Secretion of Ciliary Neurotrophic Factor by NT-501 Encapsulated Cell Technology in Patients With Retinal Degenerative Disorders

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- Thomas A. Albini has the following financial interests or relationships to disclose:
  - Received consulting fees from Adverum Biotechnologies, Allergan, B+L/Valeant Pharmaceuticals, Beaver Visitec, Clearside Biomedical, EyePoint, Genentech, Neurotech, Novartis, and Regenxbio
  - Participated in a data monitoring committee for Adverum Biotechnologies, Applied Genetic Technologies, Novartis, and Regenxbio
  - Participated in a safety review committee for Apellis and Novartis

Retinal Degenerative Diseases

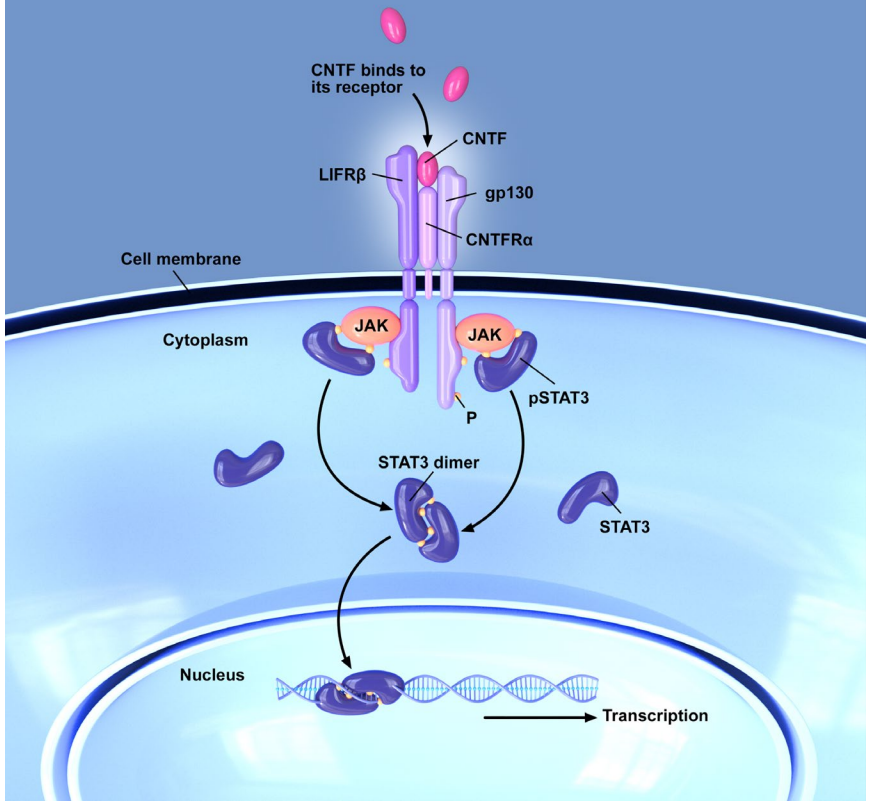
- Retinal degenerative diseases are a group of chronic conditions that are a significant cause of vision loss worldwide and impact quality of life[1,2]
- In chronic retinal degenerative diseases, damage to the retina leads to vision loss[1,2]
- Progressive death of photoreceptors and retinal pigment epithelium cells are hallmarks of these diseases[1,2]
- Despite the impact on vision loss, few effective treatments are available for chronic neurodegenerative conditions of the retina, such as macular telangiectasia type 2[3]

1. Khaboushan AS, et al. *J Transl Med*. 2024;22:227. **2.** Kaur G, Singh NK. *Neural Regen Res*. 2023;18:513-518. **3.** Ramsay E, et al. *J Control Release*. 2023;361:1-19.

Ciliary Neurotrophic Factor Is a Potent Neuroprotectant[1-3]

- In response to retinal injury, Müller glial cells release the neuroprotective factor CNTF[1]
- **CNTF protects and preserves photoreceptors[2-4]**
- In preclinical models of retinal degeneration, photoreceptors can be rescued with intravitreal injection of CNTF[2,4]

CNTF works through the JAK/STAT3 pro-survival pathway

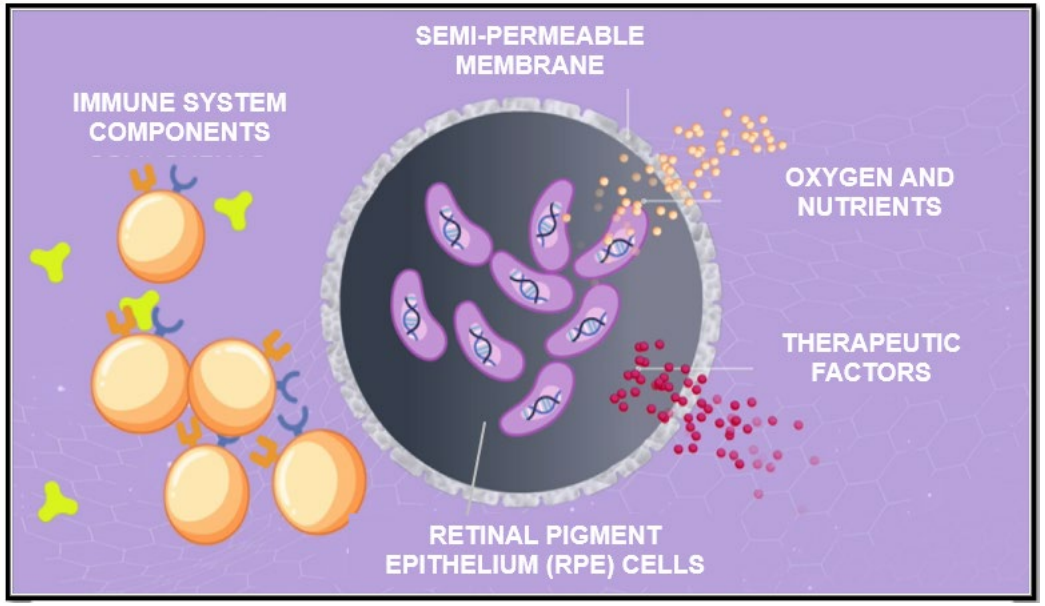


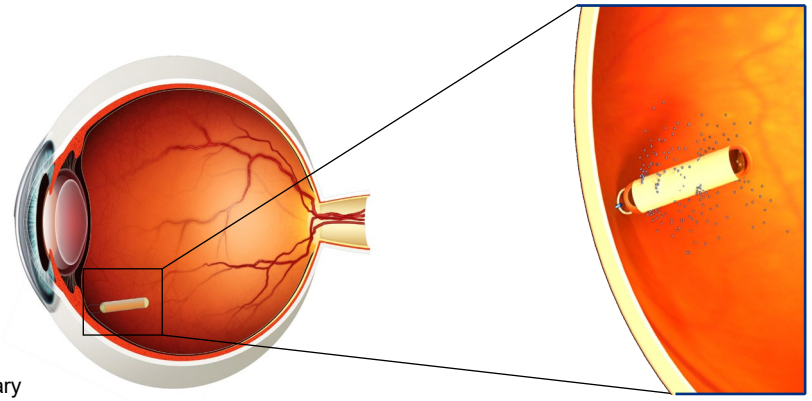
CNTF, ciliary neurotrophic factor; CNTFRα, ciliary neurotrophic factor receptor-alpha; gp130, glycoprotein 130; JAK/STAT3, Janus kinase/signal transducer and activator of transcription 3; LIFRβ, leukemia inhibitory factor ß; P, phosphorous; pSTAT3, phosphorylated signal transducer and activator of transcription 3; STAT3, signal transducer and activator of transcription 3.

1. Bringmann A, et al. *Prog Retin Eye Res*. 2009;28:423-451. **2.** Shen W, et al. *J Neurosci*. 2012;32:15715-15727. **3.** Sleeman MW, et al. *Pharm Acta Helv*. 2000;74:265-272. **4.** Tao W, et al. *Invest Ophthalmol Vis Sci*. 2002;43:3292-3298.

Encapsulated Cell Therapy Is Designed to Deliver Sustained Levels of CNTF

- Revakinagene taroretcel-lwey (NT-501) is a first-in-class encapsulated cell therapy[1,2]
  - Houses NTC-201-6A cells[1]
    - Allogeneic retinal pigment epithelial cells expressing recombinant human CNTF[1]
  - Surgically implanted into the vitreous cavity and stably anchored to the sclera[1]
  - Developed to produce long-term sustained levels of CNTF[3]
  - **NT-501 was approved by the FDA for the treatment of macular telangiectasia type 2 on March 5, 2025**



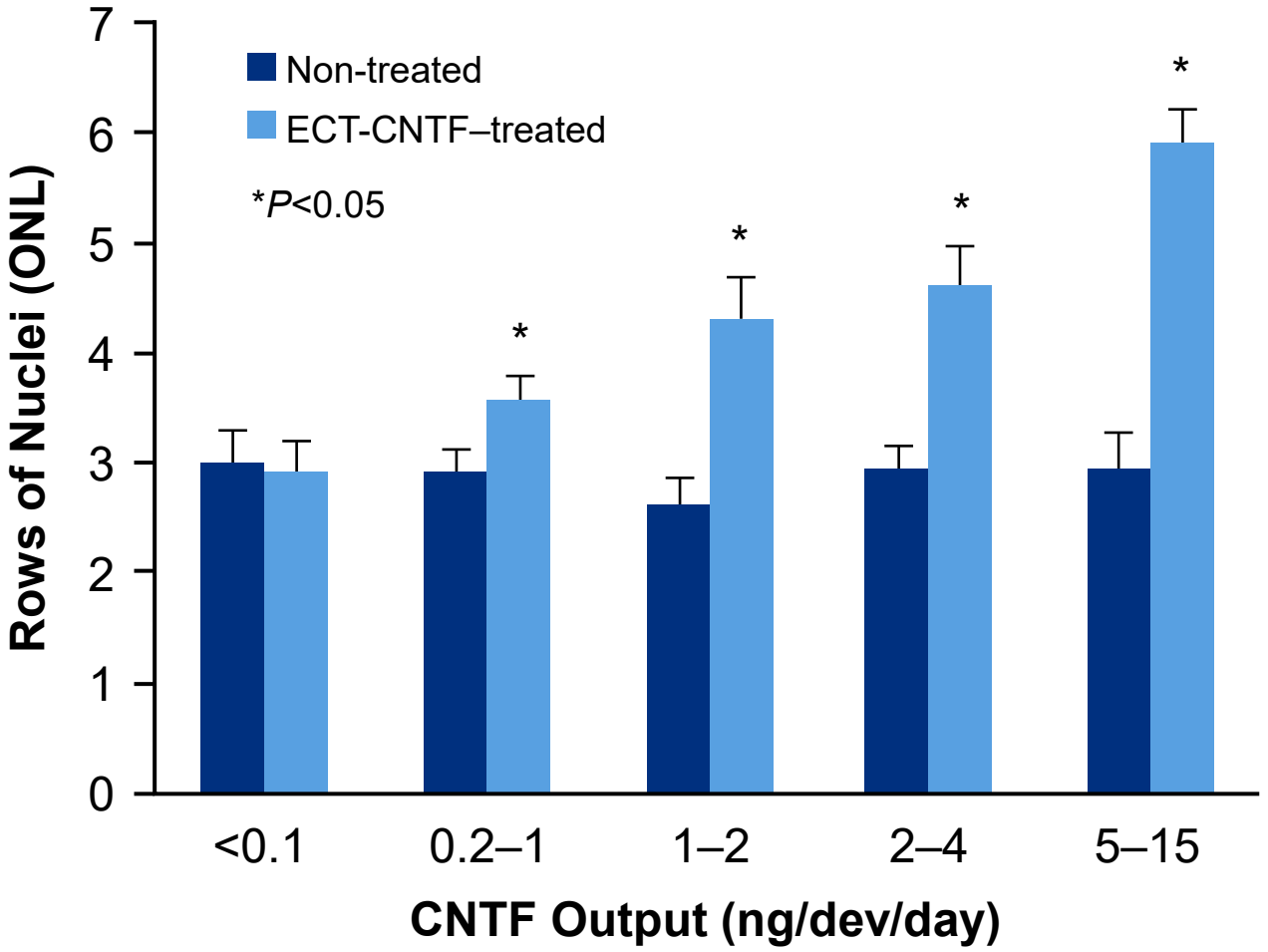


CNTF, ciliary neurotrophic factor; FDA, Food and Drug Administration; RPE, retinal pigment epithelium.

1. ENCELTO [package insert]. Cumberland, RI: Neurotech Pharmaceuticals, Inc; March 2025. **2.** Lally D, Eliott D. Phase 2 safety study of bilateral ciliary neurotrophic factor-producing revakinagene taroretcel in participants with macular telangiectasia type 2 [abstract]. Presented at: Annual EURETINA; September 19-22, 2024; Barcelona, Spain. **3.** Kauper K, et al. *Invest Ophthalmol Vis Sci.* 2023;64:3680.

CNTF Provided Photoreceptor Protection in a Preclinical Study[1]

- In the rapid retinal degeneration *rcd-1* canine model, ECT devices were intravitreally implanted into dogs at 7 weeks of age
- Doses greater than 0.2 ng/day were seen to provide photoreceptor protection, with greater protection seen at higher doses



CNTF, ciliary neurotrophic factor; dev, device; ECT, encapsulated cell therapy; ng, nanogram, ONL, outer nuclear layer.

1. Tao W, et al. *Invest Ophthalmol Vis Sci.* 2002;43:3292-3298. Figure reproduced with permission of Association for Research in Vision & Ophthalmology, from Encapsulated cell-based delivery of CNTF reduces photoreceptor degeneration in animal models of retinitis pigmentosa, Tao W, et al, 43(10), 2002; permission conveyed through Copyright Clearance Center, Inc.

Analysis of Long-term Durability of CNTF Release From NT-501

- **Objective:** To examine drug-release levels and long-term function of explanted NT-501 devices following implant durations of 0.5 to 14.5 years in people with retinal degenerative disease
- Participants were enrolled in the following trials:
  - Retinitis pigmentosa[a]: Phase 1 and three Phase 2 trials
  - Atrophic macular degeneration[b]: Phase 2 trial
  - Macular telangiectasia[c]: Phase 3 trial

CNTF, ciliary neurotrophic factor.
[a]NCT00063765, NCT00447993, NCT00447980, and NCT01530659. [b]NCT00447954. [c]NCT03319849.

Analysis of Long-term Durability of CNTF Release From NT-501

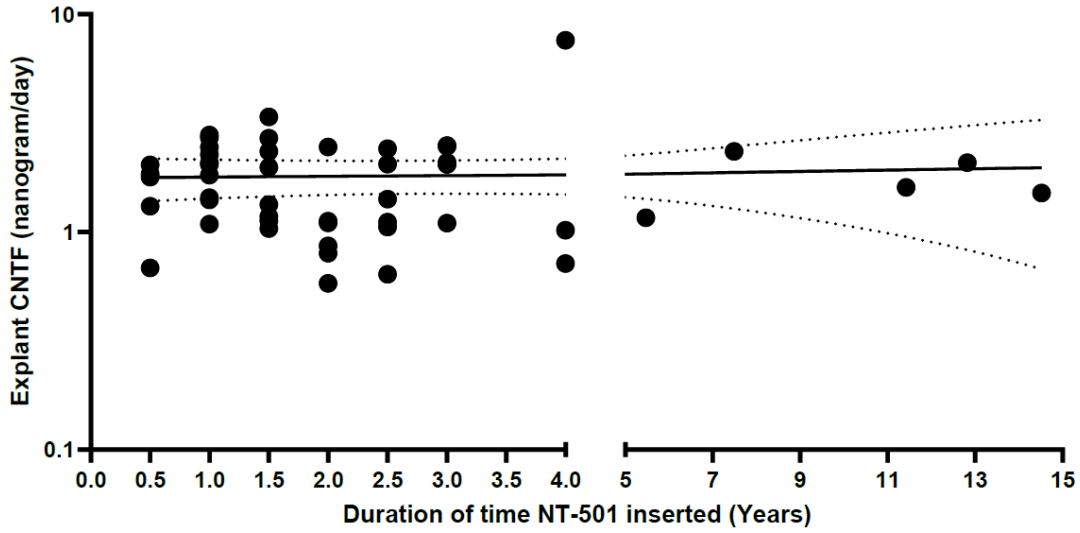
- Explanted NT-501 devices were collected and assessed for:
  - Rate and potency of CNTF produced[a]
  - Histomorphology of the encapsulated cells producing CNTF[b]
    - Samples were scored by three independent analyses on cell morphology and device cell density
- Serum from select patients were evaluated for:
  - Detectable levels of CNTF
  - Antibodies against CNTF
  - Antibodies against the NTC-201-6A cell line

CNTF, ciliary neurotrophic factor; ELISA, enzyme-linked immunosorbent assay.
[a]Assay utilized the Human CNTF Quantikine® ELISA Kit (R&D Systems), a sandwich-type ELISA. [b]Hematoxylin and eosin (H&E) staining was used to analyze cell morphology and device cell density.

Long-term CNTF Release[a] After NT-501 Implantation

- An analysis of 49 NT-501 explants from implant durations of up to 14.5 years demonstrated consistent release of CNTF
- The mean of protein release was 1.6 ng/day (95% CI, 1.4–1.8)

Secretion of CNTF by duration that NT-501 devices were implanted[b]



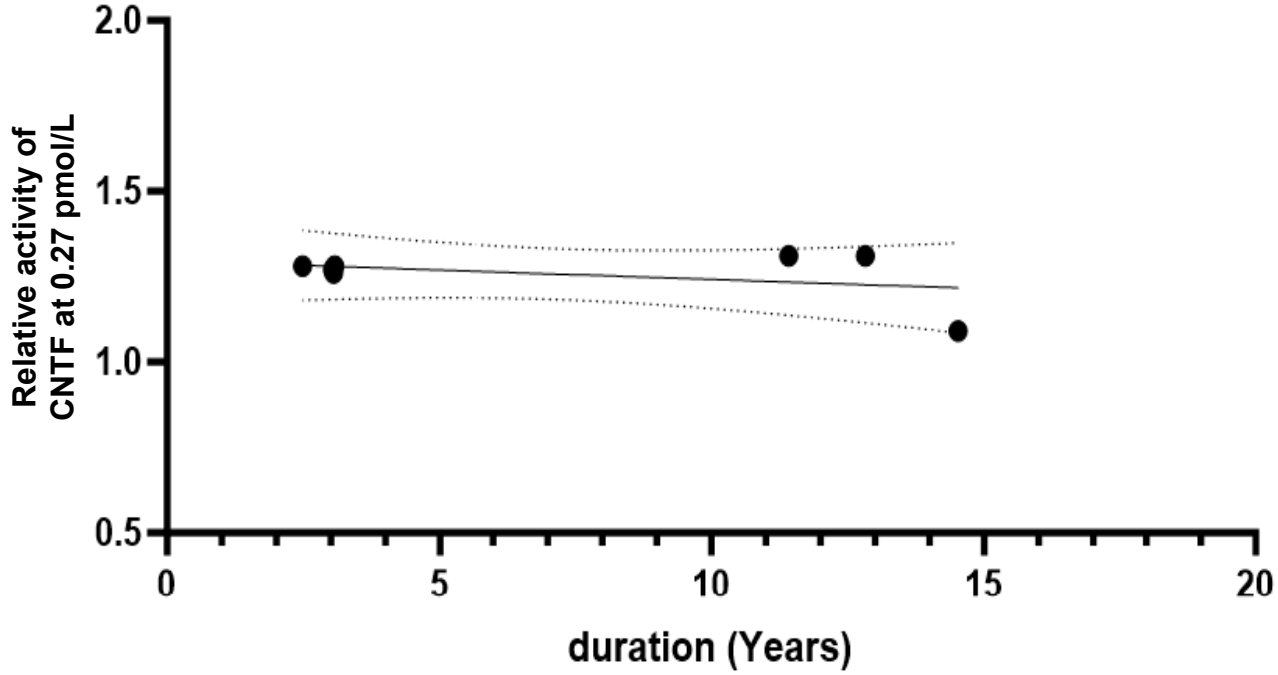
Time	0.5	1	1.5	2	2.5	3	4	5.47	7.49	11.42	12.82	14.52
n	5	10	8	6	6	6	3	1	1	1	1	1

CI, confidence interval; CNTF, ciliary neurotrophic factor; ELISA, enzyme-linked immunosorbent assay; ng, nanogram.
[a]As measured by an ELISA (Quantikine ELISA, R&D Systems). [b]Samples were grouped by the nearest half year. The solid line indicates the mean CNTF level and the dotted lines indicated the range of the 95% CI.

CNTF From Explanted Devices Compared With Reference

- Device explant pulses were tested for the specific activity of CNTF relative to a reference protein using a modification of the CNTF bioassay
- Specific activity of the samples averaged 1.25 times over that of the reference protein, indicating bioactivity
- Samples were not significantly different from each other over the duration of the implant period

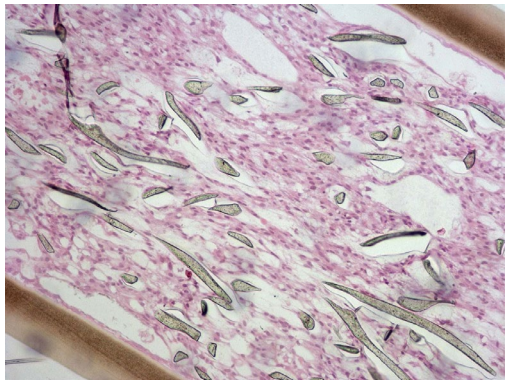
Specific activity of CNTF from patient explants compared with a reference CNTF control (n=10)[a]



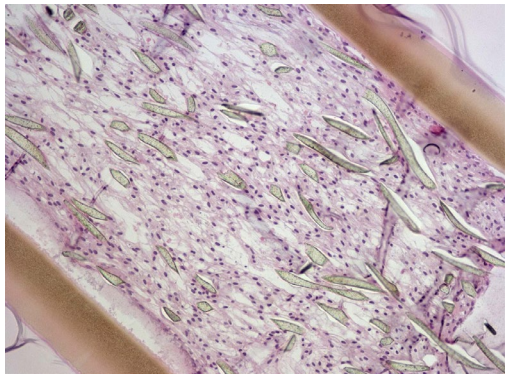
CI, confidence interval; CNTF, ciliary neurotrophic factor; EC_{50}, half-maximal effective concentration.
[a]The small volume of available sample necessitated using a single point, at historical EC_{50}, bioassay setup. The solid line indicates the mean CNTF level and the dotted lines indicates the range of the 95% CI.

NT-501 Explant Histopathology Over Time

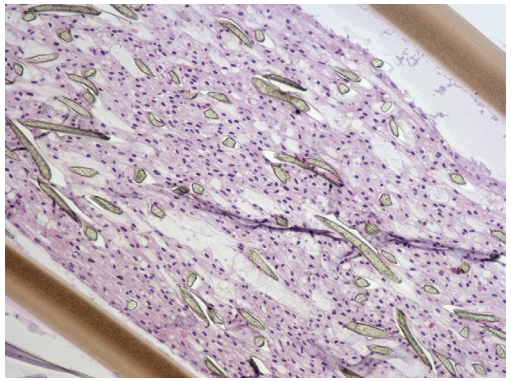
- Cell morphology from 49 NT-501 explants were similar at explant times ranging from 1 to 14.5 years
- Cell density from explants were also similar
  - This was true even for the explants with the longest implant duration



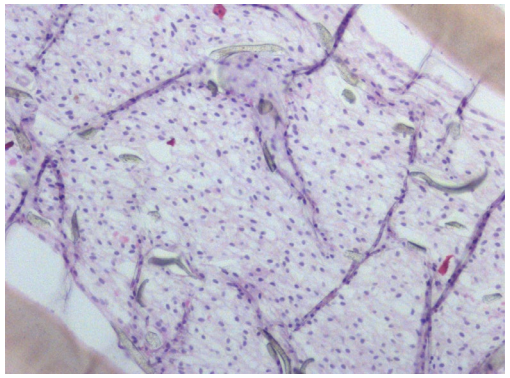
(A) Explanted after 1 year



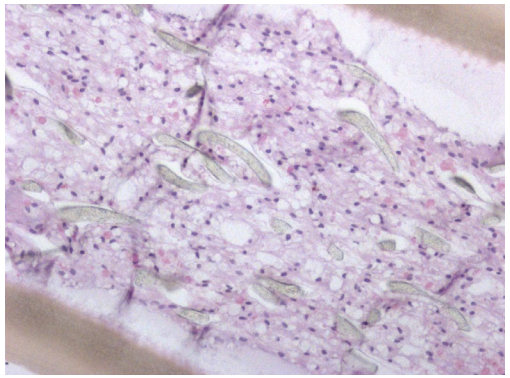
(B) Explanted after 3 years



(C) Explanted after 5.5 years



(D) Explanted after 12.9 years



(E) Explanted after 14.5 years

Figure shows representative histologic (hematoxylin and eosin–stained) sections of encapsulated NT-501 cells from NT-501 explants that had been inserted in patients for 1 to 14.5 years (A–E).

Serum Analysis From Explanted Patients

- An analysis of serum samples[a] demonstrated:
  - No detectable levels of CNTF
  - No antibody levels against CNTF over participants' baseline level
  - No antibody levels against the NTC-201-6A cell line over participants' baseline level

CNTF, ciliary neurotrophic factor; ELISA, enzyme-linked immunosorbent assay.
[a]Analyzed by ELISA.

Conclusions

- This study found that the ECT device NT-501 produced **consistent levels** of **bioactive CNTF** at time points as long as **14.5 years**
- The CNTF output (1.6 ng/day) has been shown to be **effective in slowing photoreceptor loss** in the rapid retinal degeneration *rcd-1* canine model[1]
- Histological evaluation determined that cells from NT-501 explants that had been implanted for 1 to 14.5 years were **similar in density and morphology**
- Data from this retrospective analysis support intraocular NT-501 as a promising long-term treatment option for retinal degenerative diseases

CNTF, ciliary neurotrophic factor; ECT, encapsulated cell therapy; ng, nanogram.

1. Tao W, et al. *Invest Ophthalmol Vis Sci.* 2002;43:3292-3298.

Acknowledgements

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