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No STOPS: Translational read-through of nonsense mutations for the treatment of hereditary retinal disorders

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Hereditary retinal dystrophies are a genetically heterogeneous group of rare disorders that causes vision defects, for which currently no effective cure is available. Patient screenings predict that ~12% of all pathogenic variants identified in patients are nonsense mutations. Therefore, a therapy that targets nonsense mutations has great potential to be beneficial for a substantial cohort making the approach both practical and economical. Nonsense mutations introduce a premature termination codon in the coding sequence of genes and lead to the expression of truncated, non-functional protein. Translational read-through mediates the over-read of nonsense mutations and thereby induces the expression of functional full-length proteins. We studied the biocompatibility of different translational read-through inducing drugs (TRIDs) as well as the read-through efficacies for different nonsense mutations causing retinal dystrophies with the spotlight on the Usher syndrome (USH) which is the most common form of combined deaf-blindness in man. Our data show that in comparison with classical aminoglycosides (e.g. gentamicin), designer aminoglycosides, like NB84 as well as the chemical compound Ataluren exhibit very good retinal biocompatibility. Our studies conclusively revealed read-through of different USH causing mutations and related ciliopathies, namely subtypes of the Bardet-Biedl syndrome and the Senior Loken syndrome by TRIDs in cultured cells. Furthermore, we demonstrated read-through in organotypic retina cultures, and *in vivo* in mice. In summary, our data indicate that the excellent biocompatibility combined with the ample read-through efficacies of TRIDs emphasizes the potential of designer aminoglycosides and Atalurenas a treatment option for retinal disorders caused byin-frame nonsense mutation.

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Oral glucosamine supplements as a possible ocular hypertensive agent

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The Centers for Disease Control and Prevention report that osteoarthritis affects 27 million adults in the United States. Glucosamine sulfate is a naturally occurring substance found in human cartilage and a precursor for glycosaminoglycans (GAGs). A combination of supplements, glucosamine and chondroitin sulfate, was shown in the Glucosamine/Chondroitin Arthritis Intervention Trial to aid moderate to severe osteoarthritic knee pain. Open-angle glaucoma affects more than 2 million individuals in the United States, and this number continues to increase owing to the rapid aging of the US population. Normal aqueous outflow of the eye is regulated by the content of GAGs. Researchers postulate that excessive deposits of GAG in the trabecular meshwork restrict outflow. Another theory suggests that increased release of GAG into the aqueous causes an osmotic effect, drawing more water into the anterior chamber, thus causing swelling, a decrease in pore size, and eventual increased resistance to outflow. Either of these proposed mechanisms could lead to an increased thickness of the pore lining and/or decreased outflow, resulting in increased intraocular pressure (IOP). Excessive glucosamine molecules may similarly elevate IOP. In a small retrospective clinical study, we examine the relationship between glucosamine supplementation and increased IOP in patients with glaucoma who supplement with glucosamine.

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