Exploratory Immuno-Safety Profile of EDIT-101, a First-in-Human *In Vivo* CRISPR Gene Editing Therapy for *CEP290*-Related Retinal Degeneration

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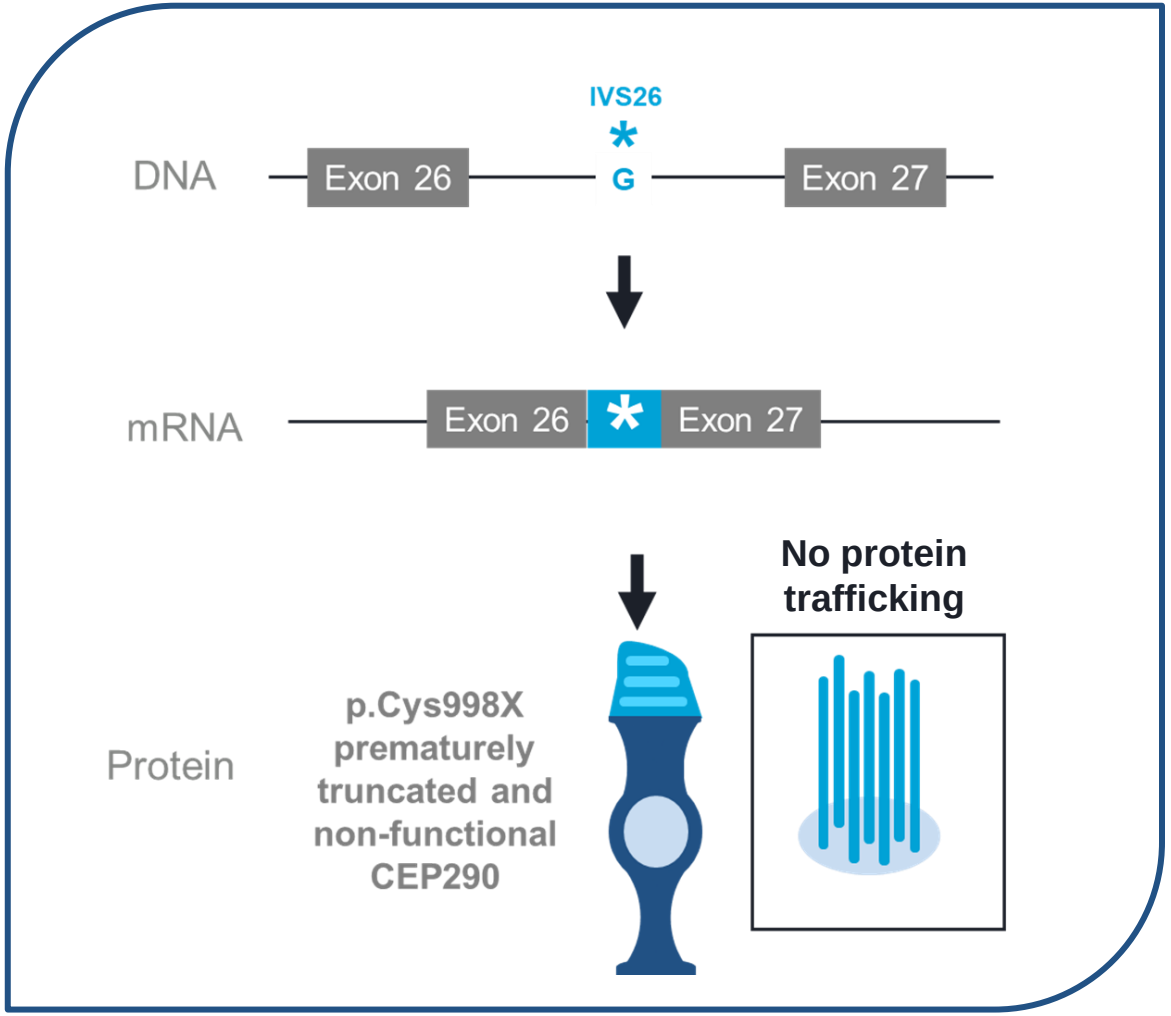
Disclosures

Brian R. Duke, Saleh El-Husayni, Michael C Jaskolka, Amanda Erlwein, Rene Myers, Mark S. Shearman, Kate Zhang, and Swati Mukherjee are all employees of Editas Medicine

CEP290-related retinal degeneration: A leading cause of early onset vision loss

Currently no approved treatments for CEP290-related retinal degeneration

- Leber Congenital Amaurosis Type 10 (LCA10) is a rare, autosomal recessive inherited disorder that causes progressive vision loss in children within the first decade of life[1,2]
- Disease is characterized by early loss of rod photoreceptors with cones being structurally intact and viable until the 4th decade of life
- LCA10 is most commonly caused by the *CEP290-IVS26* mutation, accounting for 15–20% of all cases[1]
- This mutation results in a truncated, non-functional CEP290 protein due to early translational termination

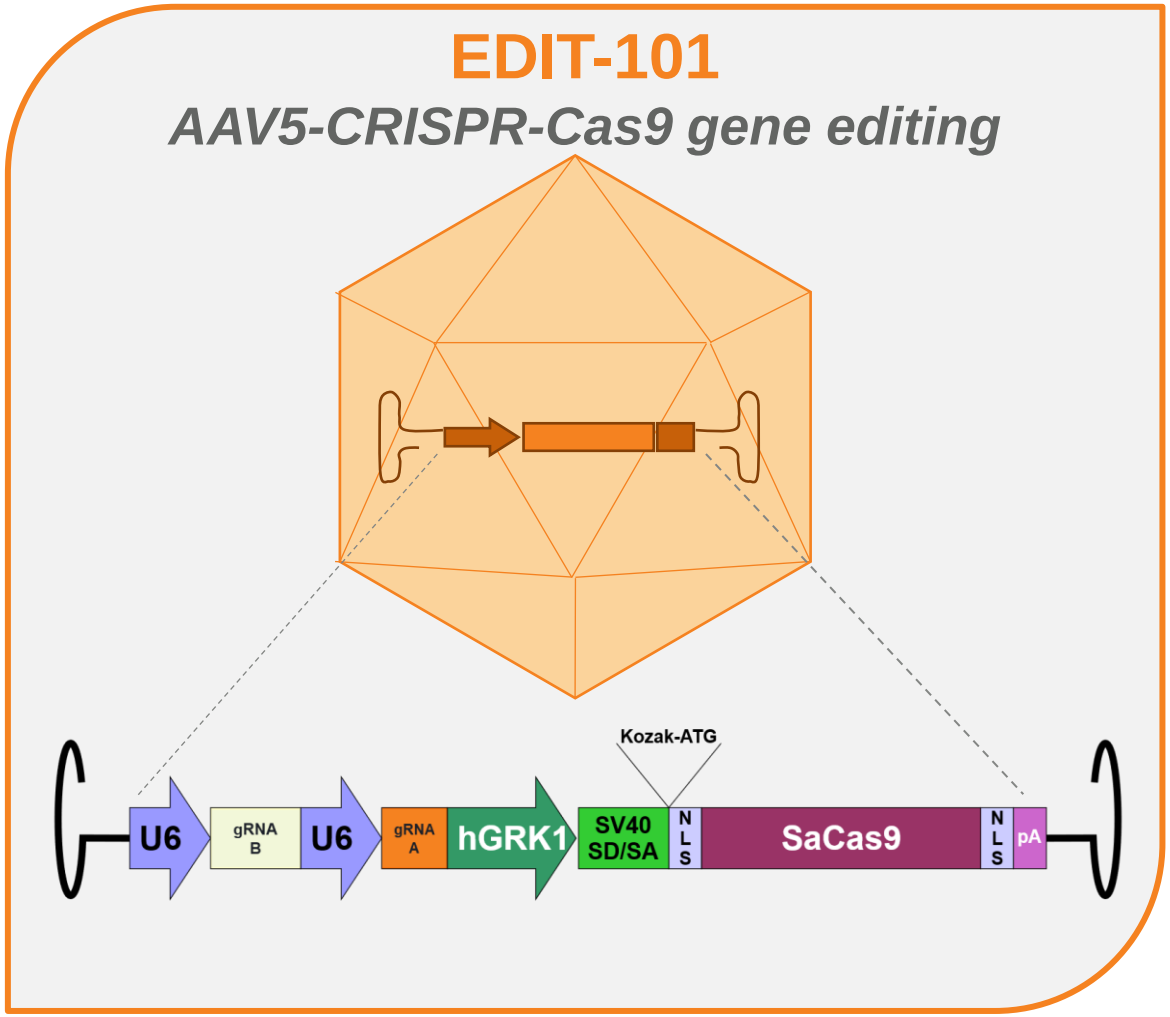


CEP290: centrosomal protein 290; CEP290-IVS26: c.2991+1655A>G mutation with intron 26; LCA10, Leber Congentital Amaurosis.

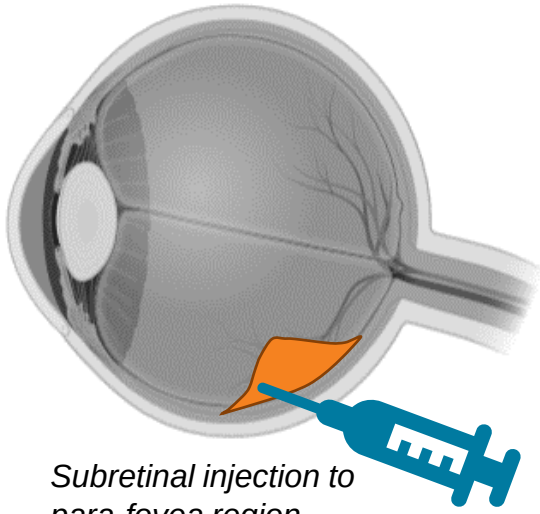
1. Kumaran N, et al. *Br J Opthalmol*. 2017;
2. Weleber RG. *LCA Gene Reviews*. 2013.

EDIT-101 is designed to specifically edit *CEP290* within photoreceptors

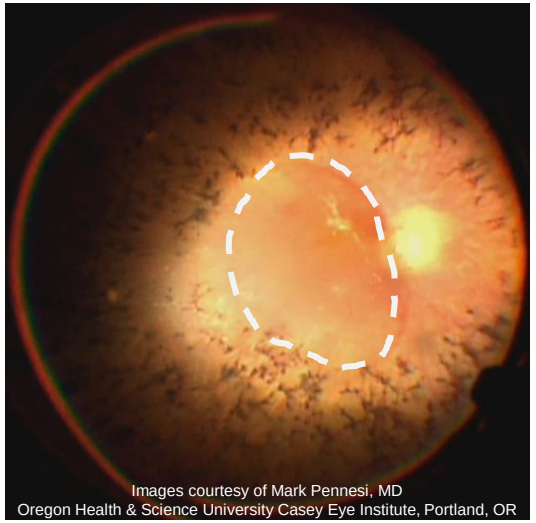
AAV5 with DNA encoding two gRNAs and SaCas9 delivered subretinally as a single dose



- **Photoreceptor-tropic** AAV5 vector
- **Highly specific** Guide RNAs
- **Restricted** SaCas9 expression in **photoreceptor cells** via human G-coupled Receptor Kinase 1 (hGRK1)
- **Local delivery to key subretinal space** targeting the structurally retained cones in the fovea, for functional restoration



Subretinal injection to para-fovea region



Images courtesy of Mark Pennesi, MD
Oregon Health & Science University Casey Eye Institute, Portland, OR

AAV5: adeno-associated virus type 5; SaCas9: *Staphylococcus aureus* CRISPR associated protein 9; hGRK1: human G-coupled Receptor Kinase 1.

Maeder ML, et al. *Nat Med*. 2019.

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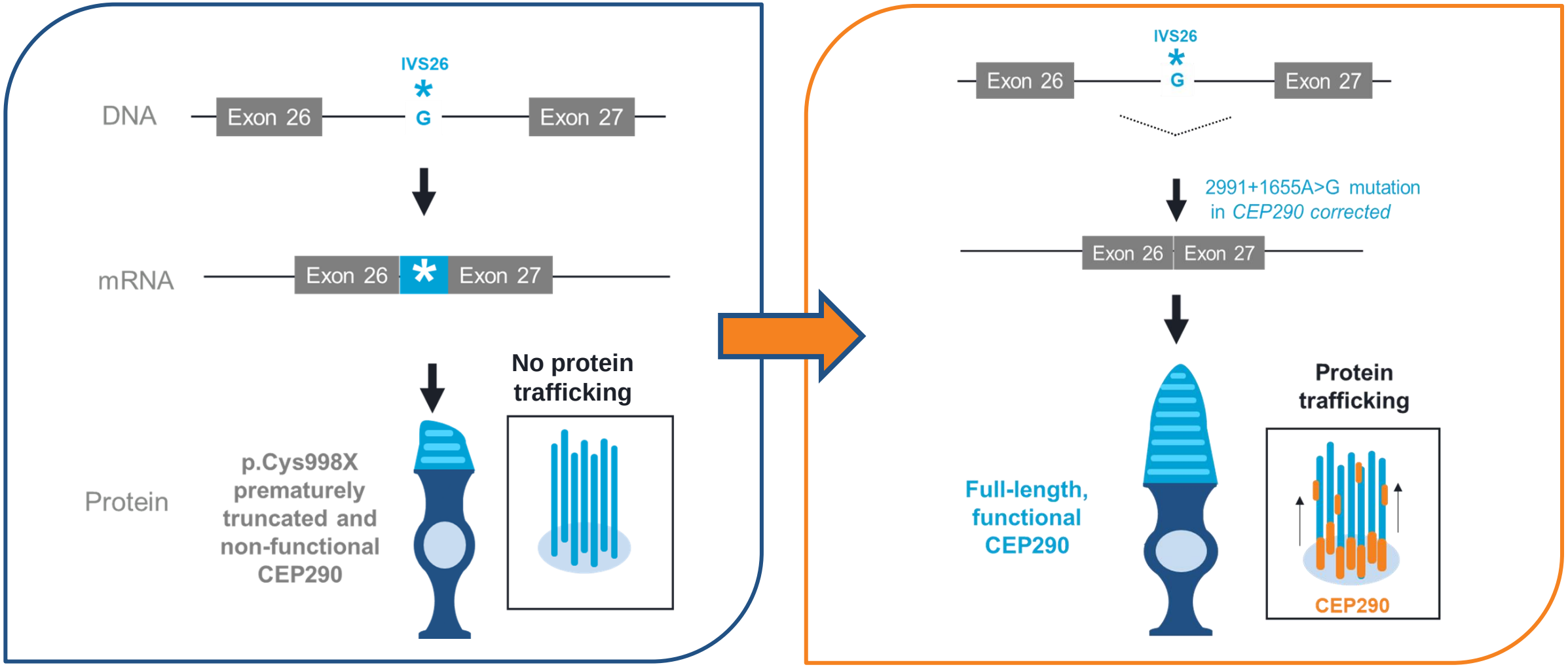

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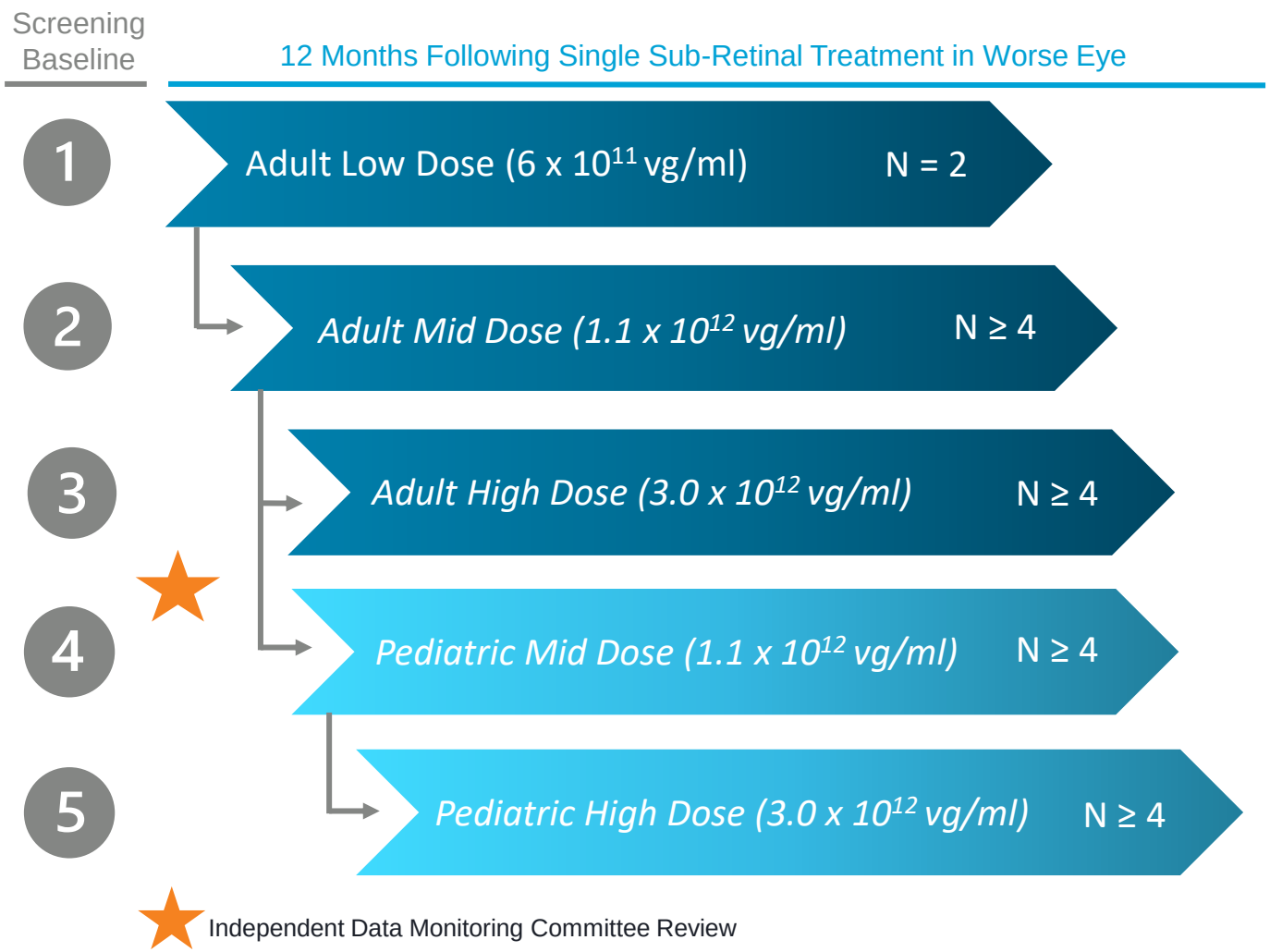
BRILLIANCE Trial

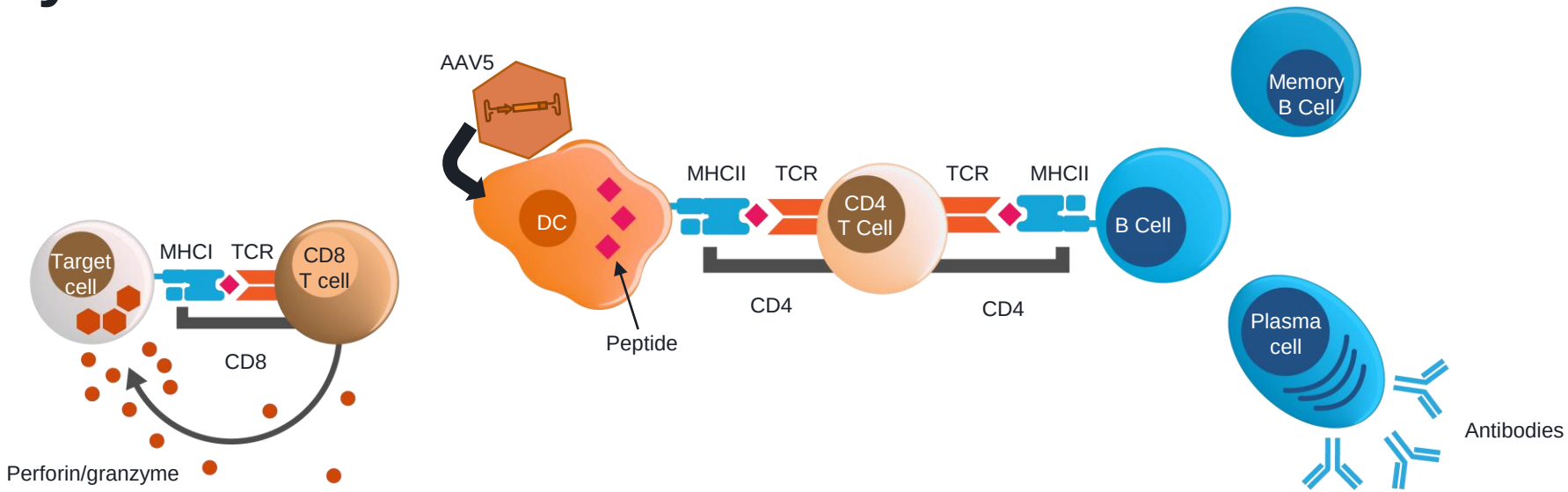
Phase 1/2, open-label, single ascending dose study for EDIT-101 (NCT03872479)



Primary Objective: Safety
Secondary Objectives: Tolerability & Efficacy
Defining Target Dose (MTD)
Immunogenicity Viral Shedding

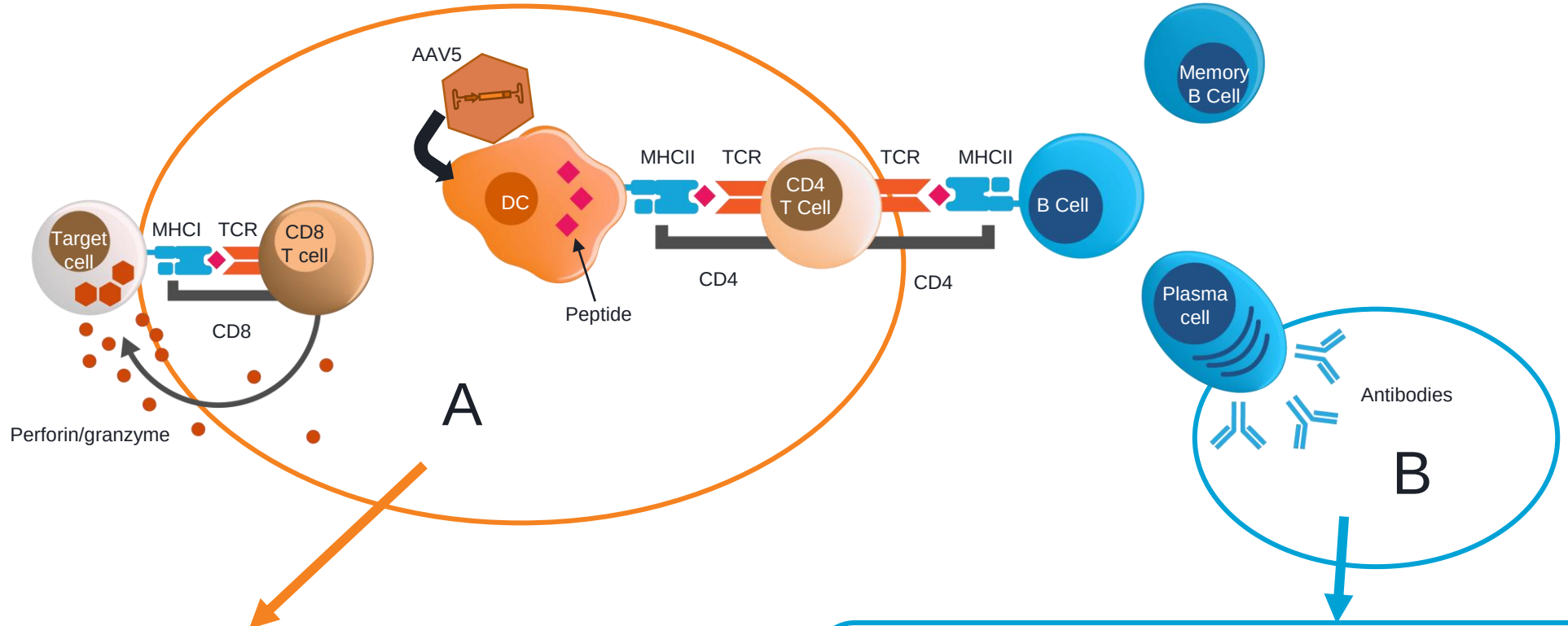
All subjects were placed on a low dose prophylactic oral prednisone regimen for 3 days prior to surgery until approx. 6 weeks following surgery

AAV gene therapy based clinical trials require monitoring adaptive immunity



AAV5: adeno-associated virus type 5; BAB: binding antibody; CD: cluster of differentiation; DC: dendritic cell; MHC: major histocompatibility complex; nAb: neutralizing antibody; PBMCs: peripheral blood mononuclear cells; SaCas9: *Staphylococcus aureus* CRISPR associated protein 9; TCR: T-cell receptor.

Cell mediated and humoral immune responses are being monitored in the BRILLIANCE trial



A. Cell Mediated Responses

- Subject PBMCs are collected and IFNγ ELISpot is performed
- Cells are stimulated with peptide pools derived from AAV5 capsid protein and SaCas9

B. Humoral Responses

- AAV5 and SaCas9 binding antibodies (BAB) are measured in subject serum using electrochemiluminescence ELISA
- AAV5 neutralizing antibodies (nAb) in subject plasma are measured using a cell-based infectivity assay

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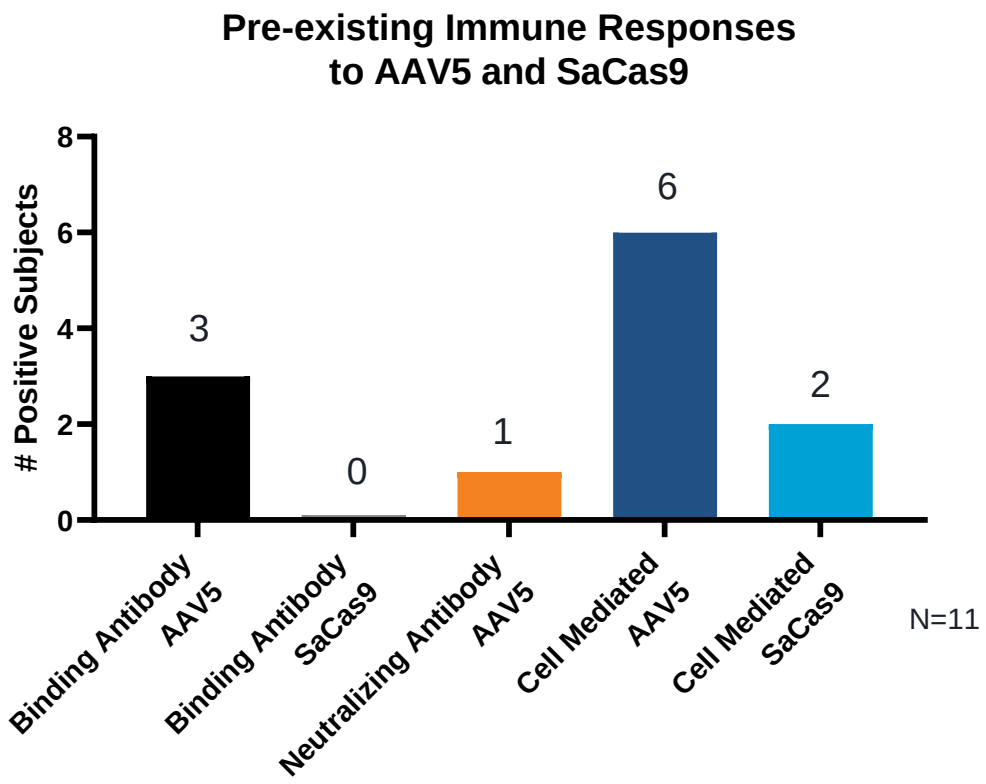
Profile of subjects with pre-existing immune response to AAV5 and SaCas9



- Pre-existing humoral immunogenicity to AAV5 was seen at screening in 3 of 11 subjects dosed. Only 1 subject's pre-existing antibodies were neutralizing
- No pre-existing humoral immunogenicity to SaCas9 was observed
- 6 of 11 subjects exhibited cell mediated responses to AAV5 at screening
- 2 subjects had pre-existing cell mediated responses to both AAV5 and SaCas9
- Pre-existing antibody responses have no clear correlation with cell mediated responses

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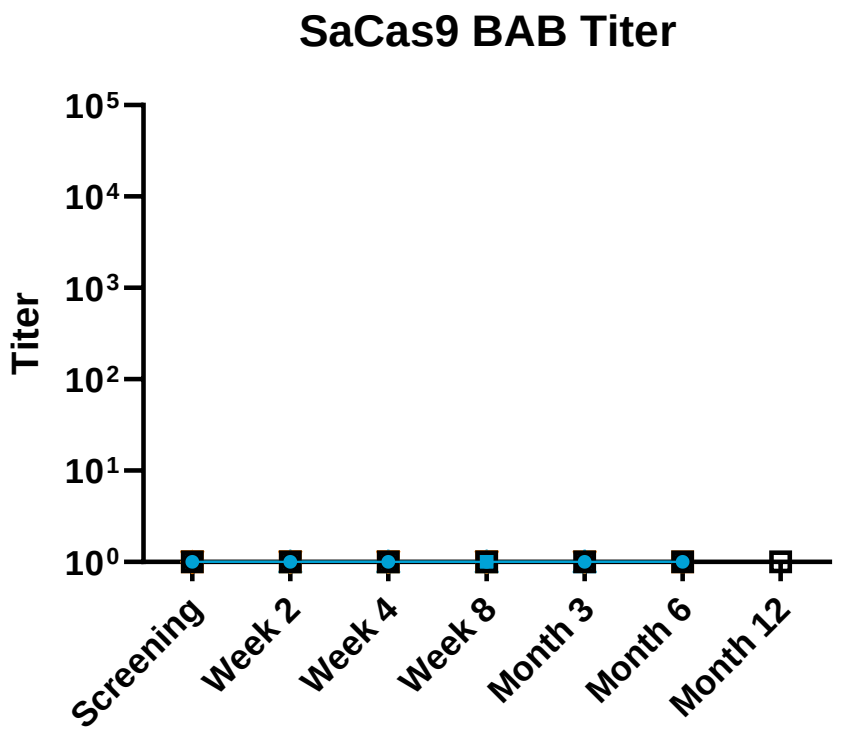
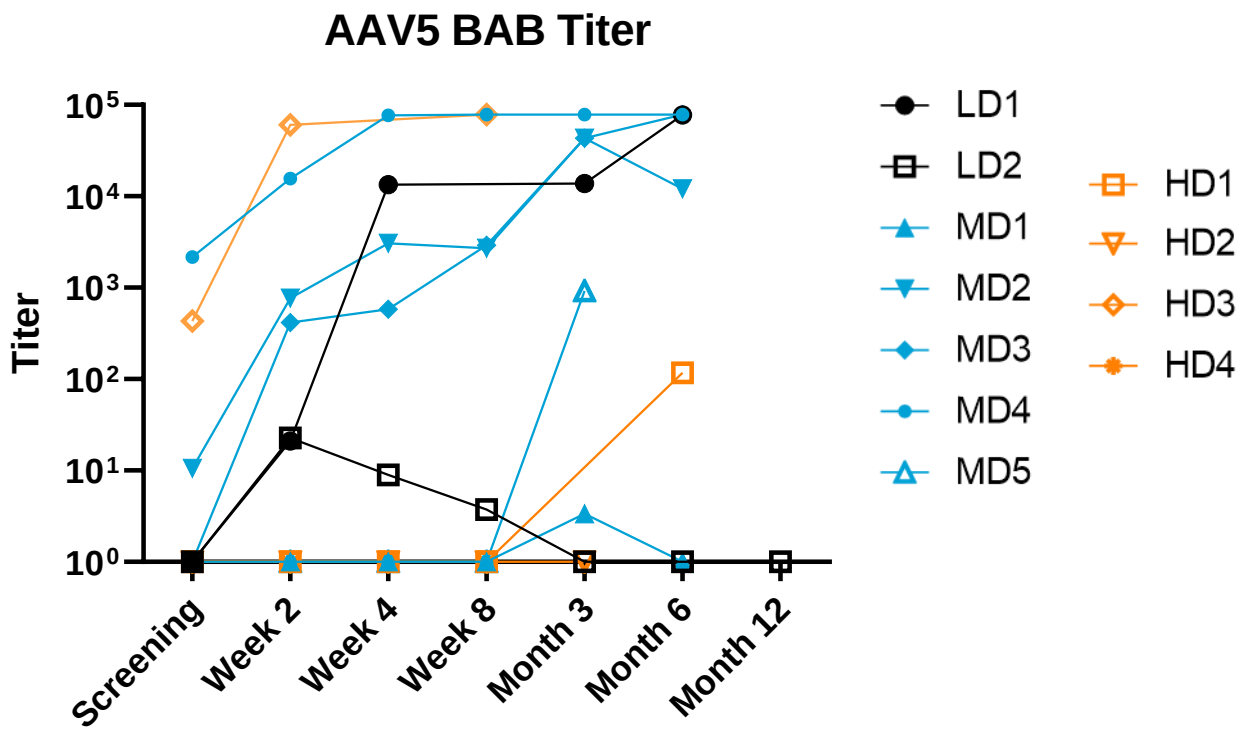
SaCas9 and AAV5 humoral response: Binding Antibodies

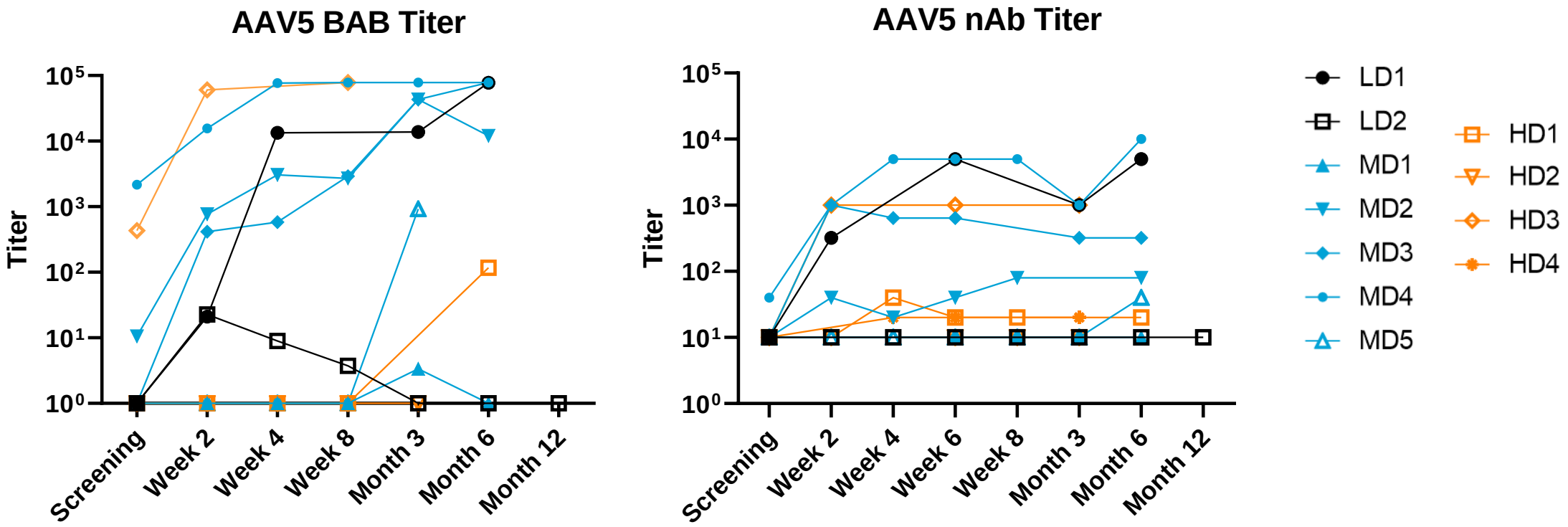




- No subjected treated with EDIT-101 developed BABs against SaCas9
- 9 of 11 subjects produce detectible levels of AAV5 BAB post dosing
- The observed titer of AAV5 BAB is independent of EDIT-101 dose level

BAB: binding antibody; HD: high dose patient; LD: low dose patient; MD: mid dose patient.

Most antibody responses to AAV5 are neutralizing



- AAV5 BAB titer positively correlate with levels of AAV5 neutralizing antibodies
- Not all antibody responses are equally neutralizing
- nAb titers are not correlated with EDIT-101 dose level and remain stable out to month 6 post-dosing

AAV5: adeno-associated virus type 5 BAB: binding antibody; HD: high dose patient; LD: low dose patient; MD: mid dose patient. nAb: neutralizing antibody.

No subject developed post-treatment cell mediated responses to EDIT-101

Cell mediated responses to AAV5 capsid and SaCas9 were assessed via IFNγ ELISpot.

A positive response to any peptide pool at ≥2 timepoints post-treatment was considered positive for the corresponding protein.

Cell Mediated Response Detection

Subject	Latest Timepoint	AAV5 Pre-Existing/Post-Treatment	SaCas9 Pre-Existing/Post-Treatment
LD1	Month 6	-/-	-/-
LD2	Month 12	**Yes/Yes**	-/-
MD1	Month 6	-/-	-/-
MD2	Month 6	-/-	-/-
MD3	Month 6	-/-	-/-
MD4	Month 6	**Yes/Yes**	-/-
MD5	Month 6	**Yes/Yes**	-/-
HD1	Month 6	**Yes/Yes**	**Yes/Yes**
HD2	Month 3	NC/**Yes**	NC/-
HD3	Month 3	**Yes/Yes**	**Yes/Yes**
HD4	Month 3	**Yes/Yes**	-/-

- Only subjects with pre-existing SaCas9 and AAV5 cell mediated responses respond post dosing
- EDIT-101 treatment does not induce new cell mediated immune responses to AAV5 and SaCas9

AAV5: adeno-associated virus type 5; HD: high dose patient; LD: low dose patient; MD: mid dose patient; NC: not collected; SaCas9: *Staphylococcus aureus* CRISPR associated protein 9.

Conclusions

Our data and patient profile indicate EDIT-101 has a favorable immunogenicity profile

Some subjects across all cohorts exhibit pre-existing immunity to AAV5 and/or SaCas9

No subject developed post-treatment cellular or humoral immunogenicity to SaCas9

EDIT-101 treatment resulted in AAV5 BAB and nAB responses in 9 of 11 subjects; antibody titers did not correlate with EDIT-101 dose level

No subject developed new post-treatment cell mediated responses to EDIT-101

AAV5: adeno-associated virus type 5; BAB: binding antibody; nAb: neutralizing antibody; SaCas9: *Staphylococcus aureus* CRISPR associated protein 9;

Acknowledgements

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Questions?