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Intravitreal α-Crystallin Chaperone Reverses Lens Opalescence in Non-Human Primates with Spontaneous Cataracts

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Purpose
The crystalline lens gradually becomes less elastic and opaque with age. These structural changes, primarily due to protein misfolding and aggregation, result clinically in presbyopia in the 40s and cataract in later life. This progressive loss of visual function is referred to as Dysfunctional Lens Syndrome (DLS). The crystallins (α, β and γ) are the most abundant lens proteins, however these proteins don't regenerate and, must remain soluble throughout life. The α-crystallins act as chaperones for the β and γ-crystallins keeping them in their native soluble confirmation. As the lens ages, the α-crystallins break down from its natural soluble dimer confirmation into monomers and lose their chaperone activity. 25-Hydroxycholesterol (25-HC) is a small molecular chaperone that binds to α-crystallin and stabilizes its natural soluble dimer confirmation.

Methods
Eight senior primates (median age 19 years) received a single 50-µL intravitreal injection of 3% 25-HC suspension through a 27-gauge needle in the study eye (SE). The uninjected, non-study eye (NSE) served as a control. The Lens Opacities Classification System (LOCS III) nuclear opalescence scores were graded by a masked observer at the slit lamp beginning 2 months before IVT and 8 weeks after. Scores were independently verified by an independent grader from lens photographs. Paired Student's 'T' tests comparing follow-up scores to baseline (Day 1) were performed.

Results
There was a statistically significant change from baseline in lens opacity in the SE beginning at day 8 and lasting to day 57. There were no significant changes in the NSE. At baseline, the average LOCS III score was 2.7 ± 0.2 and decreased maximally to 1.4 ± 0.3 by day 43. Anterior chamber inflammation was observed clinically in some eyes.

Conclusions

This study demonstrates that the small molecule α-crystallin chaperone, 25-HC, can reverse spontaneous nuclear cataract in primates, a relevant model for human cataract, and provides proof-of-concept for this lens modulation approach. However, sterols are highly insoluble, penetrate the lens poorly and cause ocular toxicity. Visus is developing non-sterol α-crystallin chaperones with more favorable pharmaceutical properties.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.

This study provides proof of concept for the treatment, or even possibly prevention, of visually significant dysfunctional lens syndrome, including cataract, in some patients without the need for more invasive intraocular surgery with next generation alpha chaperone compounds.