A Modular CRISPR/Cas9 Genome Editing Platform for Durable Therapeutic Knockout and Targeted Gene Insertion Applications

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Today’s Agenda

1. Intellia’s Modular Platform
2. Durable Gene Knockout Applications
3. Targeted Gene Insertion Persistence
Building a Full-Spectrum Genome Editing Company

CRISPR creates the therapy

Immuno-oncology
Autoimmune diseases

In Vivo
CRISPR is the therapy
Genetic diseases

Ex Vivo
CRISPR creates the therapy

Modular Platform

LNP: Lipid Nanoparticle
Intellia’s *In Vivo* Liver Editing Modular Platform Employs Non-Viral Delivery

**Lipid Nanoparticles (LNPs)**

- Target 1 gRNA
- Target 2 gRNA
- Target 3 gRNA

**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

**gRNA target site specificity defined by 20mer at 5’ end**

**Transient Cas9 expression from mRNA**
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

\[ \text{PROPRIETARY LNP DELIVERY SYSTEM} \]

\[ \text{TRANSIENT EXPRESSION} \quad | \quad \text{LARGE CARGO CAPACITY} \quad | \quad \text{REDOSING CAPABILITY} \]

\[ \text{ENABLES MULTIPLE EDITING STRATEGIES} \]

\[ \begin{align*}
\text{Remove} & \quad \text{Restore} & \quad \text{Remove / Restore} \\
\text{KNOCKOUT} & \quad \text{INSERT} & \quad \text{CONSECUTIVE EDITING} \\
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Modular Approach to Unlocking Treatment of Genetic Diseases

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**CONSECUTIVE EDITING**
- AAV
Durable Gene Knockout Applications
Transthyretin Amyloidosis (ATTR)

Caused by accumulation of misfolded transthyretin (TTR) protein, which affects nerves, heart, kidneys and eyes

50,000 hATTR patients worldwide
~200-500K wtATTR patients worldwide

2-15 years typical life expectancy from onset of symptoms

Only chronic treatment options currently available

NTLA-2001 in development for ATTR

• Employs a KO edit to reduce circulating TTR protein levels
• Aims to address hATTR and wtATTR, both polyneuropathy and cardiomyopathy, with a single course of treatment

2 Compiled from various sources

hATTR: Hereditary ATTR  
wATTR: Wild-Type ATTR
**ATTR:** Sustained >95% Serum TTR Protein Reduction After a Single Dose in NHPs

- **Control**
- **Lead LNP:** Dose Level #1 (n=3)
- **Lead LNP:** Dose Level #2 (n=3)

Therapeutically relevant serum TTR knockdown

**Single Dose**

Expect to dose first patient in Phase 1 study by year-end
Hereditary Angioedema (HAE)

Genetic disease characterized by overproduction of bradykinin, which leads to recurring, severe and unpredictable swelling in various parts of the body.

1 in 50,000 HAE patients¹

Airway obstruction is particularly dangerous because it can cause death by asphyxiation.

Attacks can occur every 7-14 days on average for untreated patients¹

Only chronic treatment options currently available

NTLA-2002 in development for HAE:

- Employs a KO edit of KLKB1 gene in hepatocytes
- Aims to reduce plasma kallikrein activity to prevent excess bradykinin production leading to HAE attacks after a single course of treatment

HAE: Rapid Path to Clinic for Next KO Development Candidate, NTLA-2002

**LNP Delivery System**

**gRNA Reprograms Genetic Target**

- Cas9 mRNA
- AAAA

**HAE Program**

- Builds on ATTR program’s infrastructure, including modular LNP delivery system
- Applies insights gained from ATTR and other research programs to liver knockout target
- Platform advances expedite progression to NHP proof-of-concept

**KLKB1 gRNA**

**TTR gRNA**

**Target-specific gRNA**

*gRNA: Guide RNA*
Achieved Sustained Therapeutically Relevant Kallikrein Activity Reduction After a Single Dose in NHPs

Kallikrein Activity Reduction

- Control
- Dose Level #1 (n=3)
- Dose Level #2 (n=3)
- Dose Level #3 (n=3)

Therapeutically relevant impact on attack rate*

Single Dose

Expect to submit IND or IND-equivalent in 2H 2021

*Banerji et al., NEJM, 2017
Partial Hepatectomy Model for Investigating Persistence of KO Genome Editing

NHP studies demonstrate sustained KO editing and target TTR protein reduction carried through regular cell turnover for 12 months
Partial Hepatectomy Model for Investigating Persistence of KO 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?
Protein Reduction Remains Unchanged Following Murine Liver Regeneration

Correlating gene editing rate similarly remains unchanged post-PHx by NGS analysis\(^1\)

![Liver regeneration timeline diagram](image)

**Serum mTTR Levels (μg/ml)**

- **Pre-Edit (Day 0)**
  - TSS Control
  - KO via CRISPR/Cas9 Gene Editing

- **Post-Edit, Pre-PHx (Day 7)**
  - TSS Control
  - KO via CRISPR/Cas9 Gene Editing

- **Post-Edit, Post-PHx Necropsy (Day 17)**
  - TSS Control
  - KO via CRISPR/Cas9 Gene Editing

* Similar results obtained for TSS control and LNP when sham surgery was performed;
\(^1\) Next generation sequencing (NGS) analysis to evaluate the frequency of insertion and deletion events (edits).
Targeted Gene Insertion Persistence
Modular Approach to Unlocking Treatment of Genetic Diseases

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Intellia THERAPEUTICS
Hemophilia B (Hem B)

Rare genetic disorder caused by missing or defective Factor IX (FIX), a blood-clotting protein encoded by the F9 gene

1 in 30,000 Male births

Primarily an X-linked disorder

Severe cases often have painful, spontaneous bleeding into joints

Patients treated chronically with replacement FIX protein

Approach for Hem B:

- Targeted transgene insertion in albumin locus
- Aims to restore Factor IX protein
- First CRISPR-mediated transgene insertion in the liver of NHPs

1 Clinical manifestations and diagnosis of hemophilia (July 2019).
Effective Modular Approach for Targeted Gene Insertion in Liver

Precise integration under control of strong promoter, leads to strong, durable expression
In Vivo Insertion of Factor 9 Gene at Albumin Intron Safe Harbor Site

Hybrid Delivery System Precisely Integrates Into the Genome
In Vivo Insertion of Factor 9 Gene at Albumin Intron Safe Harbor Site

Hybrid Delivery System Precisely Integrates Into the Genome
FIX Levels in Adult Mice Are Stable Through the Completion of a 1-Year Durability Study
Achieved Supratherapeutic Levels of FIX Activity in NHPs

- Achieved an order of magnitude of greater activity than AAV gene therapy
- By varying multiple parameters we can achieve a range of circulating FIX levels and corresponding activity:
  1. Guide RNA sequence to vary genomic insertion site
  2. AAV dose that delivers inserted gene DNA sequence
  3. LNP dose that delivers CRISPR tools

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1 Source: Representative presentations and press releases regarding clinical trials
2 CRISPR-Cas9 targeted gene insertion technology day 42 post LNP/AAV dosing across multiple guides
3 Source: National Hemophilia Foundation
All data generated with hyperfunctional FIX variant
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?
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

![Graph showing circulating hFIX levels normalized to pre-PHx levels](image)

- Episomal AAV Expression
- Targeted Insertion via CRISPR/Cas9 Gene Editing

~95% Loss with Episomal Expression

~85% Loss with Episomal Expression

1 Next generation sequencing (NGS) analysis to evaluate the frequency of insertion and deletion events (edits).
• Intellia’s non-viral LNP CRISPR/Cas9 modular platform enables rapid pipeline development for liver targets
  - NTLA-2001 for ATTR: Expect to dose first patient by year-end
  - NTLA-2002 for HAE: Plan to submit a regulatory application in 2H 2021

• Achieved supra-therapeutic levels of FIX activity in NHP to advance targeted gene insertion for hemophilia B with partner Regeneron

• Demonstrated persistence of gene KO and insertion in a PHx model of accelerated hepatocyte turnover supporting potential for single-course curative therapies

• CRISPR gene insertion has superior profile vs. AAV gene therapy