In vivo gene editing

Description

“In vivo gene editing in post-mitotic neurons of the adult brain may be a useful strategy for treating neurological diseases. Here, we develop CRISPR–Cas9 nanocomplexes and show they were effective in the adult mouse brain, with minimal off-target effects. Using this system to target Bace1 suppressed amyloid beta (A?)-associated pathologies and cognitive deficits in two mouse models of Alzheimer’s disease. These results broaden the potential application of CRISPR–Cas9 systems to neurodegenerative diseases.”

Park, H., Oh, J., Shim, G., Cho, B., Chang, Y., Kim, S., … Kim, J.. (2019). In vivo neuronal gene editing via CRISPR–Cas9 amphiphilic nanocomplexes alleviates deficits in mouse models of Alzheimer’s disease. Nature Neuroscience

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“In vivo gene editing in post-mitotic neurons of the adult brain may be a useful strategy for treating neurological diseases. here, we develop crispr–cas9 nanocomplexes and show they were effective in the adult mouse brain, with minimal off-target effects. using this system to target bace1 suppressed amyloid beta (a?)-associated pathologies and cognitive deficits in two mouse models of alzheimer’s disease. these results broaden the potential application of crispr–cas9 systems to neurodegenerative diseases.”

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Further References

Gillmore, J. D., Gane, E., Taubel, J., Kao, J., Fontana, M., Maitland, M. L., … Lebwohl, D.. (2021). CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. New England Journal of Medicine

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“BACKGROUND: transthyretin amyloidosis, also called attr amyloidosis, is a life-threatening disease characterized by progressive accumulation of misfolded transthyretin (ttr) protein in tissues, predominantly the nerves and heart. ntla-2001 is an in vivo gene-editing therapeutic agent that is designed to treat attr amyloidosis by reducing the concentration of ttr in serum. it is based on the clustered regularly interspaced short palindromic repeats and associated cas9 endonuclease (crispr-cas9) system and comprises a lipid nanoparticle encapsulating messenger rna for cas9 protein and a single guide rna targeting ttr. methods: after conducting preclinical in vitro and in vivo studies, we evaluated the safety and pharmacodynamic effects of single escalating doses of ntla-2001 in six patients with hereditary attr amyloidosis with polyneuropathy, three in each of the two initial dose groups (0.1 mg per kilogram and 0.3 mg per kilogram), within an ongoing phase 1 clinical study. results: preclinical studies showed durable knockout of ttr after a single dose. serial assessments of safety during the first 28 days after infusion in patients revealed few adverse events, and those that did occur were mild in grade. dose-dependent pharmacodynamic effects were observed. at day 28, the mean reduction from baseline in serum ttr protein concentration was 52% (range, 47 to 56) in the group that received a dose of 0.1 mg per kilogram and was 87% (range, 80 to 96) in the group that received a dose of 0.3 mg per kilogram. conclusions: in a small group of patients with hereditary attr amyloidosis with polyneuropathy, administration of ntla-2001 was associated with only mild adverse events and led to decreases in serum ttr protein concentrations through targeted knockout of ttr. (funded by intellia therapeutics and regeneron pharmaceuticals; clinicaltrials.gov number, nct04601051.).”
Mills, E. M., Barlow, V. L., Luk, L. Y. P., & Tsai, Y. H.. (2020). Applying switchable Cas9 variants to in vivo gene editing for therapeutic applications. Cell Biology and Toxicology

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“Progress in targeted gene editing by programmable endonucleases has paved the way for their use in gene therapy. particularly, cas9 is an endonuclease with high activity and flexibility, rendering it an attractive option for therapeutic applications in clinical settings. many disease-causing mutations could potentially be corrected by this versatile new technology. in addition, recently developed switchable cas9 variants, whose activity can be controlled by an external stimulus, provide an extra level of spatiotemporal control on gene editing and are particularly desirable for certain applications. here, we discuss the considerations and difficulties for implementing cas9 to in vivo gene therapy. we put particular emphasis on how switchable cas9 variants may resolve some of these barriers and advance gene therapy in the clinical setting.”
Park, H., Oh, J., Shim, G., Cho, B., Chang, Y., Kim, S., … Kim, J.. (2019). In vivo neuronal gene editing via CRISPR–Cas9 amphiphilic nanocomplexes alleviates deficits in mouse models of Alzheimer’s disease. Nature Neuroscience

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Jordan, B.. (2021). In vivo gene editing for gene therapy. Medecine/Sciences

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“In vivo gene editing has been achieved in a phase i clinical trial and results in a strong reduction of the level of a pathogenic protein. while preliminary, these results open the way for many applications in gene therapy.”
Yip, B. H.. (2020). Recent advances in CRISPR/Cas9 delivery strategies. Biomolecules

Plain numerical DOI: 10.3390/biom10060839
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“The clustered regularly interspaced short palindromic repeats (crispr)/cas9 system has revolutionized the field of gene editing. continuous efforts in developing this technology have enabled efficient in vitro, ex vivo, and in vivo gene editing through a variety of delivery strategies. viral vectors are commonly used in in vitro, ex vivo, and in vivo delivery systems, but they can cause insertional mutagenesis, have limited cloning capacity, and/or elicit immunologic responses. physical delivery methods are largely restricted to in vitro and ex vivo systems, whereas chemical delivery methods require extensive optimization to improve their efficiency for in vivo gene editing. achieving a safe and efficient in vivo delivery system for crispr/cas9 remains the most challenging aspect of gene editing. recently, extracellular vesicle-based systems were reported in various studies to deliver cas9 in vitro and in vivo. in comparison with other methods, extracellular vesicles offer a safe, transient, and cost-effective yet efficient platform for delivery, indicating their potential for cas9 delivery in clinical trials. in this review, we first discuss the pros and cons of different cas9 delivery strategies. we then specifically review the development of extracellular vesicle-mediated gene editing and highlight the strengths and weaknesses of this technology.”
Büning, H., & Schambach, A.. (2021). A first step toward in vivo gene editing in patients. Nature

Medicine

Plain numerical DOI: 10.1038/s41591-021-01476-6
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Latella, M. C., Di Salvo, M. T., Cocchiarella, F., Benati, D., Grisendi, G., Comitato, A., … Recchia, A.. (2016). In vivo Editing of the Human Mutant Rhodopsin Gene by Electroporation of Plasmid-based CRISPR/Cas9 in the Mouse Retina. Molecular Therapy – Nucleic Acids

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“The bacterial crispr/cas system has proven to be an efficient tool for genetic manipulation in various organisms. here we show the application of crispr-cas9 technology to edit the human rhodopsin (rho) gene in a mouse model for autosomal dominant retinitis pigmentosa. we designed single or double sgrnas to knock-down mutant rho expression by targeting exon 1 of the rho gene carrying the p23h dominant mutation. by delivering cas9 and sgrnas in a single plasmid we induced an efficient gene editing in vitro, in hela cells engineered to constitutively express the p23h mutant rho allele. similarly, after subretinal electroporation of the crispr/cas9 plasmid expressing two sgrnas into p23h rho transgenic mice, we scored specific gene editing as well as significant reduction of the mutant rho protein. successful in vivo application of the crispr/cas9 system confirms its efficacy as a genetic engineering tool in photoreceptor cells.”
Li, F., Wing, K., Wang, J. H., Luu, C. D., Bender, J. A., Chen, J., … Hewitt, A. W.. (2020). Comparison of CRISPR/Cas Endonucleases for in vivo Retinal Gene Editing. Frontiers in Cellular Neuroscience

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“CRISPR/cas has opened the prospect of direct gene correction therapy for some inherited retinal diseases. previous work has demonstrated the utility of adeno-associated virus (aav) mediated delivery to retinal cells in vivo; however, with the expanding repertoire of crispr/cas endonucleases, it is not clear which of these are most efficacious for retinal editing in vivo. we sought to compare crispr/cas endonuclease activity using both single and dual aav delivery strategies for gene editing in retinal cells. plasmids of a dual vector system with spcas9, sacas9, cas12a, cjcas9 and a sgrna targeting yfp, as well as a single vector system with sacas9/yfp sgrna were generated and validated in yfp-expressing hek293a cell by flow cytometry and the t7e1 assay. paired crispr/cas endonuclease and its best performing sgrna was then packaged into an aav2 capsid derivative, aav7m8, and injected intravitreally into cmv-cre:rosa26-yfp mice. spcas9 and cas12a achieved better knockout efficiency than sacas9 and cjcas9. moreover, no significant difference in yfp gene editing was found between single and dual

crispr/sacas9 vector systems. with a marked reduction of yfp-positive retinal cells, aav7m8 delivered spcas9 was found to have the highest knockout efficacy among all investigated endonucleases. we demonstrate that the aav7m8-mediated delivery of crispr/spcas9 construct achieves the most efficient gene modification in neurosensory retinal cells in vivo."
Lee, J., Kang, Y. K., Oh, E., Jeong, J., Im, S. H., Kim, D. K., … Chung, H. J.. (2022). Nano-assembly of a Chemically Tailored Cas9 Ribonucleoprotein for in Vivo Gene Editing and Cancer Immunotherapy. Chemistry of Materials

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"Cancer gene therapy based on the clustered regularly interspaced short palindromic repeat (crispr) system has been challenging due to the poor delivery and efficacy in vivo. herein, we report the development of nanoassembled ribonucleoprotein complexes (nanornp), which can efficiently block the pd-l1 immune checkpoint and induce an anti-tumor effect in vivo. we utilize crispr-associated protein 9 (cas9) that is chemically derivatized with a low-molecular weight polymer, which condenses with single-guide rna and modified dna oligonucleotides to form stabilized nanornps. delivery of the nanornp into b16 melanoma cells in vitro leads to efficient internalization and gene disruption with low cytotoxicity, leading to sustained downregulation of pd-l1. in vivo delivery in a mouse melanoma model demonstrates that the nanornp can induce indels in the target cells of the tumor at high frequencies, resulting in major suppression of tumor growth, without involving combinatorial treatment. blockade of the pd-l1 checkpoint by the nanornp in tumor tissues promotes t cell infiltration and effector cytokine release, which are characteristics of the activation of anti-tumor immunity, and inhibition of immunosuppressive myeloid cells. the current system suggests a promising strategy as an in vivo gene editing platform for cancer immunotherapy."

Category

1. General

Tags

1. CRISPR–Cas9
2. In vivo gene editing

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