

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

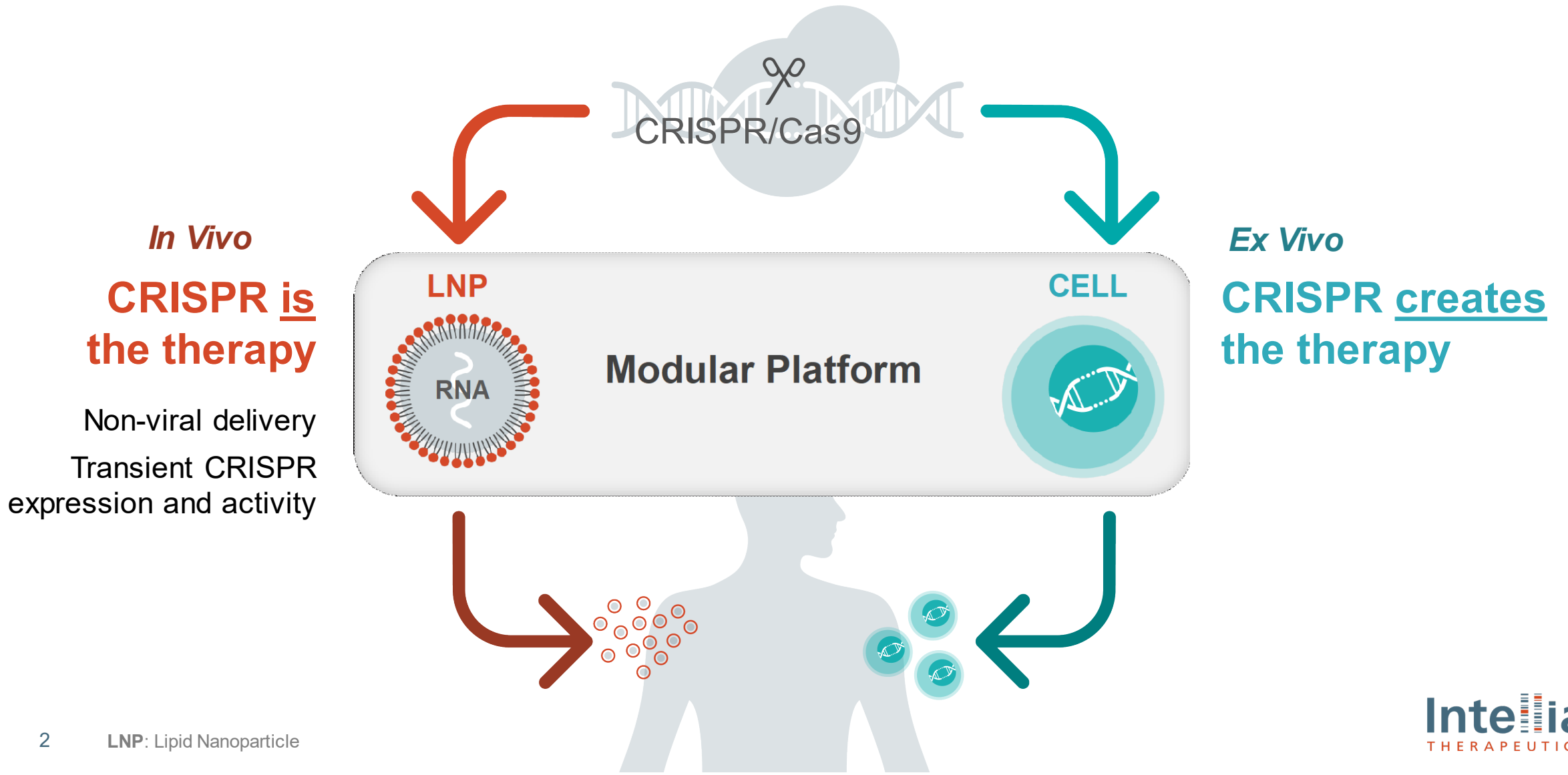


Development of *In Vivo*, Systemic CRISPR-Based Therapeutics

24th Annual Meeting of the American Society
of Gene and Cell Therapy

Laura Sepp-Lorenzino, Ph.D. | May 11, 2021

Developing CRISPR/Cas9 Genome Editing Therapies



In Vivo

CRISPR is the therapy

GENETIC DISEASES

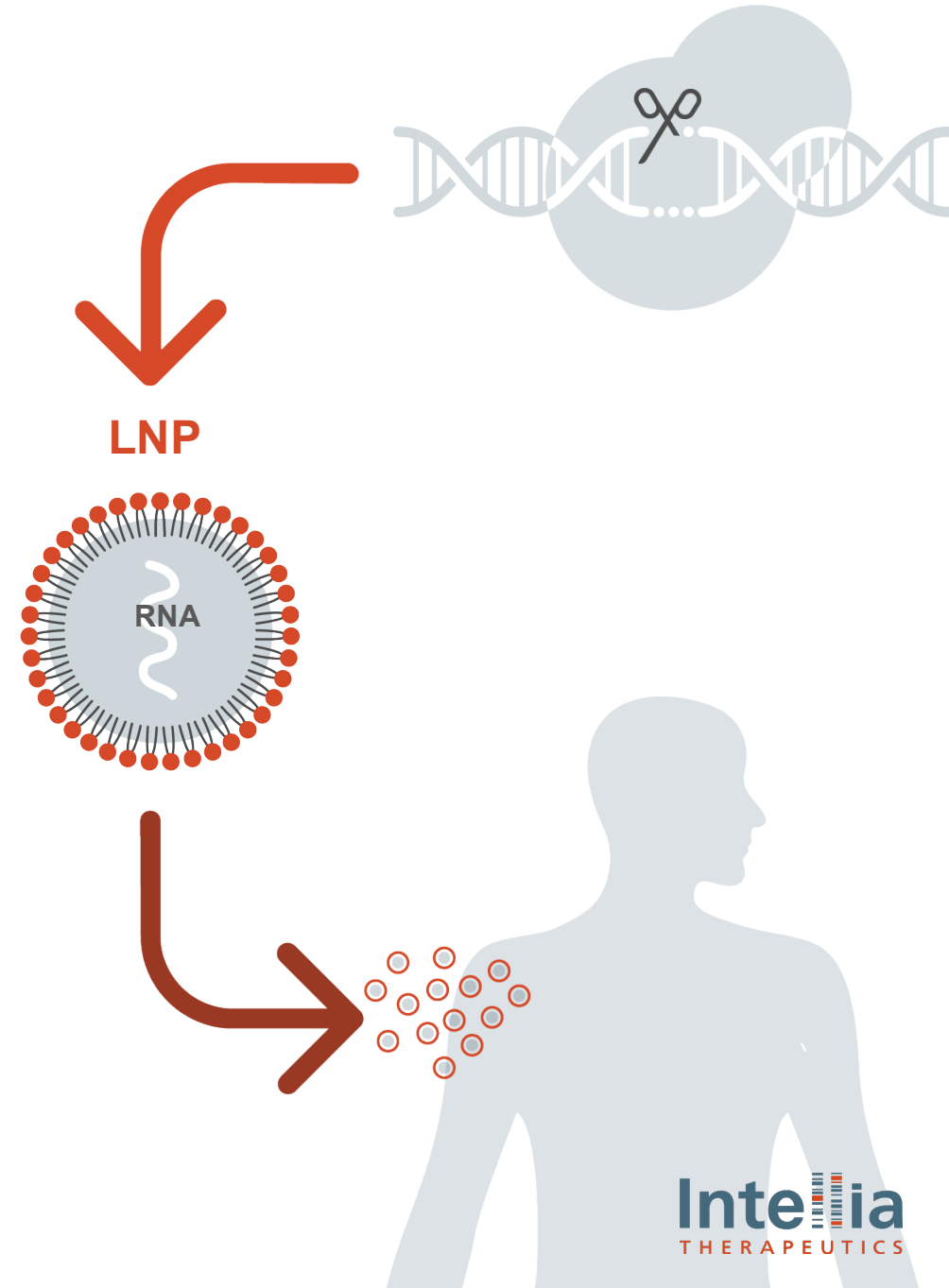
Strategic Advantages:

Systemic non-viral delivery of CRISPR/Cas9 provides transient expression

Potential curative therapy from single dose

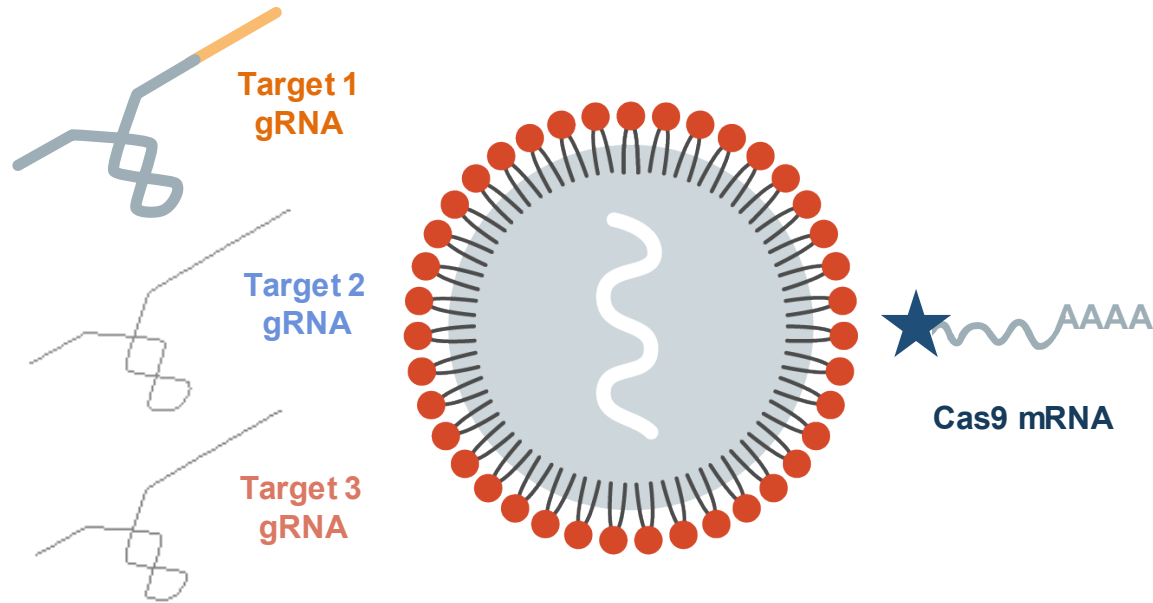
Permanent gain of function with targeted gene insertion

Delivery to multiple tissue types enabling new therapeutic applications



Intellia's *In Vivo* Liver Editing Modular Platform Employs Non-Viral Delivery

Lipid Nanoparticles (LNPs)



gRNA target site specificity
defined by 20mer at 5' end

Transient Cas9 expression
from mRNA

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

Modular Approach to Unlocking Treatment of Genetic Diseases

PROPRIETARY LNP DELIVERY SYSTEM

Transient expression

Large cargo capacity

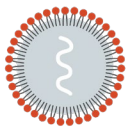
Redosing capability

ENABLES MULTIPLE EDITING STRATEGIES

Remove

KNOCKOUT

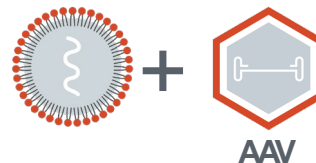
Knockout toxic or compensatory genes



Restore

INSERT

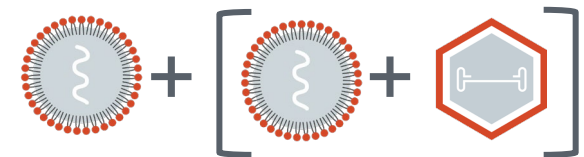
Introduce functional DNA sequence



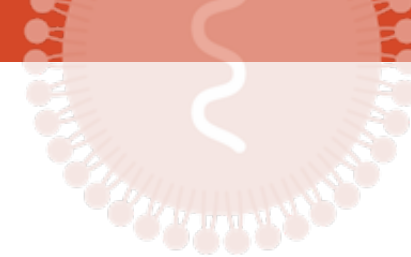
Remove / Restore

CONSECUTIVE EDITING

Any combination of knockout (KO) and insertion strategies



NTLA-2001 for Transthyretin Amyloidosis (ATTR)



ATTR

- Caused by accumulation of misfolded transthyretin (TTR) protein, which affects **nerves, heart, kidneys and eyes**
- Chronic dosing is required with current treatments
- **50,000** hATTR patients worldwide¹
- **~200-500K** wtATTR patients worldwide²

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

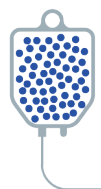
- Potential to halt and reverse disease
- Potential “one-and-done” treatment
- Expect lifelong, stable TTR reduction

NTLA-2001 Ongoing Global Phase 1 Study

Two-part, open-label, multi-center study in adults with hATTR with polyneuropathy, with plans to evaluate in a broader ATTR population of both polyneuropathy and cardiomyopathy patients

Total Enrollment:
Up to 38 patients,
age 18 to 80 years

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



PART I Single-Ascending Dose

N = Up to 30 subjects*

Up to 4
dose-escalation
cohorts

PART II Single Dose Expansion Cohort

N = 8 subjects

Administer optimal dose
selected from Part I

Potential to
advance toward
a pivotal trial for
NTLA-2001 based
on Phase 1 safety
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data

PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK and PD

- Measure serum TTR levels

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of neurologic function

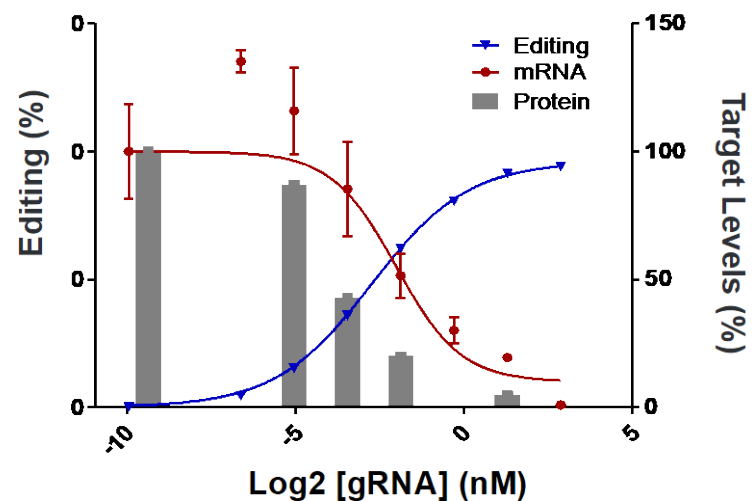
- Neuropathic impairment endpoints include NIS (Part 1 and 2) and mNIS+7 (Part 2 only)

Nonclinical Studies in Support of First-in-Human Trial Applications

Pharmacology

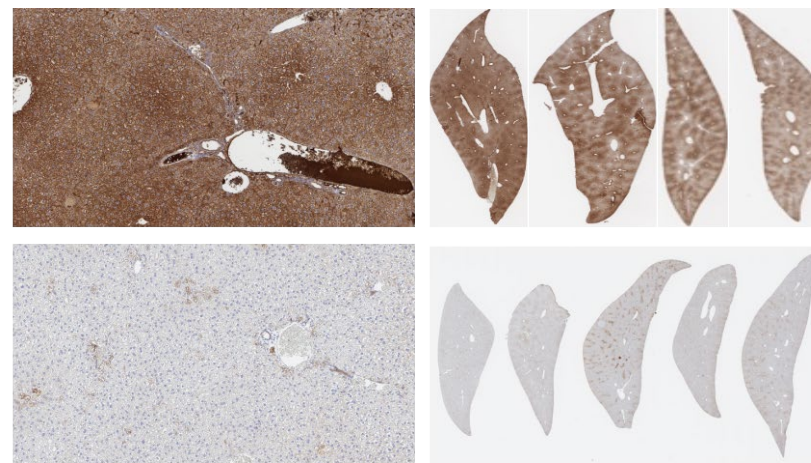
Goal: Determine on-target edit results in desired pharmacological outcome

- Primary pharmacology *in vitro*
 - Primary human hepatocytes
 - Multiple donors
- Primary pharmacology *in vivo*
 - Editing, pharmacokinetics and pharmacodynamics
 - Humanized transgenic mice
 - Cynomolgus monkeys (may require surrogate gRNA)



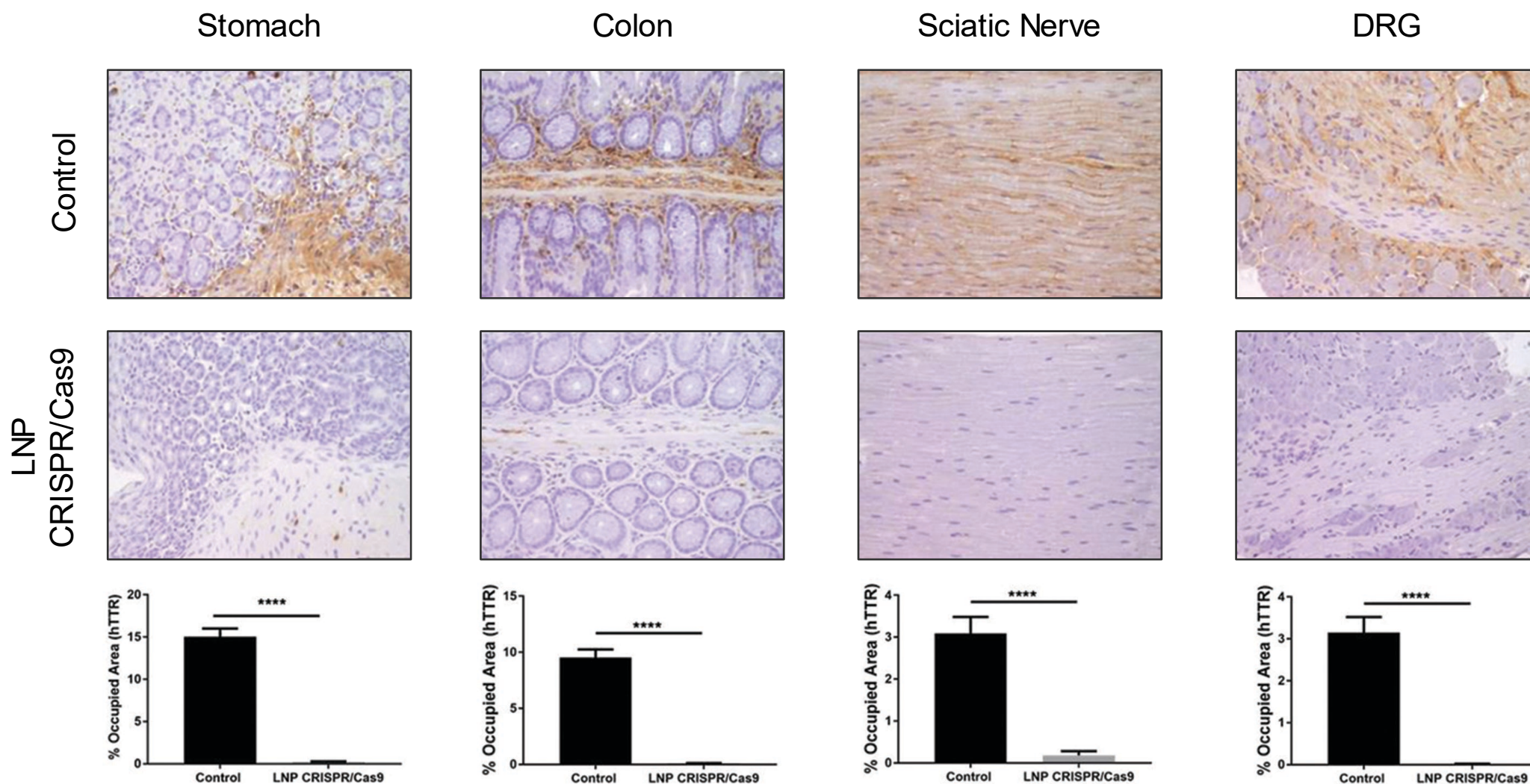
Vehicle
1 week

TTR Knockout
6 months

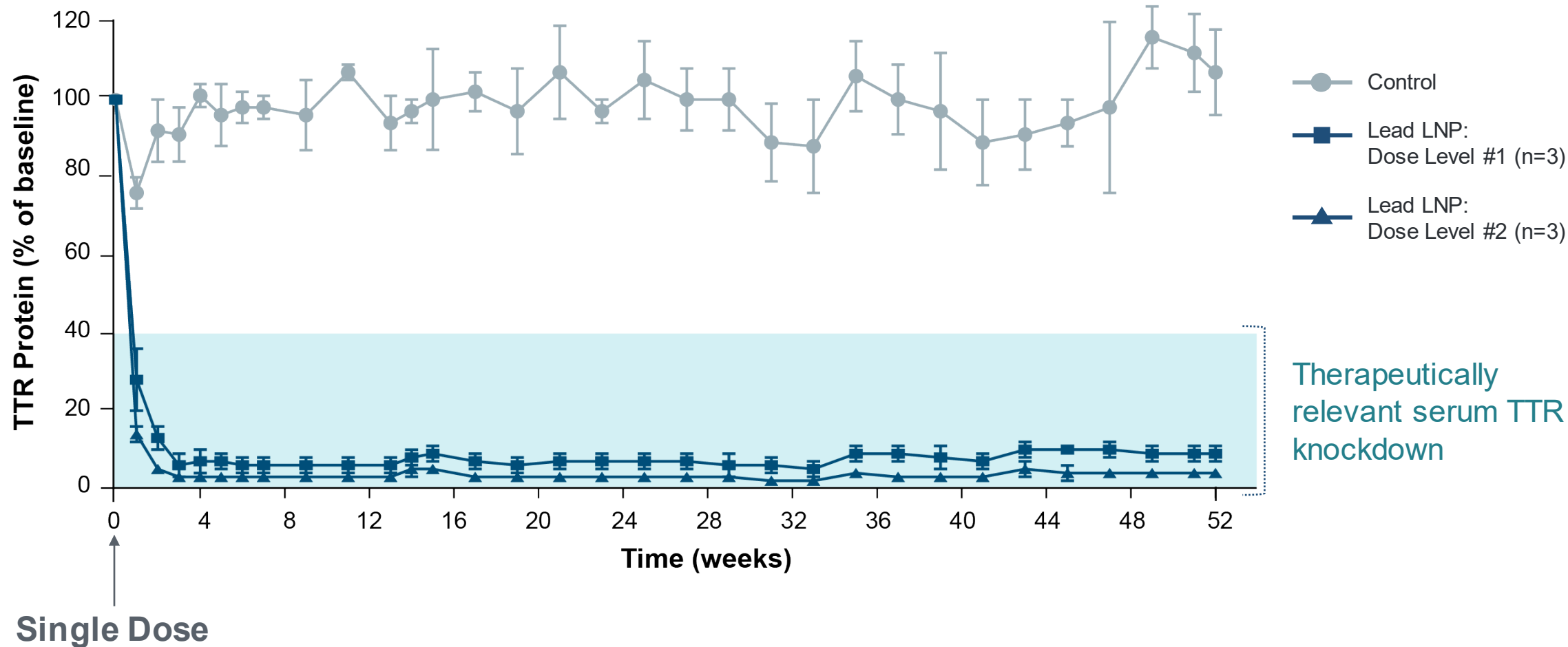


Mouse TTR Immunohistochemistry (IHC)

Decreased TTR Protein Deposition in Tissues in hV30M *TTR* Transgenic Mice

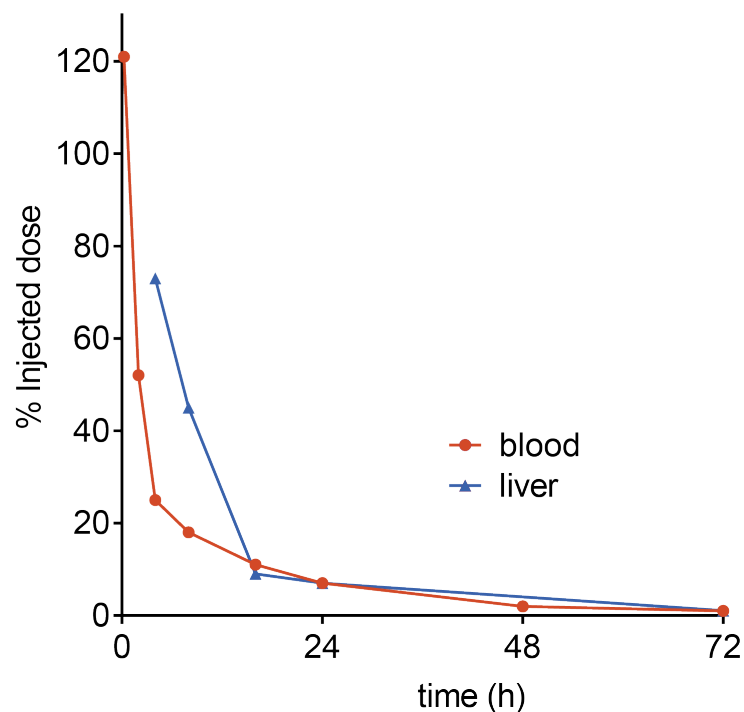


Sustained >95% Serum TTR Protein Reduction After a Single Dose in NHPs

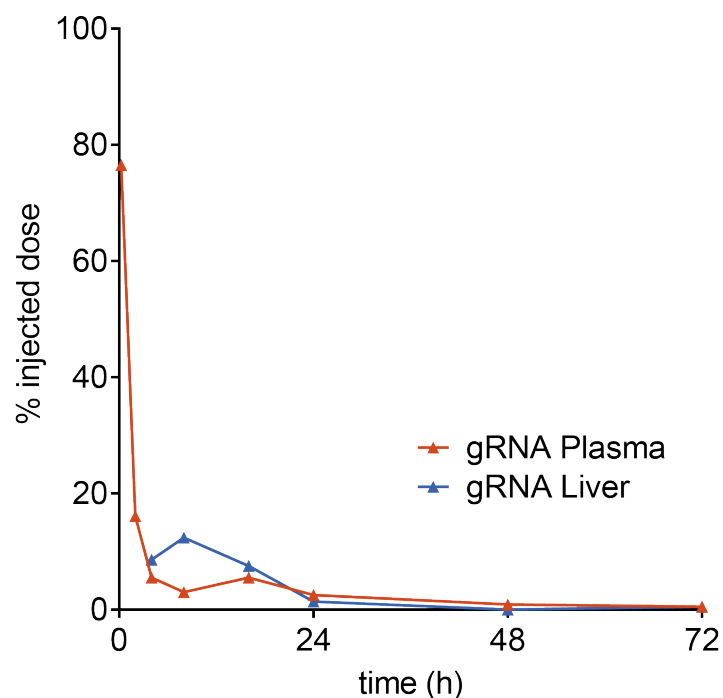


Transient Exposure to LNP and RNA Cargo After Single Administration in NHPs

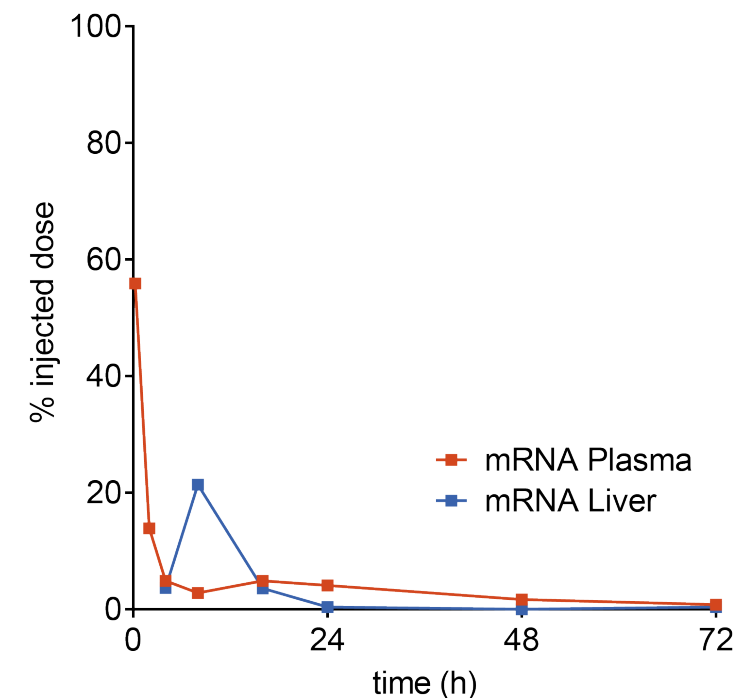
Ionizable Cationic Lipid



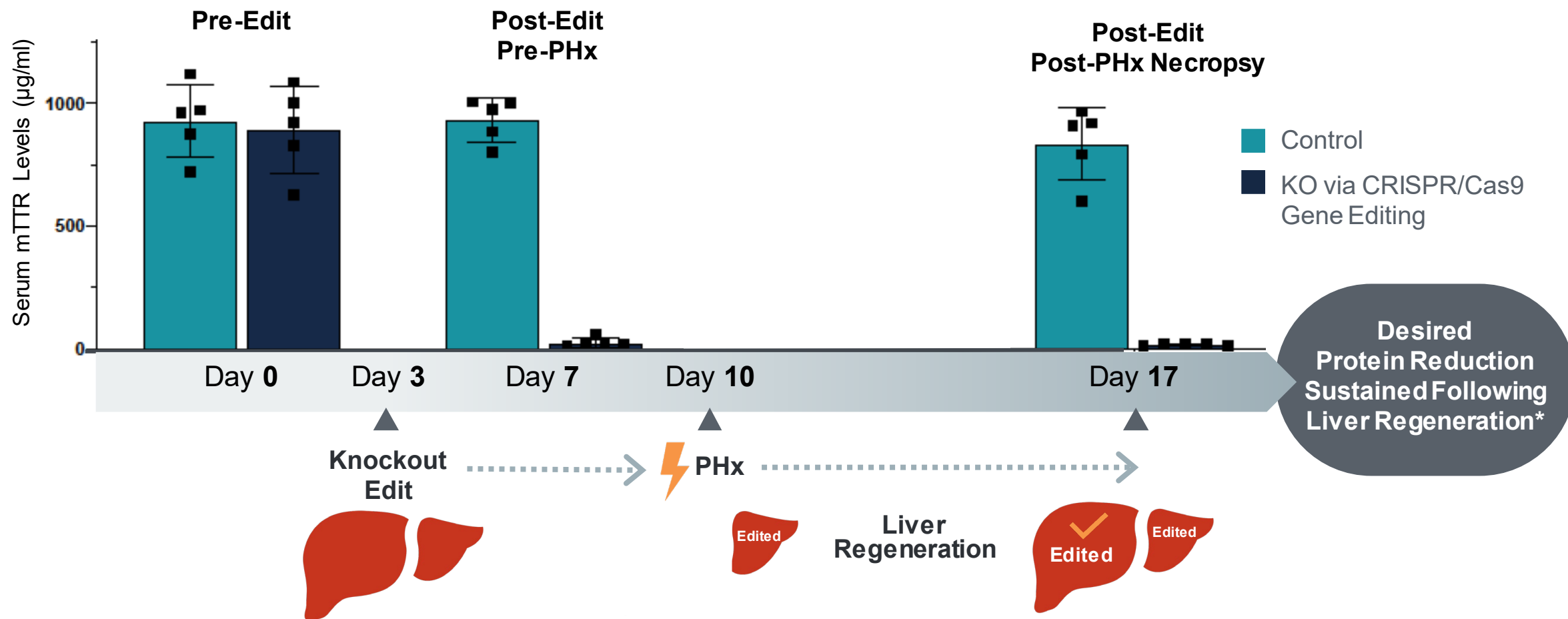
gRNA



Cas9 mRNA



Protein Reduction Remains Unchanged Following Murine Liver Regeneration



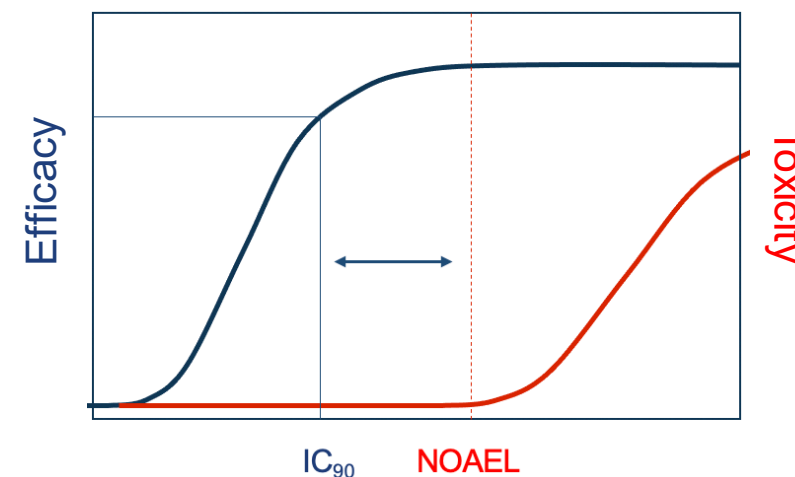
Gene editing rate similarly remains unchanged post-PHx by NGS analysis¹

Nonclinical Studies in Support of First-in-Human Trial Applications

Primary Safety and Toxicity Evaluation

Goal: Determine drug safety by evaluating adverse effect profiles, organ and tissue exposures, and margins of efficacy vs. toxicity

- Types of studies
 - Non-GLP on-target exaggerated pharmacology and duration
 - GLP single dose toxicology
 - GLP safety pharmacology
- Dose response, including multiples of therapeutic dose
 - Toxicokinetics and biodistribution
- Establish Not Observed Adverse Effect Level (NOAEL) and estimate safety margin



Non-Clinical Studies in Support of First-in-Human Trial Applications

Genotoxicity

- Orthogonal techniques used to characterize mutagenicity and large-scale chromosomal integrity
 - Potential gRNA off-target discovery and validation
 - DNA structural variants
 - Short-read NGS, long-read sequencing of long-range PCR amplicons
 - KromaTiD pinpoint DNA FISH direct visualization
- Standard ICHS2(R1) genotoxicity evaluation (bacterial Ames test) not relevant

Key Attributes for Identifying Therapeutic Guide RNA (gRNA)

High Efficacy

- Edit the genome at the intended target site
- Target site conserved across patient population
- High potency
- Edit results in desired pharmacological outcome

High Specificity

- Avoid validated unintended edits elsewhere in the genome
- Avoid DNA structural variants associated with toxicity and transformation
- Genotoxicity safety window vs. expected therapeutic exposure

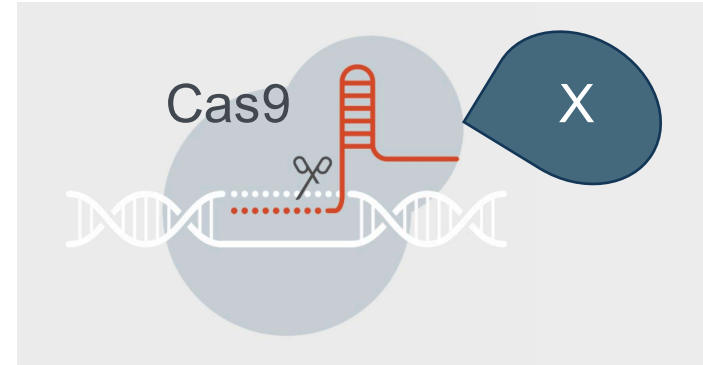
Potential Off-Target Editing with CRISPR/Cas9 is Exclusively RNA-Dependent

CRISPR Cleavase*



**gRNA sequence-dependent
off-target editing only**

Other Modalities



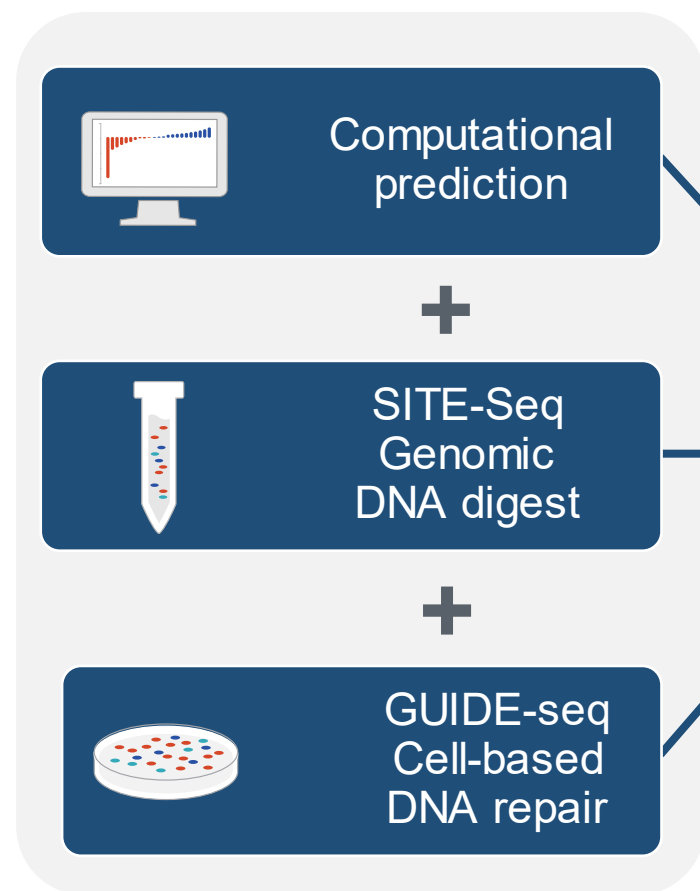
**gRNA sequence-dependent
off-target editing**

+

**Stochastic, sgRNA sequence-
independent off-targets
Dependent on X functionality**

Comprehensive gRNA Specificity Assessment: Off-Target Workflow

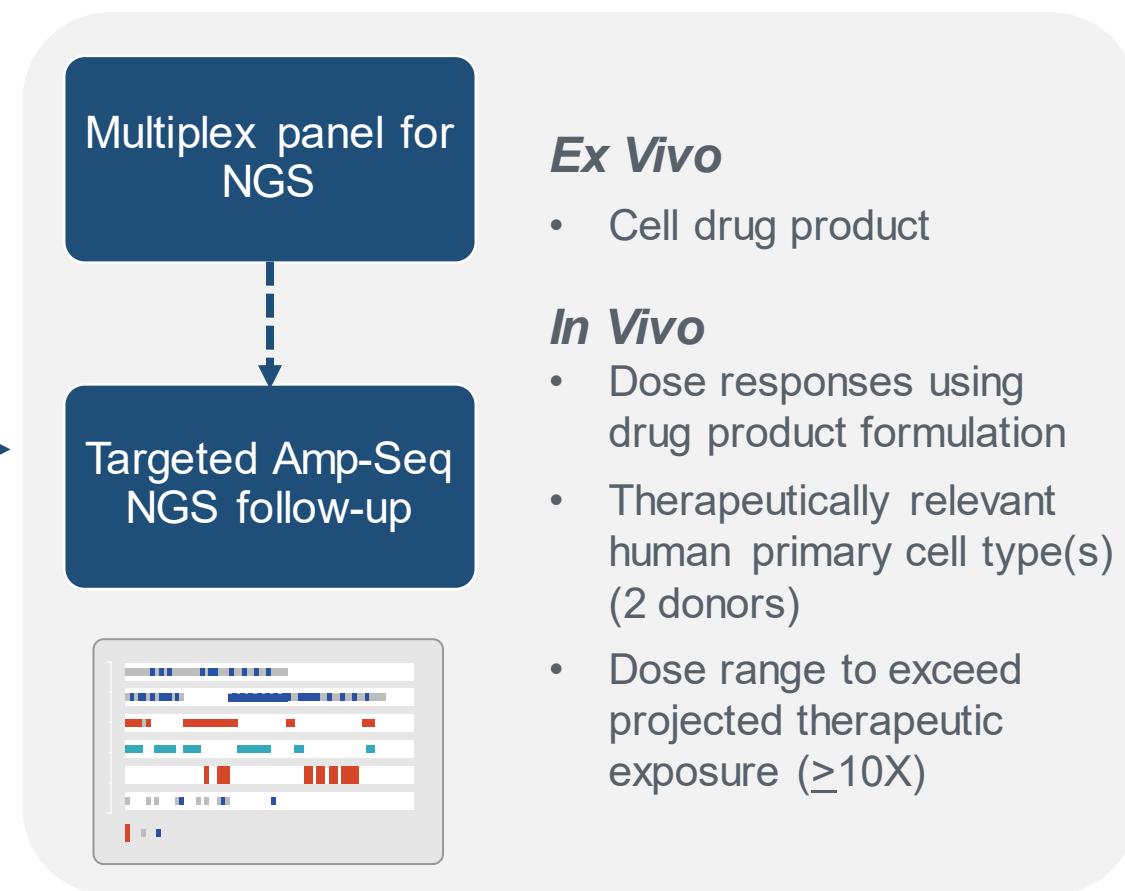
1: Discovery of Potential Off-Target Edits



Aggregate
ALL
potential
off-target
genomic loci



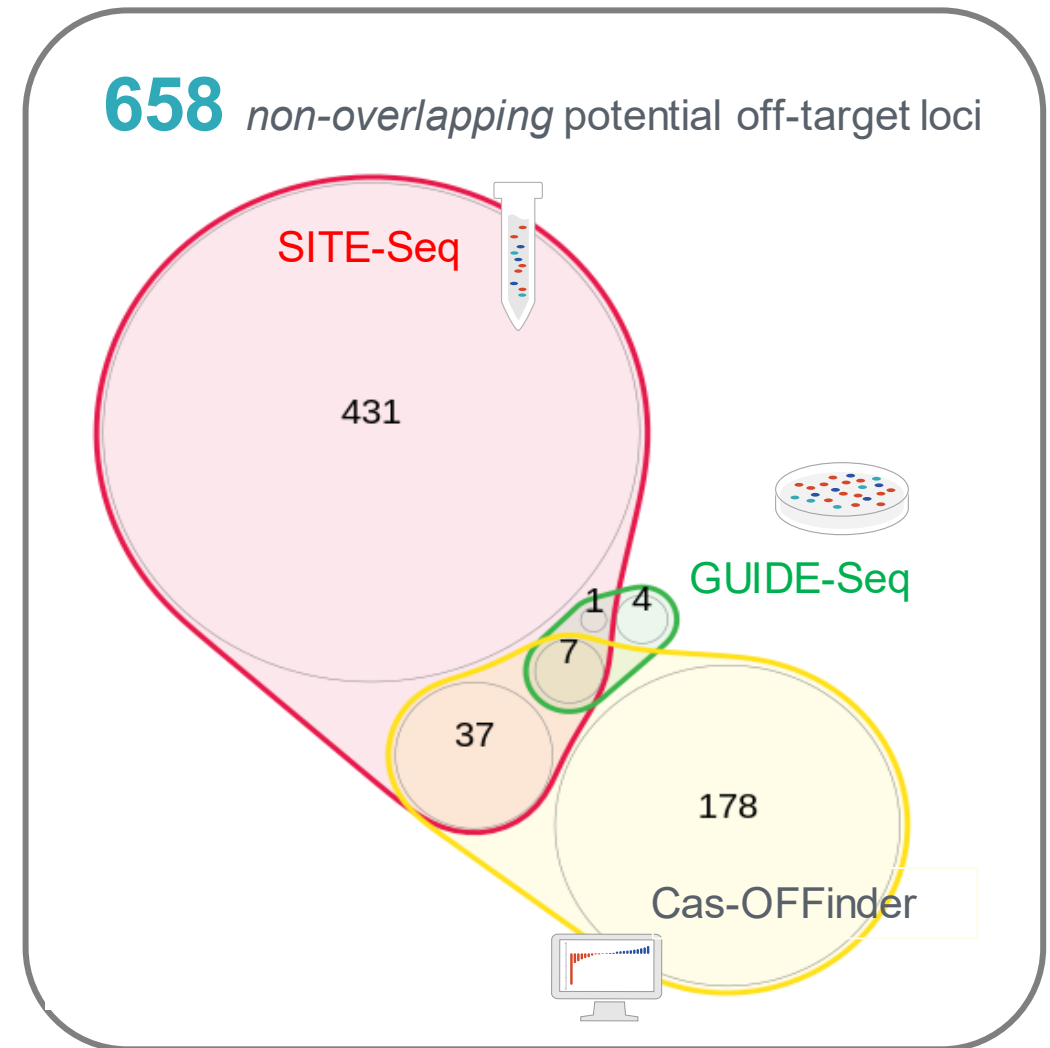
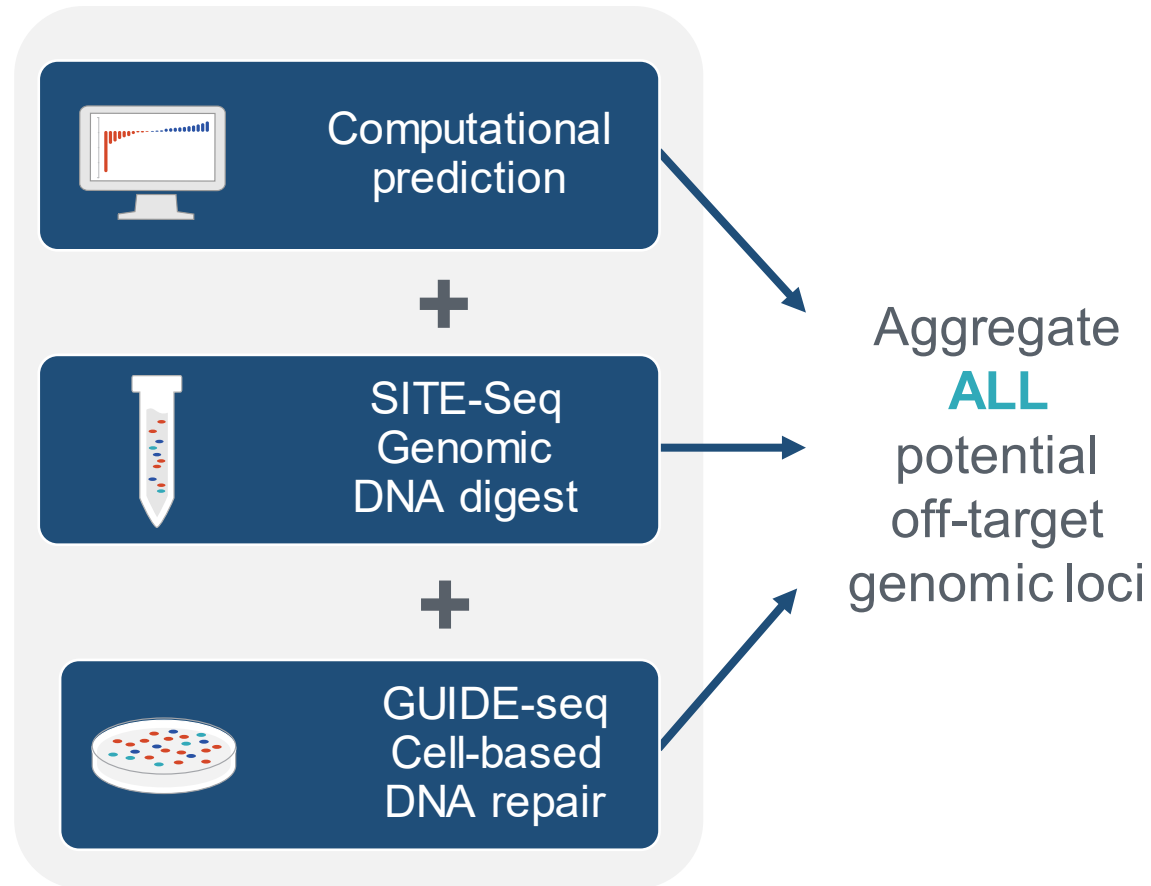
2: Validation of Off-Target Edits in Cells



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

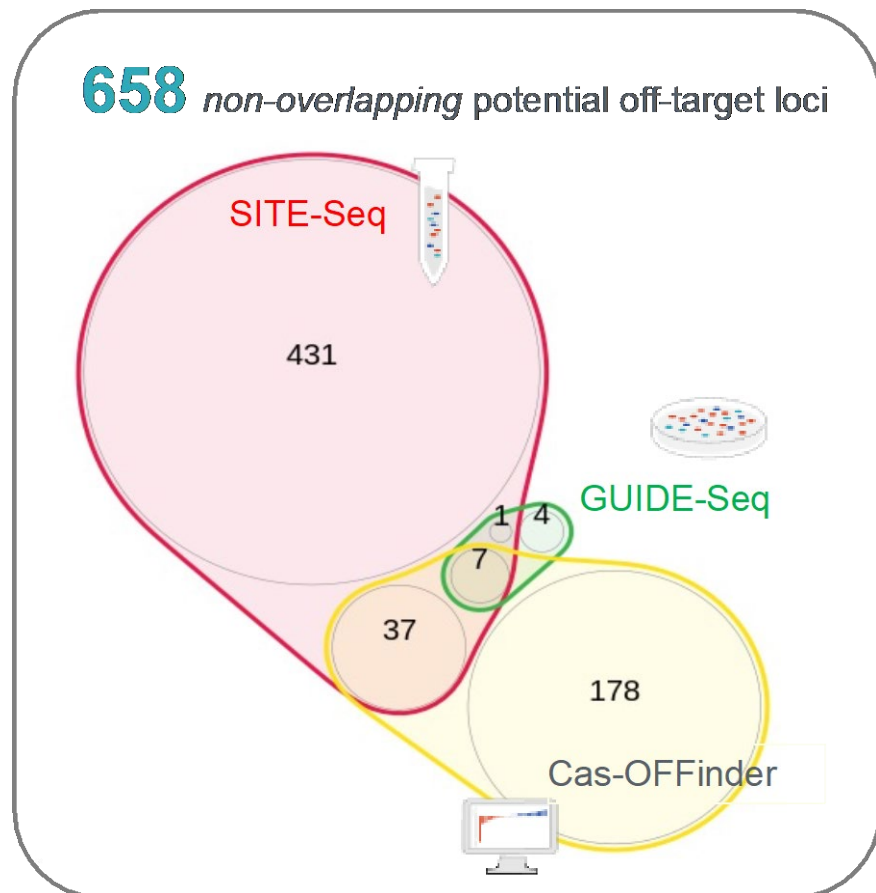
Representative Example

1: Discovery of Potential Off-Target Edits

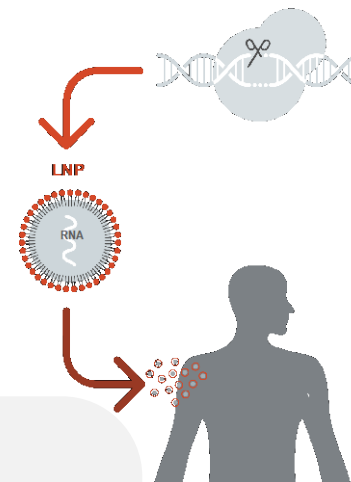
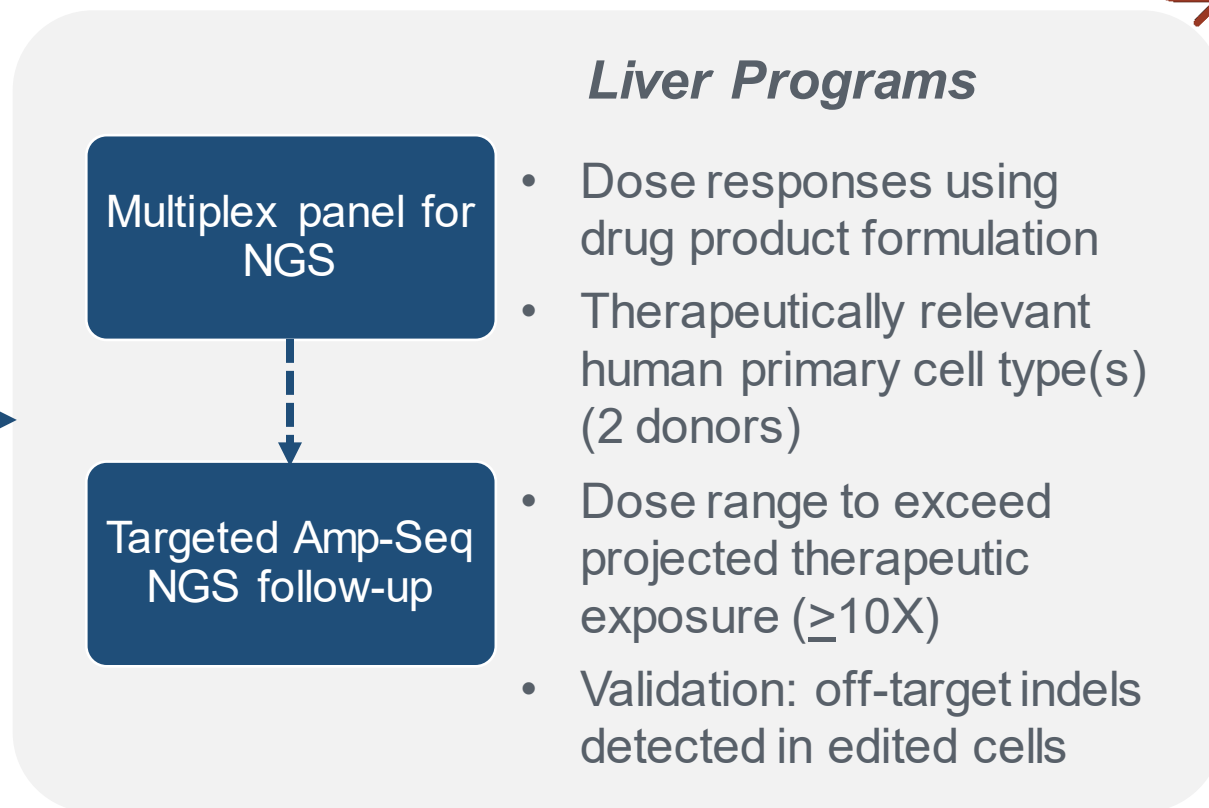


Off-Target Workflow In Practice: Representative Example

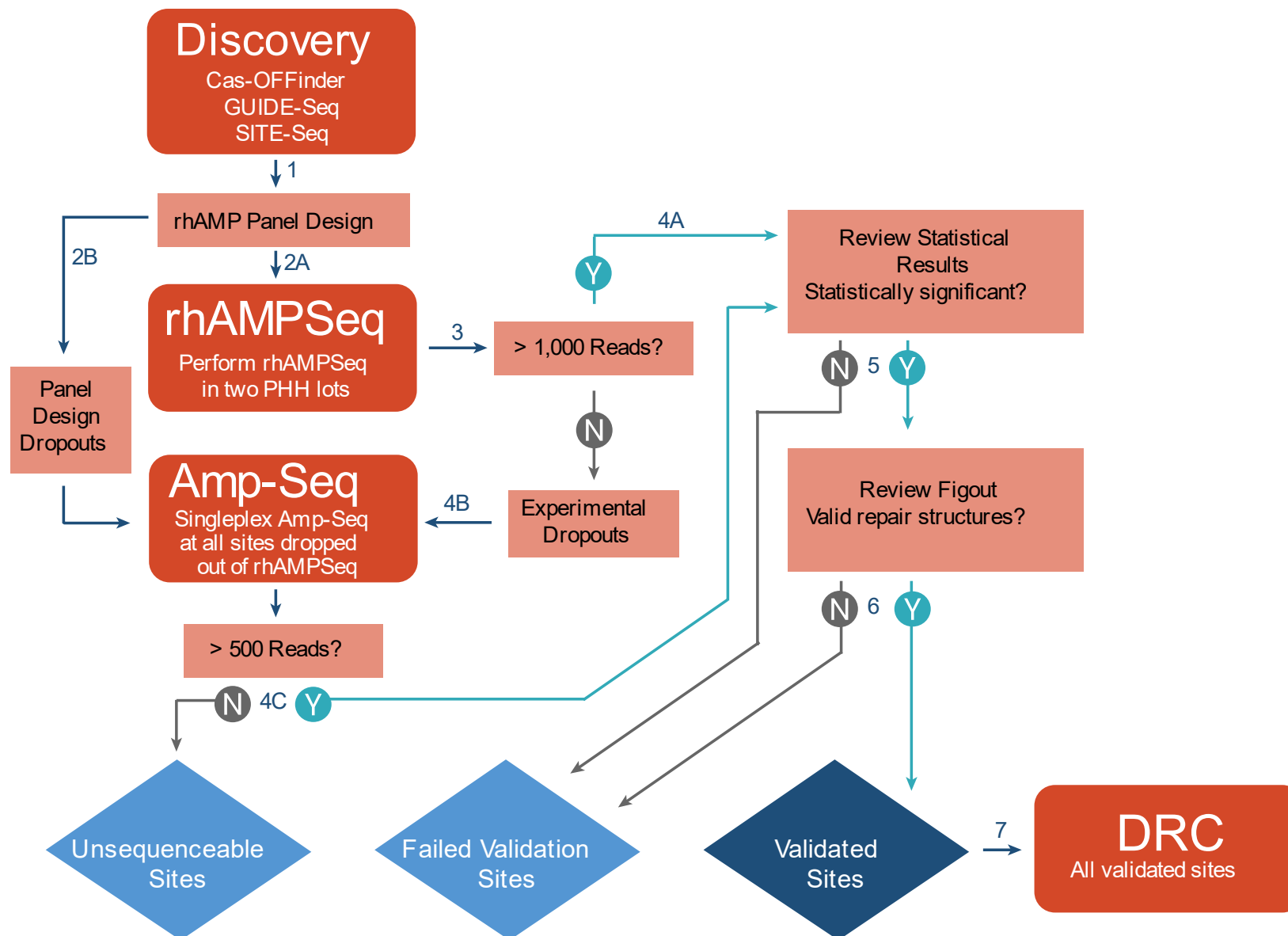
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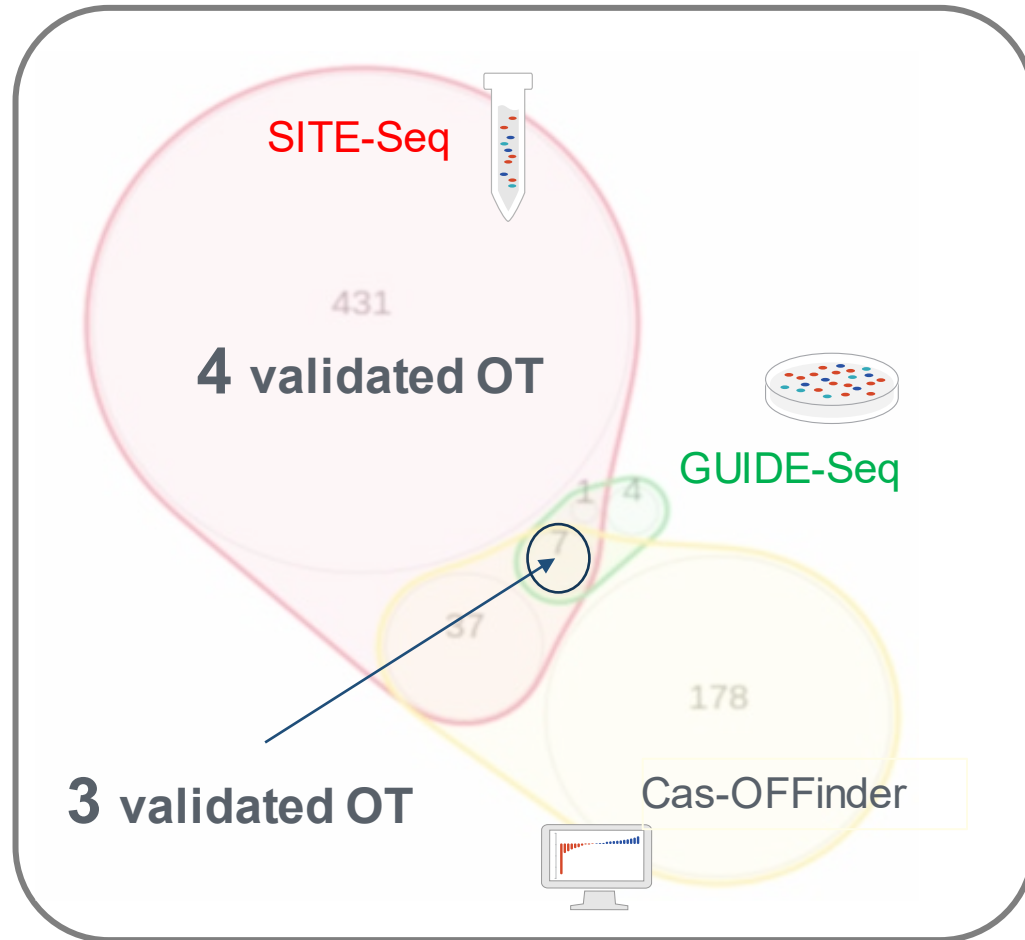
2: Validation of Off-Target Edits in Cells



Potential Off-Target Editing Characterization Workflow



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



658 potential off-target loci

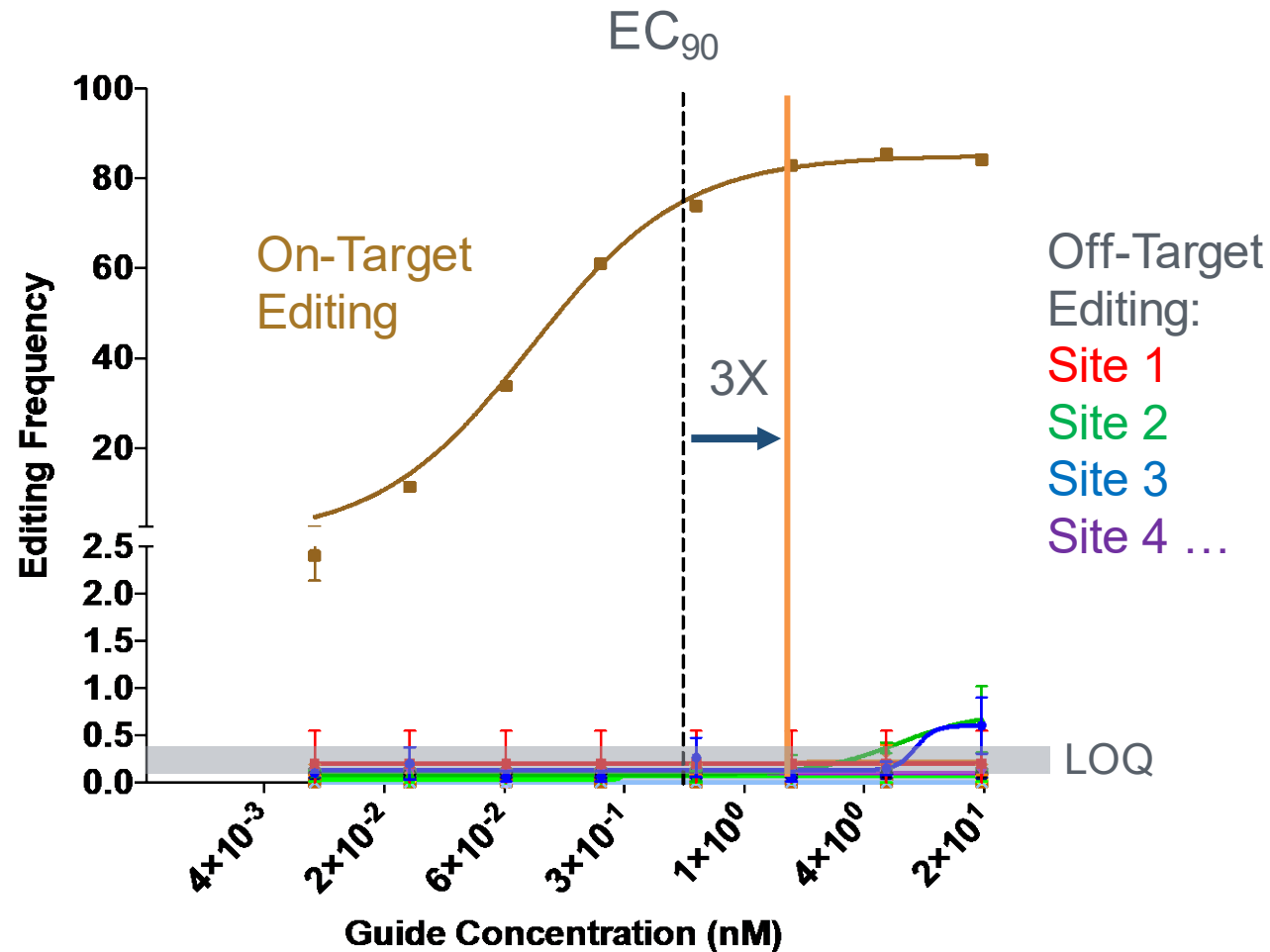


7 validated off-target (OT) loci

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 associate with cancer

Zero Detectable Off-Target Editing Observed at LNP CRISPR Concentrations Up To 3X Greater than Pharmacologic Dose



- Dose response in primary human hepatocytes (2 donors)
- Super-saturating concentrations of LNP CRISPR/Cas9 exceeding what is pharmacologically achievable *in vivo*
- Large genotoxicity safety window

Dose Range Selection for First-in-Human Studies

Minimal Recommended Starting Dose (MRSD)

- Based on non-clinical PK/PD/safety evaluation
- Standard allometric scaling
- Application of safety factors
- Consideration for pharmacological activity

$\text{NOAEL} \times \text{allometric scaling factor} = \text{Human Equivalent Dose (HED)}$

$\text{HED} / \text{safety factor} = \text{MRSD}$

Single-Ascending Dose



Pharmacological Active Dose (PAD)

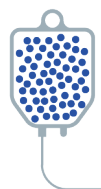
- Predicted based on *in vitro* intrinsic gRNA potency, *in vivo* data. PK modeling and allometric scaling

NTLA-2001 Ongoing Global Phase 1 Study

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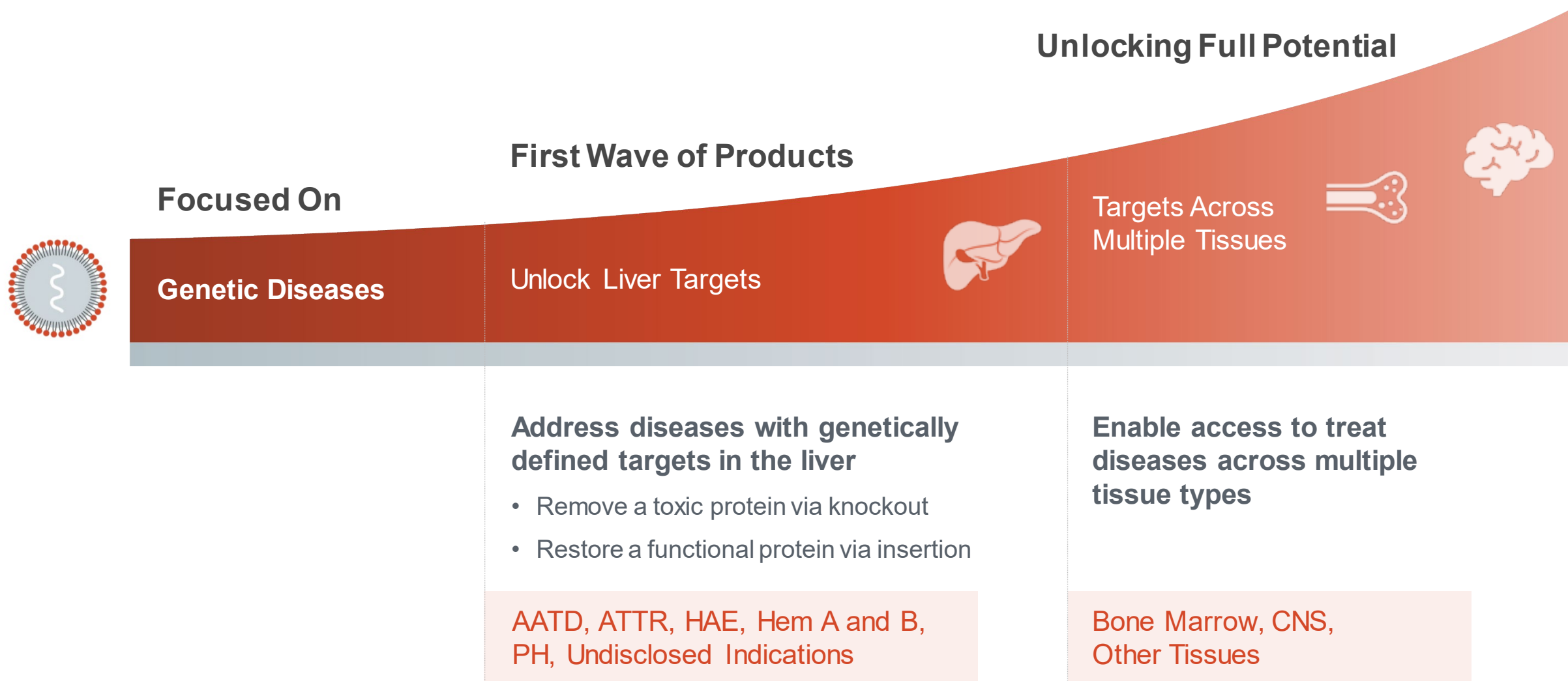
- Neuropathic impairment endpoints include NIS (Part 1 and 2) and mNIS+7 (Part 2 only)

NTLA-2001 Holds Promise to Transform the Lives of People with ATTR

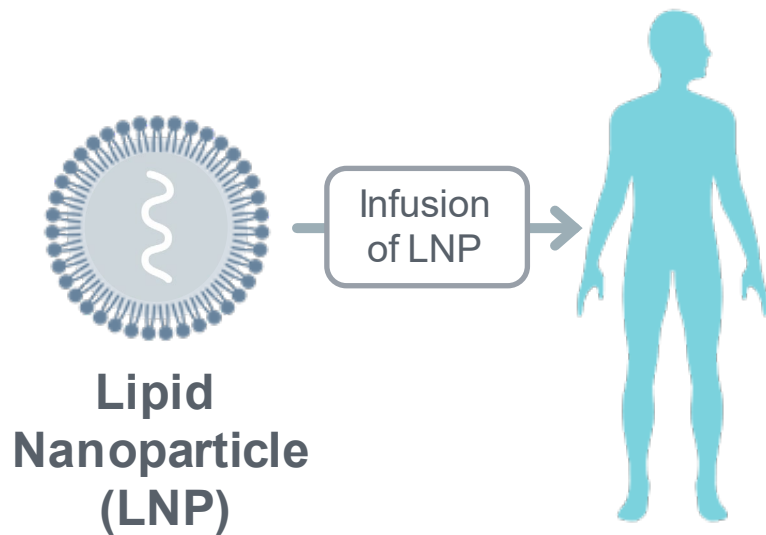
Achievements and Next Steps

- ✓ Received regulatory authorizations to initiate global Phase 1 study
- ✓ Dosed first patient with NTLA-2001 in Q4 2020
- Continue enrolling patients in global Phase 1 study to establish optimal dose
- Report interim Phase 1 data to characterize the safety and activity profile of NTLA-2001

In Vivo Pipeline Expansion Strategy



In Vivo Bone Marrow Editing for Sickle Cell Disease (SCD)



Improved safety and accessibility vs. *ex vivo* approaches

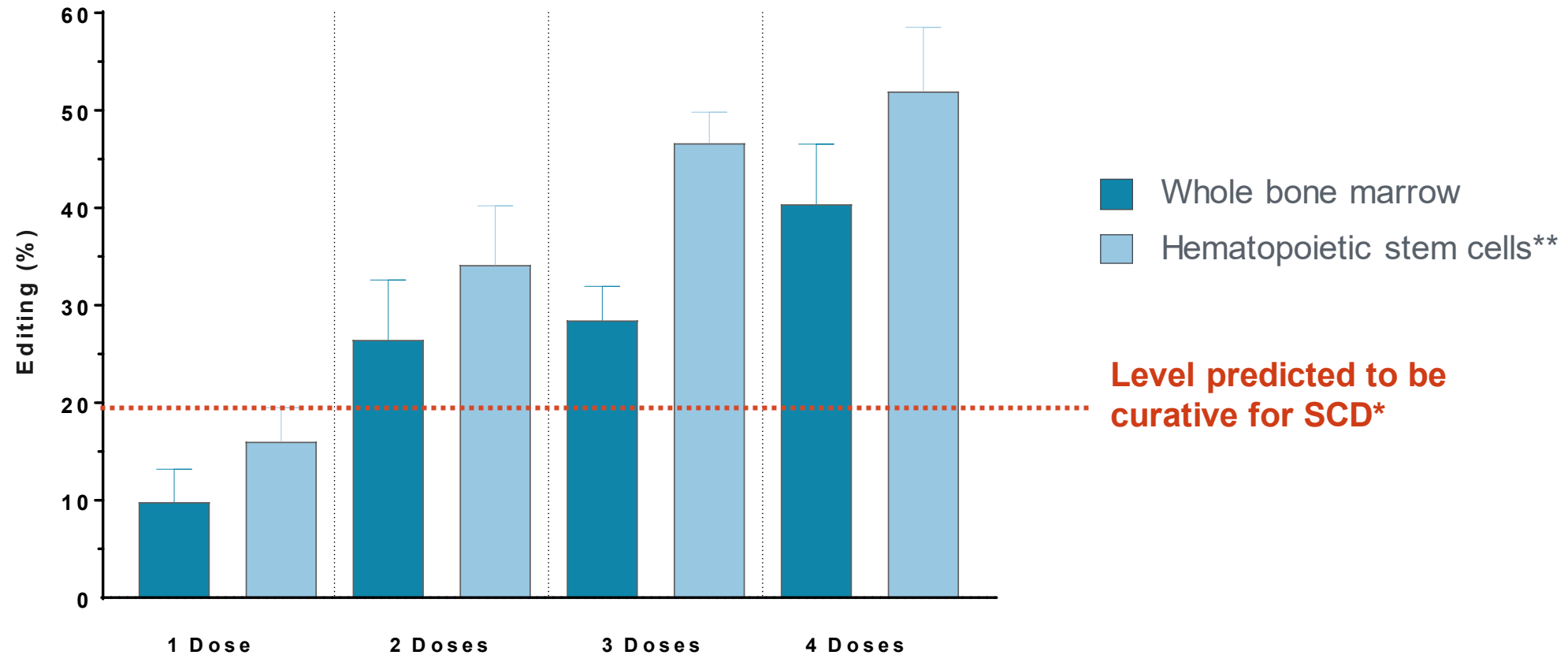
- Avoids myeloablation and associated risks of immunosuppression, malignancy, and infertility
 - Approach could become mainstream therapy for SCD
- Avoids need for complex cell manufacturing or extensive supportive care post-treatment
 - Treatment simplicity could expand access to patients in resource-poor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

Bone Marrow-Tropic LNP Enables Editing of Mouse Bone Marrow as well as Hematopoietic Stem and Progenitor Cells (HSPCs)

- Editing increases with multidosing
- Non-immunogenic LNP delivery platform may enable stepwise “treat-to-target” approach



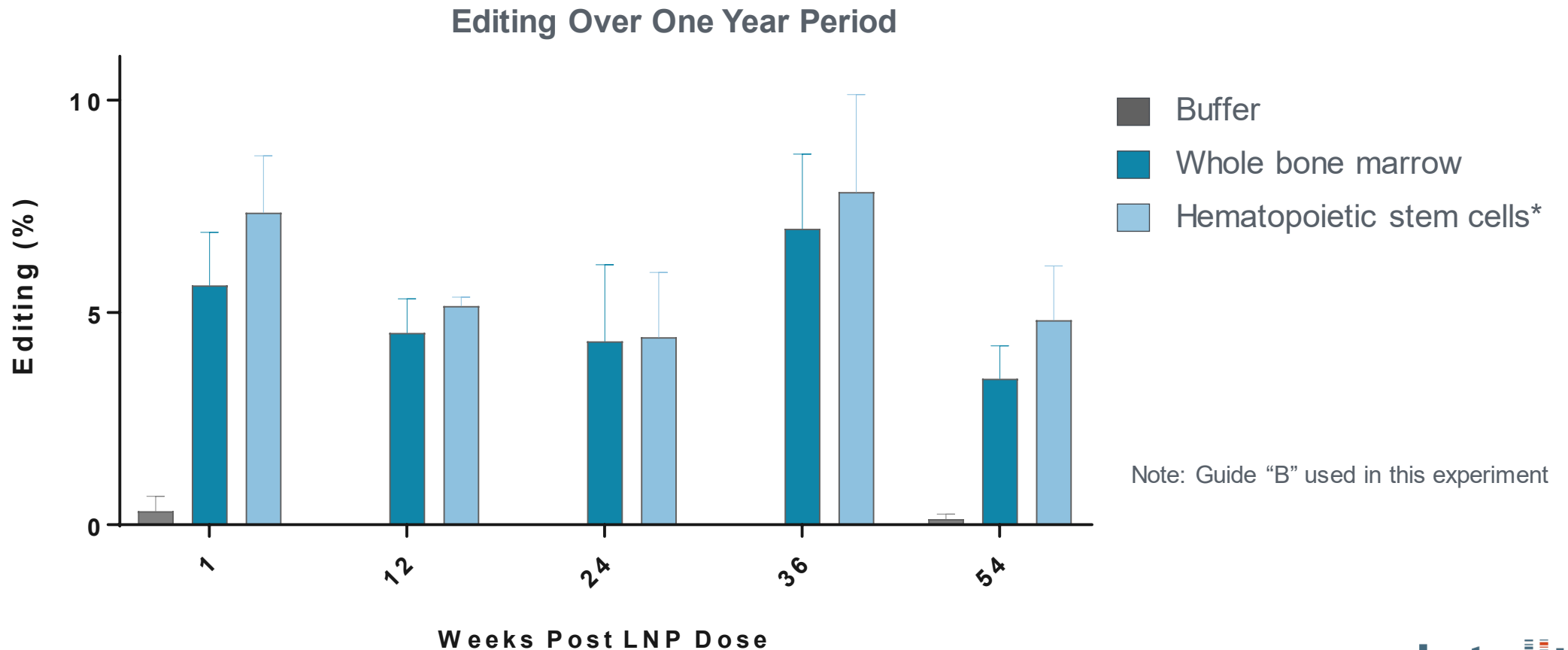
* *Blood*. 2017;130(17):1946-1948.

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

Note: Guide “B” used in this experiment

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

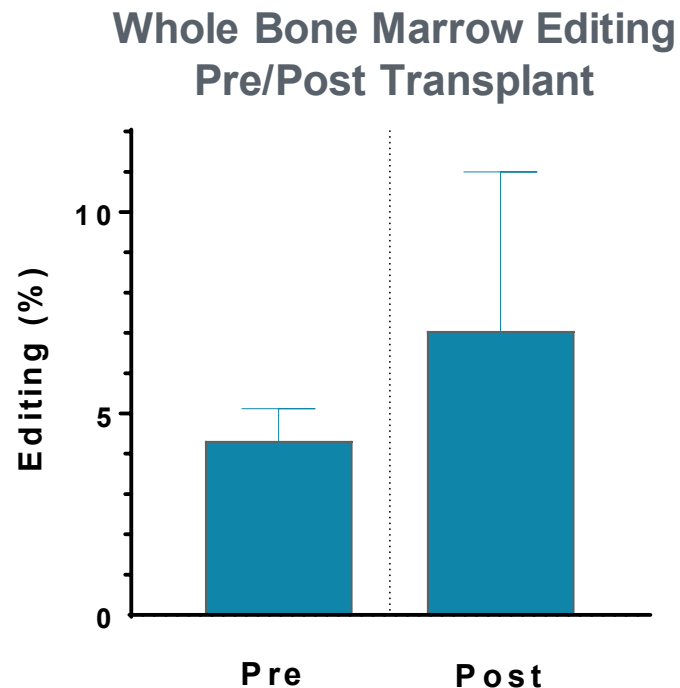


Edited HSCs Retain their Capacity to Reconstitute Primary Hematopoietic Lineages

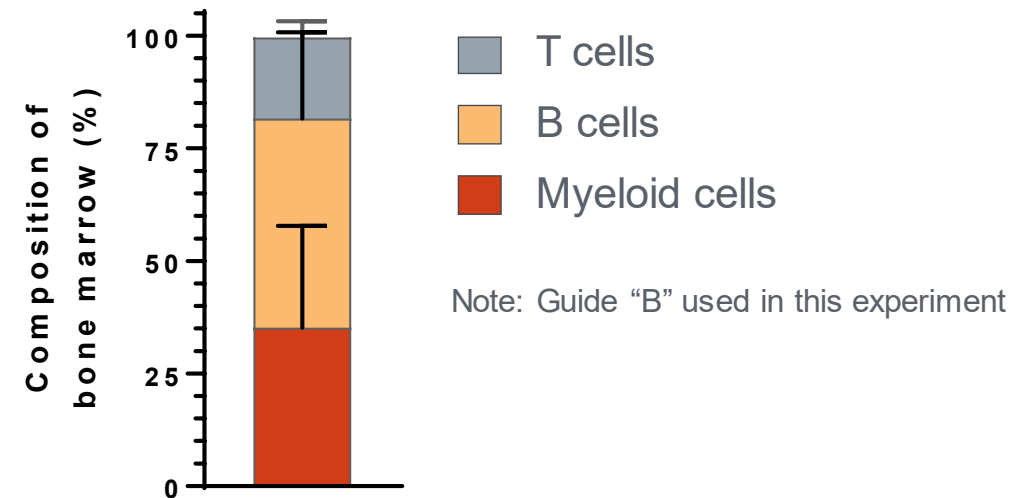
In a competitive transplant model using mice treated with a single dose of LNP, edited cells:

- ✓ Remained stable as a percentage of the bone marrow and HSC populations over a 14-week period
- ✓ Reconstituted healthy bone marrow with normal production of lymphoid and myeloid lineages

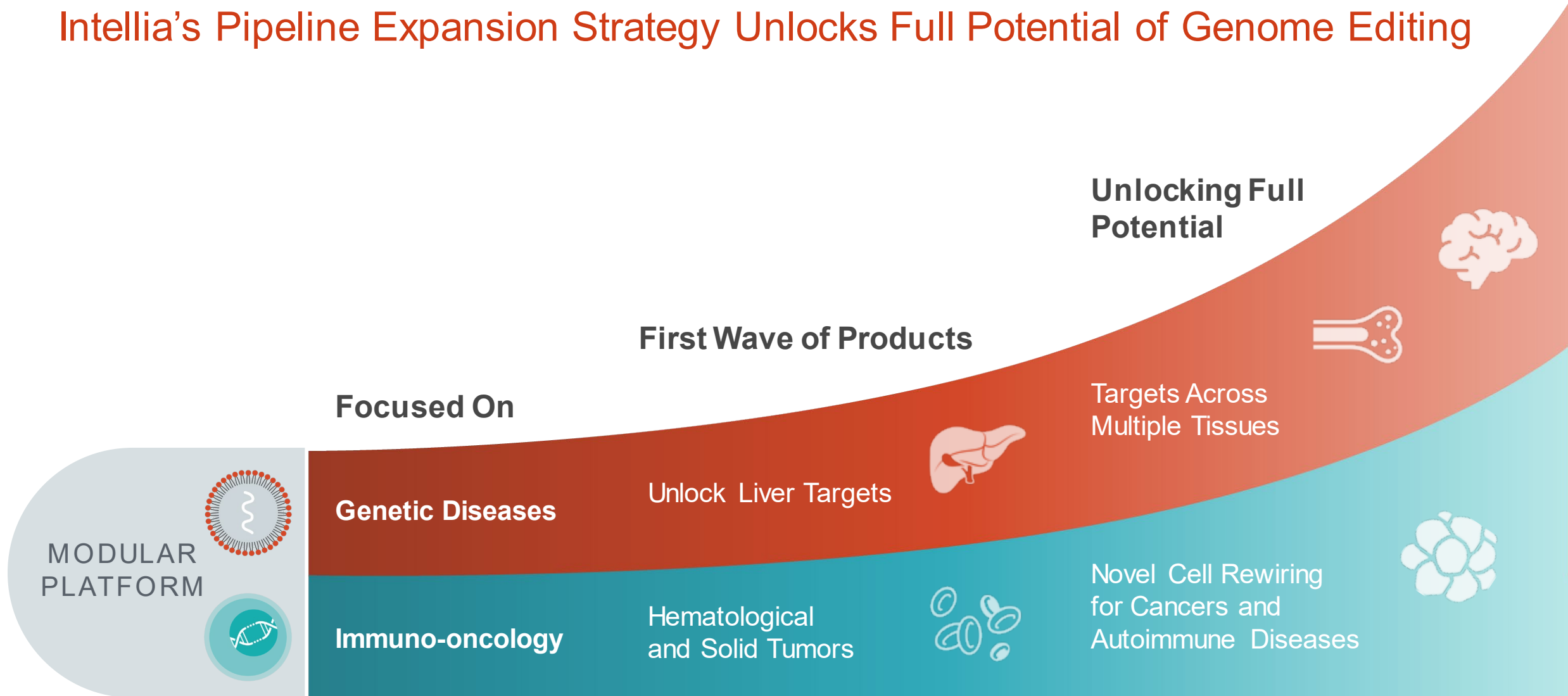
→ Nonviral approach preserves normal stem and progenitor cell function in mice



Normal Lineage Distribution



Intellia's Pipeline Expansion Strategy Unlocks Full Potential of Genome Editing



Development Pipeline Fueled by Robust Research Engine



PROGRAM	APPROACH	Research	Candidate Selection	IND-Enabling	Early-stage Clinical	Late-stage Clinical	PARTNER
<i>In Vivo</i>: CRISPR <u>is</u> the therapy							
NTLA-2001: Transthyretin Amyloidosis	Knockout						LEAD Intellia* REGENERON THERAPEUTICS
NTLA-2002: Hereditary Angioedema	Knockout						Intellia THERAPEUTICS
Hemophilia A and B	Insertion						LEAD REGENERON* Intellia THERAPEUTICS
Research Programs	Knockout, Insertion, Consecutive Edits						Intellia THERAPEUTICS
Research Programs	Various						Intellia REGENERON** THERAPEUTICS
<i>Ex Vivo</i>: CRISPR <u>creates</u> the therapy							
OTQ923 / HIX763: Sickle Cell Disease	HSC						NOVARTIS Intellia*** THERAPEUTICS
NTLA-5001: Acute Myeloid Leukemia	WT1-TCR						Intellia THERAPEUTICS
Solid Tumors	WT1-TCR						Intellia THERAPEUTICS
Undisclosed Programs	Undisclosed						Intellia THERAPEUTICS
Other Novartis Programs	CAR-T, HSC, OSC	Undisclosed					NOVARTIS Intellia*** THERAPEUTICS



Intellia

THERAPEUTICS

<https://www.intelliatx.com/careers/>