CRISPr VISION

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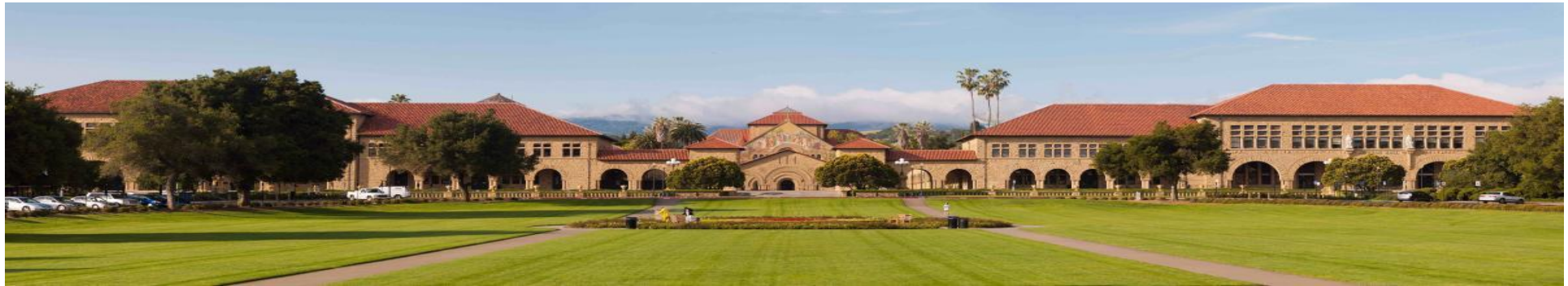


Executive Summary

PROBLEM

- Diseases of the optic nerve present a unique set of therapeutic challenges
- All optic neuropathies result in the death of Retinal Ganglion Cells (RGCs) and degeneration of the optic nerve.
- Glaucoma is the 3rd leading cause of eye disease affecting 3M Americans
- With current therapies,15% of patients develop blindness even with many years of treatment

INNOVATION

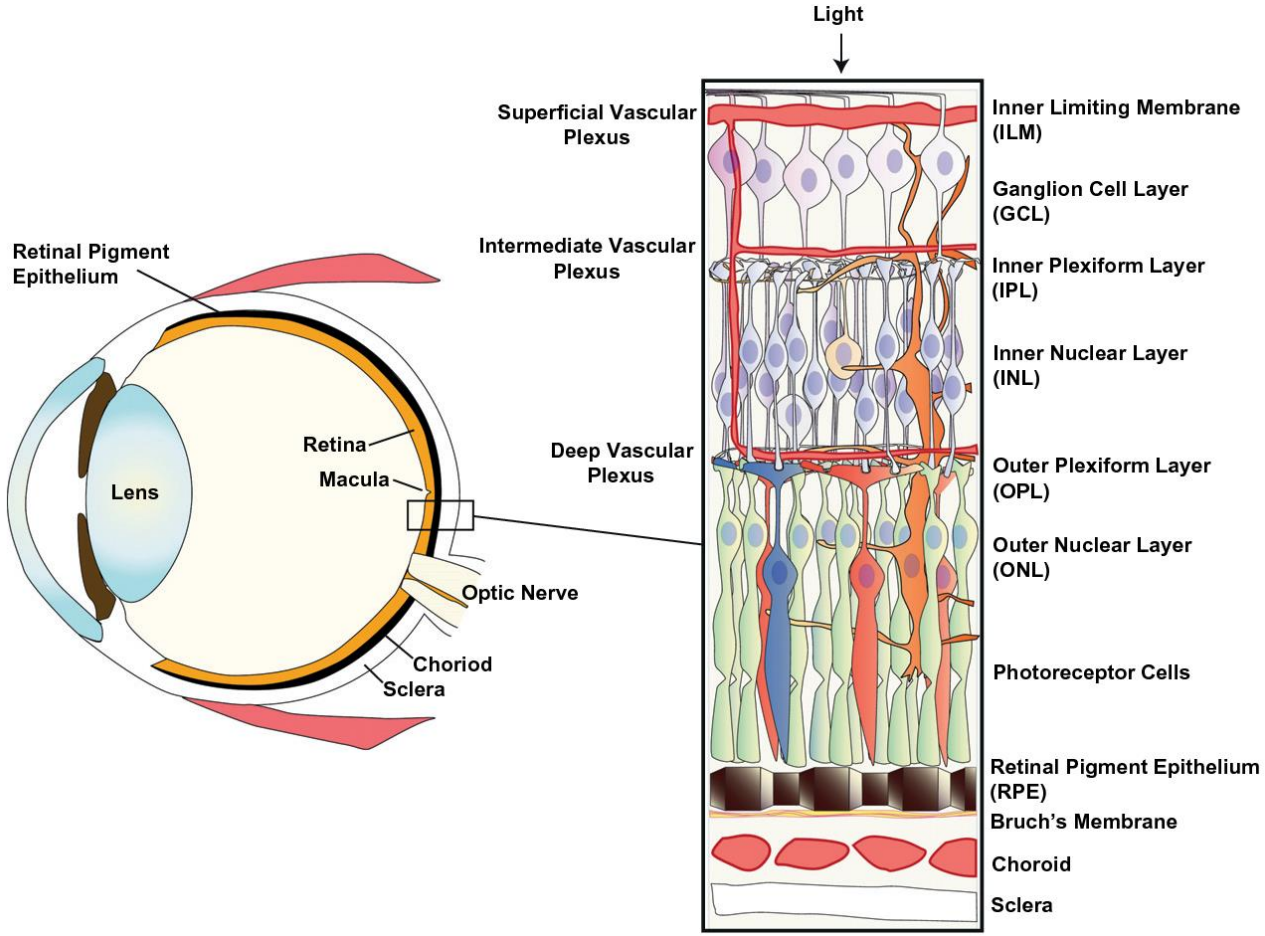
- Developed a superior, robust animal model for glaucoma – inducible and reversible
- Identified a potent and specific means to express genes in RGCs
- Uncovered multiple genes that provide protection against injury
- Demonstrated RGC-specific CRISPR/Cas gene editing through AAV delivery

SOLUTION

- An effective platform to identify, test, and develop RGC-specific gene therapies

Introduction to RGCs and Optic Nerve Disease

Retinal Ganglion Cells (RGCs) are essential neurons of the retina and form the optic nerve. They process visual information and pass it to the brain. Loss of RGC function leads to vision impairment and blindness.



Optic Nerve Disease

Disease	Prevalence
Glaucoma	3M in US (another 3M with partial condition)
Optic Neuritis	345,000 in US
Optic Atrophy	Orphan Disease
Hereditary Optic Neuropathy	Orphan Disease
Ischaemic Optic Neuropathy	Orphan Disease

RGC dysfunction is also implicated in degenerative neural diseases, such as Parkinson's and Alzheimer's

Jarrett SG, Boulton ME. Consequences of oxidative stress in age-related macular degeneration. *Mol Aspects Med*. 2012;33(4):399-417.
Martin, K., Quigley, H. Gene therapy for optic nerve disease. *Eye* **18,** 1049–1055 (2004).
DiCarlo JE, Mahajan VB, Tsang SH. Gene therapy and genome surgery in the retina. *J Clin Invest.* 2018;128(6):2177-2188.
La Morgia C, Ross-Cisneros FN, Sadun AA, Carelli V. Retinal Ganglion Cells and Circadian Rhythms in Alzheimer's Disease, Parkinson's Disease, and Beyond. Frontiers in Neurology. 2017 ;8:162.

Market Opportunity for Optic Neuropathy Therapeutics

Epidemiology of Optic Neuropathy Indications:

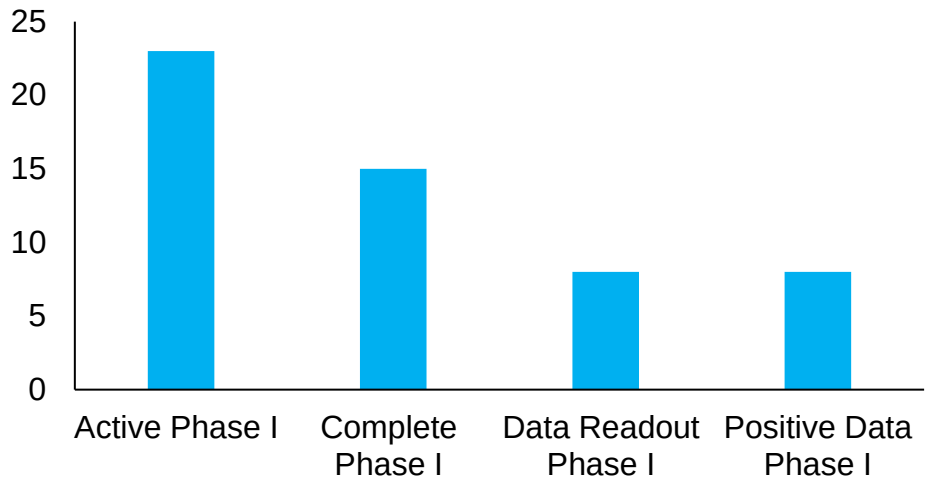
- Glaucoma:
  - 3 million US patients total
  - $2.1 Billion USD US MKT
  - 40% increase in US MKT 2020-2026
  - 15% blindness after continued treatment with 20-year onset
- Optic Neuritis:
  - 200,000 annual US cases (rare)
  - Complication of MS
  - 40-50% incidence in MS patients
  - 10% of patients do not regain vision

Ocular Gene Therapy in Clinical Trials :

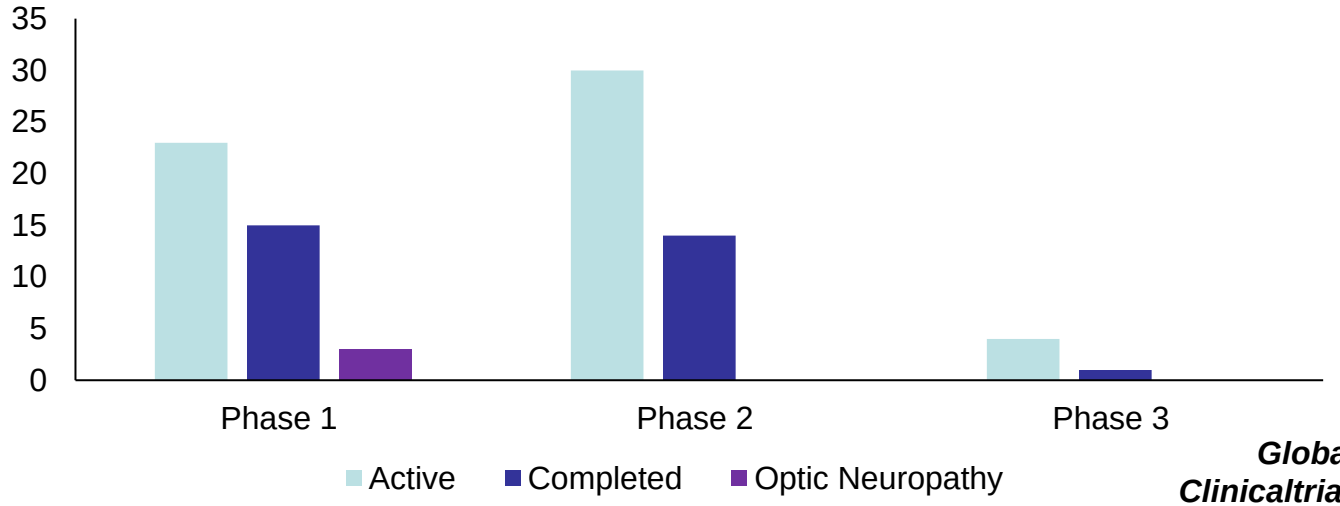
- Local delivery of gene therapy to the eye well established, ocular-tropic AAV serotypes well known and characterized
- Ocular gene therapy established as safe with 100% of read-out phase 1 trials showing positive data
- Only 8% of phase 1 clinical trials in Optic Neuropathy, 0% for later stage trials

Because of overall safety of and infrastructure for ocular gene therapy, and the relatively low prevalence of therapies for optic neuropathy in current clinical trials, there is the climate necessary to support the emergence of optic neuropathy R&D programs in the future.

Ocular Gene Therapy Safety in Phase I Trials



Opportunity for Ocular Gene Therapy Expansion to Optic Neuropathies



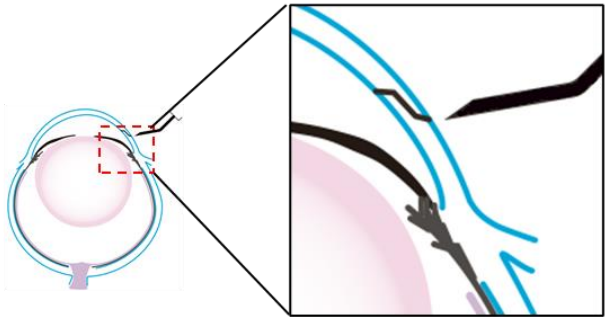
Global Data
Clinicaltrials.gov

An inducible and reversible mouse ocular hypertension model

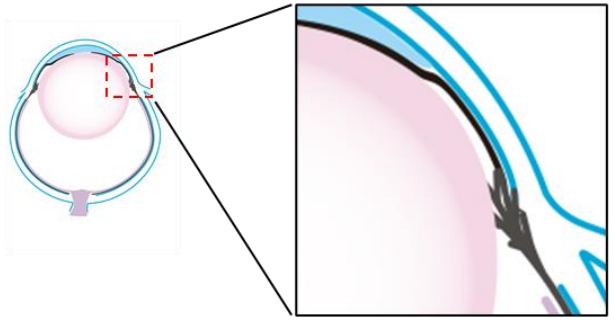
A

Intracameral Silicone Oil (SO) Injection Causing Pupillary Blocking and IOP Elevation

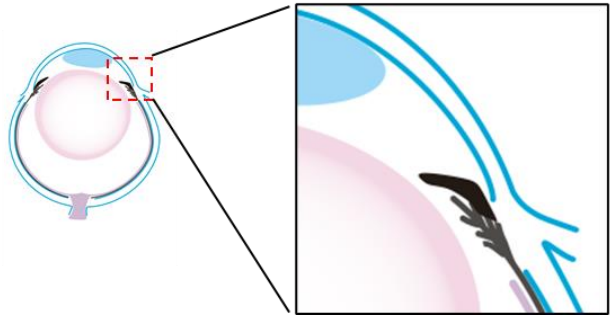
Corneal tunnel incision and SO injection



Angle closure due to IOP elevation

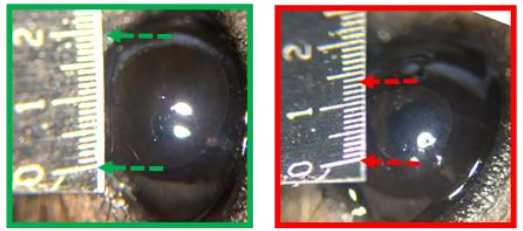


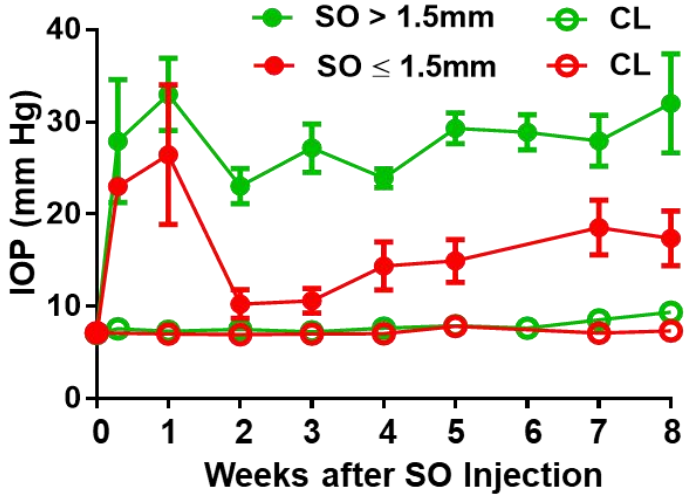
Angle reopen due to aqueous humor infiltration after pupil dilation



B

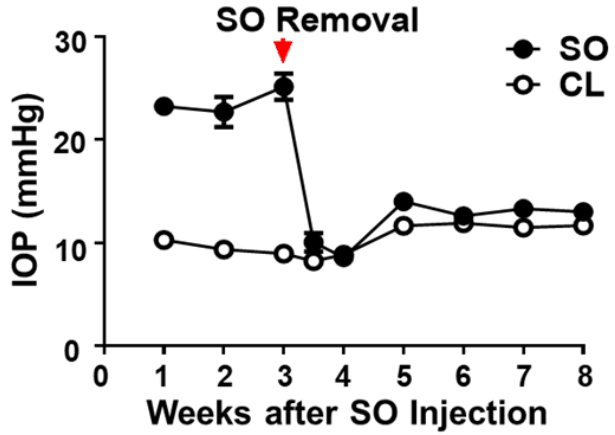
Stable IOP Elevation





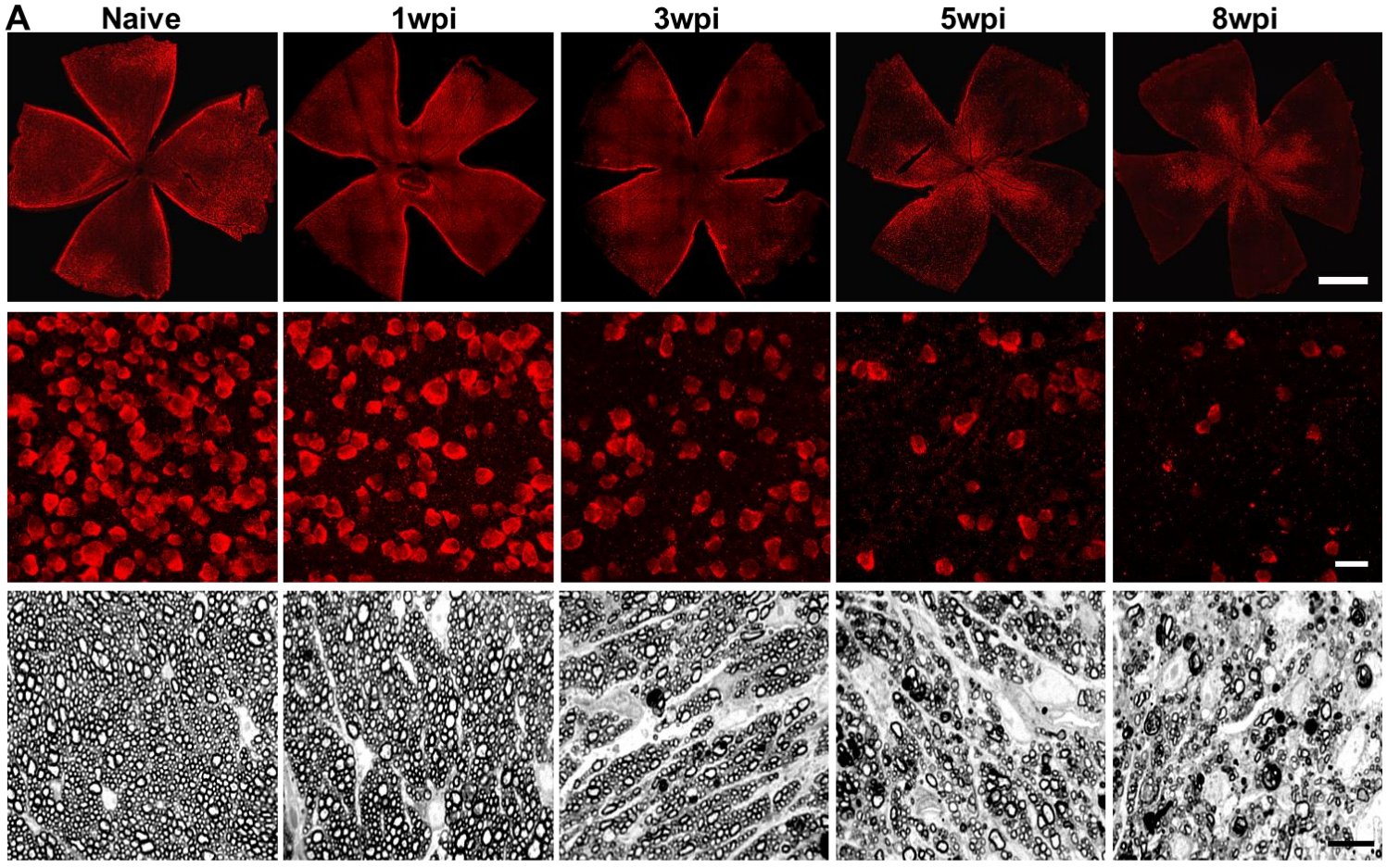
C

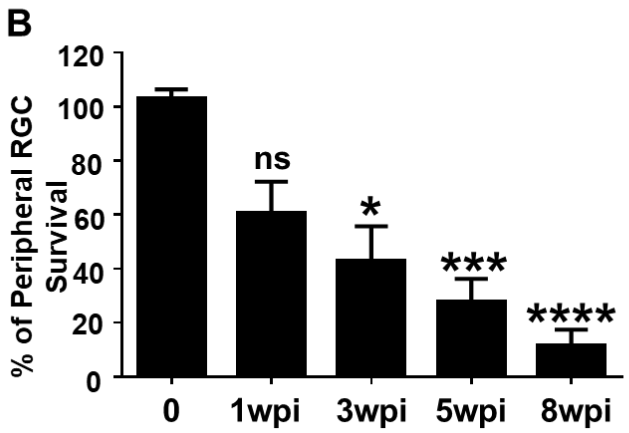
IOP lower down to normal right after SO removal

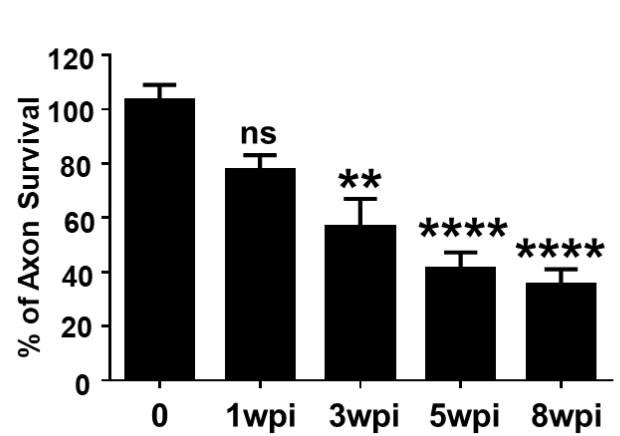


eLife 2019

Progressive RGC and Optic Nerve Degeneration in SO eyes

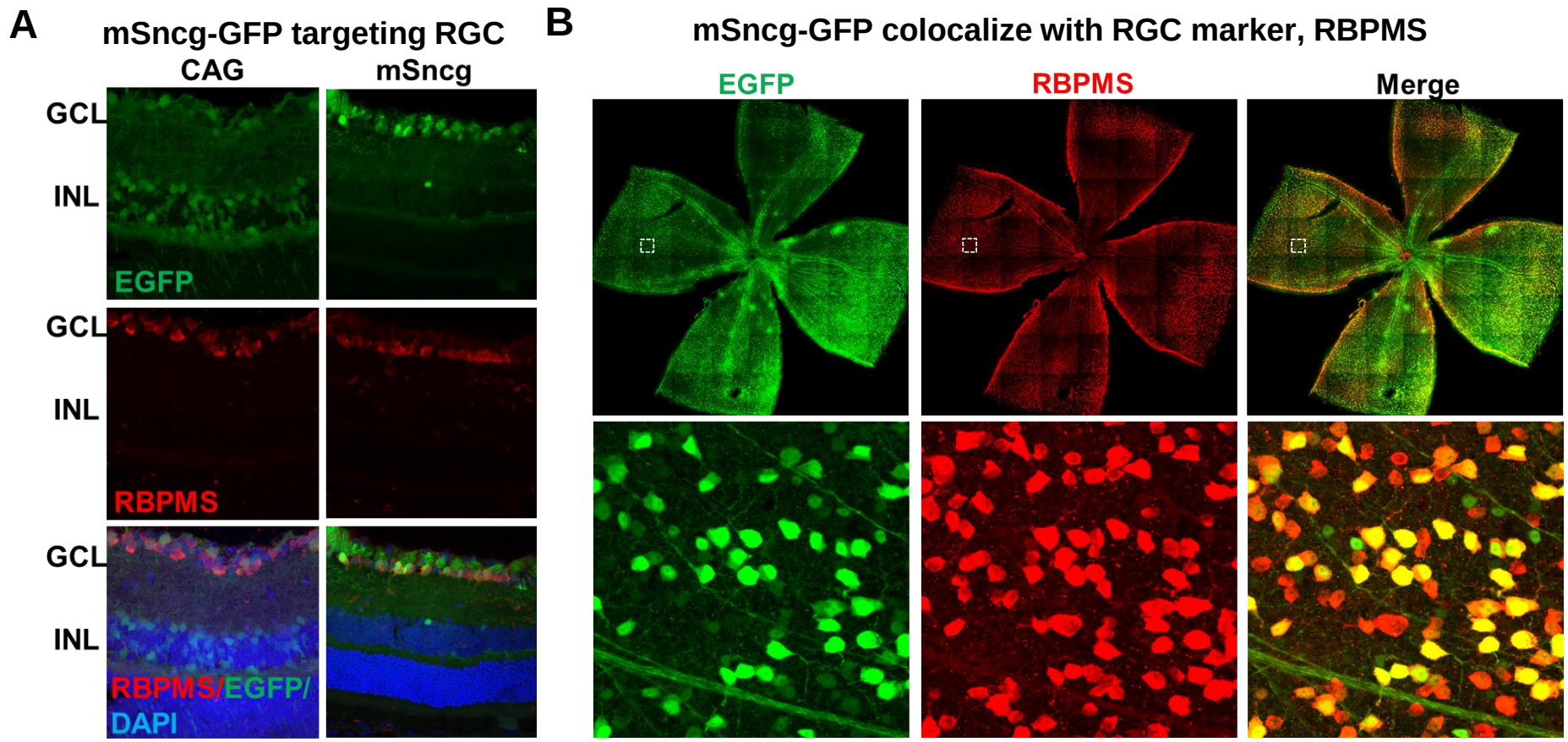






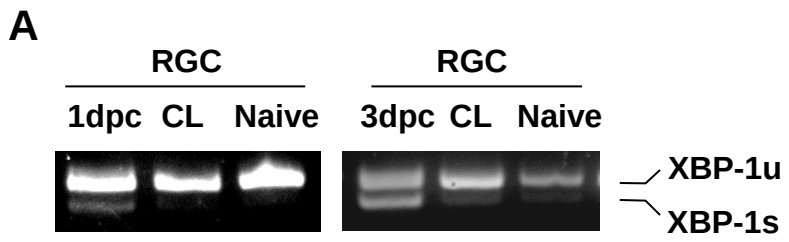
eLife 2019

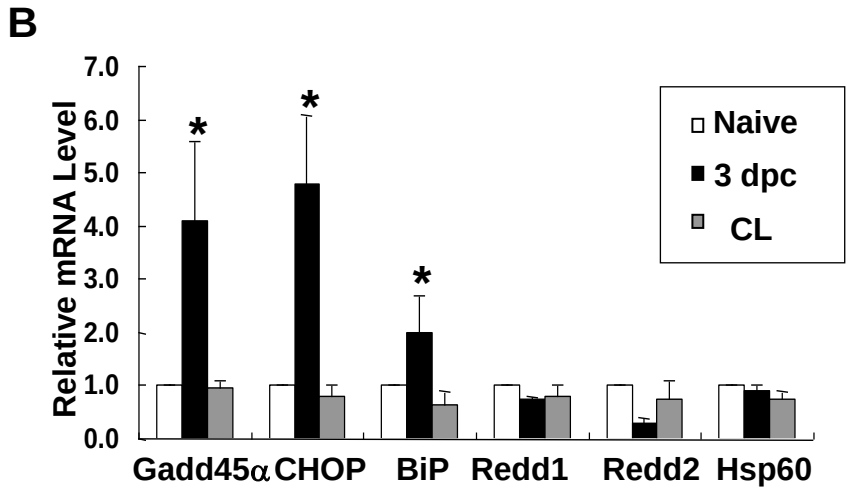
mSncg promoter drives potent transgene expression in RGCs specifically

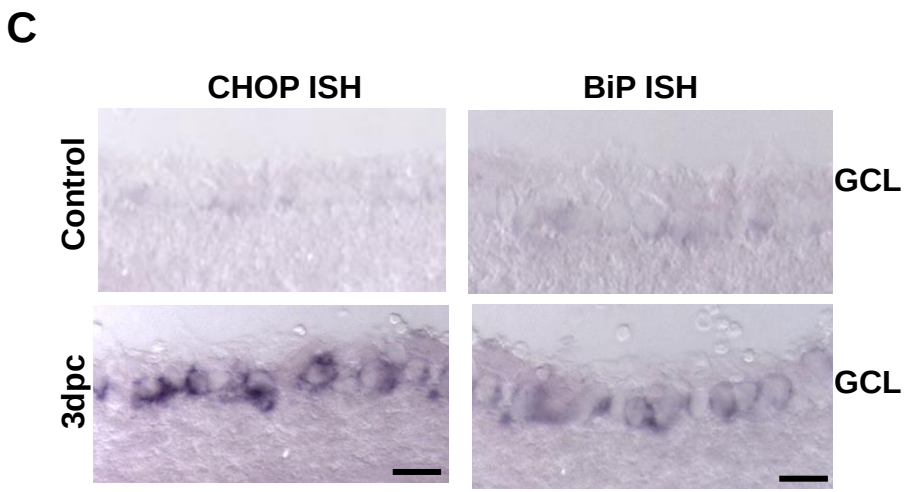


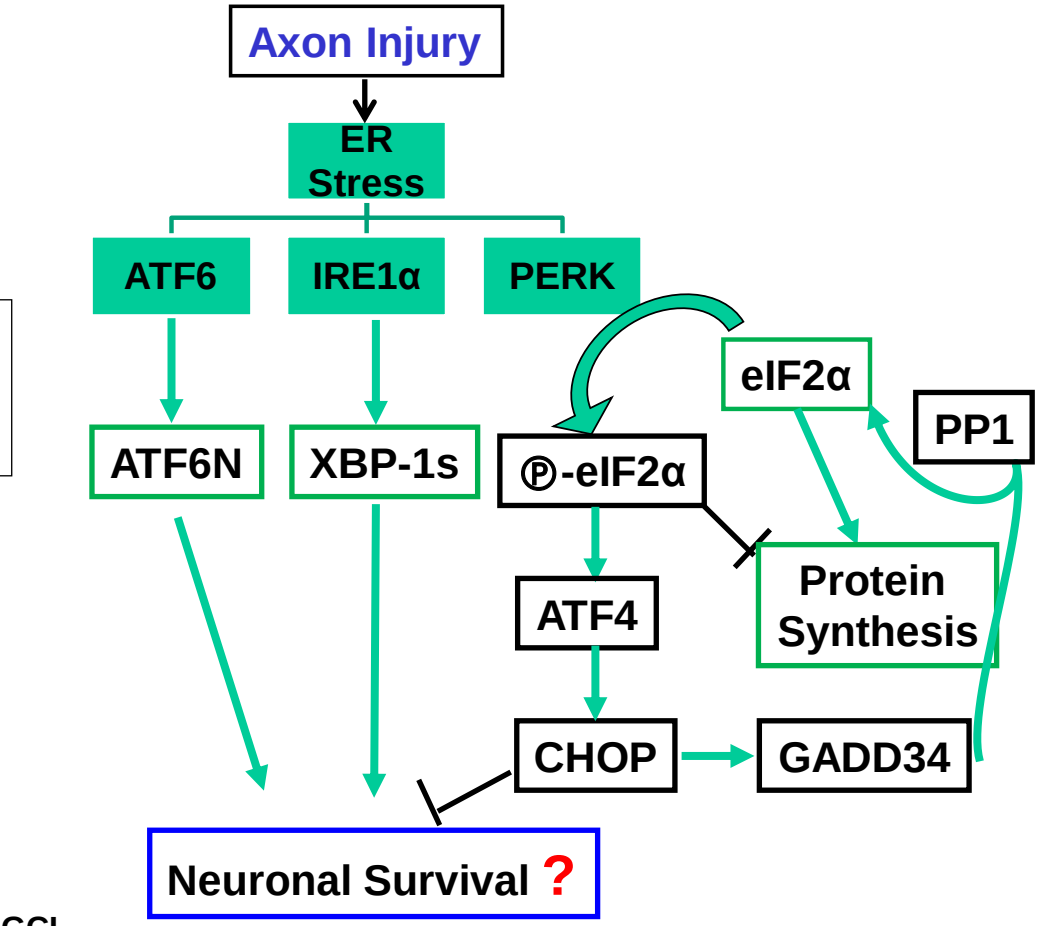
Journal of Neuroscience 2020

Optic Nerve Injury Triggers ER Stress in RGCs



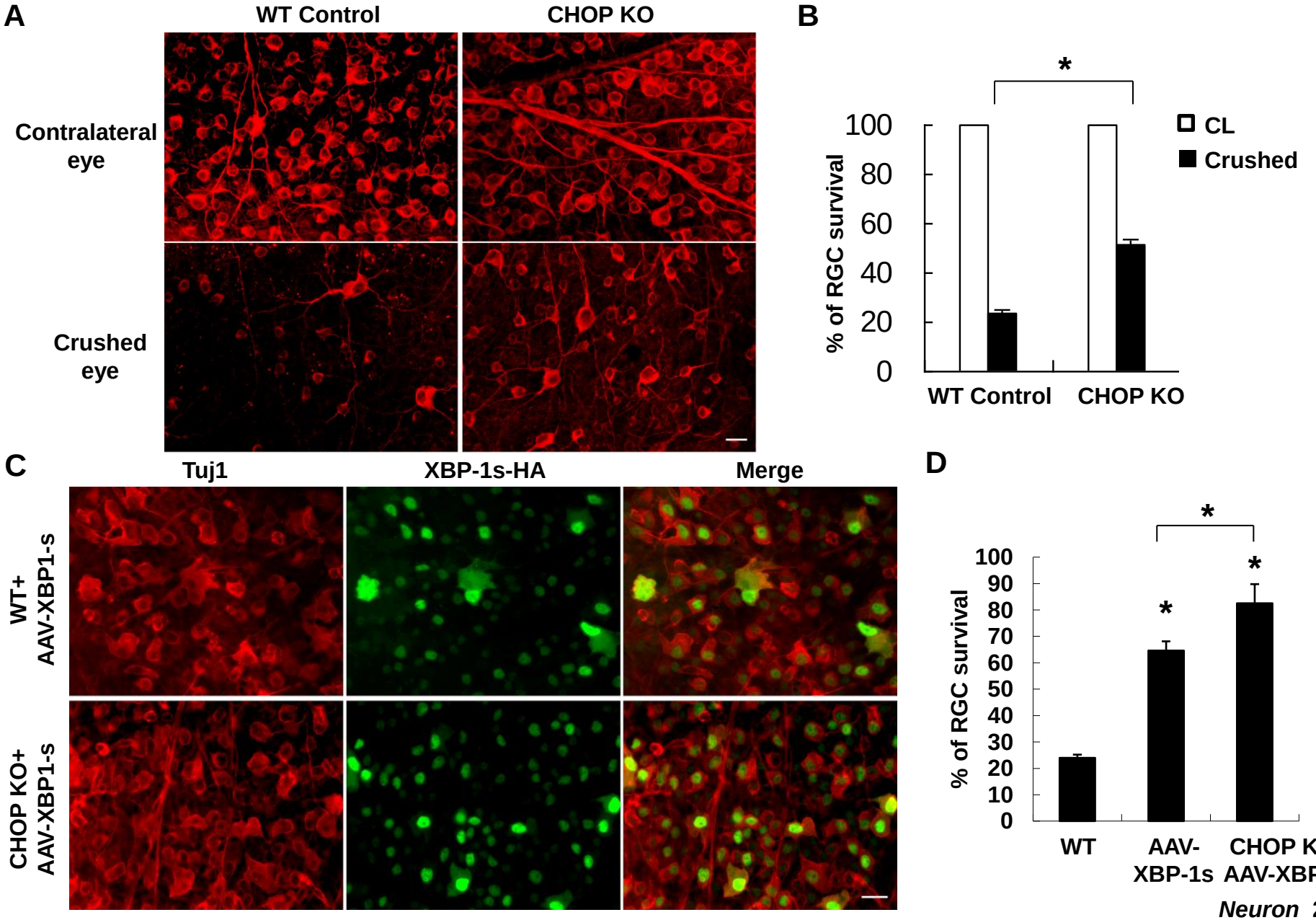






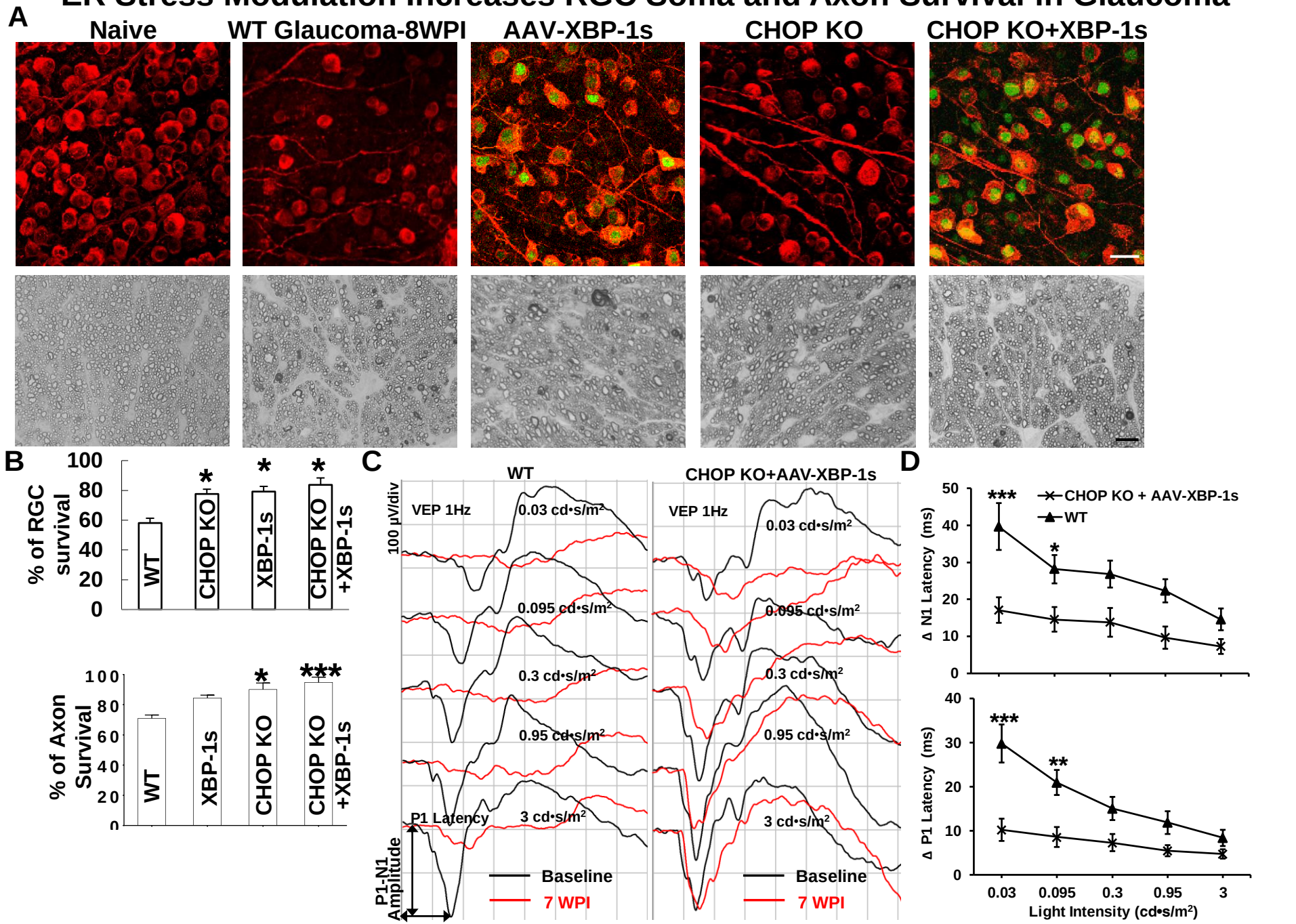
Neuron 2012

CHOP KO and XBP-1 Activation Synergistically Increase RGC Survival after ON Crush



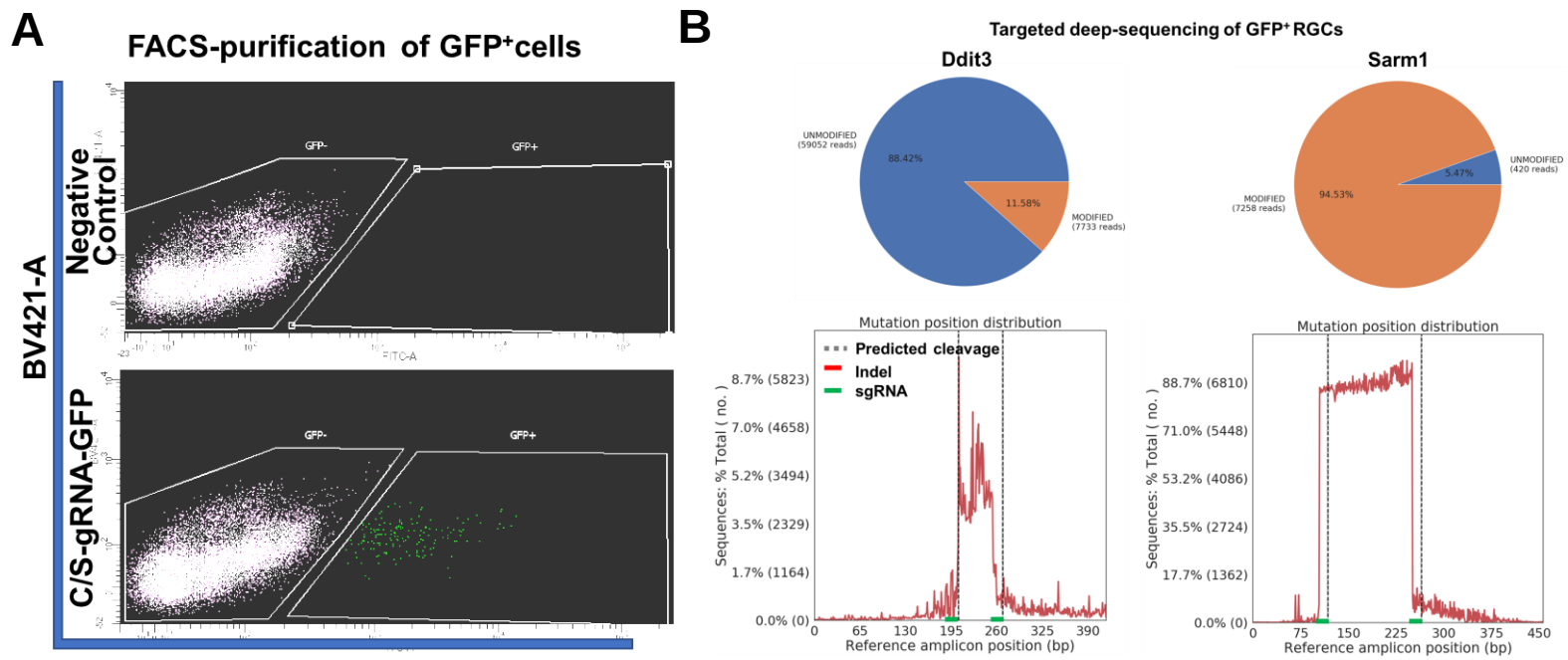
Neuron 2012

ER Stress Modulation Increases RGC Soma and Axon Survival in Glaucoma



Journal of Neuroscience 2016

mSncg promoter-mediated CRISPR/Cas9 gene editing for neuroprotection



Journal of Neuroscience 2020

Next Steps

- Evaluate potential off-target effects in RGCs and other cell types of the eye
- Evaluate effectiveness of neuroprotection of various gene-editing targets
- Validate results in human RGCs
- Complete pre-clinical data for safety and efficacy
- Develop additional therapeutic targets
- Investigate additional means of cell-specific gene expression in other cell types of the retina – opening the door to other types of eye disease