



# Creating transformative gene-based medicines for serious diseases

Corporate Overview | September 2019

# Forward-Looking Statements



*The presentation and other related materials may contain a number of “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including statements regarding CRISPR Therapeutics’ expectations about any or all of the following: (i) the safety, efficacy and clinical progress of our various clinical programs including CTX001 and CTX110; (ii) the status of clinical trials (including, without limitation, the timing of filing of clinical trial applications and INDs, any approvals thereof and the timing of commencement of clinical trials), development timelines and discussions with regulatory authorities related to product candidates under development by CRISPR Therapeutics and its collaborators; (iii) the number of patients that will be evaluated, the anticipated date by which enrollment will be completed and the data that will be generated by ongoing and planned clinical trials, and the ability to use that data for the design and initiation of further clinical trials; (iv) the intellectual property coverage and positions of CRISPR Therapeutics, its licensors and third parties as well as the status and potential outcome of proceedings involving any such intellectual property; (v) the sufficiency of CRISPR Therapeutics’ cash resources; and (vi) the therapeutic value, development, and commercial potential of CRISPR/Cas9 gene editing technologies and therapies. Without limiting the foregoing, the words “believes,” “anticipates,” “plans,” “expects” and similar expressions are intended to identify forward-looking statements. You are cautioned that forward-looking statements are inherently uncertain. Although CRISPR Therapeutics believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those projected or suggested in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others: the potential for initial and preliminary data from any clinical trial (including CTX001 and CTX110) not to be indicative of final trial results; the risk that the initial data from a limited number of patients (as is the case with CTX001 at this time) may not be indicative of results from the full planned study population; the outcomes for each CRISPR Therapeutics’ planned clinical trials and studies may not be favorable; that one or more of CRISPR Therapeutics’ internal or external product candidate programs will not proceed as planned for technical, scientific or commercial reasons; that future competitive or other market factors may adversely affect the commercial potential for CRISPR Therapeutics’ product candidates; uncertainties inherent in the initiation and completion of preclinical studies for CRISPR Therapeutics’ 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; uncertainties about regulatory approvals to conduct trials or to market products; uncertainties regarding the intellectual property protection for CRISPR Therapeutics’ technology and intellectual property belonging to third parties, and the outcome of proceedings (such as an interference, an opposition or a similar proceeding) involving all or any portion of such intellectual property; and those risks and uncertainties described under the heading “Risk Factors” in CRISPR Therapeutics’ most recent annual report on Form 10-K, and in any other subsequent filings made by CRISPR Therapeutics with the U.S. Securities and Exchange Commission, which are available on the SEC’s website at [www.sec.gov](http://www.sec.gov). Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date they are made. CRISPR Therapeutics disclaims any obligation or undertaking to update or revise any forward-looking statements contained in this presentation, other than to the extent required by law.*

# CRISPR Therapeutics Highlights



Leading gene editing company focused on translating revolutionary CRISPR/Cas9 technology into transformative therapies



**Advancing CRISPR in the clinic** with CTX001® in  $\beta$ -thalassemia and sickle cell disease



**Next-generation immuno-oncology platform** underlying wholly-owned, potentially best-in-class gene-edited allogeneic cell therapies CTX110™, CTX120™ and CTX130™



**Enabling regenerative medicine 2.0** with CRISPR/Cas9-edited allogeneic stem cells



**Advancing *in vivo* applications** based on in-licensed technologies, platform improvement and strategic partnerships

# The CRISPR/Cas9 Revolution

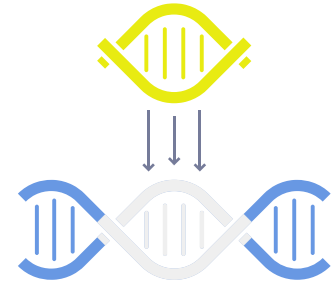
A **SPECIFIC**, **EFFICIENT** and **VERSATILE** tool for editing genes



**Disrupt**



**Delete**



**Correct or Insert**

*“If scientists can dream of a genetic manipulation,  
CRISPR can now make it happen”*

**Science**

# Our Therapeutic Programs

## GENETICALLY-DEFINED DISEASES

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### Hemoglobinopathies

Lead candidate based on *ex vivo* gene-edited hematopoietic stem cells



### *In vivo*

Pursuing *in vivo* applications via viral and non-viral approaches

## CELLULAR ENGINEERING

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### Immuno-oncology

Next-generation gene-edited allogeneic CAR-T pipeline



### Regenerative medicine

Next-generation CRISPR-enabled allogeneic stem cell-based therapies

# Our Pipeline



PROGRAM	RESEARCH	IND-ENABLING	CLINICAL	MARKETED	STATUS	PARTNER	STRUCTURE
Hemoglobinopathies							
CTX001®: β-thalassemia	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>		Enrolling	VERTEX	Collaboration
CTX001®: Sickle cell disease (SCD)	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>		Enrolling		Collaboration
Immuno-oncology							
CTX110™: Anti-CD19 allogeneic CAR-T	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>		Enrolling		Wholly-owned
CTX120™: Anti-BCMA allogeneic CAR-T	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>				Wholly-owned
CTX130™: Anti-CD70 allogeneic CAR-T	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>				Wholly-owned
Regenerative medicine							
Type I diabetes mellitus	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>			VIACYTE Regenerating Health	Collaboration
In vivo approaches							
Glycogen storage disease Ia (GSD Ia)	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>			VERTEX	Wholly-owned
Duchenne muscular dystrophy (DMD)	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>				License
Myotonic dystrophy type 1 (DM1)	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>				Collaboration
Cystic fibrosis (CF)	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div><div></div></div>				License

# Hemoglobinopathies – Devastating Blood Diseases

## Sickle Cell Disease (SCD) and $\beta$ -Thalassemia

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



Significant worldwide burden

ANNUAL BIRTHS

300K  
SCD



60K  
 $\beta$ -thalassemia

High morbidity and mortality



Anemia

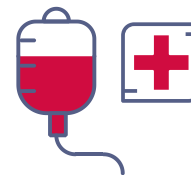


Pain



Early death

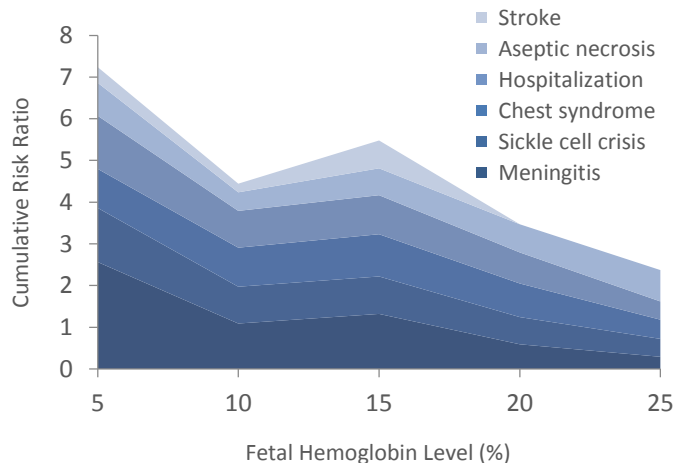
Heavy burden of patient care



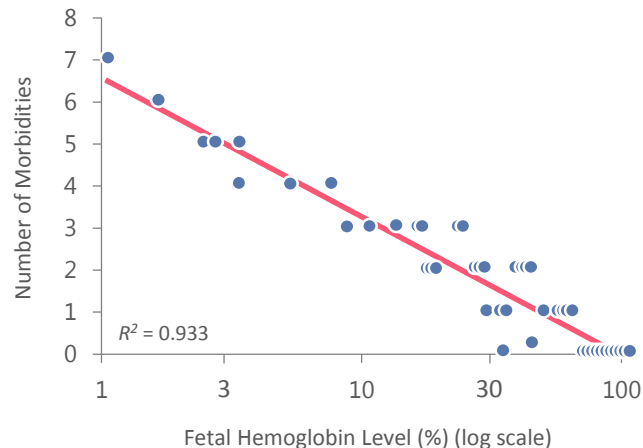
Frequent transfusions and hospitalizations

# Our Approach – Upregulating Fetal Hemoglobin

## Symptoms in SCD and $\beta$ -Thalassemia Decrease as HbF Level Increases



Powars, et al. Blood 1984



Musallam, et al. Blood 2012

- **Naturally occurring genetic variants** cause a condition known as **hereditary persistence of fetal hemoglobin (HPFH)**, which **leads to reduced or no symptoms** in patients with SCD and  $\beta$ -thalassemia
- **Our gene editing strategy aims to mimic these variants in symptomatic patients**, an approach supported by well-understood genetics



# Pioneering CRISPR Clinical Trials



Single-arm Phase 1/2 trials to assess the safety and efficacy of CTX001 in patients with  $\beta$ -thalassemia and SCD



## Patients

Up to 45 adult patients each for transfusion-dependent  $\beta$ -thalassemia and severe SCD



## Sites

Sites with extensive transplant experience in countries with significant disease burden



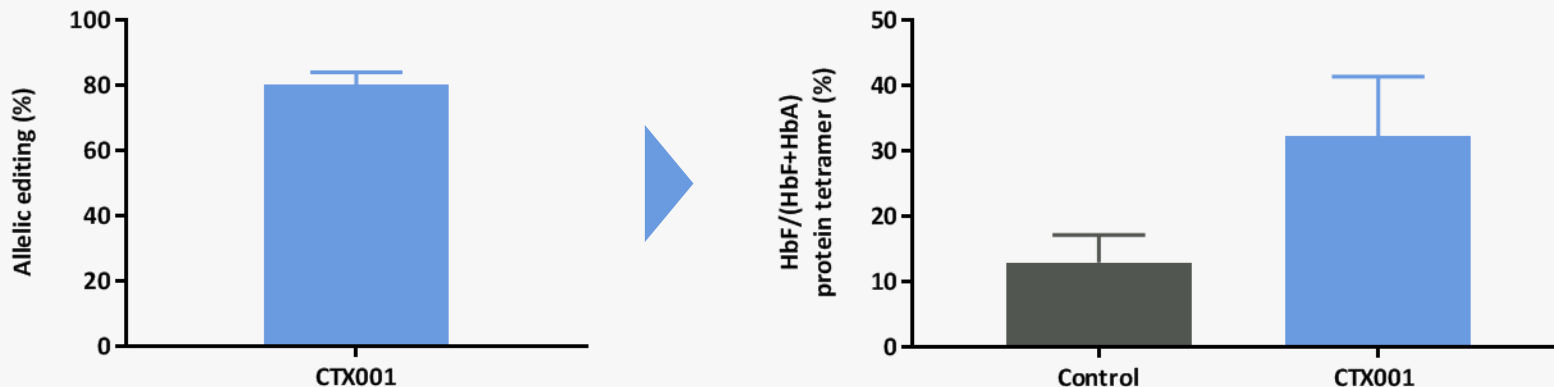
## Endpoints

HbF as a clear biomarker, and clinical correlates: transfusion burden for  $\beta$ -thal and VOCs for SCD

**Potential to expand into registrational trials**, as well as into additional age cohorts and  $\beta$ -thalassemia genotypes, if supported by safety and efficacy

# CTX001 Upregulates Fetal Hemoglobin

## High Editing Rates Lead to Robust HbF Induction

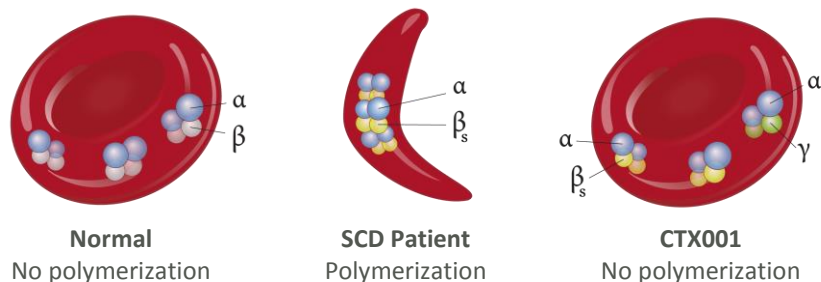


Performed at clinical scale with n=6 healthy donors

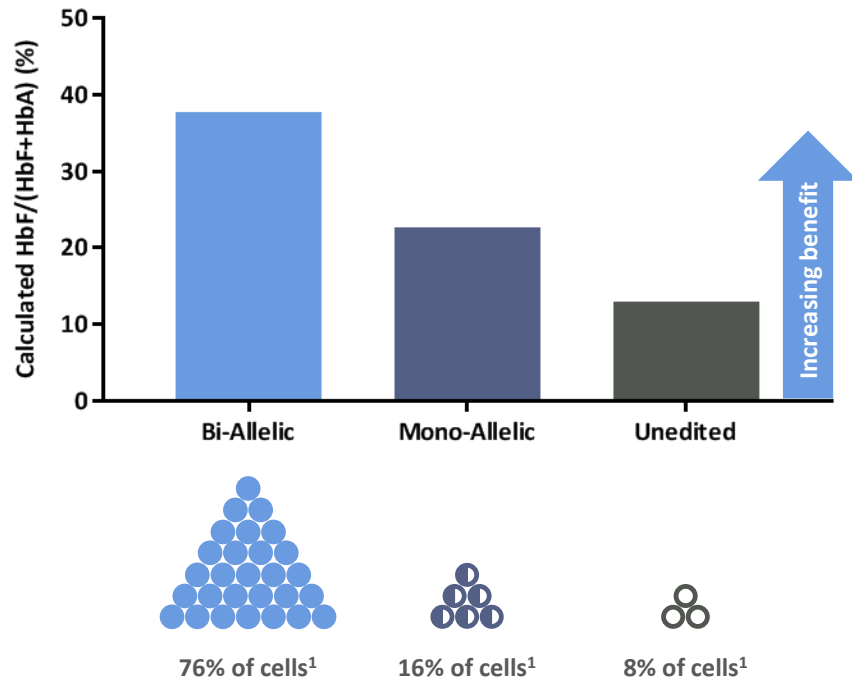
**CTX001 shows 80%** allelic editing, **>90%** of cells modified, **>30%** HbF and **no reduction in engraftment** of edited cells in mice *in vivo*

# CTX001 Aims to Treat Underlying SCD Pathophysiology

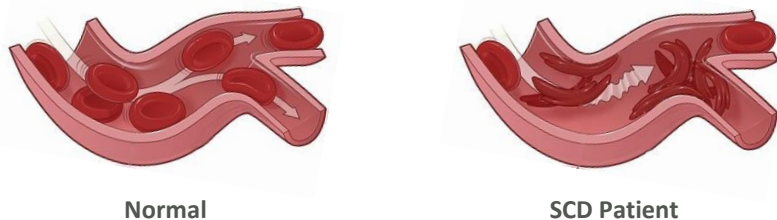
## Enough HbF to Prevent Polymerization



## Estimated HbF Expression at the Cellular Level

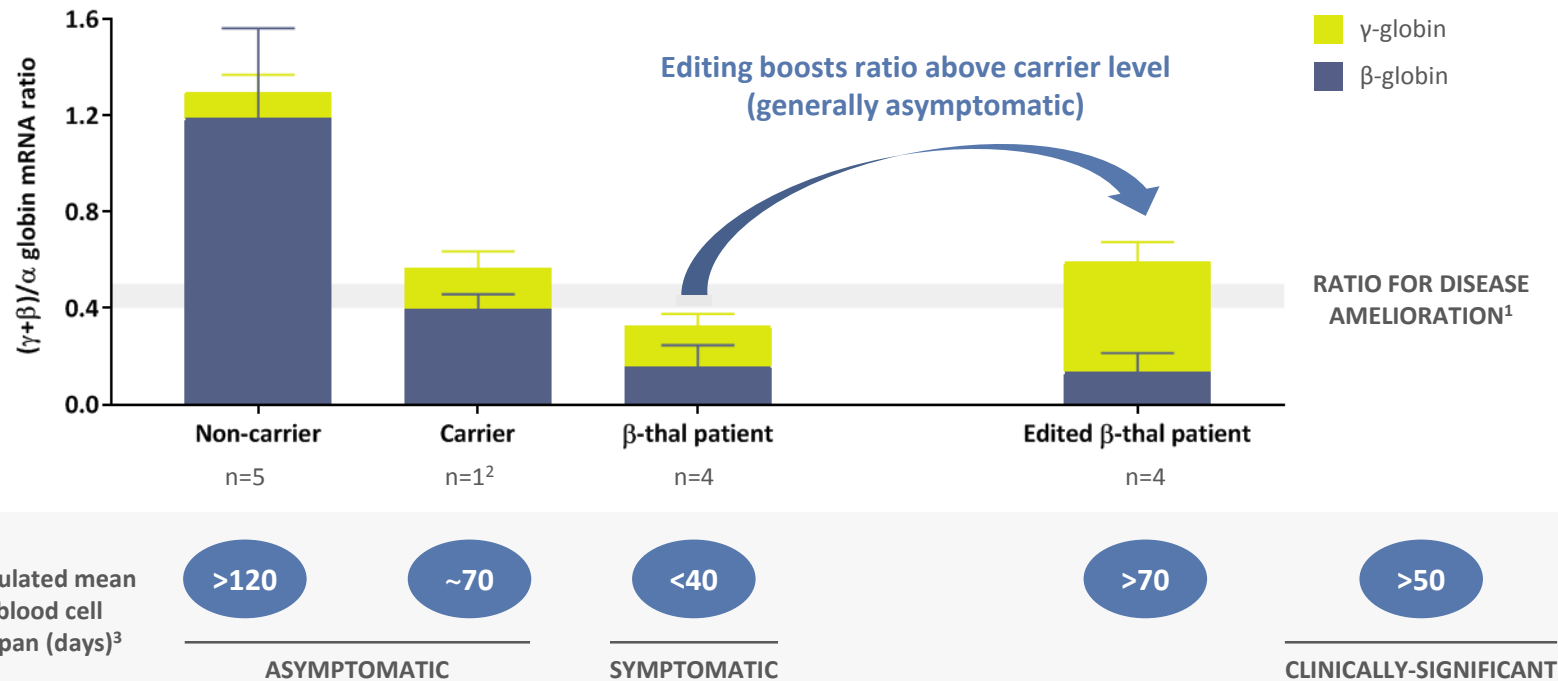


## Enough Normal Cells in Circulation to Prevent Occlusion



# CTX001 Increases HbF in $\beta$ -Thalassemia Patient Samples

## Editing Results in Increased Globin mRNA Ratio, which Correlates with Increased RBC Lifespan



1. Marinucci, *et al.* Hemoglobin 1981 and Giampaolo, *et al.* Hum Genet. 1984 2. Technical replicates 3. Calculated from Vigi, *et al.* Br J Haematol. 1969

# CRISPR Enables the Next Generation of I/O Cell Therapy



## ALLOGENEIC CAR-T

- Off-the-shelf
- More potent starting material
- More consistent product
- Broader access
- Flexible dosing (e.g., re-dosing)

## SOLID TUMOR EFFICACY

- Avoid exhaustion
- Modulate suppressive TMEs
- Target tumors with greater selectivity
- Sense and respond via genetic circuits
- Recruit endogenous immunity

# Allogeneic CAR-T Therapy Has Transformative Potential

## Before Patient Diagnosis

## After Patient Diagnosis

### Autologous: patient derived

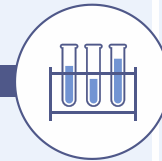


WEEK 1



Apheresis

WEEK 2



Manufacture

WEEK 3



Single  
Treatment

DAY 1: DIAGNOSIS

### Allogeneic: healthy-donor derived

HEALTHY DONOR



T Cells



Manufacture



100+ Doses



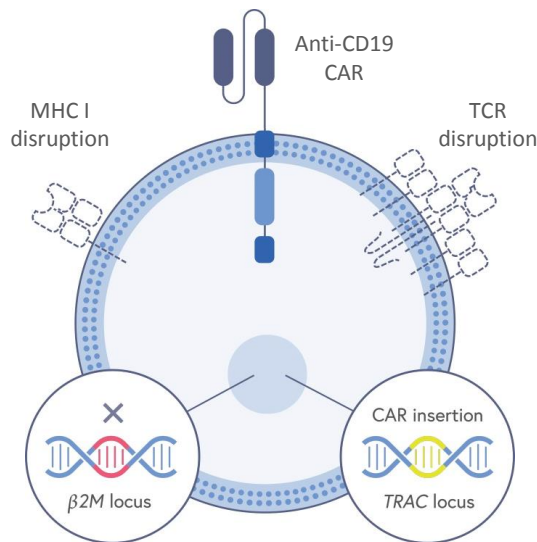
Treatment

Allogeneic CAR-T allows for immediate treatment without risk of manufacturing failure, saving patients valuable time in which their disease could progress

# CRISPR-Edited Allogeneic T Cell Design

## Initial Allogeneic CAR-T Candidate – CTX110

- **Improve persistence in the allo setting** with  $\beta 2M$  knock-out to eliminate MHC I expression

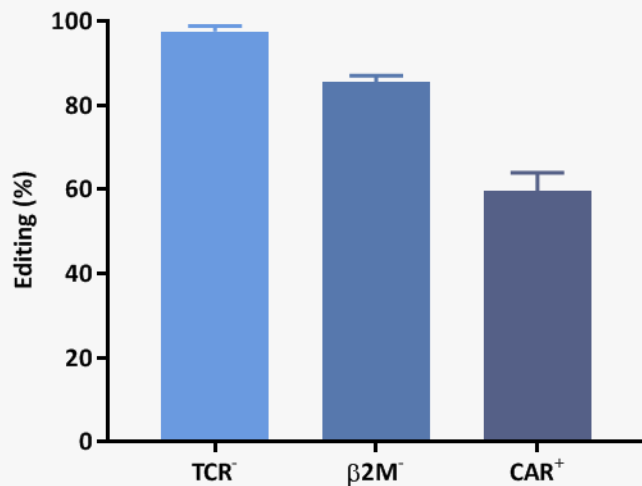


- **Prevent GvHD** via TCR disruption
- **Improve safety and potency by precise insertion** of CAR construct into TRAC locus

Multiplex editing in one step

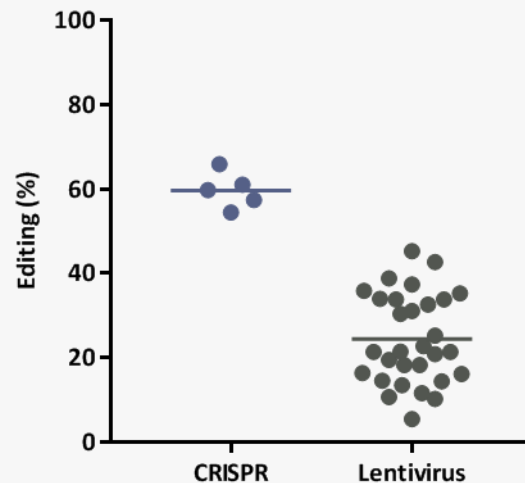
# CRISPR Editing Allows for a More Consistent Product

## Precise and Efficient Editing to Produce CTX110



**Consistently high** editing across **5 different donors**  
**>50% of cells have all three desired edits**

## Greater Consistency than Viral Approaches



**54-66%** CAR<sup>+</sup> range with CRISPR  
vs. **6-45%** for lentiviral CAR-T<sup>1</sup>

1. Maude, *et al.* NEJM 2014



# Trial of CTX110 in B-Cell Malignancies

**CRSP-ONC-001: Single-arm Phase 1/2 dose escalation and expansion study to assess the safety and efficacy of CTX110 in subjects with relapsed or refractory B-cell malignancies**



## Patients and Sites

Starting with adult patients with relapsed or refractory non-Hodgkin lymphoma; conducted at sites with CAR-T or cell therapy experience



## Lymphodepletion and Dosing

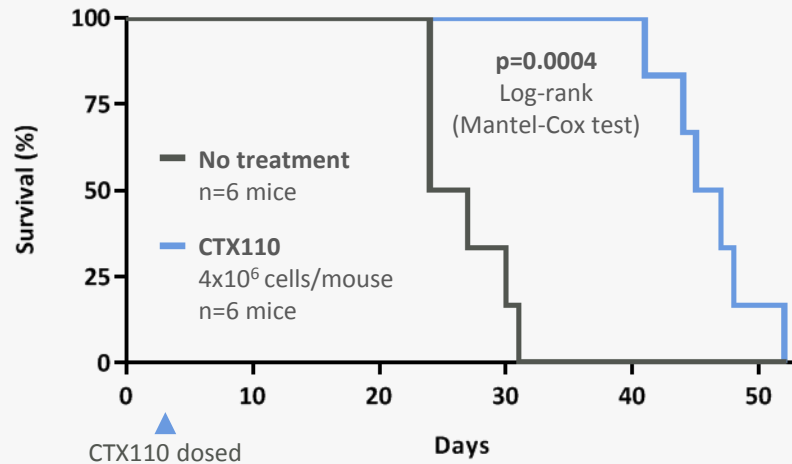
Lymphodepleting chemotherapy regimen administered before CTX110 infusion; dose escalation followed by dose expansion cohort

**Potential to expand into registrational trials, additional CD19-positive malignancies and multiple dosing if supported by safety and efficacy**

# CTX110/CTX120 – Novel Approach Against Validated Targets

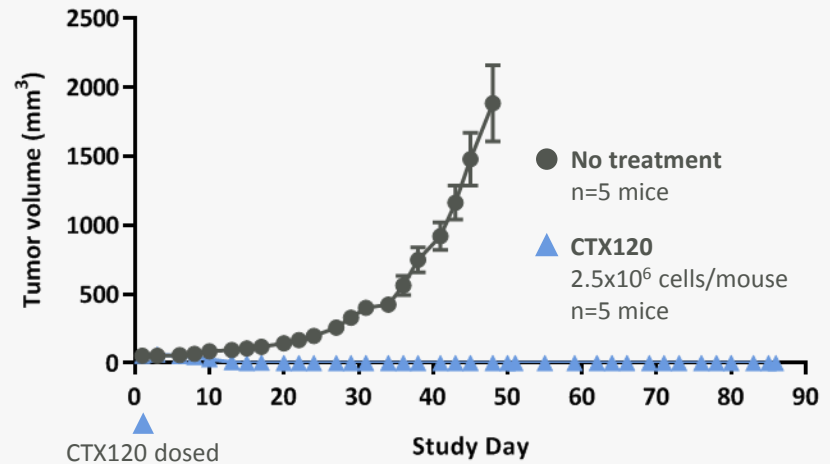
## CTX110 – Anti-CD19 Allogeneic CAR-T

Prolonged survival in disseminated Nalm6 B-ALL xenograft tumor model



## CTX120 – Anti-BCMA Allogeneic CAR-T

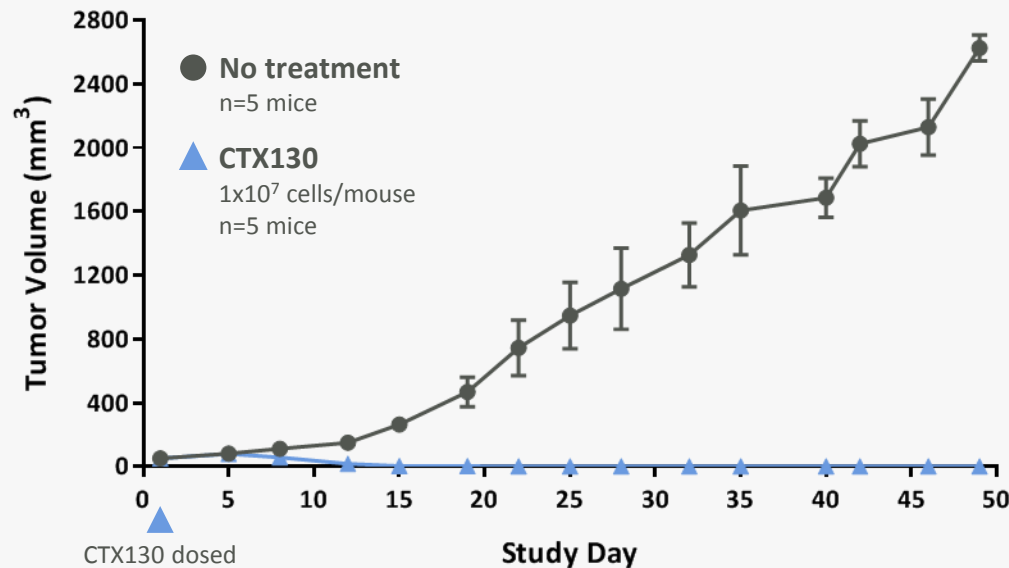
Subcutaneous RPMI-8226 multiple myeloma model completely eliminated



**Strong anti-tumor activity observed with healthy donor-derived CAR-T cells – potential for better outcomes than autologous CAR-T given poor health of patient T cells**

# CTX130 – Anti-CD70 Program as a Bridge to Solid Tumors

## Subcutaneous A498 Renal Cell Carcinoma Model Completely Eliminated



## CTX130

- Anti-CD70 allogeneic CAR-T
- Additional editing beyond TCR and  $\beta$ 2M knock-outs
- For both heme and solid tumors

## Strong rationale for targeting CD70 for solid tumors

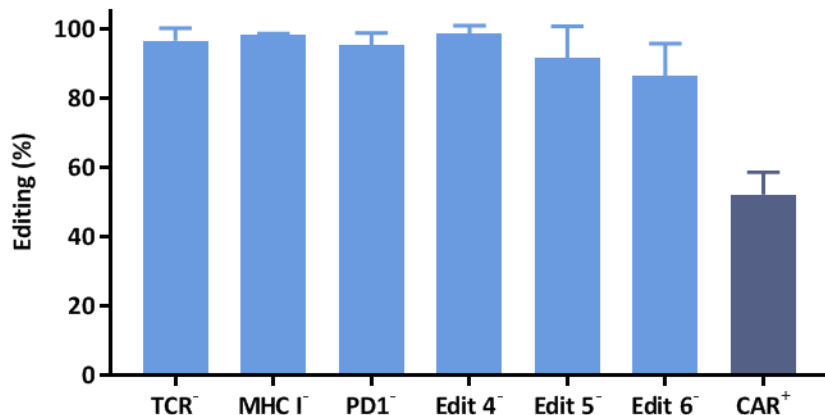
- Initial focus on clear cell renal cell carcinoma – immune-infiltrated disease and >80% CD70-positive
- Minimal CD70 expression on healthy tissues<sup>1</sup>

1. Adam, *et al.* Br J Cancer 2006

# Rapid Generation of Novel Candidates Using CRISPR

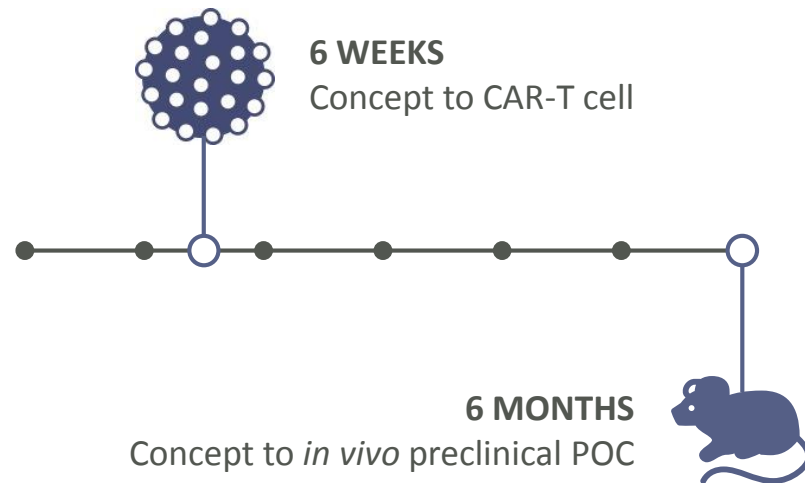
## Multiplex Editing

Single-shot sextuple knock-out plus CAR insertion performed at high efficiency



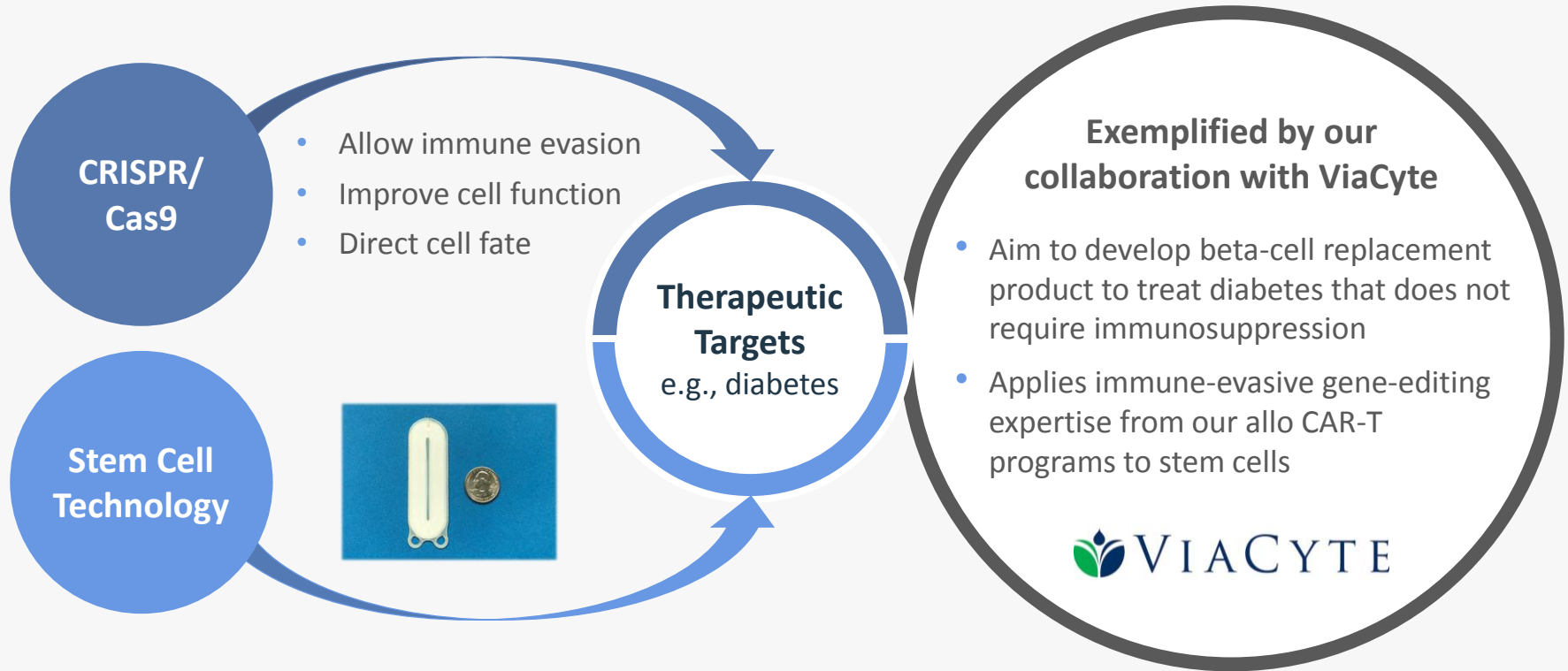
Septuple-edited CAR-T cells show **no viability decrease, no cytokine-independent growth and robust target-specific cytotoxicity**

## Speed of Discovery



# CRISPR Enables Regenerative Medicine 2.0

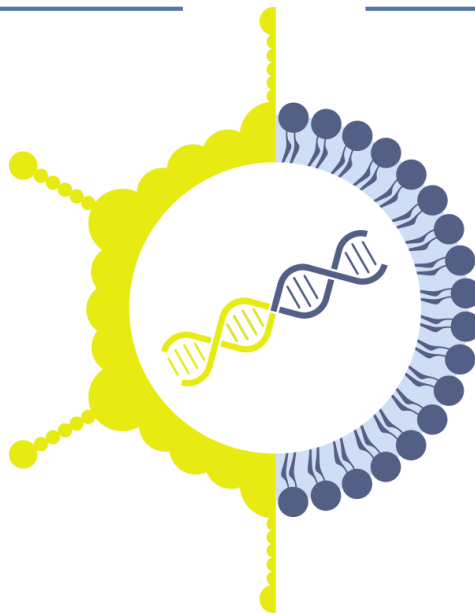
## CRISPR/Cas9 Technology Opens Broader Applications for Regenerative Medicine



# Unlocking *In Vivo* Applications of CRISPR/Cas9

## AAV Vectors for Neuromuscular Indications

- **Adeno-associated virus (AAV)** to deliver Cas9 and gRNA to muscle, the nervous system and other tissues
- Collaboration with StrideBio to improve tissue specificity and reduce immunogenicity
- Programs include DMD and DM1 in collaboration with Vertex, as well as other early research programs



## LNPs for Liver Indications

- **Lipid nanoparticles (LNPs)** containing mRNA encoding Cas9 and gRNA for delivery to the liver
- Lipid technology from MIT and mRNA technology from CureVac
- Programs include GSD Ia and other early research programs

Enabling collaborations



# Optimizing the CRISPR/Cas9 Platform

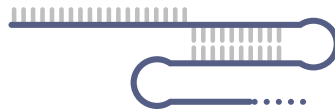
## Nuclease Engineering

Enhance CRISPR/Cas9 system through protein engineering



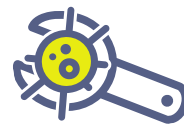
## Guide RNA Optimization

Identify optimal guide RNA formats and sequences for therapeutic editing



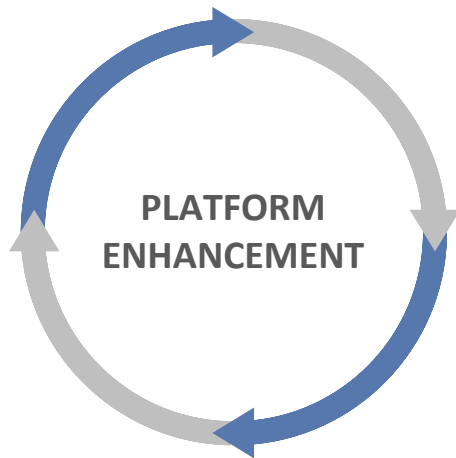
## Advanced Editing

Improve efficiency of gene correction and multiplexing



## Synthetic Biology

Engineer improved cellular therapeutics



# Strong U.S. and Global Foundational IP Position



## United States

### **Charpentier / UC Berkeley / U. Vienna granted patents of broad scope; multiple applications progressing**

- 13 patents of broad scope granted: U.S. Patent Nos. 10,000,772; 10,113,167; 10,266,850 (involved in first interference); 10,227,611; 10,301,651; 10,308,961; 10,337,029; 10,351,878; 10,358,658; 10,358,659; 10,385,360; 10,400,253 and 10,407,697
- 4 patent applications of broad scope allowed
- Over 45 additional patent applications moving forward in parallel with both broad and narrow claims
- Second interference declared June 2019 to determine who was first to invent CRISPR/Cas9 gene editing in eukaryotic cells



## Europe and Global

### **Charpentier / UC Berkeley / U. Vienna granted foundational patents, including use in eukaryotes**

- 3 patents of broad scope granted in the EU: EP2800811; EP3241902 and EP3401400
- 16 patents of broad scope granted in the United Kingdom, Germany, Japan, China, Singapore, Hong Kong, Ukraine, Israel, Australia, New Zealand, Mexico, South Africa and elsewhere
- Advancing applications globally in approximately 80 jurisdictions worldwide with both broad and narrow claims



# Building a Great Company



**EXPERIENCED**  
*Management Team*

**END-TO-END  
CAPABILITIES**  
*With ~250 Employees*

**COLLABORATIVE &  
ENTREPRENEURIAL**  
*Culture*