# CRISPR Therapeutics

*Creating transformative gene-based medicines for serious diseases*

Corporate Overview

May 2018

# Forward-Looking Statements

*This presentation and other related materials contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning: the timing of filing of clinical trial applications and INDs, any approvals thereof and timing of commencement of clinical trials, the timing, therapeutic value, development, and commercial potential of CRISPR/Cas9 gene editing technologies and therapies, the sufficiency of CRISPR's cash resources and the intellectual property coverage and positions of CRISPR, its licensors and third parties. All statements, other than statements of historical facts, included or incorporated by reference in this presentation and other related materials, including statements regarding CRISPR's strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, and objectives of management, are forward-looking statements. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "target," "should," "would," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. CRISPR may not actually achieve the plans, intentions, or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various factors, including: uncertainties regarding the intellectual property protection for CRISPR's technology and intellectual property belonging to third parties; uncertainties inherent in the initiation and completion of preclinical studies for CRISPR's product candidates; availability and timing of results from preclinical studies; whether results from a preclinical trial will be predictive of future results of the future trials; expectations for regulatory approvals to conduct trials or to market products; and those risks and uncertainties described under the heading "Risk Factors" in CRISPR's most recent annual report on Form 10-K, and in other filings that CRISPR has made or may make with the U.S. Securities and Exchange Commission.*

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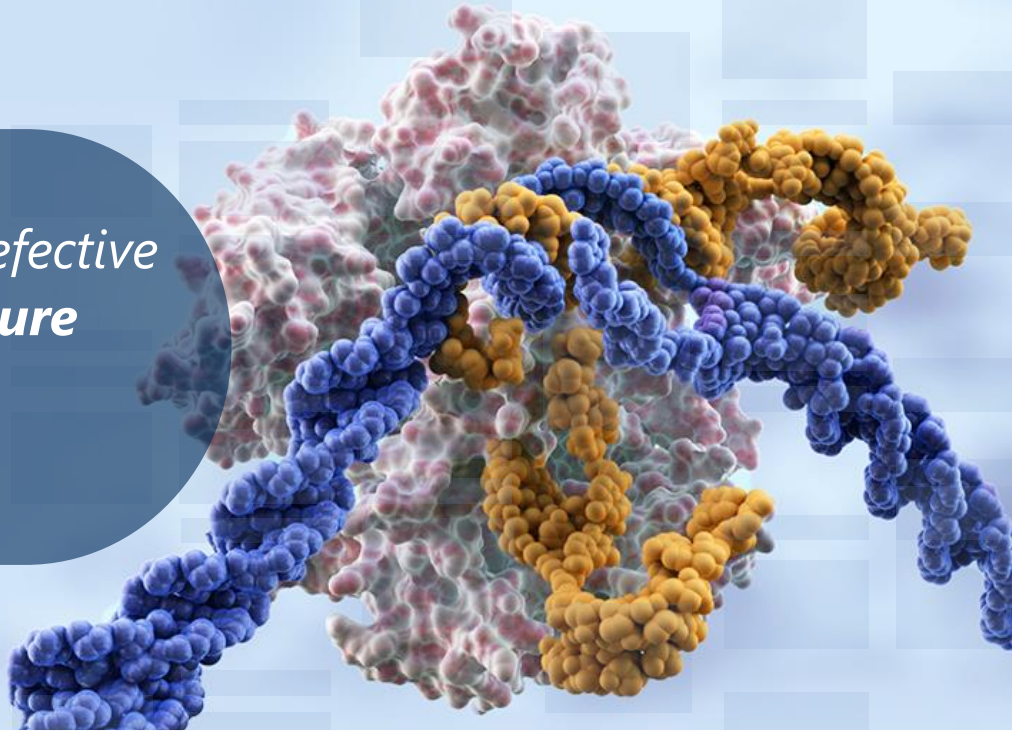
# The CRISPR/Cas9 Revolution

> *A new technology for 'editing' defective genes has raised hopes for a* ***future generation of medicines***

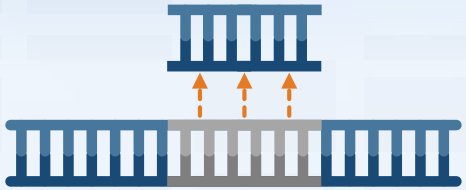
THE WALL STREET JOURNAL.



***Specific, efficient, and versatile platform***

**DISRUPTION**

**DELETION**



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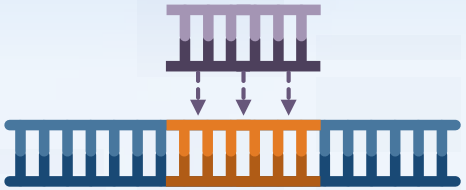


# CRISPR Therapeutics Highlights

| | |
|---|---|
| **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 |

# Our Portfolio

| Program | Editing approach | Research | IND-enabling | Ph I/II | Partner | Structure |
|---|---|---|---|---|---|---|
| ***Ex vivo:* Hematopoietic** | | | | | | |
| CTX001: β-thalassemia | Disruption | | | *First CTA Approved 1Q18* | VERTEX | Collaboration |
| CTX001: Sickle cell disease (SCD) | Disruption | | | *IND filing 1H18* | VERTEX | Collaboration |
| Hurler syndrome (MPS-1) | Correction | | | | | Wholly-owned |
| Severe combined immunodeficiency (SCID) | Correction | | | | CASEBIA | Joint venture |
| ***Ex vivo:* Immuno-oncology** | | | | | | |
| CTX101: CD19-positive malignancies | Various | | | *IND filing YE18* | | Wholly-owned |
| Anti-BCMA Allogeneic CAR-T | Various | | | | | Wholly-owned |
| Anti-CD70 Allogeneic CAR-T | Various | | | | | Wholly-owned |
| ***In vivo:* Liver** | | | | | | |
| Glycogen storage disease Ia (GSD Ia) | Correction | | | | | Wholly-owned |
| Hemophilia | Correction | | | | CASEBIA | Joint venture |
| ***In vivo:* Other organs** | | | | | | |
| Duchenne muscular dystrophy (DMD) | Disruption | | | | | Wholly-owned |
| Cystic fibrosis (CF) | Correction | | | | VERTEX | License option |

# Our Therapeutic Programs

**Hemoglobinopathies**
Ex vivo *lead candidate in genetically-defined disease*

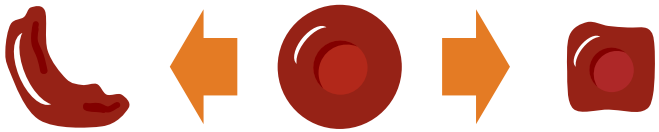
**Immuno-oncology**
*Expand cell therapy platform with allo CAR-T pipeline*

***In vivo***
*Enable* in vivo *applications through platform advancements*

# Hemoglobinopathies – Devastating Blood Diseases

## SICKLE CELL DISEASE (SCD) AND β-THALASSEMIA

**Blood disorders** caused by *mutations* in the β-globin gene



**Sickle Cell** | Normal Cell | **β-thalassemia**

### Significant worldwide burden

**300,000**

**60,000**

**Annual births** in SCD and β-thalassemia, respectively

### High morbidity and mortality

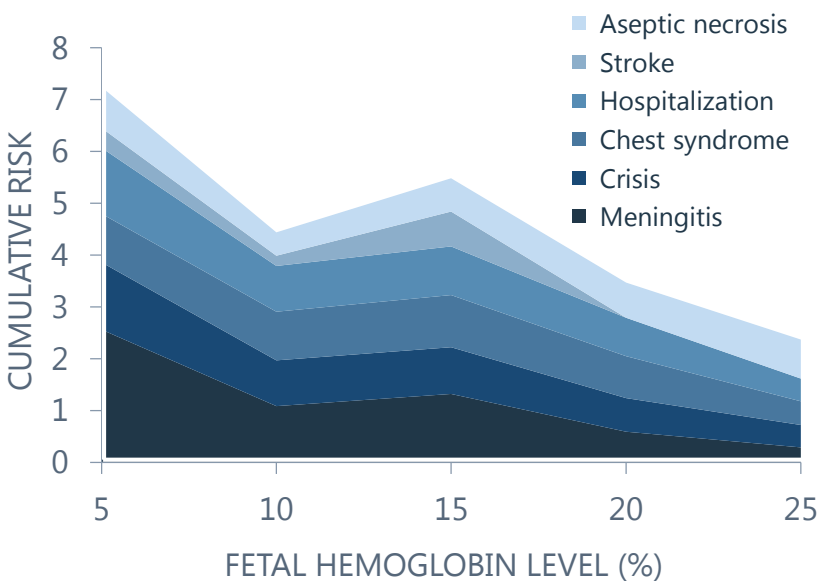
Anemia | Pain | **Early death**

### Heavy burden of patient care

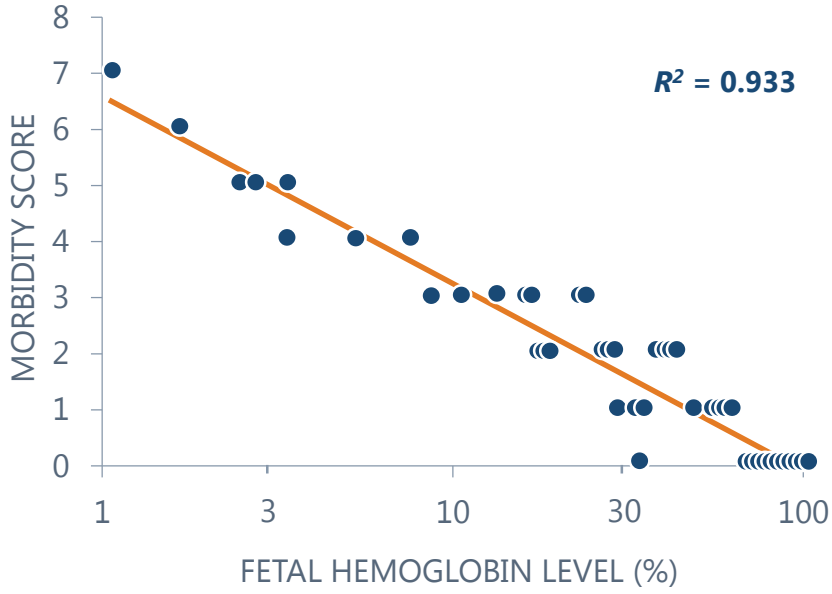
Frequent transfusions & hospitalizations

# Our Approach – Upregulating Fetal Hemoglobin

## REDUCED RISK OF EVENTS IN SICKLE CELL DISEASE[1]




## REDUCED SYMPTOMS IN β-THALASSEMIA[2]

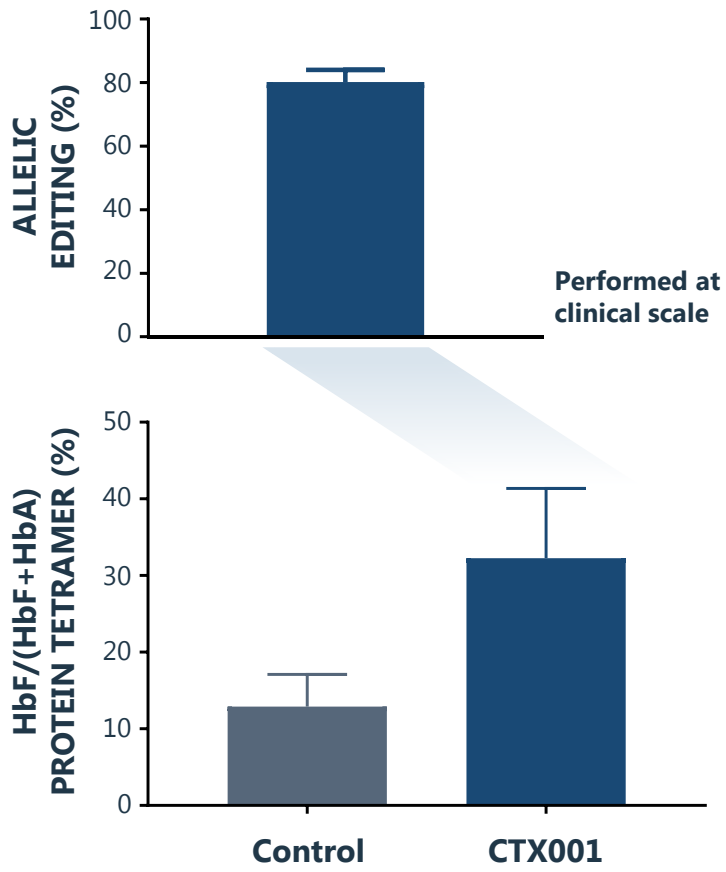



- **Naturally occurring genetic variants** cause **hereditary persistence of fetal hemoglobin** (HPFH), and **lead to reduced symptoms** in patients with sickle cell disease and β-thalassemia
- Our gene editing strategy aims to **recreate these variants** in symptomatic patients — an approach **supported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

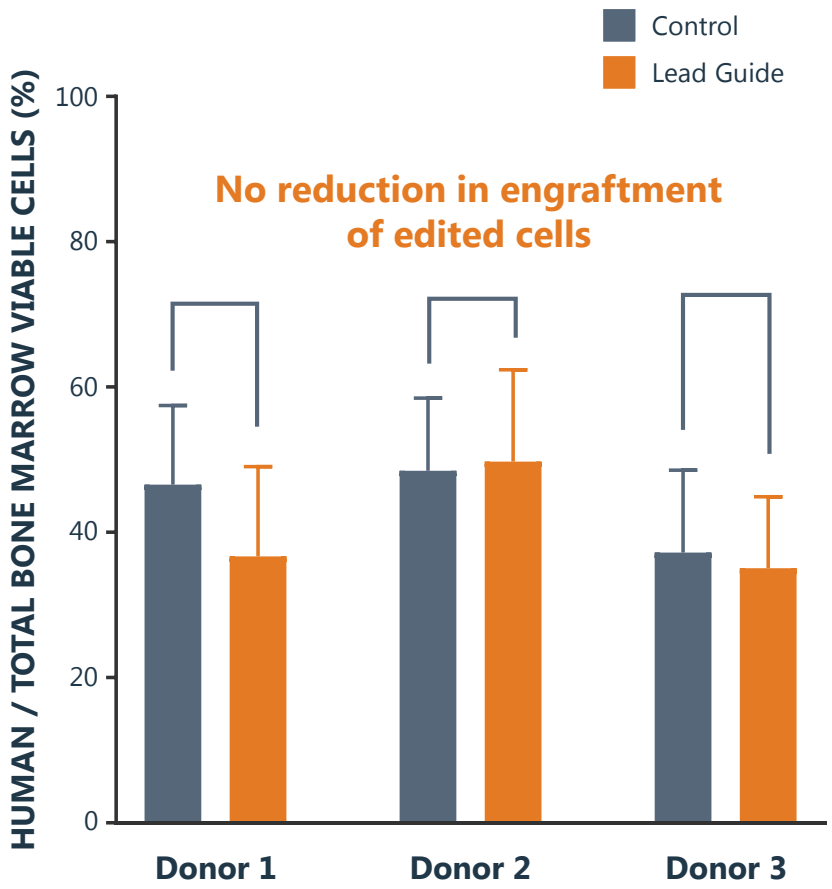
1. Powars, *et al.* Blood 1984; 2. Musallam, *et al.* Blood 2012

# CTX001 Upregulates Fetal Hemoglobin and Engrafts in Mice

## HIGH EDITING RATES LEAD TO ROBUST HbF INDUCTION[1]

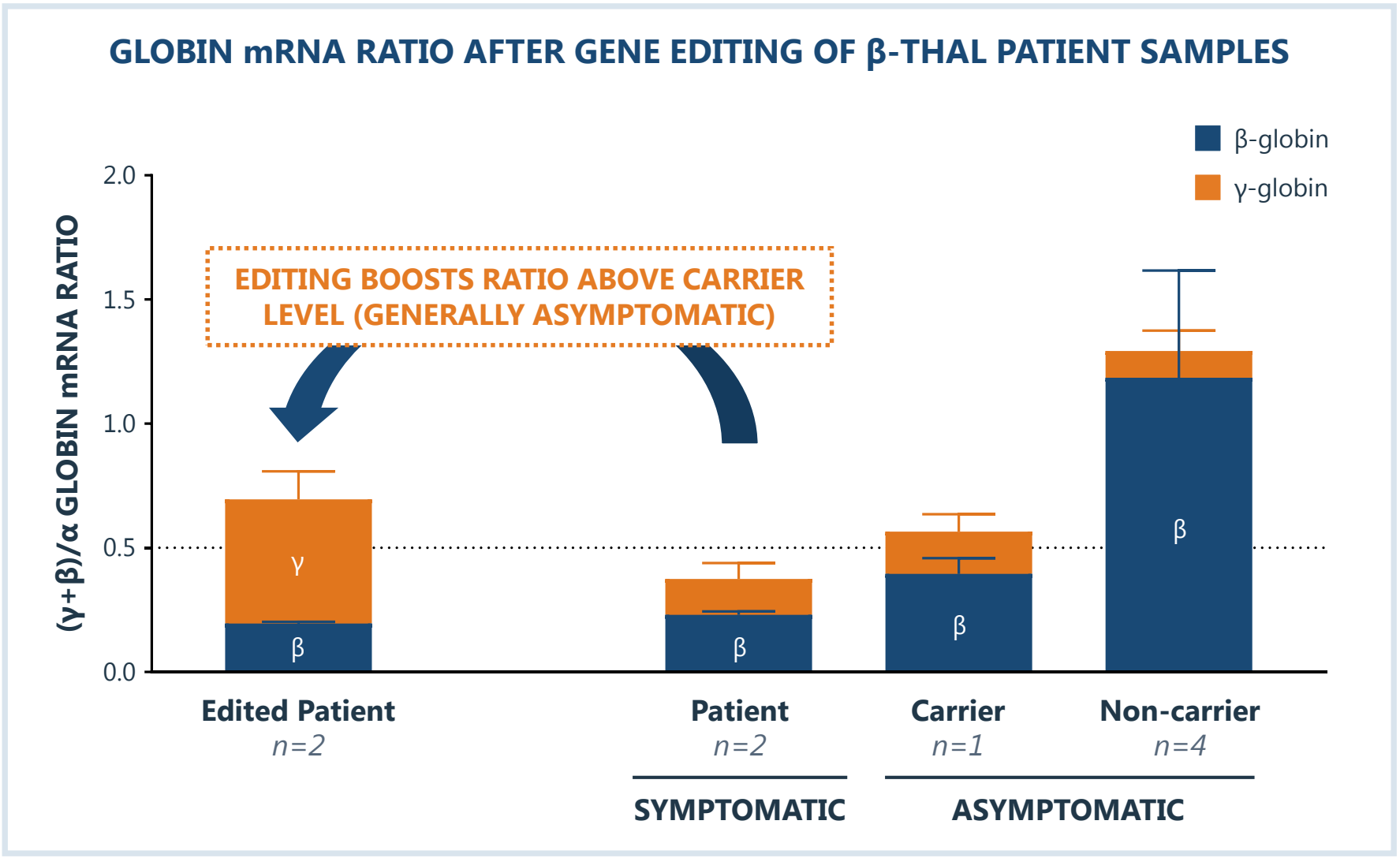



## CTX001 ENGRAFTS *IN VIVO* IN MICE[2]

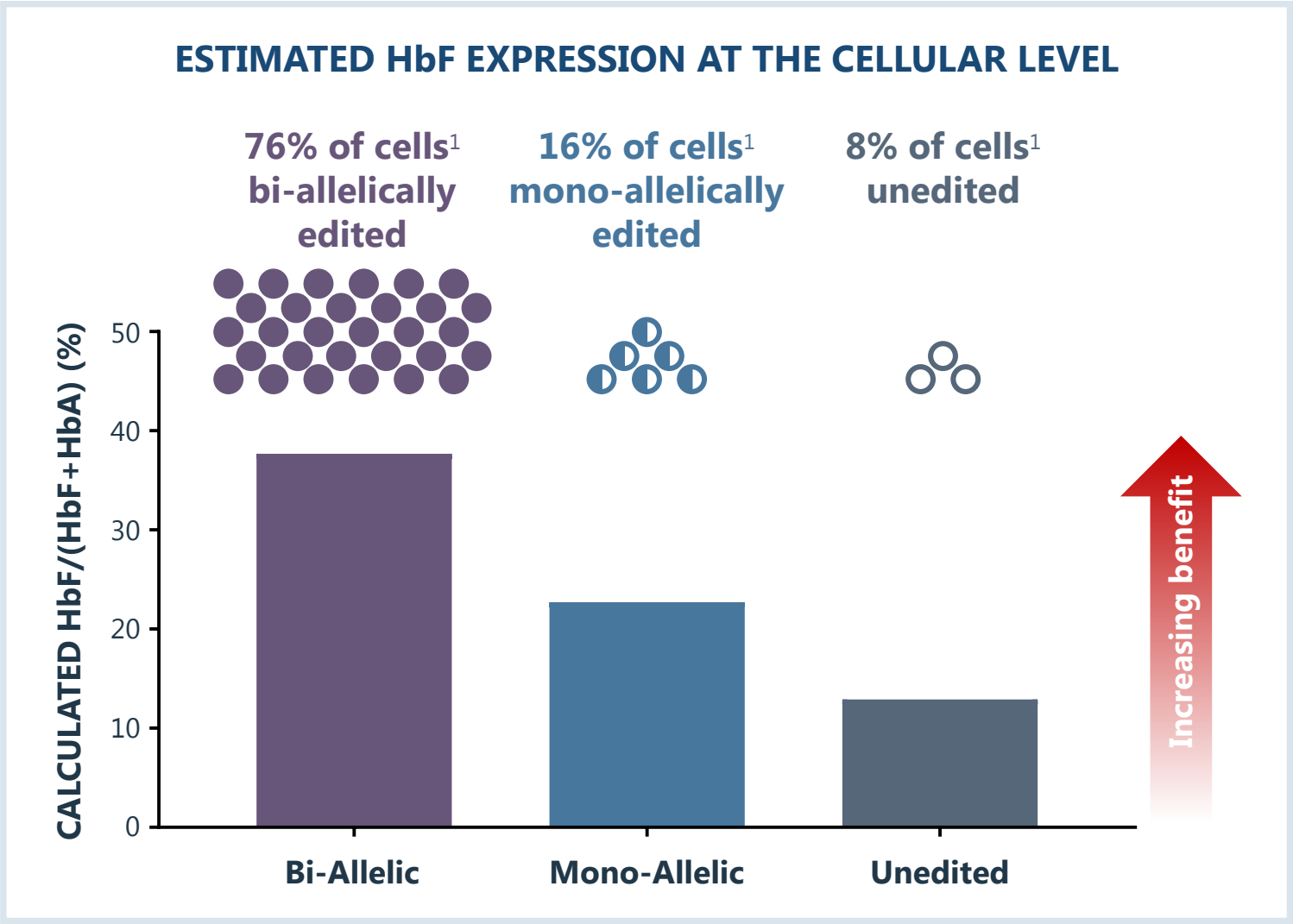



1. n=6 healthy donors; 2. 16-week engraftment data

# β-thal: Editing Increases Globin Expression to Carrier Levels



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




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

# Pioneering CRISPR Clinical Trial

**CTX001-111**

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

**Patients**

Up to 30 adult transfusion-dependent patients

**Sites**

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

**Endpoints**

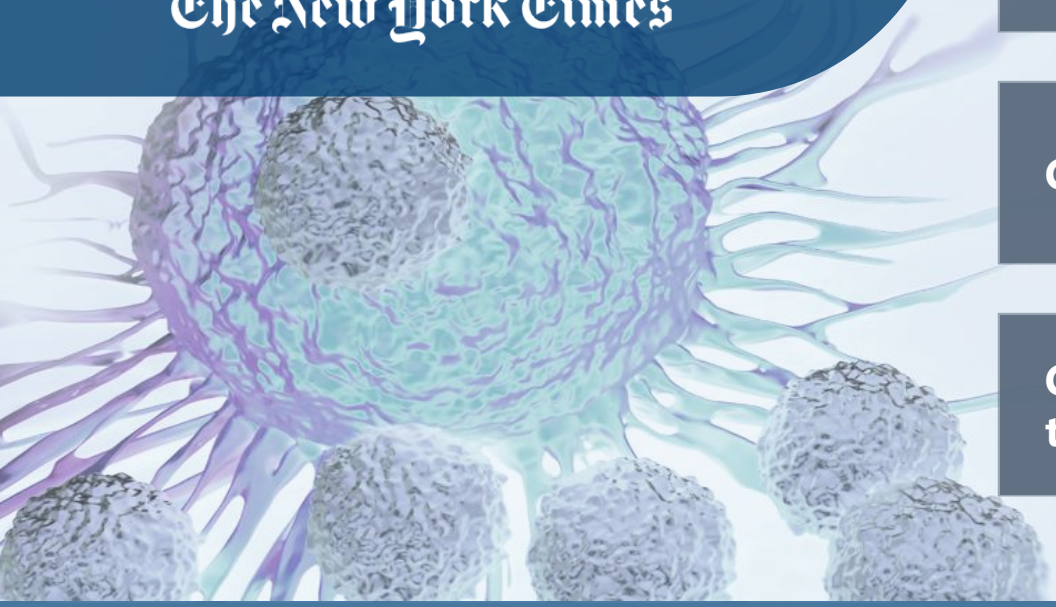
HbF levels and transfusion requirements are clinically relevant and easily measurable

**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

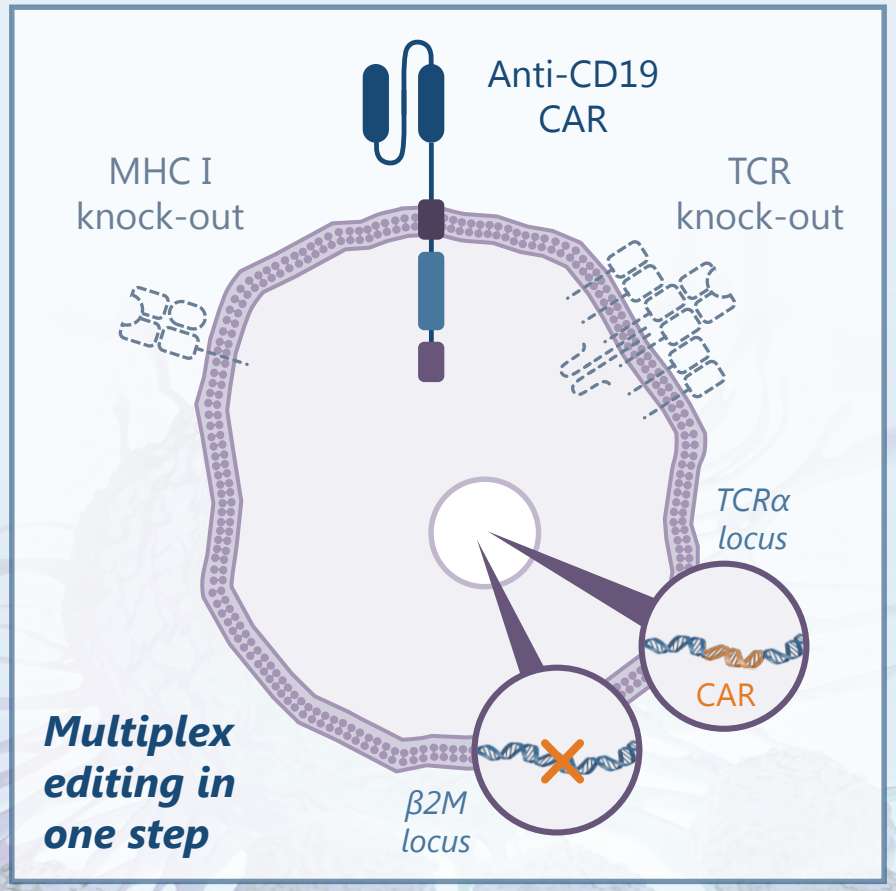


. . . But there are still **significant limitations** to autologous CAR-T

- **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

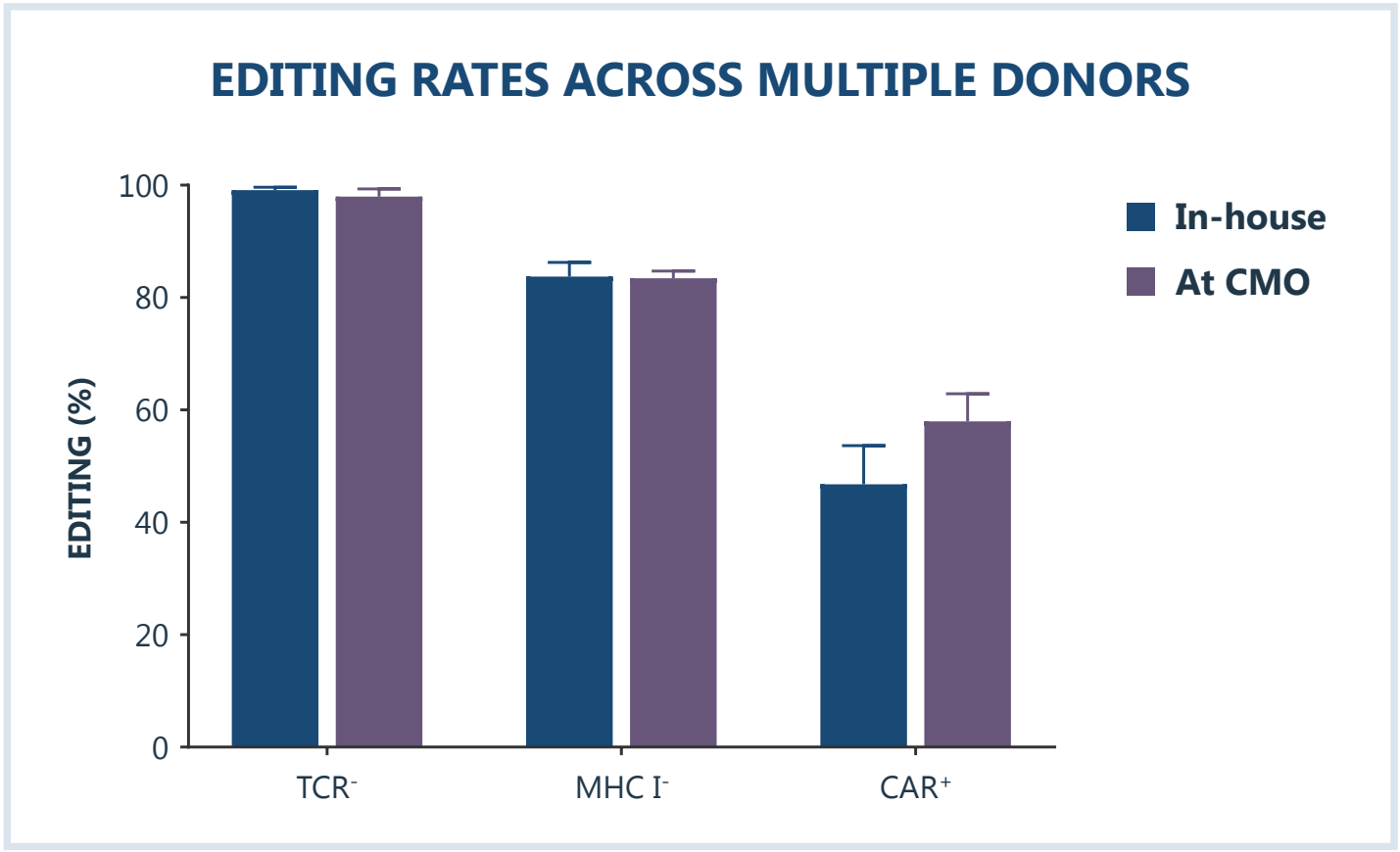
**CTX101** – our initial immuno-oncology product candidate




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**

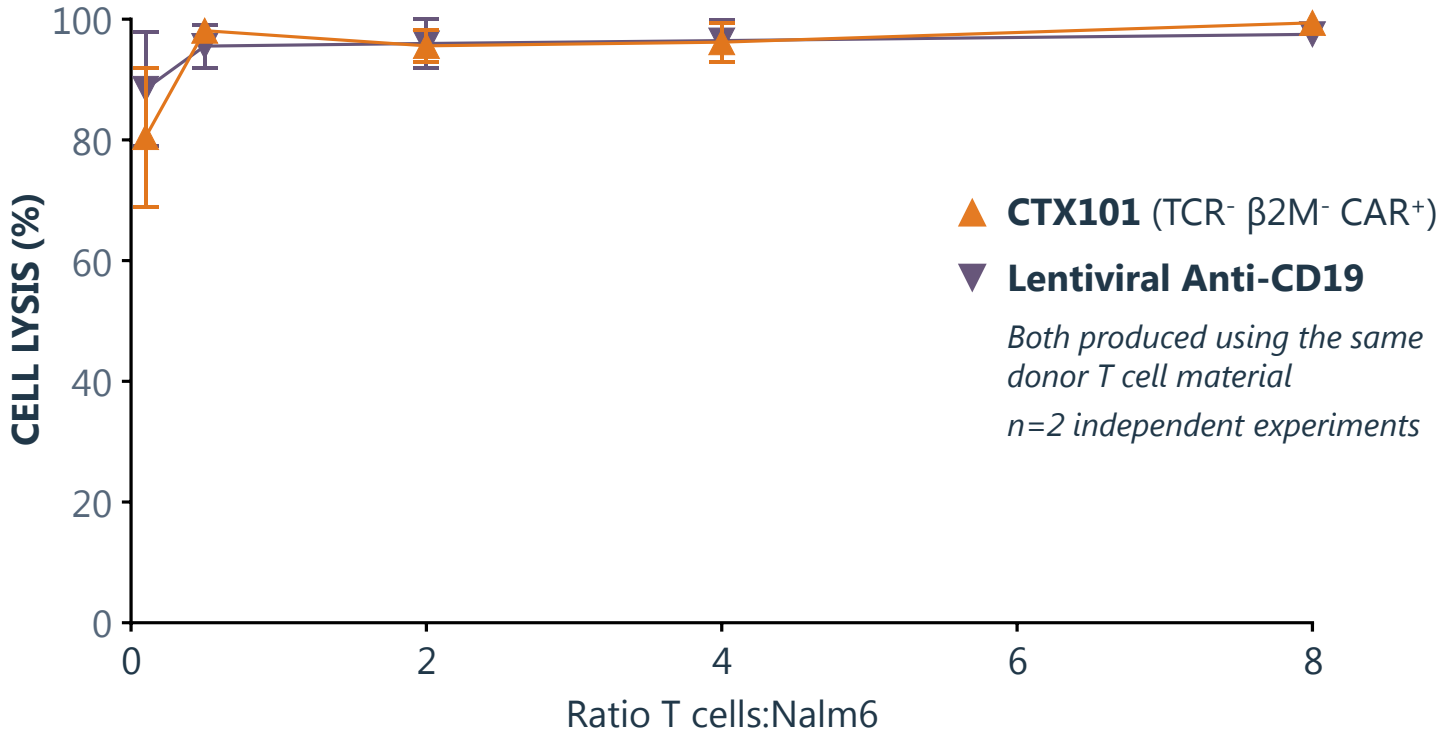
# Equal or Better Editing Rates Achieved After Tech Transfer




**Process development and manufacturing initiated for CTX101 – IND-enabling studies underway**

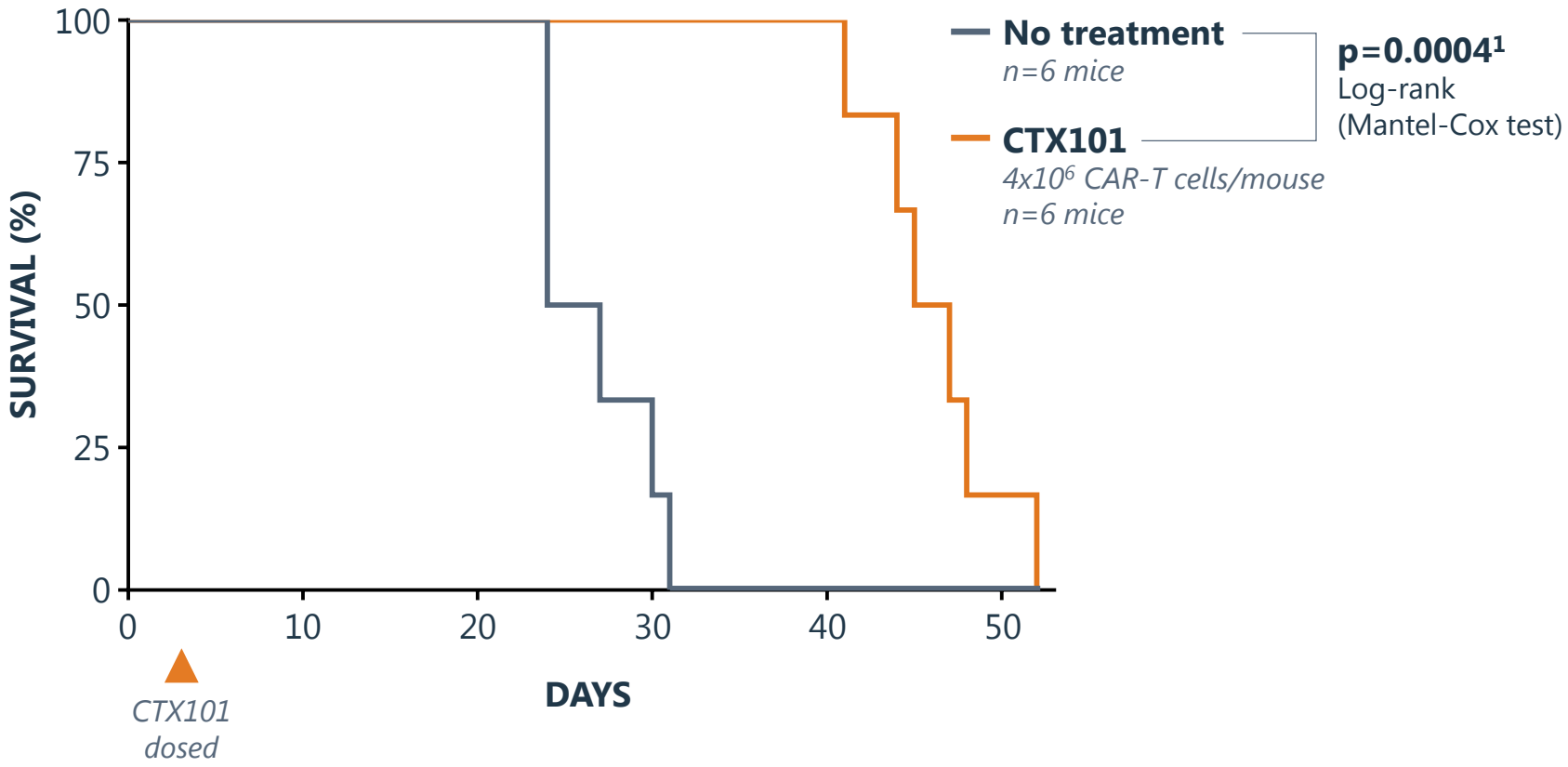
# CTX101 Eliminates CD19-Expressing Tumor Cells *In Vitro*

## CTX101 COMPARES FAVORABLY TO LENTIVIRAL "AUTOLOGOUS" CAR-T



# CTX101 Prolongs Survival in a CD19+ Tumor Model *In Vivo*

## PROLONGED SURVIVAL IN DISSEMINATED NALM6 B-ALL MODEL



# Numerous Opportunities Beyond CTX101

**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***

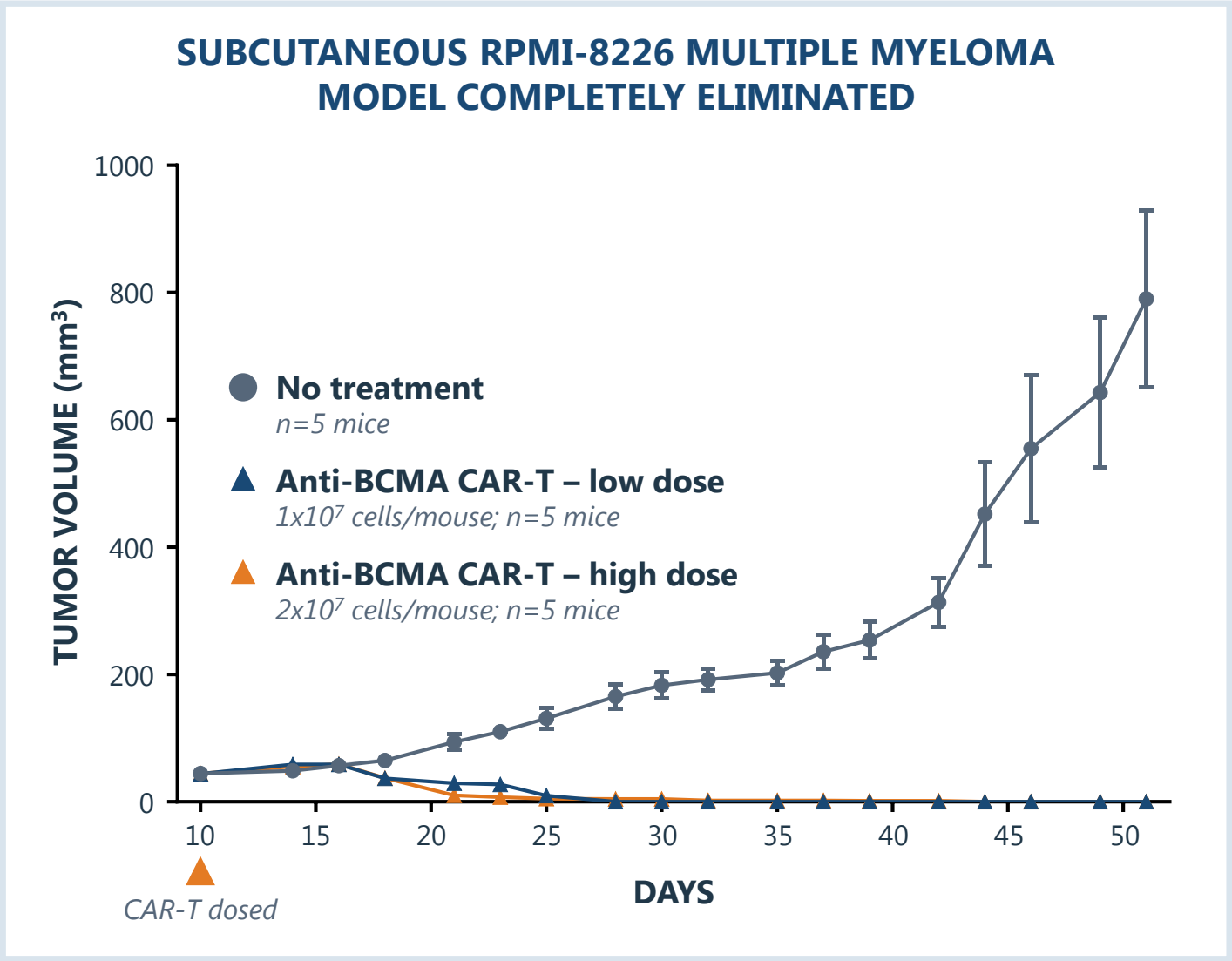
**Unlock the full potential of CRISPR**

Multiplex editing to enable more complex products

***Switches, neoantigens, bispecifics***

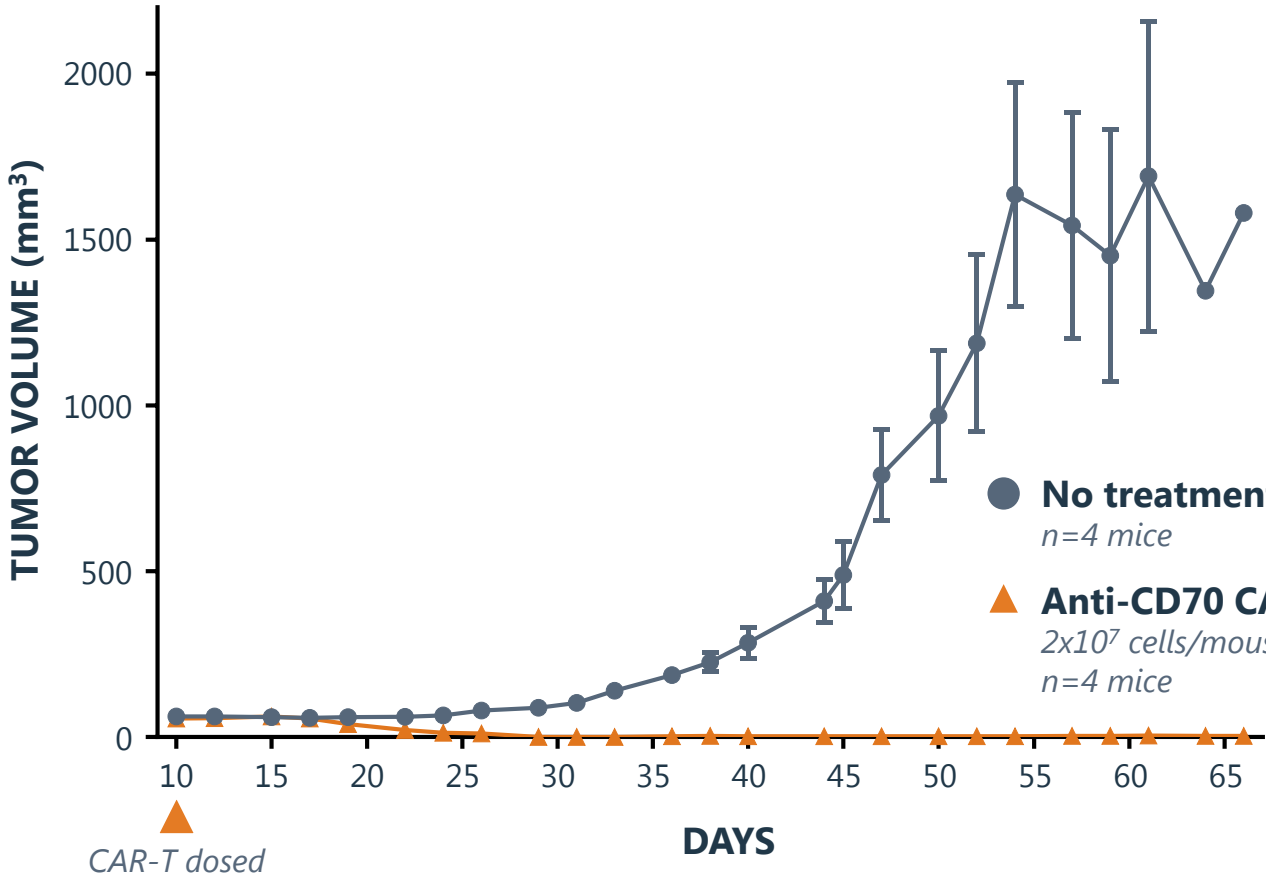
**Collaborations with Neon and MGH to identify and exploit new targets**

# Gene-Edited Allo CAR-T Targeting BCMA



# Gene-Edited Allo CAR-T Targeting CD70

## SUBCUTANEOUS A498 RENAL CELL CARCINOMA MODEL COMPLETELY ELIMINATED




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

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

CRISPR THERAPEUTICS

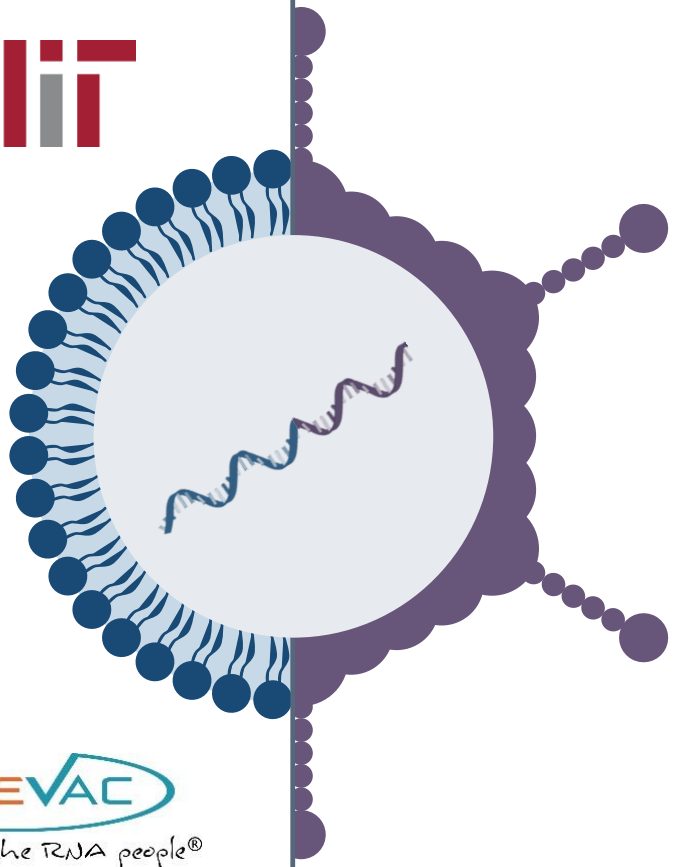
## NON-VIRAL

**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)

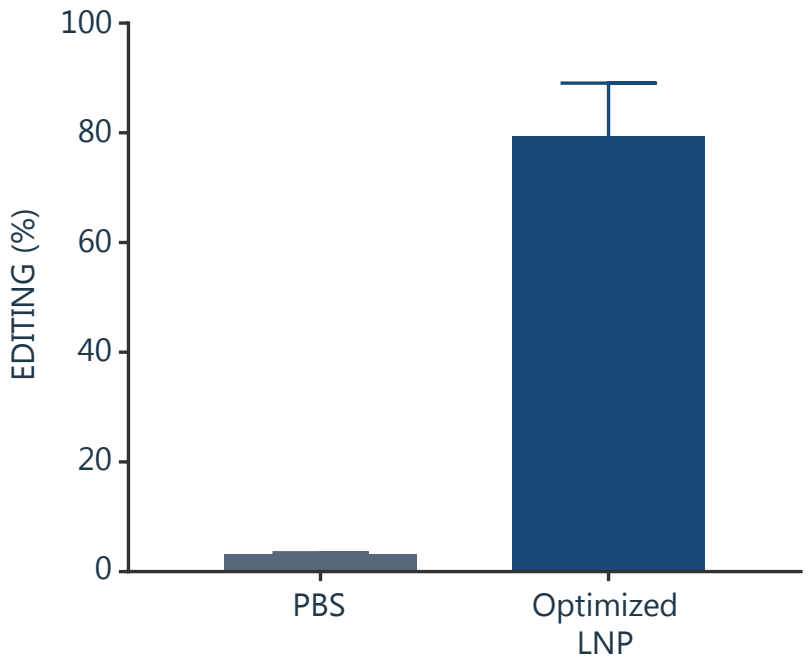
- Improved tissue specificity
- Reduced immunogenicity
- Self-inactivation

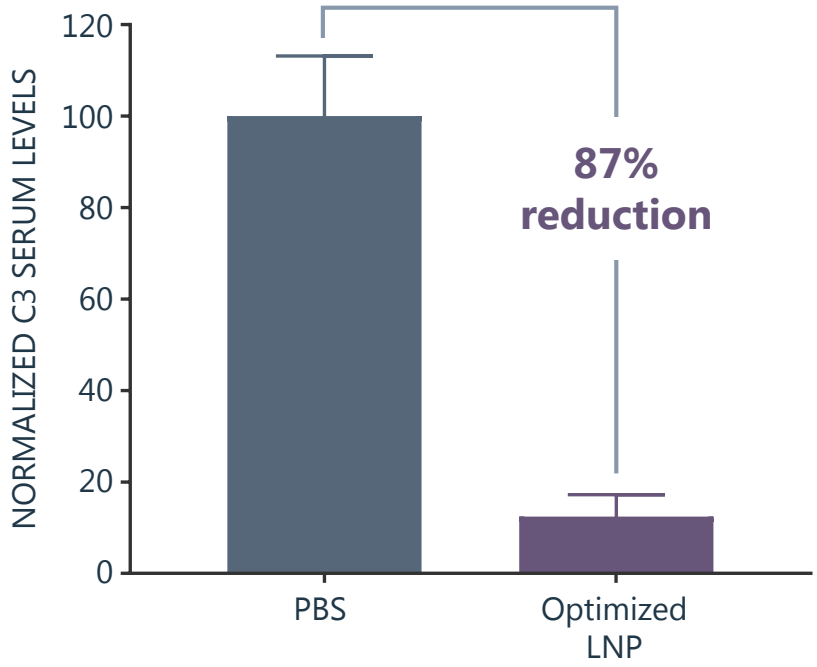
stridebio

# 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**

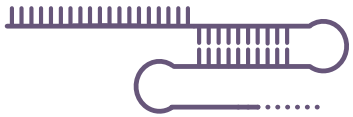
# Optimizing the CRISPR/Cas9 Platform

## NUCLEASE ENGINEERING

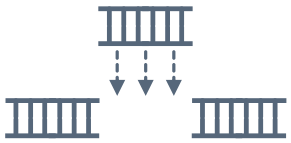
Enhance CRISPR/Cas9 system through protein engineering

## 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

| | Foundational IP estate | | Broad IP estate |
|---|---|---|---|
| **Patent Filings** | **EMMANUELLE CHARPENTIER** | **UC BERKELEY / U. VIENNA** | **BROAD INSTITUTE** |
| **Human Therapeutics Licensees** | CRISPR THERAPEUTICS | Intellia THERAPEUTICS via CARIBOU BIOSCIENCES | editas MEDICINE |
| **Strategic Investors** | Celgene, gsk | | |
| **Partners & Total Deal Size** | BAYER, VERTEX, >$3B | NOVARTIS, REGENERON, >$3B | JUNO THERAPEUTICS, Allergan, <$2B |

- 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

# Strong US and Global Foundational IP Position

## 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*

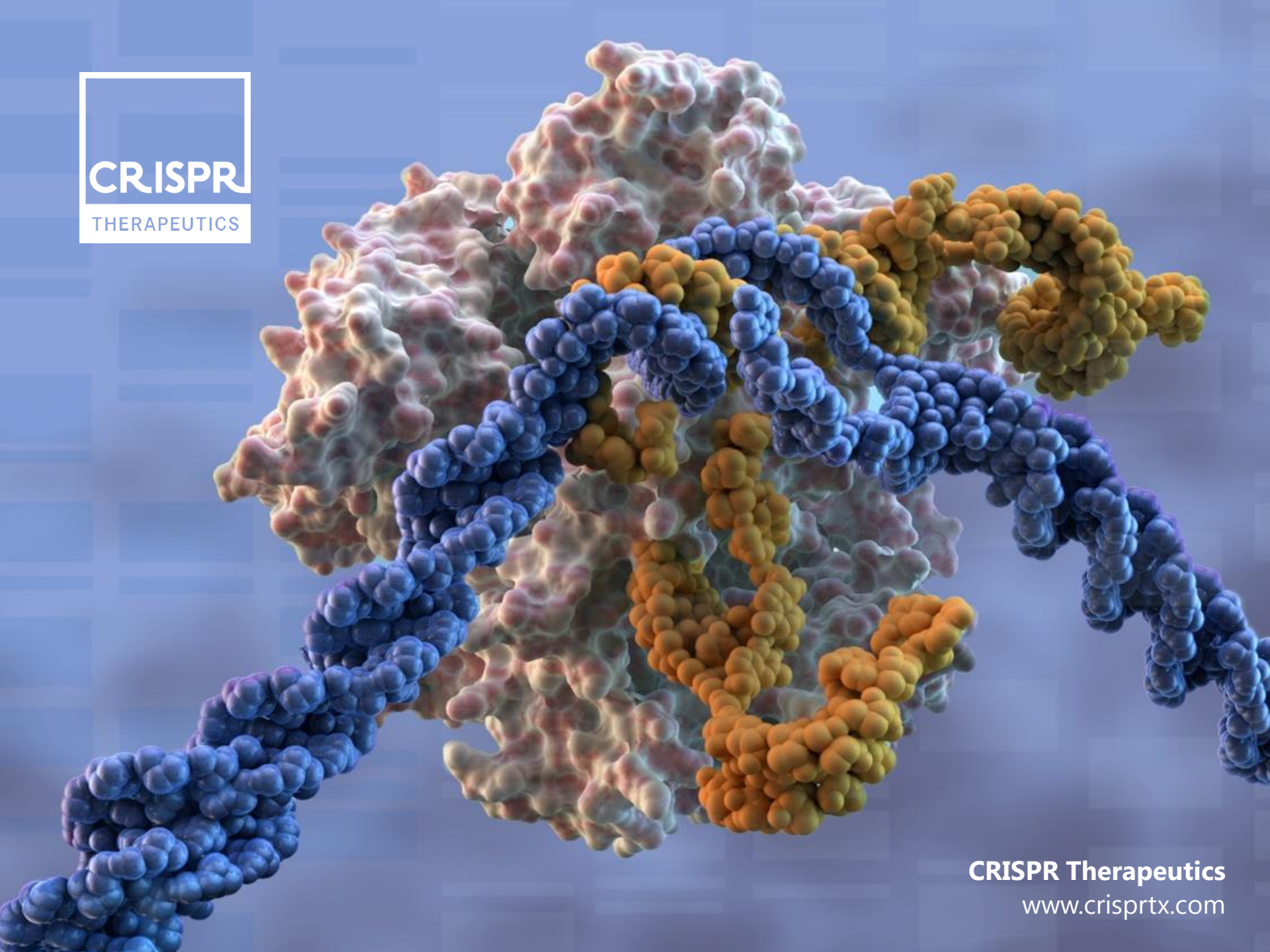
**TONY HO, MD**
Head of Research & Development
*Head of Oncology Innovation, AstraZeneca*

**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*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