Discovery of EDIT-101 for the Treatment of Leber's Congenital Amaurosis Type 10

Precision Genome Editing with Programmable Nucleases

January 2018

Charlie Albright
Chief Scientific Officer

Forward Looking Statements

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of The Private Securities Litigation Reform Act of 1995. All statements, other than statements of historical facts, contained in this presentation, 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. Forward-looking statements in this presentation include statements regarding the Company's goals of submitting of an IND for the LCA10 program by mid-2018, initiating an LCA10 natural history study in mid-2017, achieving preclinical proof-of-concept for additional programs and establishing alliances. 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 and clinical trials and clinical development of the Company's product candidates; whether interim results from a clinical trial will be predictive of the final results of the trial or the results of future trials; expectations for regulatory approvals to conduct trials or to market products; availability of funding sufficient for the Company's foreseeable and unforeseeable operating expenses and capital expenditure requirements; 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 presentation represent the Company's views as of the date of this presentation. 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 presentation.

Acknowledgements

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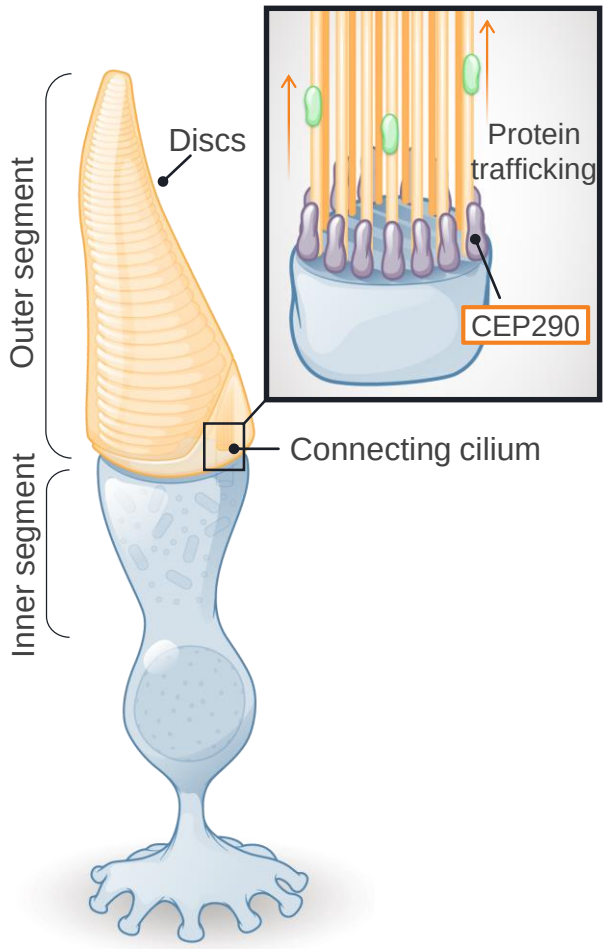
Towards a CRISPR Medicine for LCA10

- Editing corrects splicing defect in cells from LCA10-IVS26 patients and restores full-length mRNA and protein
- EDIT-101 gRNAs are highly specific
- EDIT-101 and NHP-specific construct efficiently edit photoreceptors in transgenic mice and NHPs, respectively
- Immunogenicity studies suggest low levels of anti-Cas9 antibodies in humans

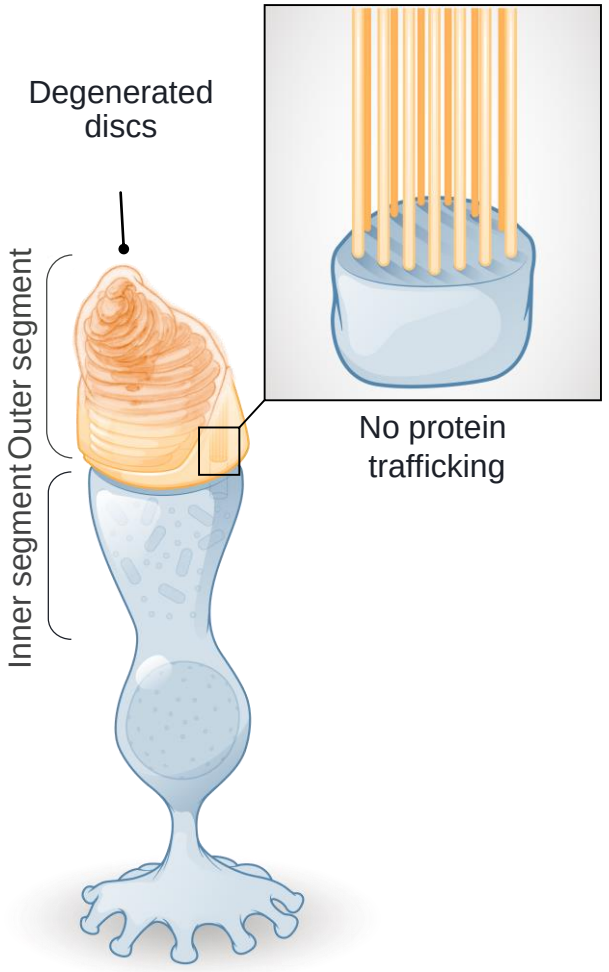
CEP290 gene editing medicine has the potential to have a major impact on vision in LCA10 patients

CEP290 Essential for Ciliary Trafficking and Phototransduction

WT Photoreceptor

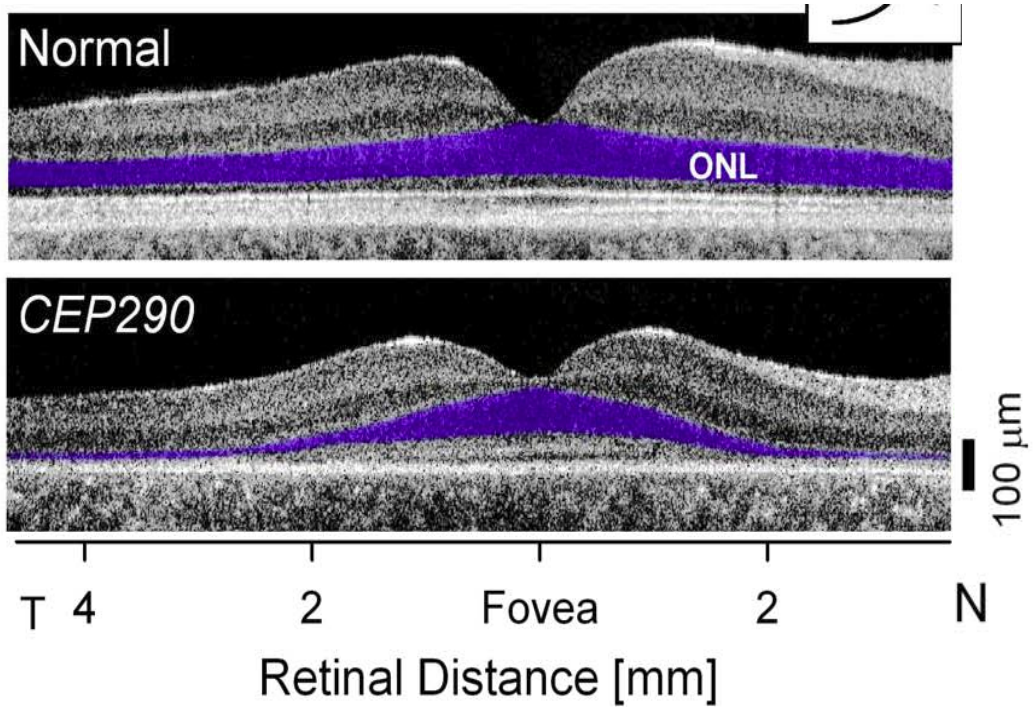


LCA10 Photoreceptor



Photoreceptors Survive in LCA10 Patients

Outer nuclear layer
= photoreceptors

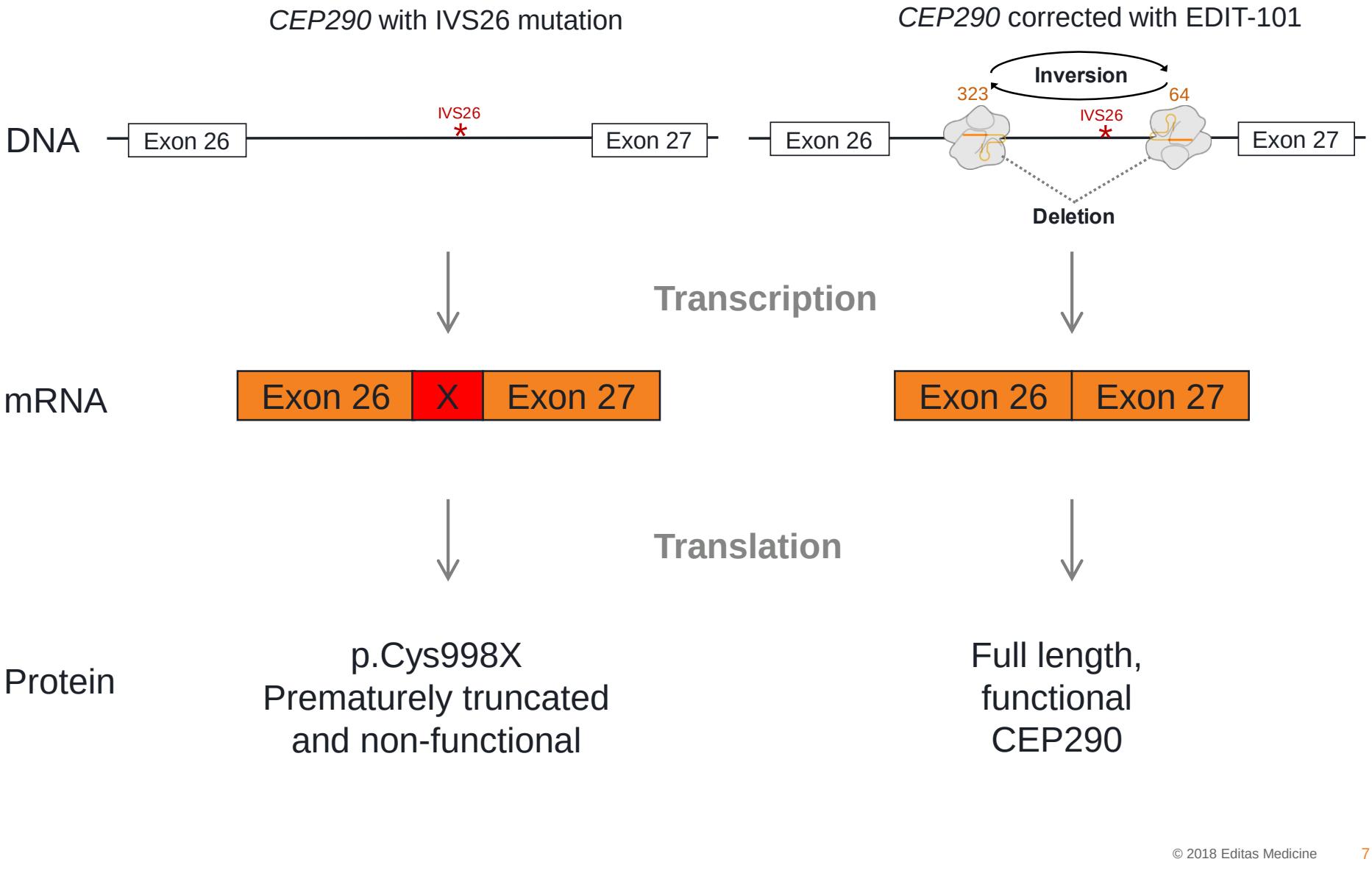


Boye et al., PLOS ONE 2014

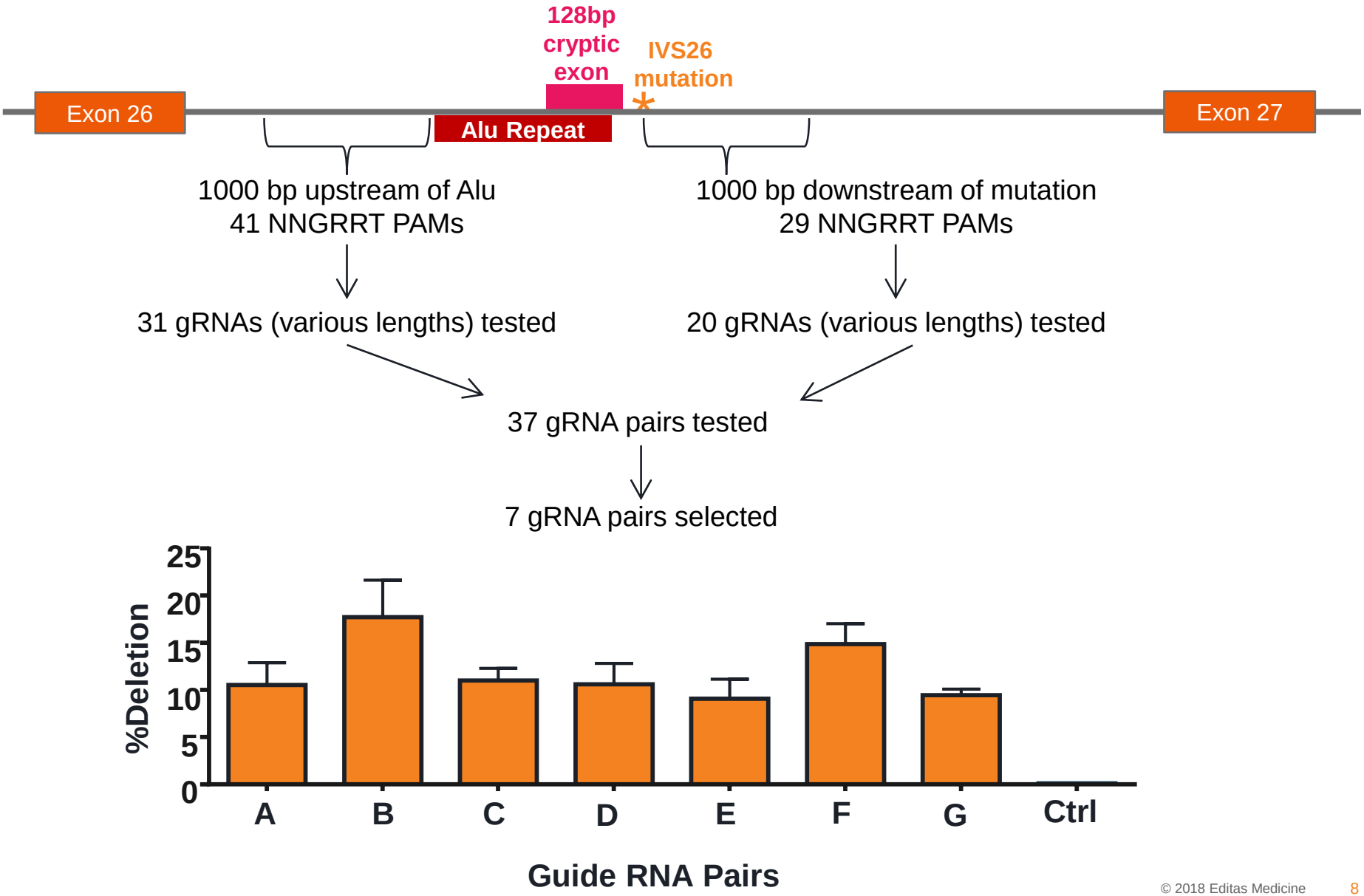
- It is estimated that visual acuity can be achieved with ~10% of functioning photoreceptors[1,2]

1.Geller, Sieving and Green, *J. Opt. Soc. Am.*, 1992
2.Geller and Sieving, *Vision Res.*, 1993

Gene Editing to Repair *CEP290* Splicing Defect



Identification of gRNAs that Remove IVS26 Mutation



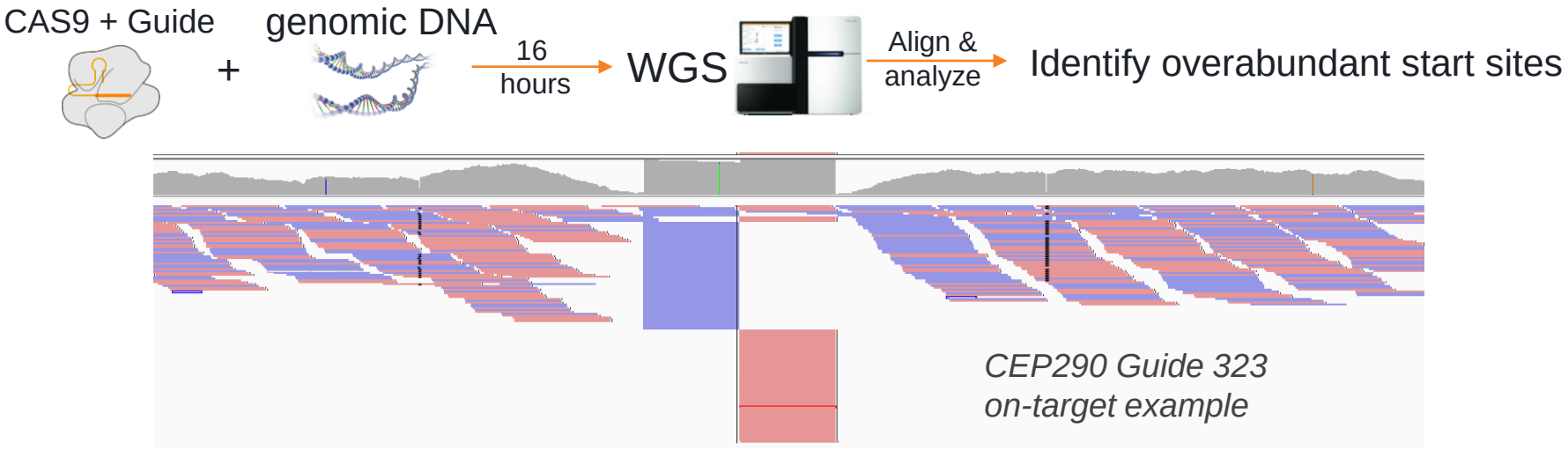
Comprehensive Specificity Assessment for Genome Editing Medicines: METHODS

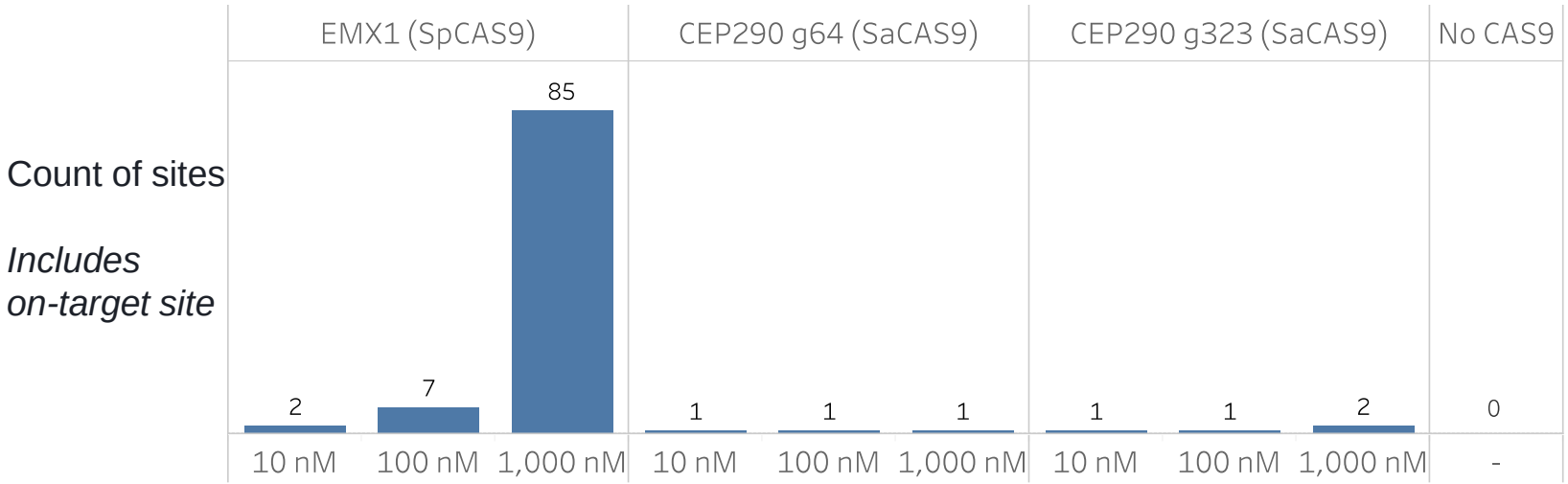
		DETECTION	
		Discovery →	Verification
SCOPE	Small DNA changes *(within a single chromosome, up to ~100 base pairs)*	*In silico* modeling	Measure effect of enzyme activity on 'discovered' sites (Targeted PCR and UDiTaS)
		Biochemical approaches (Digenome)	
		Cellular approaches (GUIDE-Seq)	
	Large DNA changes *(within or between chromosomes)*	*In silico* modeling	Measure effect of enzyme activity on 'discovered' large changes (ddPCR and UDiTaS)
		Cellular approaches (UDiTaS)	

Robust Specificity Analysis in Multiple Model Systems Identifies Molecules with No Detectable Off Targets

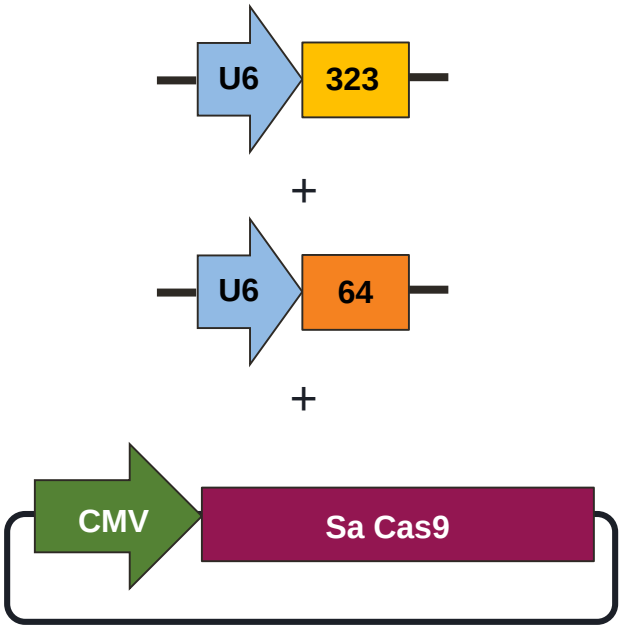
gRNA	Genome-Wide Cell BAsed Discovery Assay (GUIDE-seq)					Targeted Measurement Assays		
	Cell Type 1	Cell Type 2	Cell Type 3	Cell Type 4	**# Off-target sites**	Cell 1 # of sites assayed	Cell 4 # of sites assayed	**# Off-target sites**
11	✓	✓	✓	✓	**4**	3	6	**1**
64	✓	✓	✓	✓	**0**	63	83	**0**
323	✓	✓	✓	✓	**0**	58	92	**0**
490	✓		✓	✓	**0**	48	74	**0**
492	✓		✓	✓	**1**	56	95	**1**
496	✓		✓	✓	**0**	58	72	**0**
502	✓		✓	✓	**8**	12	12	**6**
504	✓		✓	✓	**0**	53	71	**0**
Non-Specific Control				✓	**59**			

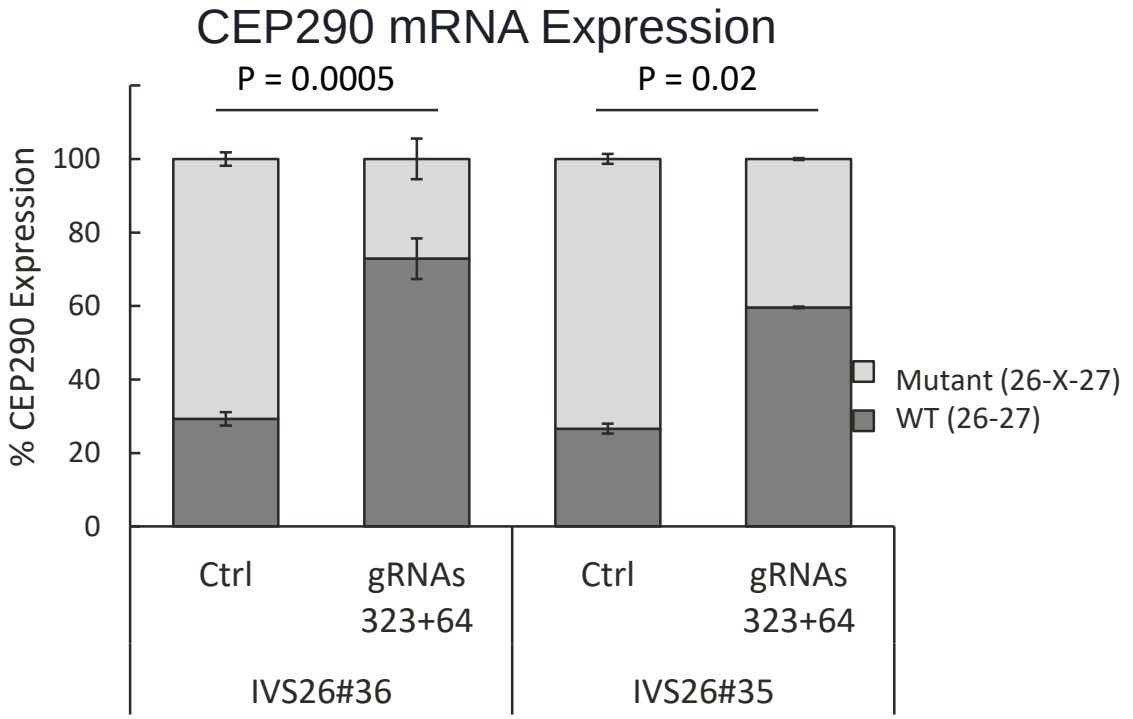
Digenome Assay with Lead Guides (64 and 323)

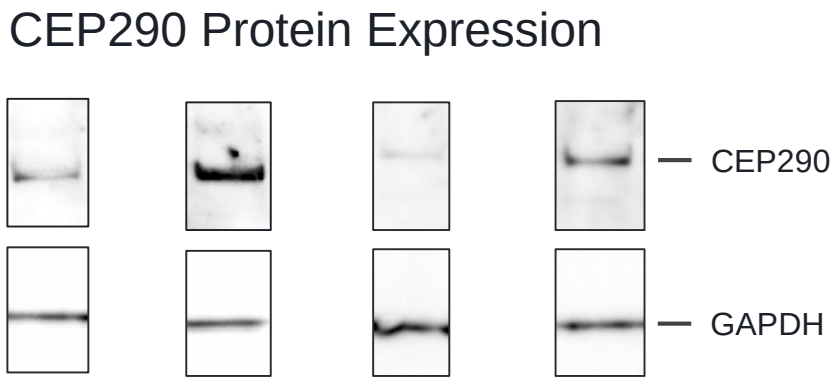




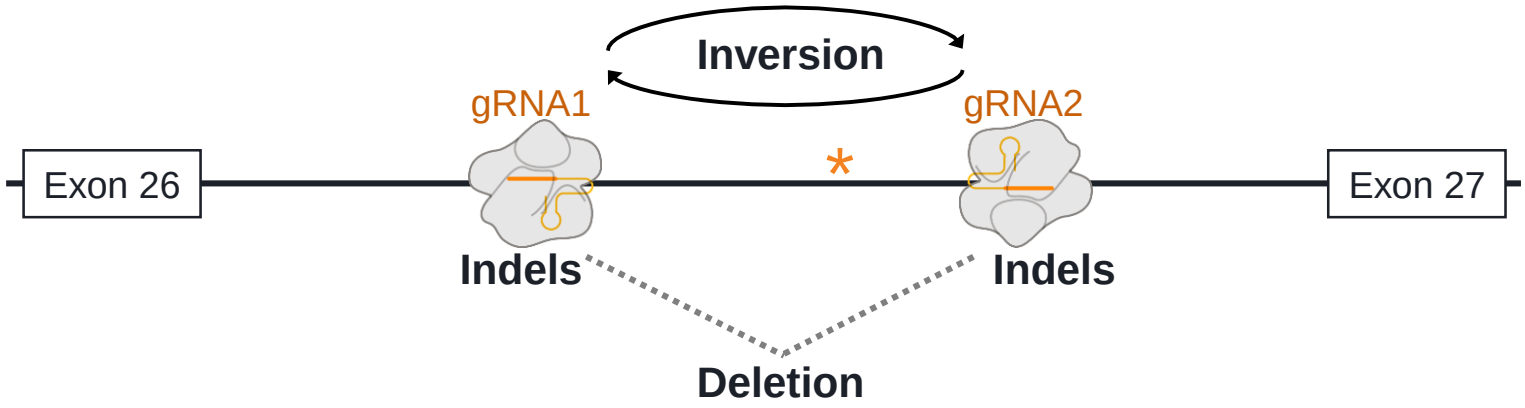
Editing Corrects CEP290 Splicing and Restores mRNA and Protein Expression

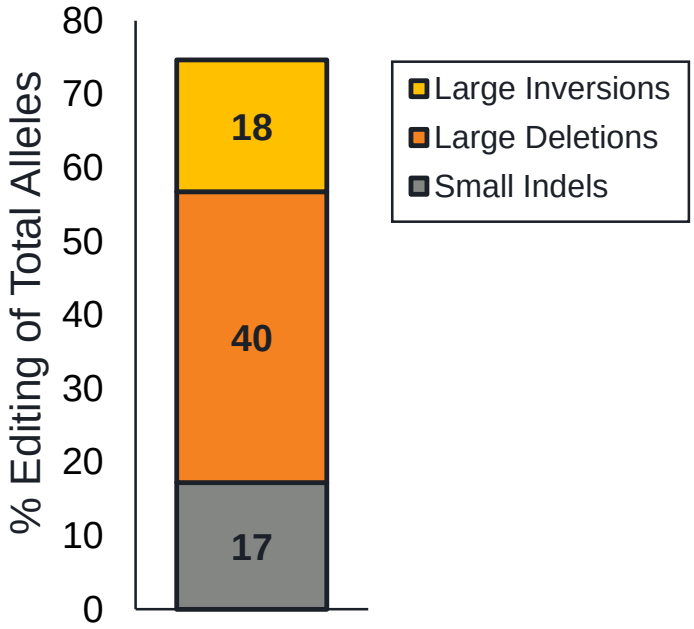




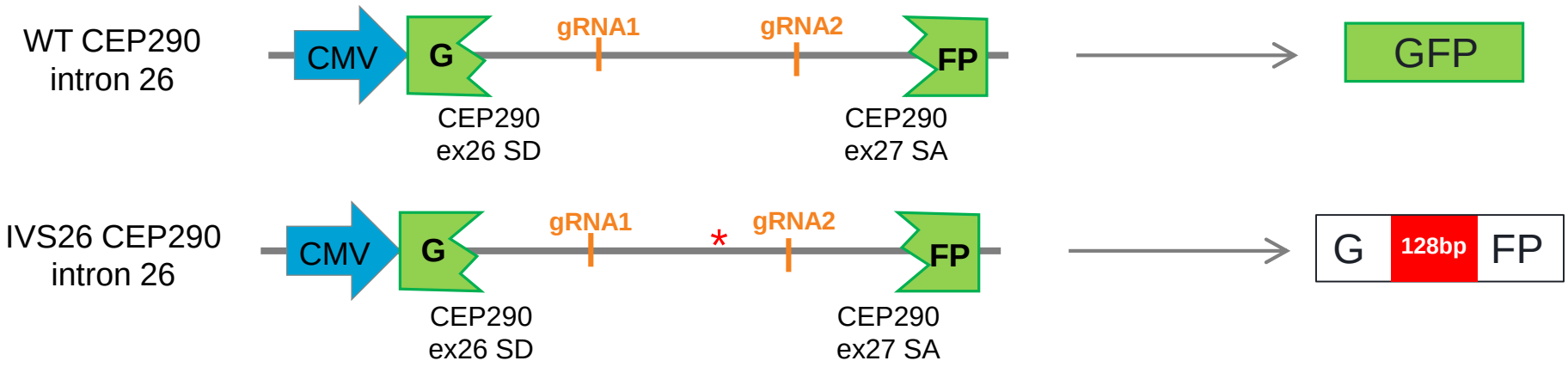


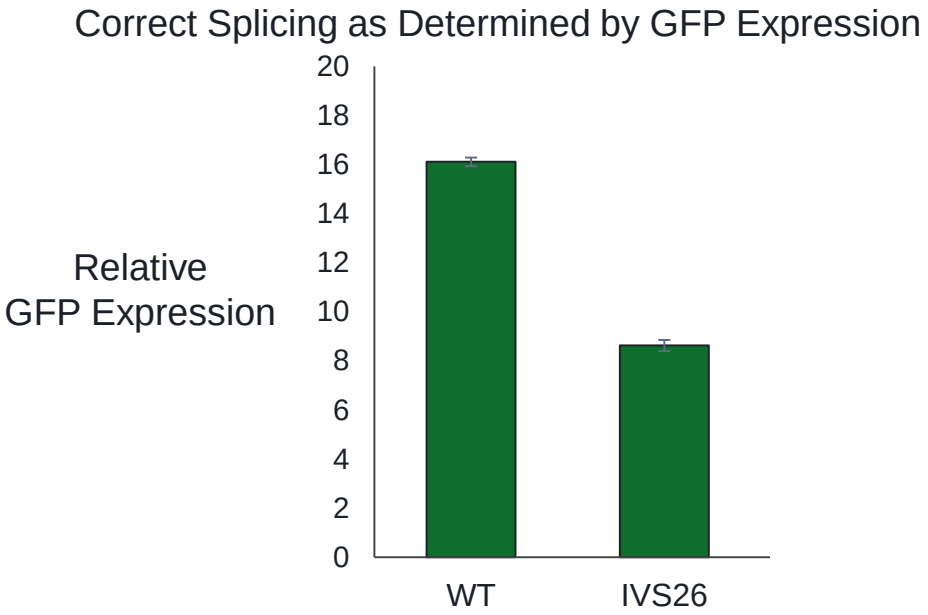
Editing Causes Inversions, Deletions, and Indels



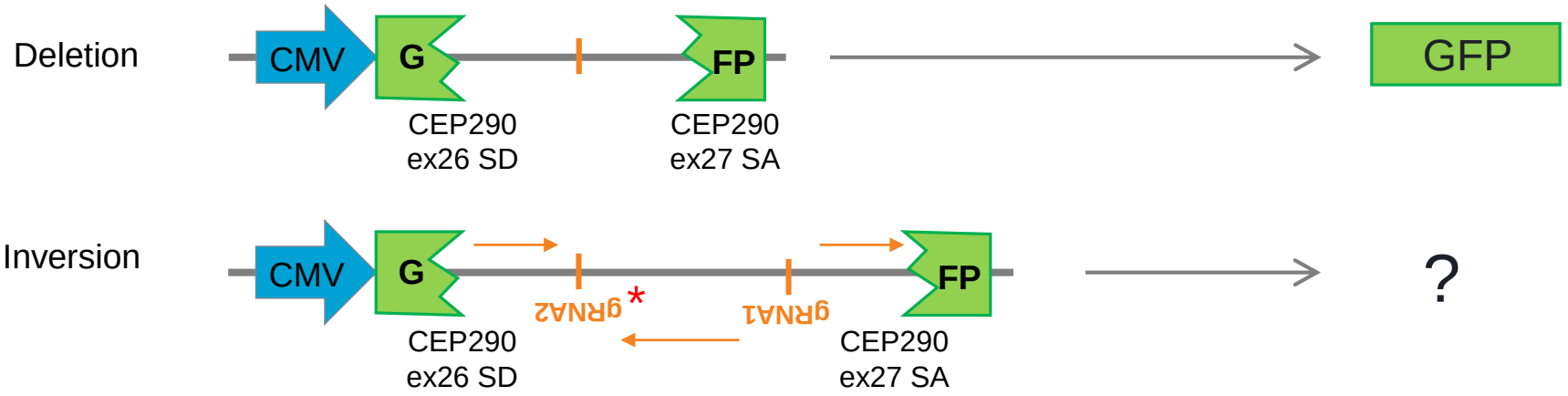


LCA10-IVS26 Mutation Decreases Splicing in a Reporter System

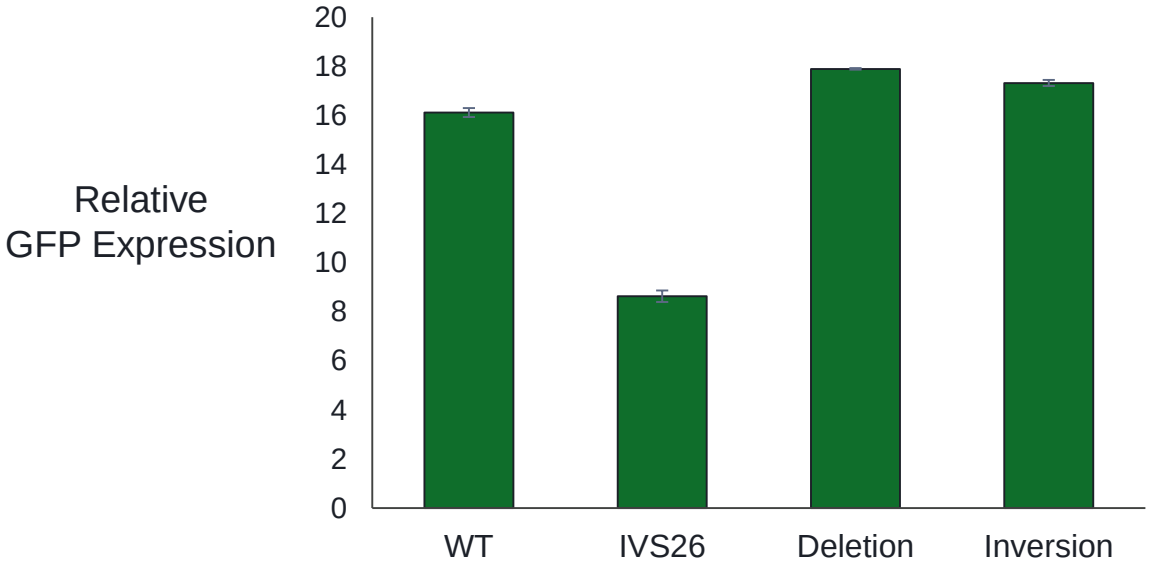




Targeted Deletions and Inversions Correct Splicing

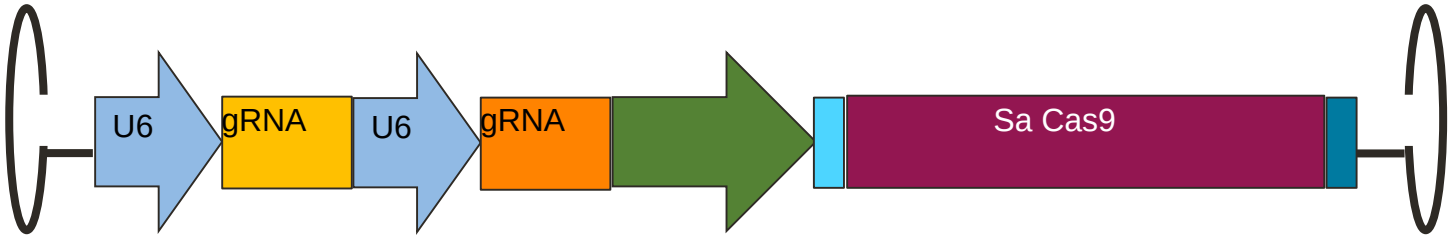


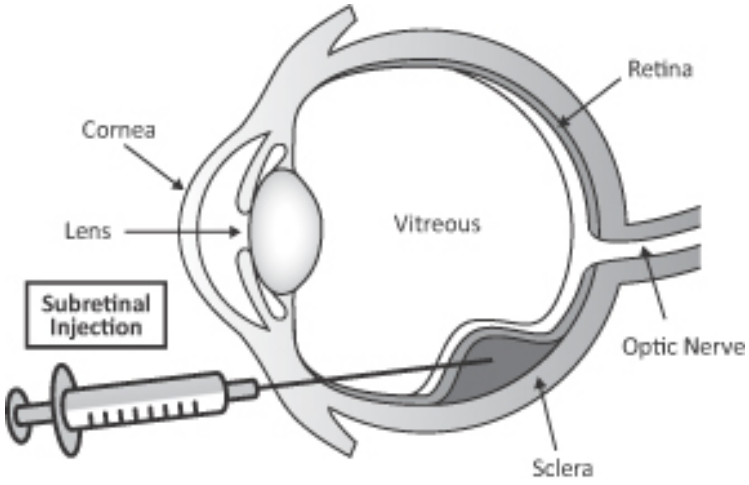
Correct Splicing as Determined by GFP Expression



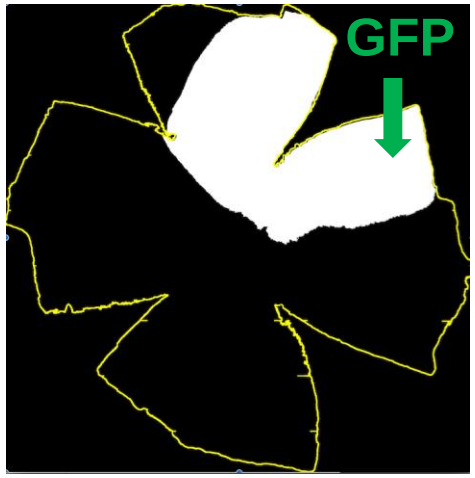
EDIT-101: gRNAs plus SaCas9 in AAV5

AAV5

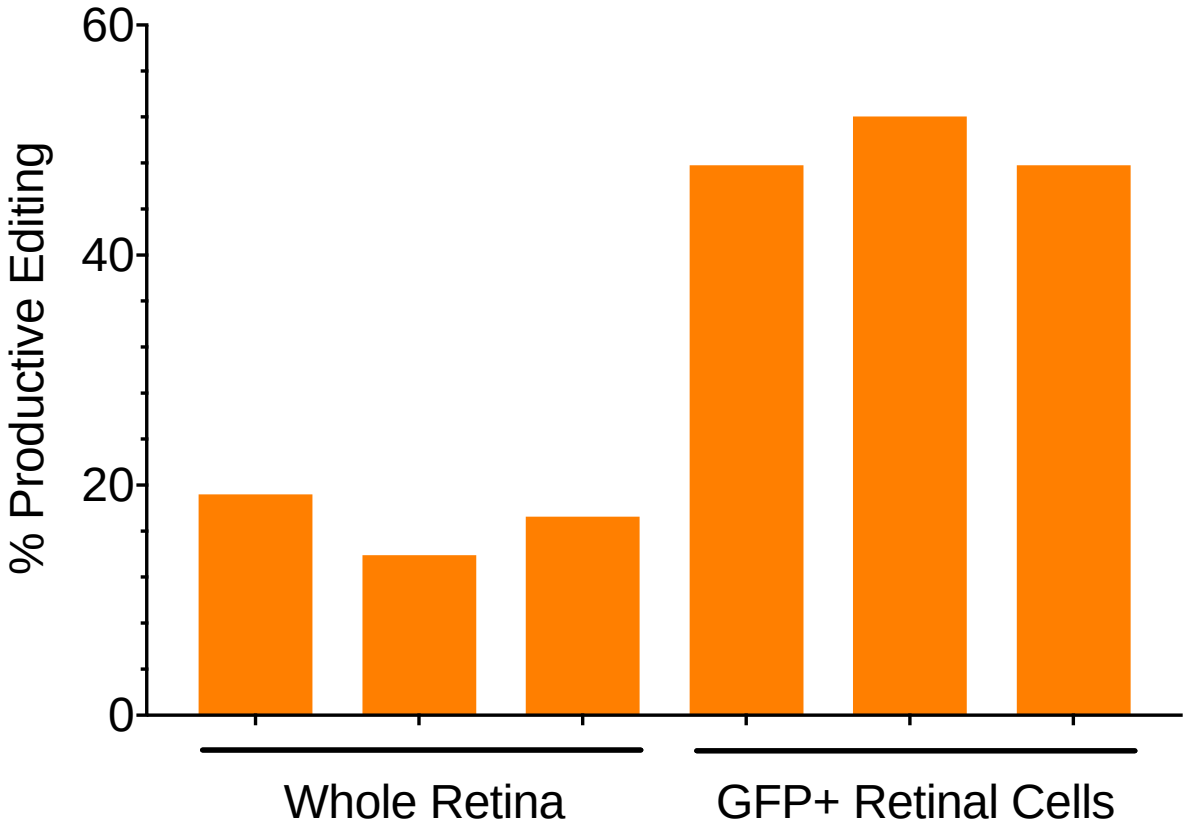




Efficient Transduction and Editing of Mouse Retina by Subretinal Delivery of EDIT-101

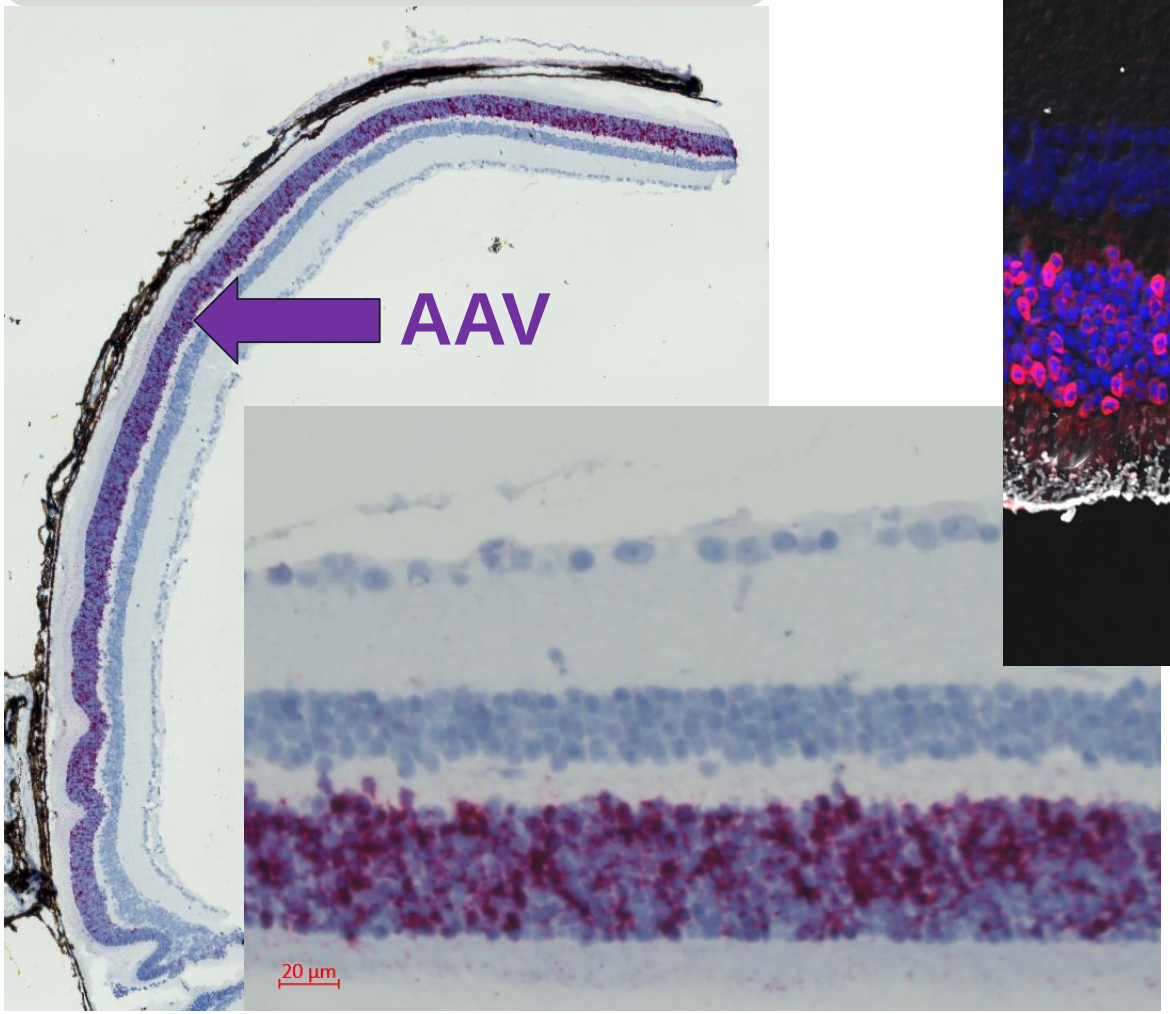


Transduction efficiency by SR in mouse retina:
24% (FACs) –
30% (Histo)

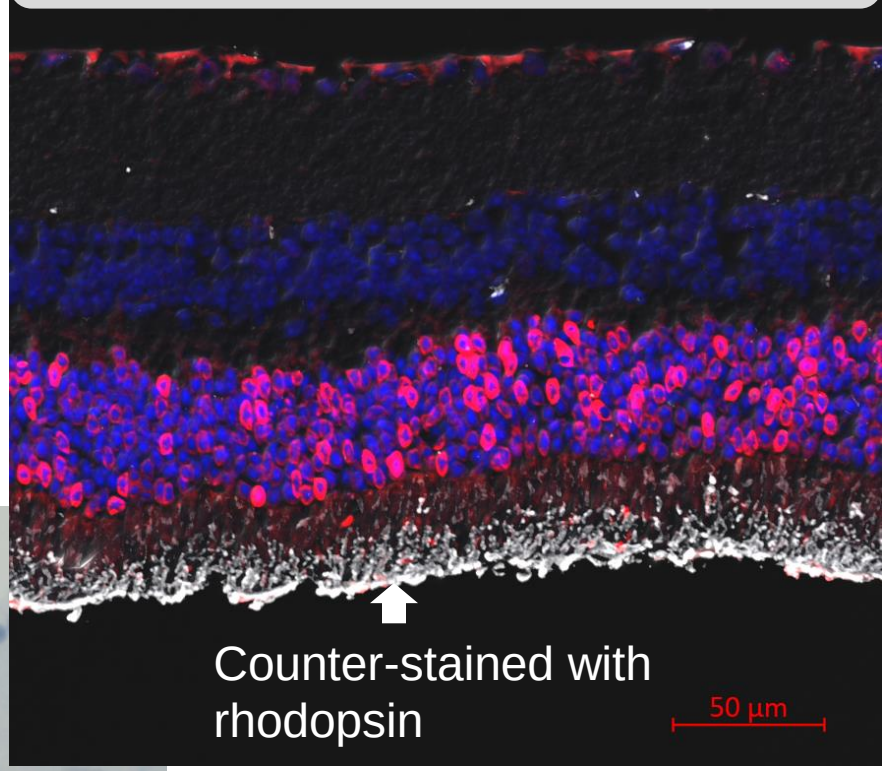


Efficient Transduction of Photoreceptor Cells with EDIT-101 in HuCEP290 KI Mice

ISH of AAV Vector Genome

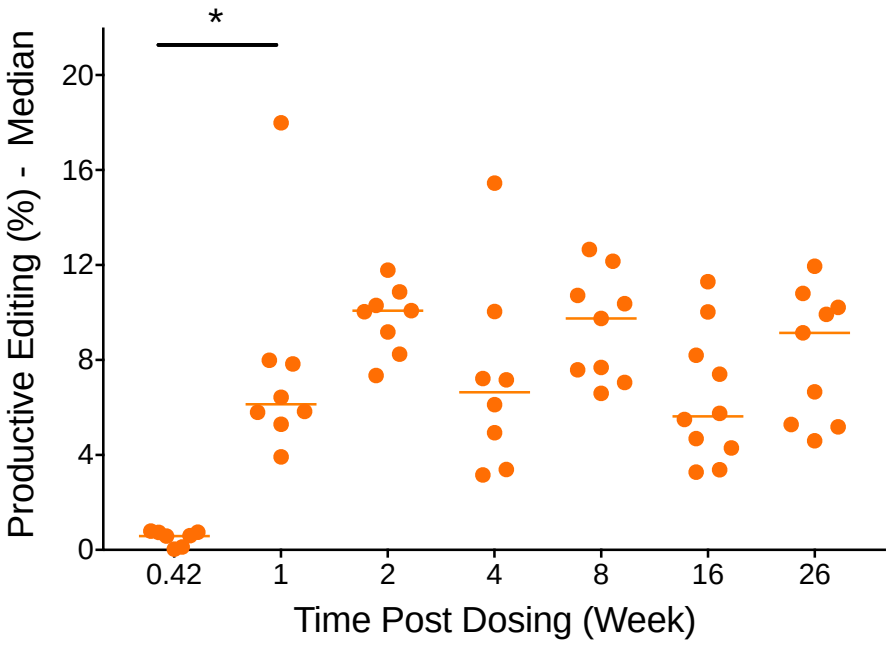


IHC of Cas9 Protein

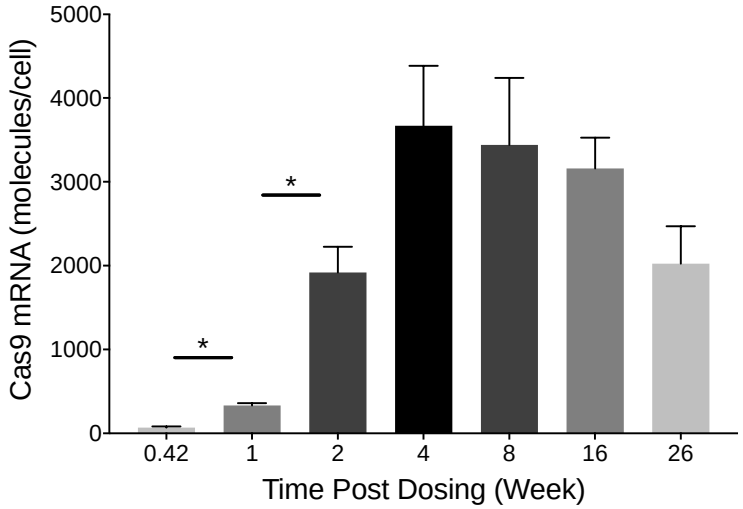


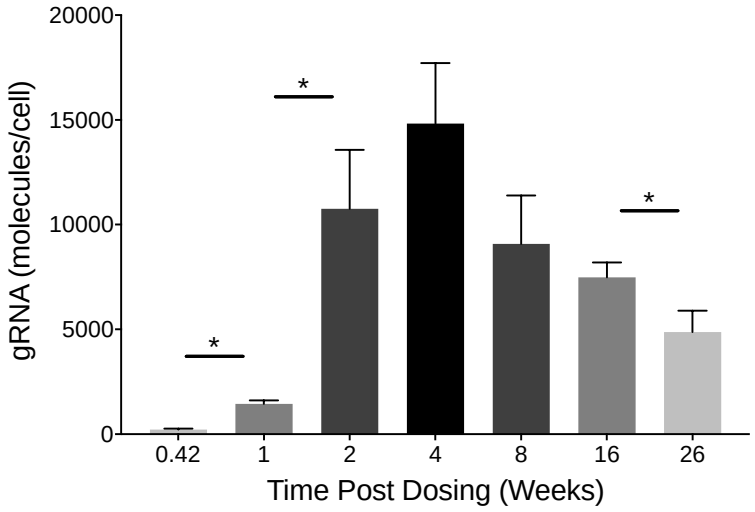
Rapid Onset and Stable CEP290 Gene Editing by EDIT-101 in HuCEP290 IVS26 KI Mice

Stable CEP290 Gene Editing Over Time

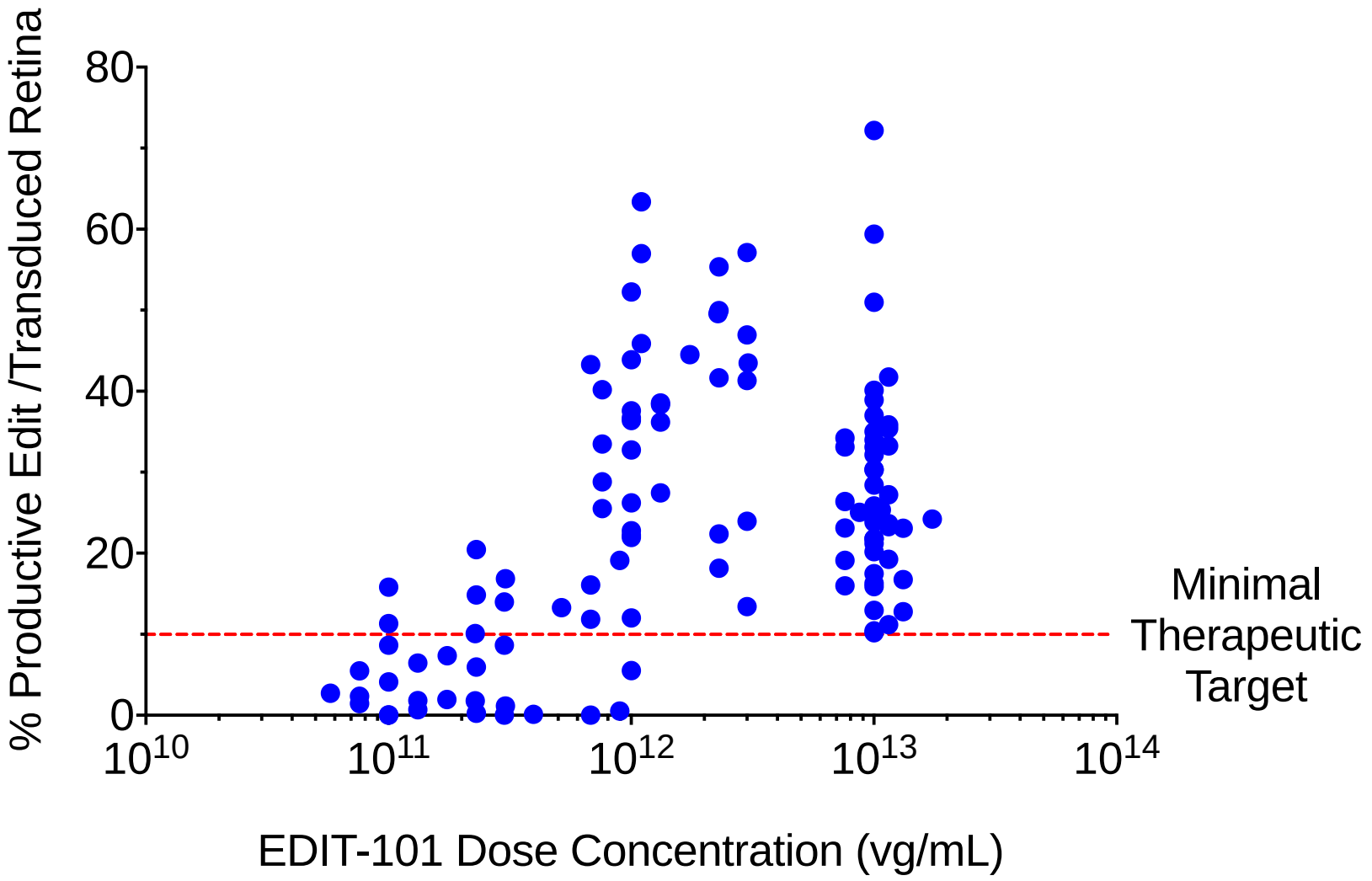


CRISPR/Cas9 Expression Decreased Over Time

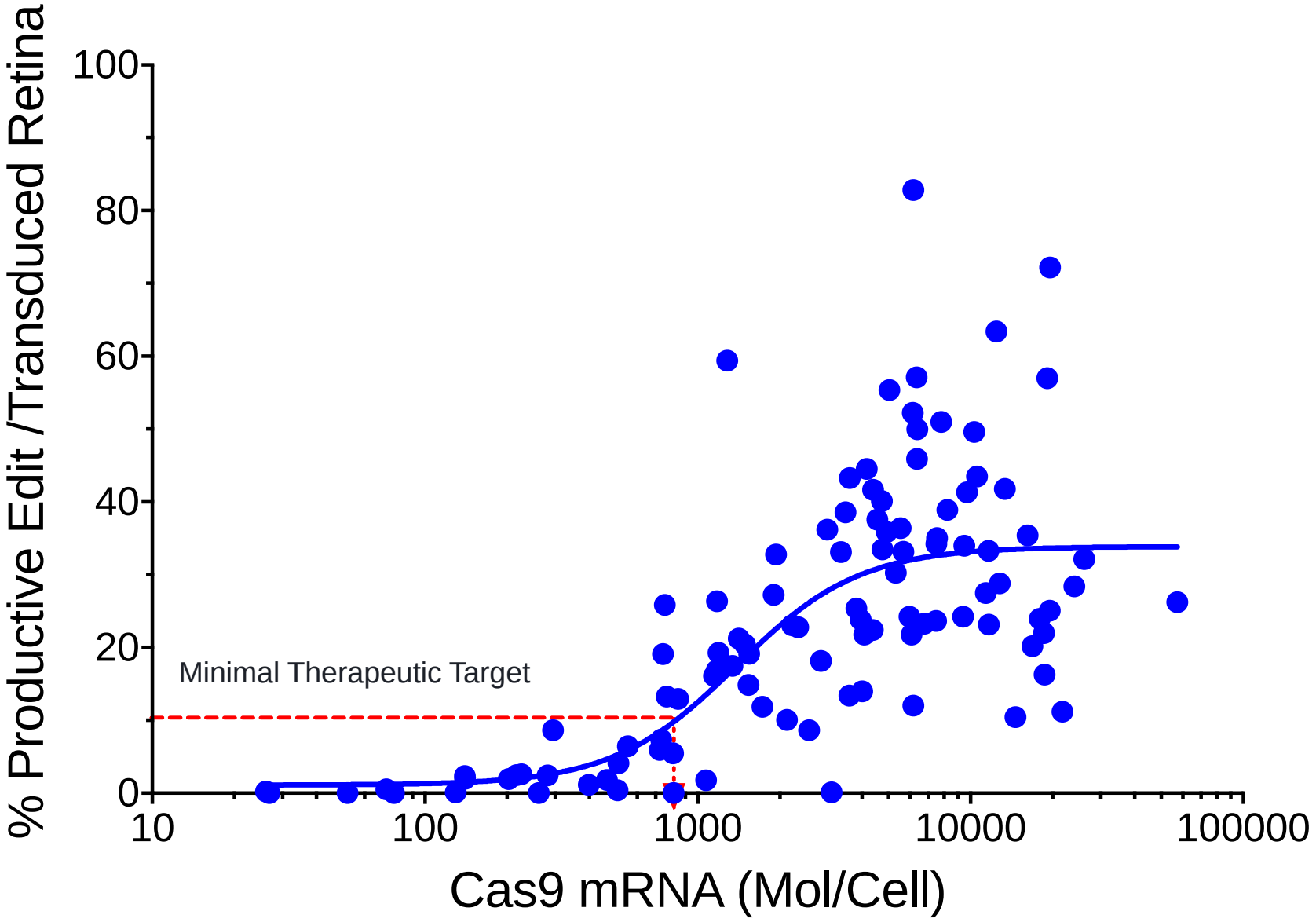




Dose Response of EDIT-101 in HuCEP290 KI Mice



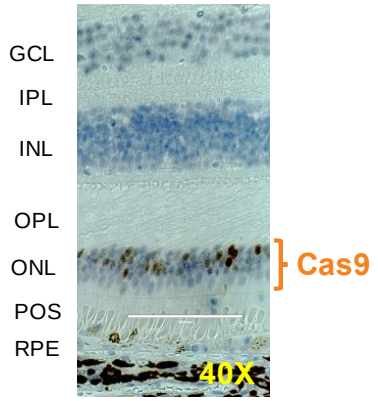
Correlation of Productive CEP290 Editing Efficiency and Expression Levels of Cas9 mRNA



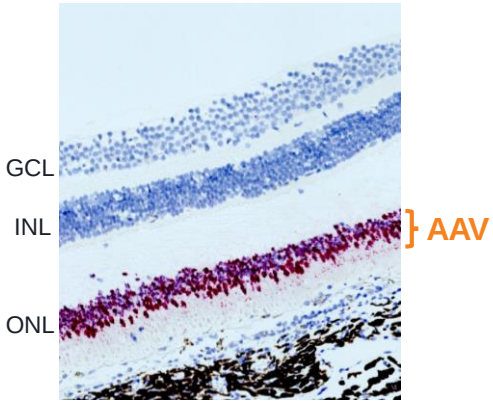
Retinal Structural Differences Between Mice and NHPs and Adjusted Productive Editing

Monkey Retina

Cas9 IHC



ISH of AAV vector genome

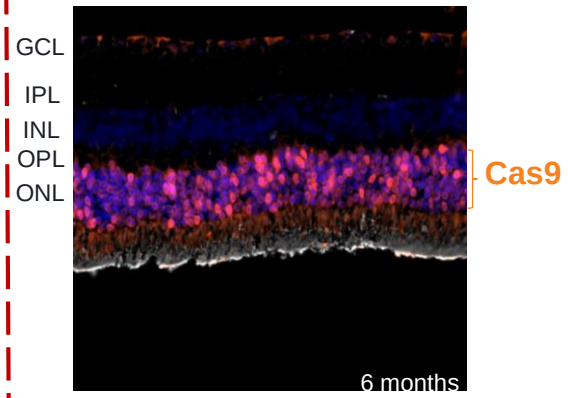


AAV5-cynoCEPgRNAs-GRK1-SaCas9

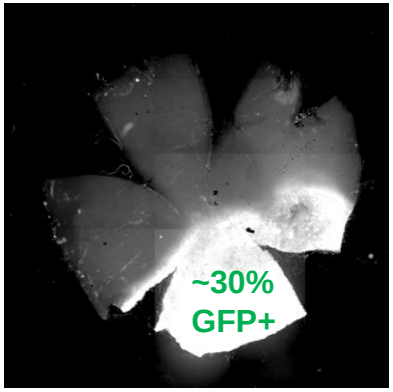
- Macula
- Photoreceptors: 25-30% cells
- Most foveal photoreceptors are cones
- 8mm retinal punch covering most of the bleb collected for analysis but only photoreceptors (25-30%) express GRK1

Mouse Retina

Cas9 IF



AAV5-GRK1-GFP

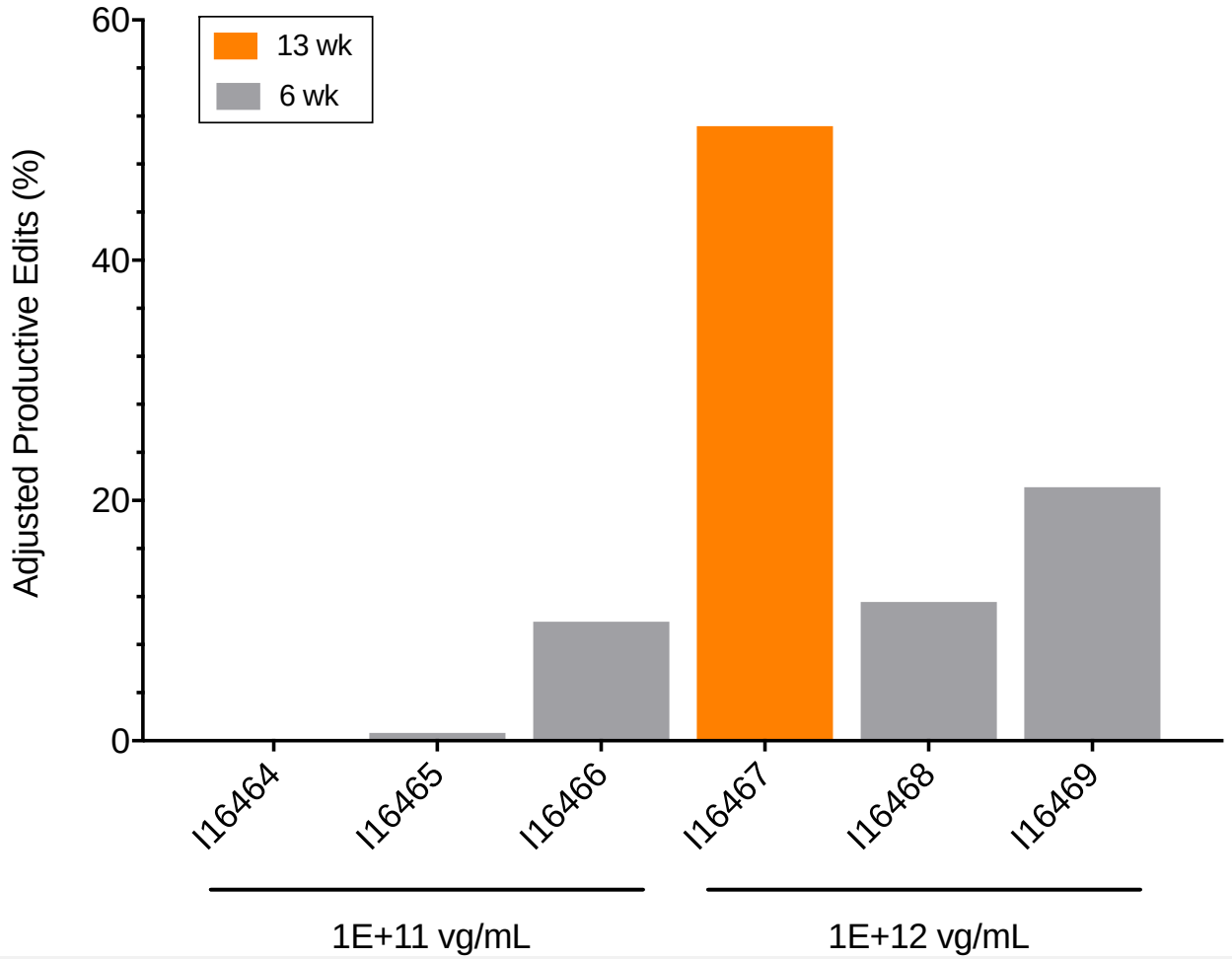


EDIT-101

- No Macula
- Photoreceptors: 85-90% cells
- 97% of photoreceptors are rods
- Entire retina collected for analysis but only 30% neural retina transduced with 1µl AAV5 vector

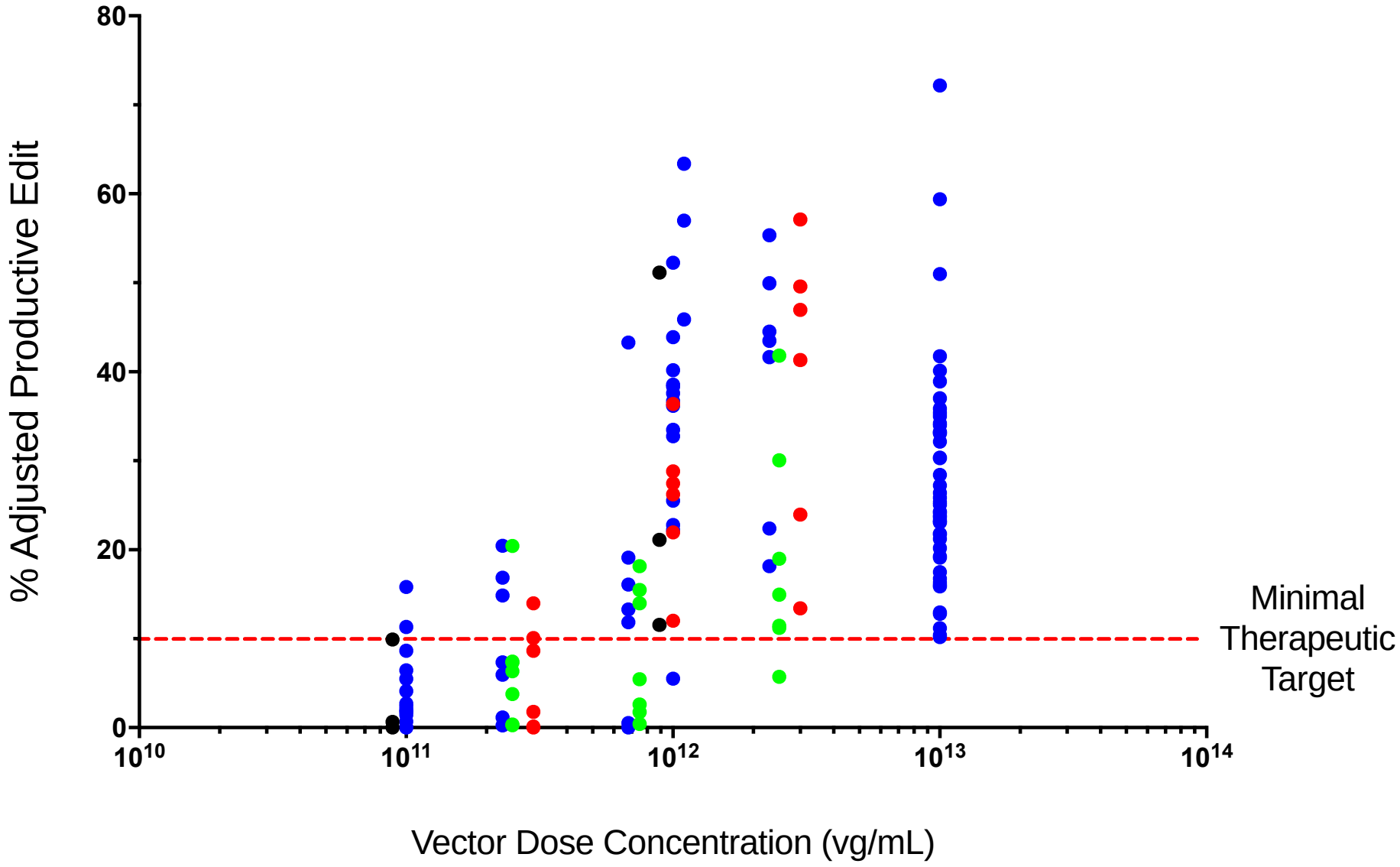
In both species, quantified productive edits (inversions and deletions) must be multiplied by 3.5x to determine total productive editing in photoreceptors

Productive Editing Exceeds Therapeutic Threshold in NHPs



Based on demonstration that Cas9 expression is limited to photoreceptors cells, level of productive editing in photoreceptors may be as high as 50%

Editing Efficiency Comparison: EDIT-101 in Mice vs Surrogate NHP Vectors in NHPs

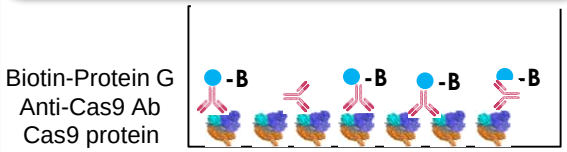


Immunogenicity Analysis

- What is the prevalence of pre-existing humoral or cellular immunity to Cas9 proteins in humans and preclinical species?
- Does *in vivo* delivered CRISPR/Cas9 system induce a humoral or cellular immune response to Cas9 proteins in humans and preclinical species?
- Will the pre-existing or induced humoral or cellular responses affect efficacy or safety?
- Scientists at Editas and FDA are collaborating to address these questions.

Assay to Detect Anti-Cas9 Antibodies in Human Serum in Accordance with FDA Guidance

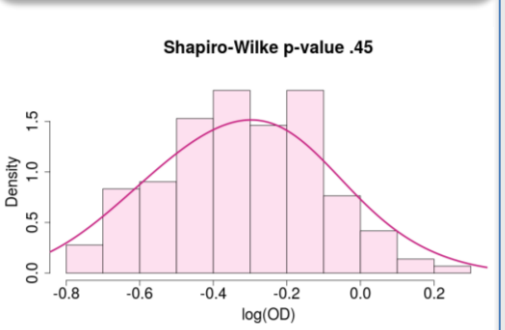
An ELISA assay was developed using anti-SaCas9 and anti-SpCas9 antibodies



Training set: 48 human donors

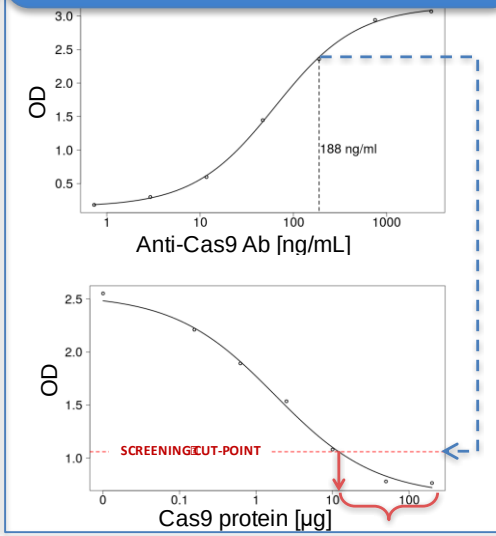
- Validate assay (Sensitivity, Selectivity and Precision)
- Set cut point for screening assay
- Set cut point for confirmatory assay

Determine Screening Cut-point



Determine normality of distribution
Outlier evaluation

Determine [Cas9] for the Confirmatory Competition Assay



Sample set: 200 human donors

- Determine the prevalence of anti-Cas9 antibodies in a sample of US population
- SAMPLES TESTED POSITIVE IN SCREENING ASSAY ARE SUBJECTED TO THE **CONFIRMATORY** ASSAY

Pre-existing human anti-Cas9 antibodies

Human anti-Cas9 antibodies	SaCas9	SpCas9
Screening assay	19% (38/200)	4.5% (9/200)
Confirmatory assay	5.5% (11/200)	1.5% (1/200)

These results show low levels of pre-existing anti-Cas9 antibodies in humans

Humoral Response to Cas9 and AAV5 Capsid

	SaCas9	SpCas9	AAV5 Capsid
Pre-existing human anti-Cas9	5.5% (11/200)	1.5% (1/200)	
Pre-existing NHP anti-Cas9	10/20		
Induced NHP anti-Cas9	1/6		
Pre-existing NHP anti-AAV5			5/20
Induced NHP anti-AAV5			5/6

Collaboration between Zuben Sauna (OTAT/CBER/FDA) and Editas Medicine

Towards a CRISPR Medicine for LCA10

- Editing corrects splicing defect in cells from LCA10-IVS26 patients and restores full-length mRNA and protein
- EDIT-101 gRNAs are highly specific
- EDIT-101 and NHP-specific construct efficiently edit photoreceptors in transgenic mice and NHPs, respectively
- Immunogenicity studies suggest low levels of anti-Cas9 antibodies in humans

CEP290 gene editing medicine has the potential to have a major impact on vision in LCA10 patients