CRISPR THERAPEUTICS

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. 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.

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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 β-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

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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

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Our Therapeutic Programs

GENETICALLY-DEFINED DISEASES

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

Immuno-oncology

Next-generation gene-edited allogeneic CAR-T pipeline

Regenerative medicine

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

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Our Pipeline

Hemoglobinopathies

Immuno-oncology

Regenerative medicine

In vivo approaches

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

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Hemoglobinopathies – Devastating Blood Diseases

Sickle Cell Disease (SCD) and β-Thalassemia

Blood disorders caused by mutations in the β-globin gene

Sickled Normal Cell Thalassemic

Significant worldwide burden

ANNUAL BIRTHS

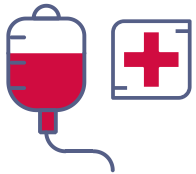
300K
SCD

60K
β-thalassemia

High morbidity and mortality

Anemia Pain Early death

Heavy burden of patient care



Frequent transfusions and hospitalizations

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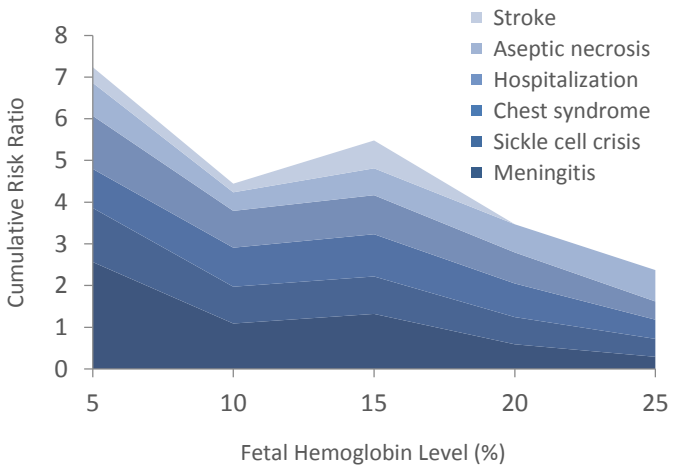
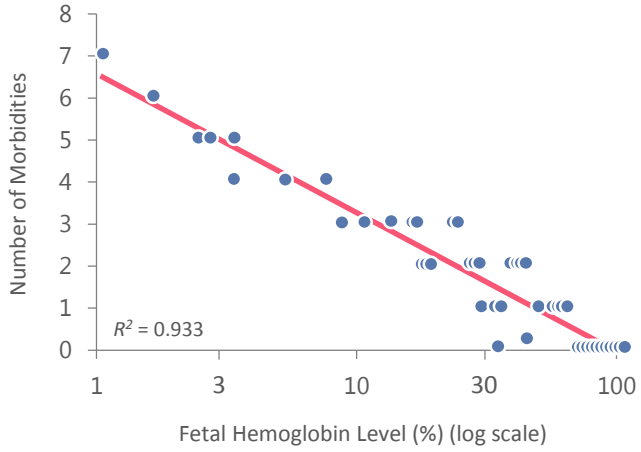
Our Approach – Upregulating Fetal Hemoglobin

Symptoms in SCD and β-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 β-thalassemia
- **Our gene editing strategy aims to mimic these variants in symptomatic patients,** an approach supported by well-understood genetics

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Pioneering CRISPR Clinical Trials

CLIMB THAL-111 CLIMB SCD-121

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

Patients

Up to 45 adult patients each for transfusion-dependent β-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 β-thal and VOCs for SCD

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

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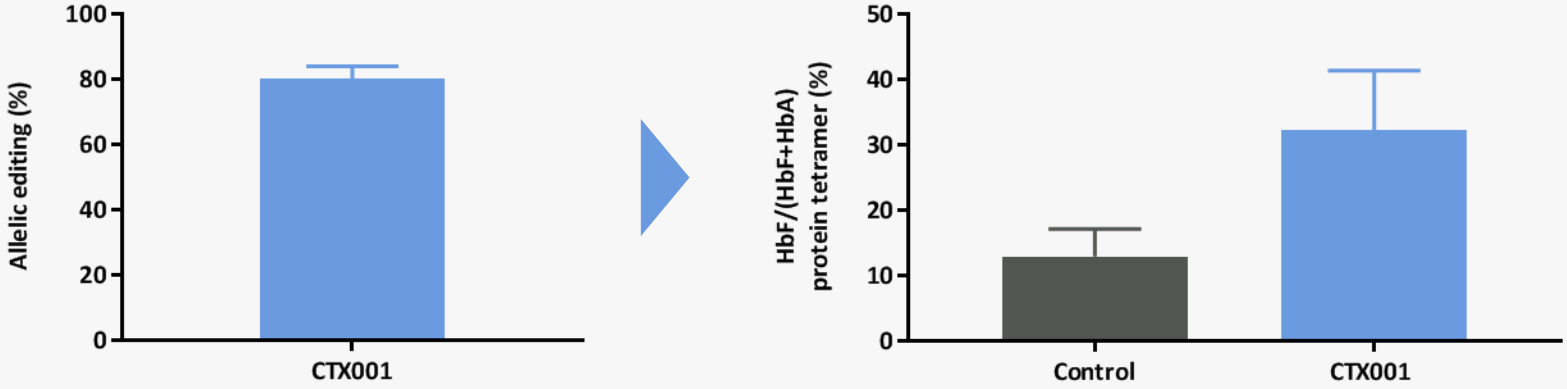
CTX001 Upregulates Fetal Hemoglobin

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*

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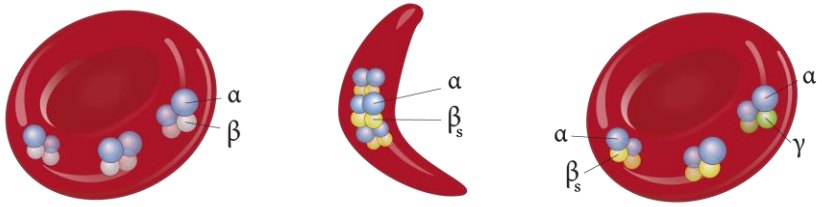
CTX001 Aims to Treat Underlying SCD Pathophysiology

Enough HbF to Prevent Polymerization

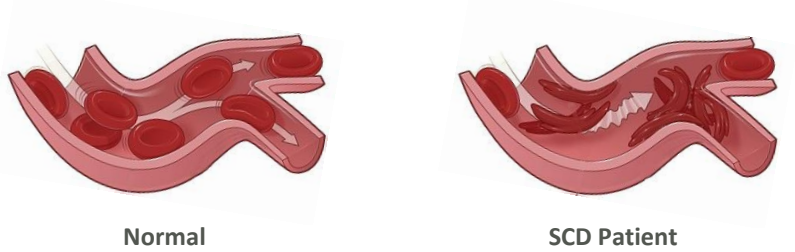


Normal
No polymerization

SCD Patient
Polymerization

CTX001
No polymerization

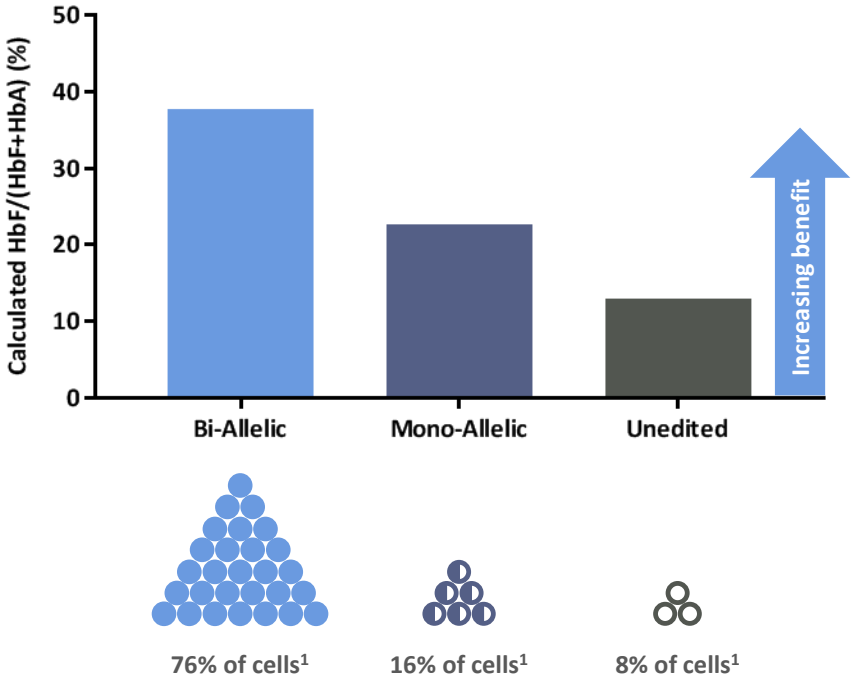
Enough Normal Cells in Circulation to Prevent Occlusion



Normal

SCD Patient

Estimated HbF Expression at the Cellular Level



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

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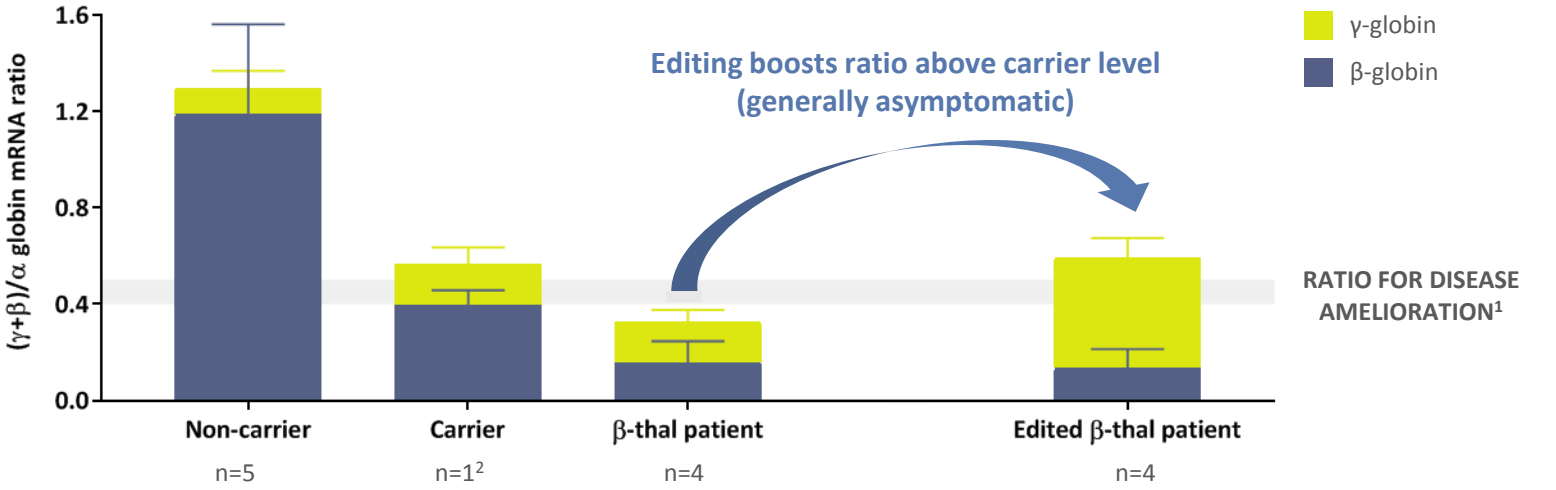
CTX001 Increases HbF in β-Thalassemia Patient Samples

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

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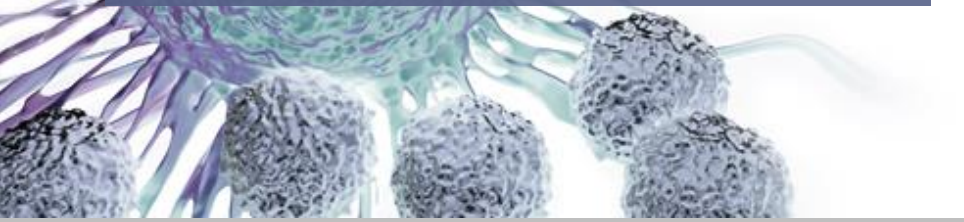
CRISPR Enables the Next Generation of I/O Cell Therapy

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



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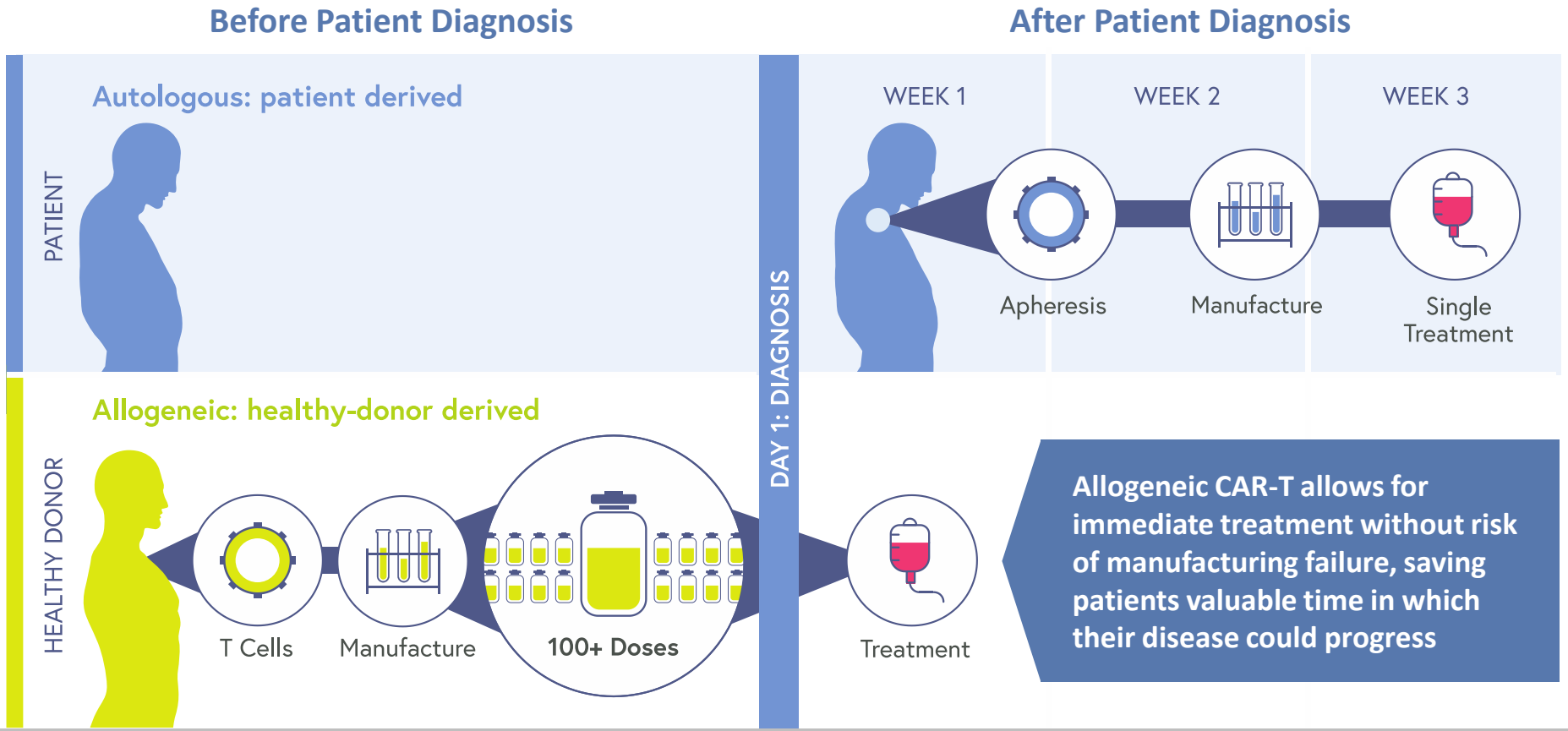
Allogeneic CAR-T Therapy Has Transformative Potential



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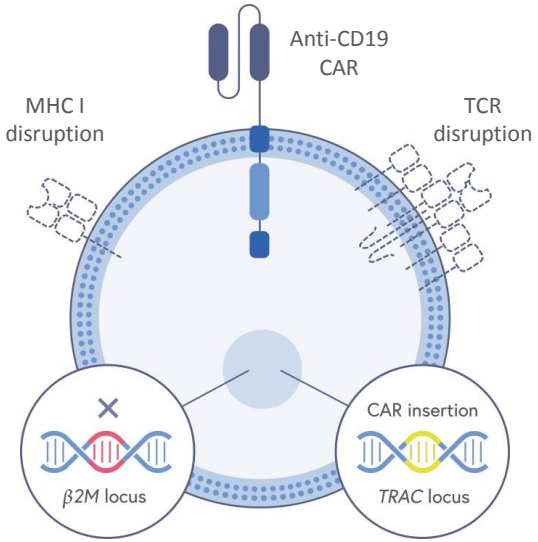
CRISPR-Edited Allogeneic T Cell Design

Initial Allogeneic CAR-T Candidate – CTX110

- **Improve persistence in the allo setting** with β2M 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

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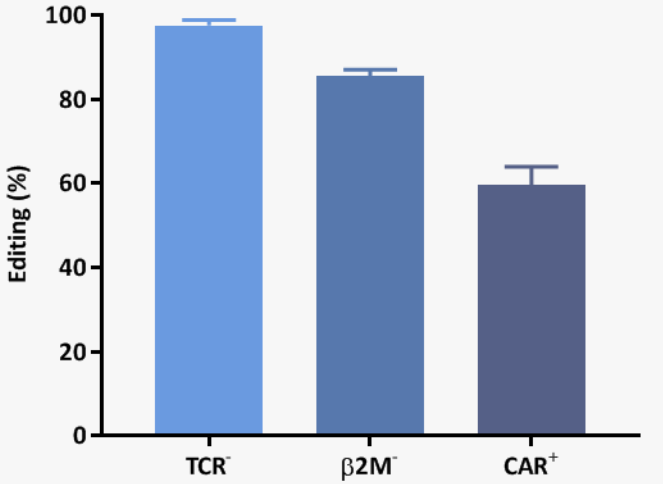
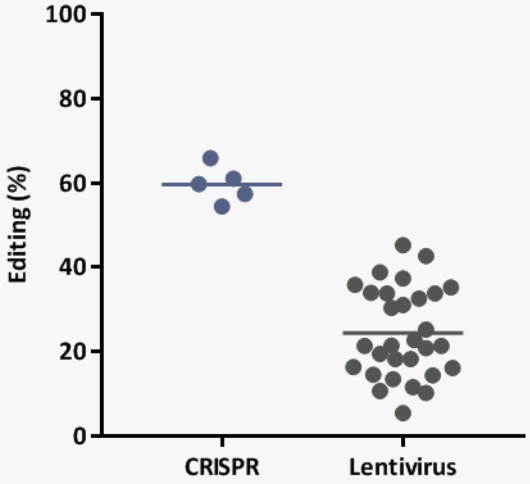
CRISPR Editing Allows for a More Consistent Product

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+ range with CRISPR
vs. **6-45%** for lentiviral CAR-T[1]

1. Maude, *et al*. NEJM 2014

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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

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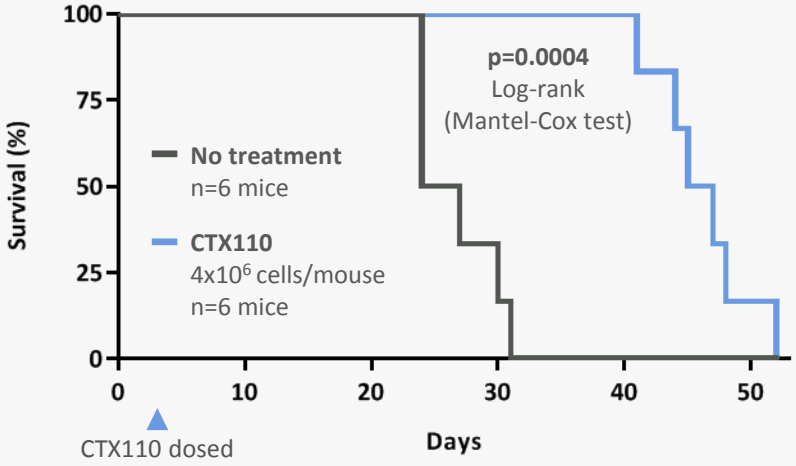
CTX110/CTX120 – Novel Approach Against Validated Targets

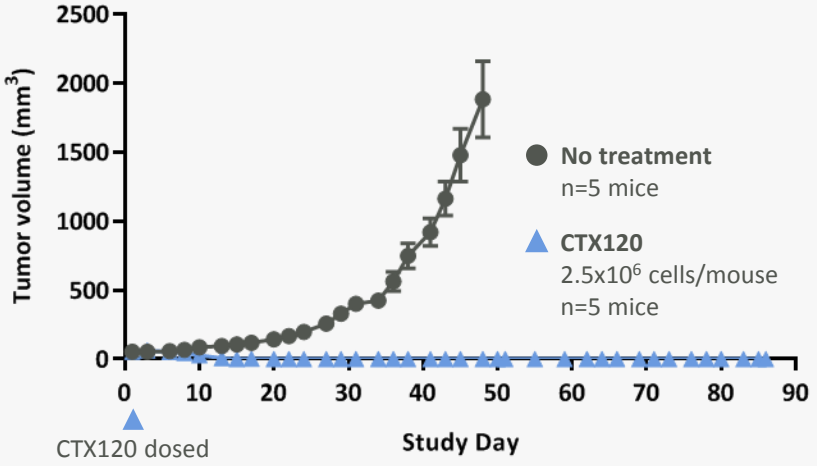
CTX110 – Anti-CD19 Allogeneic CAR-T

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

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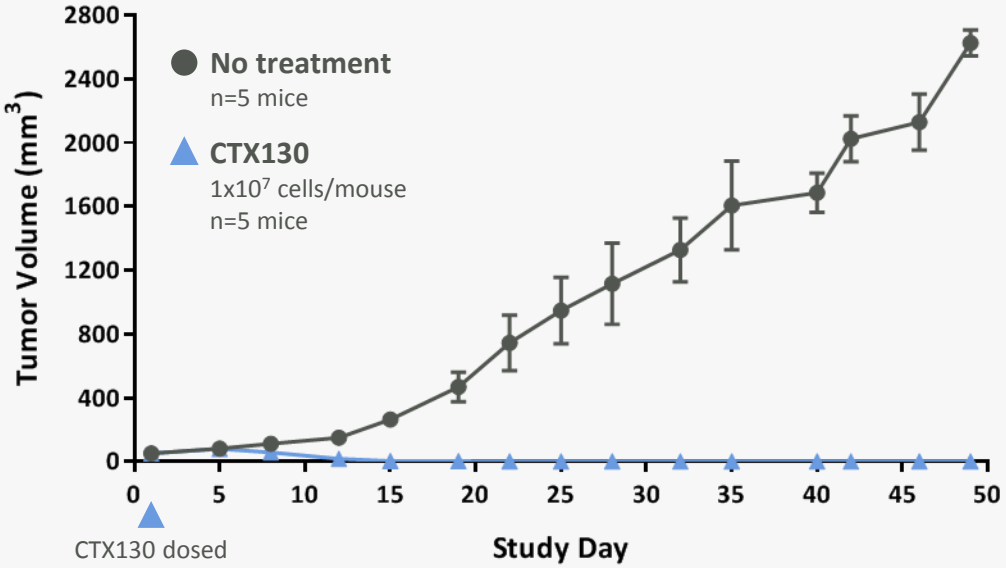
CTX130 – Anti-CD70 Program as a Bridge to Solid Tumors

Subcutaneous A498 Renal Cell Carcinoma Model Completely Eliminated



CTX130

- Anti-CD70 allogeneic CAR-T
- Additional editing beyond TCR and β2M 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[1]

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

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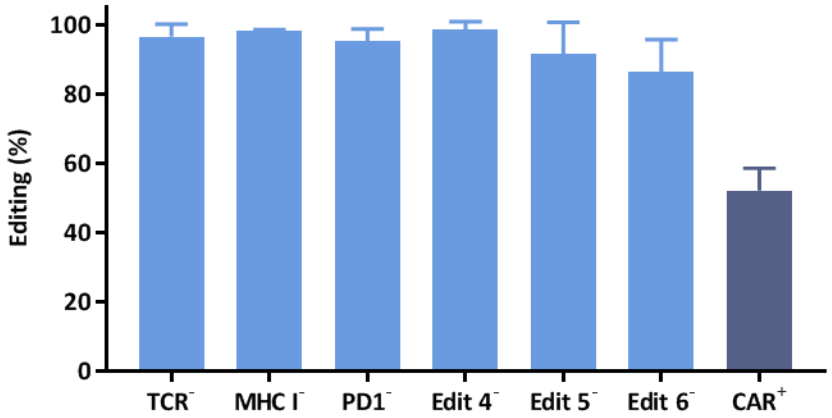
Rapid Generation of Novel Candidates Using CRISPR

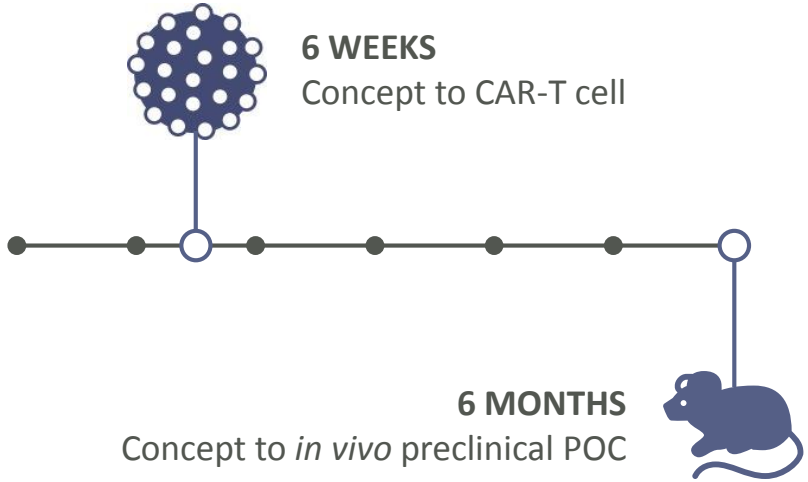
Multiplex Editing

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



6 WEEKS
Concept to CAR-T cell

6 MONTHS
Concept to *in vivo* preclinical POC

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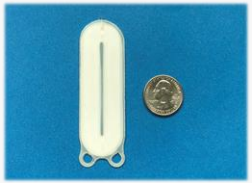
CRISPR Enables Regenerative Medicine 2.0

CRISPR/Cas9 Technology Opens Broader Applications for Regenerative Medicine

CRISPR/ Cas9

- Allow immune evasion
- Improve cell function
- Direct cell fate

Stem Cell Technology



Therapeutic Targets
e.g., diabetes

Exemplified by our collaboration with ViaCyte

- Aim to develop beta-cell replacement product to treat diabetes that does not require immunosuppression
- Applies immune-evasive gene-editing expertise from our allo CAR-T programs to stem cells

VIACYTE

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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

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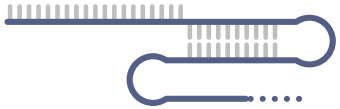
Optimizing the CRISPR/Cas9 Platform

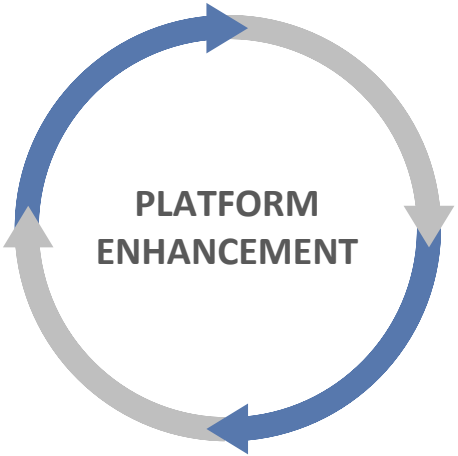
Nuclease Engineering

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

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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

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Building a Great Company

EXPERIENCED
Management Team

END-TO-END CAPABILITIES
With ~250 Employees

COLLABORATIVE & ENTREPRENEURIAL
Culture