



# CRISPR Therapeutics

*Creating transformative gene-based medicines for serious diseases*

Corporate Overview

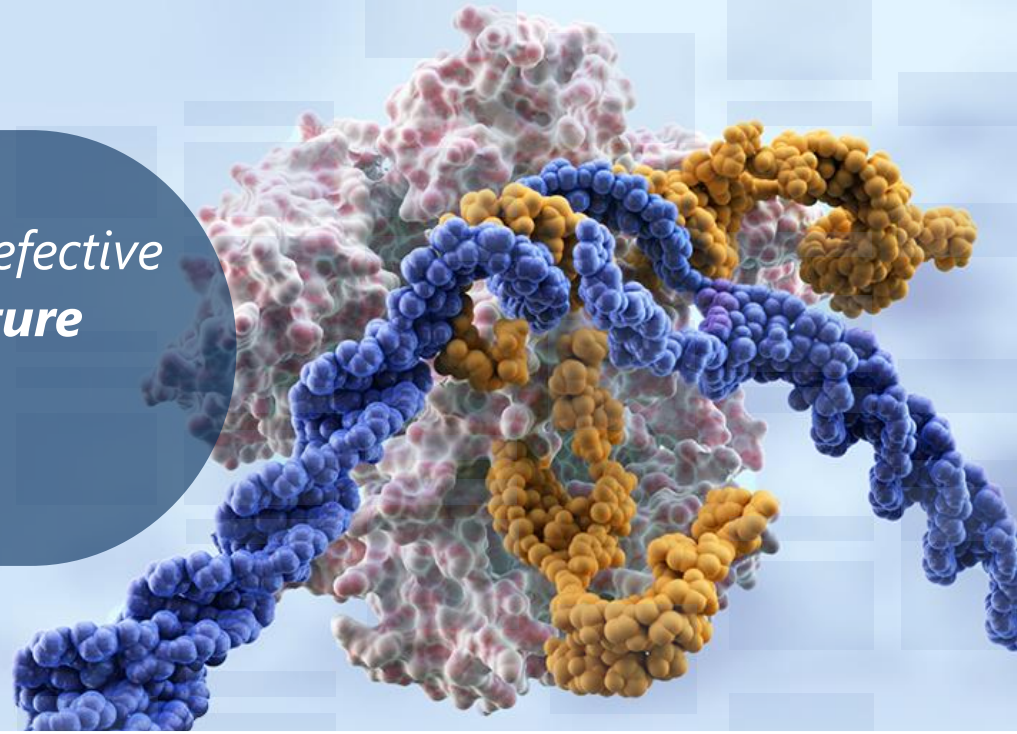
June 2018



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“A new technology for ‘editing’ defective genes has raised hopes for a **future generation of medicines**”  
THE WALL STREET JOURNAL.

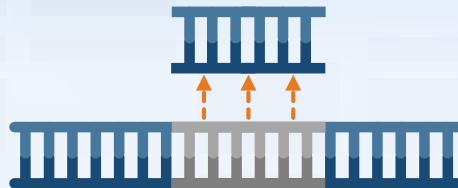


*Specific, efficient, and versatile platform*

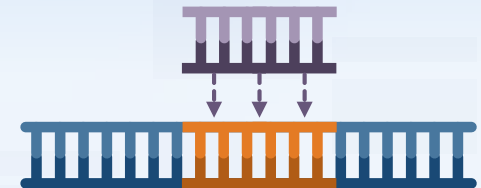
► DISRUPTION



► DELETION



► CORRECTION



# CRISPR Therapeutics Highlights



## LEADING GENE-EDITING COMPANY

Rapidly translating revolutionary CRISPR/Cas9 technology into transformative therapies



## PIONEERING CRISPR IN THE CLINIC

Filed first company-sponsored CTA for a CRISPR-based therapeutic; CTX001 on track to initiate trials in 2018 in hemoglobinopathies



## NEXT-GENERATION I/O PLATFORM

Advancing wholly owned, potentially best-in-class gene-edited allogeneic CAR-T products toward the clinic



## ADVANCING *IN VIVO* APPLICATIONS

Pursuing select *in vivo* indications enabled by in-licensed technologies, platform improvement, and strategic partners



















## UNIQUE CASEBIA JOINT VENTURE

50% ownership of Casebia broadens our pipeline and supports our platform improvement efforts; funded by ~\$265M from Bayer



## STRONG IP & FINANCIAL POSITION

Strong IP and robust financial position: \$341.8 million in cash as of 3/31/18

Program	Editing approach	Research	IND-enabling	Ph I/II	Partner	Structure
<b>Ex vivo: Hematopoietic</b>						
CTX001: $\beta$ -thalassemia	Disruption			First CTA Approved 1Q18		Collaboration
CTX001: Sickle cell disease (SCD)	Disruption			IND filing 1H18		Collaboration
Hurler syndrome (MPS-1)	Correction					Wholly-owned
Severe combined immunodeficiency (SCID)	Correction					Joint venture
<b>Ex vivo: Immuno-oncology</b>						
CTX110: CD19-positive malignancies	Various			IND filing YE18		Wholly-owned
CTX120: Anti-BCMA Allogeneic CAR-T	Various					Wholly-owned
CTX130: Anti-CD70 Allogeneic CAR-T	Various					Wholly-owned
<b>In vivo: Liver</b>						
Glycogen storage disease Ia (GSD Ia)	Correction					Wholly-owned
Hemophilia	Correction					Joint venture
<b>In vivo: Other organs</b>						
Duchenne muscular dystrophy (DMD)	Disruption					Wholly-owned
Cystic fibrosis (CF)	Correction					License option



## **Hemoglobinopathies**

*Ex vivo lead candidate in genetically-defined disease*



## **Immuno-oncology**

*Expand cell therapy platform with allo CAR-T pipeline*

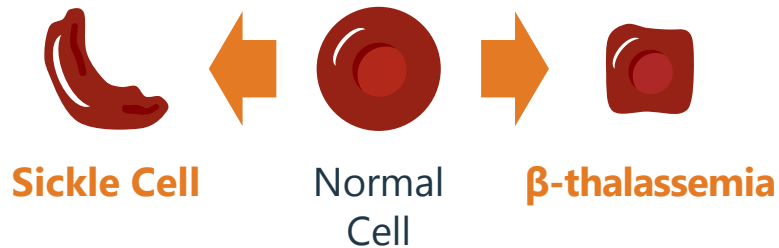


## ***In vivo***

*Enable in vivo applications through platform advancements*

## SICKLE CELL DISEASE (SCD) AND $\beta$ -THALASSEMIA

**Blood disorders** caused by *mutations* in the  $\beta$ -globin gene



**Significant worldwide burden**

**300,000** Annual births  
in SCD and  $\beta$ -  
thalassemia,  
respectively

**60,000**

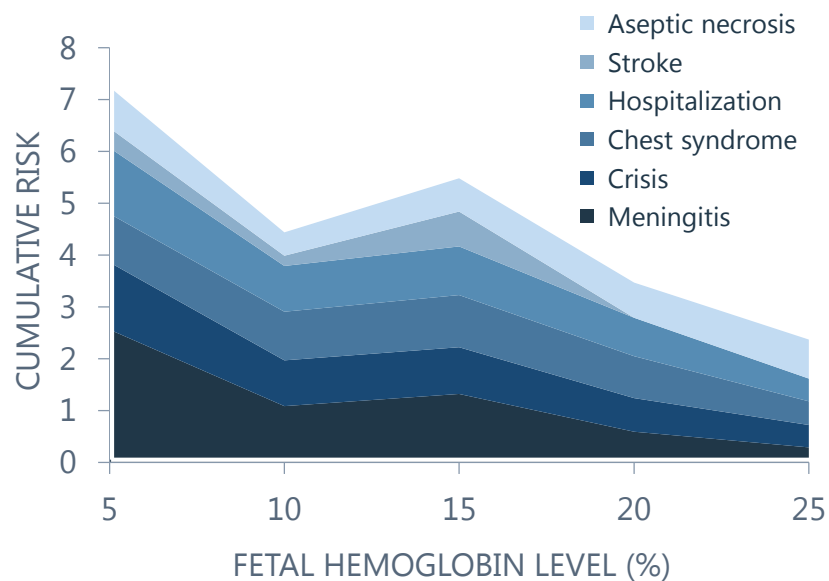
**High morbidity and mortality**



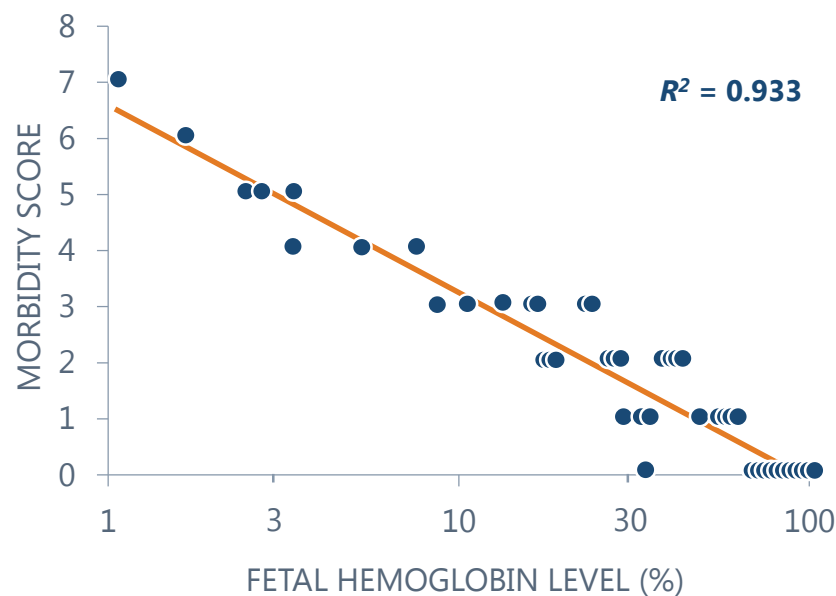
**Heavy burden of patient care**



## REDUCED RISK OF EVENTS IN SICKLE CELL DISEASE<sup>1</sup>



## REDUCED SYMPTOMS IN $\beta$ -THALASSEMIA<sup>2</sup>

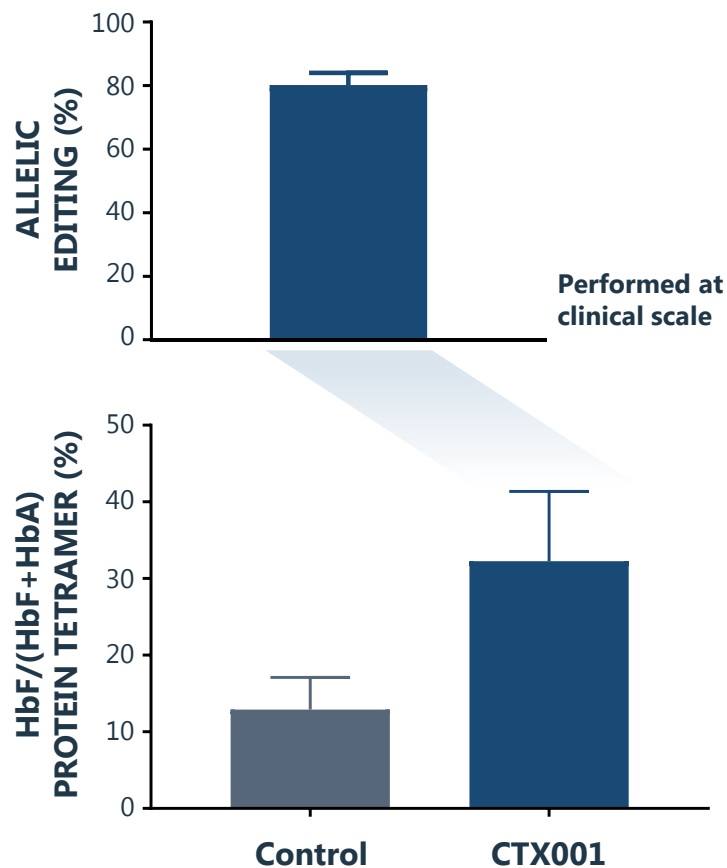


- › **Naturally occurring genetic variants** cause **hereditary persistence of fetal hemoglobin (HPFH)**, and **lead to reduced symptoms** in patients with sickle cell disease and  $\beta$ -thalassemia
- › Our gene editing strategy aims to **recreate these variants** in symptomatic patients — an approach **supported by well-understood genetics**

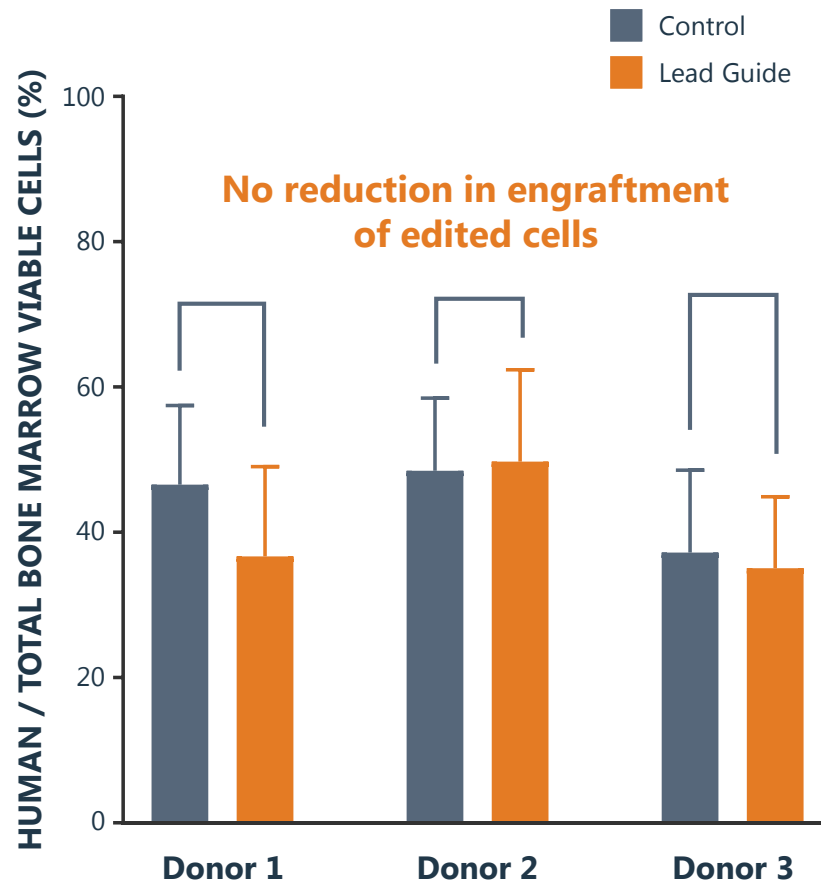
1. Powars, *et al.* Blood 1984; 2. Musallam, *et al.* Blood 2012

# CTX001 Upregulates Fetal Hemoglobin and Engrafts in Mice

## HIGH EDITING RATES LEAD TO ROBUST HbF INDUCTION<sup>1</sup>



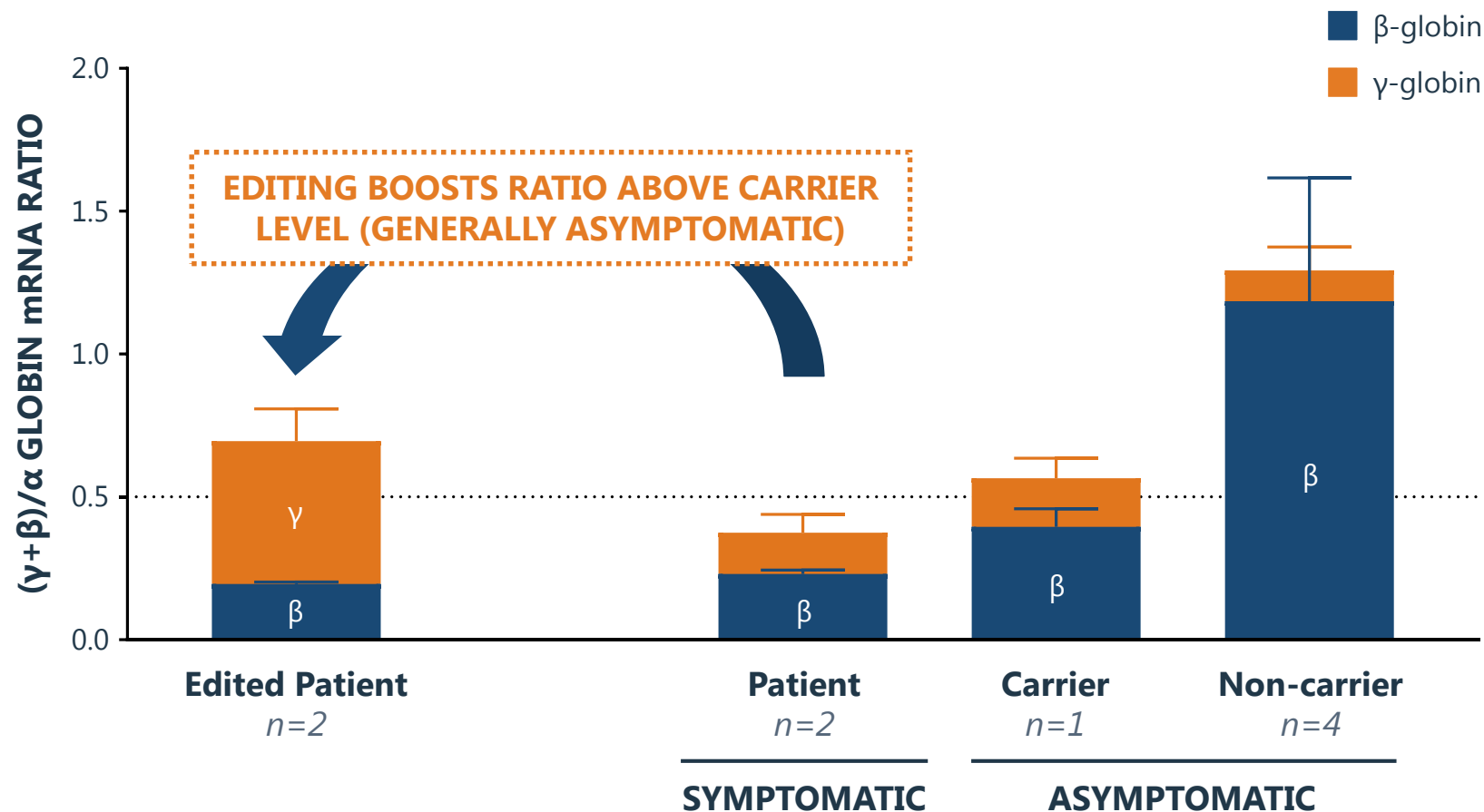
## CTX001 ENGRAFTS *IN VIVO* IN MICE<sup>2</sup>



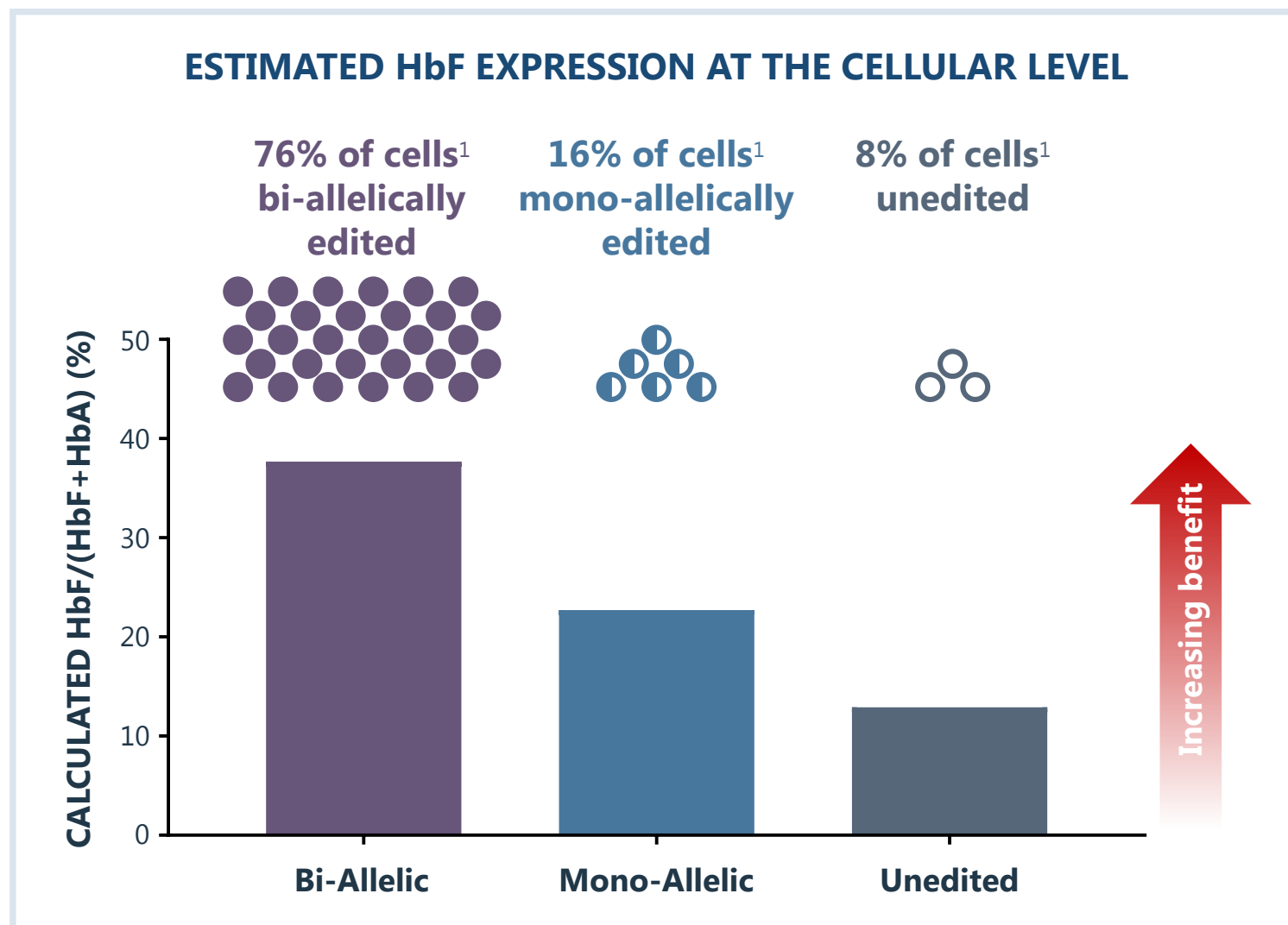
1. n=6 healthy donors; 2. 16-week engraftment data

# $\beta$ -thal: Editing Increases Globin Expression to Carrier Levels

## GLOBIN mRNA RATIO AFTER GENE EDITING OF $\beta$ -THAL PATIENT SAMPLES



# SCD: Bi-Allelic Editing Leads to High HbF Protein Levels



1. n=163 single erythroid colonies derived from edited CD34<sup>+</sup> cells from healthy donors

## CTX001-111

*A single arm Phase 1/2 study to assess the safety and efficacy of CTX001 in patients with  $\beta$ -thalassemia*



### Patients

Up to 30 adult  
transfusion-dependent  
patients



### Sites

Sites with extensive  
transplant experience in E.U.  
countries with significant  
disease burden



### Endpoints

HbF levels and transfusion  
requirements are clinically  
relevant and easily  
measurable

**Potential to expand into a registrational trial**, as well as to additional  
genotype and age cohorts, if supported by safety and efficacy

# Autologous CAR-T is Transformative, but has Limitations

CAR-T has generated **tremendous excitement** . . .

“*The first-ever treatment that genetically alters a patient’s own cells to fight cancer, a milestone that is **expected to transform treatment in the coming years***”

*The New York Times*

. . . But there are still **significant limitations** to autologous CAR-T

**Patients progress or die while waiting**

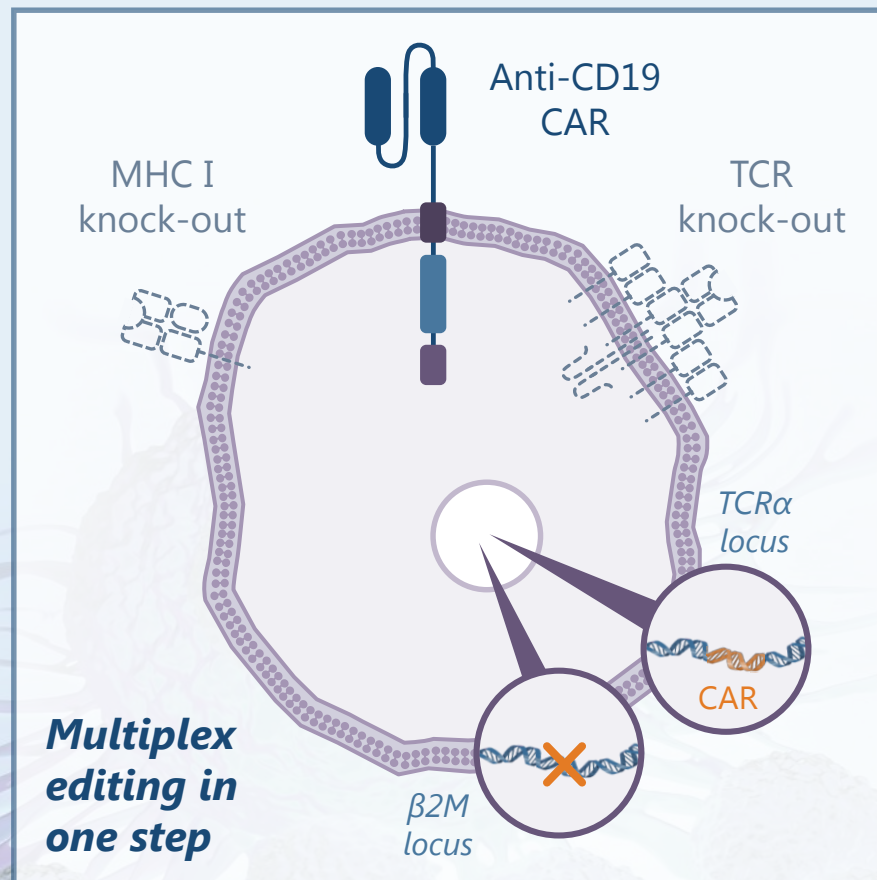
**Patient-to-patient variability**

**Costly, complicated manufacturing**

**Commercial challenges of bespoke therapy**

# Our Approach: Gene-Edited Allogeneic CD19 CAR-T

**CTX110** – our initial immuno-oncology product candidate



CRISPR enables an allogeneic approach that **remedies issues with autologous CAR-T**

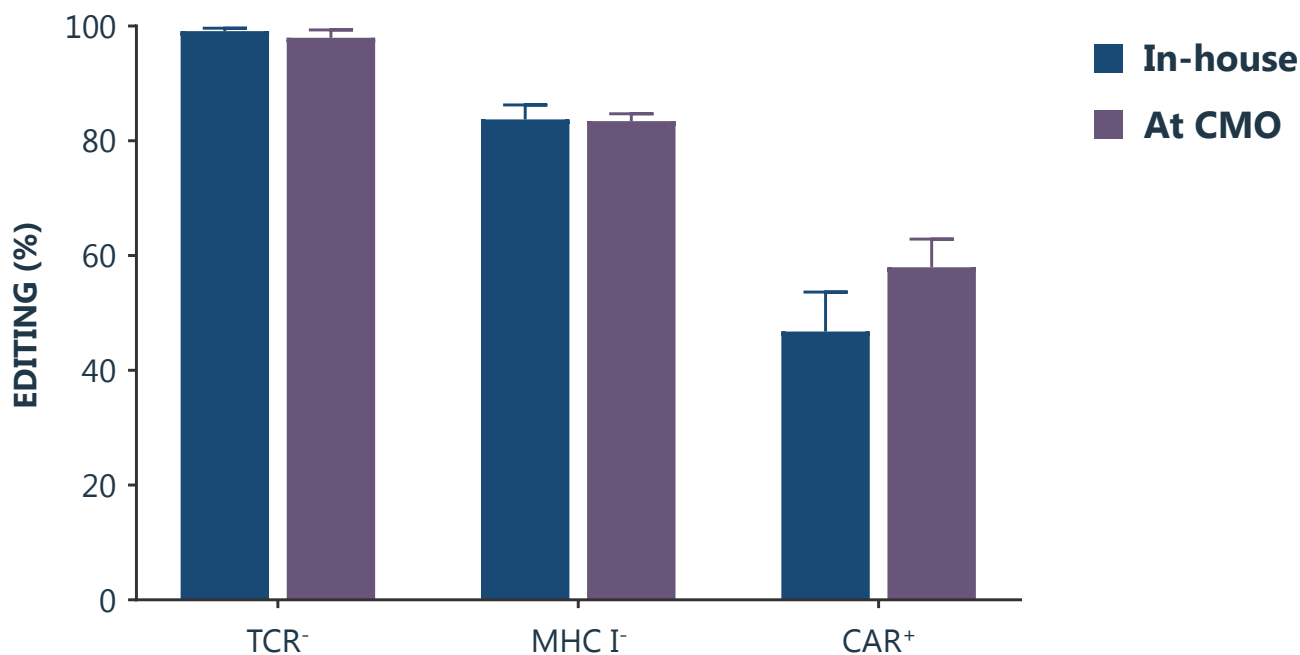
**Product available immediately**

**Consistent healthy-donor lymphocytes**

**Low COGs and simpler manufacturing**

**Off-the-shelf product – broader access**

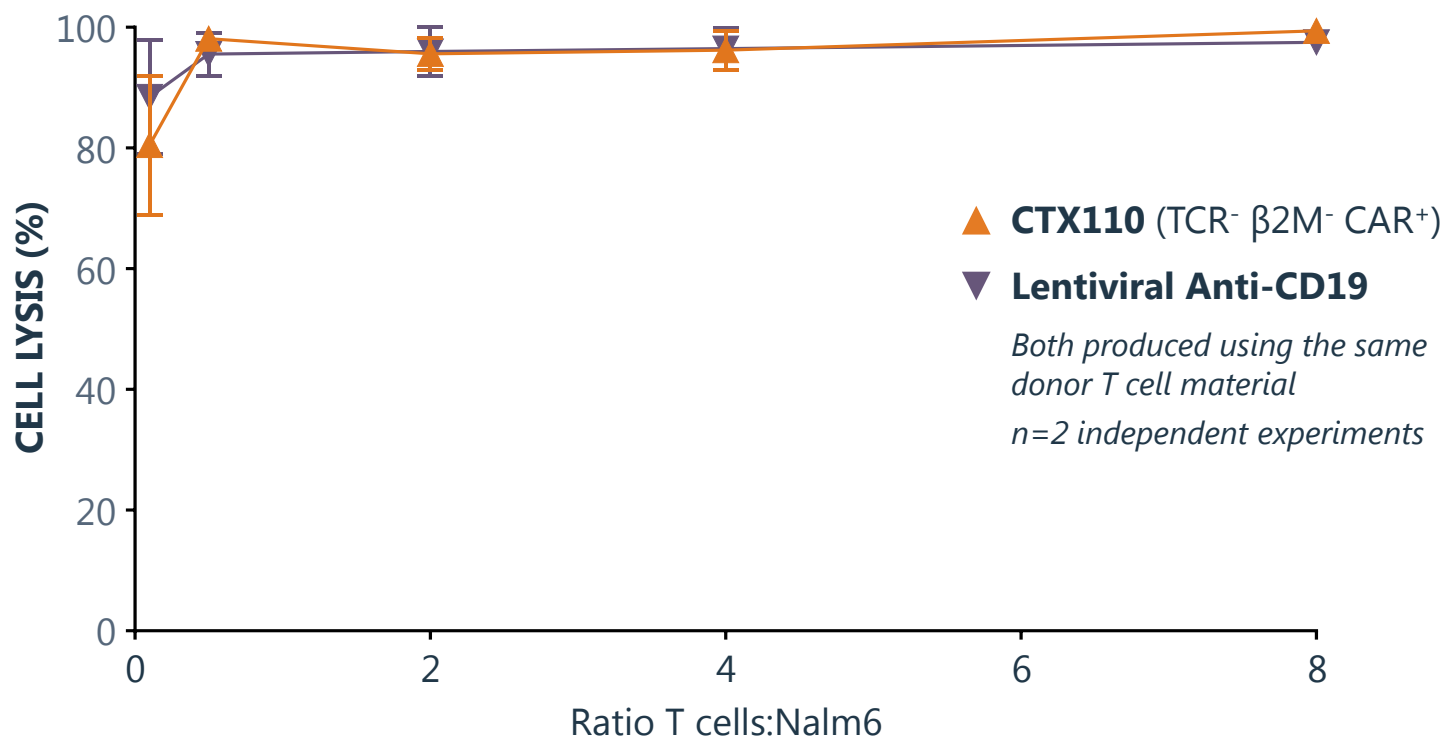
## EDITING RATES ACROSS MULTIPLE DONORS



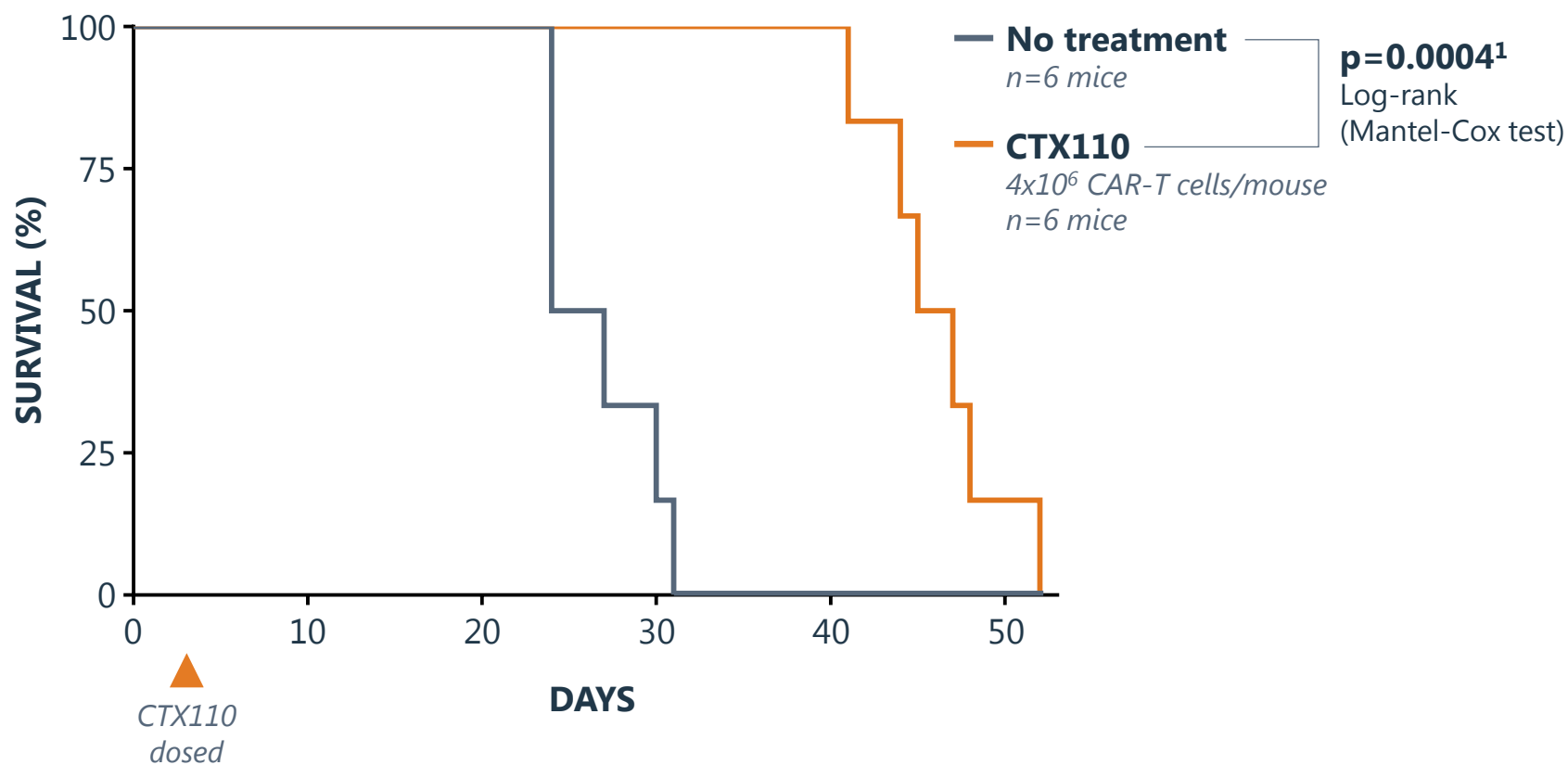
**Process development and manufacturing initiated for CTX110 –  
IND-enabling studies underway**

# CTX110 Eliminates CD19-Expressing Tumor Cells *In Vitro*

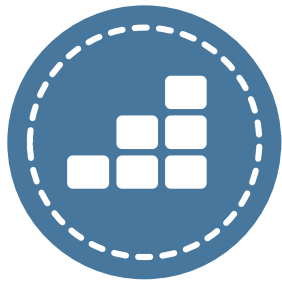
## CTX110 COMPARES FAVORABLY TO LENTIVIRAL "AUTOLOGOUS" CAR-T



## PROLONGED SURVIVAL IN DISSEMINATED NALM6 B-ALL MODEL



# Numerous Opportunities Beyond CTX110



## Make rapid entry using validated tumor targets

Healthy-donor allo approach  
in well-validated tumor targets

***CD19, BCMA***



## Expand into solid with novel targets and advanced editing

Precise edits to make CAR-T  
effective in solid tumors

***CD70, resistance to tumor  
microenvironment***



## Unlock the full potential of CRISPR

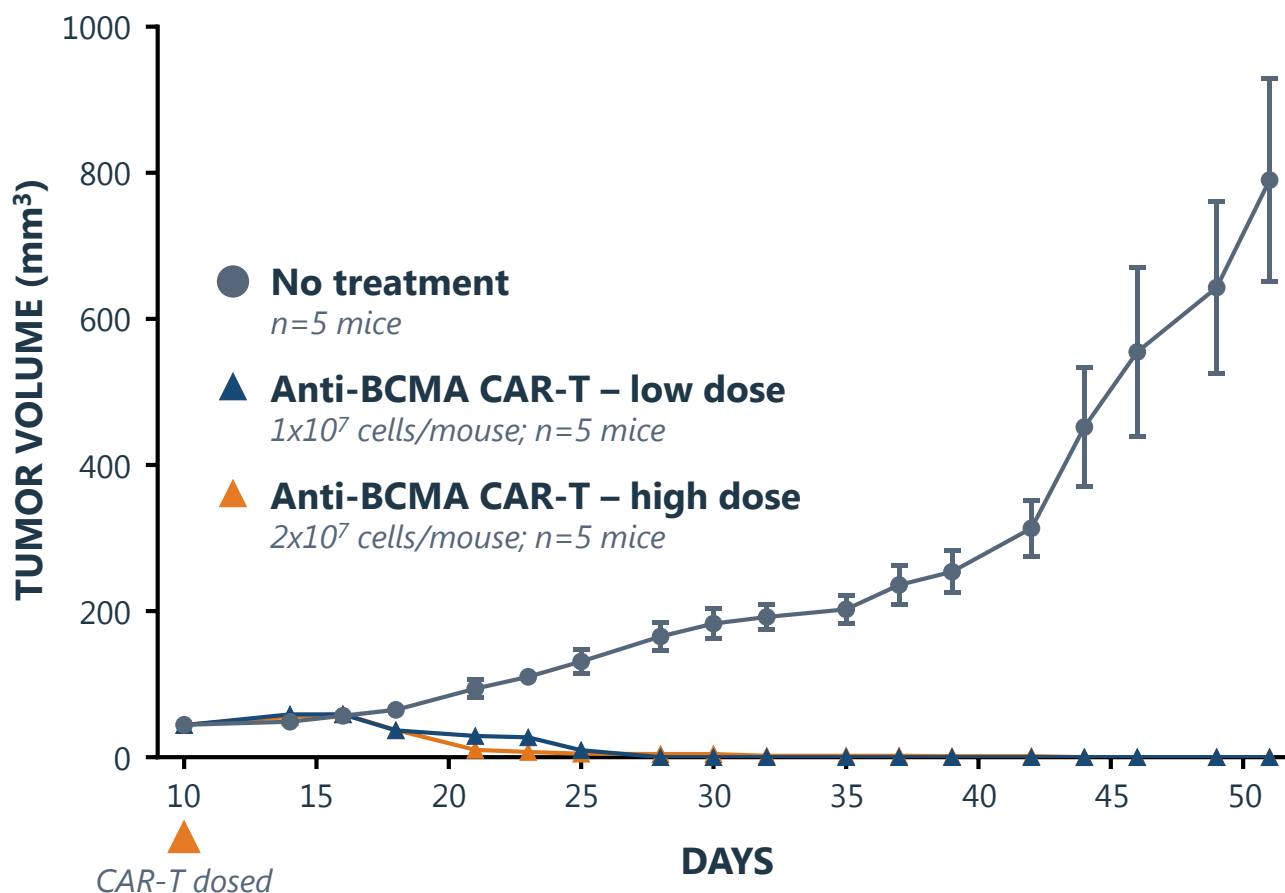
Multiplex editing to enable  
more complex products

***Switches, neoantigens,  
bispecifics***

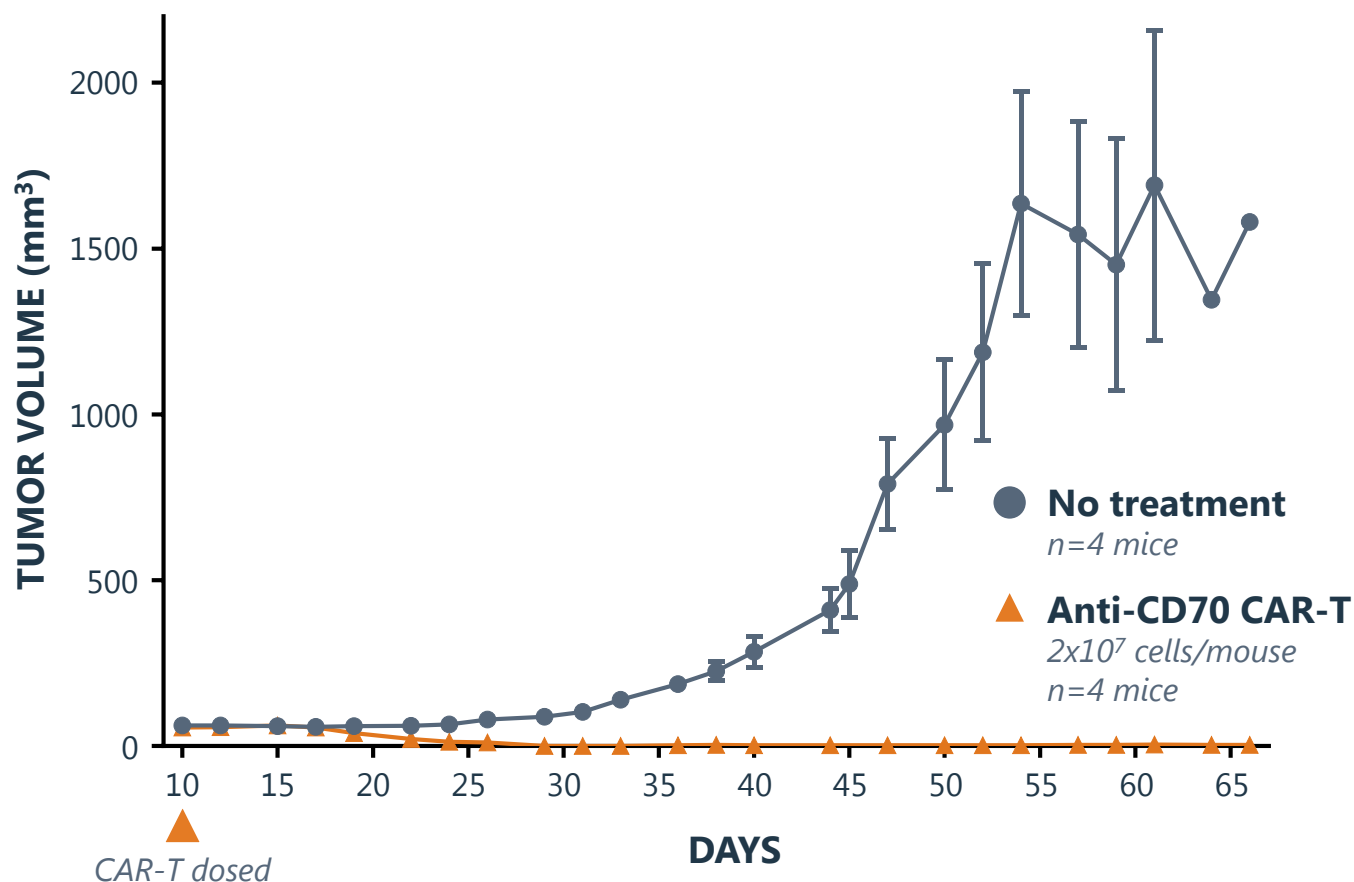


**Collaborations with Neon and MGH  
to identify and exploit new targets**

## SUBCUTANEOUS RPMI-8226 MULTIPLE MYELOMA MODEL COMPLETELY ELIMINATED



## SUBCUTANEOUS A498 RENAL CELL CARCINOMA MODEL COMPLETELY ELIMINATED



- > **85% CAR<sup>+</sup>** using a proprietary single chain made in-house
- > **99% TCR knock-out** even before purification

# Delivering CRISPR/Cas9 to Unlock *In Vivo* Applications

## NON-VIRAL

### Lipid Nanoparticles (LNPs)

- › Increased potency
- › Expansion beyond liver delivery
- › Improved tolerability



### Messenger RNA (mRNA)

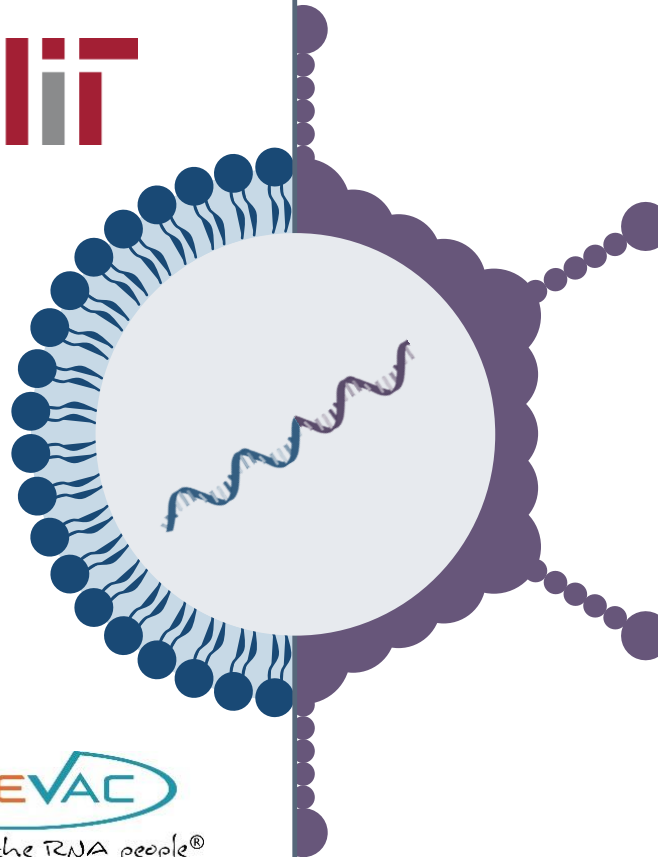
- › Controlled duration of expression
- › Tissue specificity
- › Increased potency



## VIRAL

### Adeno-Associated Virus (AAV)

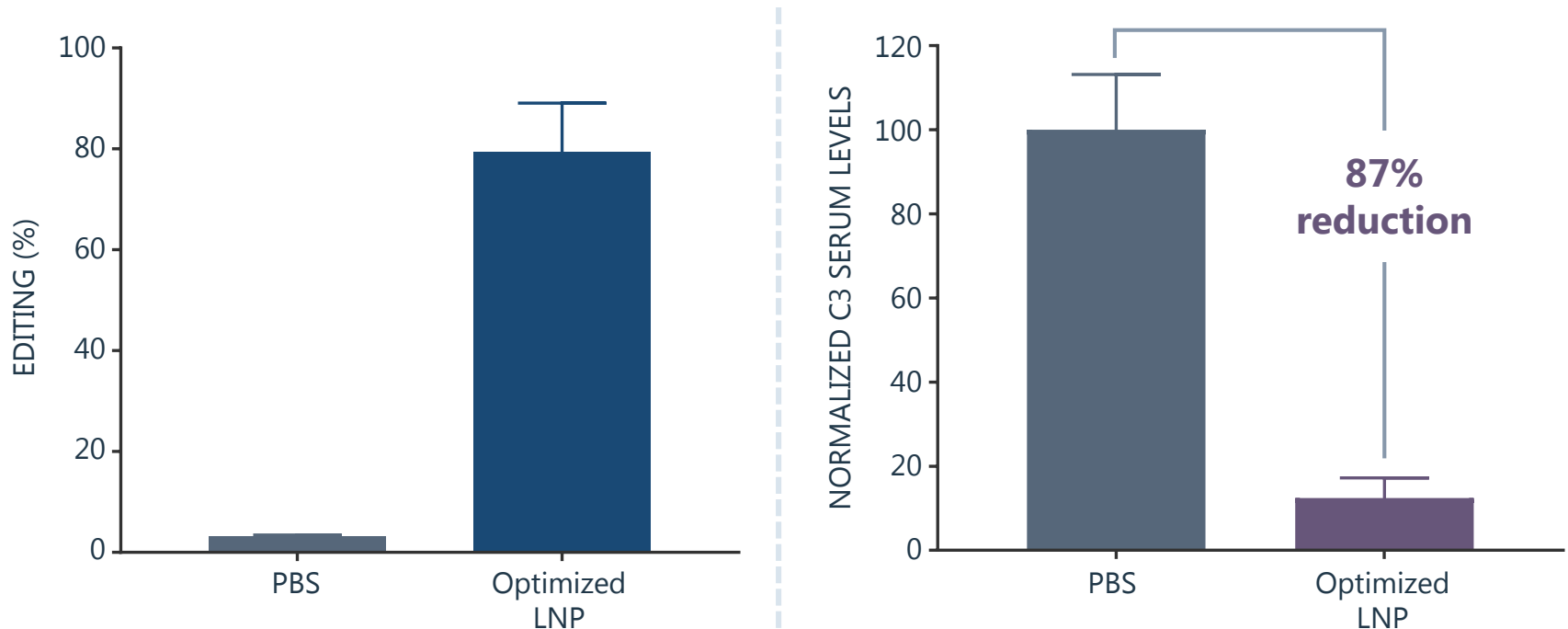
- › Improved tissue specificity
- › Reduced immunogenicity
- › Self-inactivation



# Potent Liver Editing Using Proprietary LNP Technology

## SIGNIFICANT DECREASE IN SERUM C3 LEVELS AFTER EDITING *IN VIVO*

*Editing and serum protein quantified in five mice following intravenous LNP dose*



**~80% editing in mouse livers and 87% reduction in serum C3 protein using  
just 1 mg/kg total RNA**

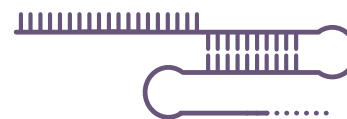
## NUCLEASE ENGINEERING

Enhance CRISPR/Cas9 system through protein engineering

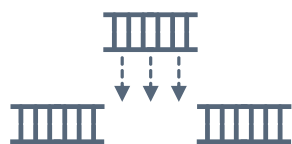


## GUIDE RNA OPTIMIZATION

Identify optimal guide RNA formats and sequences for therapeutic editing



## PLATFORM ENHANCEMENT



## ADVANCED EDITING

Improve efficiency of gene correction and multiplexing



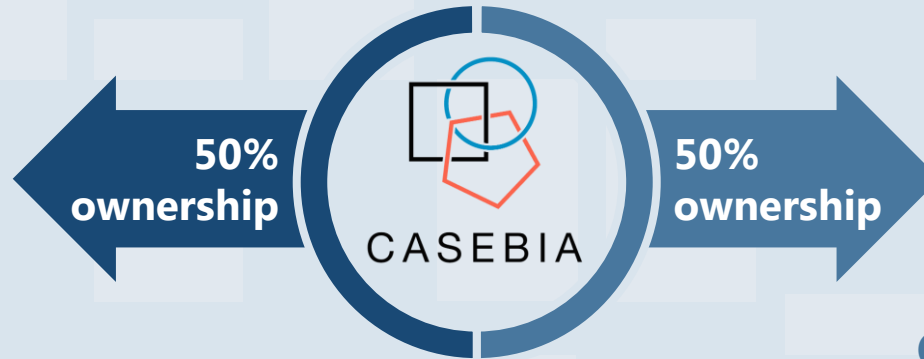
## STEM CELL ENGINEERING

Expand applications of gene-edited stem cells to treat disease

# Fifty-Percent Ownership of Casebia Therapeutics



**Committed IP**  
*for select indications*



**Committed \$370M**  
*\$265M to Casebia and  
\$105M to CRISPR*

## THERAPEUTIC FOCUS AREAS



Hematology



Cardiology



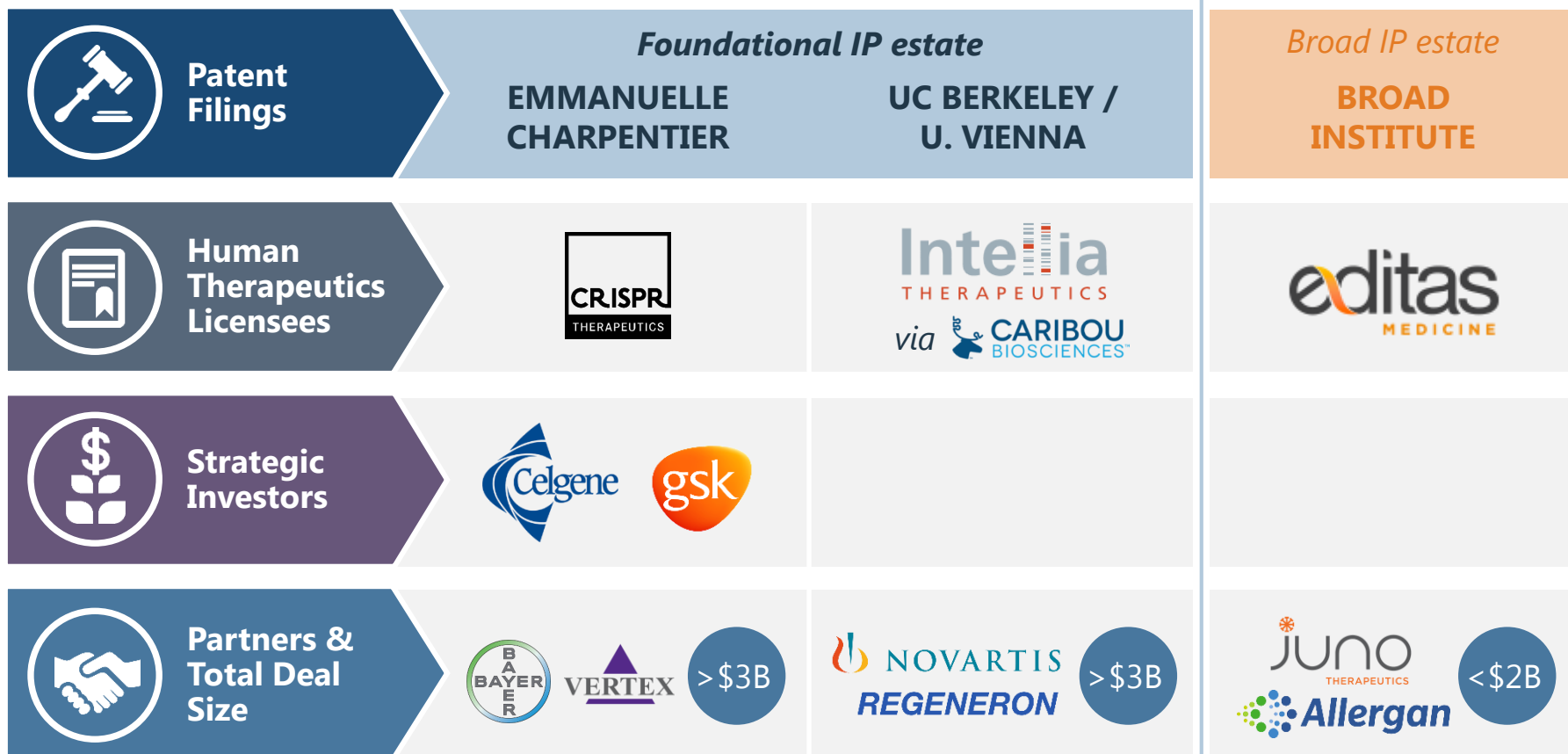
Ophthalmology

**Joint research on  
platform technology**  
– protein engineering,  
delivery, etc.



**CRISPR has full access  
at no cost to *all new* IP**  
for use within the field of  
human therapeutics

# Foundational Intellectual Property Landscape



- › Direct license to foundational IP covering all human therapeutic fields; term through 2033
- › Four large pharma partnerships indicate strength of the Charpentier / Berkeley foundational IP estate
- › Access to Vilnius IP estate through invention management agreement

## UNITED STATES

### UC-CRISPR appealing interference decision in Federal Appeals Court

- › Appeal ongoing to overturn Feb 2017 PTAB decision to end the first interference on technical grounds



#### Next steps

- › Appeal decision expected in 2018
- › Multiple patent applications moving forward in parallel – both narrow and broad claims

## EUROPE AND GLOBAL

### UC-CRISPR granted foundational patents, including use in eukaryotes

- › 3 patents granted between E.U. and U.K. include single-guide RNA & uses in all settings
- › Patents of broad scope granted in China, Australia, New Zealand, Singapore, Mexico



#### Next steps

- › Advancing applications globally in ~80 jurisdictions worldwide based on arguments developed in Europe

# Experienced Management Team

**SAM KULKARNI, PHD**

Chief Executive Officer

*Partner, McKinsey & Company*

**RODGER NOVAK, MD**

President & Chairman

*Head of Anti-Infectives R&D, Sanofi*

**TONY HO, MD**

Head of Research & Development

*Head of Oncology Innovation, AstraZeneca*

**JIM KASINGER, JD**

General Counsel & Corporate Secretary

*General Counsel, Moderna*

**LAWRENCE KLEIN, PHD**

Head of Business Development & Strategy

*Associate Partner, McKinsey & Company*

**MIKE TOMSICEK, MBA**

Chief Financial Officer

*Chief Financial Officer, Abiomed*

**SHELBY WALKER, JD**

Head of Intellectual Property

*Chief IP Counsel, Dyax*

McKinsey & Company

SANOFI 

AstraZeneca 

moderna™  

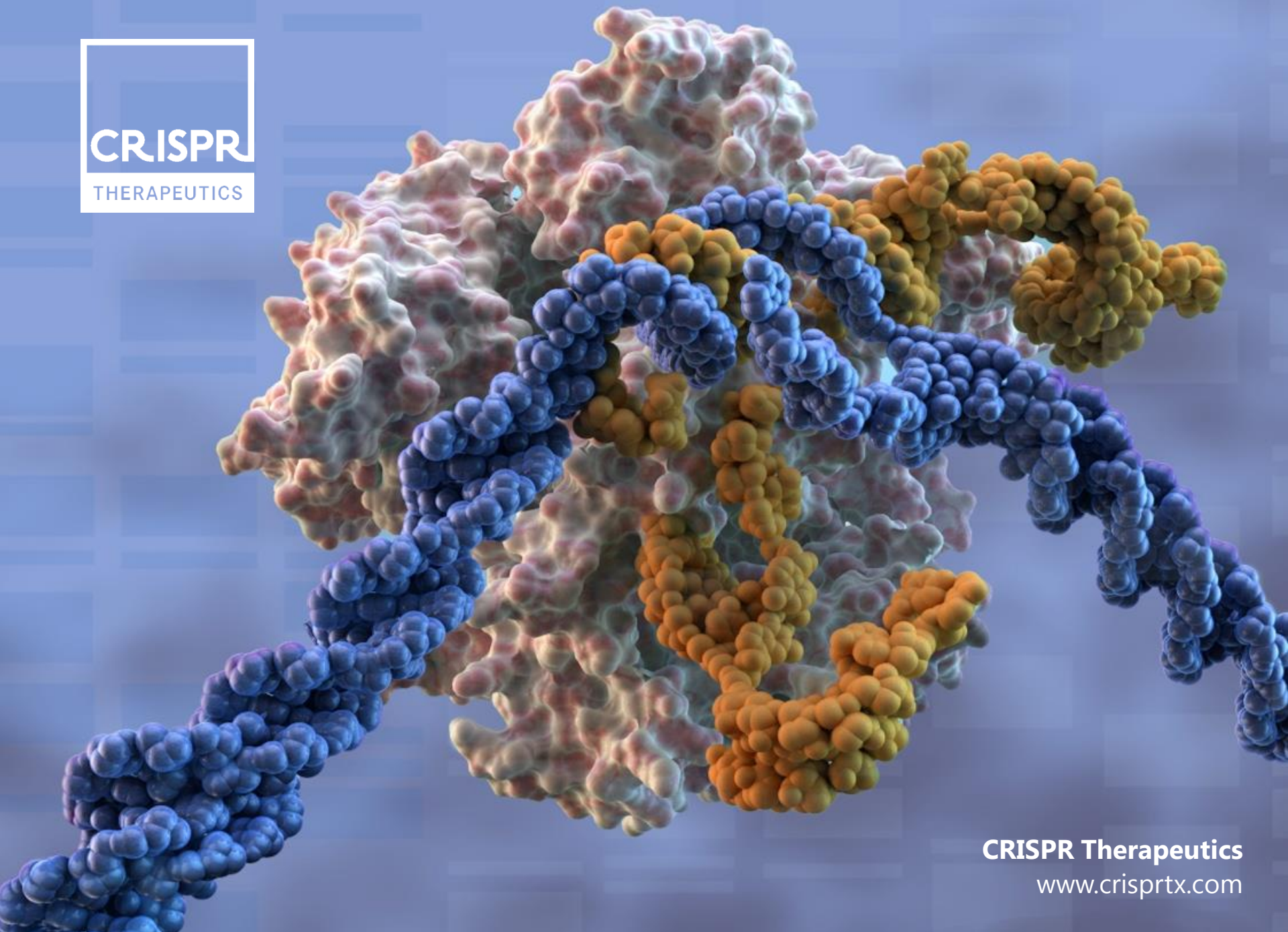

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