CRISPR THERAPEUTICS

Creating transformative gene-based medicines for serious diseases

Corporate Overview | January 2019

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CRISPR Therapeutics Highlights

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

Pioneering 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

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

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					*Initiate trial in 1H 2019*		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* and other genetic diseases**							
Glycogen storage disease Ia (GSD Ia)							Wholly-owned
Duchenne muscular dystrophy (DMD)							Wholly-owned
Cystic fibrosis (CF)						VERTEX	License option
Hurler syndrome (MPS I)							Wholly-owned

CASEBIA THERAPEUTICS **Through Casebia, our joint venture with Bayer, we have 50% ownership of additional programs in SCID, hemophilia A and IPEX**

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

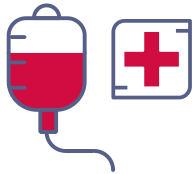
300K
SCD

60K
β-thalassemia

High morbidity and mortality

Anemia Pain Early death

Heavy burden of patient care



Frequent transfusions and hospitalizations

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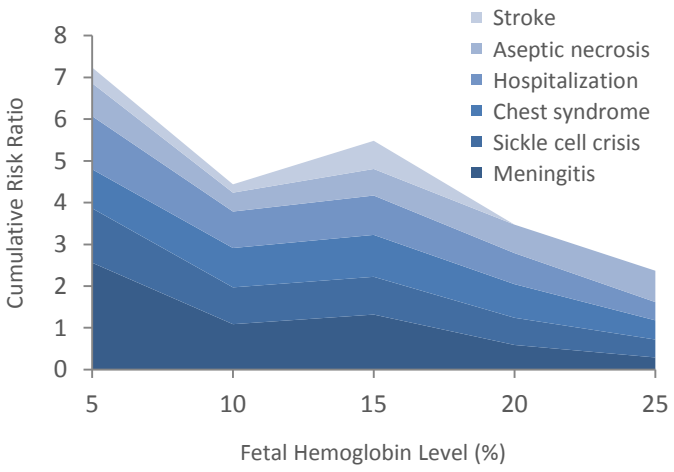
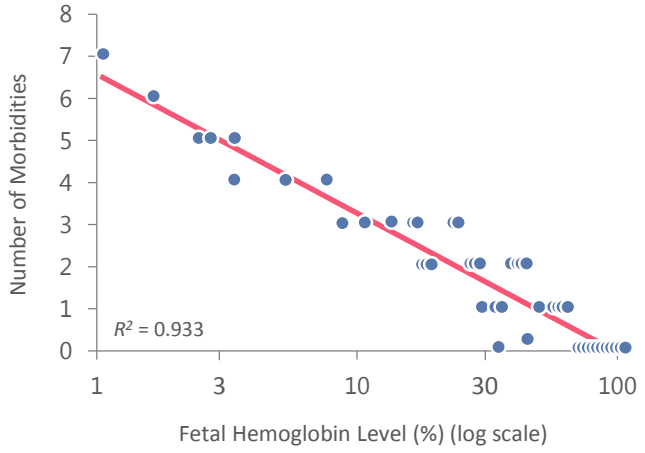
Our Approach – Upregulating Fetal Hemoglobin

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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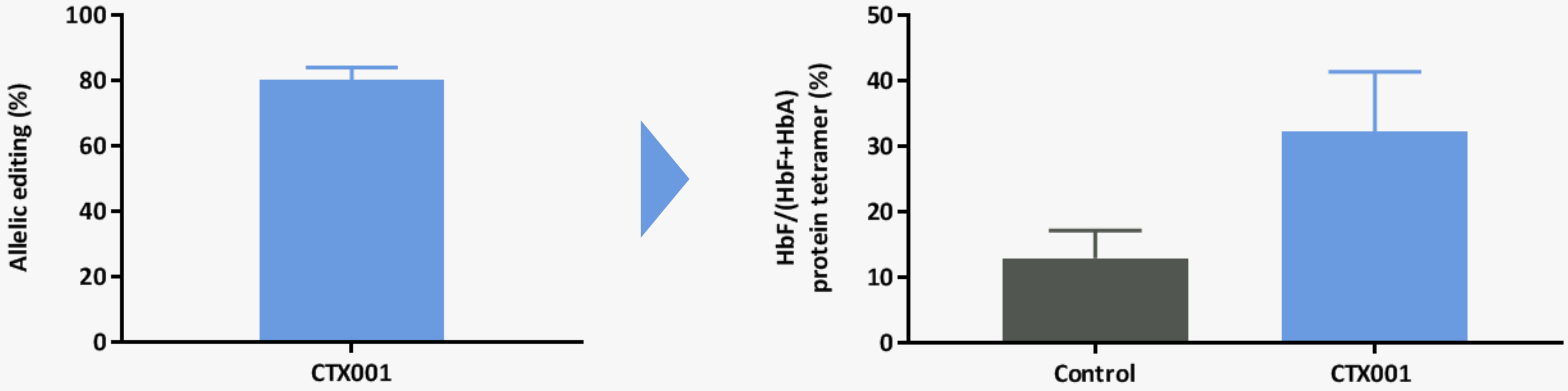
CTX001 Upregulates Fetal Hemoglobin

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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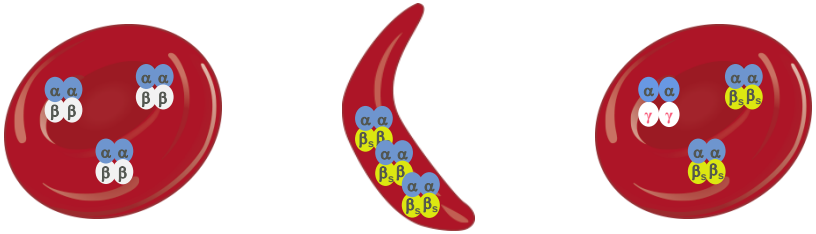
CTX001 Aims to Treat Underlying SCD Pathophysiology

Enough HbF to Prevent Polymerization

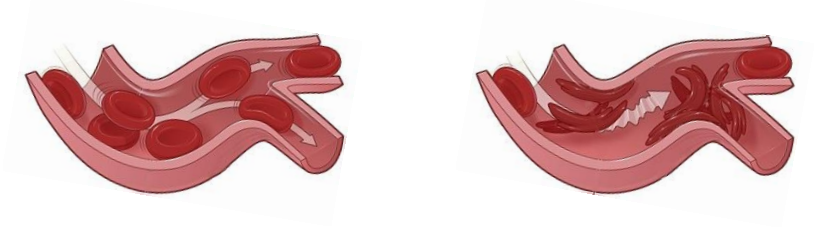


Normal
No polymerization

SCD Patient
Polymerization

CTX001
No polymerization

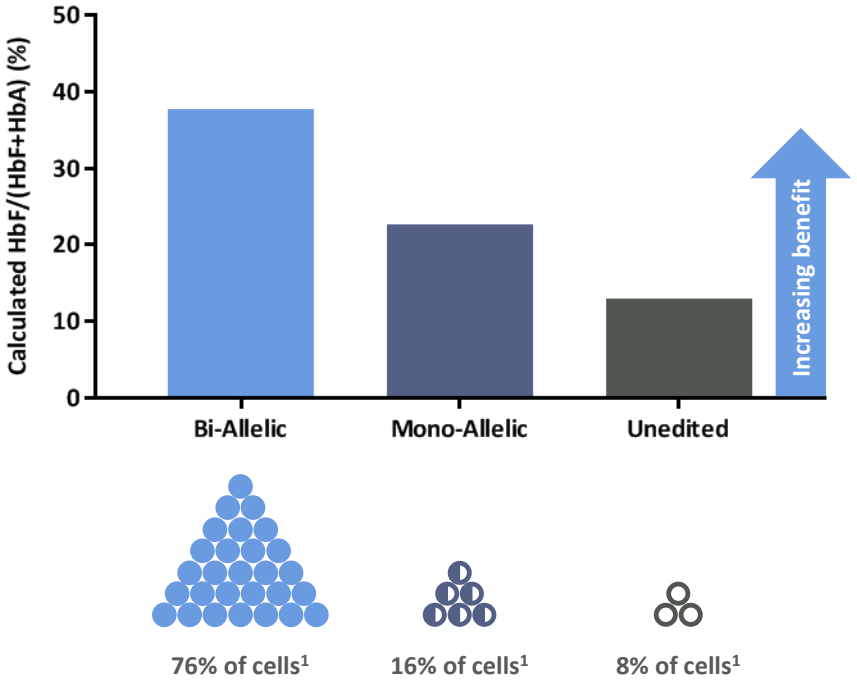
Enough Normal Cells in Circulation to Prevent Occlusion



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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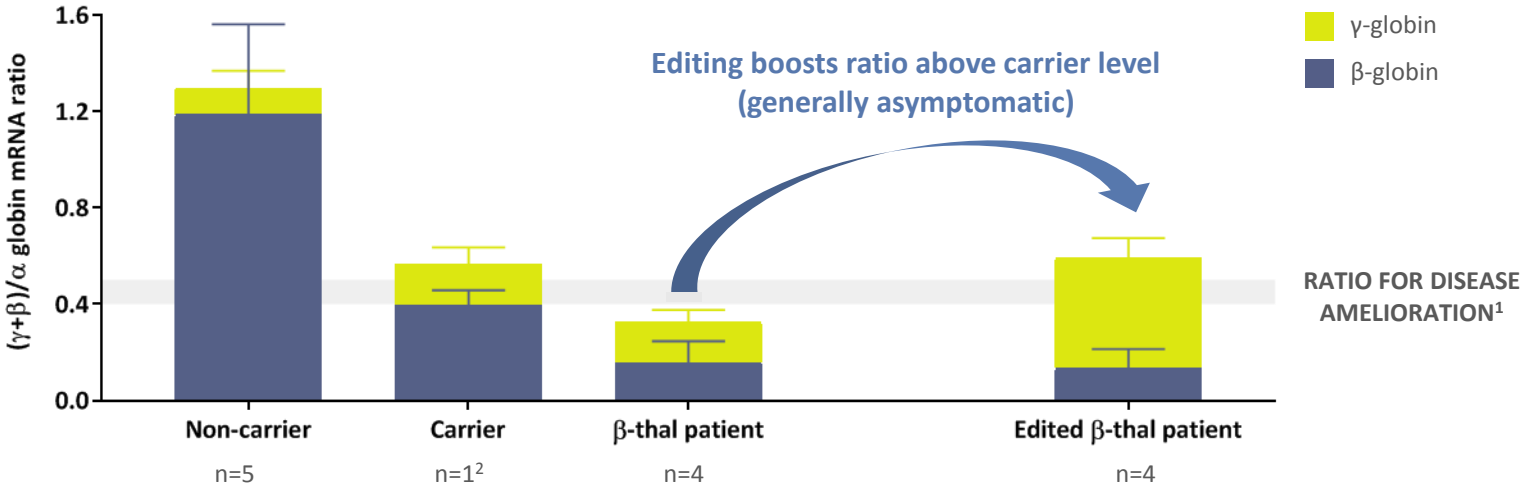
CTX001 Increases HbF in β-Thalassemia Patient Samples

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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Pioneering CRISPR Clinical Trials

CTX001-111 and CTX001-121

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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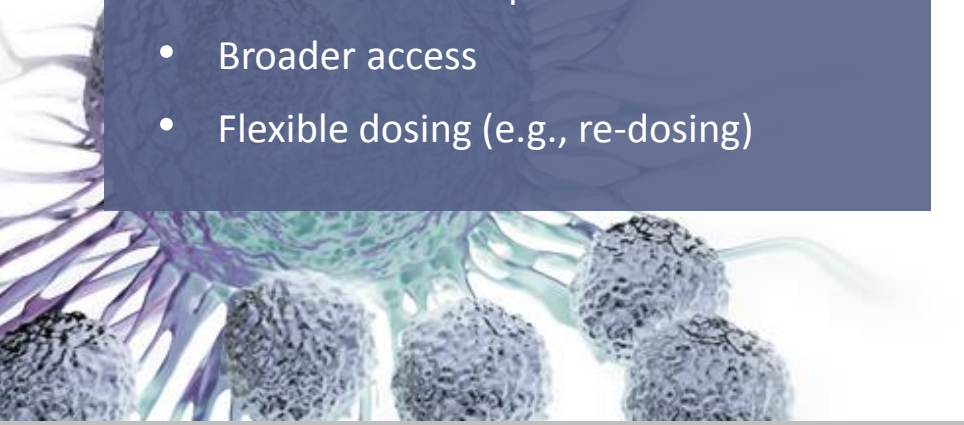
CRISPR Enables the Next Generation of I/O Cell Therapy

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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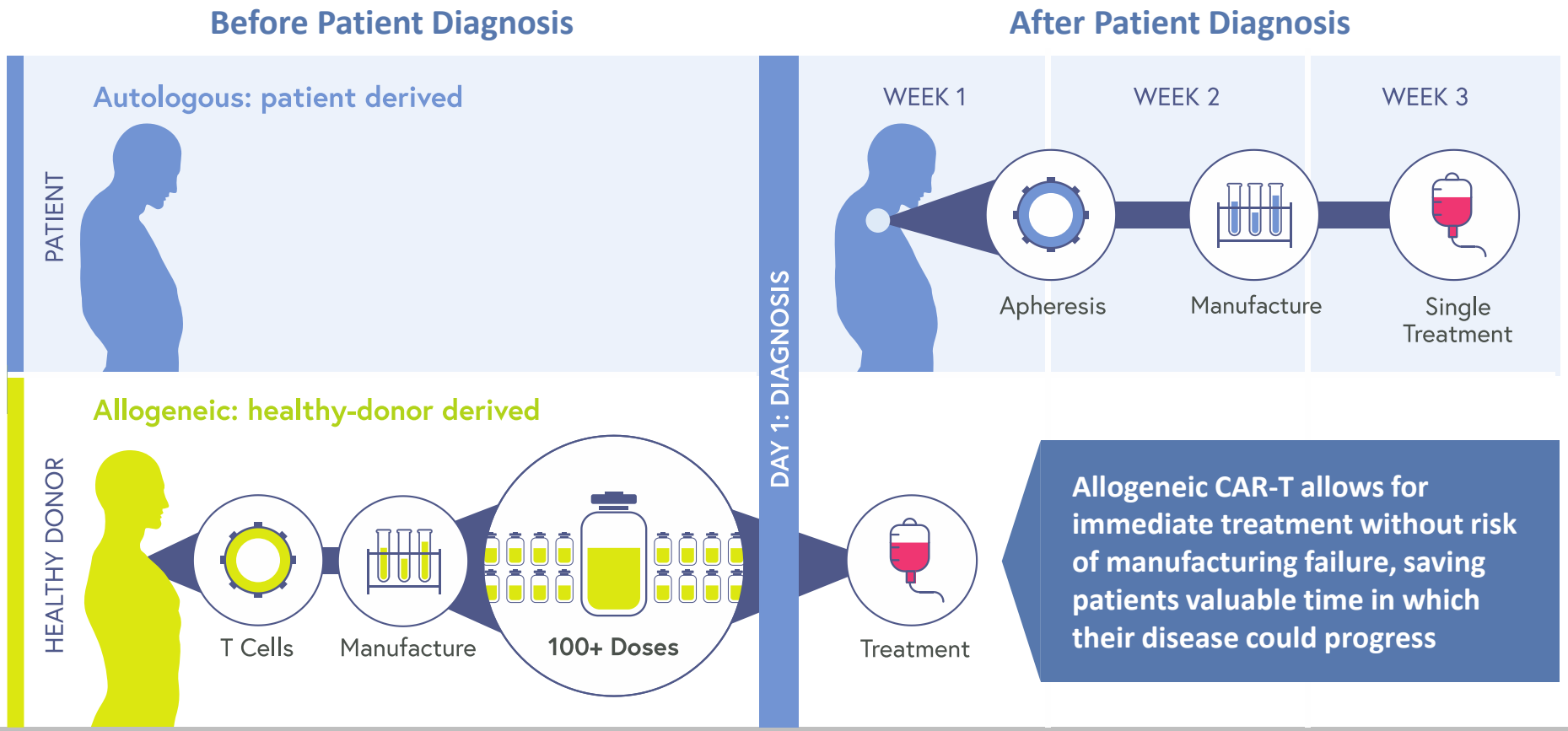
Allogeneic CAR-T Therapy Has Transformative Potential



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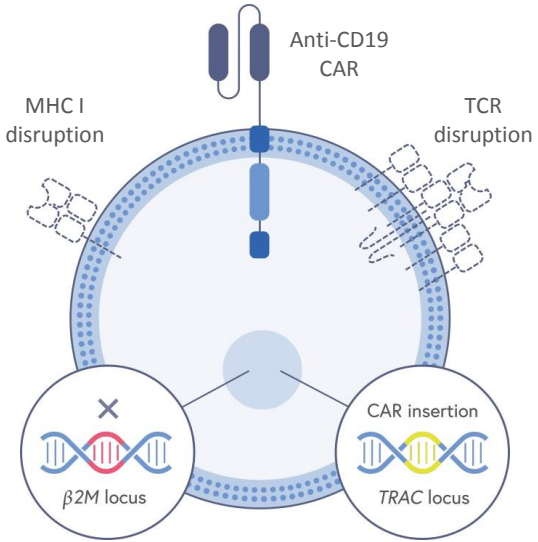
CRISPR-Edited Allogeneic T Cell Design

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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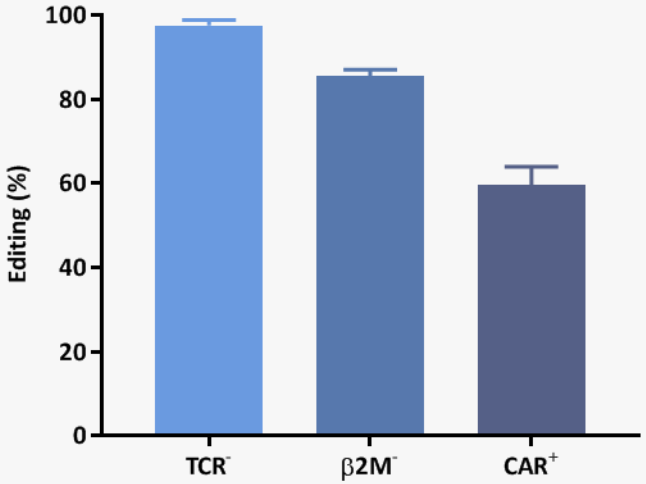
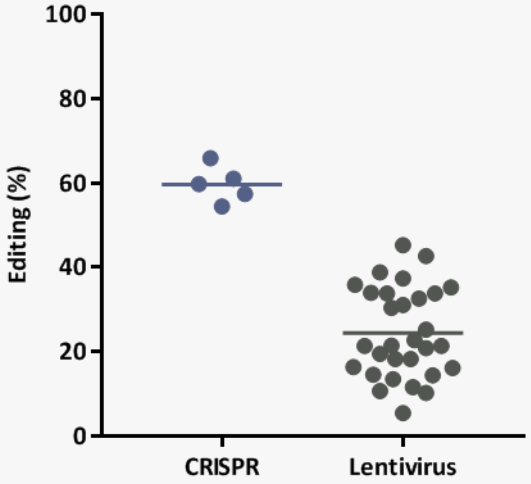
CRISPR Editing Allows for a More Consistent Product

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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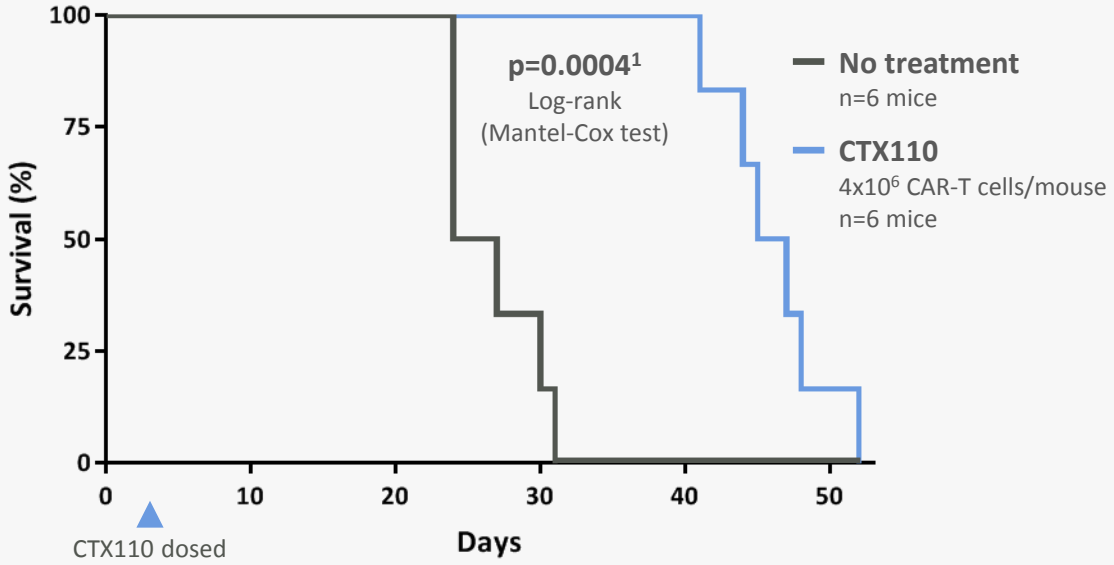
CTX110 – Anti-CD19 Lead Program Advancing to the Clinic

Prolonged Survival in Disseminated Nalm6 B-ALL Xenograft Tumor Model



CTX110

- Anti-CD19 allogeneic CAR-T
- TCR and β2M knock-outs
- For CD19-positive malignancies, such as lymphomas and leukemias

Lead immuno-oncology program

- Novel approach against a validated tumor target
- Targeting trial initiation in 1H 2019

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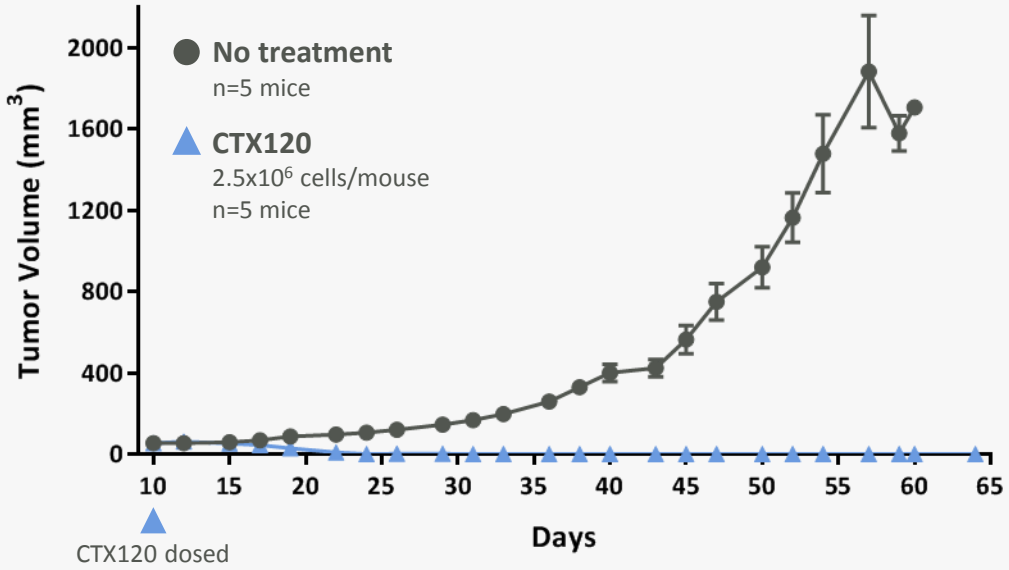
CTX120 – Strong Rationale for Anti-BCMA Allo CAR-T

Subcutaneous RPMI-8226 Multiple Myeloma Model Completely Eliminated



CTX120

- Anti-BCMA allogeneic CAR-T
- TCR and β2M knock-outs
- For multiple myeloma

Strong rationale in multiple myeloma

- Validated tumor target
- Potential for better outcomes than autologous CAR-T given poor health of patient T cells following many prior lines of therapy

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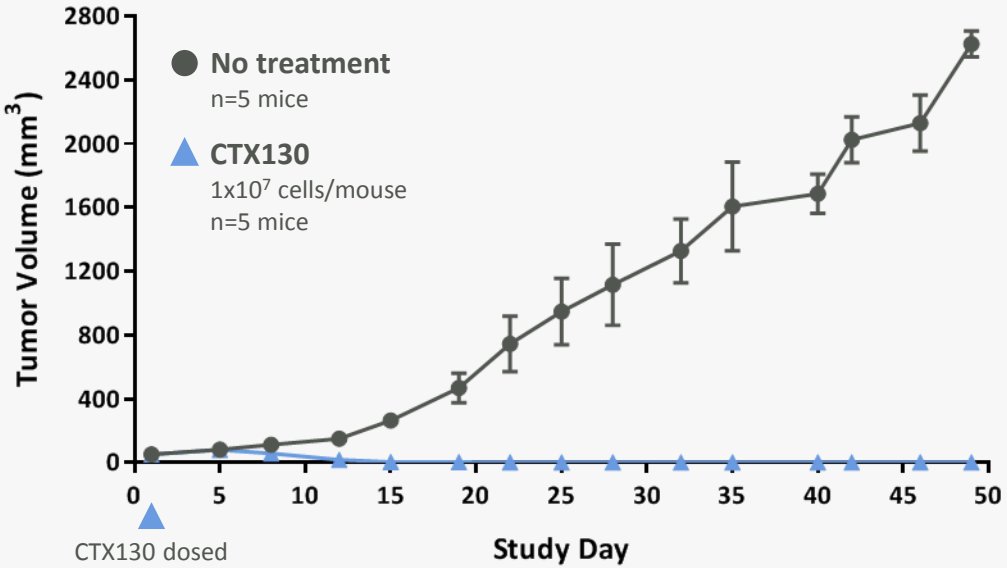
CTX130 – Anti-CD70 Program as a Bridge to Solid Tumors

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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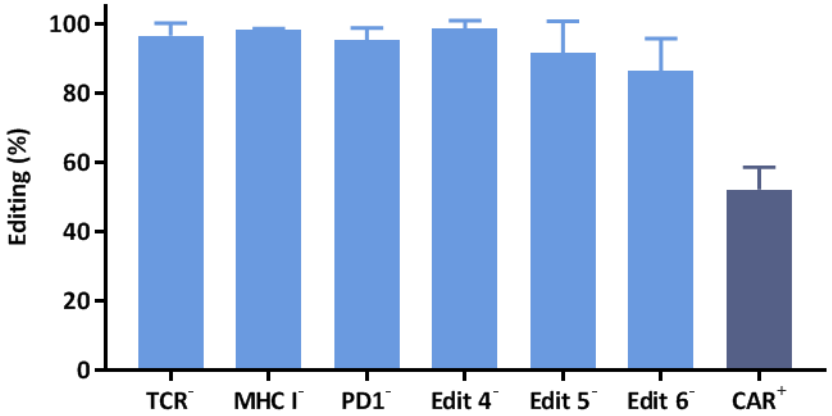
Rapid Generation of Novel Candidates Using CRISPR

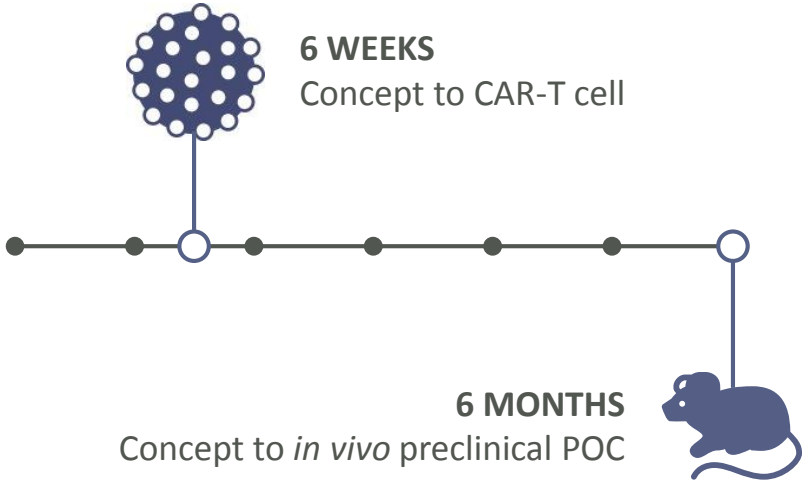
Multiplex Editing

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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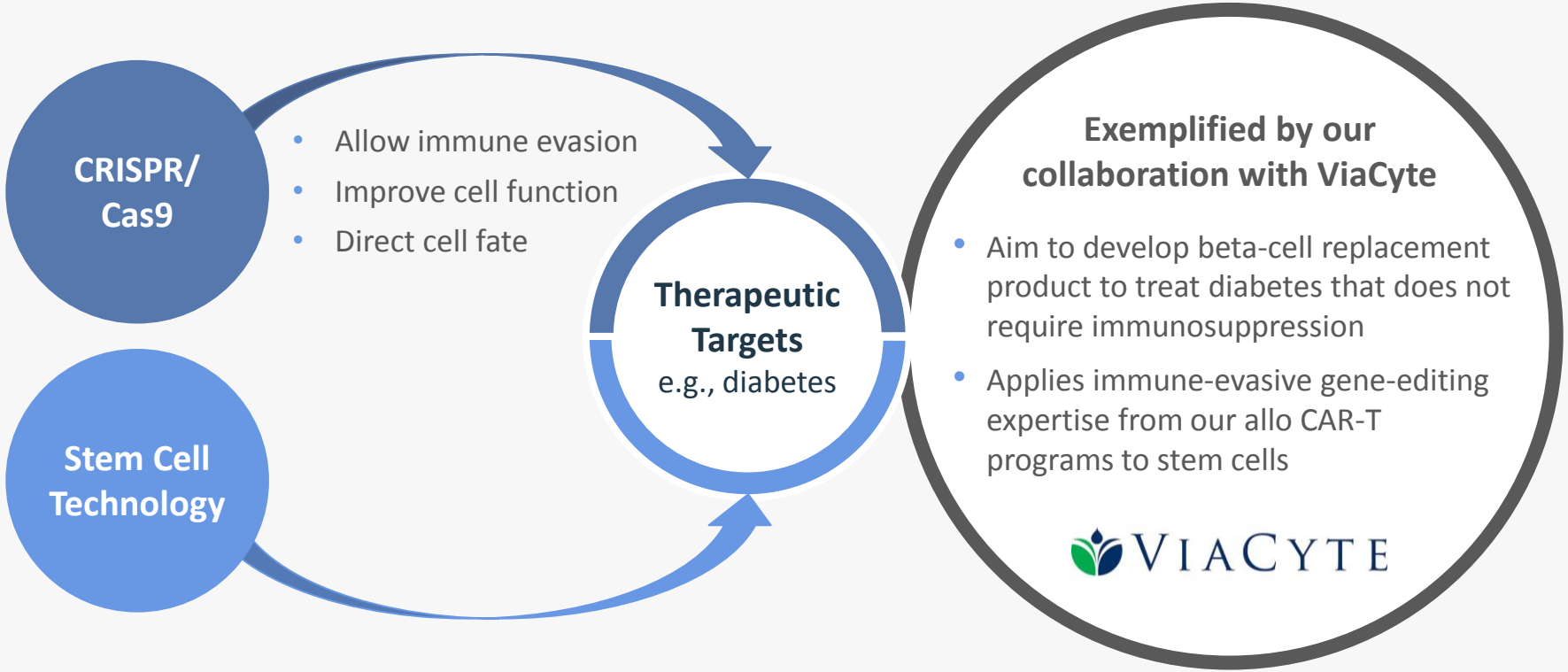
CRISPR Enables Regenerative Medicine 2.0

CRISPR/Cas9 Technology Opens Broader Applications for Regenerative Medicine



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Delivering CRISPR/Cas9 to Unlock *In Vivo* Applications

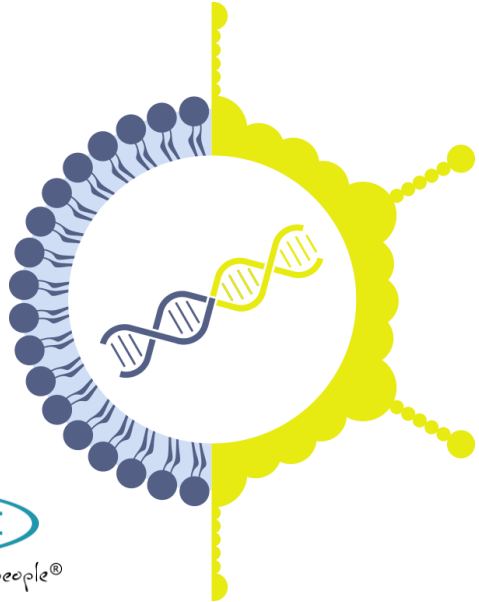
Non-Viral

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

CASEBIA THERAPEUTICS

- **Broadens our pipeline –** 50%-owned by CRISPR Therapeutics and funded by $265 MM from Bayer
- **Enhances our platform improvement efforts** – joint research and full access to new IP at no cost

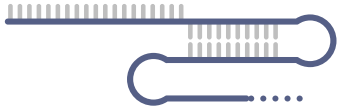
Optimizing the CRISPR/Cas9 Platform

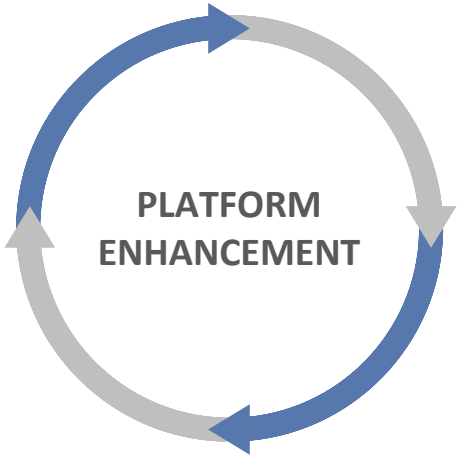
Nuclease Engineering

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

- 2 patents of broad scope granted (No. 10,000,772 and 10,113,167)
- Multiple patent applications moving forward in parallel with both broad and narrow claims
- Federal Appeals Court affirmed PTAB decision to end the first interference on technical grounds, without any determination on inventorship of CRISPR/Cas9 gene editing in eukaryotic cells

Europe, China and Global

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

- 4 patents granted between EU and U.K. include single-guide RNA and uses in all settings
- Patents of broad scope granted in Japan, China, Singapore, Australia, New Zealand, Mexico 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 >170 Employees

COLLABORATIVE & ENTREPRENEURIAL
Culture