Beam Therapeutics

PRECISION GENETIC MEDICINES THROUGH BASE EDITING

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Beam Therapeutics and Base Editing

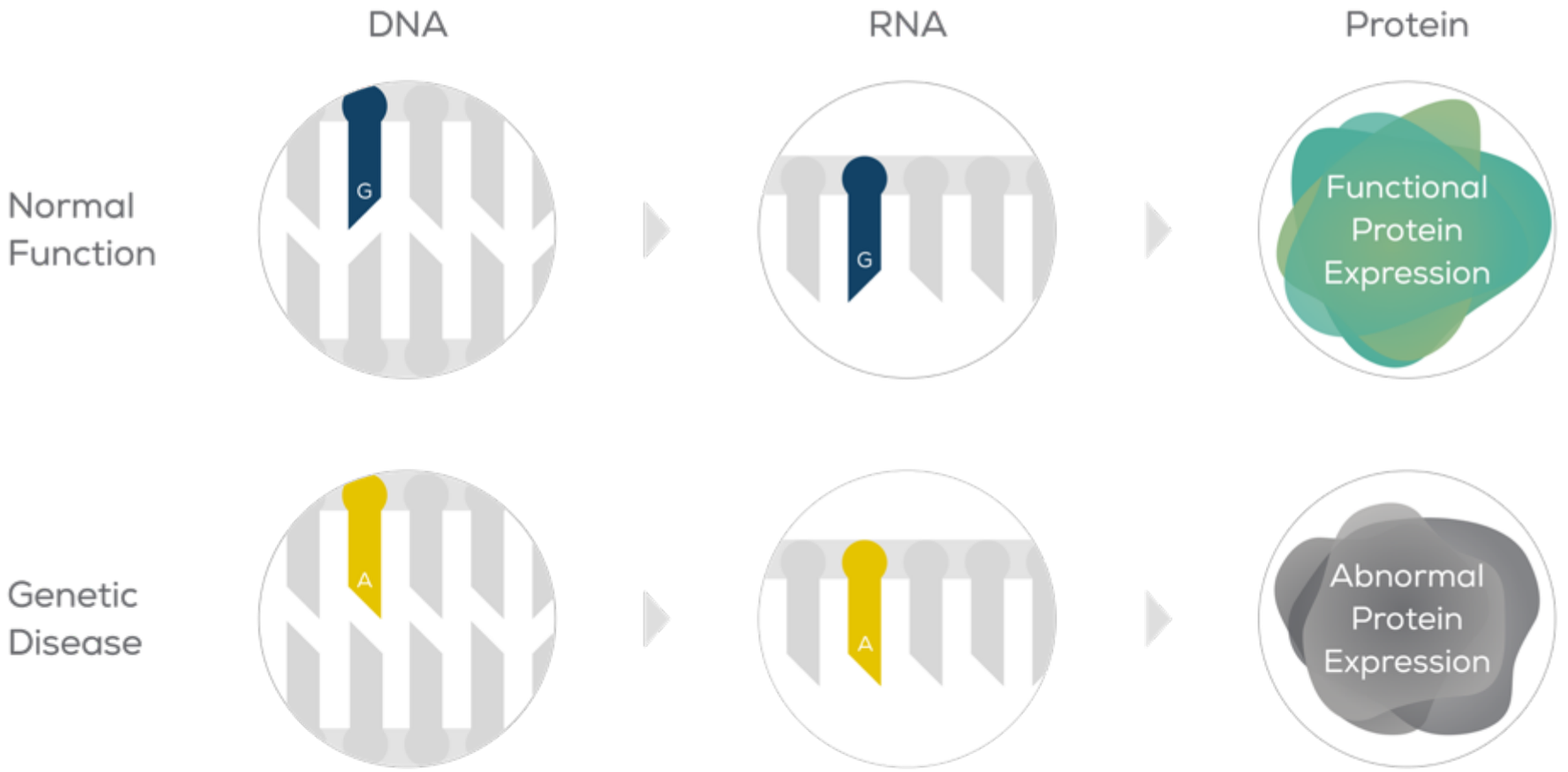
Beam is developing **precision genetic medicines** through **base editing**

- **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

OVER HALF

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

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Noura S. Abul-Husn, M.D., Ph.D., Xiping Cheng, M.D., Ph.D., Alexander H. Li, Ph.D., Yurong Xin, Ph.D., Claudia Schurmann, Ph.D., Panayiotis Stevis, Ph.D., Yashu Liu, Ph.D., Julia Kozlitina, Ph.D., Stefan Stender, M.D., Ph.D., G. Craig Wood, M.S., Ann N. Stepanchick, Ph.D., Matthew D. Still, et al.

GENETICS

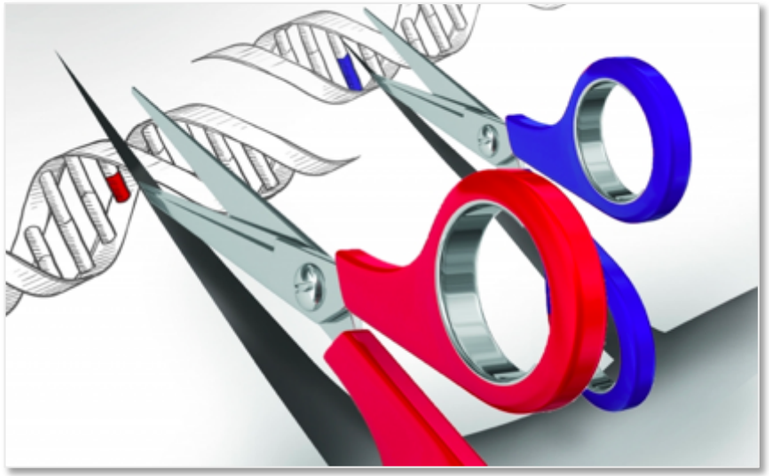
Gene mutation defends against Alzheimer's disease

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

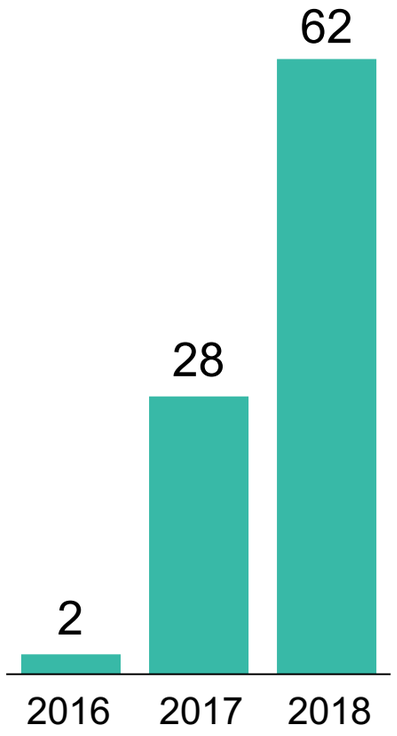
Beam THERAPEUTICS

Gene Correction	Gene Regulation	Gene Silencing	Gene Reprogramming	Multiplex Editing
Direct correction of point mutations Insertion of protective mutations or clinical variants	Editing regulatory elements to raise/lower gene expression	Introduction of STOP codons or disruption of splice sites	Changing protein function (binding, catalysis, signaling) by altering key amino acids	Editing multiple locations without translocations or deletions

Rapid expansion of base editing technology since 2016, including in vivo validation

Editing POC in vivo

Base editing papers



2018

nature medicine
Treatment of a metabolic liver disease by in vivo genome base editing in adult mice
Lukas Villiger[1], Hiu Man Grisch-Chan[2], Helen Lindsay[3,4], Femke Ringnalda[1], Chiara B. Pogliano[5], Gabriella Allegri[2], Ralph Fingerhut[2,8], Johannes Häberle[4,6,7], Joao Matos[5], Mark D. Robinson[3,4], Beat Thöny[2,7] and Gerald Schwank[1]*

Circulation
Reduced Blood Lipid Levels With In Vivo CRISPR-Cas9 Base Editing of ANGPTL3
Alexandra C. Chadwick, Niklaus H. Evitt, Wenjian Lv, and Kiran Musunuru

nature COMMUNICATIONS
Improving the DNA specificity and applicability of base editing through protein engineering and protein delivery
Holly A. Rees[1,2,3], Alexis C. Komor[1,2,3], Wei-Hsi Yeh[1,2,3,4,5], Joana Caetano-Lopes[6,7], Matthew Warman[6,7], Albert S.B. Edge[4,5,8] & David R. Liu[1,2,3]

Programmable base editing of zebrafish genome using a modified CRISPR-Cas9 system
Yihan Zhang[1,2], Wei Qin[1], Xiaochan Lu[1], Jason Xu[2], Haigen Huang[2], Haipeng Bai[1], Song Li[1] & Shuo Lin[1,2]

Highly efficient RNA-guided base editing in rabbit
Zhiquan Liu[1], Mao Chen[1], Siyu Chen[1], Jichao Deng[1], Yuning Song[1], Liangxue Lai[1,2] & Zhanjun Li[1]

Targeting fidelity of adenine and cytosine base editors in mouse embryos
Hye Kyung Lee[1], Michaela Willi[1], Shannon M. Miller[2,3,4], Sojung Kim[1], Chengyu Liu[5], David R. Liu[2,3,4] & Lothar Hennighausen[1]

nature biotechnology
Adenine base editing in mouse embryos and an adult mouse model of Duchenne muscular dystrophy
Seuk-Min Ryu[1,2,4], Taeyoung Koo[1,4], Kyoungmi Kim[1,3,4], Kayeong Lim[1,2,4], Gayoung Baek[1], Sang-Tae Kim[1], Heon Seok Kim[1,2], Da-eun Kim[1,2], Hyunji Lee[1], Eugene Chung[1,2] & Jin-Soo Kim[1,2]

Optimized base editors enable efficient editing in cells, organoids and mice
Maria Paz Zafra[1,11], Emma M Schatoff[1,2,11], Alyna Katti[1,3], Miguel Foronda[1], Marco Breinig[4], Anabel Y Schweitzer[4], Amber Simon[1], Teng Han[1,3], Sukanya Goswami[1], Emma Montgomery[1], Jordana Thibado[3], Edward R Kastenhuber[3,6], Francisco J Sánchez-Rivera[3], Junwei Shi[2,8], Christopher R Vakoc[7], Scott W Lowe[5,9], Darjus F Tschaharganeh[4] & Lukas E Dow[1,3,10]

Improving cytidine and adenine base editors by expression optimization and ancestral reconstruction
Luke W Koblan, Jordan L Doman, Christopher Wilson, Jonathan M Levy, Tristan Tay, Gregory A Newby, Juan Pablo Maianti, Aditya Raguram & David R Liu

Genome Biology
CRISPR-SKIP: programmable gene splicing with single base editors
Michael Gapinske[1], Alan Luu[2,3†], Jackson Winter[1], Wendy S. Woods[1], Kurt A. Kostan[1], Nikhil Shiva[1], Jun S. Song[2,3*] and Pablo Perez-Pinera[1,4*]

Cell Discovery
www.nature.com/celldisc
Efficient RNA-guided base editing for disease modeling in pigs
Zhifang Li[1], Xiaoyue Duan[1], Xiaomeng An[1], Tao Feng[1,2], Pan Li[1], Linlin Li[1], Jun Liu[1], Panxue Wu[1], Dengke Pan[1], Xuguang Du[1] and Sen Wu[1]

2017

nature
Programmable base editing of A·T to G·C in genomic DNA without DNA cleavage
Nicole M. Gaudelli[1,2,3], Alexis C. Komor[1,2,3]†, Holly A. Rees[1,2,3], Michael S. Packer[1,2,3]†, Ahmed H. Badran[1,2,3], David I. Bryson[1,2,3]† & David R. Liu[1,2,3]

nature methods
CRISPR-STOP: gene silencing through base-editing-induced nonsense mutations
Cem Kuscu, Mahmut Parlak, Turan Tufan, Jiekun Yang, Karol Szlachta, Xiaolong Wei, Rashad Mammadov & Mazhar Adli

nature biotechnology
Increasing the genome-targeting scope and precision of base editing with engineered Cas9-cytidine deaminase fusions
Y Bill Kim[1,2], Alexis C Komor[1,2], Jonathan M Levy[1,2], Michael S Packer[1,2], Kevin T Zhao[1,2] & David R Liu[1–3]

Highly efficient RNA-guided base editing in mouse embryos
Kyoungmi Kim, Seuk-Min Ryu, Sang-Tae Kim, Gayoung Baek, Daesik Kim, Kayeong Lim, Eugene Chung, Sunghyun Kim & Jin-Soo Kim

Science
RNA editing with CRISPR-Cas13
David B. T. Cox1, Jonathan S. Gootenberg, Omar O. Abudayyeh, Brian Franklin, Max J. Kellner

Arteriosclerosis, Thrombosis, and Vascular Biology
In Vivo Base Editing of PCSK9 as a Therapeutic Alternative to Genome Editing
Alexandra C. Chadwick, Xiao Wang, Kiran Musunuru

2016

nature
Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage
Alexis C. Komor[1,2], Yongjoo B. Kim[1,2], Michael S. Packer[1,2], John A. Zuris[1,2] & David R. Liu[1,2]

Science
Targeted nucleotide editing using hybrid prokaryotic and vertebrate adaptive immune systems
Keiji Nishida,[1] Takayuki Arazoe,[1] Nozomu Yachie,[2,3,4] Satomi Banno,[1] Mika Kakimoto,[1] Mayura Tabata,[1] Masao Mochizuki,[1] Aya Miyabe,[1] Michihiro Araki,[1] Kiyotaka Y. Hara,[5] Zenpei Shimatani,[1] Akihiko Kondo[1,6]*

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

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

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

Broad portfolio strategy

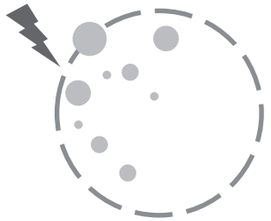
Beam THERAPEUTICS

Invest Broadly in Delivery

…To Enable Wide Range of Strategic Franchises

CURRENT FOCUS | *EXPANSION POTENTIAL*

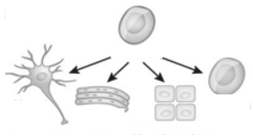
Ex Vivo Electroporation



Hematology

Oncology

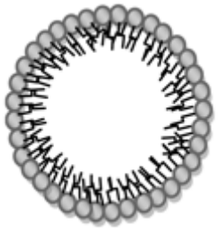
Immunology



iPS cells

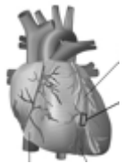
Xenotransplant

In Vivo LNP

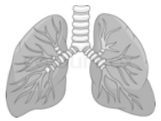


Liver Genetic Disease

CV Risk

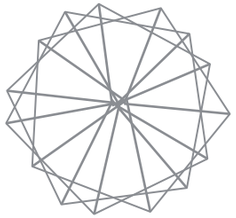


Antiviral



Lung

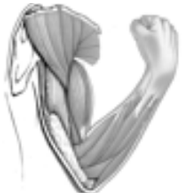
AAV



Eye

CNS

Muscle

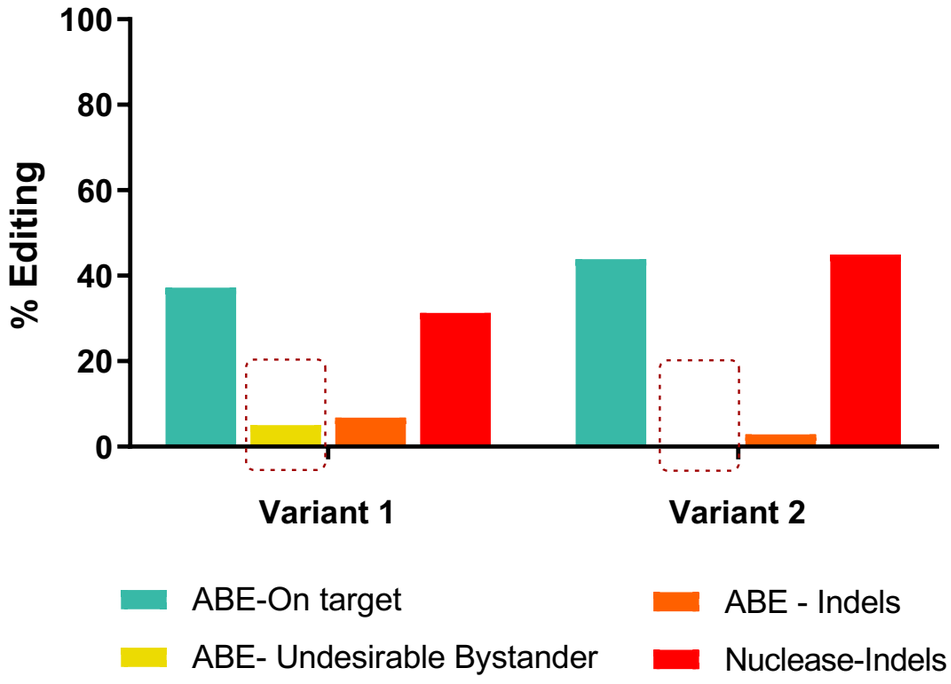


Liver: Optimization improved editing precision and efficiency

Pediatric Liver Disease

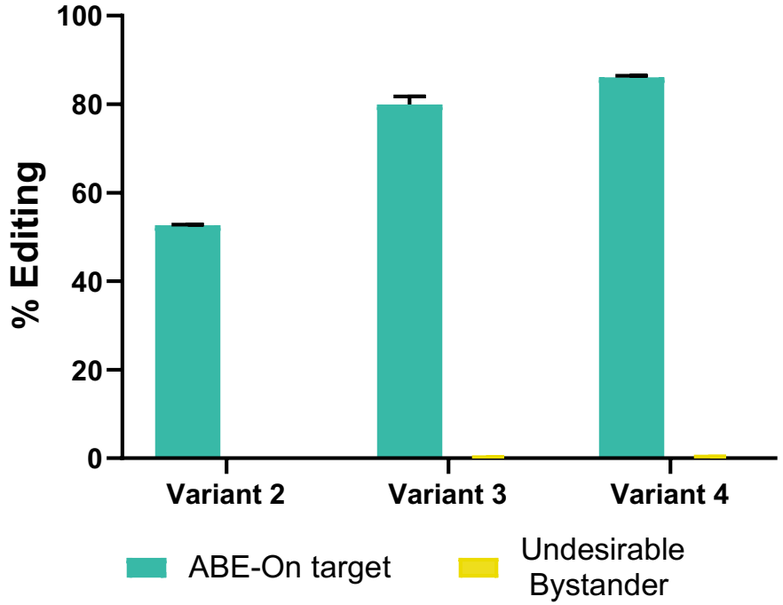
- Genetic liver disease with high unmet medical need in children
- **>80% precision correction** of one of the two most prevalent mutations in the disease with A-to-G editor
- Editing levels expected to be therapeutic

Initial optimization eliminated bystander editing



Editing in HEK293T cells

Subsequent optimization increased editing rates

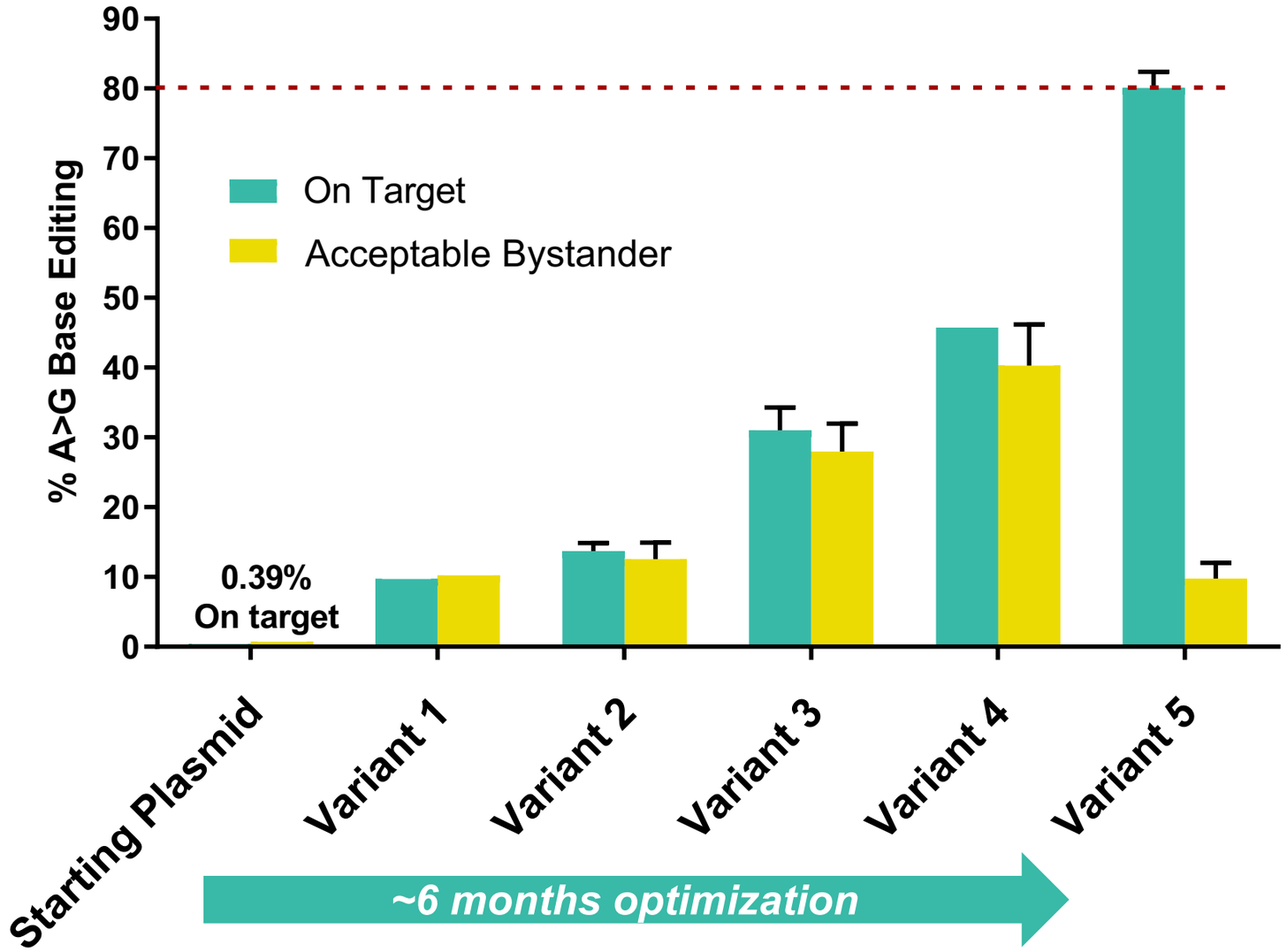


Editing in HEK293T cells

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



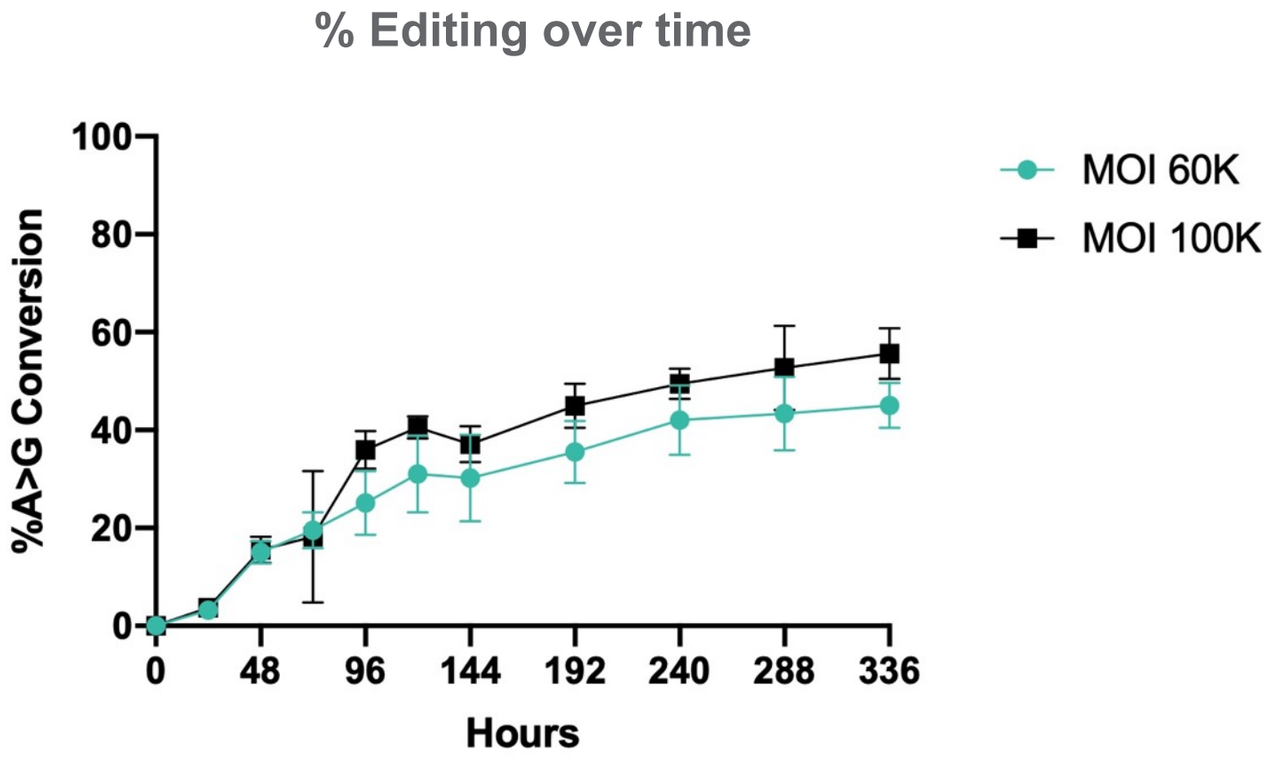
Editing in HEK293T cells

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)

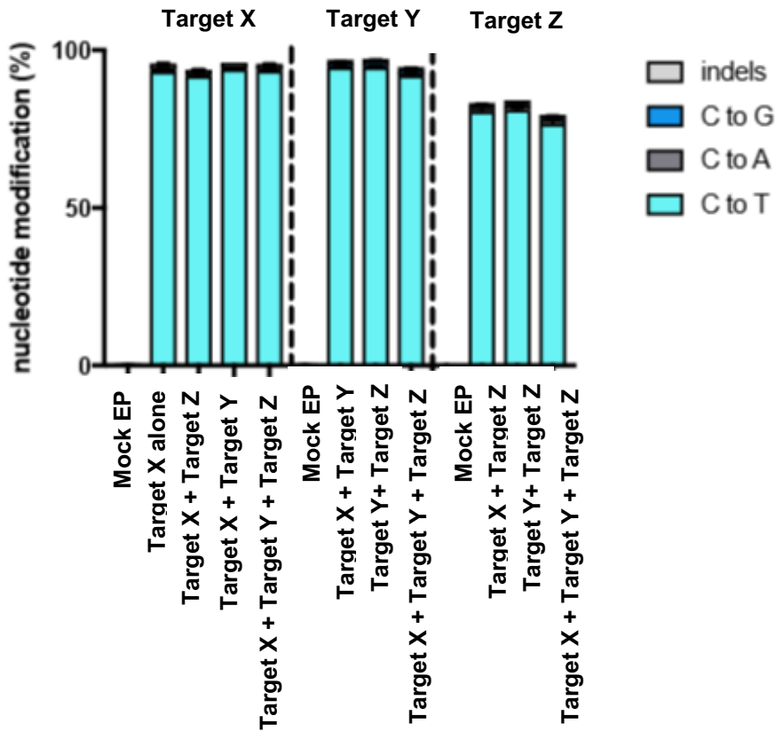
- Delivery of editor to RPE cells via split AAV2 infection yields high editing rates with A-to-G editor



Editing in RPE cells

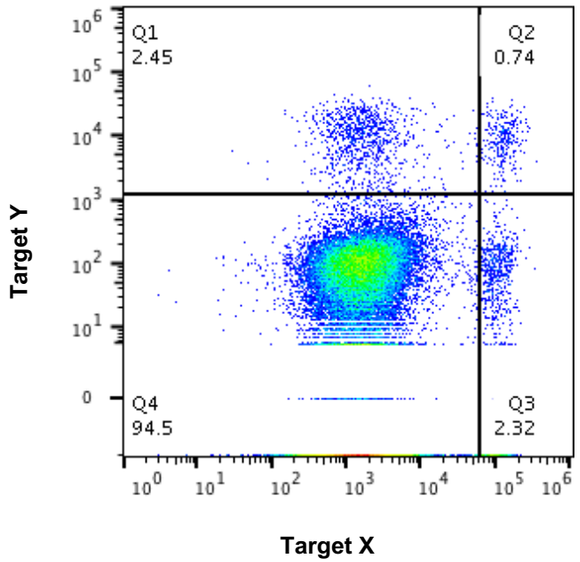
Oncology: Multiplex editing for allogeneic cell therapy, with no detectable translocations

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

Type	Mock (%)	BE4-treated (%)	Cas9-treated (%)
On-target modification (*Target X*/*Target Y*/ *Target Z*)	0	89.9 / 97.9 / 89.1	53.0 / 77.2 / 55.2
Target X-A / Target Y-A	0	0	0.925
Target X-A / Target Y-B	0	0	0.353
Target X-A / Target Z-A	0	0	1.647
Target X-A / Target Z-B	0	0	0.508
*Target X-B / Target Y-A**	0	0	0.505

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

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

Beam THERAPEUTICS