



# ***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.*

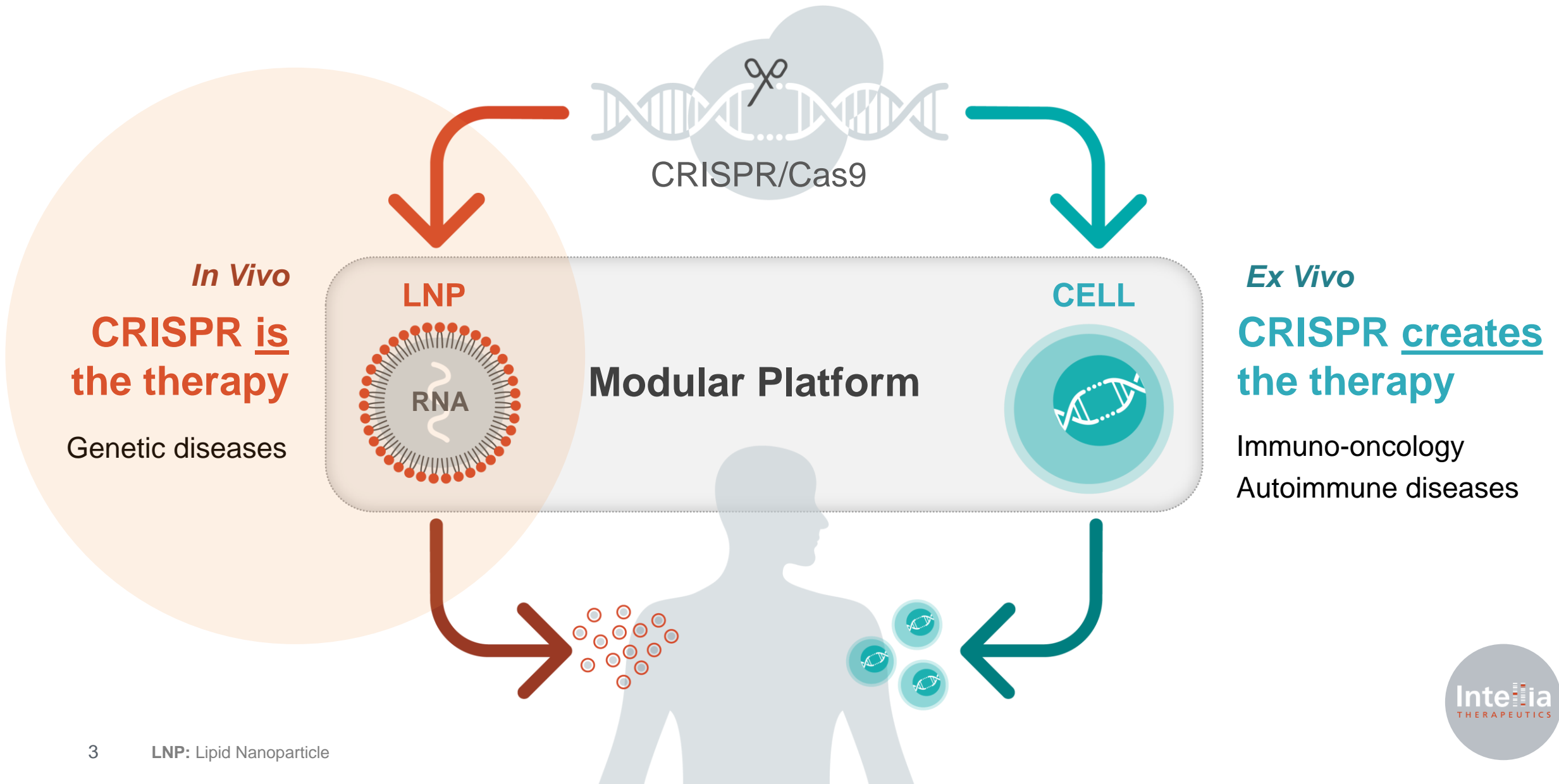
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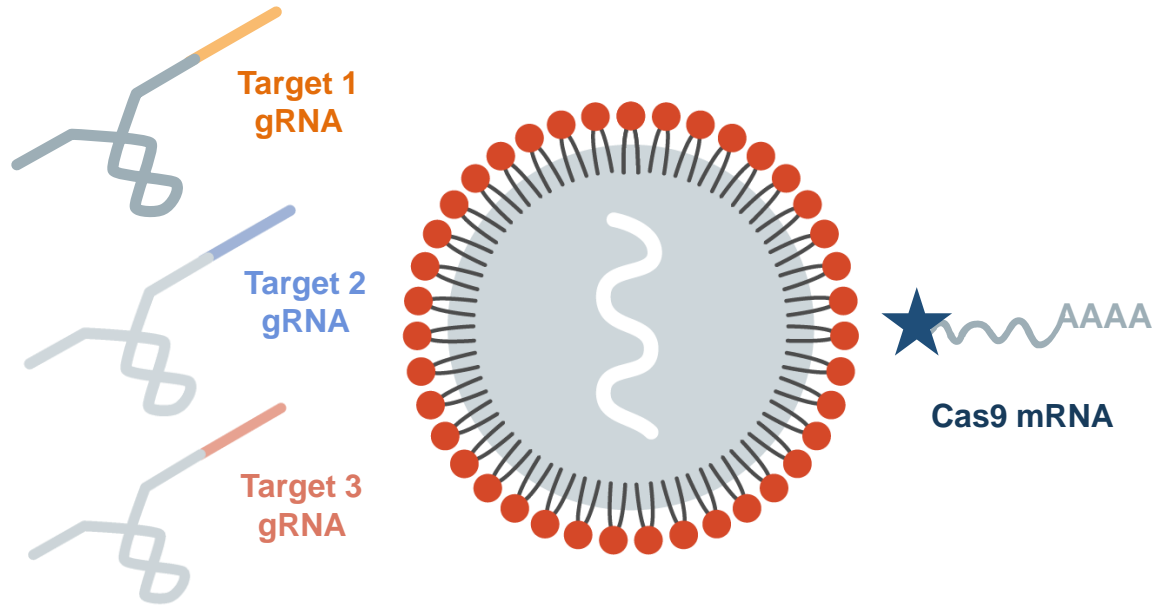


# Intellia Therapeutics is a Full-Spectrum Genome Editing Company



# 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

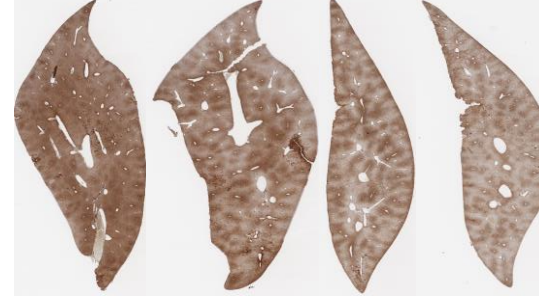
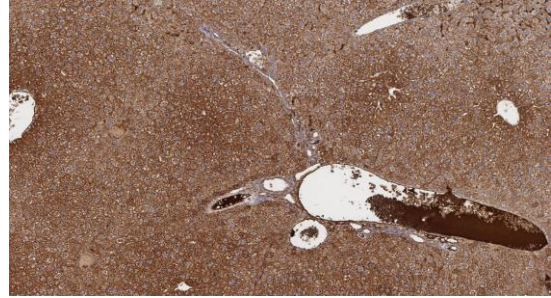
- ✓ Clinically-proven delivery to liver
- ✓ Large cargo capacity
- ✓ Transient expression
- ✓ Biodegradable
- ✓ Low immunogenicity
- ✓ Well-tolerated
- ✓ Redosing capability
- ✓ Scalable synthetic manufacturing
- ✓ Tunable



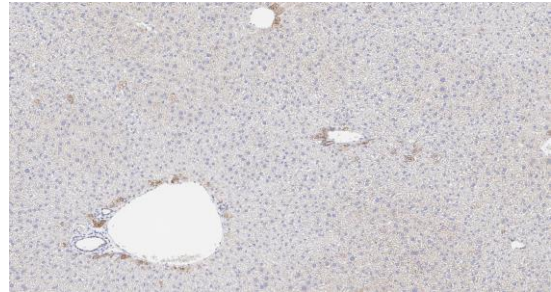
# Effective Transthyretin (TTR) Liver Knockout (KO) in Mice After Single LNP Dose

## Mouse TTR Immunohistochemistry (IHC)

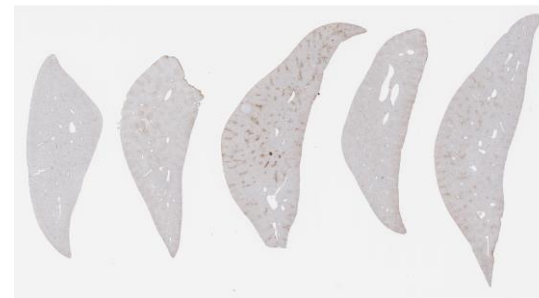
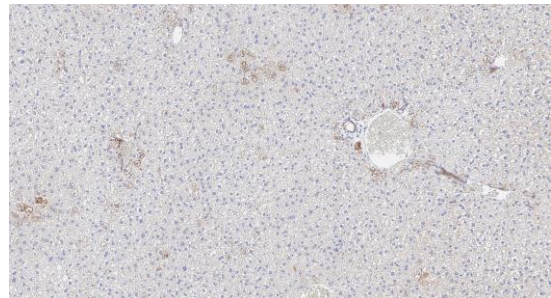
**Vehicle**  
1 week



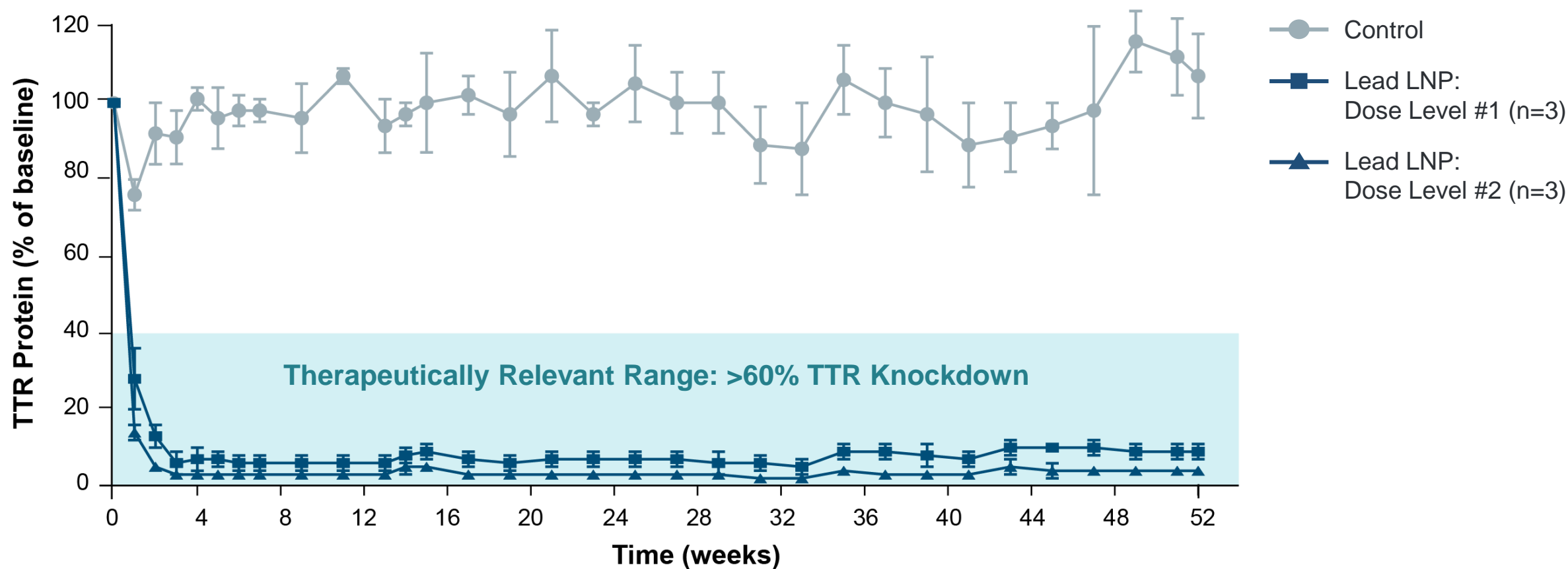
**TTR Knockout**  
1 week



**TTR Knockout**  
6 months

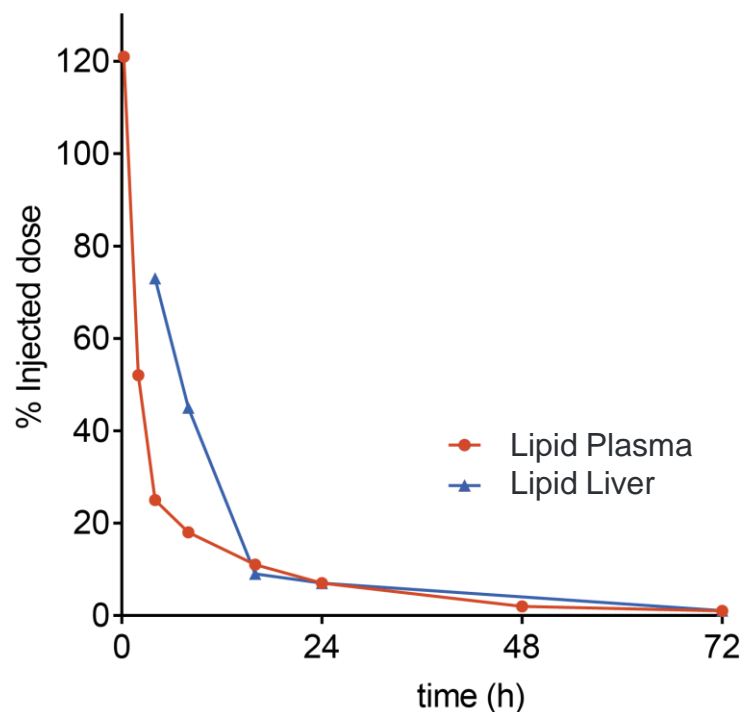


## Year-Long, >95% Serum TTR KO After a Single Dose in NHPs

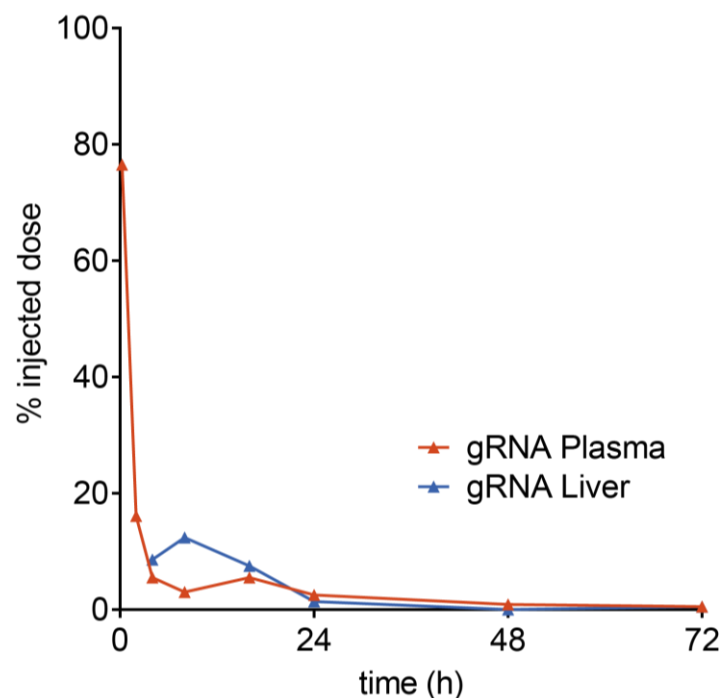


# Transient Exposure to LNP and RNA Cargo After Single Administration in NHPs

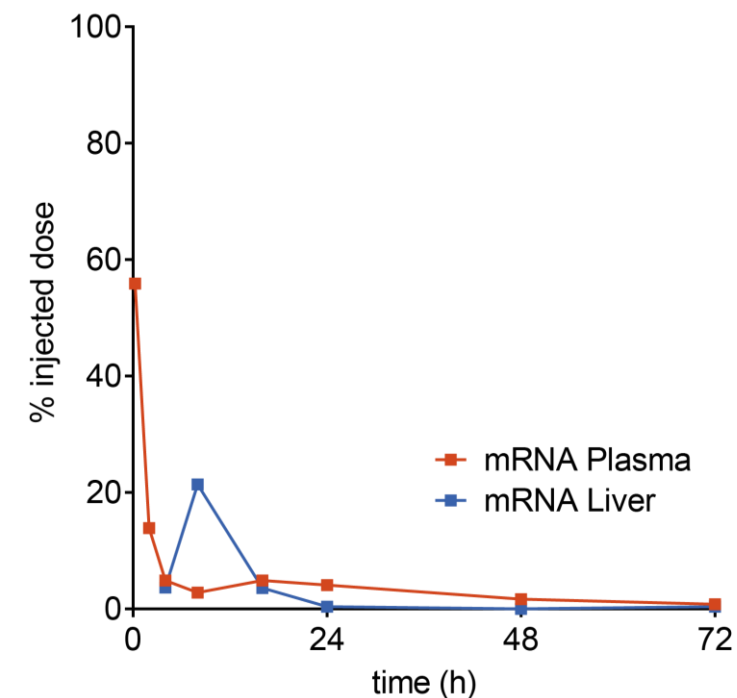
## Ionizable Cationic Lipid



## gRNA



## Cas9 mRNA



# Disease and Target Selection Leverages Platform Modularity



## Platform Modularity



Liver LNP  
Delivery



Editing  
Tool



## Liver Target and Disease



Unmet  
Need



Causative  
Gene



Path to the  
Clinic and  
Registration



# 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<sup>1</sup>

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

Attacks can occur every

## 7-14 days

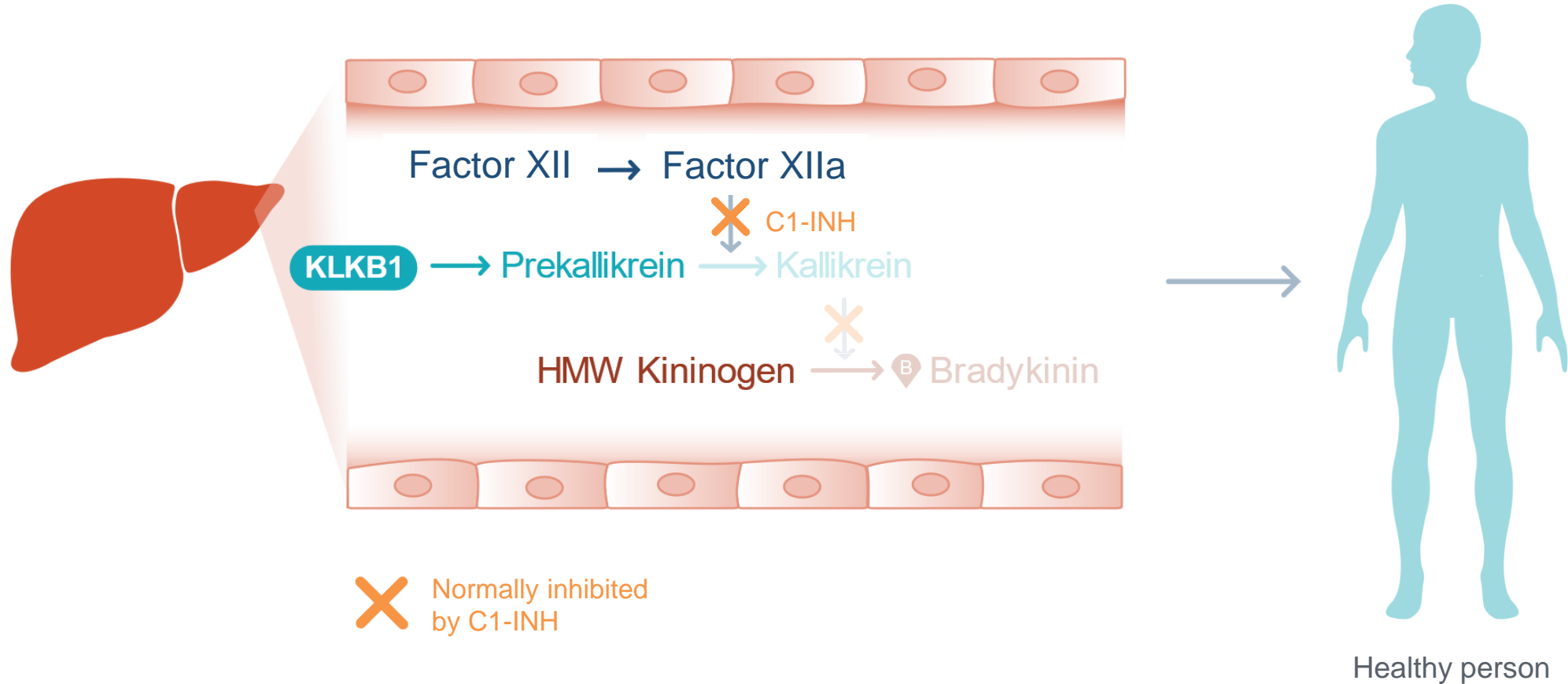
on average for untreated patients<sup>1</sup>

**Only chronic treatment options** currently available

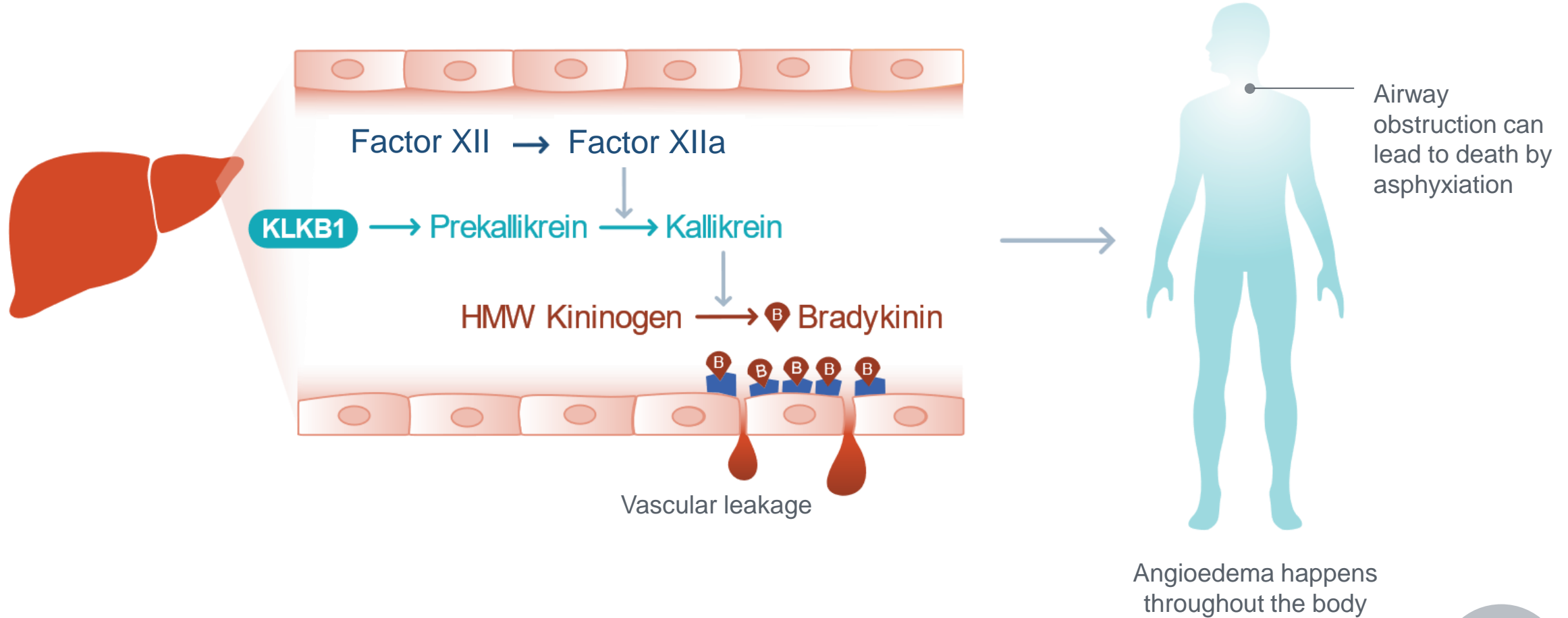
## Approach for HAE

- 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

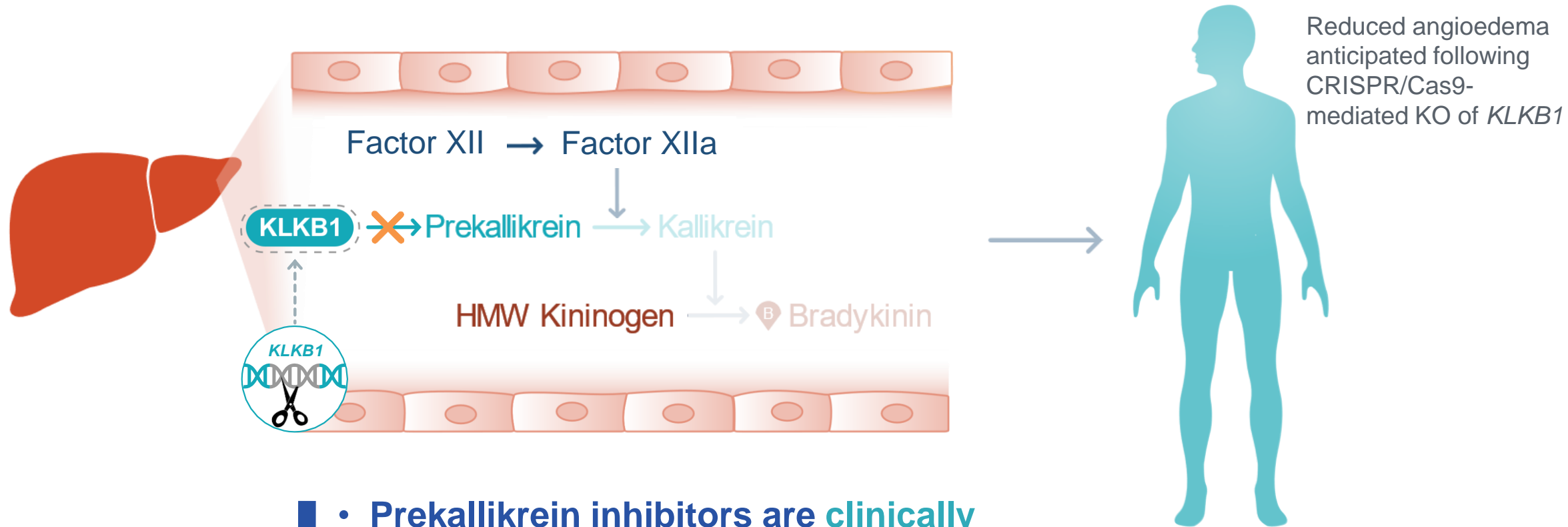
# C1 Esterase Inhibitor (C1-INH) Regulates the Release and Buildup of Bradykinin



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

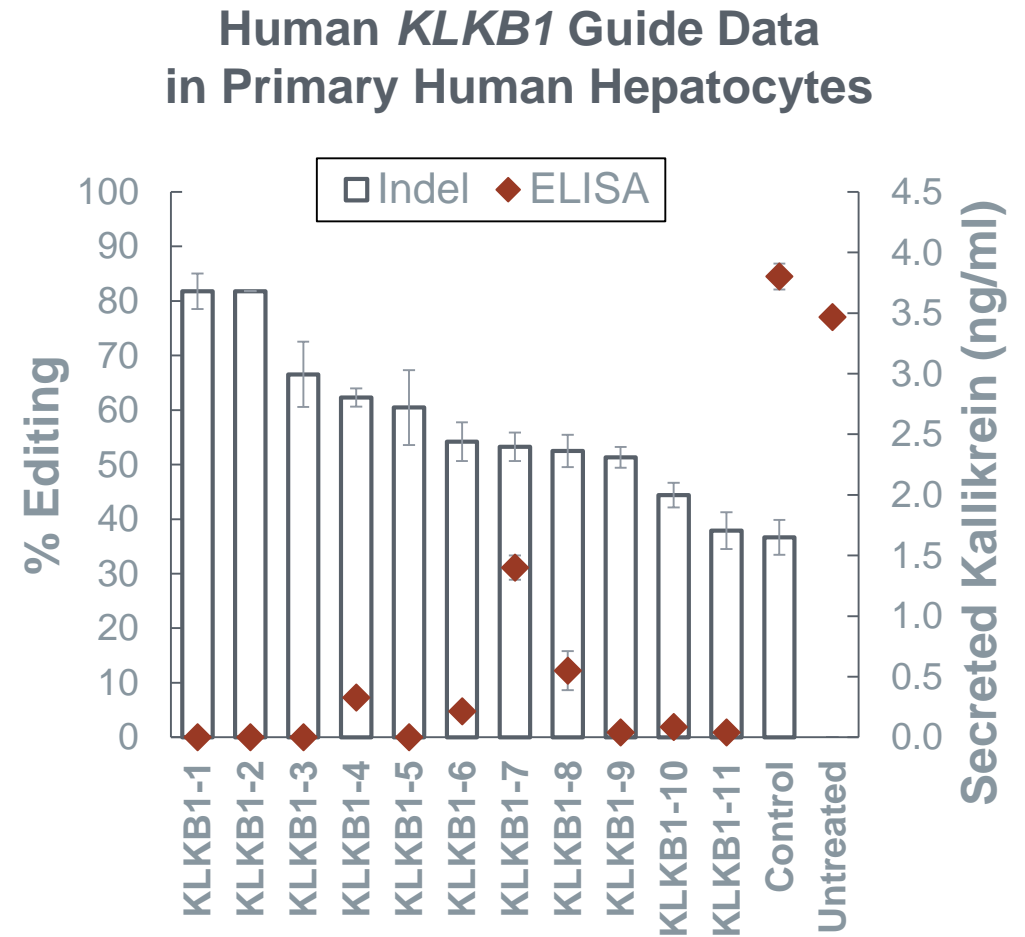
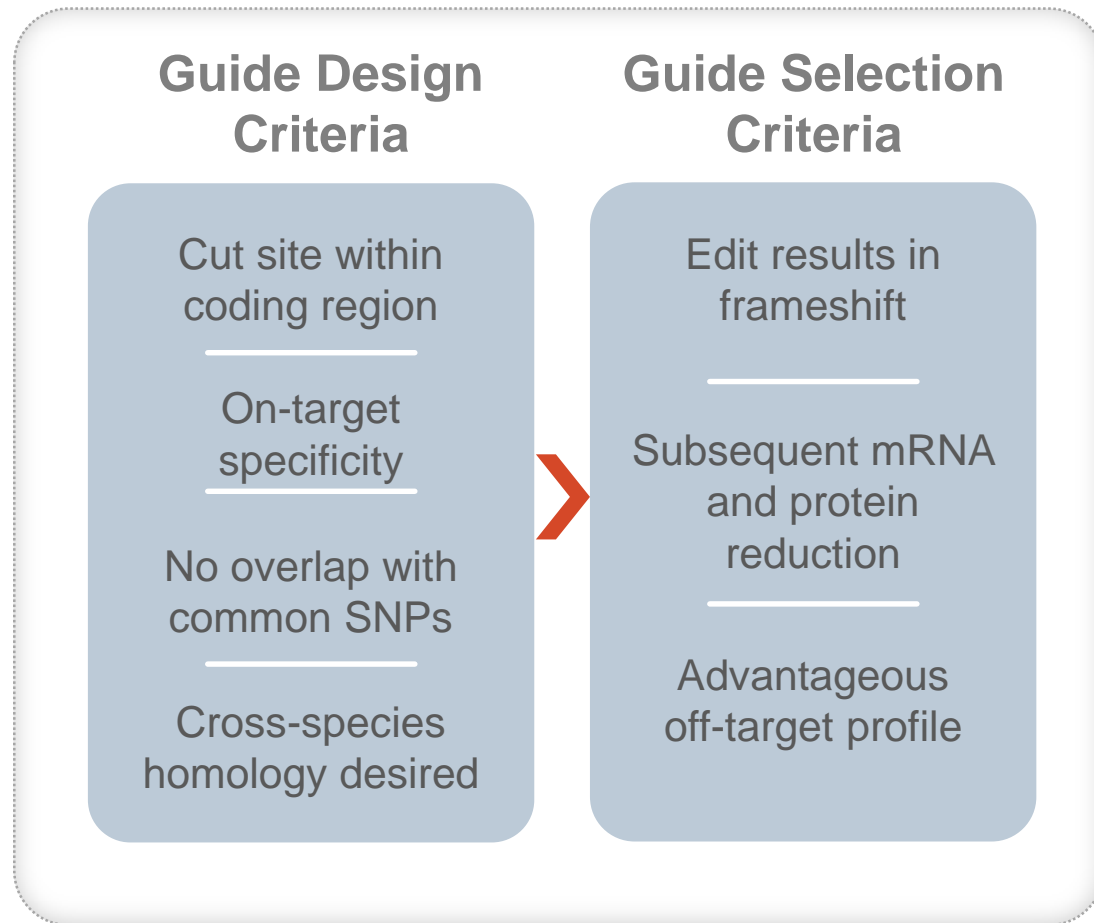


# CRISPR/Cas9-Mediated KO of *KLKB1* Reduces the Undesired Bradykinin Activity in People with HAE

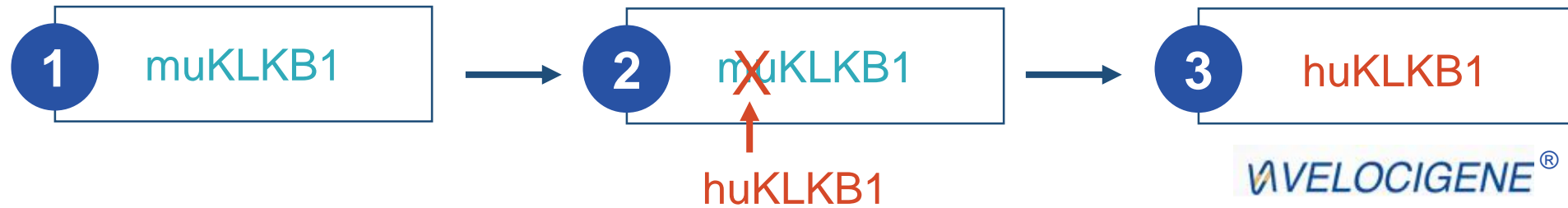


- Prekallikrein inhibitors are **clinically validated** in preventing HAE attacks
- *KLKB1* KO is **expected to be safe**, as human nulls show no associated pathology\*

# Intellia's Industrialized Guide Qualification Platform Enables Efficient Selection of *KLKB1* Human Lead Guides

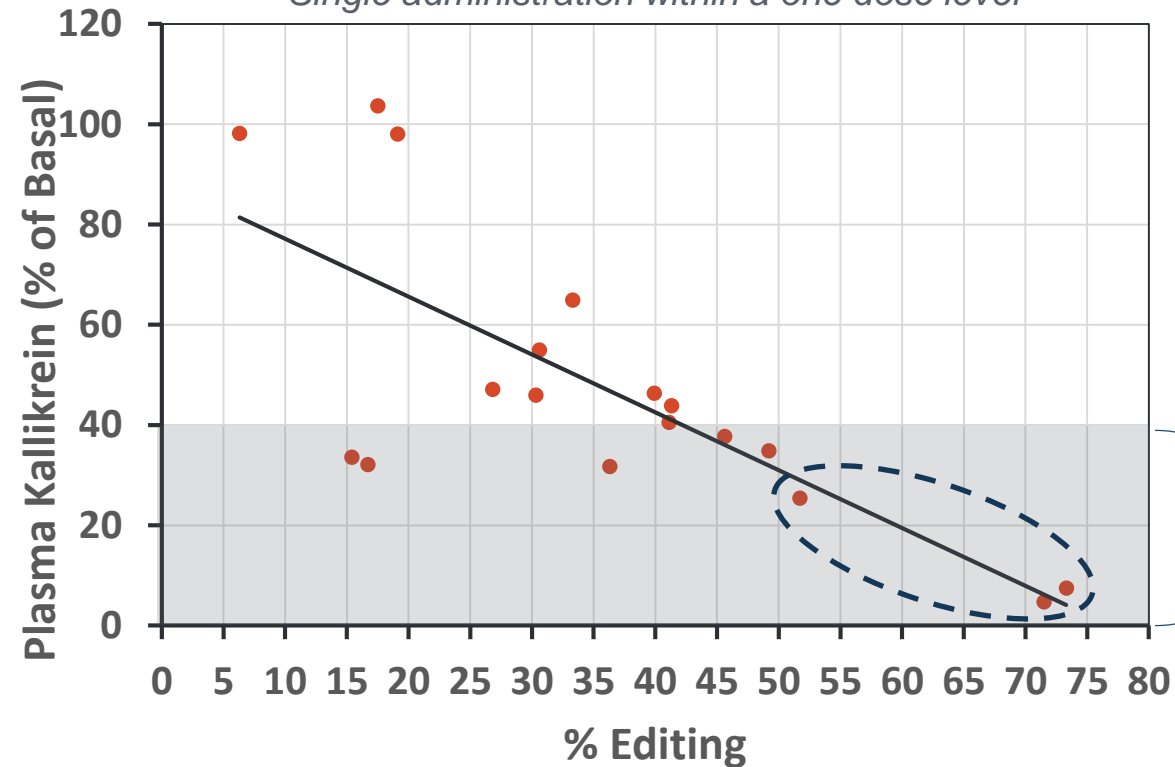


# Humanized *KLKB1* Mice Enable Further Selection of Lead Human Guides



## *KLKB1* Editing vs. Serum Protein Reduction

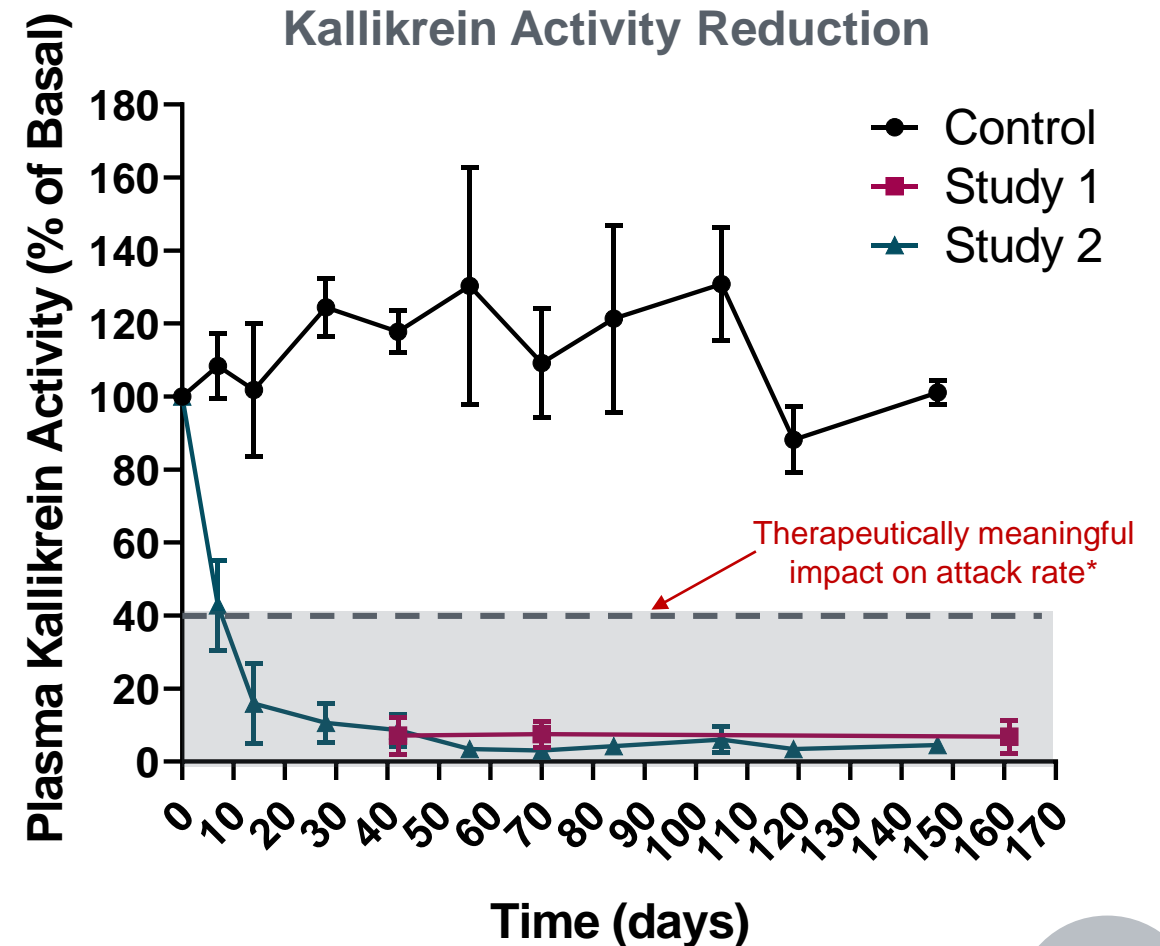
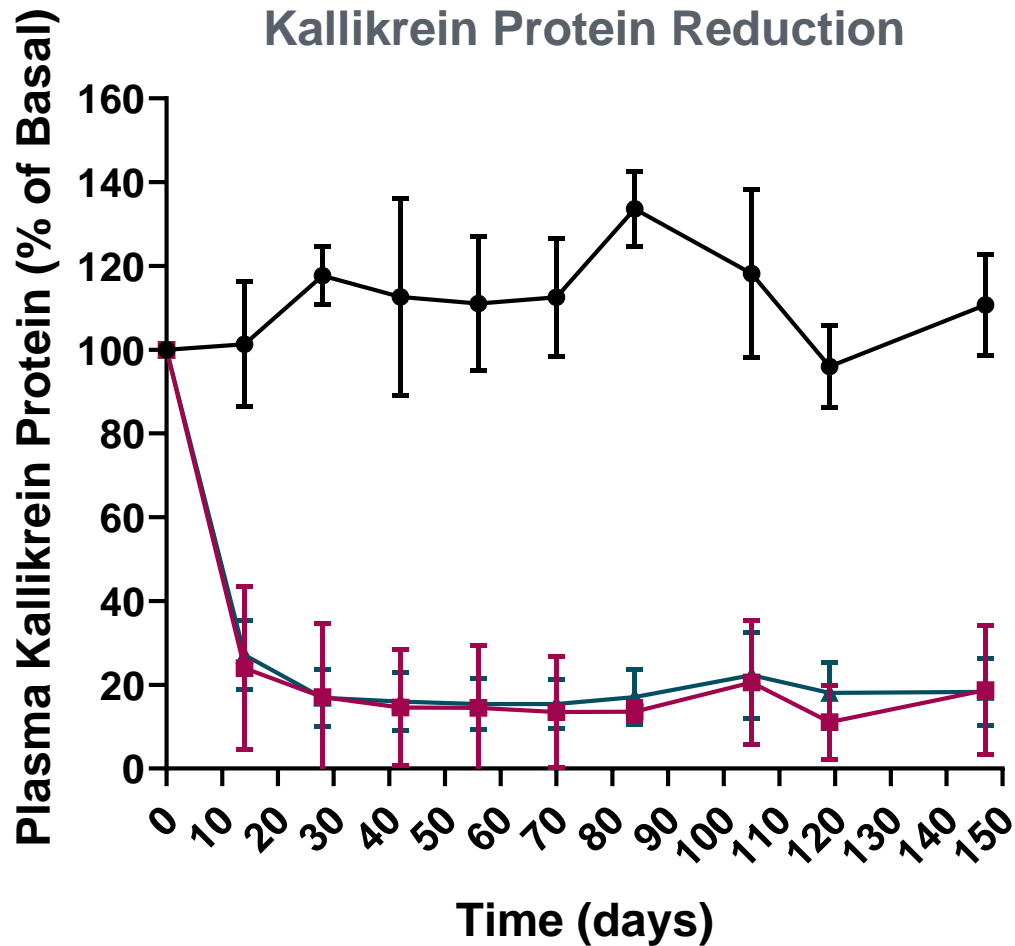
*Single administration within a one dose level*



Target protein reduction



## KLKB1 KO by Single Dose LNP in NHPs Results in Reproducible and Durable Decrease in Serum Kallikrein Protein Levels and Activity



# *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**



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