Creating transformative gene-based medicines for serious diseases

Corporate Overview | May 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
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”
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
# Our Pipeline

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<th>PROGRAM</th>
<th>RESEARCH</th>
<th>IND-ENABLING</th>
<th>CLINICAL</th>
<th>MARKETED</th>
<th>STATUS</th>
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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
Our Approach – Upregulating Fetal Hemoglobin

Symptoms in SCD and β-Thalassemia Decrease as HbF Level Increases

- 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

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

Performed at clinical scale with n=6 healthy donors

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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

**Estimated HbF Expression at the Cellular Level**

- Bi-Allelic
  - Estimated HbF expression: 50%
- Mono-Allelic
  - Estimated HbF expression: 40%
- Unedited
  - Estimated HbF expression: 10%

**Enough Normal Cells in Circulation to Prevent Occlusion**

- Normal
  - No occlusion
- SCD Patient
  - Occlusion

1. n=163 single erythroid colonies derived from edited CD34+ cells from healthy donors
CTX001 Increases HbF in β-Thalassemia Patient Samples

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

Calculated mean red blood cell lifespan (days)³

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<th>Condition</th>
<th>Mean Lifespan</th>
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<td>ASYMPOTOMATIC</td>
<td>&gt;120</td>
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<td>SYMPTOMATIC</td>
<td>&lt;40</td>
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<td>CLINICALLY-SIGNIFICANT</td>
<td>&gt;50</td>
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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*
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

Autologous: patient derived

After Patient Diagnosis

WEEK 1
Apheresis

WEEK 2
Manufacture

WEEK 3
Single Treatment

Allogeneic: healthy-donor derived

T Cells
Manufacture
100+ Doses

Day 1: Diagnosis

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 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
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

- No treatment
  - n=6 mice
- CTX110
  - 4x10^6 CAR-T cells/mouse
  - n=6 mice

p=0.0004^\dagger
Log-rank (Mantel-Cox test)

CTX110

- Anti-CD19 allogeneic CAR-T
- TCR and \( \beta2M \) knock-outs
- For CD19-positive malignancies, such as lymphomas and leukemias

Lead immuno-oncology program

- Novel approach against a validated tumor target
- On track to initiate clinical trial in 1H 2019
Subcutaneous RPMI-8226 Multiple Myeloma Model Completely Eliminated

No treatment
n=5 mice

CTX120
2.5x10^6 cells/mouse
n=5 mice

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

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

Subcutaneous A498 Renal Cell Carcinoma Model Completely Eliminated

- No treatment
  n=5 mice
- CTX130
  1x10⁷ cells/mouse
  n=5 mice

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

Rapid Generation of Novel Candidates Using CRISPR

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

Speed of Discovery
6 WEEKS
Concept to CAR-T cell

6 MONTHS
Concept to in vivo preclinical POC

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

- 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

PLATFORM ENHANCEMENT
Strong U.S. and Global Foundational IP Position

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

- 3 patents of broad scope granted: U.S. Patent Nos. 10,000,772, 10,113,167 and 10,227,611
- 2 patent applications of broad scope allowed, including the patent application involved in the first interference
- 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

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

- 5 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, 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 >190 Employees

COLLABORATIVE &
ENTREPRENEURIAL
Culture

CRISPR Therapeutics | www.crisprtx.com