Complement C3-Targeted Gene Therapy
Restricts Onset and Progression of
Neurodegeneration in Chronic Mouse
Glaucoma

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Dysregulation of the complement system is implicated in neurodegeneration, including human and
animal glaucoma. Optic nerve and retinal damage in glaucoma is preceded by local complement
upregulation and activation, but whether targeting this early innate immune response could have
therapeutic benefit remains undefined. Because complement signals through three pathways that
intersect at complement C3 activation, here we targeted this step to restore complement balance in
the glaucomatous retina and to determine its contribution to degeneration onset and/or progression.
To achieve this, we combined adeno-associated virus retinal gene therapy with the targeted C3
inhibitor CR2-Crry.

We show that intravitreal injection of AAV2.CR2-Crry produced sustained Crry overexpression in
the retina and reduced deposition of the activation product complement C3d on retinal ganglion
cells and the inner retina of DBA/2J mice. This resulted in neuroprotection of retinal ganglion cell
axons and somata despite continued intraocular pressure elevation, suggesting a direct restriction of
neurodegeneration onset and progression and significant delay to terminal disease stages.

Our study uncovers a damaging effect of complement C3 or downstream complement activation in
glaucoma, and it establishes AAV2.CR2-Crry as a viable therapeutic strategy to target pathogenic
C3-mediated complement activation in the glaucomatous retina.

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