CRISPR Therapeutics

Creating transformative gene-based medicines for serious diseases

Corporate Overview

May 2017

Forward Looking Statements

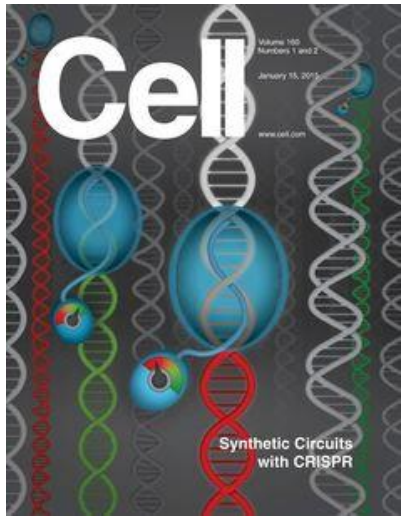
This document contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to statements concerning the timing of our preclinical studies and the intellectual property protection 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 quarterly report on form 10-Q, 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.

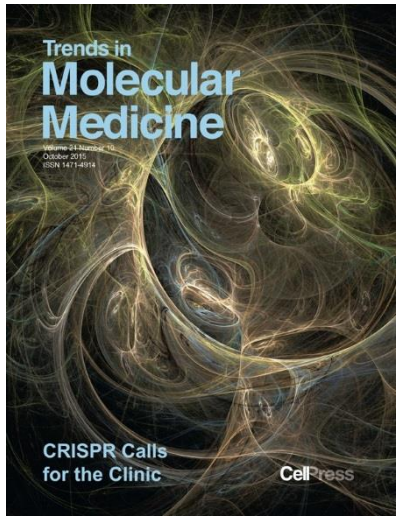
In addition, the forward-looking statements included in this document represent the Company's views as of the date of this document. The Company anticipates that subsequent events and developments will cause its views to change. However, while the Company may elect to update these forward-looking statements 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 & public offering; 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

SAM KULKARNI, PHD
President and Chief Business Officer
Partner, McKinsey & Company

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

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

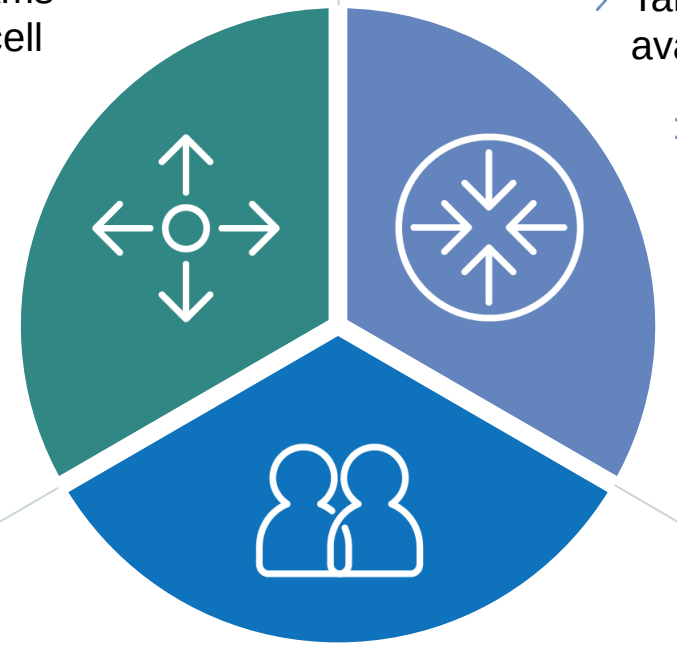
VERSANT ventures
Abingworth partners in life science investing
SR·one™
BAYER
NEA
Celgene
VERTEX

STRATEGY PROGRAMS INTELLECTUAL PROPERTY FINANCES

Differentiated Business Strategy

FOCUS ON *EX VIVO* APPROACHES

- Rapidly advance lead programs in β-thalassemia and sickle cell disease with hematopoietic stem cell editing *ex vivo*
- Leverage our *ex vivo* gene editing capabilities in other indications
- Expand into immuno-oncology through T-cell editing (unencumbered)



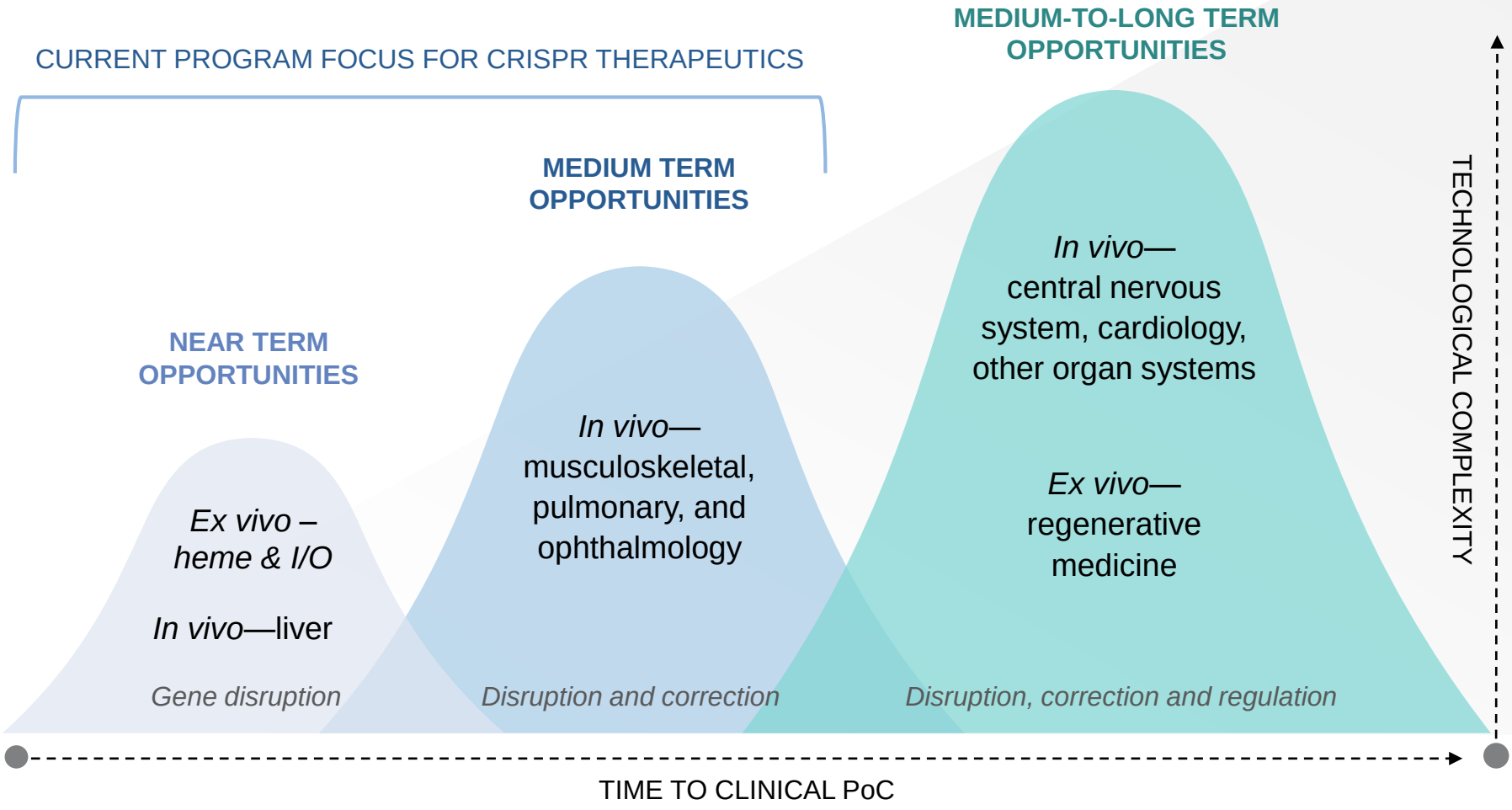
PURSUE SELECT *IN VIVO* APPLICATIONS

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

LEVERAGE CASEBIA (JV WITH BAYER) AND COLLABORATION WITH VERTEX

- Broaden our ability to pursue additional indications beyond our lead programs
- Co-invest with Casebia in delivery and other enabling technologies
- Access expertise in hemophilia (Bayer), cystic fibrosis (Vertex), and other areas

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

- 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

- $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

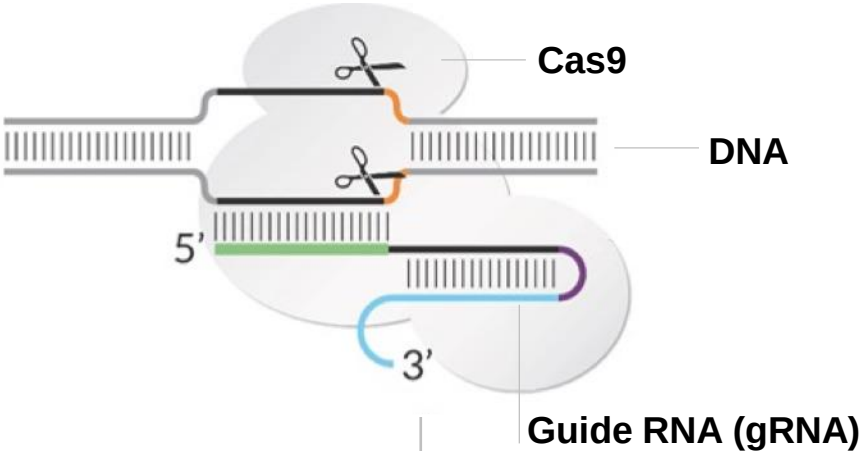
= Fully CRISPR owned
= Co-owned
= Out-licensed

	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 (commercial lead in the U.S.)

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

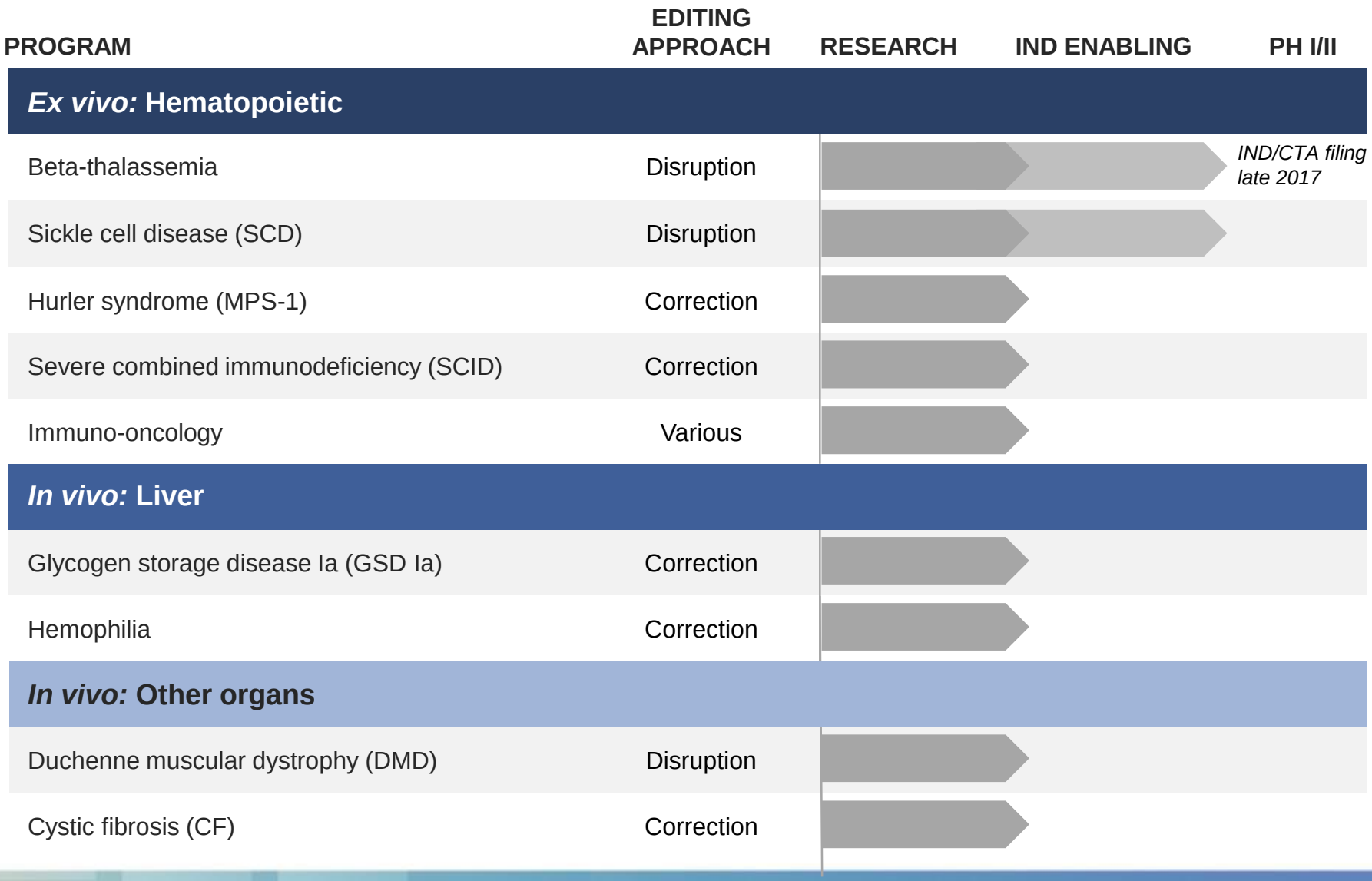
Versatile

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

Successful clinical translation will require expertise in:

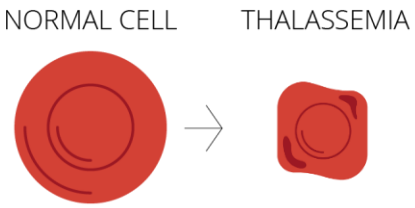
- Effective delivery of nucleic acids and proteins
- Pharmacology models for gene-based therapies
- GMP manufacturing of nucleic acids, viral vectors, and/or modified stem cells

Our Current Product Development Pipeline



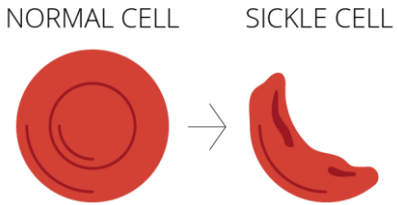
Hemoglobinopathies – Red Blood Cell Disorders

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)

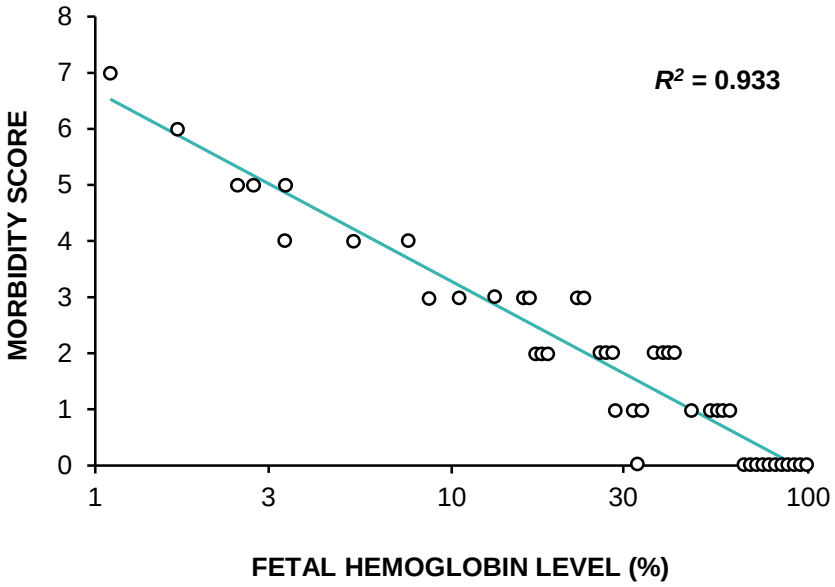
SICKLE CELL DISEASE



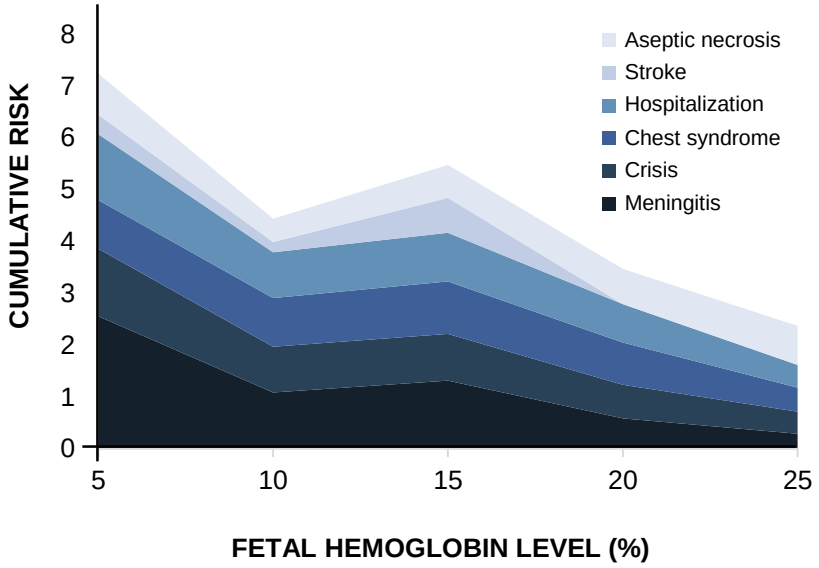
- Significant worldwide burden (300,000 births annually)
- Caused by a single DNA base pair mutation
- Devastating morbidity & mortality (anemia, pain, early death)
- High burden of patient care (sickle cell crises, chronic morbidity)

Increased Fetal Hemoglobin Alleviates Symptoms

BETA-THALASSEMIA
reduced symptoms[1]



SICKLE CELL DISEASE
reduced symptoms[2]

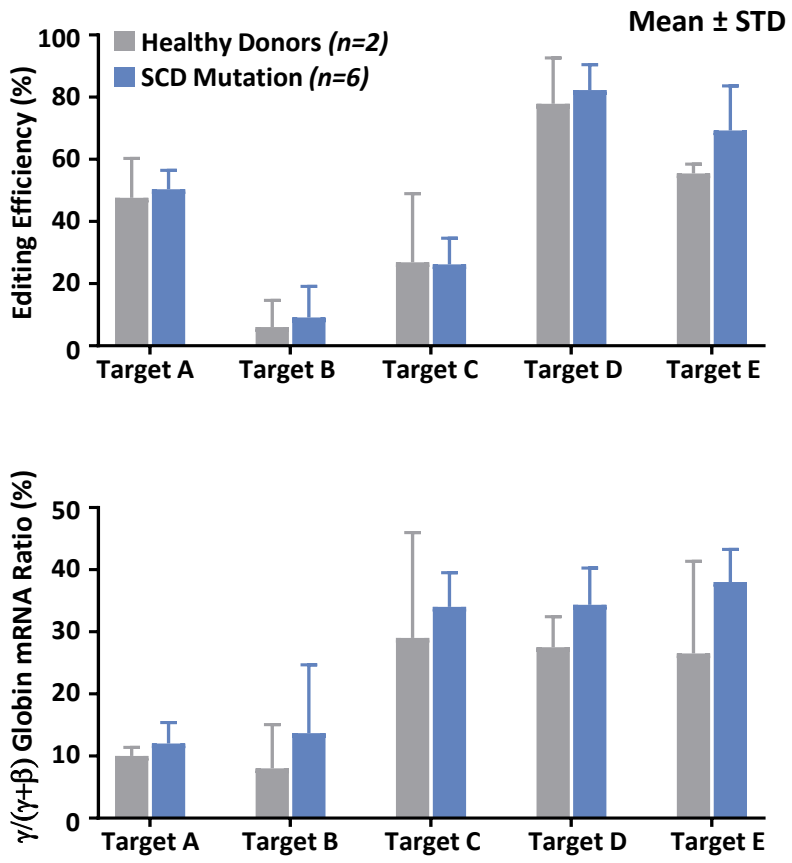


- Genetic variants occur naturally that cause HbF to persist into adulthood (hereditary persistence of fetal hemoglobin), which alleviate symptoms in patients with β-thalassemia and sickle cell
- Our gene editing strategy aims to recreate these variants in symptomatic patients — an approach supported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

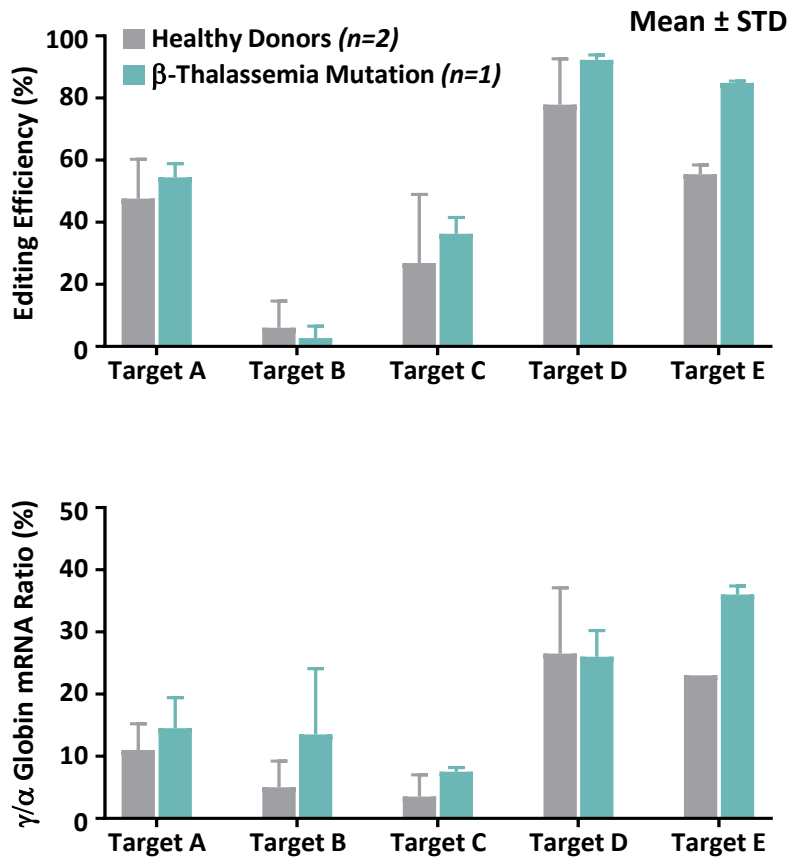
1. Musallam et al. Blood 2012; 2. Powars et al., Blood 1984

CRISPR to Re-Create HPFH Variants and Reactivate HbF

Sickle Cell and Healthy Donor



β-thalassemia and Healthy Donor



› *High γ-globin expression upon erythroid differentiation*

IND/CTA-enabling Studies Currently Underway

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

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 CTA IN LATE 2017[1]

GLP / TOXICOLOGY STUDIES

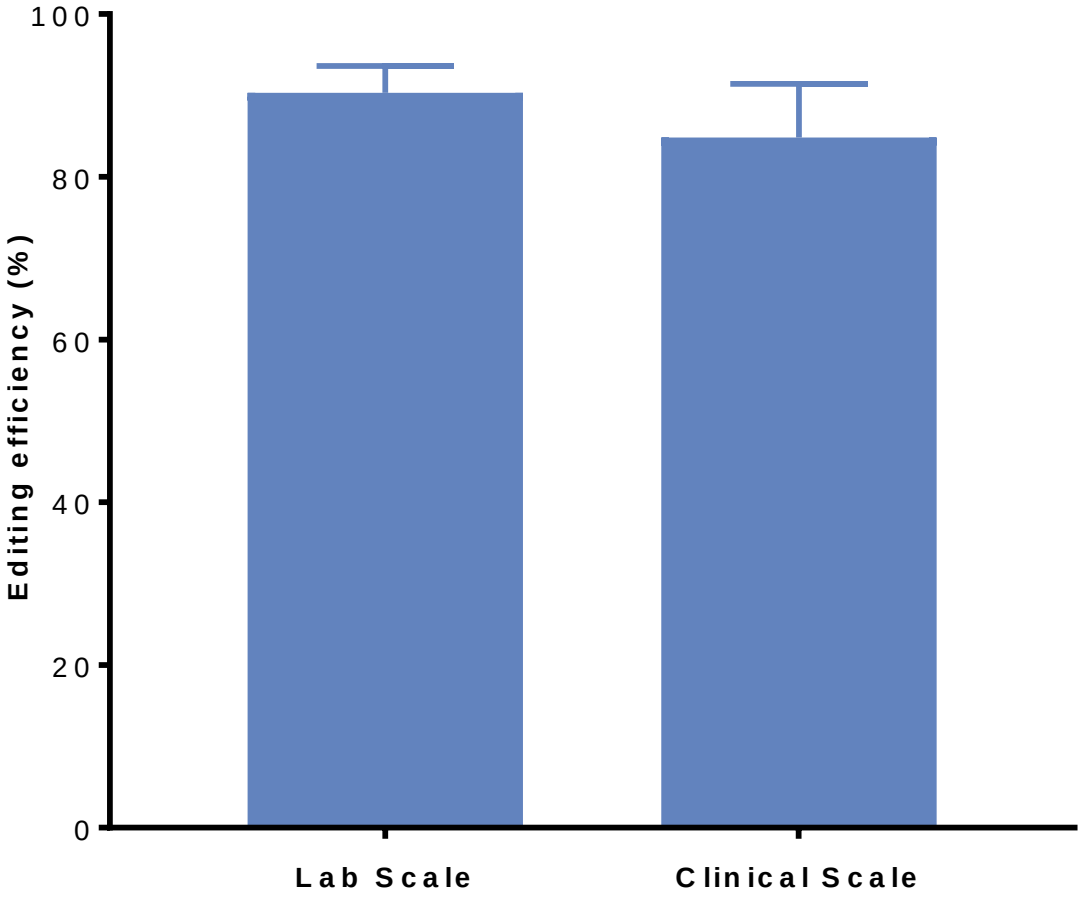
- Determine whether edited cells cause any adverse effects
- Determine risk for toxicity and tumorigenicity

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; CTA (Clinical Trial Application)

Editing is Highly Efficient at Clinical Scale



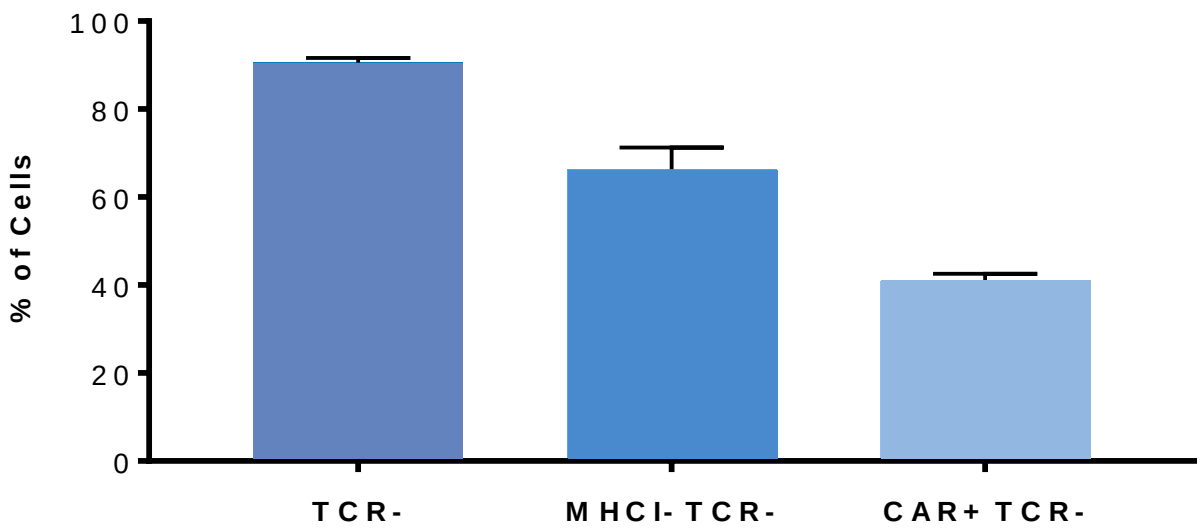
IND/CTA preparation updates

- 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

Data presented at ASH Annual Meeting (Dec 2016)

First CRISPR Allogeneic CAR-T Construct

MULTIPLEXED CRISPR/Cas9 GENE INSERTION AND DISRUPTION IN HUMAN PRIMARY T-CELLS



- **25%** of cells **TCR- MHCI- CAR+**
- Achieved in **single electroporation**
- Sufficient editing level for **efficient manufacturing**

- **Knock-out TCR** to prevent GvHD
- High efficiency **~90%** knock-out increases safety

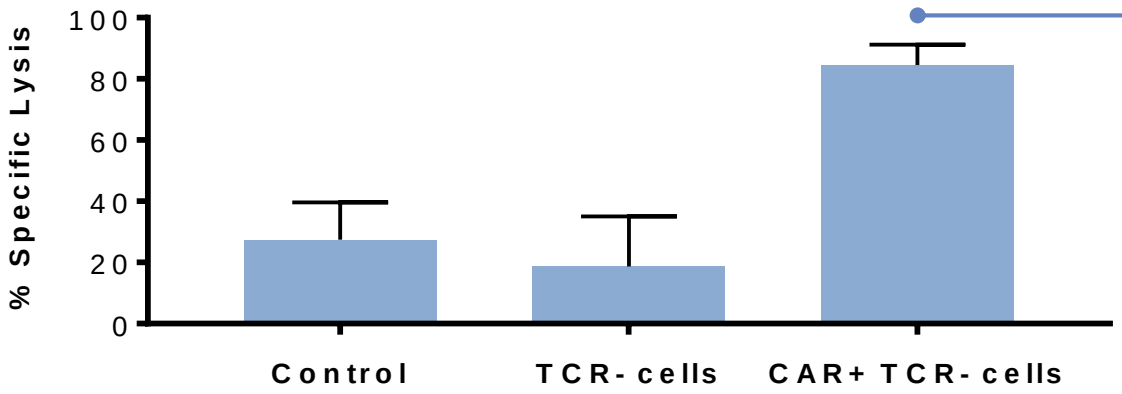
- **Knock-out MHC I** to increase persistence
- **~65%** of cells resistant to host immune clearance

- **Insert CAR site-specifically** to increase safety and potency
- **~40%** of cells CAR positive, higher than reported lentiviral rates

CAR-T Cells Are Functional in *In Vitro*

CRISPR CAR-T CELLS KILL TUMOR CELLS …

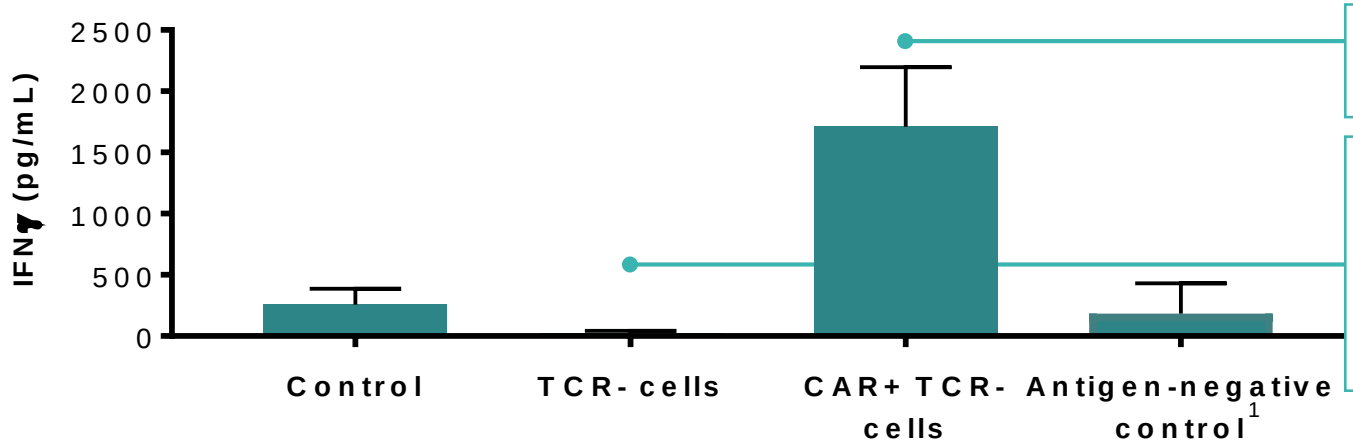
% lysis of tumor cells (average of 3 independent experiments with 2 separate donors)



Robust tumor cell lysis by CAR-T cells

… AND SECRETE INTERFERON ONLY UPON ANTIGEN+ CELL ENGAGEMENT

IFNγ secretion (average of 3 independent experiments with 2 separate donors)



Strong IFN secretion by CAR-T cells

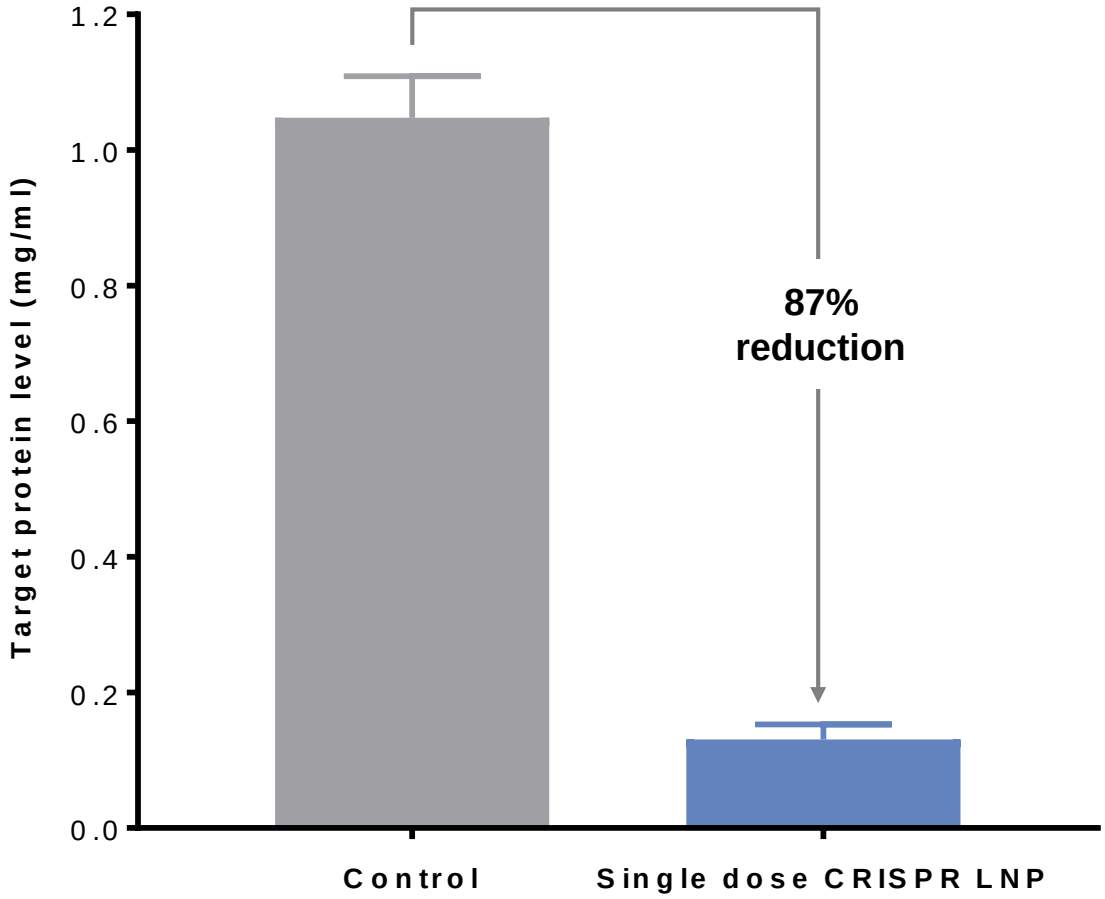
IFN drop after TCR KO may correlate with lower non-specific T-cell activity – i.e., reduced GvHD

1. CAR+ TCR- T-cells against antigen-negative cell line (2 independent experiments with 2 separate donors)

In Vivo Delivery of CRISPR/Cas9 Using Lipid Nanoparticles

***IN VIVO* EDITING IN MOUSE LIVER VIA LIPID NANOPARTICLES (LNPs)**

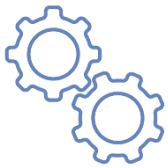
Serum level of target protein 72 hours after dosing



LNPs being optimized for delivery to liver

- LNPs from various sources tested and optimized LNP from MIT licensed exclusively
- LNPs do not provoke an immune response, increasing safety and making repeat dosing possible
- Effect achieved at therapeutically-relevant doses

Components of Platform Development

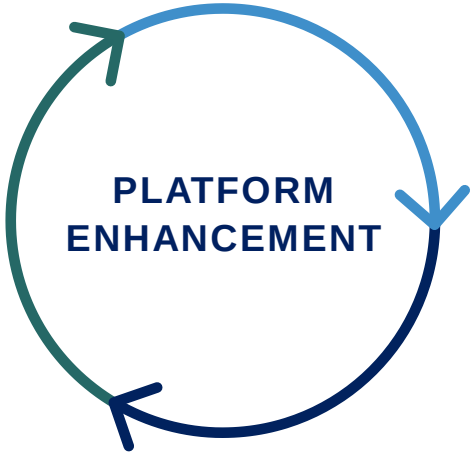


OPTIMIZATION

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

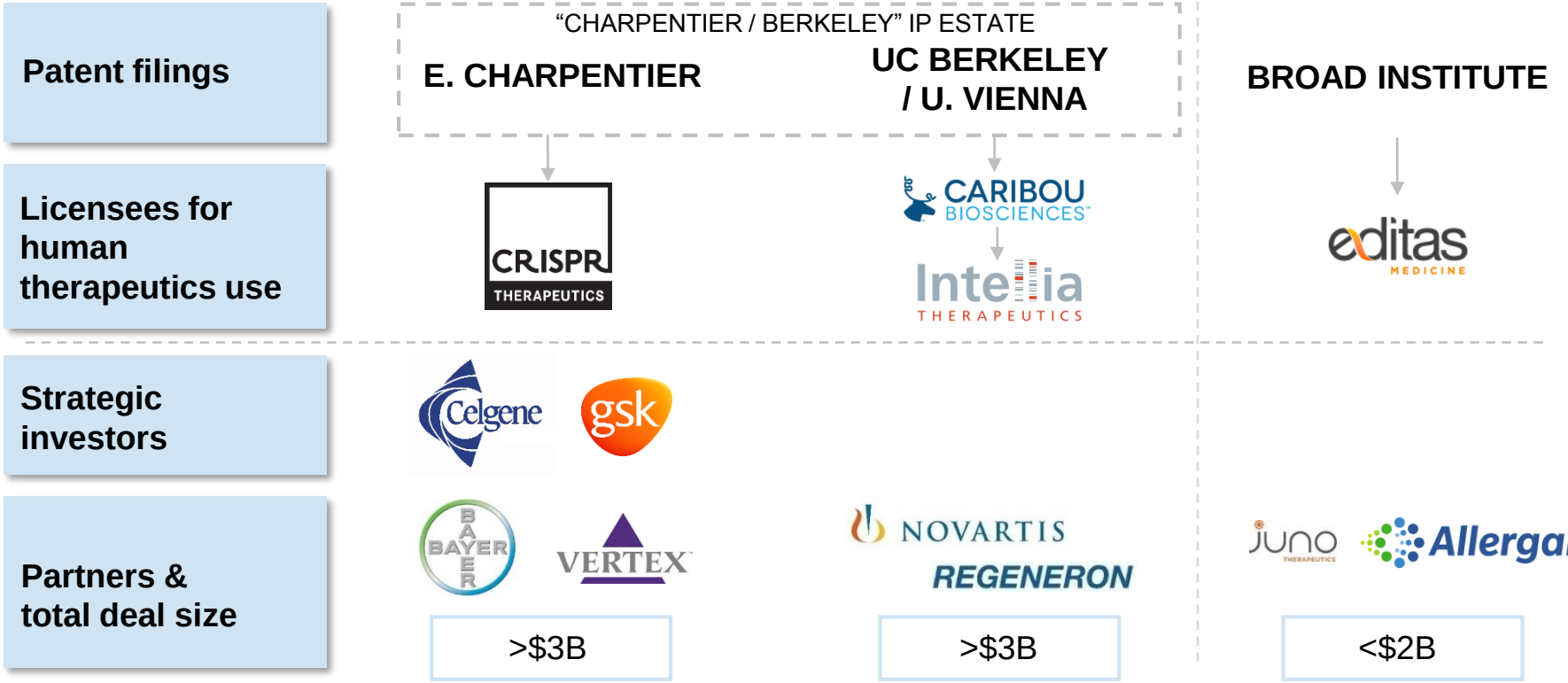
CORRECTION

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 human therapeutic fields; Patent term through 2033
- Four large pharma partnerships indicate strength of the Charpentier/Berkeley IP estate
- Access to Vilnius IP estate through Invention management agreement

Global Patent Coverage

EUROPE AND OTHER JURISDICTIONS: COMMANDING IP POSITION

- **Mar. 2016:** First U.K. patent awarded to UC-CRISPR (Patent #2518764)
- **Feb. 2017:** Second U.K. patent granted to UC-CRISPR (Patent #2537000)
- **May. 2017:** E.U. patent granted to UC-CRISPR (Appl. #13793997)

E.U. and U.K. patents

Foundational patents in E.U. and U.K. to UC-CRISPR including use in Eukaryotes

- E.U. and U.K. patents granted in spite of multiple Third Party Observations (TPOs) by Broad *et al.*
- Patents include single-guide RNA and uses in all settings (incl. eukaryotic cells)
- Broad's related E.U. patents have been opposed by numerous parties

Other jurisdictions

Advancing in other jurisdictions based on arguments developed in E.U. and U.K.

- Corresponding applications are being advanced globally based on E.U. and U.K. patents, portfolio includes 80 jurisdictions worldwide
- Wide-ranging patent granted in China

U.S. Patent Coverage

UNITED STATES: CASES PROCEEDING UNDER FIRST-TO-INVENT

- **Dec. 2015:** U.S. patent office examiners determined case allowable
- **Jan. 2016:** U.S. interference with Broad Inst. cases declared
- **Feb. 2017:** First interference ended on technical grounds (UC-CRISPR claims are broader in scope)
- **Apr. 2017:** UC-CRISPR appeals interference decision in Federal Appeals Court

CRISPR/Cas for genome editing in Eukaryotic cells

UC-CRISPR's claims in all cell types:

- UC-CRISPR has patent applications covering uses of CRISPR/Cas gene editing not limited by cellular environment
- Broad Inst. purposely limited their claims to uses in eukaryotes and argued 'no interference'
- Third party claims on use in Eukaryotes rejected citing prior art of Charpentier/Doudna

Path Forward

Appeal Interference and Parallel Prosecution:

- Appeal Board decision in Federal Appeals Court (expected ~12-18 months)
- Pursuing multiple patent applications in parallel – both narrow and broad claims

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, MaxCyte, StrideBio, MIT)
- 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; ~$289M 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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