CASSS WCBP2023

Realizing the Promise of CRISPR Therapeutics: *In Vivo* and Cell Therapy Applications

Laura Sepp-Lorenzino, Ph.D.

January 24, 2023

Shanna, living with HAE; Milton, who has ATTR-CM; and Nancy and her father, Il Hyung, who have ATTR-PN

The CRISPR-based therapeutics referenced in this presentation are investigational, and have not been approved by regulatory authorities

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Intellia THERAPEUTICS

Today's Agenda

CRISPR/Cas9 Genome Editing

Guide RNA Identification & Characterization

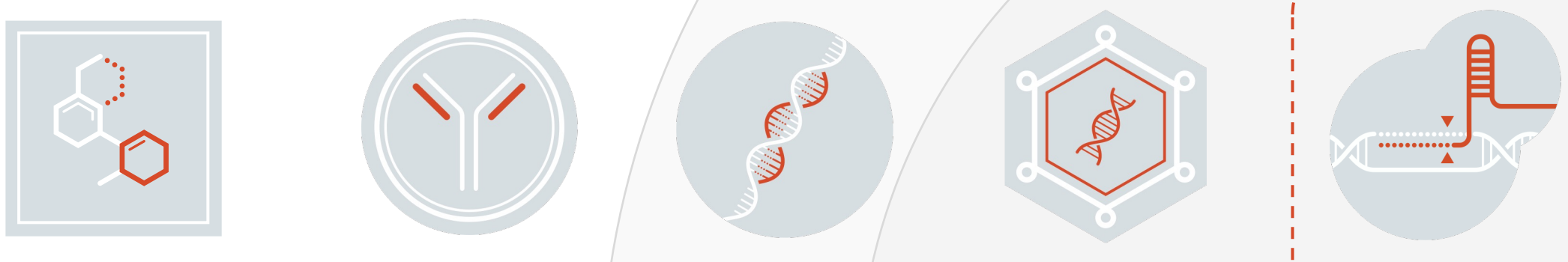
In Vivo Therapeutic Applications

Engineered Cell Therapies

Intellia THERAPEUTICS

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

INNOVATION TIMELINE



Small Molecule Drugs | Biologics | RNAi / ASO | Gene Therapy | Genome Editing

PROTEINS RNA DNA

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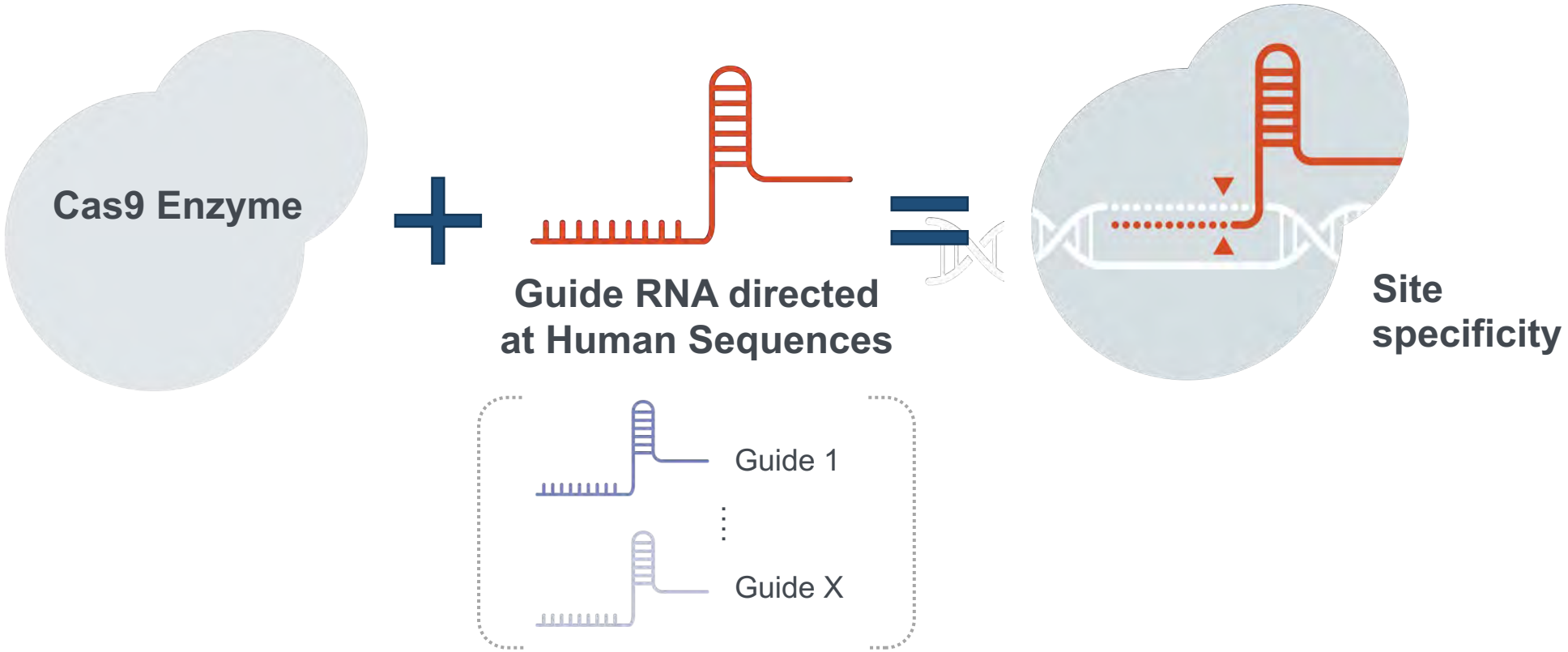
CRISPR/Cas9: Precise and Modular Approach for Editing the Genome

Potential to modify any gene within the genome



Potent / Selective / Simple / Any Gene / One or Multiple Edits / Permanent Change

CRISPR = clustered regularly interspaced short palindromic repeats

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Building a Full-spectrum Genome Editing Company

CRISPR-based Modular Platform

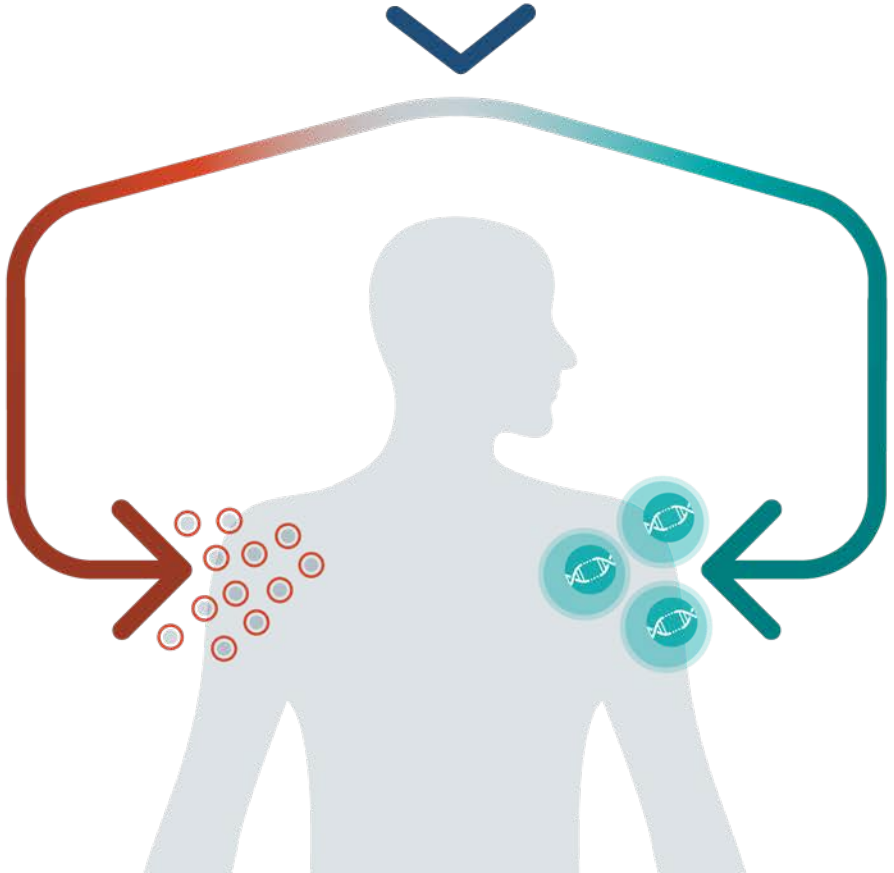
EMPLOY NOVEL EDITING AND DELIVERY TOOLS

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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World-class Genome Editing Platform Allows for Unsurpassed Capabilities

Proprietary CRISPR-based Modular Platform

Editing Tools	Delivery Tools
CRISPR/Cas9 Spy, HiFi Spy, Nme2	LNPs
C>T base editor	AAVs
DNA writer	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

- Knockouts, insertions, corrections or deletions
- Multiplicity of edits

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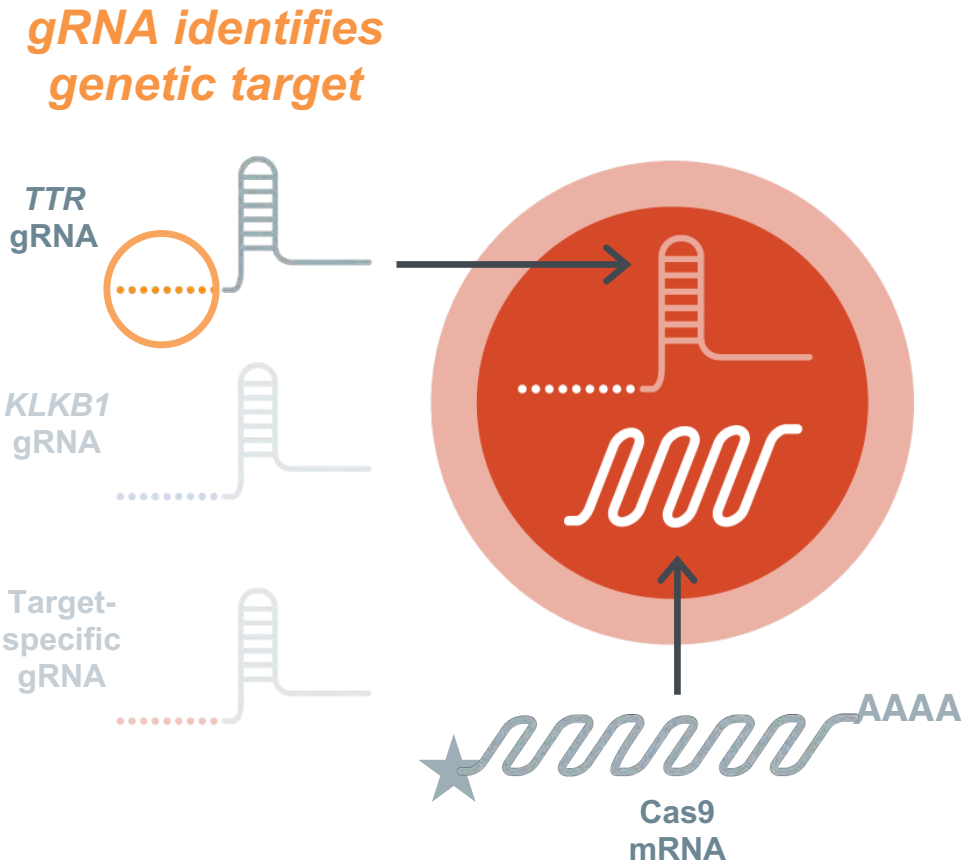
Modular Delivery Platform Enables Rapid and Reproducible Path to Clinical Development

LNP Delivery System:



Key Advantages of LNP Delivery

- Large cargo capacity
- Transient expression
- Biodegradable
- Used for *in vivo* and *ex vivo* applications
- Clinically proven delivery to liver
- Low immunogenicity
- Well-tolerated
- Redosing capability
- Tunable to other tissues
- Scalable synthetic manufacturing

LNP: lipid nanoparticle; **gRNA**: guide RNA; **mRNA**: messenger RNA

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Broad 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* REGENERON
NTLA-2002: Hereditary Angioedema	Knockout					Intellia
NTLA-2003: AATD-Liver Disease	Knockout					Intellia
NTLA-3001: AATD-Lung Disease	Insertion					Intellia
Hemophilia B	Insertion					Intellia REGENERON* LEAD
Hemophilia A	Insertion					Intellia REGENERON* LEAD
Research Programs	Knockout, Insertion, Consecutive Edits					Intellia
Research Programs	Various					Intellia REGENERON** SPARINGVISION
***Ex Vivo:* CRISPR creates the therapy**						
OTQ923 / HIX763: Sickle Cell Disease	HSC					Intellia*** NOVARTIS
NTLA-6001: CD30+ Lymphomas	Allo CAR-T					Intellia
Acute Myeloid Leukemia / Solid Tumors	Allo WT1-TCR					Intellia
Research Programs	Allo – Undisclosed					Intellia
Research Programs	Various					Intellia AVENCELL kyverna ONK
Other Novartis Programs	CAR-T, HSC, OSC	Undisclosed				Intellia*** NOVARTIS

* Lead development and commercial party; ** Rights to certain *in vivo* targets; *** Milestones & royalties only

AATD: alpha-1 antitrypsin deficiency; **CAR-T**: chimeric Antigen Receptor T Cells; **HSC**: hematopoietic stem cells; **OSC**: ocular stem cells; **TCR**: T cell receptor

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Today's Agenda

CRISPR/Cas9 Genome Editing

Guide RNA Identification & Characterization

In Vivo Therapeutic Applications

Engineered Cell Therapies

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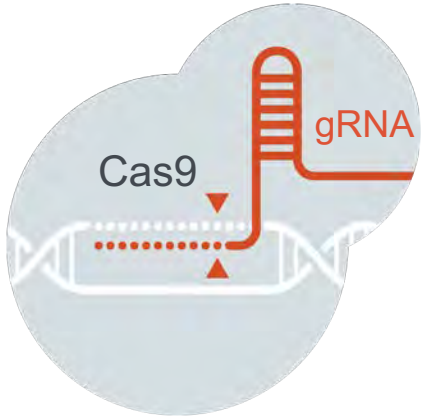
Canonical CRISPR/Cas9 Genome Modification



- PAM and gRNA-dependent double strand break (DSB)
- Repaired by host mechanisms
  - NHEJ in all cells
  - HDR in proliferating cells
  - Both stimulated by DSB

KNOCKOUT

Inactivation/deletion of disease-causing DNA sequence

REPAIR

Correction of “misspelled” disease-driving DNA sequence

INSERT

Insert new DNA sequence to manufacture therapeutic protein

gRNA: Guide RNA; **NHEJ**: Non-homologous end joining; **HDR**: Homology directed repair

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Key Attributes for Identifying Therapeutic Guide RNAs (gRNA)

High Precision

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

High Accuracy

- Avoid validated unintended edits elsewhere in the genome ("*off-target*")
- Avoid DNA structural variants (SV) associated with toxicity or transformation
- Wide genotoxicity safety window vs. expected therapeutic exposure

Potential Off-Target Editing with Canonical Cas9 is Exclusively gRNA-Dependent

Canonical CRISPR Cleavase*

gRNA sequence-dependent off-target editing only

*Cas9 adopts an auto-inhibited conformation until properly bound to target site

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Two Classes of Potential Unintended Genome Editing with CRISPR/Cas9

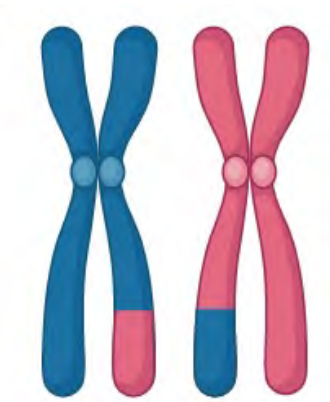
Off-target DNA Editing (mutagenesis) - Safety

Indel formation at unintended loci in the human genome

DNA Structural Variants (SV) (chromosomal integrity) - Safety

Imperfect restoration of chromosome structure

1. Inter-chromosomal translocations
2. Intra-chromosomal
   - DNA inversions
   - DNA duplications
   - large deletions



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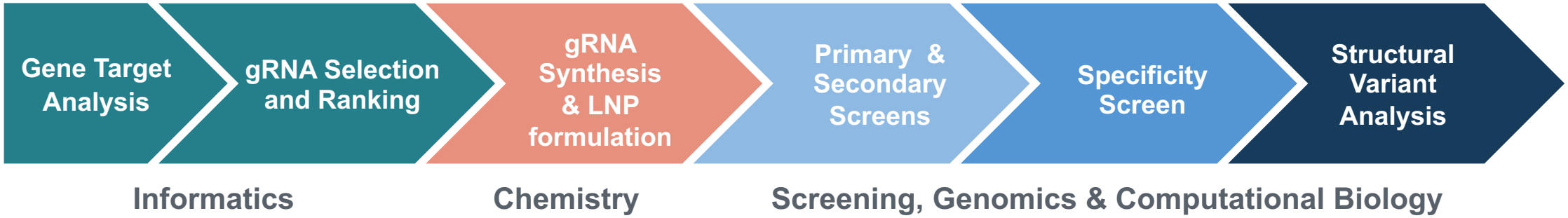
Intellia's gRNA Selection and Qualification Platform



Goal is to select gRNAs with the highest on-target editing activity and no detectable off-target potential at multiples of intended human therapeutic dose

NGS: Next-Generation Sequencing

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Appropriate Technologies are Required To Evaluate the On-Target Activity and Safety of Gene and Cell Therapy Products

Next-generation sequencing technologies provide methods to characterize intended and unintended genomic changes in Gene and Cell Therapy Products

Objective	*Methodology*
Detection of insertions and deletions (indels) at known genomic loci	Amplicon Sequencing
Discovery methods to identify the potential for off-target editing	SITE-Seq, GUIDE-Seq, ONE-Seq, CIRCLE-Seq, RGEN-Seq etc.
Multiplexed approaches to evaluate indels across many loci	rhAmpSeq, Hybrid Capture, etc.
Methods to assess chromosomal structural integrity: structural variants and large genomic changes	Short-read NGS technology characterization, Long-read sequencing, Pinpoint DNA FISH direct visualization technology

Each assay is appropriately validated and qualified for its corresponding use, with their level of analytical sensitivity and specificity, accuracy, and precision

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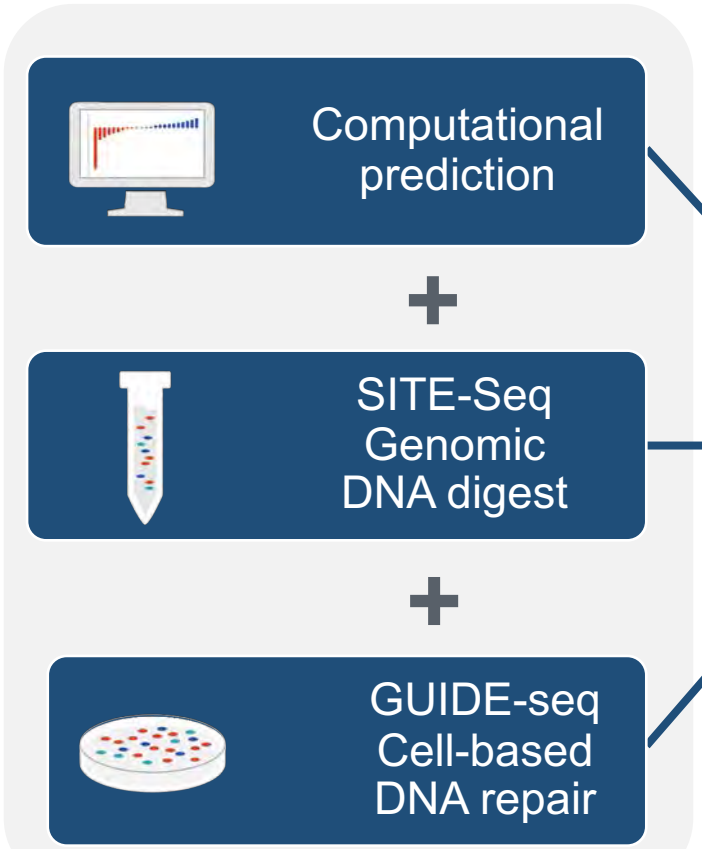
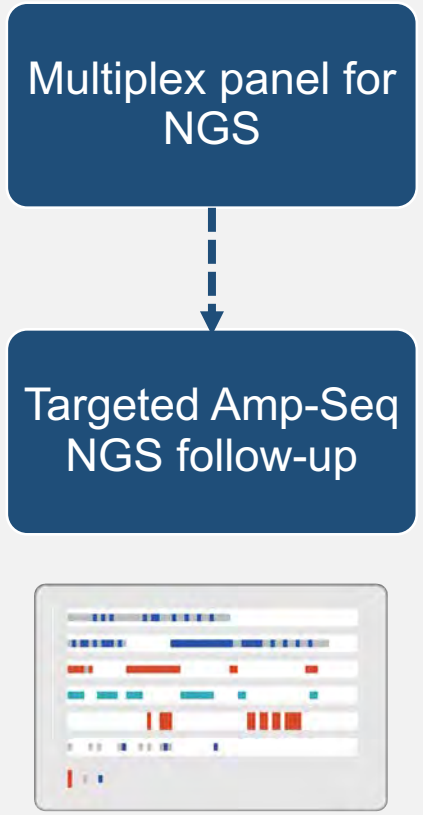
Comprehensive gRNA Specificity Assessment: An Off-Target Workflow

1: Discovery of Potential Off-Target Edits



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

2: Cell-based **Validation** of True Off-Target Edits by Deep Sequencing



Ex Vivo

- Cell drug product

In Vivo

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

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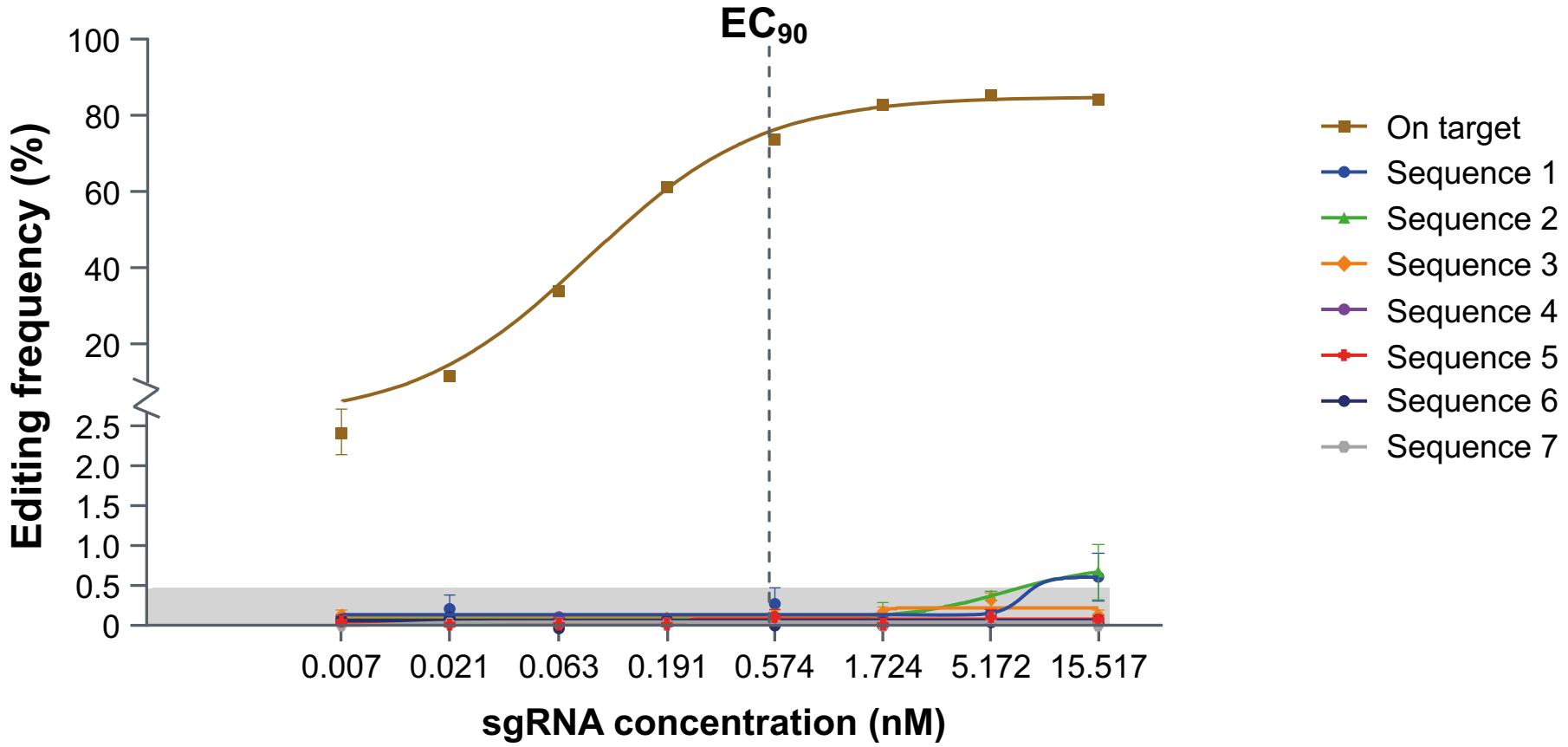
No Detected Validated Off Targets at the Multiples of the Intended Human Dose in Primary Human Hepatocytes



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

Gillmore *et al. New England Journal of Medicine* **385**:493-502 (2021)

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Today's Agenda

CRISPR/Cas9 Genome Editing

Guide RNA Identification & Characterization

In Vivo Therapeutic Applications

Engineered Cell Therapies

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In Vivo

CRISPR is the therapy

GENETIC DISEASES

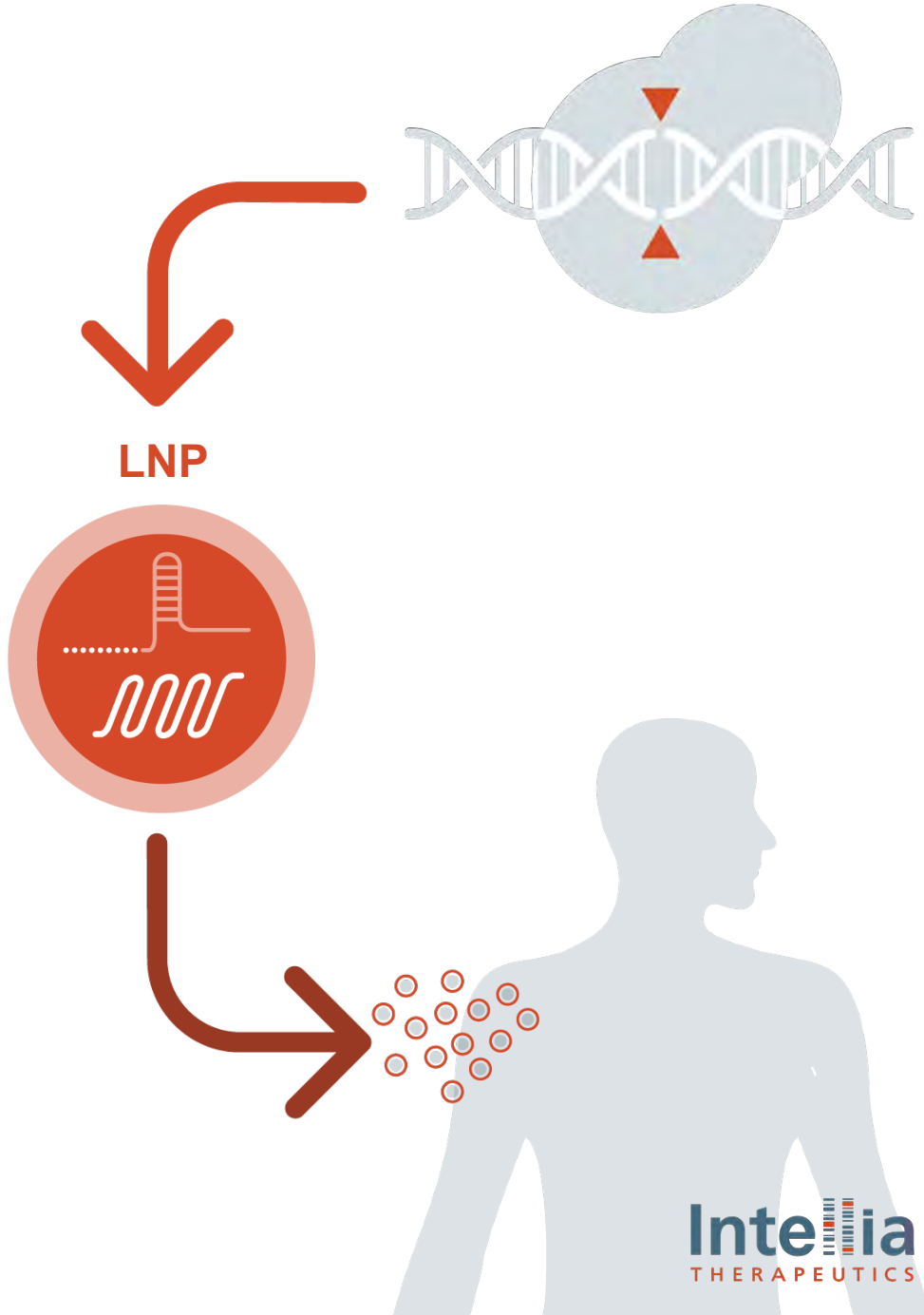
Strategic Advantages:

Potential curative therapy from single dose

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

Potential for permanent gene knockout or gain of function by targeted insertion

Capable of delivering to multiple tissue types for various therapeutic applications



LNP: lipid nanoparticle

Multiple Safety Features Built In for *In Vivo* CRISPR Therapeutic Applications

Target Validation
Technical Feasibility
Unmet Need

gRNA Accuracy & Precision

Liver Delivery

Transient CRISPR Expression

Benefit : Risk Assessment

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NTLA-2001 for Transthyretin (ATTR) Amyloidosis

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NTLA-2001 for Transthyretin (ATTR) Amyloidosis

About ATTR Amyloidosis

- Caused by accumulation of misfolded transthyretin (TTR) protein
- Primarily affects the nerves and/or the heart
- Chronic dosing is required with current treatment options

Our Approach

Knock out *TTR* gene with a single-dose CRISPR-based treatment

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

Key Advantages

Potential to:

- Halt and reverse disease with deep and consistent TTR reduction
- Be a single-dose treatment
- Expect lifelong, stable TTR reduction

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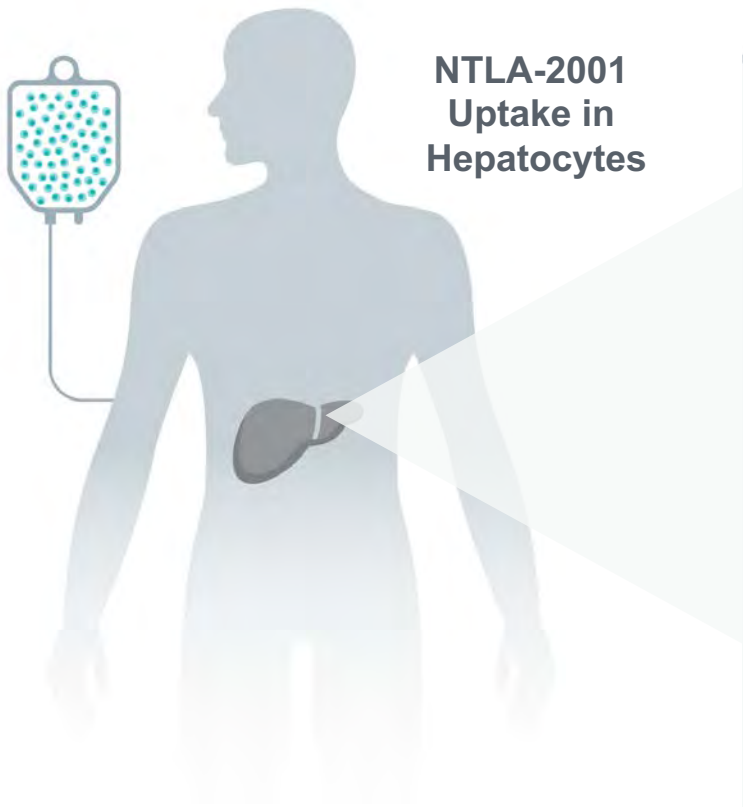
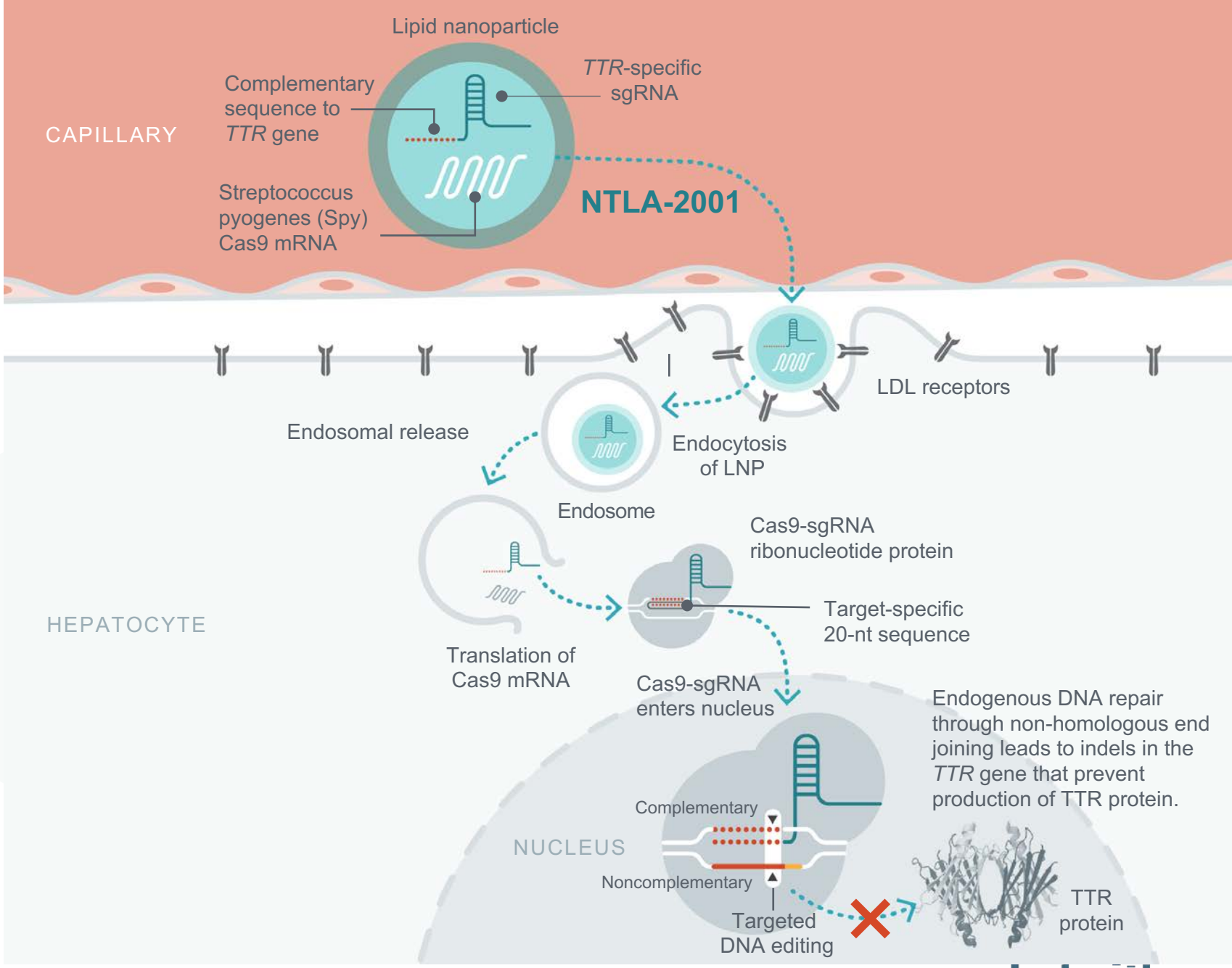
Case Study: NTLA-2001

In vivo CRISPR/Cas9 candidate for Transthyretin (ATTR) Amyloidosis



NTLA-2001 Uptake in Hepatocytes



This presentation includes the therapeutic hypothesis for an investigational product not yet approved by regulatory authorities

LNP; lipid nanoparticle sgRNA; single guide RNA; TTR, transthyretin

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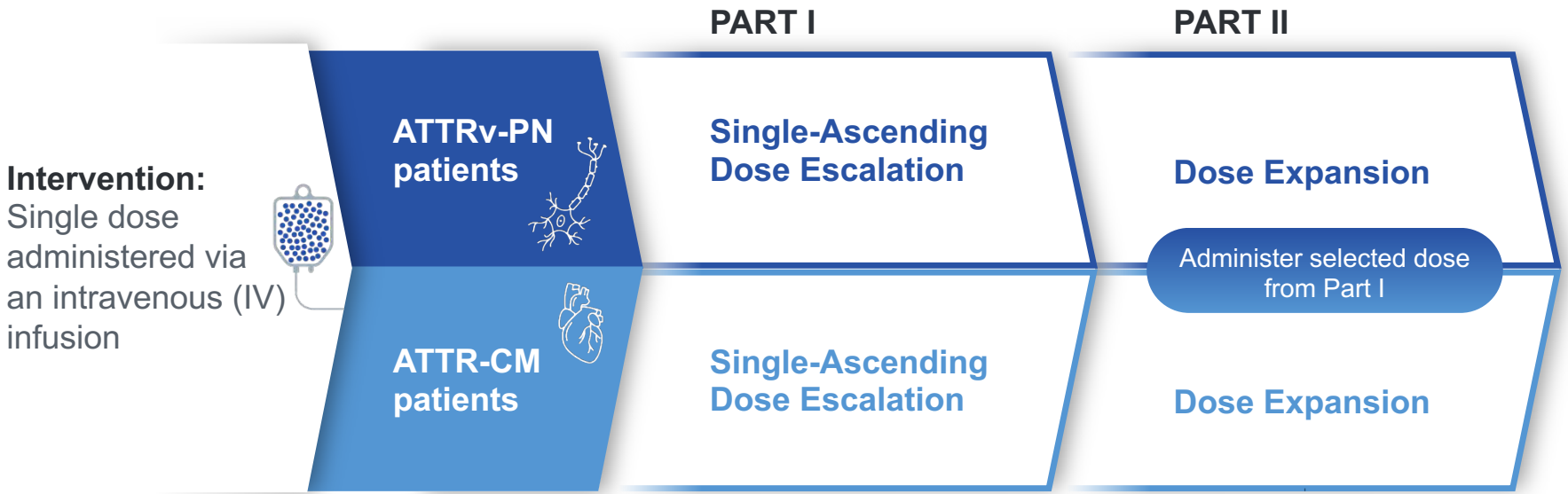
NTLA-2001 Phase 1 Study

Two-part, open-label, multi-center study in adults with hereditary ATTR amyloidosis 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

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NTLA-2001 Was Generally Well Tolerated in ATTRv-PN and ATTR-CM Patients in Dose-Escalation Portion of the Phase 1 Study

- 27 patients dosed across both PN and CM arms
- Majority of adverse events were mild in severity
- Majority of infusion-related reactions were considered mild, resolving without clinical sequelae; all patients received a complete study dose
- Maximally tolerated dose was not reached

Note: Refer to adverse event tables for additional details.
This slide includes data for investigational products not yet approved by regulatory authorities.
ATTR-CM: ATTR amyloidosis with cardiomyopathy; **ATTRv-PN**: hereditary ATTR amyloidosis with polyneuropathy

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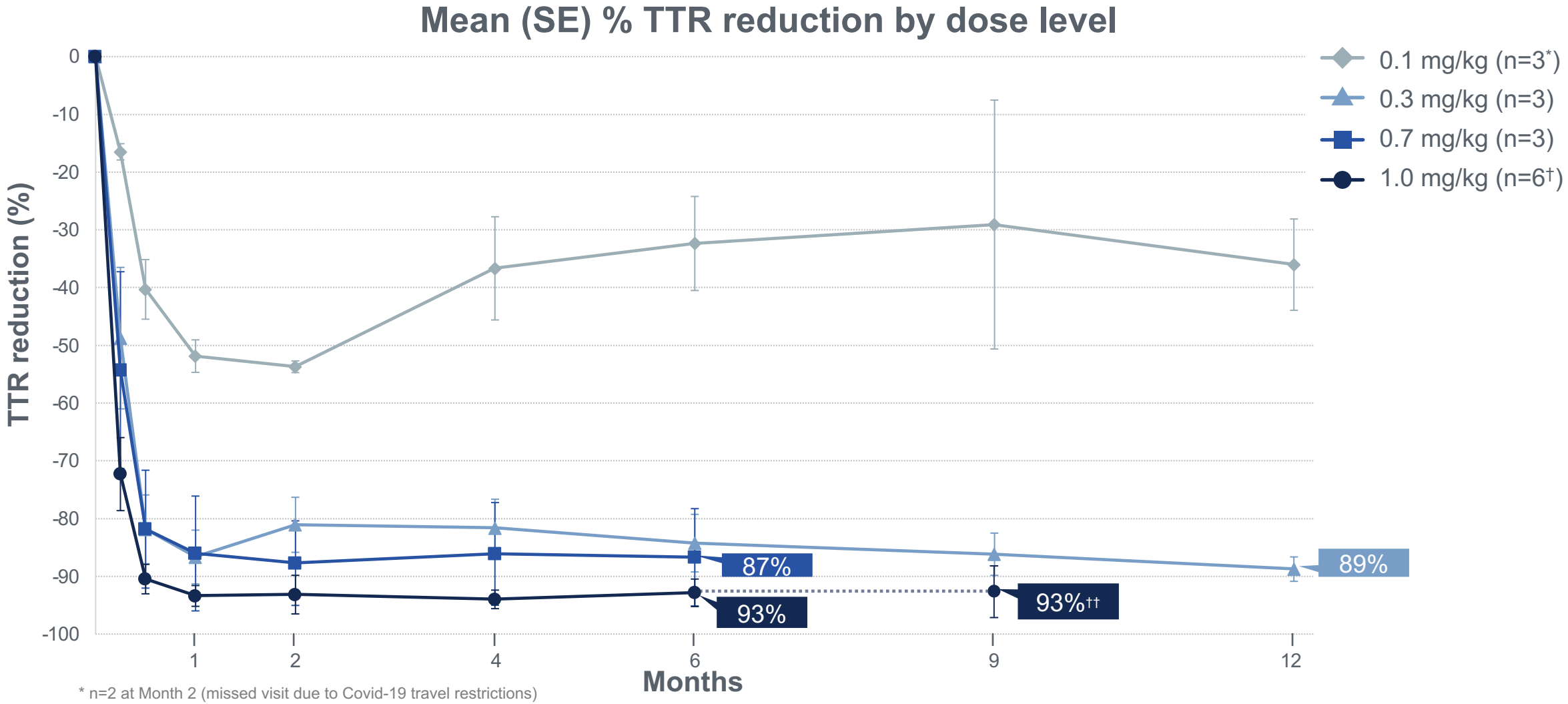
ATTRv-PN Arm: Dose-Responsive Rapid and Deep Serum TTR Reduction Sustained Through 6-12 Months



* n=2 at Month 2 (missed visit due to Covid-19 travel restrictions)
† n=5 at Month 2 (missed visit due to Covid-19 travel restrictions)
†† n=3 have reached Month 9 follow-up
Data disclosed: June 24, 2022

This slide includes data for investigational products not yet approved by regulatory authorities.
SE: standard error; **TTR**: transthyretin; **ATTRv-PN**: hereditary ATTR amyloidosis with polyneuropathy

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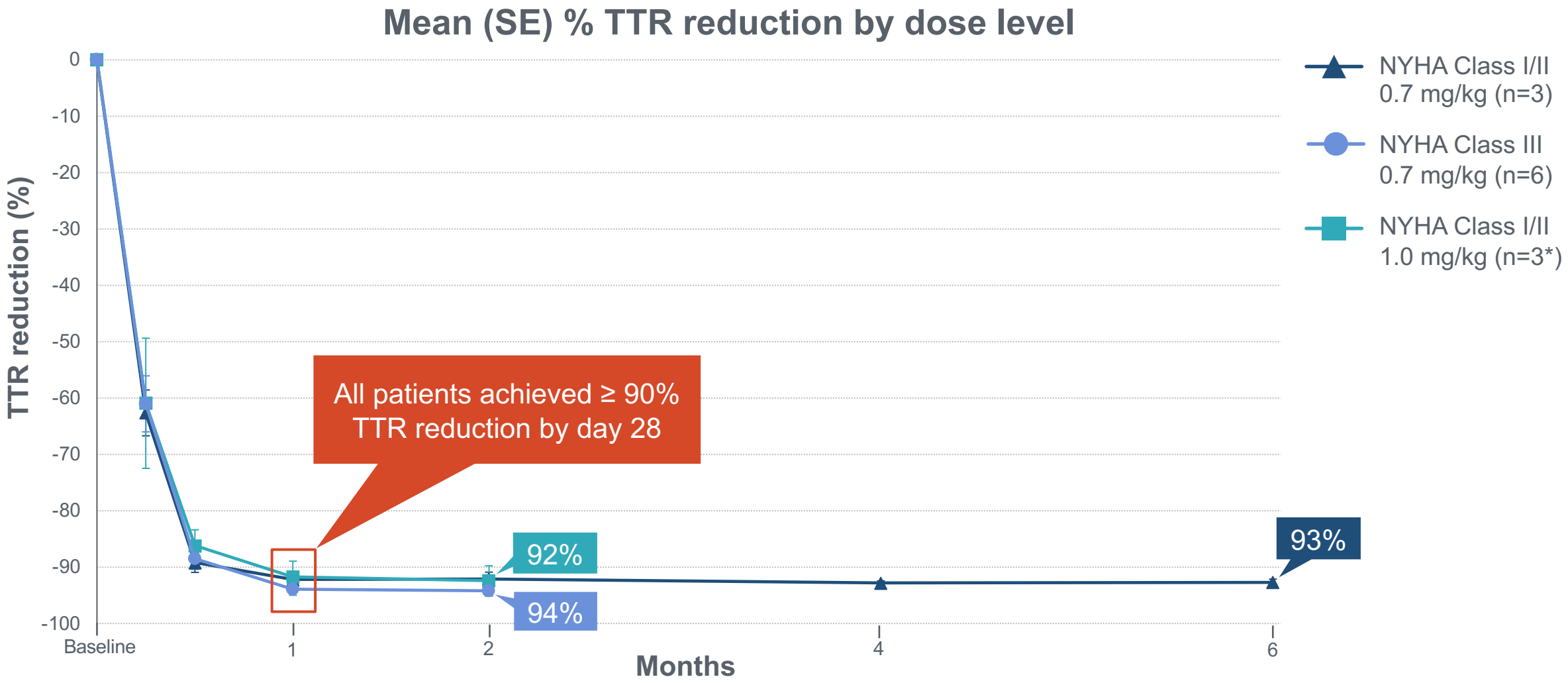
ATTR-CM Arm: Rapid and Deep Serum TTR Reduction Sustained Through 2-6 Months Across All Patients



Data cut-off: August 25, 2022; Data disclosed: November 5, 2022

* n=2 at Month 2 (missed patient visit)

This slide includes data for investigational products not yet approved by regulatory authorities.

SE: standard error; **TTR**: transthyretin; **ATTR-CM**: ATTR amyloidosis with cardiomyopathy; **NYHA**: New York Heart Association

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Shanna and their sons, Oren and Damian, all living with HAE

NTLA-2002 for Hereditary Angioedema (HAE)

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NTLA-2002 for Hereditary Angioedema (HAE)

About HAE

- Genetic disease characterized by recurring, severe and unpredictable swelling in various parts of the body
- Despite availability of existing therapies, significant unmet need persists
- Chronic dosing is required with current treatment options

Our Approach

Knock out *KLKB1* gene with a single dose

- Reduce kallikrein activity to prevent attacks

Key Advantages

Potential to:

- Be a single-dose treatment
- Provide extensive and continuous reduction in kallikrein activity
  - Intended to minimize the risk of breakthrough attacks
- Eliminate significant treatment burden

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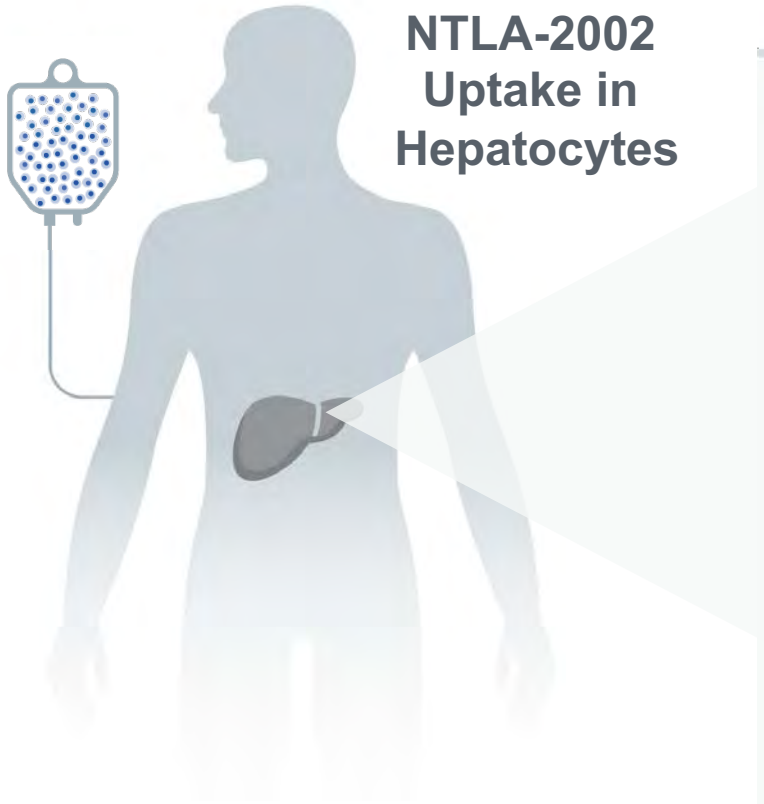
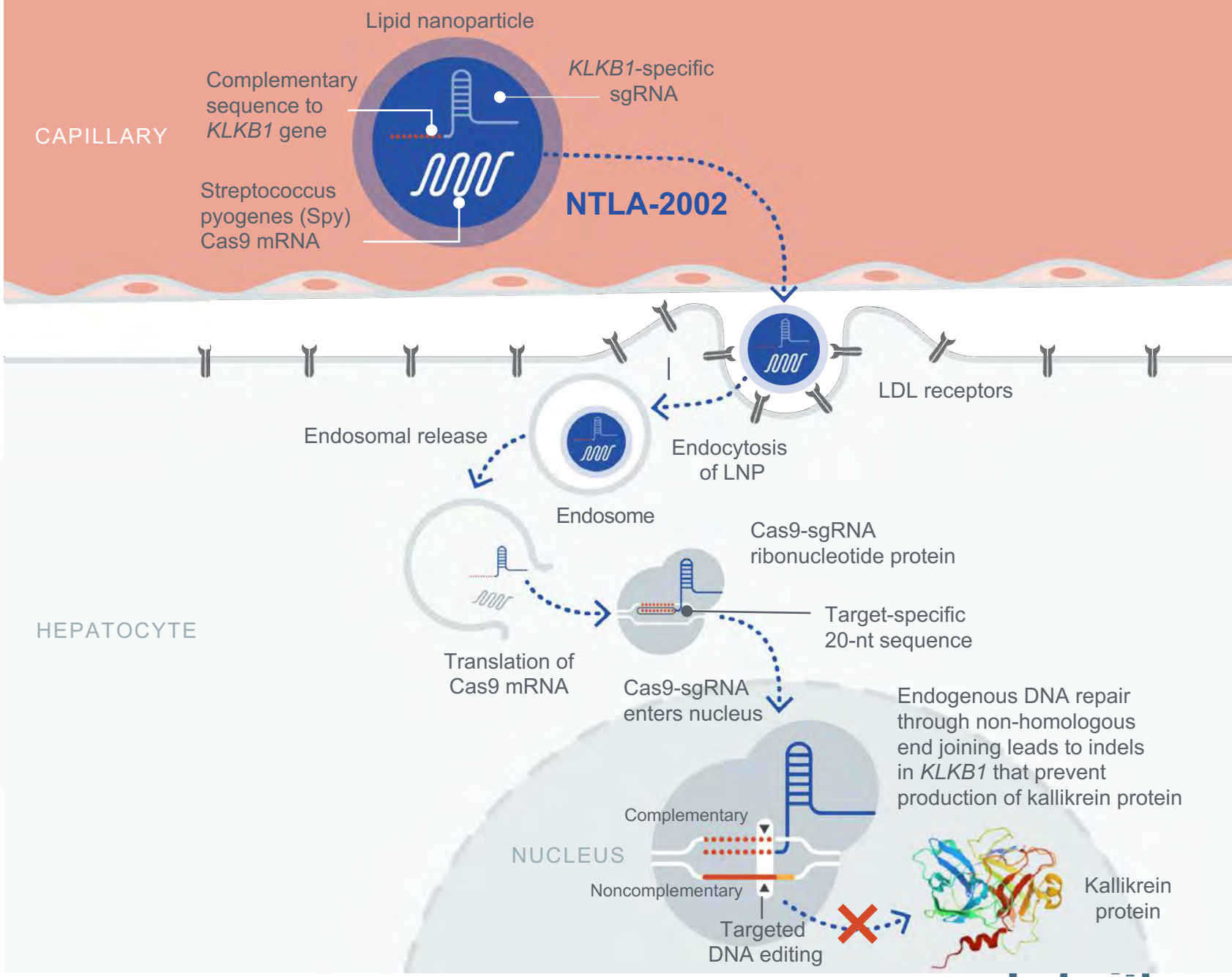
NTLA-2002 is a novel, investigational CRISPR/Cas9-based *in vivo* gene editing therapy



NTLA-2002 Uptake in Hepatocytes



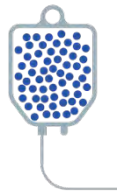
LNP, Lipid Nanoparticle; **sgRNA**, Single Guide RNA

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

- 75 mg (n=3)
- 50 mg (n=4)
- 25 mg (n=3)

PHASE 2
Expansion study to confirm recommended dose

Randomized

- 50 mg* (n=10)
- 25 mg* (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
* Subject to regulatory feedback
PK: pharmacokinetics; **PD**: pharmacodynamics

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NTLA-2002 Was Generally Well-Tolerated in the Phase 1 Portion of the Study

- 10 patients dosed across three dose levels
- Most frequent AEs were infusion-related reactions and fatigue across all dose levels
- Majority of adverse events were mild in severity
- No treatment-emergent SAEs or ≥ Grade 3 TEAEs were observed

Note: Refer to adverse event tables for additional details.
This slide includes data for investigational products not yet approved by regulatory authorities.
AE: adverse event; **SAE**: serious adverse event; **TEAE**: treatment-emergent adverse event

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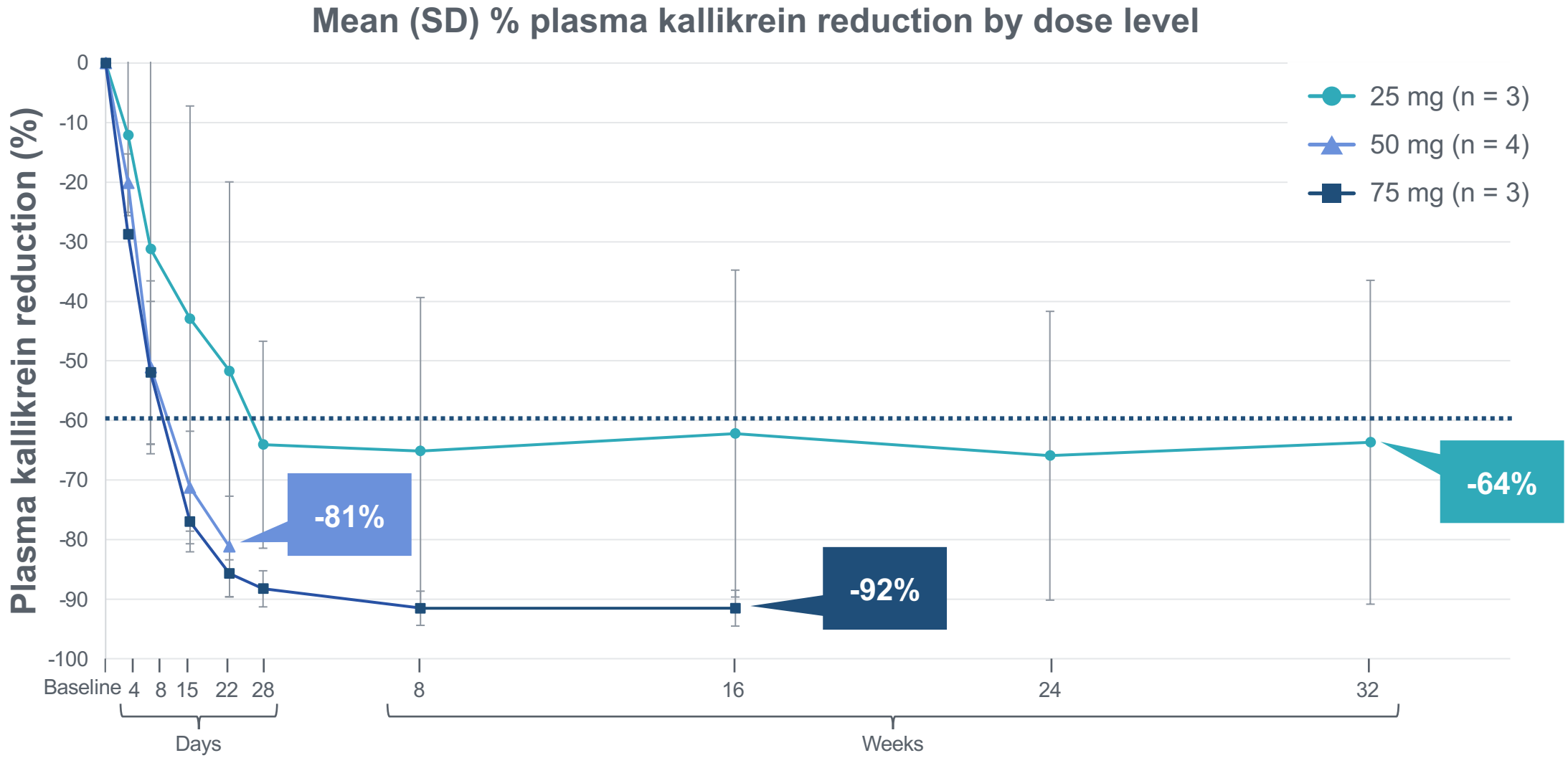
NTLA-2002 Resulted in Rapid and Deep Plasma Kallikrein Reduction at All Dose Levels



Dashed line represents targeted minimum reduction
Data disclosed: November 12, 2022
This slide includes data for investigational products not yet approved by regulatory authorities.
SD: standard deviation

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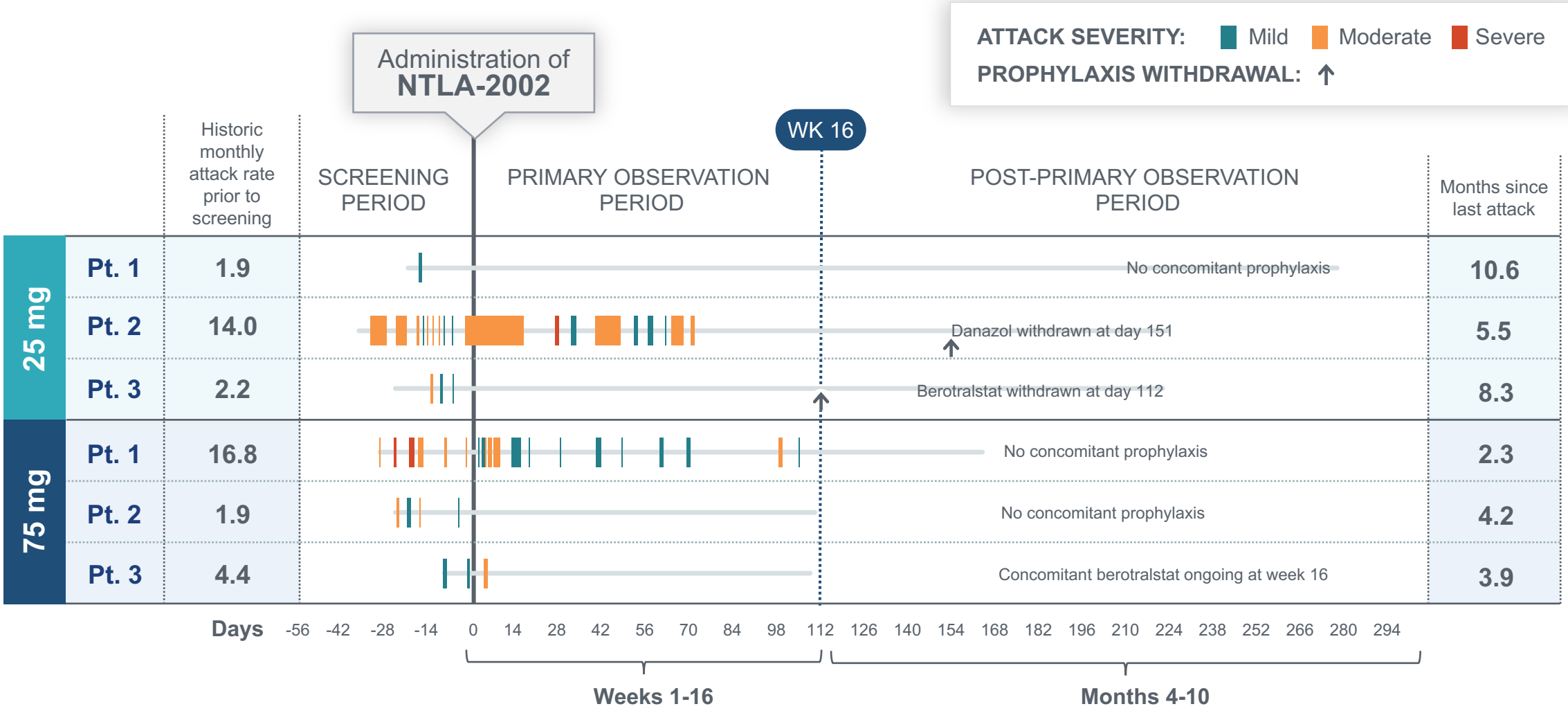
All Patients Have an Ongoing Attack-Free Interval Ranging 2.3 to 10.6 Months



Data cut-off: September 28, 2022; Data disclosed: November 12, 2022
This slide includes data for investigational products not yet approved by regulatory authorities.

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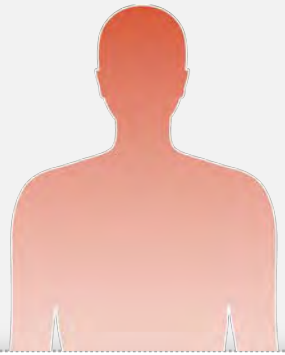
Platform proof-of-concept enables next wave of clinical programs

ACHIEVED HUMAN PROOF-OF-CONCEPT



✓ **NTLA-2001:**
ATTR Amyloidosis*

✓ **NTLA-2002:**
Hereditary Angioedema

NEXT WAVE OF CLINICAL PROGRAMS

NTLA-2003 for AATD	**NTLA-3001** for AATD	Hemophilia A**	Hemophilia B**

Types of edits: knockout or insertion

* In collaboration with Regeneron – Intellia-led
** In collaboration with Regeneron – Regeneron-led

AATD: Alpha-1 Antitrypsin Deficiency

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Significant opportunities to unlock full potential of *in vivo* platform

CRITERIA USED TO SELECT POTENTIAL FUTURE CANDIDATES:

Unmet need • Population size • Technical feasibility

Potential Liver Development Programs*

Rare Diseases**

- Lysosomal storage diseases
- Metabolic diseases
- Blood disorders

Prevalent Diseases**

- Dyslipidemia
- Hypertension
- NASH
- Viral diseases

Unlocking Full Potential of Genome Editing

Target Tissues


Bone marrow


CNS/PNS


Eye***


Heart


Skeletal muscle

Expansion into tissue-specific diseases

* This is a selection of potential liver targets and does not represent all future opportunities
** Individual targets could be developed by Intellia, Regeneron or through collaborations
*** In collaboration with SparingVision

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Today's Agenda

CRISPR/Cas9 Genome Editing

Guide RNA Identification & Characterization

In Vivo Therapeutic Applications

Engineered Cell Therapies

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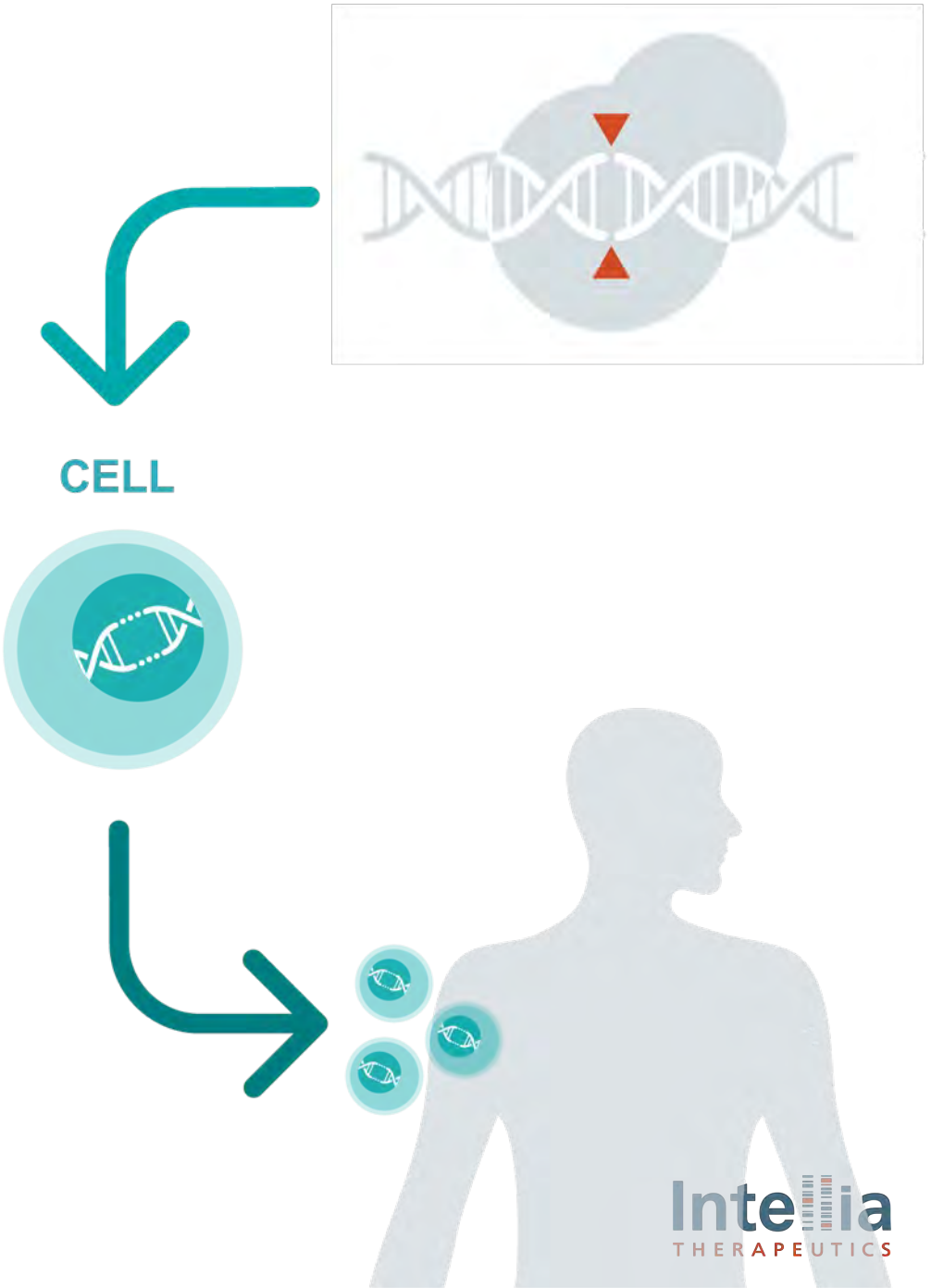
Ex Vivo

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

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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; **LNP**: lipid nanoparticle; **HSC**: hematopoietic stem cells; **CAR**: chimeric antigen receptor

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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.
DSB: double strand break

Highly Efficient Allo CAR-T Cell Engineering at Bioreactor Scale (N=4 Donors)

Allo-CD30 CAR-T Research Process

DAY 0
Thaw

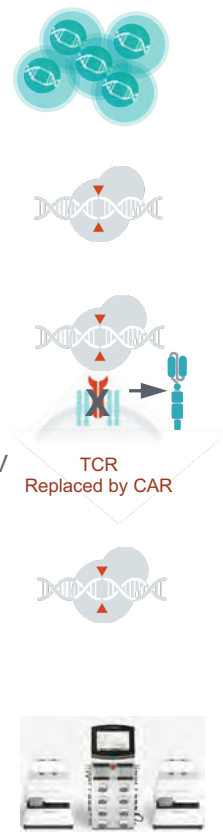
Step 1
KO 1
Activate

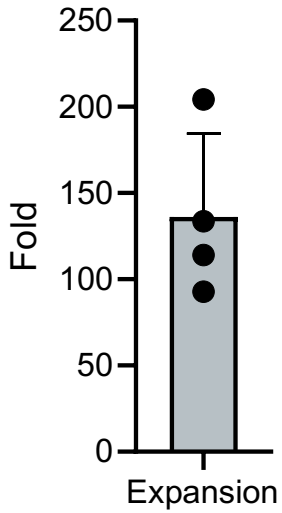
Step 2
TRAC KO/KI
CD30 CAR-T AAV

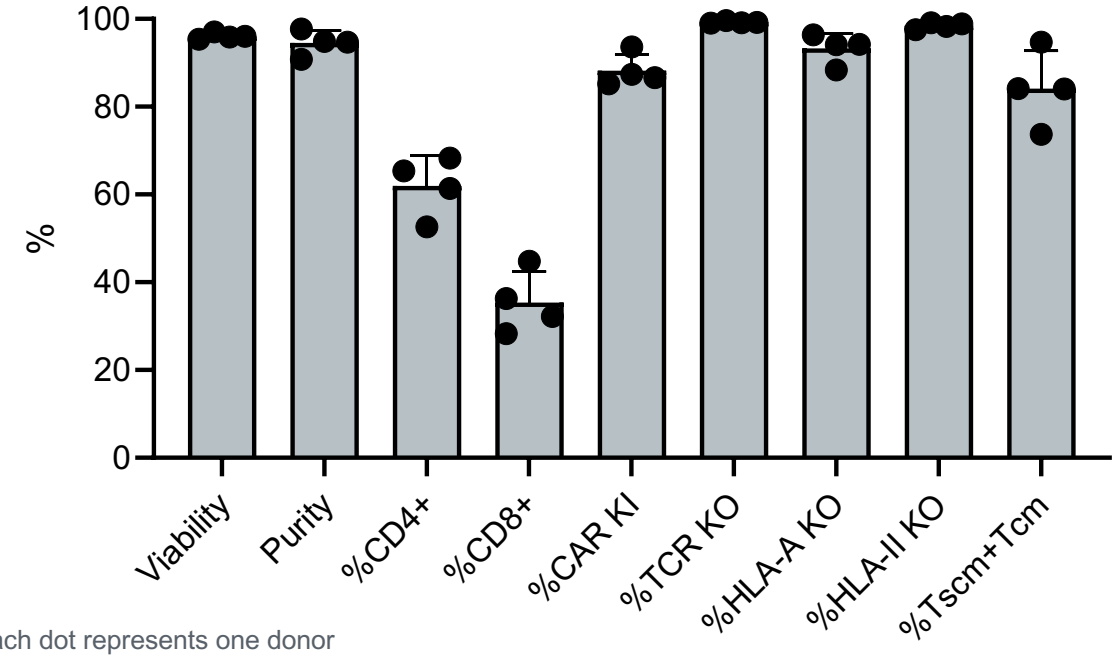
Step 3
KO 3

Step 4
Cell Expansion

Day 10-11
Harvest



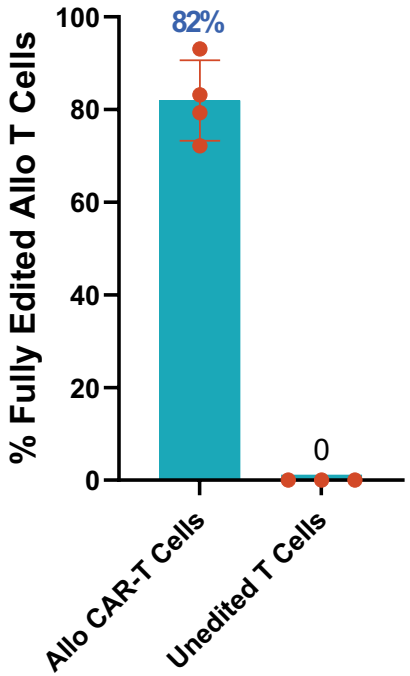




Each dot represents one donor

CAR: CD30-specific CAR

Allo CAR-T Cells
(3 KOs + 1 Insertion)



- **Highly efficient KO (>90%) using a sequential LNP-based CRISPR/Cas9 KO protocol**
- **High CAR insertion rates (>80%) via AAV-mediated insertion into the TRAC locus**
- **100 - 200-fold expansion of T cells with high Tscm memory phenotype (>70%)**

Editing/memory data shown is CD8+ Subset, CD4+ is comparable

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Immune Concerns Unaddressed by Current Allogeneic Solutions

Approach	Employ intense lymphodepletion regimen	Knockout (KO) HLA-I (B2M)	KO HLA-I & express NK inhibitor^	**Intellia's Approach** KO HLA-II & HLA-A
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	✗	✓	✓	✓

^Example: **HLA-E**: Human leukocyte antigen class E
B2M: Beta-2-microglobulin
Slide based on preclinical data disclosed by Intellia; Cell product to be further explored in additional preclinical and clinical studies.

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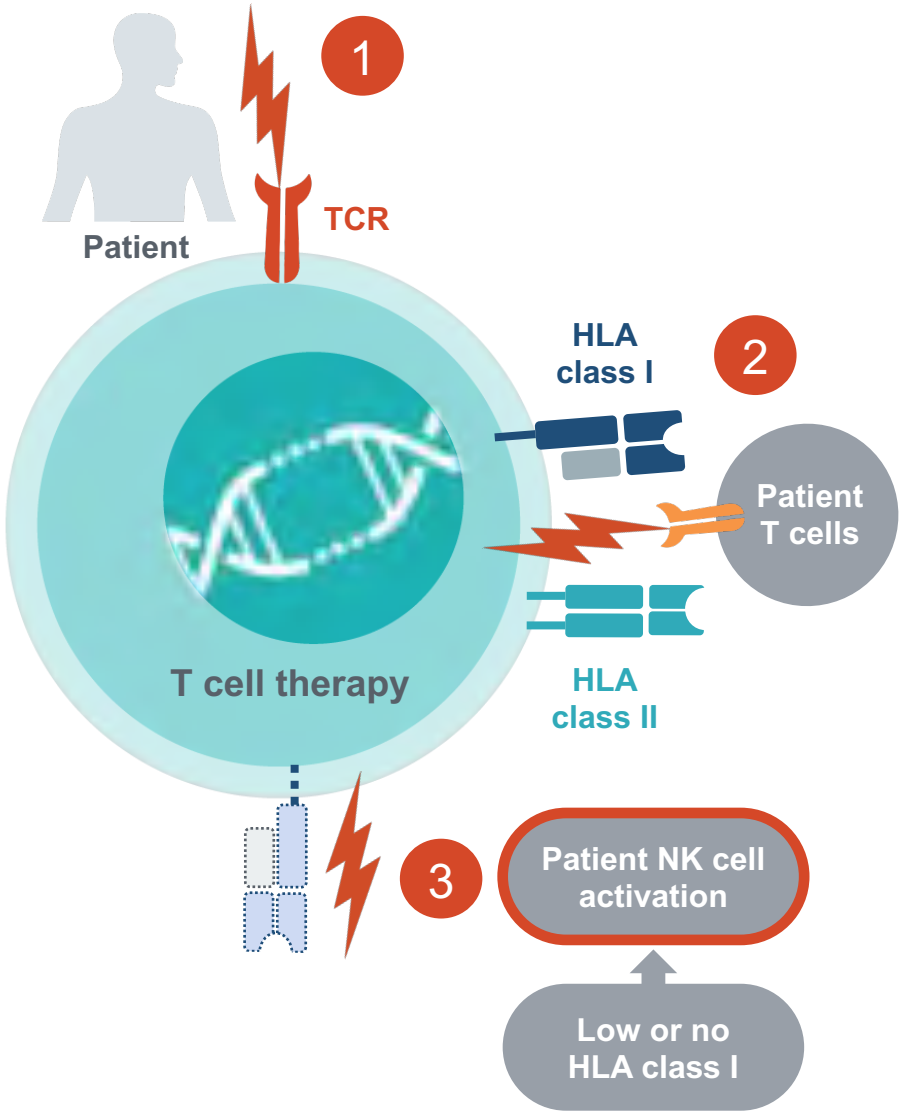
Three Immune Concerns Must Be Addressed by Allogeneic Cell Therapies



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

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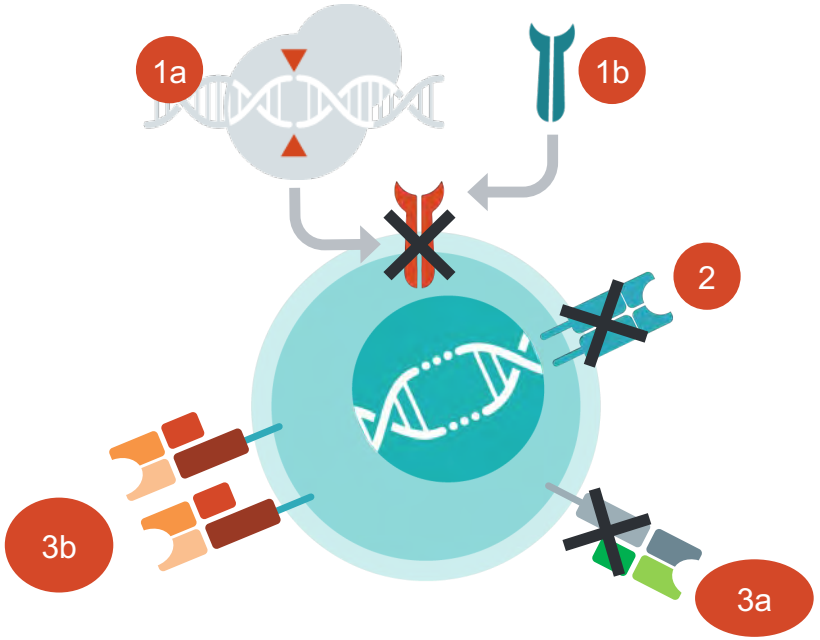
Intellia's Differentiated Allogeneic Approach Aims to Address All Three Immune Concerns



Key Potential Advantages

- ✓ Approach is applicable to CAR and TCR
- ✓ Solves for host NK and T cell rejection
- ✓ Avoids long-term immunosuppression

Intellia's Editing Strategy	Main Objective of Edit
1a Knockout endogenous TCR	**Prevent graft-versus-host disease (GvHD)**
1b Insert target CAR or TCR	**Direct T cell for tumor killing**
2 Knockout HLA Class II	**Prevent CD4-mediated rejection**
3a Knockout HLA-A only	**Prevent CD8-mediated rejection**
3b Retain HLA-B, HLA-C and HLA-E	**Block NK cell activation and avoid NK-mediated rejection**

NK: natural killer; **TCR**: T cell receptor; **CAR**: chimeric antigen receptor

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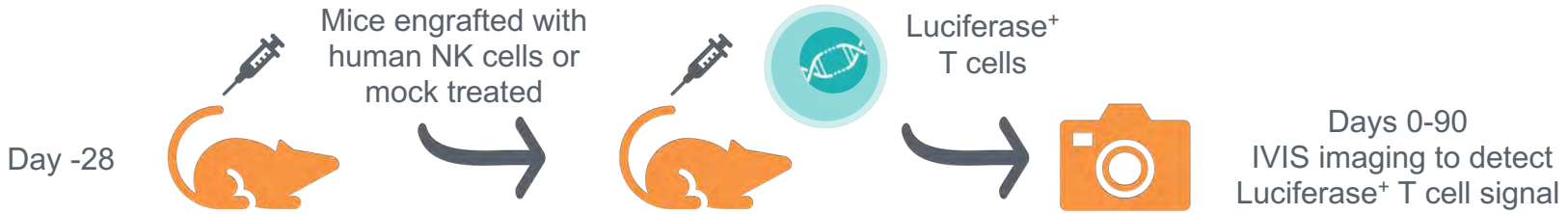
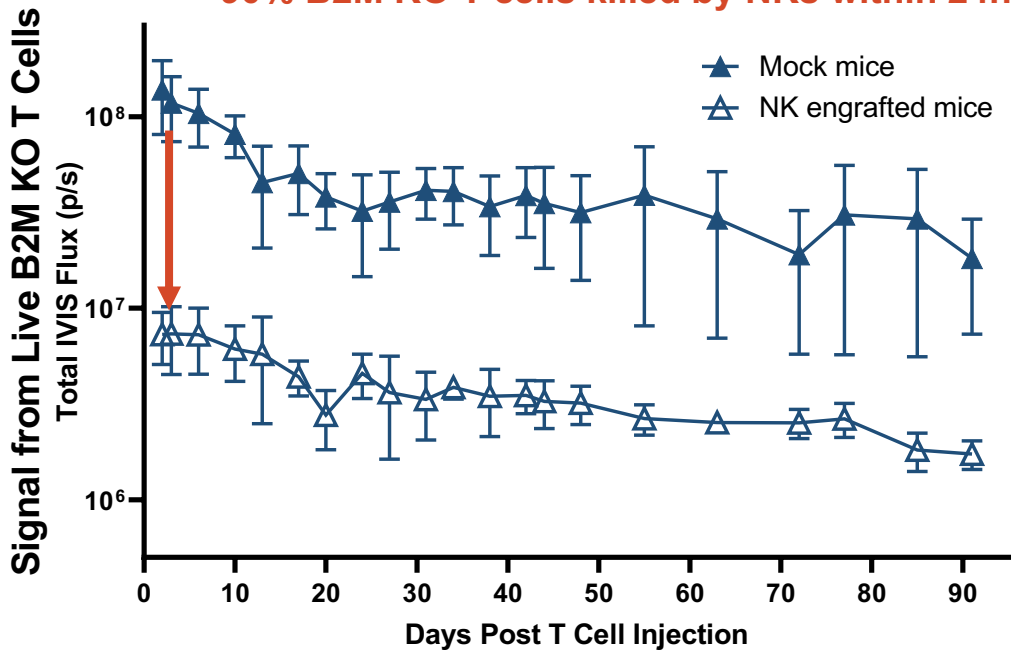
Allo TCR-T Cells Resisted NK Cell Killing for at Least 90 Days *In Vivo*



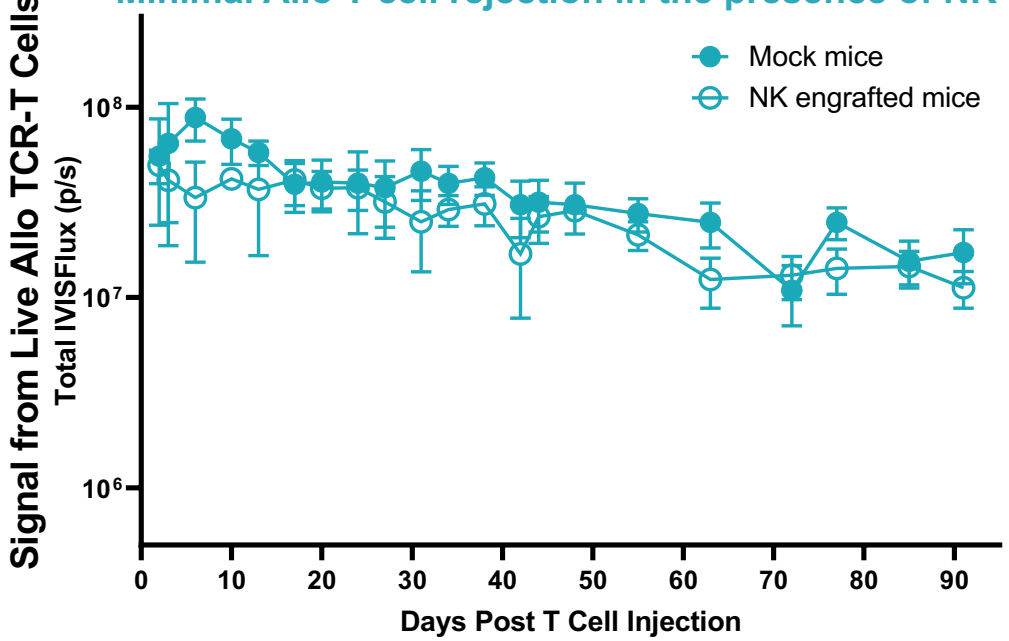
B2M Knockout T cells

>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



Yong Zhang et al., ESGCT 2021, Talk 2C

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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

TCR: T cell receptor; **AML**: acute myeloid leukemia

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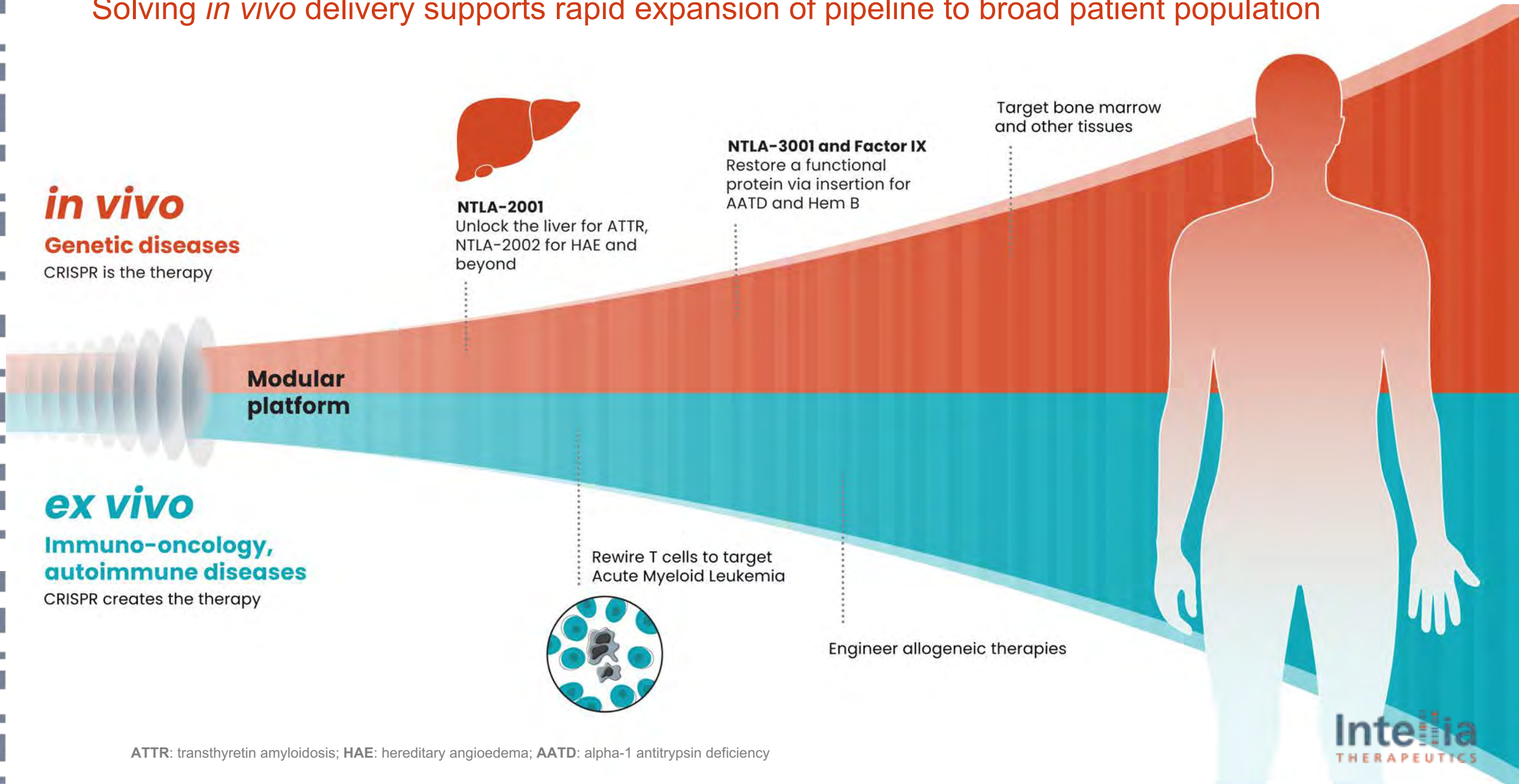
Unlocking the full potential of CRISPR

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



ATTR: transthyretin amyloidosis; **HAE**: hereditary angioedema; **AATD**: alpha-1 antitrypsin deficiency

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