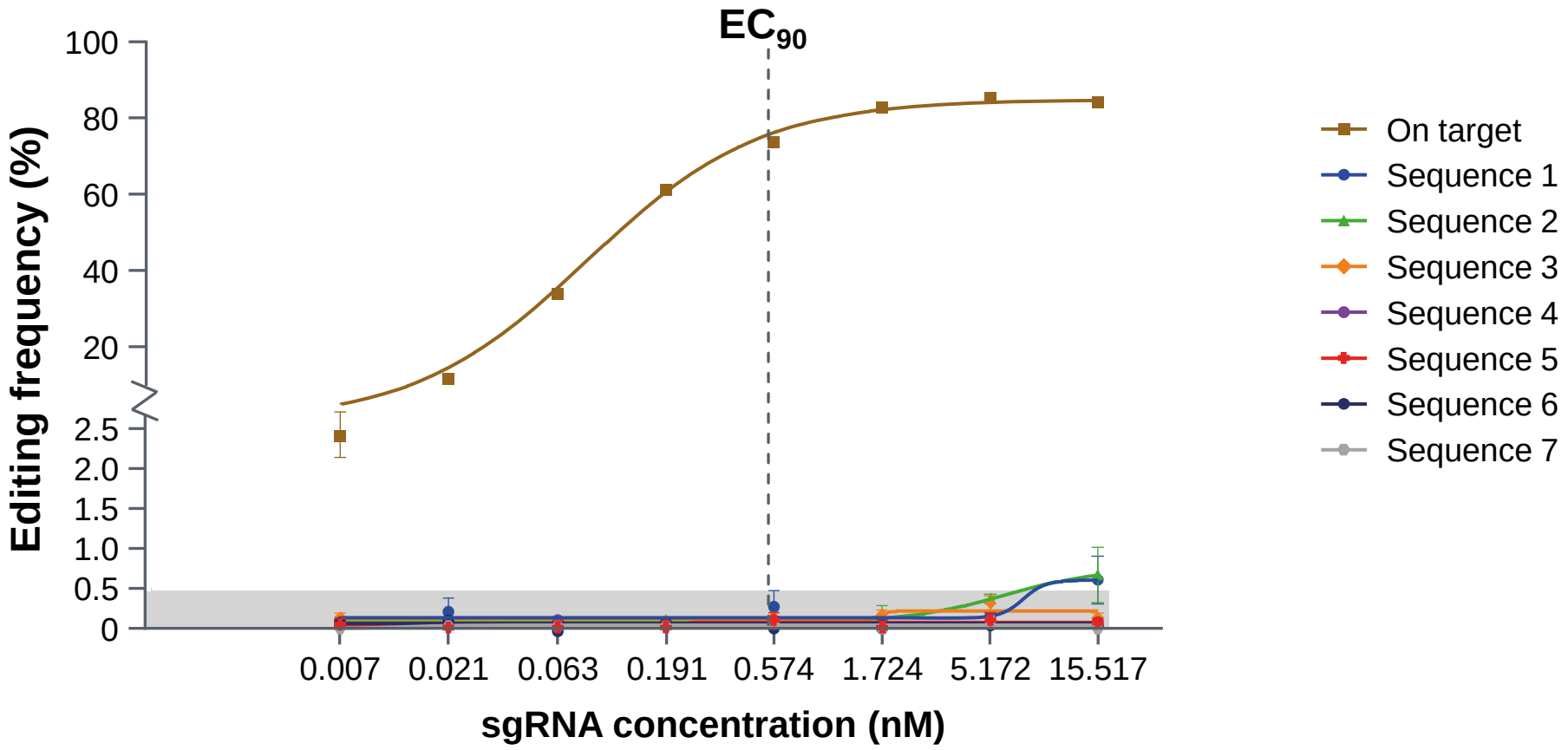
2 in introns and 5 in intergenic regions

- SITE-Seq discovered **100%**
- GUIDE-Seq and Cas-OFFinder discovered the same 3 out of 7 validated off-target loci **43%**
- Eliminate gRNA with validated off-target indels in regions of the genome associated with cancer

Data above is a representative example

Intellia THERAPEUTICS

In Vitro: No detectable off-target editing with pharmacologic concentration of sgRNA



EC_{90}, concentration inducing 90% of maximal effect; sgRNA, single guide RNA

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Strategic Collaborations

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Growing Intellia's Impact on Patients Through Strategic Collaborations and Business Development

Increasing shareholder value:

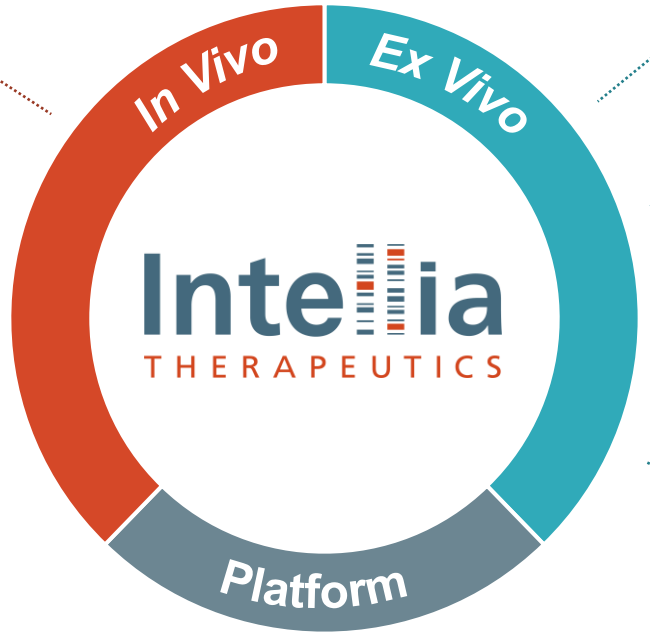
- Leveraging our technology while retaining rights to key areas of focus
- Accelerate development of programs outside key areas of focus
- Expand our pipeline with valuable rights in future commercial success
- Access external expertise to enhance our platform

Genetic diseases

REGENERON

Ophthalmology

SPARINGVISION
GENOMIC MEDICINES FOR OCULAR DISEASES



rewrite
THERAPEUTICS

Immuno-oncology (IO)

AVENCELL

IO (NK Cells)

ONK
THERAPEUTICS

Autoimmune diseases (CD19)

kyverna

Sickle cell disease and IO

NOVARTIS

Intellia
THERAPEUTICS

Foundational Partnerships Provided Access to R&D Capabilities

REGENERON

- Up to 15 *in vivo* targets with a mix of co-developed and licensed programs
  - Liver-centric product development
- **ATTR:** First selected Co/Co program
  - Intellia is lead party; Regeneron will share 25% of costs and profits
- **Hemophilia A and B**: Co/Co agreements based on targeted insertion capabilities
  - Regeneron is lead party; Regeneron will share 65% of costs and profits
- *In vivo* targets exclusively developed by Regeneron:
  - Up to $320M in milestones per target
  - High single-to-low-double-digit royalties
- Non-exclusive license to certain platform IP on up to 10 *ex vivo* CRISPR products in defined cell types

NOVARTIS

- Advancing Phase 1/2 study for sickle cell disease based on CRISPR/Cas9-edited HSCs
- Research collaboration term concluded in December 2019
- Novartis selected various CAR-T, HSC and OSC targets for development
  - Up to $230M in milestone payments per product
  - Mid single-digit royalties
  - All non-selected targets revert to Intellia

Intellia THERAPEUTICS

Intellia, Cellex and Blackstone Launch AvenCell to Develop Allogeneic Universal CAR-T Cell Therapies, With $250M Committed Funding

Concurrent Cellex deal enables expansion and acceleration of Intellia's ex vivo pipeline with expanded manufacturing capabilities

Intellia THERAPEUTICS

- Rights to **two Co/Co options** in U.S. and key European countries on allogeneic universal CAR-T products
  - Intellia leads U.S. commercialization
- Additional **validation** of Intellia's proprietary allogeneic platform
- Hold substantial **equity stake** in NewCo
- **Access to Cellex cell therapy manufacturing site and allogeneic cell donations** via a preferred relationship
  - Supports Intellia's wholly owned *ex vivo* pipeline
  - Expanded capacity to handle additional pipeline growth

AVENCELL

- Expansion of **existing Intellia-GEMoaB collaboration**
- Combines **GEMoaB's switchable universal CAR-T cell technology** with **Intellia's allogeneic platform** enabled by advanced CRISPR engineering
- Addition of **validating partner** Blackstone and **infusion of $250M capital** to prosecute pipeline
- Clinical-stage autologous products from GEMoaB with **near-term milestones**
- **Seasoned management team**
- Access to Cellex cell therapy **manufacturing site**

Intellia

THERAPEUTICS