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Nanoparticle-mediated ABCA4 delivery rescues the degenerative Stargardt's phenotype

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Mutations in the photoreceptor-specific flippase ABCA4 are associated with autosomal recessive Stargardt's disease (STGD1), cone-rod dystrophy, retinitis pigmentosa, and increased susceptibility to age-related macular degeneration, all diseases for which there are no curative therapies. Gene replacement is a logical strategy for ABCA4-associated disease, particularly given the current success of adeno-associated viral (AAV)-mediated ocular gene delivery. However, the large size of the ABCA4 cDNA (6.8 kbp) has thus far prevented significant progress in the development of clinically viable genetic treatments. Here we take advantage of an optimized non-viral DNA nanoparticle (NP) technology which does not suffer from the capacity limitations of AAV vectors to deliver ABCA4 to the Abca4-/- mouse model of Stargardt's disease. In contrast to many other non-viral approaches, these NPs drive long-term gene expression after subretinal delivery, making them an excellent choice for chronic retinal degenerations such as Stargardt's. We show persistent transgene expression (up to 8 months post-injection-PI) and distribution of transduced ABCA4 throughout retina, not just in the site of injection. Critically, we also observe significant correction of functional and structural Stargardt's phenotypes after delivery of ABCA4 NPs. These data suggest that DNA NPs may be an excellent, clinically relevant gene delivery approach for genes too large for traditional viral vectors.

Biography

Muna I. Naash earned her Masters and Ph.D. in Biochemistry, the latter from Baylor College of Medicine. Her post-doctoral fellowship was in the Department of Ophthalmology at Baylor College of Medicine in Houston. Dr. Naash currently holds Edith Kinney Gaylord Presidential Professorship position in the Department of Cell Biology and a former Director of the Cell Biology Graduate Program at the University of Oklahoma Health Sciences Center (OUHSC). She also holds an Adjunct Faculty status at the Oklahoma Center for Neuroscience and a member of the Cancer Center at OUHSC and the Graduate College. One of her research program is to unravel the mechanisms of visual loss in animal models of retinal diseases and the development of non-viral gene therapy. She has published close to 100 papers in reputed journals and serving as ad hock or members on several study sections and reviewed for numerous journals.

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