Efficient and Durable Ocular Gene Silencing of TTR after Single Intravitreal Administration of siRNA Conjugates

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Abstract

- Ocular transthyretin produced locally in retinal pigment epithelium (RPE) and ciliary epithelia (CE) can cause amyloid deposits, resulting in significant visual impairment, including blindness, in approximately 10% of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) patients.
- Liver transplantation does not resolve ocular amyloidosis and liver-directed therapies are not expected to be efficacious against ocular manifestations.
- Silencing the expression of TTR in the eye using RNAI Therapeutics would represent a novel treatment approach for development.
- Here we show that siRNA conjugates targeting TTR can be delivered to the relevant cell types in the eye and produce efficient and durable gene silencing after single intravitreal administration.
- Preclinical efficacy and safety of siRNA conjugates in rodents and nonhuman primates will be presented.

Figure 1. Aynlam Advancements in Conjugate-Based siRNA Delivery

Figure 2. RNAI Therapeutics for hATTR Amyloidosis

Figure 3. TTR is Produced in the Eye as Well as the Liver

Figure 4. Two Sites of TTR Production in the Eye

Figure 5. Ocular TTR Silencing by Differentially Modified siRNA Conjugates in Rat After Single Intravitreal Injection

Figure 6. Robust TTR Silencing in Both CE and RPE in Rat

Figure 7. TTR Ocular Activity in hATTR Transgenic Mice

Figure 8. Ocular TTR Silencing by siRNA Conjugates in Non-Human Primates (NHP)

Figure 9. Ocular TTR Silencing by OC Optimized Conjugates in NHP

Safety of Ocular siRNA Conjugates in NHP

Ophthalmoscopic Examination Summary (Days 7, 3, 10)

Histopathology Summary (Day 31)

Ocular Opportunity for RNAI Therapeutics

- The siRNA conjugates specifically designed for ocular delivery show robust and durable RNAI activity
  - Silencing demonstrated at both sites of ocular TTR expression (RPE and CE)
  - Encouraging initial safety results
  - Successful translation to higher species
  - RNAI therapeutics directed to disease-causing, intracellular gene targets represent a significant opportunity for further development

References

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6. Hare et al. ARCH OPHTHALMACOL. 2018;128: 206.