Development of AGN 151587 (EDIT-101), a gene editing approach to restore vision in Leber Congenital Amaurosis Type 10

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Chief Technology Officer

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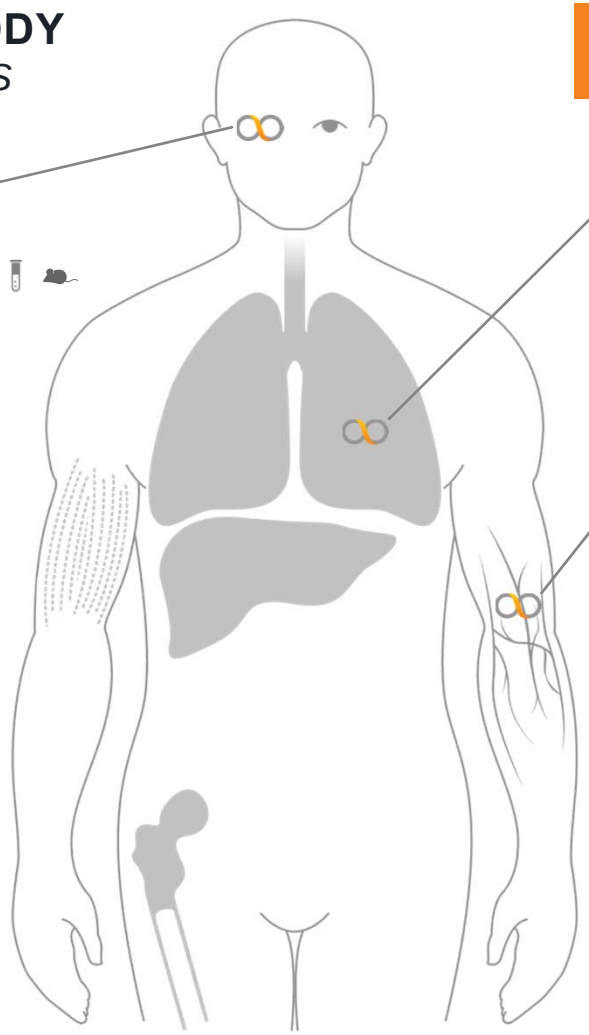
Developing Best-in-Class CRISPR Medicines

EDITING INSIDE THE BODY
IN VIVO *CRISPR MEDICINES*

OCULAR DISEASES
- Leber congenital amaurosis 10*
- Usher syndrome 2A
- Retinitis pigmentosa
- Ocular HSV



EDITING OUTSIDE THE BODY
ENGINEERED CELL MEDICINES

CANCER
- Autologous T cell medicines**
- Allogeneic cell medicines

BLOOD DISEASES
- Sickle cell disease
- Beta-thalassemia

EARLY DISCOVERY
- Liver – AATD
- Muscle – DMD
- Lung – CF

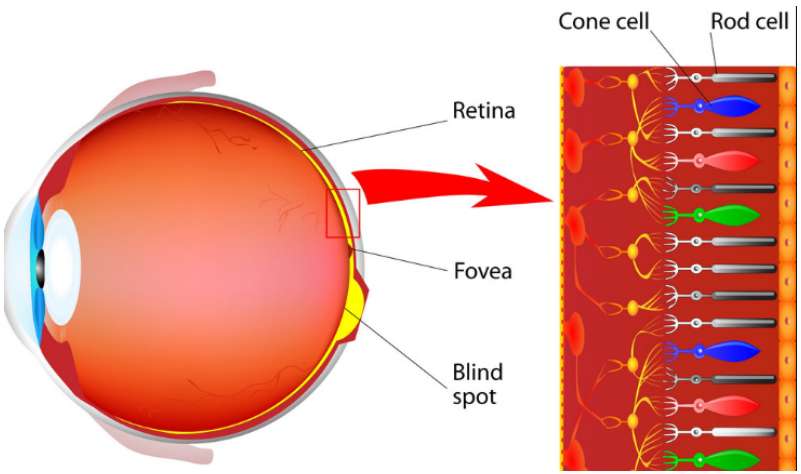
in vitro proof of biology
in vivo proof of concept
AAV delivery

*EDIT-101 (AGN-151587) partnered with Allergan; **Partnered with Celgene; LCA10: Leber congenital amaurosis 10; HSV: herpes simplex virus; CF: cystic fibrosis; DMD: Duchenne muscular dystrophy; AATD: alpha-1 antitrypsin deficiency; AAV: adeno-associated virus

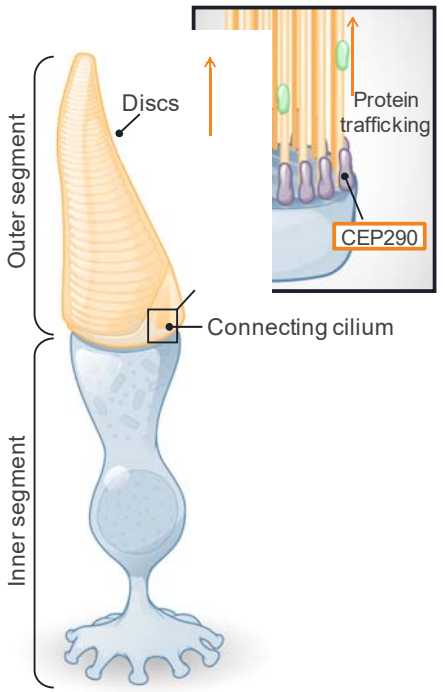
Considerations for an in vivo Editing Experimental Medicine

DISEASE BIOLOGY	▪ Unmet need, editing strategy, differentiation, and therapeutic editing target
IDENTIFY EDITING MOIETY IN CELLS	▪ Guide RNA and protein selection ▪ On-target and off-target editing in relevant tissue
IN VIVO PHARMACOLOGY	▪ Delivery, dose-response, animal models, and human dose prediction
SAFETY AND TOLERABILITY	▪ IND-enabling studies, translational biomarkers, immunogenicity
CLINICAL DEVELOPMENT	▪ Endpoints, biomarkers, doses, study design

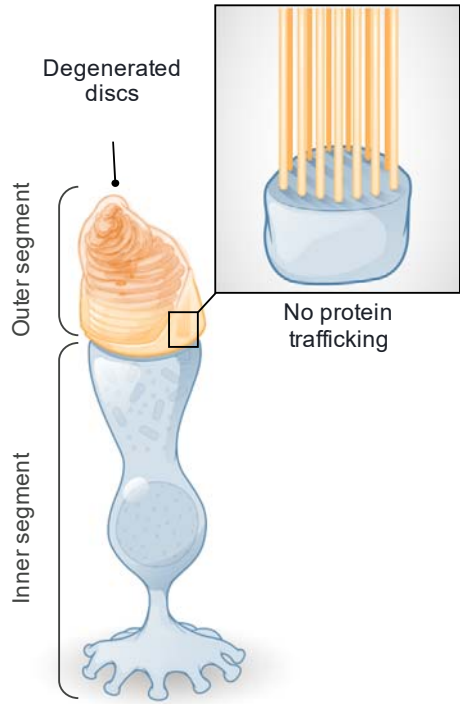
Leber Congenital Amaurosis 10



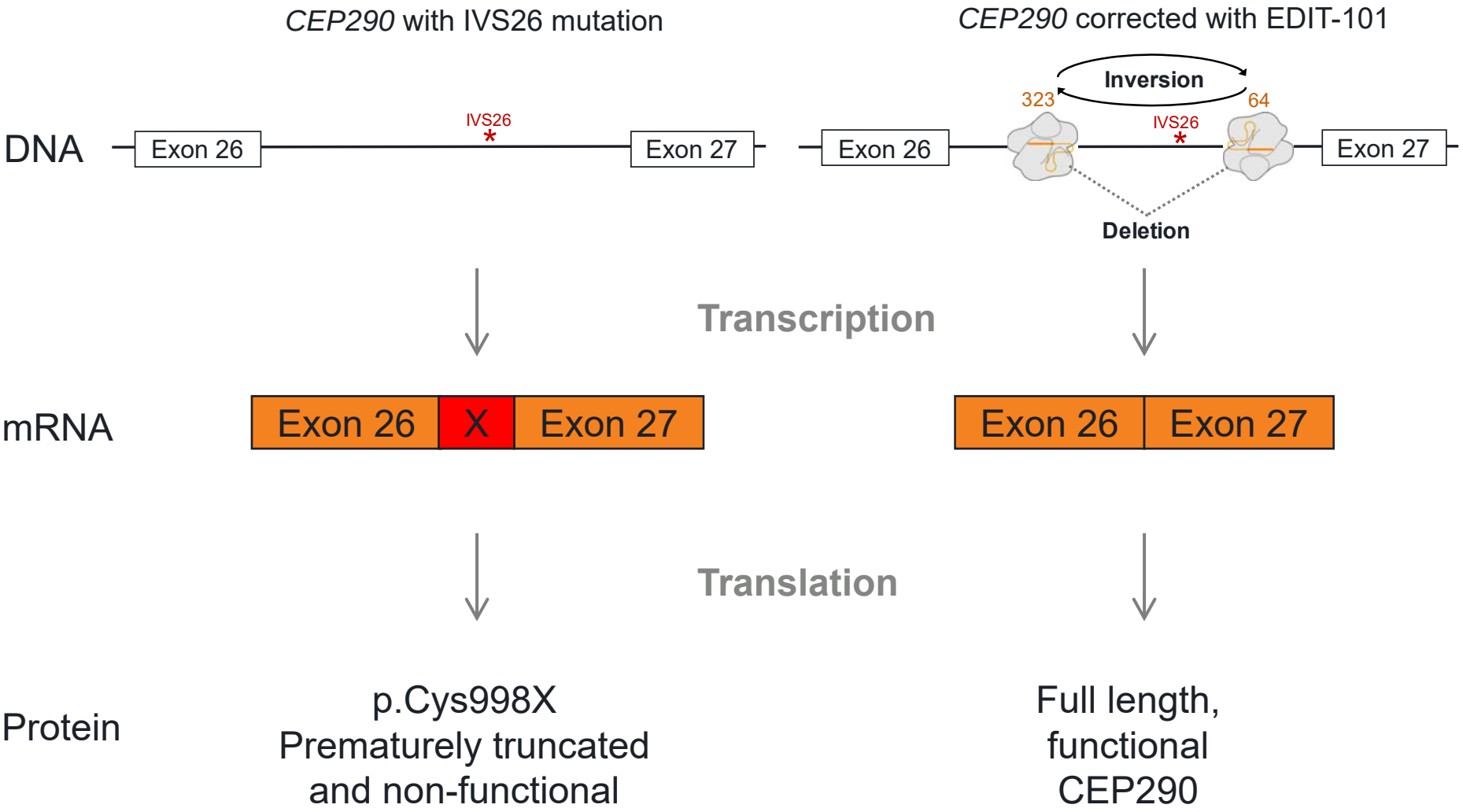
WT Photoreceptor



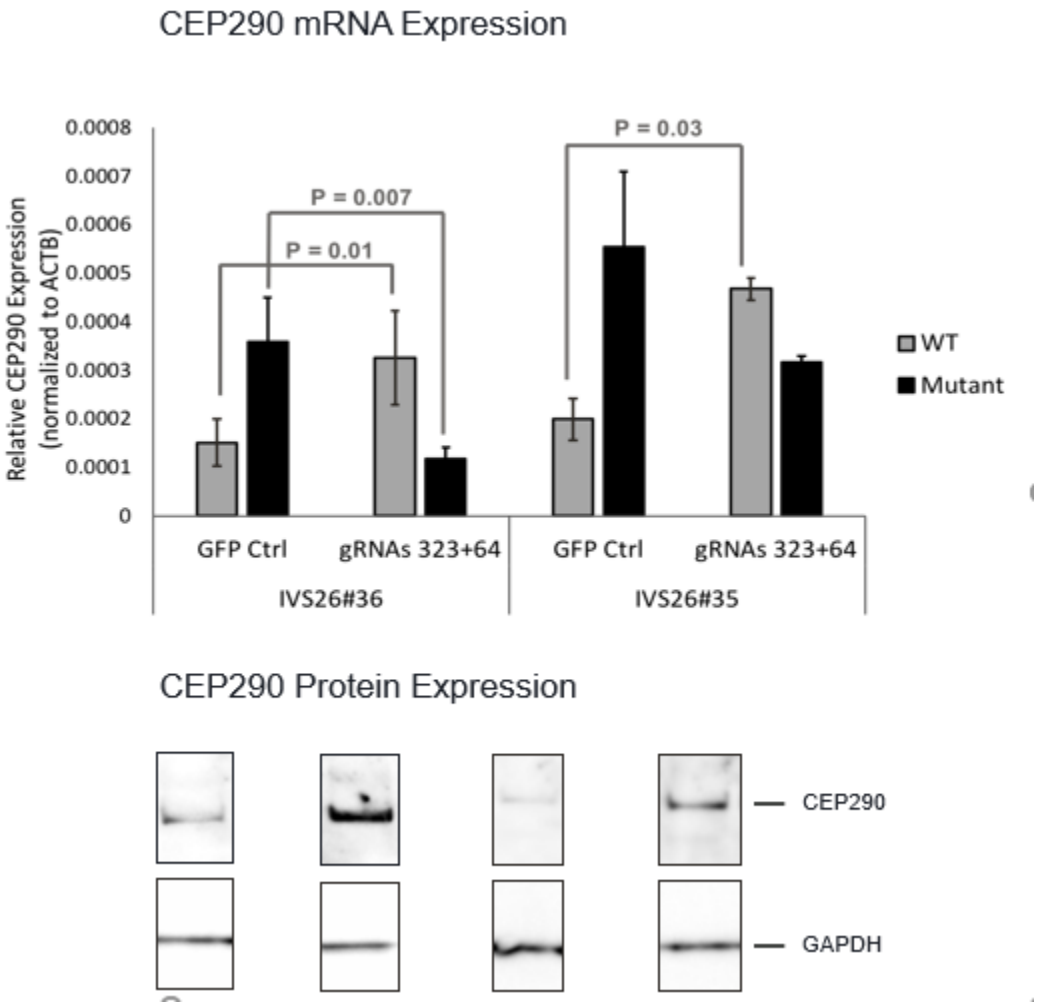
LCA10 Photoreceptor



Gene Editing to Repair *CEP290* Splicing Defect

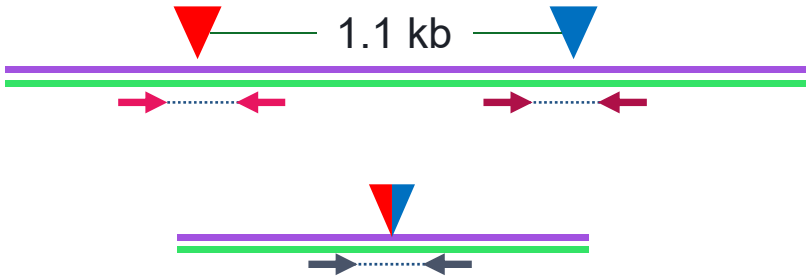


Editing Corrects CEP290 Splicing Thereby Restoring mRNA and Protein Expression



From LCA10 patient fibroblasts

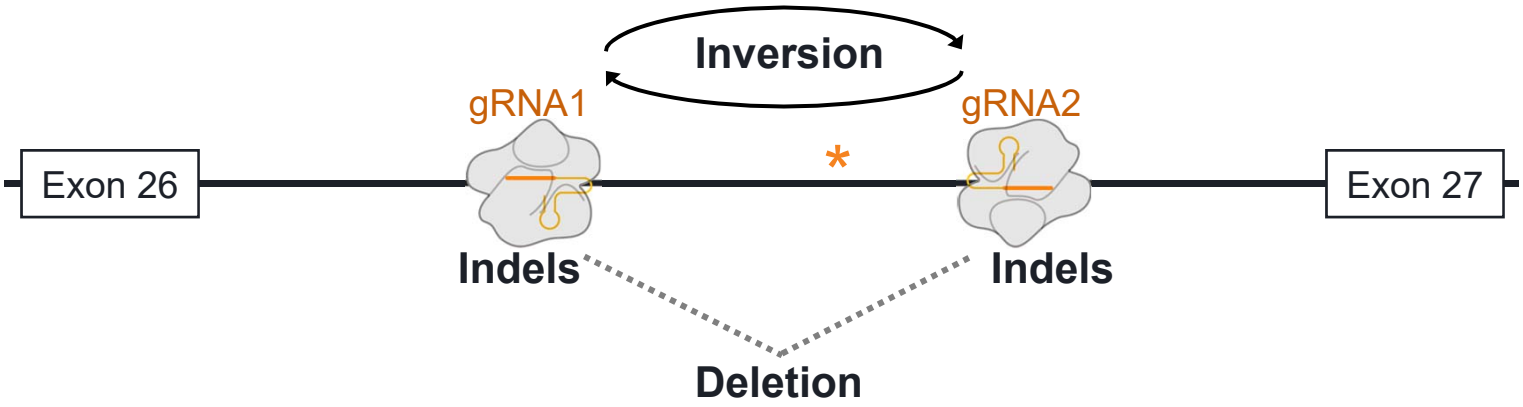
Challenges with PCR-NGS Assays When Making Multiple Edits

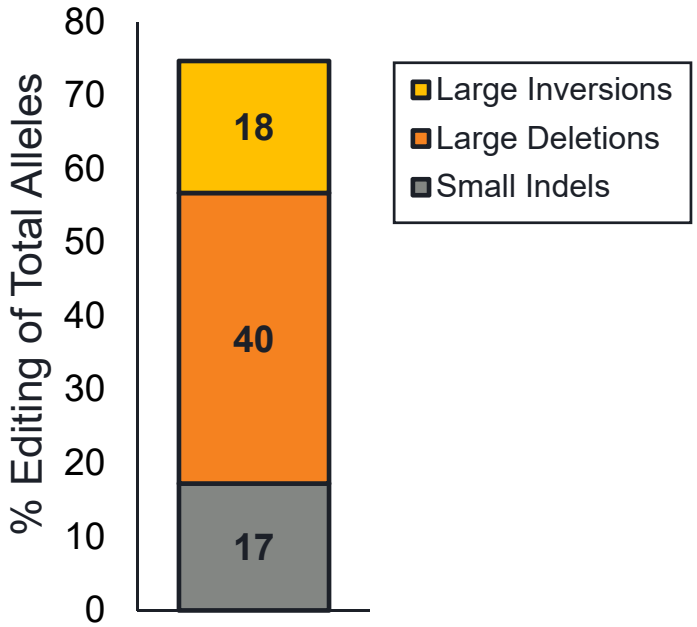


3 PCR assays needed to measure editing at CEP290 intron 26 locus

Even with rigorous standards it is difficult to cross compare 3 assays

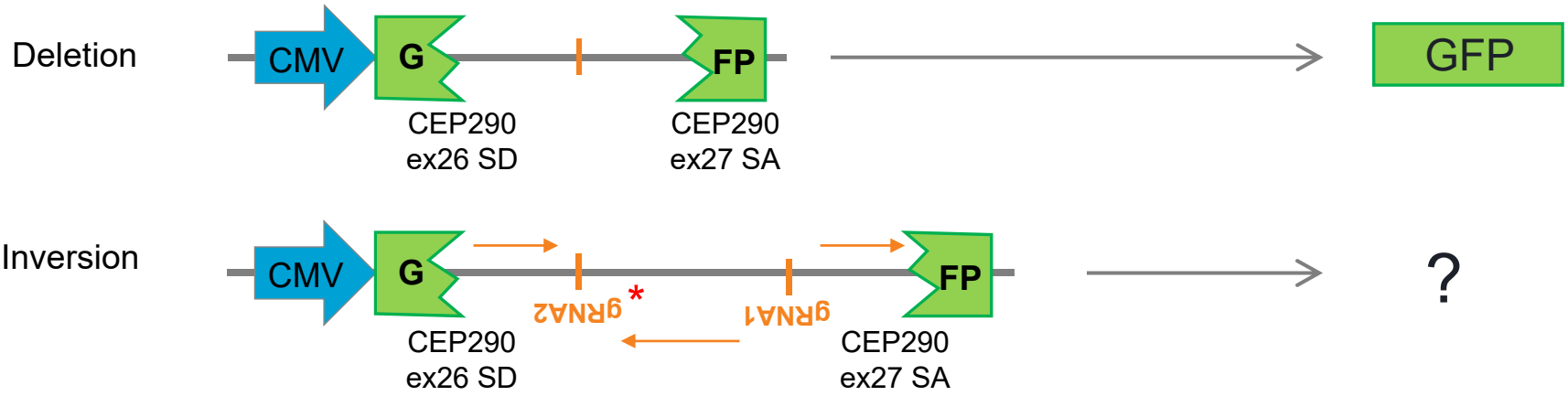
Editing Causes Inversions, Deletions, and Indels



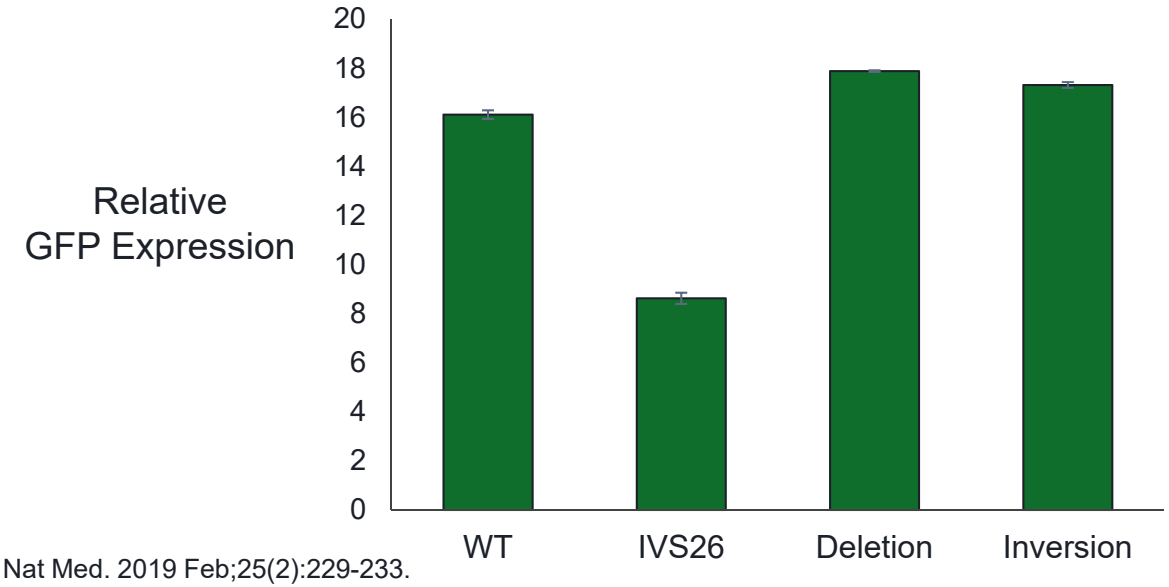


Maeder et al. Nat Med. 2019 Feb;25(2):229-233.

Targeted Deletions and Inversions Correct Splicing



Correct Splicing as Determined by GFP Expression



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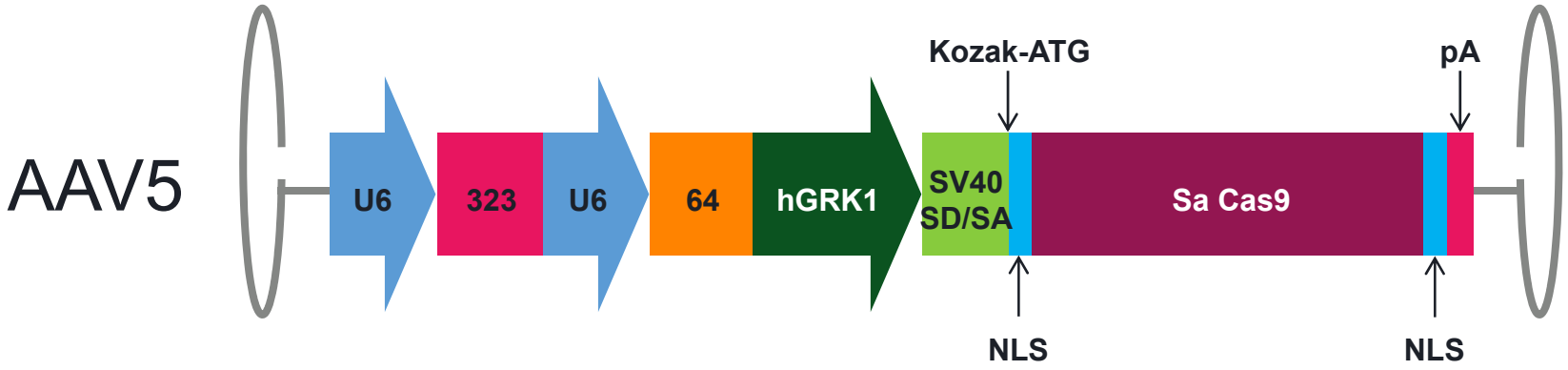
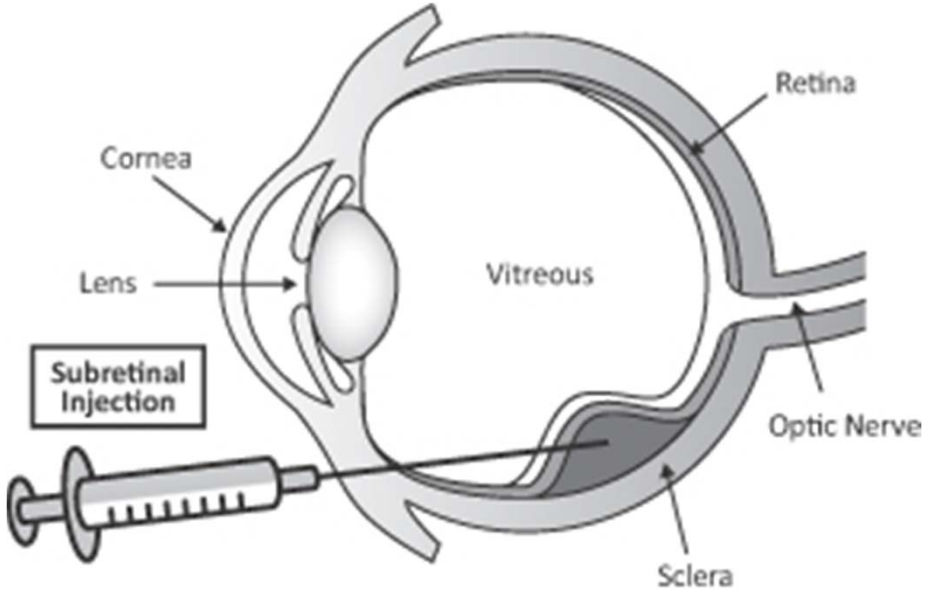
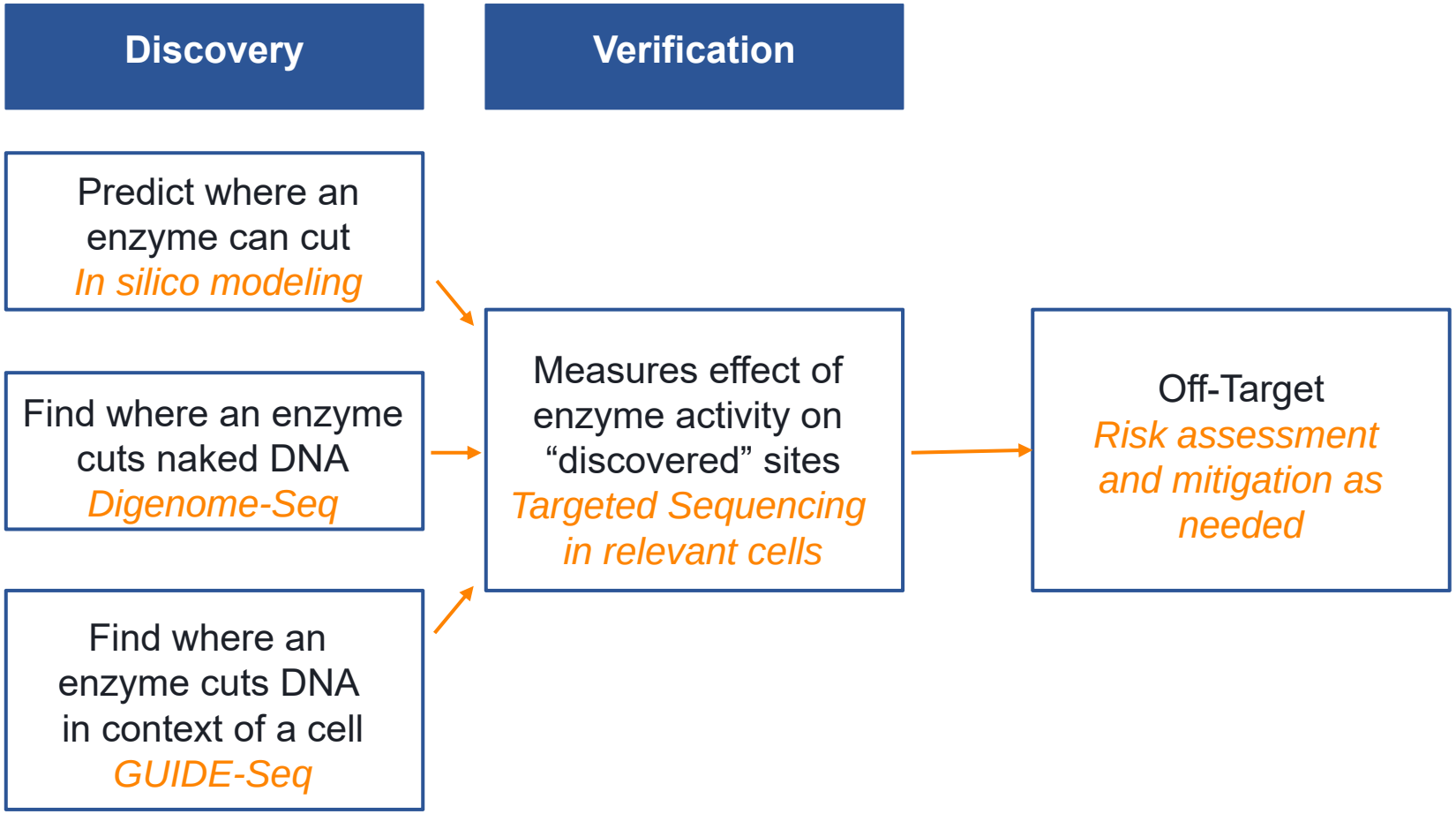
AGN-151587: gRNAs Plus SaCas9 in AAV5

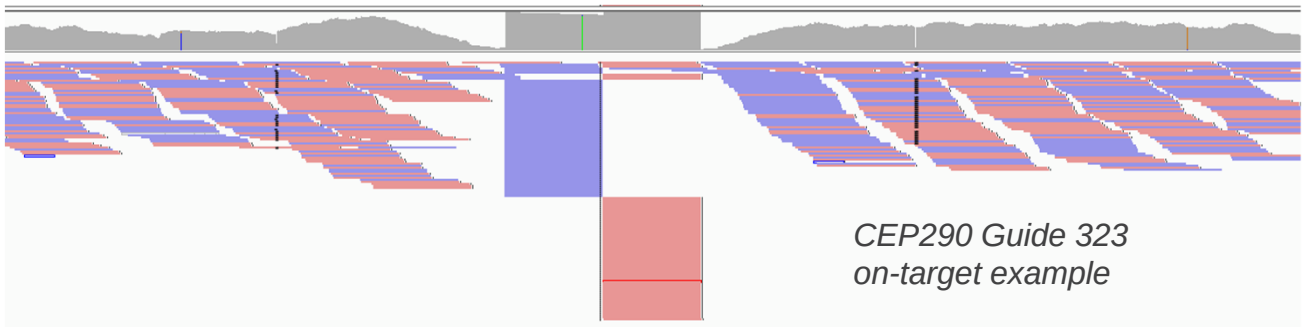


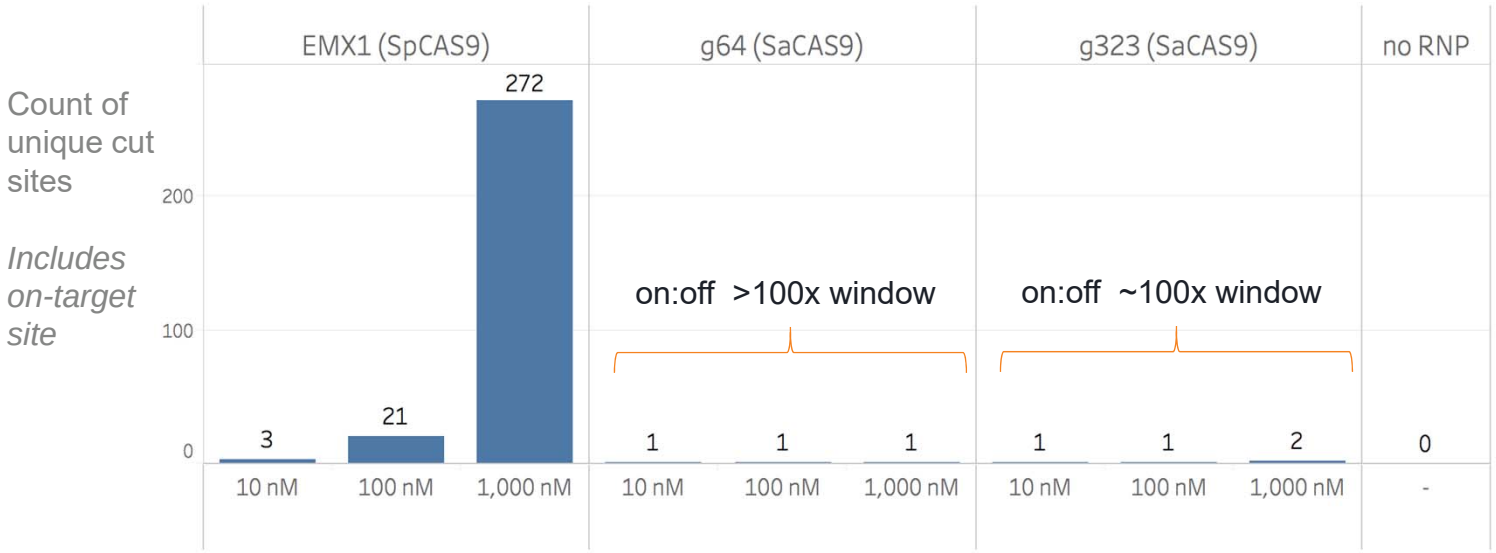


Comprehensive Specificity Assessment



Digenome-Seq Assay





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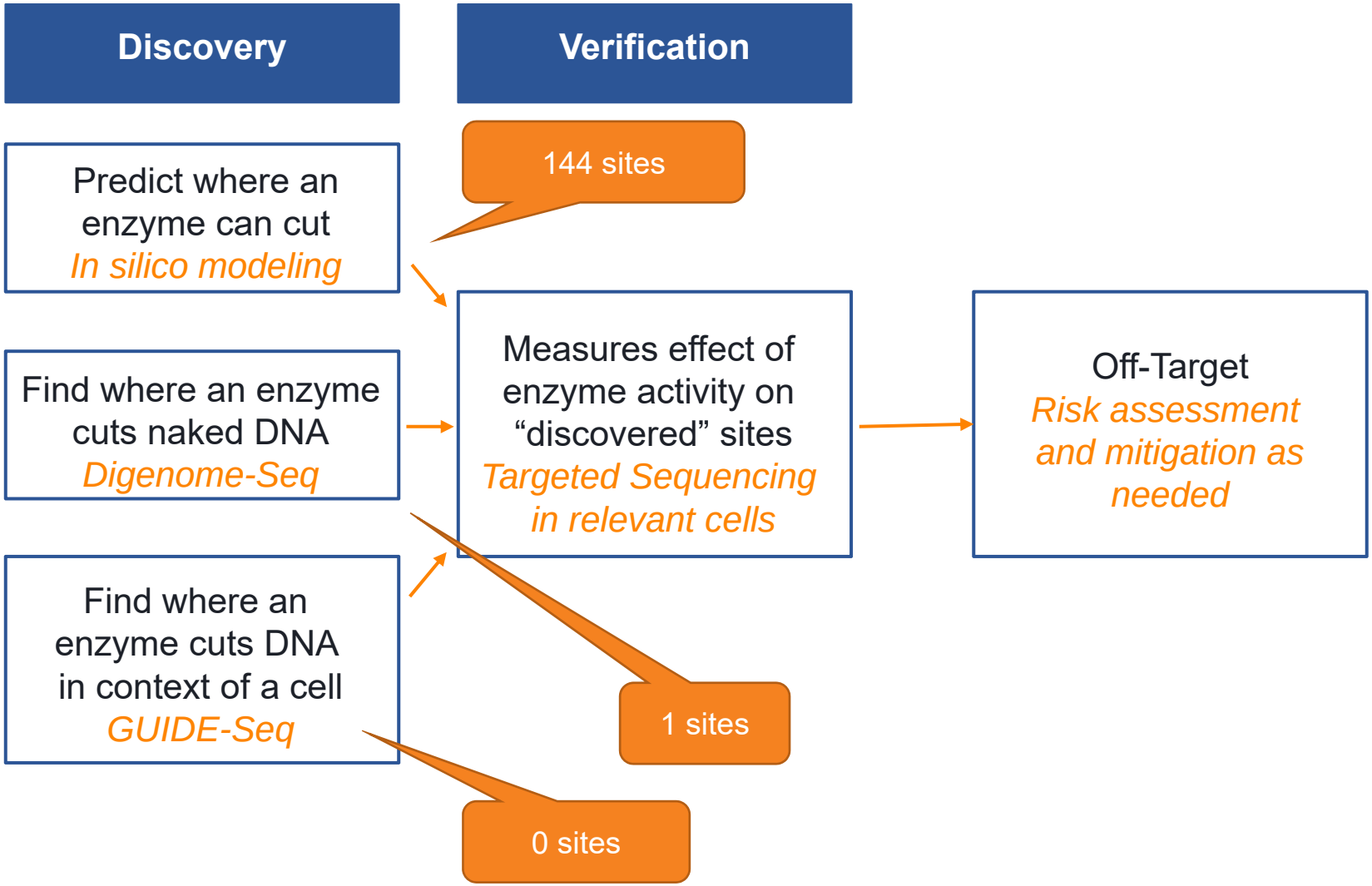
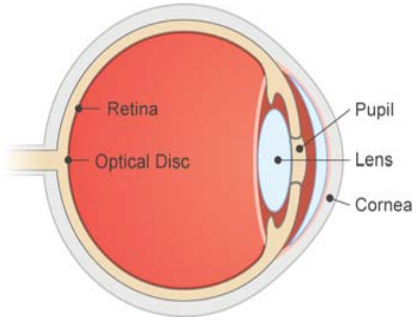


Human Retinal Explant Model



Human Eyes 3-5 hrs Post-Mortem

Remove Neural Retina

3 mm punches

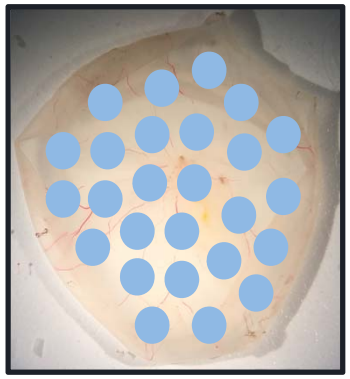
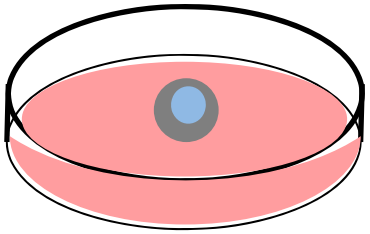
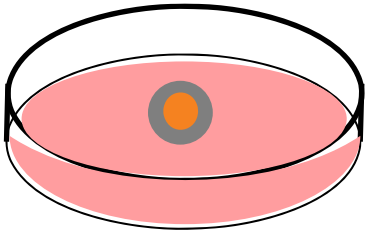


Plate 3 mm punches with photoreceptor side down



24-well format



Harvest **28 days** post-transduction

Histology

UDiTaS to measure Editing

Specificity verification panel

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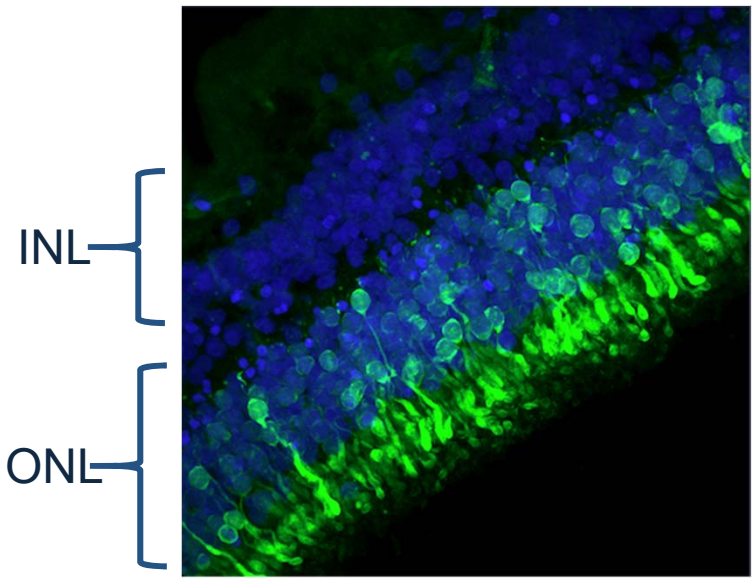
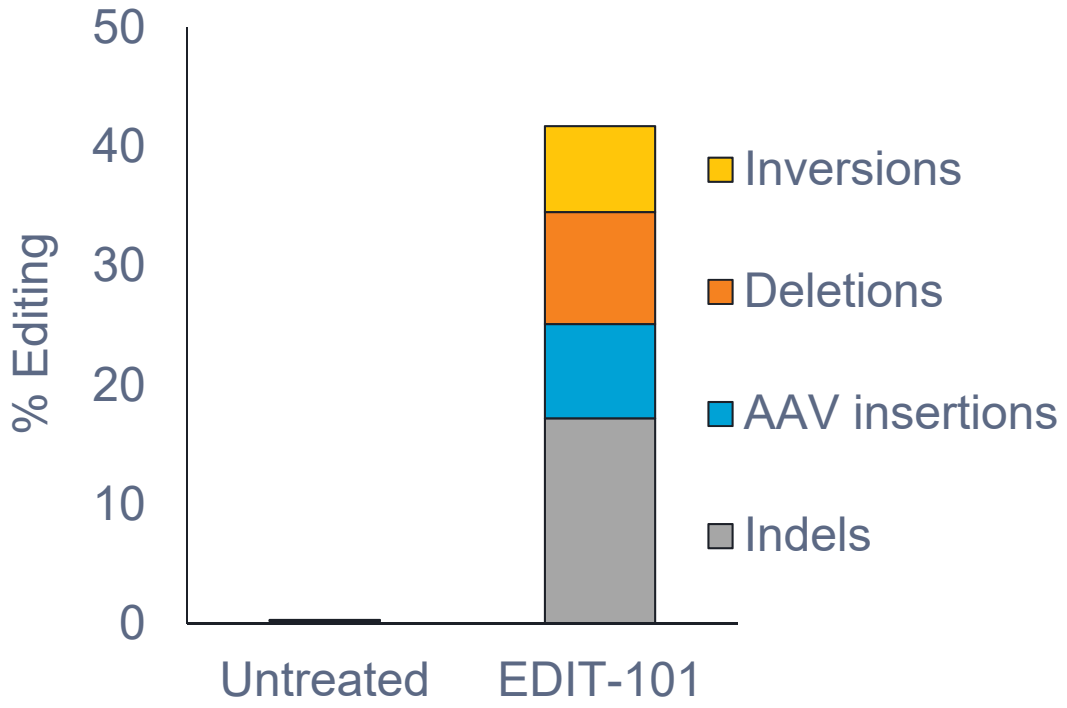
Human retinal explant model [2]

AAV5-GRK1-GFP (5e11 vg)



EDIT-101 (5e11 vg)



28 Day Post Transduction

Specificity assessment, verification phase using targeted PCR with NGS readout

Retinal Explant #1	Retinal Explant #2	ARPE-19	U-2 OS	
147: 2 On-target, 144 *In Silico*, 1 Digenome				Candidate off-target sites
3	3	3	3	Fail — Assay Design (3 sites in repetitive regions)
5	15	7	5	Fail — Assay QC (142 in at least 2 samples)
128	122	126	127	Pass — Below LLoD <0.1% (no editing)
9	5	9	10	Pass — Above LLoD, no difference vs. to control
2	2	2	2	Verified — Verified editing at sites

Both on-target sites identified and no off-target candidate sites verified

Considerations for an in vivo editing experimental medicine

DISEASE BIOLOGY	▪ Unmet need, editing strategy, differentiation, and therapeutic editing target
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IN VIVO PHARMACOLOGY	▪ Delivery, dose-response, animal models, and human dose prediction
SAFETY AND TOLERABILITY	▪ IND-enabling studies, translational biomarkers, immunogenicity
CLINICAL DEVELOPMENT	▪ Endpoints, biomarkers, doses, study design

Initiated LCA10 Phase 1/2 Clinical Trial

LCA10 PHASE 1/2 TRIAL

brilliance

DESIGN

Open-label, dose escalation study
to evaluate safety, tolerability, and efficacy

PATIENTS

~18 patients with IVS26 mutation*

COMPARATOR

Patient's own baseline value
for each efficacy measure

FOLLOW-UP

Core measurements
every 3 months for 1st year

*Intervening sequence 26 in CEP290 gene containing the c.2991+1655A>G mutation

Views on Human Germline Editing

- Somatic cell gene editing has the potential to transform the lives of patients living with serious disease; Editas Medicine is only working on somatic cell gene editing
- Germline gene editing in human clinical settings is currently prohibited across much of the world
- In addition to scientific concerns, robust ethical and legal frameworks are not yet developed for germline gene editing in human settings
- As this topic concerns all of humanity, it is important that we all engage and listen to diverse stakeholders, including members of the patient, caregiver, regulatory, biotechnology, legal, academic, ethical, and faith communities to determine if, and under which conditions, the status quo should change
- To allow this process to develop in the years ahead, we support a global moratorium on clinical applications of human germline editing

Acknowledgements

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