Creating transformative gene-based medicines for serious diseases

Corporate Overview | June 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>
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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

- 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.

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


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**
- Normal: No polymerization
- SCD Patient: Polymerization
- CTX001: No polymerization

**Estimated HbF Expression at the Cellular Level**

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<th>Bi-Allelic</th>
<th>Mono-Allelic</th>
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<td>Calculated HbF/(HbF+HbA) (%)</td>
<td>40</td>
<td>20</td>
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**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

- Editing boosts ratio above carrier level (generally asymptomatic)
- Calculated mean red blood cell lifespan (days): 3
- 2. Technical replicates
Pioneering CRISPR Clinical Trials

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

**PATIENT**

- Autologous: patient derived

**HEALTHY DONOR**

- Allogeneic: healthy-donor derived
- T Cells
- Manufacture
- 100+ Doses

After Patient Diagnosis

**WEEK 1**
- Apheresis

**WEEK 2**
- Manufacture

**WEEK 3**
- Single Treatment

**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. 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

\[ p=0.0004^{1} \]

(Log-rank test, Mantel-Cox test)

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
- 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

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

Subcutaneous A498 Renal Cell Carcinoma Model Completely Eliminated

- No treatment
  - n=5 mice

- CTX130
  - 1x10^7 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 tissues¹
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

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- **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
**Strong U.S. and Global Foundational IP Position**

**United States**

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

- 5 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; and 10,301,651
- 5 patent applications of broad scope allowed
- Over 40 additional 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 and Global**

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

- 6 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