Project Title : Restoring vision by inhibition of zinc release

Abstract: Retinal ganglion cells (RGCs), the projection neurons of the eye, cannot regenerate their the optic nerve has been injured, and soon begin to die. Within an hour after the optic nerve is injured, mobile Zn^{2+} increases several-fold in the terminals of retinal amacrine cells (AC) in the inner plexiform layer and continues to rise over the first day, while accumulating more slowly within RGCs themselves. Zn^{2+} accumulation in AC terminals involves the Zn^{2+} transporter protein ZnT-3 that is responsible for Zn^{2+} import into synaptic vesicles, and knockout of ZnT3 blocks Zn^{2+} accumulation while promoting RGC survival and axon regeneration. Intravitreal injection of Zn^{2+} chelators enables many RGCs to survive for months after nerve injury and regenerate axons. Importantly, the therapeutic window for Zn^{2+} chelation extends for several days. Of great interest, intraocular injection of tetanus toxin prevents the translocation of Zn^{2+} from the AC processes to the RGCs while increasing the Zn^{2+} in AC processes, and mimics the protective effect of Zn^{2+} chelation. These results suggest that exocytotic release of mobile Zn^{2+} from the AC processes is critical for the deleterious effects of Zn^{2+} accumulation. These results point to the viability of targeted secretion inhibition as a therapeutic strategy for promoting neuronal survival and axon regeneration after optic nerve injury. The specific question to be addressed in this project is whether a botulinum toxin based strategy can be used to block Zn^{2+} secretion from AC processes following optic nerve injury and effectively promote axonal regeneration and neuronal survival.