proceedings

Abstract

A Novel Retinal Gene Therapy Strategy for Batten Disease and Beyond †

Maura Schwartz, Alex Campbell, Joseph Caporale, Megan Baird, Isabella Palazzo, Shibi Likhite, Andrew Fischer and Kathrin Meyer *

The Abigail Wexner Research Institute at Nationwide Children's Hospital, Center for Gene Therapy, Columbus, OH 43205, USA; Maura.Schwartz@nationwidechildrens.org (M.S.); Warren.Campbell@osumc.edu (A.C.); Joseph.Caporale@nationwidechildrens.org (J.C.); Megan.Baird@nationwidechildrens.org (M.B.); palazzo.7@osu.edu (I.P.); Shibi.Likhite@nationwidechildrens.org (S.L.); Andrew.Fischer@osumc.edu (A.F.)

* Correspondence: Kathrin.Meyer@nationwidechildrens.org

† Presented at the 1st International Electronic Conference on Brain Sciences, 10–25 November 2020; Available online: https://sciforum.net/conference/IECBS.

Keywords: ret and a; neuraminidase; AAV9; gene therapy; Batten Disease

Batten Disease is a fatal lysosomal storage disorder characterized by cognitive and motor deficits, vision impairment, and seizures. Loss of vision is a hallmark of 10 of the 13 Batten Disease subtypes. Our group has pioneered AAV9 gene therapy treatments, achieving widespread transduction of the brain and spinal cord. Two clinical trials are currently ongoing at the Nationwide Children's Hospital delivering this vector via cerebrospinal fluid (CSF) to the brain and spinal cord for treatment of the lethal neurodegenerative aspects of Batten Disease. However, AAV9 transduction of the retina after CSF delivery is limited, and there is a critical need for a solution that prevents vision loss and further improves quality of life for Batten Disease patients.

Similar to most genetic ocular diseases, photoreceptor degeneration is the most commonly cited pathology in patients. However, recent studies suggest that in some subtypes of Batten Disease, expression must be rescued also within the deeper layers of the retina that are difficult to reach with therapeutic vectors (inner nuclear layer, INL). We performed the single-cell RNA sequencing of mice and non-human primate retinas in collaboration with Dr. Fischer (OSU), and concluded that Batten Disease vision-specific gene therapy needs to target a wide range of cells, including the INL, which is a major challenge for the translation of a vision-specific therapy to the clinic.

We have recently discovered that the administration of neuraminidase (NA), a sialidase enzyme, prior to or in combination with AAV9.GFP, drastically increases transduction throughout the murine C57Bl/6 retina, including the INL and all the way through to the photoreceptor layer. Our preliminary data indicate GFP expression in almost all, if not all, retinal cell types using this method. Importantly, we have confirmed the successful targeting of INL bipolar cells, a notoriously difficult cell-type to transduce, and up to a 40% increase in Müller glia transduction. Preliminary histological examination indicates no damage or alterations in retinal integrity.

While additional testing in large animal models is required and scheduled to occur in a WT pig model in Autumn 2020, this remarkable discovery suggests that it may now be possible to target every cell-type of the retina with a single AAV vector. This is especially important in regard to the treatment of Batten Disease, but has many additional implications. Current retinal therapies that require a more invasive subretinal delivery to photoreceptors could now opt for the safer intravitreal delivery strategy. In addition, this strategy would be highly useful in the field of optogenetics, where investigators continue

Citation: Schwartz, M.; Campbell, A.; Caporale, J.; Baird, M.; Palazzo, I.; Likhite, S.; Fischer, A.; Meyer, K. A Novel Retinal Gene Therapy Strategy for Batten Disease and Beyond. *Proceedings* **2021**, *71*, 5. https://doi.org/10.3390/IECBS-08470

Published: 18 November 2020

to struggle to find an efficient way to express light-sensitive opsins in cells of the INL to restore sight in individuals that have already lost their photoreceptors.

Supplementary Materials: The following are available online at www.mdpi.com/2504-3900/71/1/5/s1.