Early Testing of CNTF for Glaucoma

Based on the results of preclinical studies, this neurotrophic factor is a candidate for clinical use.

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The search for treatments that promote the survival and regeneration of retinal ganglion cells (RGCs) independent of IOP-lowering effects remains a major goal for basic and clinical research in glaucoma.[1] Neurotrophic factors affect the survival, proliferation, differentiation, and function of neuronal cells. Ciliary neurotrophic factor (CNTF) has begun to bridge the gap between laboratory and human studies.

> "In preclinical models, CNTF provides a neuroprotective effect in RGCs against severe stress such as optic nerve trauma."

CNTF's FUNCTION

CNTF is a well-studied neurotrophic factor shown to act as an injury-activated signal to protect neural tissues, including the retina. CNTF is expressed in the retina under stressful conditions such as experimental ocular hypertension[2] and optic nerve trauma,[3] where it directly stimulates intracellular signaling called the *Jak-STAT cascade* in retinal Müller glial cells, RGCs, and astrocytes. It is thought that the activation of the STAT3 signaling pathway directly mediates the neuroprotective effect of CNTF on neuronal cells. Also, glial cells activated by STAT signaling are associated with the protection of neurons from neuronal degeneration.[4]

NEUROPROTECTION AND REGENERATION

Animal models of retinal degeneration have suggested that CNTF has a neuroprotective effect on photoreceptors. The injection of CNTF protein into the vitreous cavity[5] and the intraocular adenovirus-mediated gene transfer of CNTF[6,7] prevent the death of photoreceptor cells in rodent models of retinal degeneration. Similarly, in preclinical models, CNTF provides a neuroprotective effect in RGCs against severe stress such as optic nerve trauma.[8] Long-term delivery using adeno-associated virus serotype 2 (AAV2) vectors that express a secretable form of CNTF make long-term delivery to RGCs possible. An intravitreal injection of AAV2-CNTF 1 week before trauma to the optic nerve enhanced RGC survival almost fourfold compared with control retinas 7 weeks after the treatment.[8,9] Similarly, the intravitreal administration of AAV2-CNTF in laser-

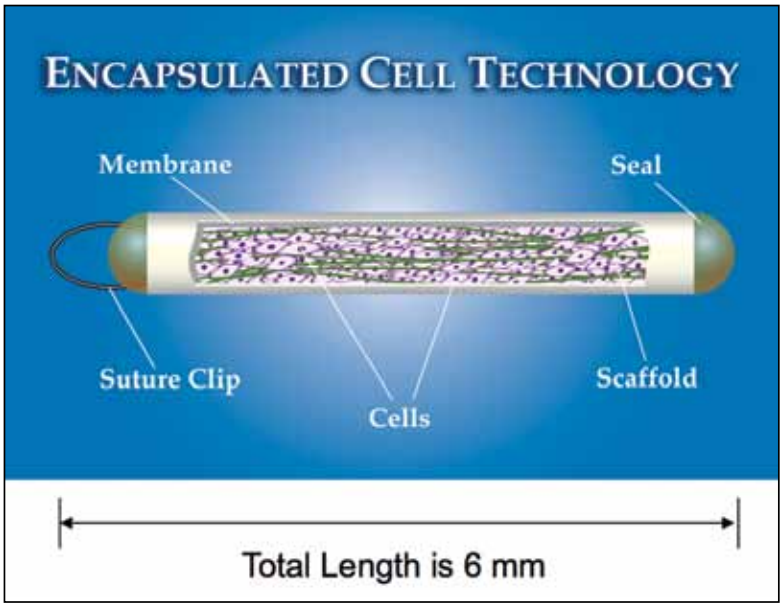

Figure 1. Neurotech's NT-501 intravitreal implant.

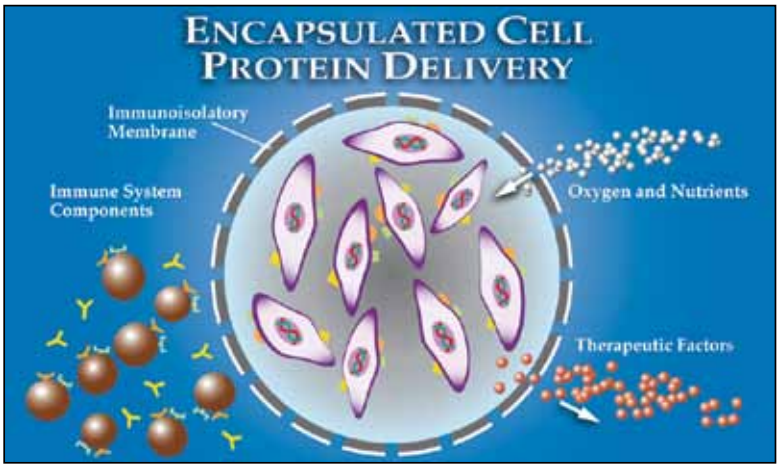

Figure 2. A small capsule of human cells engineered to secrete CNTF is enclosed in a semipermeable membrane that allows CNTF secretion into the vitreous.

induced glaucoma can exert a significantly protective effect against axon loss in the optic nerve.[10]

Interestingly, CNTF has an additional positive effect: it promotes axon regeneration after optic nerve damage in preclinical models. Purified RGCs extensively elongate their neurites in the presence of CNTF in culture.[11,12] In vivo, CNTF enhances RGC axon regeneration in the optic nerve. The intravitreal application of CNTF[13] and AAV2-CNTF injection[8] substantially enhanced the regeneration of damaged axons into a sciatic nerve graft after optic nerve axon transection.

CLINICAL TESTING

Can CNTF slow the progression of visual field loss or even restore vision in patients with glaucoma or other optic neuropathies? Recently, another method of long-term CNTF delivery to the retina has been developed: an intravitreal implant (NT-501 implant; Neurotech, Inc.; Figure 1). A small capsule of human cells engineered to secrete CNTF is enclosed in a semipermeable membrane that allows CNTF secretion into the vitreous (Figure 2). In phase 2 trials, the implant was found to be safe in human testing without significant serious adverse events in patients with retinitis pigmentosa and age-related macular degeneration.[14] The data also showed that CNTF secretion was maintained at similar levels even after 2 years,[14] suggesting that long-term drug delivery is feasible in the human eye.

Would CNTF work in humans to support RGC survival or encourage optic nerve regeneration? A phase 1 trial in glaucoma recently completed enrollment and is expected to complete 18 months of follow-up by September 2013 (www.clinicaltrials.gov # NCT01408472). Although phase 1 trials are designed to evaluate safety in the patient population being studied, any hint of efficacy will be expected to drive investigation in later-phase trials.

CONCLUSION

Much work will have to be done to cycle back and forth between human testing and preclinical development. The premise of moving promising candidate therapies from the laboratory to the clinic, however, raises the hope of identifying new treatments for glaucoma patients. ■

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