Project Title: Enhancing Optic Nerve Regeneration after Trauma
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Background:
Objective: Study whether manipulation of Kruppel like factors (KLFs) in retinal ganglion cells (RGCs) will enhance axon growth and regenerative potential of RGCs in traumatic optic neuropathy (TON).

Hypothesis: The developmental regulation of KLFs underlies the loss of intrinsic axon growth ability in RGCs, and that manipulation of expression levels of multiple KLF family members will further enhance axon growth and the regenerative potential of RGCs in vivo, especially if combined with other manipulations that also enhance axon growth.

Specific Aims: 1) Determine whether manipulating the expression of multiple KLFs enhances axon regeneration at a rate greater than KLF4 by itself, determine whether simultaneously enhancing pro-regenerative signaling through the manipulation of key signaling pathways further improves regeneration, and determine whether simultaneously blocking the negative effects of glial associated axon growth inhibitors by blocking rho-rho kinase signaling in RGC growth cones further improves regeneration. 2) Determine whether delivery of magnetic nanoparticles (MNPs) carrying pro-growth signaling molecules (specifically agonist anti-trk antibodies) can be used to enhance axon growth in vivo and whether this manipulation can interact with and enhance the regenerative potential of the manipulations in Aim one.

Study Design: Dr. Goldberg addresses ways of alleviating TON resulting from the severing of RGC axons that leads to vision loss. The PI’s strategy is based on manipulating key transcription factors, KLFs that influence the RGC axon regenerative capacity that is generally lost postnatally. Although many efforts are directed toward protecting RGCs from death following eye/brain injury (e.g., in combat-related injuries), the PI will investigate the novel approach of trying to reconnect RGCs with the brain. The work will be done using an optic nerve crush rat model, which is well justified and validated.

Relevance: Military personnel run a high risk of incurring ocular nerve damage. This work will inform genetic and transcriptional manipulations to rescue dying neurons and promote optic nerve axon regeneration. If vision can be restored, even in a fractional way, it would be a major advance in treating TON, as well as chronic optic neuropathies such as nonarteritic anterior ischemic optic neuropathy and glaucoma. If successful, these studies will lay the groundwork for a novel strategy to protect the retina and optic nerve from acute damage (e.g., following explosions and pressure wave injuries) by regenerating the axons of the RGCs and re-establishing connections to the brain through the optic nerve.