TITLE: Gene therapy for blue cone monochromacy caused by C203R mutation

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RESEARCH PROJECT DESCRIPTION

Blue cone monochromacy (BCM) is an X-linked congenital vision disorder characterized by complete loss or severely reduced L- and M- cone function. BCM patients display poor visual acuity, severely impaired color discrimination, myopia, nystagmus, and minimally detectable cone-mediated electroretinogram. The two most common causes of BCM are deletions encompassing the L/M-opsin promoter, abolishing expression of both L- and M-opsin, or the presence of a deleterious C203R missense mutation either in a single *OPN1LW/MW* hybrid gene or in multiple *OPN1LW/MW* genes.

Using M-opsin knockout (*Opn1mw*$^{-/-}$) mice as a model for BCM, we showed that AAV-mediated expression of human M- or L-opsin promoted regrowth of cone outer segments and rescues M-cone function in the treated *Opn1mw*$^{-/-}$ dorsal retinas, providing proof-of-concept for gene augment therapy. However, BCM caused by C203R appears to display a dominate-negative phenotype and may not be treated by simple gene replacement. We hypothesize that combination of reducing the C203R with siRNA and introducing a “harden” copy of normal L/M opsin resistant to siRNA could lead to a more appropriate level of normal opsin expression and have a better treatment effect. Medical students will perform cell culture experiments assessing the effectiveness of siRNAs in reducing the levels of target mRNA and protein using Q-RT-PCR and western blot analysis. Effective siRNAs will be tested in C203R knock-in mice. Funding for the project is provided by BCM Foundation.

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