Beam Therapeutics and Base Editing

▸ A new approach to genome editing
  – Single base editing precision (A, C, G, T)
  – No cutting of DNA or RNA strands
  – Enables diverse therapeutic strategies

▸ Singular leadership position in base editing
  – World class founding and management team
  – IP leadership including licenses from Harvard, Broad, and Editas Medicine
  – $87M Series A and $135M Series B

▸ Rapidly emerging pipeline of base editing programs
  – 10 active programs
  – All major delivery technologies (ex vivo, LNP, AAV)
  – Potential for initial wave of multiple IND filings
The power of a single letter

>3 Billion bases (A, G, C, T) in the human genomic code

Even a single letter can be the difference between health and disease
The power of a single letter

Other genetic variations – also often single base changes – are known to **protect against disease**

**OVER HALF** of genetic changes driving disease are **POINT MUTATIONS**

**Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease**
Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

**A Protein-Truncating HSD17B13 Variant and Protection from Chronic Liver Disease**

**Gene mutation defends against Alzheimer’s disease**
Rare genetic variant suggests a cause and treatment for cognitive decline.
A new approach to genome editing

Nuclease editing
- Creation of double-strand DNA break at a target location to disrupt, delete, or insert gene sequences

Base editing
- Direct conversion of one base pair to another at a target location, without double-strand breaks
Base editing – a new way of editing using CRISPR

- Base editors use **separate targeting and editing elements** to improve control and specificity
  - Modified CRISPR → guide RNA-driven targeting
  - Tethered deaminase → single base editing

- **Modular system** allows mixing & matching of elements

- **Key advantages:**
  - Highly efficient editing (30-90%)
  - Low level of insertions/deletions (<1-5%)
  - Activity in dividing and non-dividing cells
  - No need for delivering DNA template
Base editing enables diverse therapeutic strategies

- **Gene Correction**: Direct correction of point mutations. Insertion of protective mutations or clinical variants.
- **Gene Regulation**: Editing regulatory elements to raise/lower gene expression.
- **Gene Silencing**: Introduction of STOP codons or disruption of splice sites.
- **Gene Reprogramming**: Changing protein function (binding, catalysis, signaling) by altering key amino acids.
- **Multiplex Editing**: Editing multiple locations without translocations or deletions.
Rapid expansion of base editing technology since 2016, including in vivo validation

Pubmed search for “Base editing” OR “Nucleotide editing” NOT “Homology directed repair” by Title/Abstract followed by removing all “Review” and “Comment” by Publication Type
Beam’s strategy to become the leader in precision genetic medicines

1. Build **foundational capabilities** to extend Beam’s leadership position in Base Editing

2. Establish a **broad pipeline across all validated delivery modalities** in parallel (ex vivo, LNP, AAV)

3. Accelerate **lead programs to the clinic** to early human POC

**Base editing is a broad, best-in-class technology for precision genetic medicine**

ASGCT 2019
Broad portfolio strategy

Invest Broadly in Delivery

...To Enable Wide Range of Strategic Franchises

CURRENT FOCUS

Ex Vivo Electroporation

In Vivo LNP

AAV

EXPANSION POTENTIAL

Hematology

Oncology

Immunology

diabetes

iPS cells

Xenotransplant

Liver

Genetic Disease

Blood

CV Risk

Antiviral

Eye

CNS

Muscle

Lung

ASGCT 2019
Liver: Optimization improved editing precision and efficiency

Pediatric Liver Disease

- Genetic liver disease with high unmet medical need in children
- >80% precision correction of one of the two most prevalent mutations in the disease with A-to-G editor
- Editing levels expected to be therapeutic

Initial optimization eliminated bystander editing

Subsequent optimization increased editing rates

Editing in HEK293T cells
Liver: Optimization campaign significantly improved editing efficiency on a challenging target

Genetic Liver Disease
- Genetic liver disease with high unmet medical need
- 80% precision correction with A-to-G editor (variant 5)
- Editing levels expected to be therapeutic

Editing in HEK293T cells

~6 months optimization

Genetic Liver Disease

Editing in HEK293T cells

ASGCT 2019
Precise correction of point mutation via AAV delivery in primary retinal cells

Genetic Eye Disease

- Genetic condition leading to progressive blindness with high unmet need
- 50% correction with A-to-G editor
- Editing levels expected to be therapeutic (recessive condition)

Delivery of editor to RPE cells via split AAV2 infection yields high editing rates with A-to-G editor
Oncology: Multiplex editing for allogeneic cell therapy, with no detectable translocations

Multiplex Editing (3 Targets) for Allogeneic CAR-T

- 95% multiplex editing in donor T-cells of several targets simultaneously

95% Knockdown of Multiplex Targets

- Multiplex editing results in successful knockdown of targets

No Detectable Translocations

- Unlike for Cas9-treated cells, no BE4-induced rearrangements in triple-edited T cells are detectable using a sensitive, unbiased translocation detection assay (Uditas™)

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<tr>
<th>Type</th>
<th>Mock (%)</th>
<th>BE4-treated (%)</th>
<th>Cas9-treated (%)</th>
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Beam’s potential to become a leader in precision genetic medicine

- Base editing is emerging as a powerful next-generation editing technology
- Beam has established a world class team and foundational capabilities in next-generation gene editing technologies
- Beam has secured significant funding to move our rapidly-advancing pipeline of wholly-owned programs to the clinic
- Our goal is to build a leading precision genetic medicine company over the long term
Thank You