CRISPR Therapeutics
Creating transformative gene-based medicines for serious diseases

Corporate Overview
October 2018
Forward-Looking Statements

This presentation and other related materials contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning: the timing of filing of clinical trial applications and INDs, any approvals thereof and timing of commencement of clinical trials, the timing, therapeutic value, development, and commercial potential of CRISPR/Cas9 gene editing technologies and therapies, the sufficiency of CRISPR’s cash resources and the intellectual property coverage and positions of CRISPR, its licensors and third parties. All statements, other than statements of historical facts, included or incorporated by reference in this presentation and other related materials, including statements regarding CRISPR’s strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “target,” “should,” “would,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. CRISPR may not actually achieve the plans, intentions, or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various factors, including: uncertainties regarding the intellectual property protection for CRISPR’s technology and intellectual property belonging to third parties; uncertainties inherent in the initiation and completion of preclinical studies for CRISPR’s 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; expectations for regulatory approvals to conduct trials or to market products; and those risks and uncertainties described under the heading “Risk Factors” in CRISPR’s most recent annual report on Form 10-K, and in other filings that CRISPR has made or may make with the U.S. Securities and Exchange Commission.

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A new technology for ‘editing’ defective genes has raised hopes for a future generation of medicines.

The Wall Street Journal.
CRISPR Therapeutics Highlights

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<th>LEADING GENE-EDITING COMPANY</th>
<th>Rapidly translating revolutionary CRISPR/Cas9 technology into transformative therapies</th>
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<td>PIONEERING CRISPR IN THE CLINIC</td>
<td>Filed first company-sponsored CTA for a CRISPR-based therapeutic; CTX001 on track to initiate trials in 2018 in hemoglobinopathies</td>
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<td>NEXT-GENERATION I/O PLATFORM</td>
<td>Advancing wholly owned, potentially best-in-class gene-edited allogeneic CAR-T products toward the clinic</td>
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<td>ADVANCING IN VIVO APPLICATIONS</td>
<td>Pursuing select <em>in vivo</em> indications enabled by in-licensed technologies, platform improvement, and strategic partners</td>
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<tr>
<td>UNIQUE CASEBIA JOINT VENTURE</td>
<td>50% ownership of Casebia broadens our pipeline and supports our platform improvement efforts; funded by ~$265M from Bayer</td>
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<td>STRONG IP &amp; FINANCIAL POSITION</td>
<td>Strong IP and robust financial position: ~$320 million in cash as of June 30, 2018</td>
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## Our Portfolio

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<th>Program</th>
<th>Editing approach</th>
<th>Research</th>
<th>IND-enabling</th>
<th>Ph I/II</th>
<th>Partner</th>
<th>Structure</th>
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<td><strong>Ex vivo: Hematopoietic</strong></td>
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<td>CTX001: β-thalassemia</td>
<td>Disruption</td>
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<td><strong>CTA Approved</strong></td>
<td>VERTEX, Collaboration</td>
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<tr>
<td>CTX001: Sickle cell disease (SCD)</td>
<td>Disruption</td>
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<td>VERTEX, Collaboration</td>
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<td>Hurler syndrome (MPS-1)</td>
<td>Correction</td>
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<td>Wholly-owned</td>
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<td>Severe combined immunodeficiency (SCID)</td>
<td>Correction</td>
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<td>Joint venture</td>
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<td><strong>Ex vivo: Immuno-oncology</strong></td>
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<td>CTX110: Anti-CD19 allogeneic CAR-T</td>
<td>Various</td>
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<tr>
<td>CTX120: Anti-BCMA allogeneic CAR-T</td>
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<td>Wholly-owned</td>
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<tr>
<td>CTX130: Anti-CD70 allogeneic CAR-T</td>
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<td><strong>Ex vivo: Regenerative Medicine</strong></td>
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<td>Viacyte, Collaboration</td>
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<td><strong>In vivo: Liver</strong></td>
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<td>Glycogen storage disease Ia (GSD Ia)</td>
<td>Correction</td>
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<td>Hemophilia</td>
<td>Correction</td>
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<td>Joint venture</td>
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<td><strong>In vivo: Other organs</strong></td>
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<tr>
<td>Duchenne muscular dystrophy (DMD)</td>
<td>Disruption</td>
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<td>Wholly-owned</td>
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<td>Cystic fibrosis (CF)</td>
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<td><strong>License option</strong></td>
<td>VERTEX</td>
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Our Therapeutic Programs

Hemoglobinopathies
Ex vivo lead candidate in genetically-defined disease

Immuno-oncology
Expand cell therapy platform with allo CAR-T pipeline

Regenerative Medicine
Advance the next generation of stem cell-based therapies

In vivo
Enable in vivo applications through platform advancements
SICKLE CELL DISEASE (SCD) AND β-THALASSEMIA

Blood disorders caused by mutations in the β-globin gene

Significant worldwide burden

300,000 Annual births in SCD and β-thalassemia, respectively

60,000

High morbidity and mortality

Heavy burden of patient care

Anemia Pain Early death

Frequent transfusions & hospitalizations
Our Approach – Upregulating Fetal Hemoglobin

- Naturally occurring genetic variants cause hereditary persistence of fetal hemoglobin (HPFH), and lead to reduced symptoms in patients with sickle cell disease and β-thalassemia.

- Our gene editing strategy aims to recreate these variants in symptomatic patients — an approach supported by well-understood genetics.

CTX001 Upregulates Fetal Hemoglobin and Engrafts in Mice

HIGH EDITING RATES LEAD TO ROBUST HbF INDUCTION\(^1\)

- **ALLELIC EDITING (%)**
  - Control: 80%
  - CTX001: 100%
  - Performed at clinical scale

- **HbF/(HbF+HbA) PROTEIN TETRAMER (%)**
  - Control: 10%
  - CTX001: 20%

CTX001 ENGRAFTS IN VIVO IN MICE\(^2\)

- **HUMAN / TOTAL BONE MARROW VIABLE CELLS (%)**
  - Donor 1: Control: 40%, CTX001: 50%
  - Donor 2: Control: 45%, CTX001: 60%
  - Donor 3: Control: 35%, CTX001: 55%

1. n=6 healthy donors; 2. 16-week engraftment data

No reduction in engraftment of edited cells
**β-thal: Editing Increases Globin Expression to Carrier Levels**

**GLOBIN mRNA RATIO AFTER GENE EDITING OF β-THAL PATIENT SAMPLES**

- **Non-carrier** ($n=4$)
  - $\gamma$-globin/α-globin ratio: 0.5
  - % Globin: $\beta$
- **Carrier** ($n=1$)
  - $\gamma$-globin/α-globin ratio: 0.5
  - % Globin: $\beta$
- **Patient** ($n=2$)
  - $\gamma$-globin/α-globin ratio: 1.0
  - % Globin: $\beta$
- **Edited Patient** ($n=2$)
  - $\gamma$-globin/α-globin ratio: 2.0
  - % Globin: $\beta$

**EDITING BOOSTS RATIO ABOVE CARRIER LEVEL (GENERALLY ASYMPTOMATIC)**
SCD: Bi-Allelic Editing Leads to High HbF Protein Levels

ESTIMATED HbF EXPRESSION AT THE CELLULAR LEVEL

- 76% of cells bi-allelically edited
- 16% of cells mono-allelically edited
- 8% of cells unedited

CALCULATED HbF/(HbF+HbA) (%)

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

**CTX001-111 and CTX001-121**

*Single-arm Phase 1/2 studies 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-thal and severe SCD
- **Sites**: Sites with extensive transplant experience in countries with significant disease burden
- **Endpoints**: HbF levels and transfusion requirements are clinically relevant and easily measurable

**Potential to expand into registrational trials**, as well as into additional age cohorts and β-thal genotypes, if supported by safety and efficacy
Autologous CAR-T is Transformative, but has Limitations

CAR-T has generated **tremendous excitement** . . .

“. . . But there are still **significant limitations** to autologous CAR-T

<table>
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<th>Limitations</th>
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<tr>
<td>Patients progress or die while waiting</td>
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<td>Patient-to-patient variability</td>
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<td>Costly, complicated manufacturing</td>
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<td>Commercial challenges of bespoke therapy</td>
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*The first-ever treatment that genetically alters a patient’s own cells to fight cancer, a milestone that is expected to transform treatment in the coming years* — The New York Times
Our Approach: Gene-Edited Allogeneic CD19 CAR-T

**CTX110** – our initial immuno-oncology product candidate

CRISPR enables an allogeneic approach that remedies issues with autologous CAR-T

- Product available immediately
- Consistent healthy-donor lymphocytes
- Low COGs and simpler manufacturing
- Off-the-shelf product – broader access

**Multiplex editing in one step**

MHC I knock-out

Anti-CD19 CAR

TCR knock-out

β2M locus

TCRα locus

CAR
Staged Approach to Realize Potential of CRISPR in I/O

Make rapid entry using validated tumor targets
Healthy-donor allo approach in well-validated tumor targets

**CD19, BCMA**

Expand into solid with novel targets and advanced editing
Precise edits to make CAR-T effective in solid tumors

**CD70, resistance to tumor microenvironment**

Unlock the full potential of CRISPR
Multiplex editing to enable more complex products

**Switches, neoantigens, bispecifics**

Collaborations with Neon and MGH to identify and exploit new targets
Equal or Better Editing Rates Achieved After Tech Transfer

Process development and manufacturing initiated for CTX110 – IND-enabling studies underway
CTX110 Eliminates CD19-Expressing Tumor Cells *In Vitro*

**CTX110 COMPARES FAVORABLY TO LENTIVIRAL “AUTOLOGOUS” CAR-T**

![Graph showing cell lysis comparison between CTX110 and Lentiviral Anti-CD19 CAR-T cells.](image)

- **CTX110** (TCR- β2M- CAR+)
- **Lentiviral Anti-CD19**

*Both produced using the same donor T cell material
n=2 independent experiments*
CTX110 Prolongs Survival in a CD19+ Tumor Model \textit{In Vivo}

**PROLONGED SURVIVAL IN DISSEMINATED NALM6 B-ALL MODEL**

**No treatment**
- $n=6$ mice

**CTX110**
- $4 \times 10^6$ CAR-T cells/mouse
- $n=6$ mice

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

$CTX110$ dosed
CTX120: Gene-Edited Allo CAR-T Targeting BCMA

SUBCUTANEOUS RPMI-8226 MULTIPLE MYELOMA MODEL COMPLETELY ELIMINATED

- **No treatment**
  - n=5 mice

- **CTX120 – low dose**
  - 2.5x10^6 cells/mouse; n=5 mice

- **CTX120 – high dose**
  - 1x10^7 cells/mouse; n=5 mice
CTX130: Gene-Edited Allo CAR-T Targeting CD70

SUBCUTANEOUS A498 RENAL CELL CARCINOMA MODEL COMPLETELY ELIMINATED

- **No treatment**
  - \( n=5 \text{ mice} \)

- **CTX130**
  - \( 1 \times 10^7 \text{ cells/mouse} \)
  - \( n=5 \text{ mice} \)

**Graphs**

- **Tumor Volume (mm\textsuperscript{3})**
- **Study Day**

- **CTX130 dosed**
CRISPR/Cas9 Enables Regenerative Medicine 2.0

CRISPR/Cas9 TECHNOLOGY OPENS BROADER APPLICATIONS FOR REGENERATIVE MEDICINE

CRISPR/Cas9 ENABLES CELLULAR ENGINEERING TO:
› Improve immune evasion
› Improve cell function
› Direct cell fate

EXEMPLARY BY OUR COLLABORATION WITH VIACYTE

› Combines our gene editing capabilities and ViaCyte’s stem cell capabilities to develop a beta-cell replacement product to treat diabetes
› Applies immune-evasive gene editing expertise from our allogeneic CAR-T programs to stem cells to avoid the need for immunosuppression

Therapeutic Targets e.g., diabetes

Regen Med
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
Fifty-Percent Ownership of Casebia Therapeutics

Committed IP for select indications

50% ownership

Casebia

50% ownership

Bayer

Committed $370M
$265M to Casebia and $105M to CRISPR

THERAPEUTIC FOCUS AREAS

- Hematology
- Cardiology
- Ophthalmology

Joint research on platform technology – protein engineering, delivery, etc.

CRISPR has full access at no cost to all new IP for use within the field of human therapeutics

CRISPR Therapeutics

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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

STEM CELL ENGINEERING
Expand applications of gene-edited stem cells to treat disease

PLATFORM ENHANCEMENT
## Foundational Intellectual Property Landscape

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<th>Patent Filings</th>
<th>Foundational IP estate</th>
<th>Broad IP estate</th>
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<tr>
<td>EMMANUELLE CHARPENTIER</td>
<td>UC BERKELEY / U. VIENNA</td>
<td>BROAD INSTITUTE</td>
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<th>Human Therapeutics Licensees</th>
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<td>CRISPR THERAPEUTICS</td>
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<tr>
<td>via CARIBOU BIOSCIENCES</td>
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<th>Strategic Investors</th>
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<td>Celgene</td>
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<th>Partners &amp; Total Deal Size</th>
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<td>BAYER</td>
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- Direct license to foundational IP covering all human therapeutic fields; term through 2033
- Four large pharma partnerships indicate strength of the Charpentier / Berkeley foundational IP estate
- Access to Vilnius IP estate through invention management agreement
## Strong U.S. and Global Foundational IP Position

### UNITED STATES

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

- First patent of broad scope granted (U.S Patent No. 10,000,772)
- 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 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 ~80 jurisdictions worldwide with both broad and narrow claims
## Experienced Management Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
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| **SAM KULKARNI, PHD** | Chief Executive Officer  
Partner, McKinsey & Company                                        |
| **RODGER NOVAK, MD** | President & Chairman  
Head of Anti-Infectives R&D, Sanofi                                 |
| **TONY HO, MD** | Head of Research & Development  
Head of Oncology Innovation, AstraZeneca                             |
| **JIM KASINGER, JD** | General Counsel & Corporate Secretary  
General Counsel, Moderna                                              |
| **LAWRENCE KLEIN, PHD** | Head of Business Development & Strategy  
Associate Partner, McKinsey & Company                                |
| **RICHARD SCHWARTZ, PHD** | Head of Technical Operations  
SVP, Manufacturing, Synlogic Therapeutics                             |
| **MIKE TOMSICEK, MBA** | Chief Financial Officer  
Chief Financial Officer, Abiomed                                       |
| **SHELBY WALKER, JD** | Head of Intellectual Property  
Chief IP Counsel, Dyax                                                   |

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