# CRISPR Therapeutics

*Creating transformative gene-based medicines for serious diseases*

Corporate Overview

January 2017

# Forward Looking Statements

*This document contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to statements concerning the timing of our preclinical studies and the intellectual property protection of our technology. All statements, other than statements of historical facts, contained in this document, including statements regarding the Company'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. The Company 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 inherent in the initiation and completion of preclinical studies for the Company'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; uncertainties regarding the intellectual property protection for our technology; and other factors discussed in the "Risk Factors" section of the Company's most recent registration statement on Form S-1 (file no. 33-213577), which is on file with the Securities and Exchange Commission, and in other filings that the Company may make with the Securities and Exchange Commission in the future.*

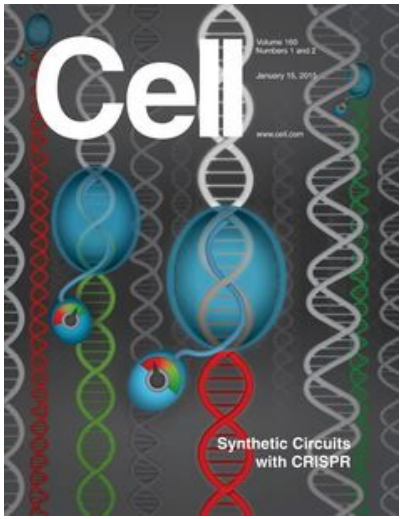
*In addition, the forward-looking statements included in this document represent the Company's views as of the date of this document. The Company anticipates that subsequent events and developments will cause its views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date of this document.*

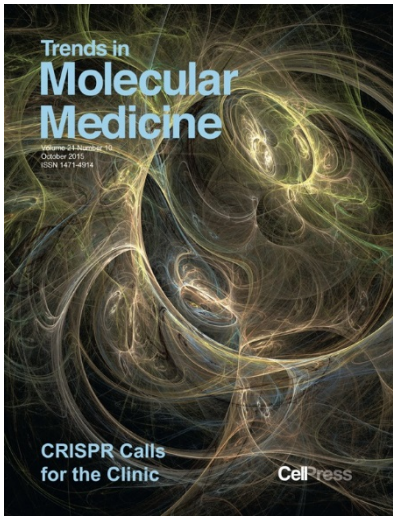
# CRISPR Therapeutics Highlights

| | |
|---|---|
| **LEADING GENE-EDITING COMPANY** | Formed in late 2013 with an exclusive license to foundational CRISPR IP directly from Emmanuelle Charpentier for human therapeutic use |
| **EXPERIENCED MANAGEMENT TEAM** | Management team with years of relevant experience in product development and clinical translation |
| **STRONG TRANSLATIONAL FOCUS** | Focus on translation of CRISPR/Cas9 technology into transformative gene-based medicines |
| **DIVERSIFIED DEVELOPMENT PORTFOLIO** | Targeting a broad range of diseases including *ex vivo* hematology, immuno-oncology, and liver-related indications |
| **COLLABORATIONS WITH BAYER AND VERTEX** | Leading collaborations with >$350M committed by partners and access to distinctive capabilities |
| **STRONG FINANCIAL POSITION** | >$400M raised in CRISPR from blue chip VCs, strategic partners & other investors; up to $300M committed in our Bayer JV, Casebia |

# CRISPR/Cas9: The Next Medical Breakthrough






*"A new technology for 'editing' defective genes has raised hopes for a future generation of medicines"*

THE WALL STREET JOURNAL.

# Our Leadership Team

**RODGER NOVAK, MD**
Chief Executive Officer & Director
*Head Anti-infectives R&D, Sanofi*

**SVEN ANTE (BILL) LUNDBERG, MD**
Chief Scientific Officer
*Head of Translational Medicine, Alexion*

**SAM KULKARNI, PHD**
Chief Business Officer
*Partner, McKinsey & Company*

**MARC BECKER**
Chief Financial Officer
*Global VP Finance, Genzyme-Sanofi*

**TYLER DYLAN-HYDE, PHD**
Chief Legal Officer
*Partner, Morrison & Foerster*

**CHAD COWAN, PHD**
Head of Research
*Assoc. Professor Harvard Medical School*

**KALA SUBRAMANIAN, PHD**
Strategic Development and Operations
*Global Head of Program Mgmt., Novartis*

# Our Scientific Founders, Advisors, and Investors

**EMMANUELLE CHARPENTIER**

- Alexander v. Humboldt Prof, Director, Max Planck Institute for Infection Biology, Berlin
- Foundational work on CRISPR/Cas genome editing
- 25 plus highly prestigious awards for CRISPR/Cas work

**STEPHEN ELLEDGE**

- Professor at Harvard Medical School, Department of Genetics
- Renowned expert in DNA repair and DNA damage response
- Lasker Award Winner 2015

**CRAIG MELLO**

- Professor at University of Massachusetts Medical
- Howard Hughes Medical Investigator
- Nobel Laureate-discovery of RNAi

**MATTHEW PORTEUS**

- Associate Professor at Divisions of Hematology/Oncology and Human Gene Therapy, Stanford School of Medicine
- Renowned expert in gene editing and bone marrow transplantation

**DAN ANDERSON**

- Associate Professor MIT Koch Institute
- Widely recognized as a leader in development of nanoparticles
- Distinguished early work on CRISPR/Cas *in vivo* delivery

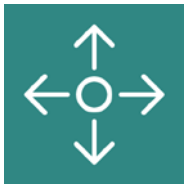
**INVESTORS**

VERSANT ventures
Abingworth partners in life science investing
SR·one™
BAYER
NEA
Celgene
VERTEX

**STRATEGY** PROGRAMS INTELLECTUAL PROPERTY FINANCES

# Corporate and Business Strategy

**Creating transformative gene-based medicines for serious human diseases**



## FOCUS ON THE HEMATOPOIETIC SYSTEM THROUGH *EX VIVO* APPROACHES

- Rapidly advance lead programs in beta-thalassemia and sickle cell disease
- Leverage our hematopoietic *ex vivo* gene editing capabilities in other indications

## PURSUE SELECT INDICATIONS REQUIRING *IN VIVO* APPROACHES

- Target the liver using readily available delivery technologies
- Optimize delivery technologies for indications outside the liver (e.g., musculoskeletal)

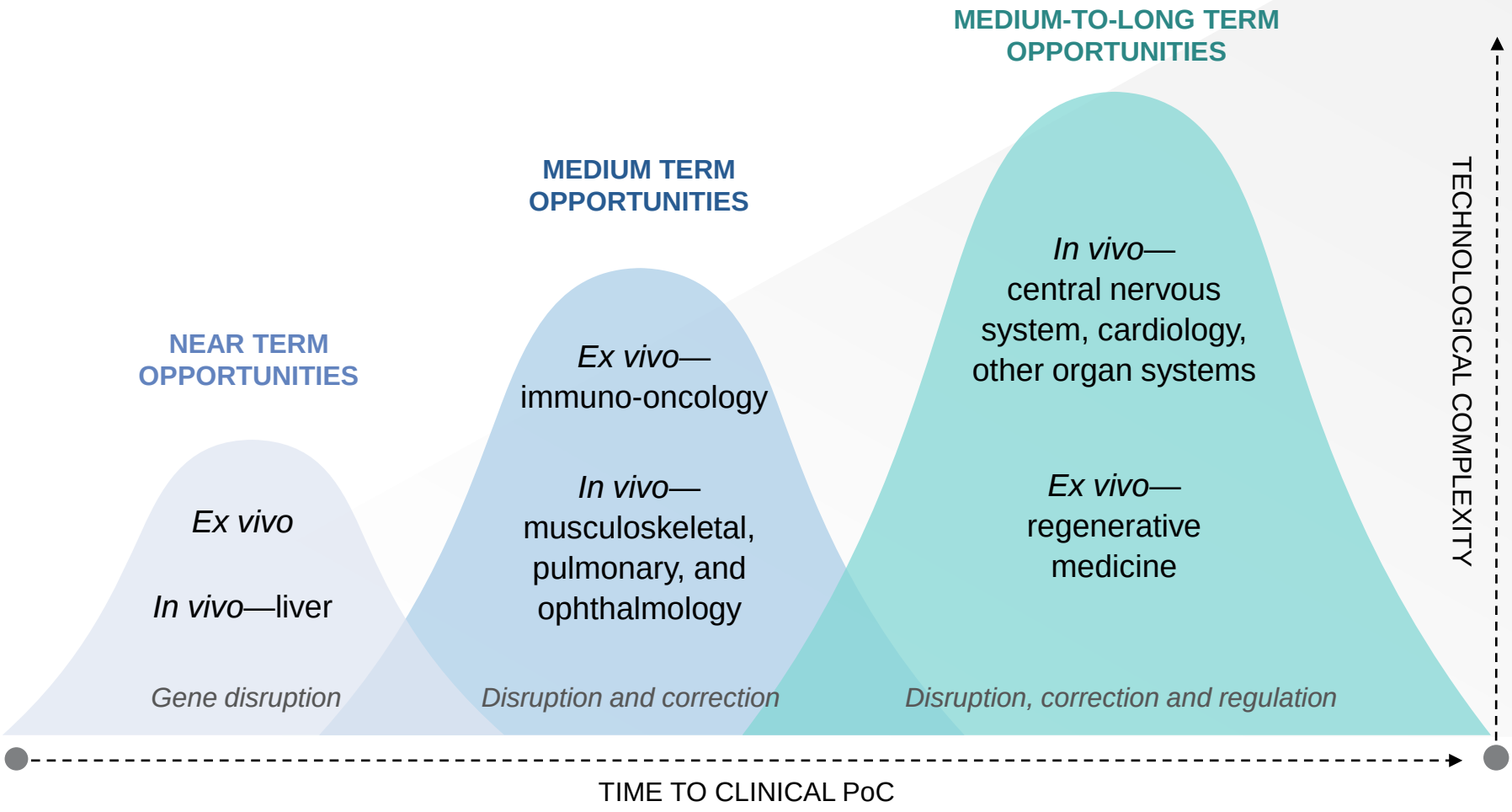
## FOSTER AND LEVERAGE OUR COLLABORATIONS WITH BAYER AND VERTEX

- Broaden our ability to pursue additional indications beyond our lead programs
- Access expertise in hemophilia (Bayer), cystic fibrosis (Vertex), and other areas

## ADVANCE OUR LEADING POSITION IN THE FIELD OF GENE EDITING

- Invest in the enhancement of our CRISPR/Cas9 platform
- Collaborations bring resources and expertise for platform enhancement

# Progression of CRISPR/Cas9 Applications



# Leading Partnerships with Bayer and Vertex

**GIVEN THE IMMENSE POTENTIAL OF CRISPR/CAS9, WE PARTNERED TO:**

- Broaden the range of indications we can simultaneously pursue
- Access industry-leading expertise and enabling technologies in specific therapeutic areas
- Increase our ability to invest in platform enhancements to support our programs

BAYER × CRISPR THERAPEUTICS

CASEBIA

- Joint venture - Casebia Therapeutics, 50-50 ownership
- $70M up-front and $35M in IPO to CRISPR Therapeutics, $265M committed JV funding
- High-complexity, high-reward disease areas – hematology, ophthalmology, cardiology
- Access to protein engineering, delivery technology, and therapeutic-area expertise

VERTEX

- $105M up-front, $2.5B+ in potential milestones, plus royalties and research funding
- Co-development/co-commercialization of hemoglobinopathies; 50-50 profit split; CRISPR lead commercializing party in the US
- Research collaboration on cystic fibrosis and additional undisclosed targets

# High-Level View of Our Portfolio

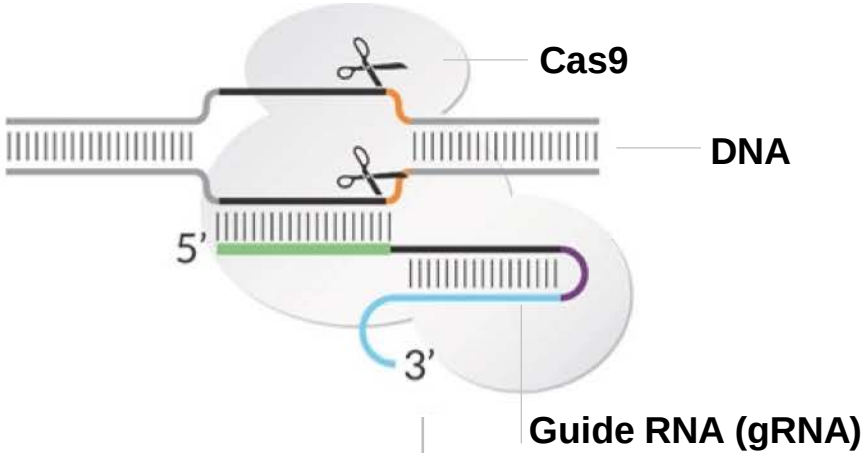
= Fully CRISPR owned
= Co-owned
= Out-licensed

| | HEMATOPOIETIC SYSTEM | LIVER DELIVERY | OTHER ORGAN SYSTEMS |
|---|---|---|---|
| CRISPR THERAPEUTICS | Hemoglobinopathies[1] | | |
| | Hurler syndrome (MPS-1) | Glycogen storage disease Ia (GSD Ia) | |
| | Immuno-oncology | | Duchenne muscular dystrophy (DMD) |
| CASEBIA | Severe combined immuno-deficiency (SCID) | Hemophilia | |
| | | | Other programs (ophthalmology, cardiology) |
| VERTEX | | | Cystic Fibrosis (CF) |
| | | | Other programs (not disclosed) |

1. 50-50 Co-development and co-commercialization with Vertex

STRATEGY **PROGRAMS** INTELLECTUAL PROPERTY FINANCES

# CRISPR/Cas9 Mechanism of Action




**DISRUPTION**

Hemoglobinopathies

Immuno-oncology

DMD

**CORRECTION**

Hurler syndrome

SCID

GSD Ia

Hemophilia

Cystic fibrosis

**GENE REGULATION**

Future programs

# CRISPR: Transformative Gene Editing Platform

## Efficient

- **Rapid guide RNA selection** given ease of design and testing
- **Durability of edits** opens potential for curative therapies

## Specific

- **Single DNA base-pair resolution** in cutting possible
- **Robust DNA-RNA base pairing** drives specificity
- **Ability to rapidly screen** for gRNAs without ‘off-target’ cutting

## Versatile

- **Disruption, correction, and gene regulation** all possible
- **Ability to ‘multiplex’,** or edit multiple genes at once

**Successful clinical translation will require expertise in:**

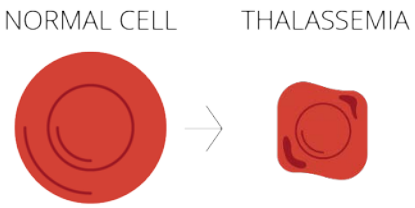
- Effective delivery of nucleic acids and proteins
- Pharmacology models for gene-based therapies
- GMP manufacturing of nucleic acids, viral vectors, and/or modified stem cells

# Our Current Product Development Pipeline

| PROGRAM | EDITING APPROACH | RESEARCH | IND ENABLING | PH I/II |
|---|---|---|---|---|
| ***Ex vivo:* Hematopoietic** | | | | |
| Beta-thalassemia | Disruption | | | *IND/CTA filing in late 2017* |
| Sickle cell disease (SCD) | Disruption | | | |
| Hurler syndrome (MPS-1) | Correction | | | |
| Severe combined immunodeficiency (SCID) | Correction | | | |
| Immuno-oncology | Various | | | |
| ***In vivo:* Liver** | | | | |
| Glycogen storage disease Ia (GSD Ia) | Correction | | | |
| Hemophilia | Correction | | | |
| ***In vivo:* Other organs** | | | | |
| Duchenne muscular dystrophy (DMD) | Disruption | | | |
| Cystic fibrosis (CF) | Correction | | | |

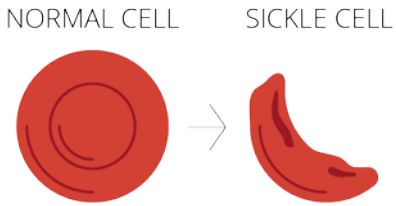
# Hemoglobinopathies – Red Blood Cell Disorders

## BETA-THALASSEMIA




- Significant worldwide burden (60,000 births annually)
- Caused by a variety of different genetic mutations
- Severe cases have debilitating symptoms (anemia, heart failure)
- High burden of patient care (frequent transfusions, allo-HSCT)

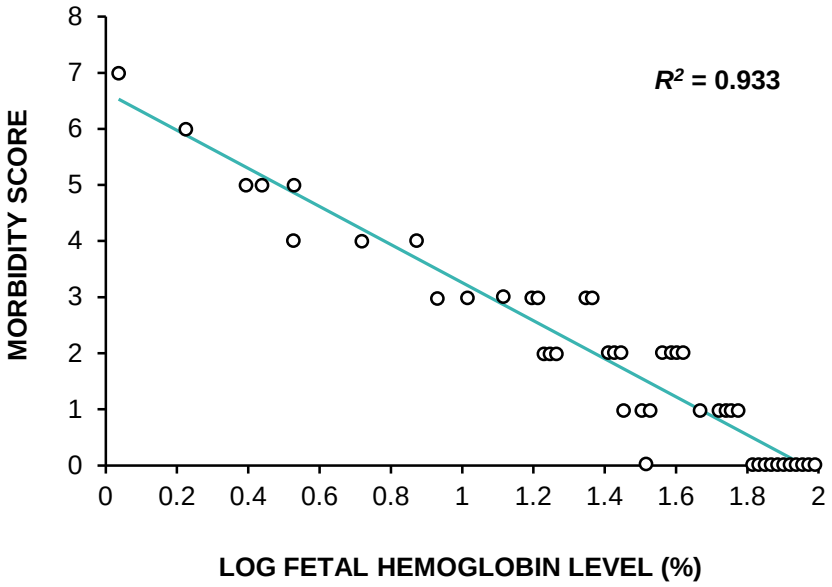
## SICKLE CELL DISEASE



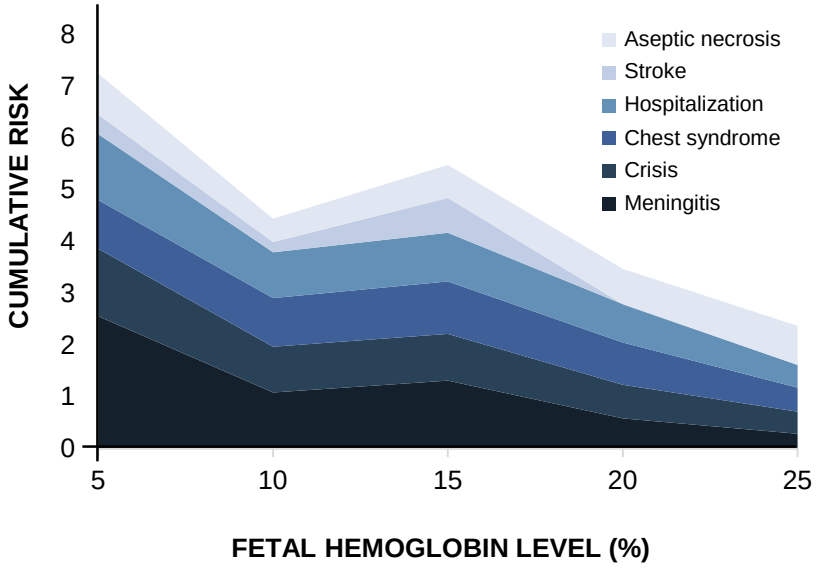

- Significant worldwide burden (300,000 births annually)
- Caused by a single DNA base pair mutation
- Devastating morbidity & mortality (anemia, pain, early death)
- High burden of patient care (sickle cell crises, chronic morbidity)

# Increased Fetal Hemoglobin Alleviates Symptoms

**BETA-THALASSEMIA**
reduced symptoms[1]




**SICKLE CELL DISEASE**
reduced symptoms[2]




- Genetic variants occur naturally that cause HbF to persist into adulthood, which alleviate symptoms in patients with Beta-thalassemia and sickle cell
- Our gene editing strategy aims to recreate these variants in symptomatic patients — an approach supported by well-understood genetics

1. Musallam et al. Blood 2012; 2. Powars et al., Blood 1984

# IND-enabling Studies are Currently Underway

= data follows

**1**

***IN VITRO***
**PROOF-OF-CONCEPT**

- Desired gene edits can be made with high efficiency
- Off-target cutting activity not detectable above threshold
- Edits cause healthy and patient-derived cells to produce HbF

**2**

***IN VIVO***
**ENGRAFTMENT STUDIES**

- Test ability of edited cells to repopulate in immuno-compromised mouse model
- Assess homing to the marrow, engraftment and differentiation of edited cells
- Ensure effect is stable and durable

Today

**TARGET IND/CTA IN LATE 2017[1]**

**GLP / TOXICOLOGY STUDIES**

- Determine whether edited cells cause any adverse effects
- Determine risk for toxicity and tumorigenicity

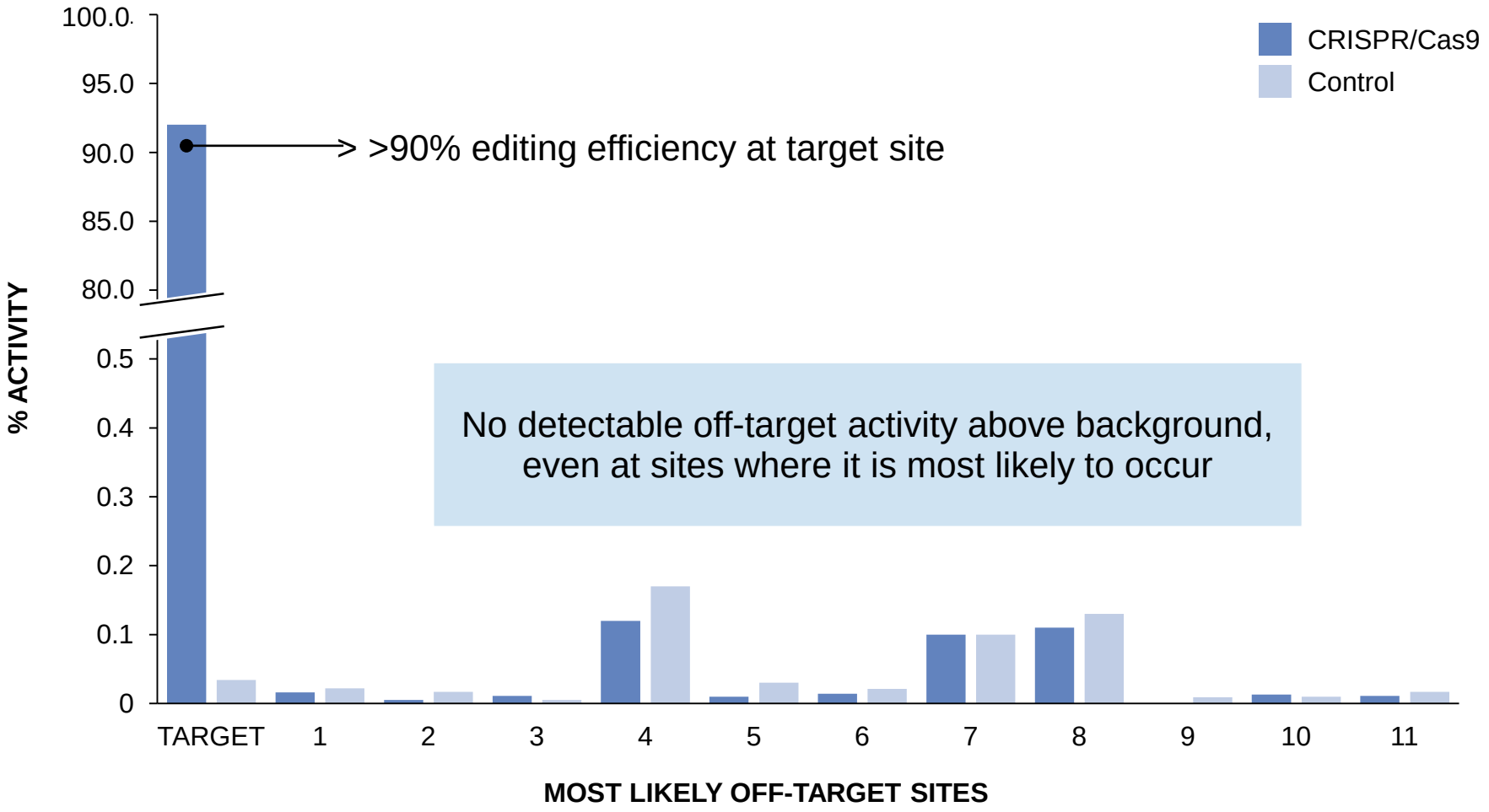
**3**

**Process development and manufacturing**

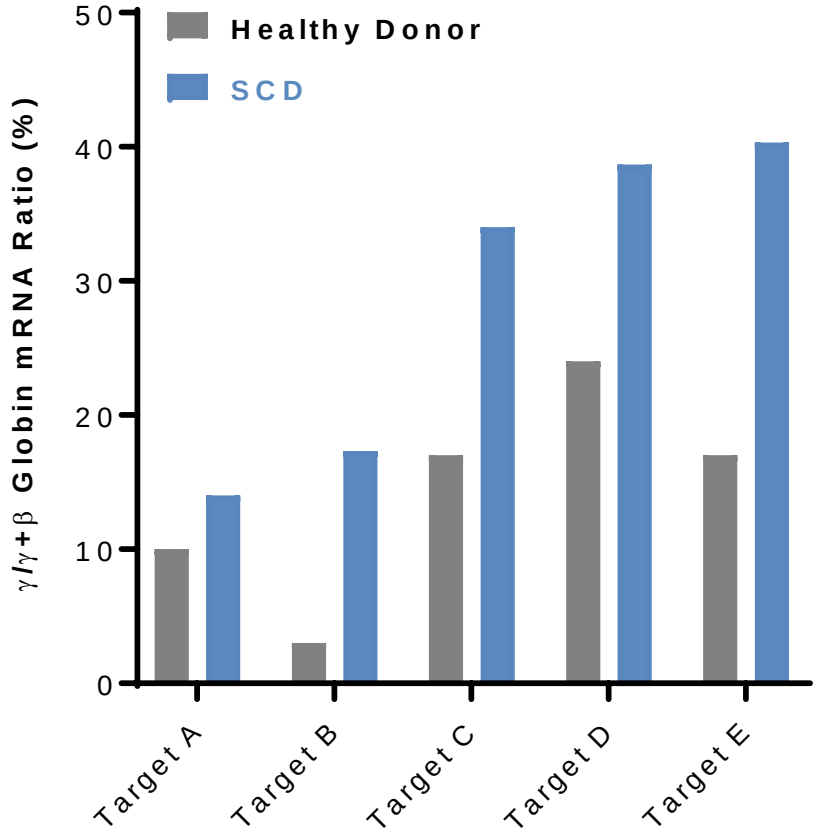
(Process development for GMP manufacturing of human $CD34^+$ cells, Cas9 and guide RNAs on-going)

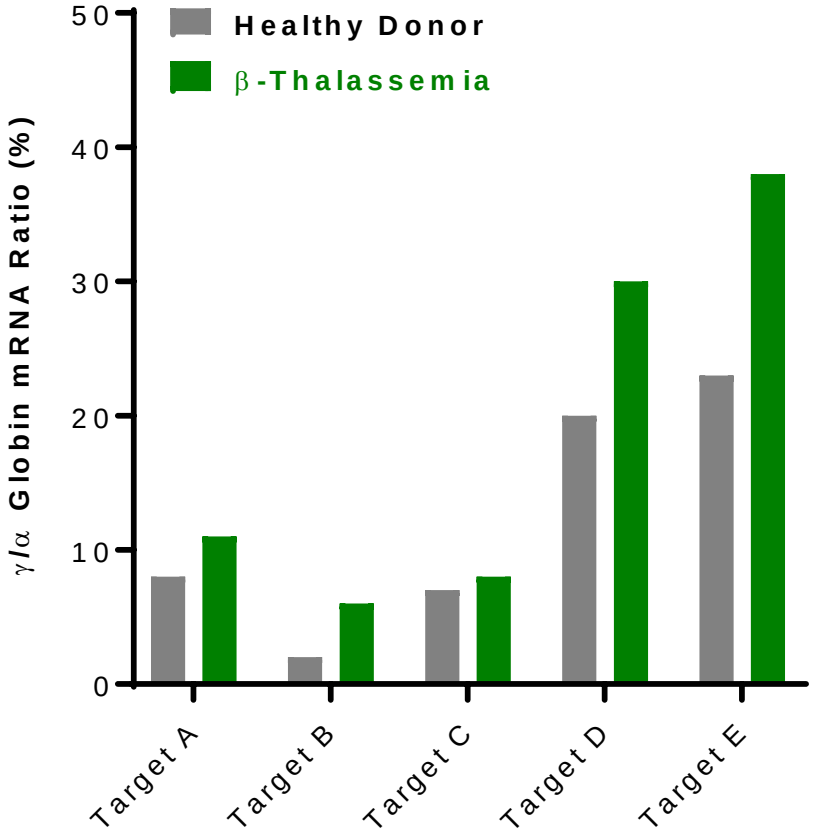
1. IND/CTA Filing For Beta-thalassemia

# 1 Candidate Guides are Efficient and Specific



# 1 Natural Variants Reactivate HbF in Patient Cells



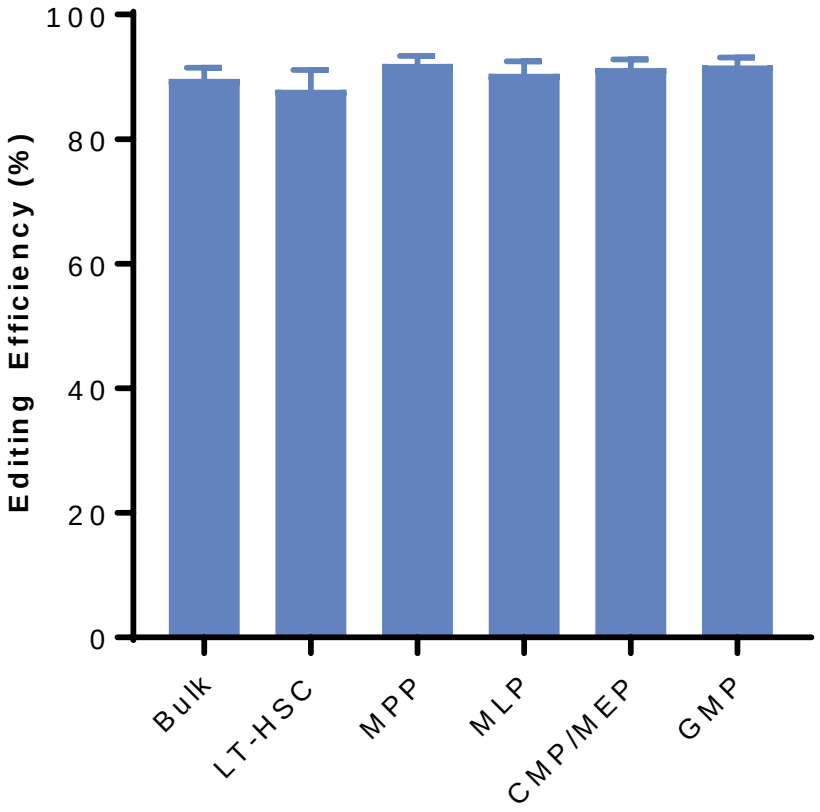




- Several target edits cause significant levels of HbF mRNA to be produced in erythroid cells
- HbF upregulation is more pronounced in SCD and β-thal patient-derived cells

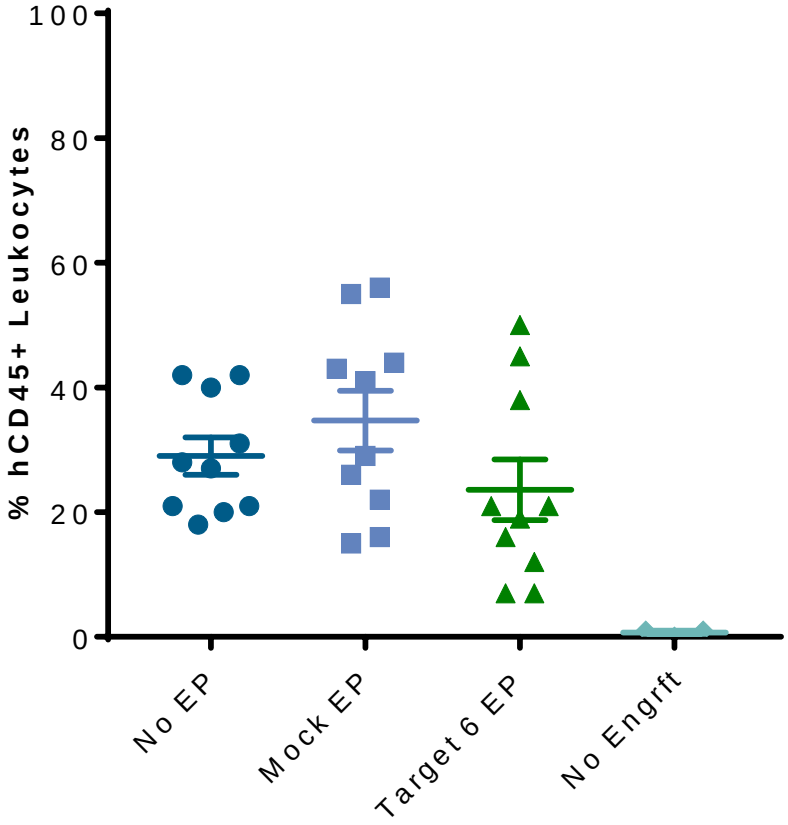
Data presented at ASH Annual Meeting (Dec 2016)

# 2 Edited cells have engraftment potential

**Long-term stem cells (LT-HSC) are edited at high-efficiency, comparable to other subsets …**

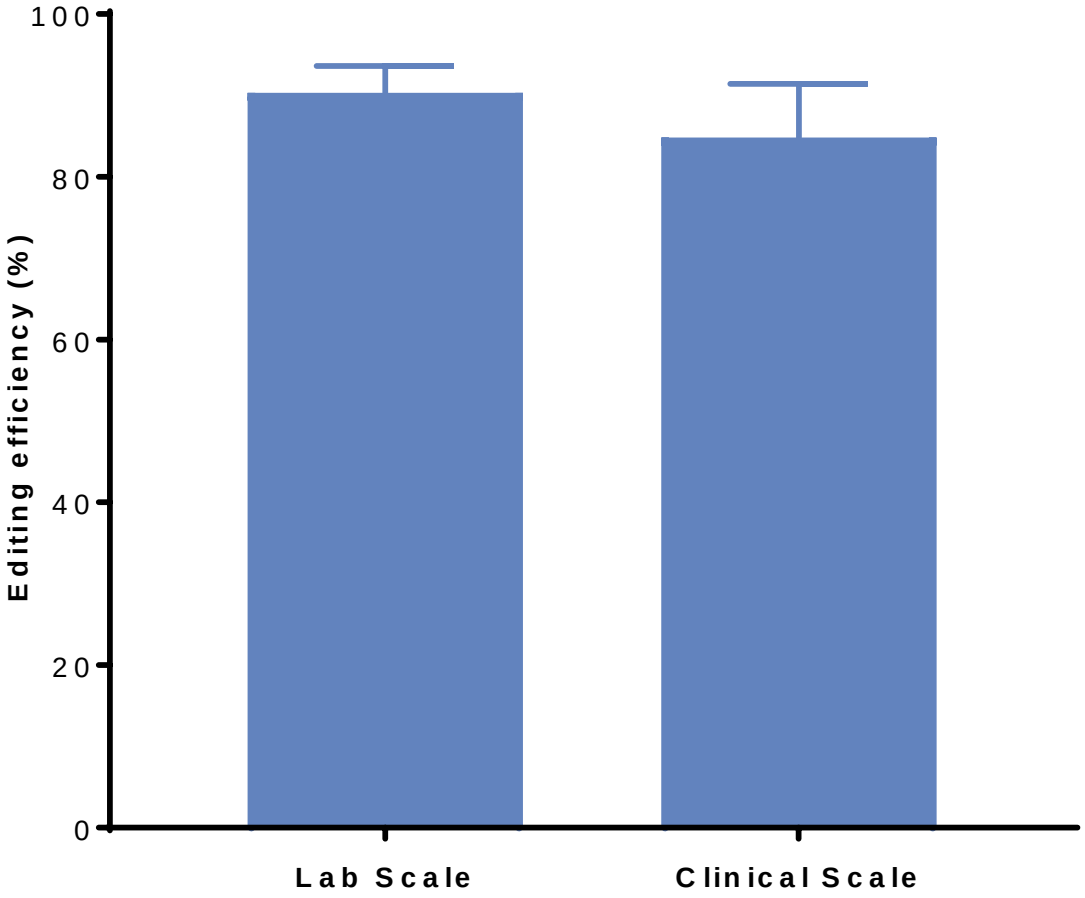



**… and retain the ability to engraft and repopulate in mice**




Data presented at ASH Annual Meeting (Dec 2016)

# 3 Editing is highly efficient at clinical scale




Data presented at ASH Annual Meeting (Dec 2016)

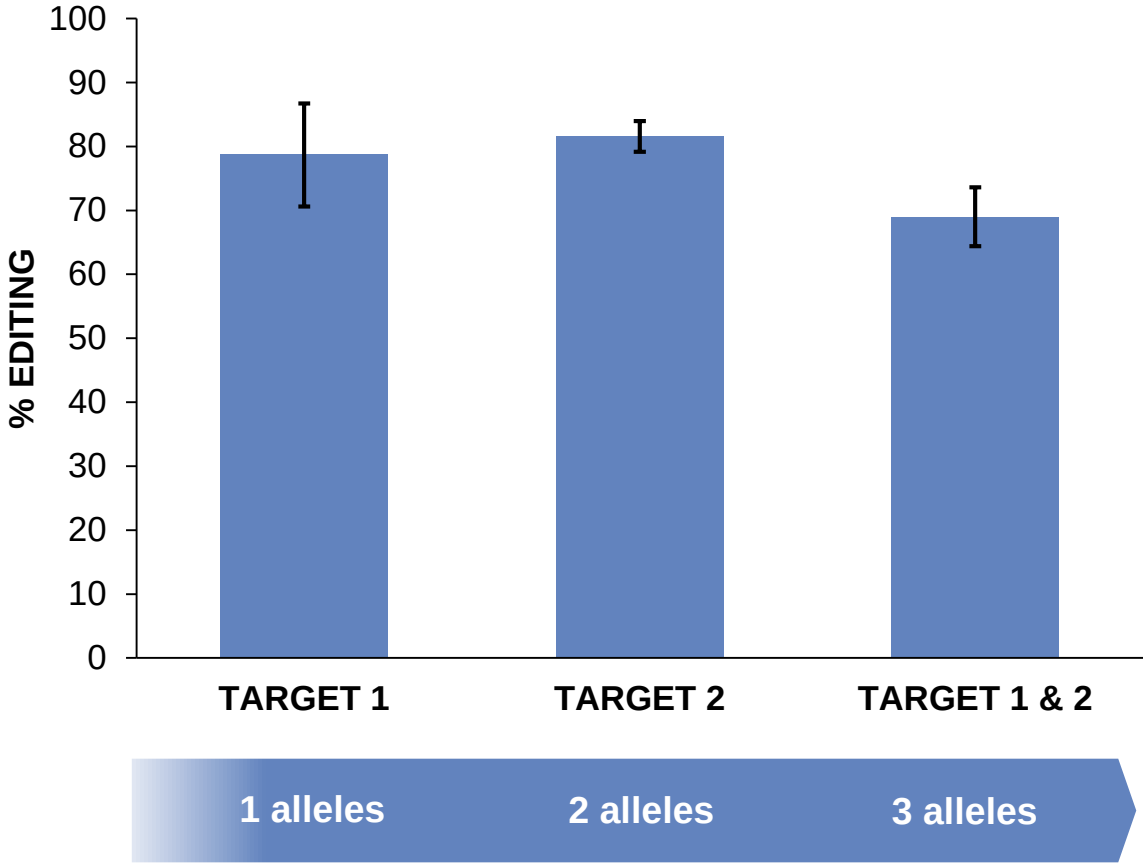
## IND/CTA preparation updates

- Processes successfully transferred to a GMP-capable facility
- Multiple clinical-scale runs completed with no significant loss of efficiency versus lab scale
- GLP/toxicology studies initiated - biodistribution and general toxicology studies in NSG mice

# Gene Editing in T-cells: Immuno-Oncology

**MULTIPLEX EDITING EFFICIENCY FOR ALLOGENEIC T-CELL THERAPIES**

% human primary T-cells negative for target after editing




**Advantages over other editing approaches (e.g., TALENs)**

- Higher efficiency than published reports
- Ability to multiplex larger numbers of edits
- Allows more rapid testing of various genetic edits
- More straightforward to engineer and apply

# *In Vivo* and *Ex Vivo* Gene Editing: Duchenne Muscular Dystrophy (DMD)

### *IN VIVO* APPROACH

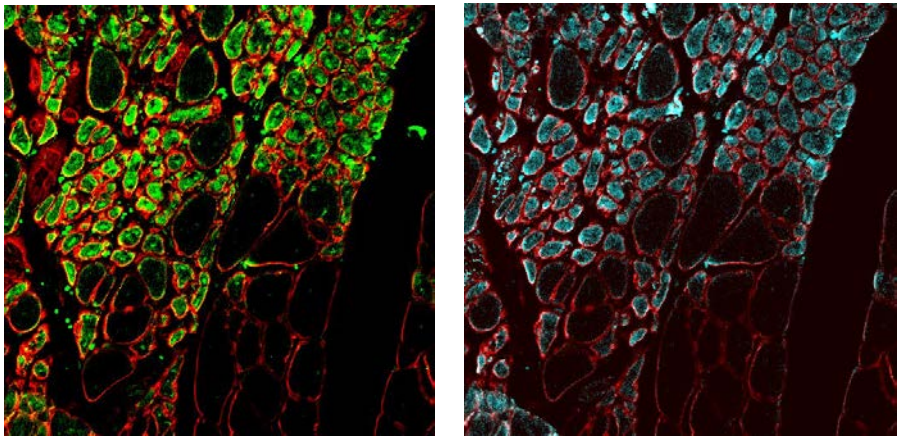
- Administration of Cas9 nuclease and guide RNAs via delivery vectors to generate functional form of dystrophin gene
- Similar to AAV gene therapy approaches in development, with potentially higher potency and durability of gene editing

### *EX VIVO* APPROACH

- Exclusive license to Anagenesis P2MC Muscle Stem Cell technology
- Approach: DMD patient cells can be re-programmed into stem cells, gene corrected using CRISPR and re-administered

### ANAGENESIS STEM CELL TECHNOLOGY

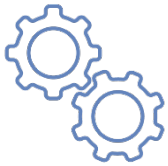
**PoC in *mdx*/Rag Mouse Model**



Laminin GFP  Laminin Dystrophin

- Muscle stem cells (Green) administered to DMD mice generate muscle cells (Red) and express the missing DMD protein dystrophin (Cyan)

# Components of Platform Development

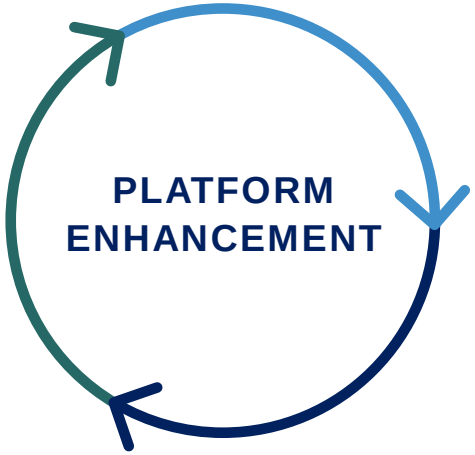


**OPTIMIZATION**

Enhance function of the CRISPR/Cas9 system through protein and nucleic acid engineering

**GUIDE RNA SELECTION**

Identify optimal RNA sequences to guide genomic editing




**CELLULAR ENGINEERING**

Improve power of gene-edited stem cells as a therapeutic strategy

**DELIVERY**

Enhance ability to specifically introduce editing machinery into target tissues

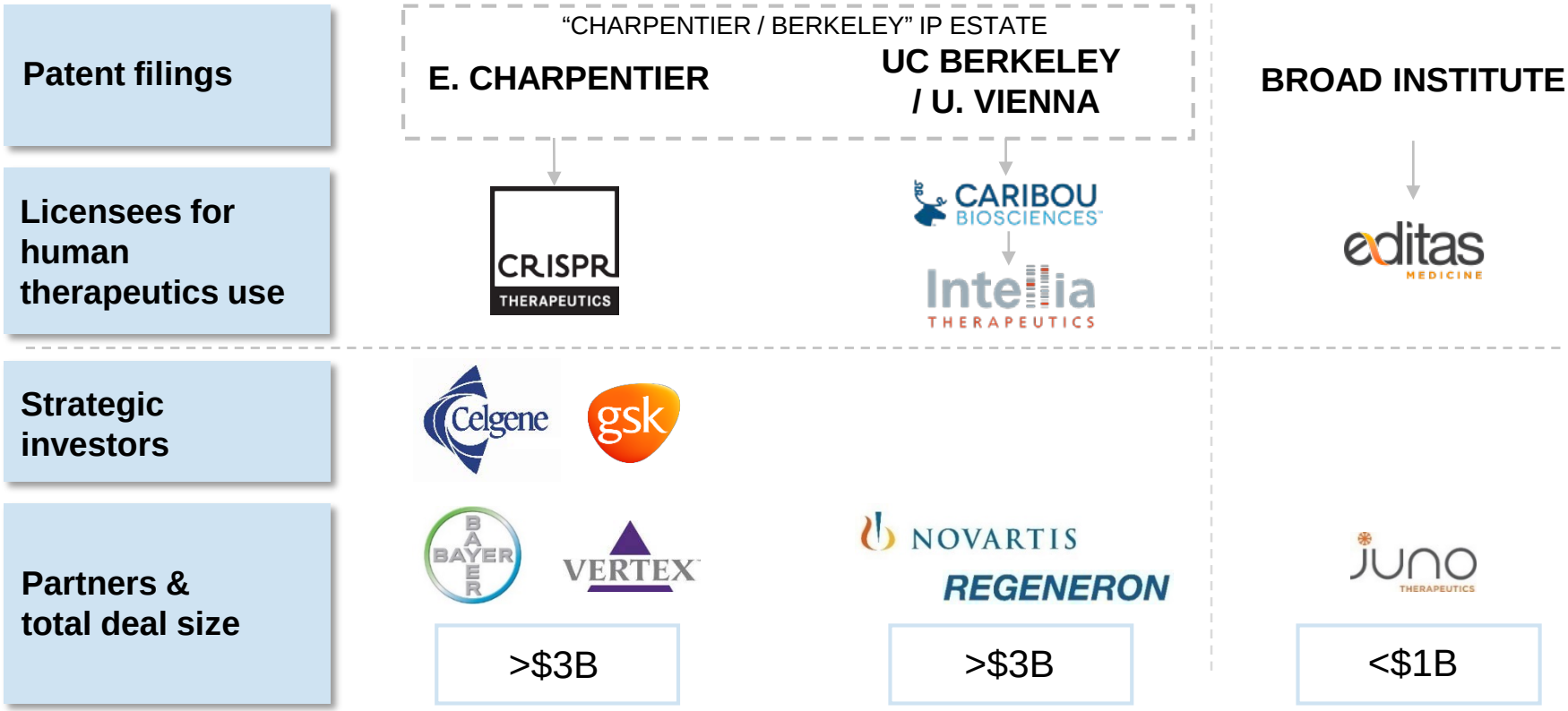
**CORRECTION**

Increase efficiency of gene correction approaches

STRATEGY PROGRAMS **INTELLECTUAL PROPERTY** FINANCES

# Direct Access to Foundational CRISPR IP

## CRISPR IP LANDSCAPE




- Direct license to foundational IP covering all therapeutic fields
- Four large pharma partnerships indicate strength of the Charpentier/Berkeley IP estate
- Potential 20-year patent term through 2033 with possible extensions

# Interference Proceedings: Status and Timeline

**UNITED STATES**

**CASES PROCEEDING UNDER FIRST-TO-INVENT**

**DECEMBER. 23, 2015**
U.S. patent office examiners determined case allowable

**JANUARY 11, 2016**
U.S. interference with Broad cases declared

**2016**
Motions phase of interference now ongoing

**2017**
Priority phase of interference would begin

**YEAR** 2015 2016 2017

**CASES PROCEEDING UNDER FIRST-TO-FILE**

**2016 - 2017**
Advancing European case based on arguments developed in UK

**MARCH 2, 2016**
Accelerated single-guide RNA claims. UK patent granted.

**EUROPE**

In addition to the U.S. and Europe, we are also pursuing extensive global coverage for foundational IP. The PCT and supplemental direct applications cover approximately 80 countries worldwide.

# Strengthening our Intellectual Property Position

## PROGRAM-SPECIFIC IP

- Specific gRNAs, DNA templates and editing strategies
- Methods for treating cells *ex vivo* or formulations for *in vivo* delivery

## SUPPORTING TECHNOLOGIES

- Delivery technologies – viral vectors, lipid nanoparticle
- Technologies to increase gene correction efficiency
- Methods for editing and differentiating stem cells

## CORE PLATFORM IP

- Optimization of CRISPR components, including gRNA modifications and engineered Cas9 variants
- Cas9 orthologs and supporting methods of use

### Strengthening our position through owned patents and in-licensing

- 80+ new patent applications submitted, others in-process
- In-licensing specific technologies (e.g. Anagenesis)
- Continuous enablement of our portfolio

STRATEGY PROGRAMS INTELLECTUAL PROPERTY **FINANCES**

# Strong Financial Position

$97M IPO proceeds
$38M additional equity funding

**IPO & Crossover Investors**

Institutional investors, life sciences specialist funds and strategic partners

$175M raised from partners
($110M non-dilutive, $65M equity)

**Partners**

VERTEX

BAYER

$95M raised from VCs (Series A-B) and insiders

**VC Funding**

VERSANT ventures

NEA New Enterprise Associates

Abingworth investors in life sciences & healthcare

SR·one Unique Insight. Creating value.

Celgene

- Capital raised > $400M;  >$300M current cash position
- Additional funding through milestones, research reimbursements, and $300M Casebia funding
- Cash reach >2 years

CRISPR THERAPEUTICS

# Transformative Gene-based Medicines

for Serious Diseases.

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