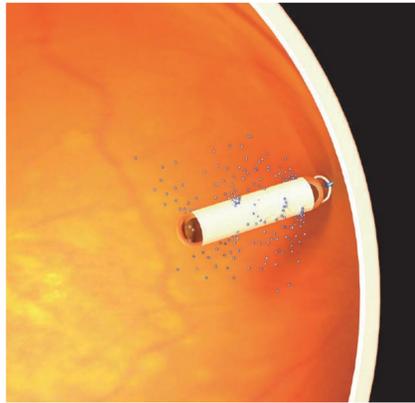


# Continuous Intraocular Drug Delivery over 5 ½ Years: Ciliary Neurotrophic Factor (CNTF) Production by Encapsulated Cell Technology Implants Treating Patients with Retinitis Pigmentosa and Geographic Atrophy

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## 1. OBJECTIVE

We have previously reported the pharmacokinetics of ciliary neurotrophic factor (CNTF) delivered over 2 years by an intraocular encapsulated cell technology (ECT) implant in patients with retinitis pigmentosa (RP) and geographic atrophy (GA). This is a follow-up evaluation of patients implanted up to a 5.5 - year period.



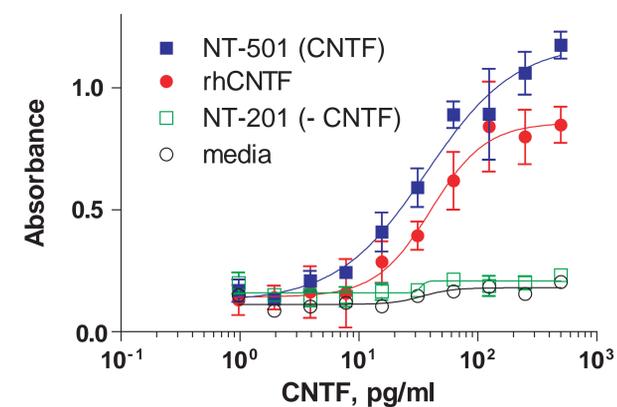
## 2. METHODS AND MATERIALS

All study patients received an ECT-CNTF implant, designated NT-501, in one eye. For the phase 1 RP (CNTF1) study, the protocol mandated explant of all patients at 6 months. For the phase 2 studies, including phase 2 GA (CNTF2), and phase 2 late and early stage RP (CNTF3, and CNTF4), explants were optional and occurred at 12, 18 and 24 months. Several additional patients from the CNTF4 study chose to be explanted at 30 (n=6), 44 (n=1), 54 (n=1) and 66 (n=1) months post implant. The rate of CNTF secretion from the explants and the corresponding vitreous CNTF levels, if available, were evaluated at each time point. Serum samples from these patients were evaluated for CNTF, anti-CNTF antibodies and antibodies to the encapsulated cells.

## 3. RESULTS

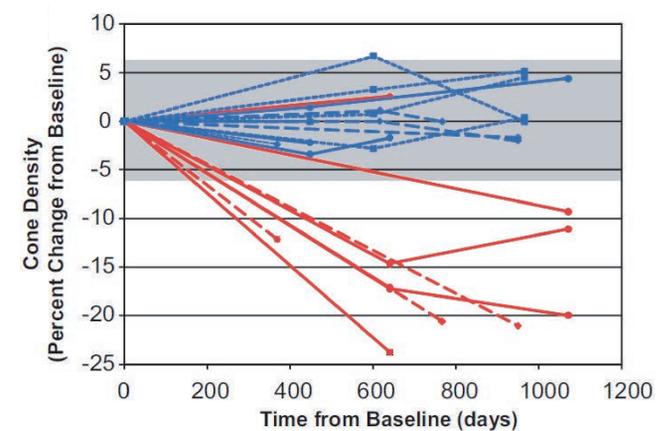
Cumulatively, the data demonstrates NT-501 implants produce CNTF continuously over a 5.5 year period. The range of explant CNTF production rate at each time point was statistically equivalent between the 0.5 year and 5.5 year implant period. The mean rates of CNTF production over this period varied between approximately 1 ng/day to 2 ng/day, a rate shown to be effective in protecting cone photoreceptors in RP patients (<sup>1</sup>Talcott et al. IOVS, 2011). Encapsulated cells, subjectively evaluated following H&E staining of explant capsules, were viable and at a high population density, similar to the pre-implant condition. CNTF, anti-CNTF antibodies and antibodies to the encapsulated cells were not detected in the serum of patients.

### Potency and Bioactivity of NT-501 Produced CNTF



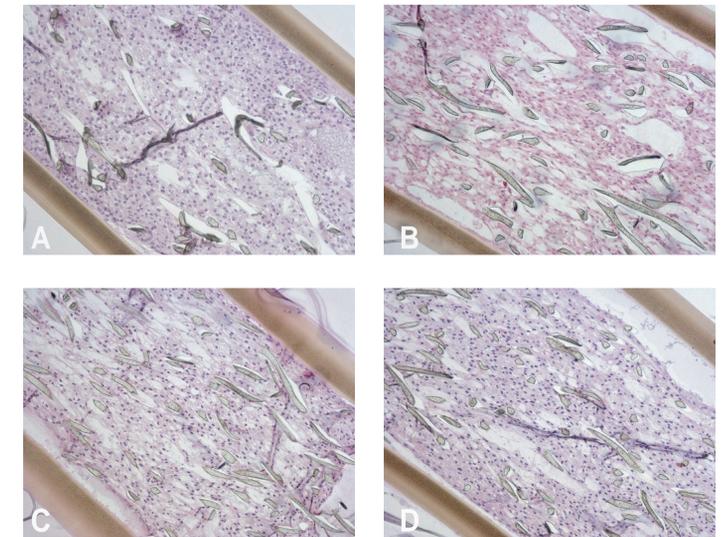
**Figure 1.** Prior to implant, the bioactivity/potency of CNTF produced from clinical lots of NT-501 devices was determined using a TF-1.CN5a1 cell proliferation assay. NT-501-produced CNTF consistently generated a more robust cell growth response compared to rhCNTF. This observation is not surprising considering NT-501 derived CNTF is made from human mammalian cells and has not been subjected to the purification process.

### NT-501 Preserves Photoreceptor Density in RP<sup>1</sup>



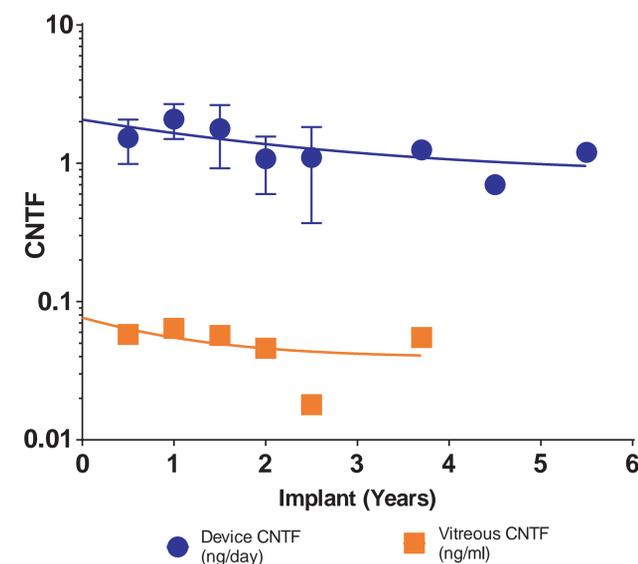
**Figure 2.** Cone photoreceptor density evaluated over time by adaptive optics scanning laser ophthalmoscopy (AOSLO). Retinitis pigmentosa patients (n=3) treated with CNTF-secreting NT-501 implants were evaluated using AOSLO at repeated regions of interest (ROI) to determine individual cone density and spacing. Overall, cone density in the ROI's of sham treated eyes decreased by 9%-24% while 100% of the cone density in ROI's of CNTF-implant eyes remained stable over the course of the treatment period.

### Long-Term Cell Viability of NT-501 Implants



**Figure 4.** Representative histologic (H&E) sections of encapsulated NT-501 cells 2-weeks prior to implant (A), following 1-year implant (B), 3-year implant (C) and 5.5-year implant period (D). Cell viability and distribution are excellent in all evaluated samples showing no evidence of decline in cell mass comparing pre-implant and explanted samples over a 5.5 year study period.

### Intraocular, Steady-State Delivery of CNTF in Human Patients



**Figure 3.** Intraocular delivery of CNTF over course of 5.5 years in human patients with RP or AMD. Explant device conditioned supernatant as well as 100 microliter samples of vitreous from each patient were analyzed to determine concentrations of CNTF as a function of treatment time. Both device explant and vitreous CNTF levels remain constant over period of 6-months to 5.5 years in human patients.

**Table 1.** The kinetic rates from device explant and human vitreous for ECT produced CNTF fit the equation:

$$\ln \text{ECT-Device, Vit}_t = -k t + \ln \text{ECT-Device, Vit}_0$$

where ECT-Device, Vit is the CNTF device or vitreous level at time t or time 0 (6 month implant) and k is the decay rate constant. The fitted kinetic constants and half life ( $t_{1/2}$ ) determinations describe the delivery profile of CNTF produced by ECT implants and concentrations detected in human vitreous samples over time. MRT = mean residence time or time to clear 69% of drug from vitreous.

Compartment	$t_{1/2}$ (years)	k (years <sup>-1</sup> )	MRT (years)
Device Explant	5.5	0.120	NA
Vitreous	4.7	0.144	6.8

## 4. CONCLUSIONS

The current study demonstrates that intraocular NT-501 implants maintain a favorable pharmacokinetic for the treatment of chronic retinal degenerative diseases without systemic exposure for over a half decade.

## 5. REFERENCES

<sup>1</sup> Talcott et al, Longitudinal study of cone photoreceptor during retinal degeneration and in response to ciliary neurotrophic factor treatment. *IOVS*, 2011; 52:2219-2226

