In Vivo Liver Delivery of CRISPR/Cas9 Using Lipid Nanoparticles Enables Gene Knockout Across Multiple Targets and Species

Keystone Symposium: Engineering the Genome
Jessica Seitzer | February 9, 2020

Disclosure: Employee of Intellia Therapeutics, Inc.
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Intellia Therapeutics is a Full-Spectrum Genome Editing Company

CRISPR is the therapy
Genetic diseases

In Vivo

CRISPR/Cas9

Modular Platform

LNP: Lipid Nanoparticle

Ex Vivo

CRISPR creates the therapy
Immuno-oncology
Autoimmune diseases
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

Transcriptase Cas9 expression from mRNA
gRNA target site specificity defined by 20mer at 5’ end
Effective Transthyretin (TTR) Liver Knockout (KO) in Mice After Single LNP Dose

Mouse TTR Immunohistochemistry (IHC)

Vehicle
1 week

TTR Knockout
1 week

TTR Knockout
6 months
Year-Long, >95% Serum TTR KO After a Single Dose in NHPs

Therapeutically Relevant Range: >60% TTR Knockdown

Control

Lead LNP:
Dose Level #1 (n=3)

Lead LNP:
Dose Level #2 (n=3)
Transient Exposure to LNP and RNA Cargo After Single Administration in NHPs

Ionizable Cationic Lipid

- Lipid Plasma
- Lipid Liver

% injected dose vs. time (h)

gRNA

- gRNA Plasma
- gRNA Liver

% injected dose vs. time (h)

Cas9 mRNA

- mRNA Plasma
- mRNA Liver

% injected dose vs. time (h)
Liver LNP Delivery  Editing Tool  Unmet Need  Causative Gene  Path to the Clinic and Registration

Platform Modularity

Liver Target and Disease

Disease and Target Selection Leverages Platform Modularity
Prekallikrein (KLKB1) KO for 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 patients

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

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

**Only chronic treatment options** currently available

**Approach for HAE**

- Aim to reduce overproduction of bradykinin to prevent HAE attacks with a single course of treatment
- Employ a knockout edit of KLKB1 gene in hepatocytes

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C1 Esterase Inhibitor (C1-INH) Regulates the Release and Buildup of Bradykinin

Healthy person

KLKB1 → Prekallikrein → Kallikrein

Factor XII → Factor XIIa

HMW Kininogen → Bradykinin

Normally inhibited by C1-INH
C1-INH Deficiency Results in Unregulated Release and Buildup of Bradykinin, Activating Endothelial Cells and Leading to Angioedema

Airway obstruction can lead to death by asphyxiation

Angioedema happens throughout the body
CRISPR/Cas9-Mediated KO of *KLKB1* Reduces the Undesired Bradykinin Activity in People with HAE

- Prekallikrein inhibitors are **clinically validated** in preventing HAE attacks
- *KLKB1* KO is expected to be **safe**, as human nulls show no associated pathology*

*Fletcher Syndrome, PMID 20424433*
Intellia’s Industrialized Guide Qualification Platform Enables Efficient Selection of *KLKB1* Human Lead Guides

**Guide Design Criteria**
- Cut site within coding region
- On-target specificity
- No overlap with common SNPs
- Cross-species homology desired

**Guide Selection Criteria**
- Edit results in frameshift
- Subsequent mRNA and protein reduction
- Advantageous off-target profile

### Human *KLKB1* Guide Data in Primary Human Hepatocytes

<table>
<thead>
<tr>
<th>KLKB1-1</th>
<th>KLKB1-2</th>
<th>KLKB1-3</th>
<th>KLKB1-4</th>
<th>KLKB1-5</th>
<th>KLKB1-6</th>
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<th>KLKB1-10</th>
<th>KLKB1-11</th>
<th>Control</th>
<th>Untreated</th>
</tr>
</thead>
</table>

**% Editing**

- Indel
- ELISA

**Secreted Kallikrein (ng/ml)**

- 0.0
- 0.5
- 1.0
- 1.5
- 2.0
- 2.5
- 3.0
- 3.5
- 4.0
- 4.5

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Humanized KLKB1 Mice Enable Further Selection of Lead Human Guides

KLKB1 Editing vs. Serum Protein Reduction

Single administration within a one dose level

Target protein reduction

VelociGene® is a registered trademark of Regeneron Pharmaceuticals, Inc.
KLKB1 KO by Single Dose LNP in NHPs Results in Reproducible and Durable Decrease in Serum Kallikrein Protein Levels and Activity

Kallikrein Protein Reduction

Kallikrein Activity Reduction

Therapeutically meaningful impact on attack rate*

*Banerji et al., NEJM, 2017
KLKB1
Knockout
Key
Takeaways

• Modularity of Intellia's platform enables independent, one-time therapeutic approaches for multiple targets

• Editing of KLKB1 gene results in therapeutically relevant reduction of kallikrein activity in NHPs

• Kallikrein activity reduction sustained for at least 22 weeks in NHPs, in a highly reproducible manner across studies

• Expect to nominate a development candidate for HAE in 1H 2020