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

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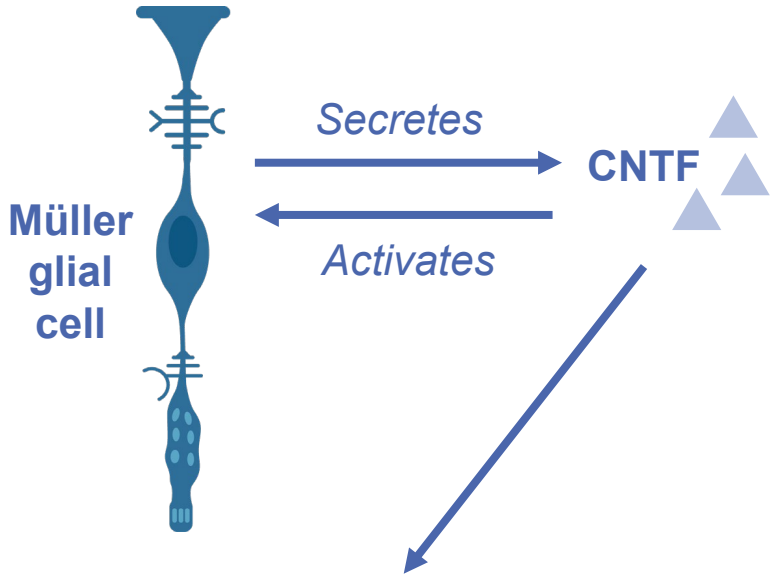
# Retinal Degenerative Diseases

- 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.

# CNTF Protects and Preserves Photoreceptors

- Under pathological conditions, Müller glial cells can protect photoreceptors from cell death through the production of neurotrophic factors, including CNTF[1]
- Neuroprotective factors, including CNTF, provide structural and neuroprotective support by activating cell survival pathways[1-3]
- ECT enables continual release of CNTF to the retina over long periods of time, without triggering an immune response[4-6]

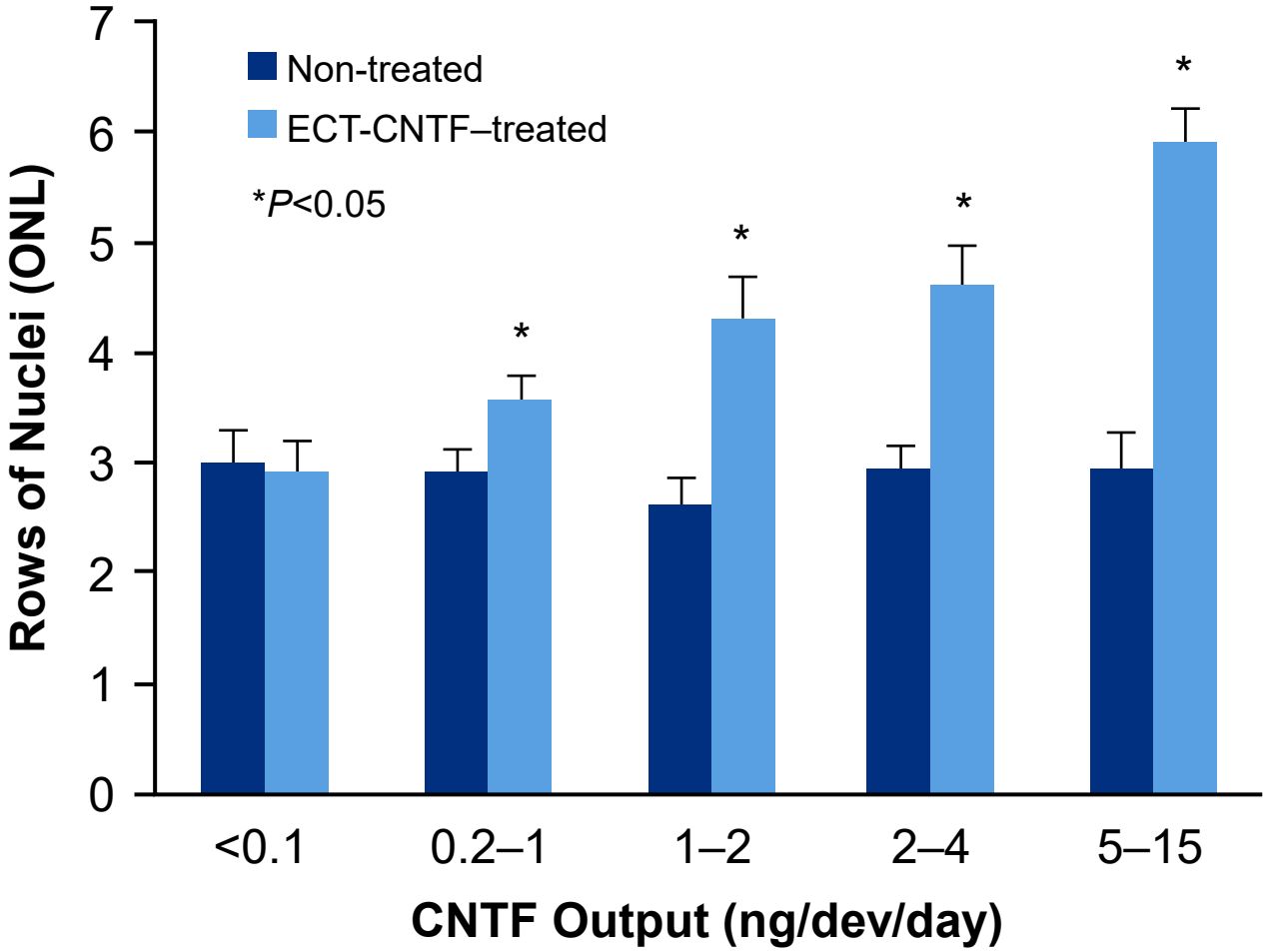



CNTF, ciliary neurotrophic factor; ECT, encapsulated cell therapy.

**1.** Bringmann A, et al. *Prog Retin Eye Res*. 2006;25:397-424. **2.** Rhee KD, et al. *Proc Natl Acad Sci U S A*. 2013;110:E4520-E4529. **3.** Cayouette M, et al. *J Neurosci*. 1998;18:9282-9293. **4.** Wen R, et al. *Prog Retin Eye Res*. 2012;31:136-151. **5.** Tao W. *Expert Opin Biol Ther*. 2006;6:717-726. **6.** 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

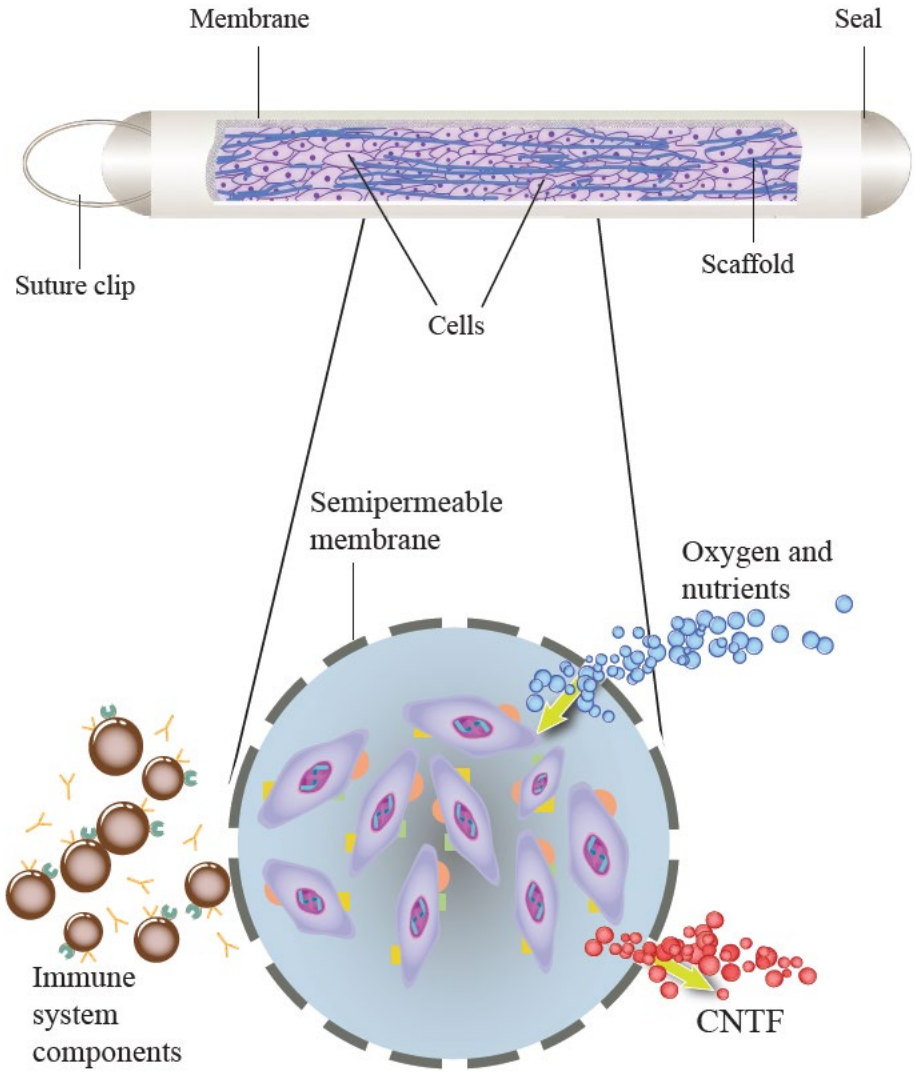



CNTF, ciliary neurotrophic factor; dev, device; ECT, encapsulated cell therapy; ng, nanogram, ONL, outer nuclear layer;.

**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.

# Encapsulated Cell Therapy Enables Long-term CNTF Delivery

- Revakinagene taroretcel-lwey (formerly known as NT-501) is a first-in-class ECT[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 release long-term sustained levels of CNTF[3]
  - **Revakinagene taroretcel-lwey was approved by the FDA for the treatment of MacTel on March 5, 2025[1]**




CNTF, ciliary neurotrophic factor; ECT, encapsulated cell therapy; FDA, Food and Drug Administration; MacTel, macular telangiectasia type 2.
**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.

# Assessing the Long-term Durability of Revakinagene Taroretcel-lwey

- **Objective:** To examine drug-release levels and long-term function of explanted revakinagene taroretcel-lwey 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 age-related macular degeneration[b]: Phase 2 trial
  - MacTel[c]: Phase 3 trial

MacTel, macular telangiectasia type 2.
[a]NCT00063765, NCT00447993, NCT00447980, and NCT01530659. [b]NCT00447954. [c]NCT03319849.





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# Analysis of Long-term Durability of CNTF Release From Revakinagene Taroretcel-lwey

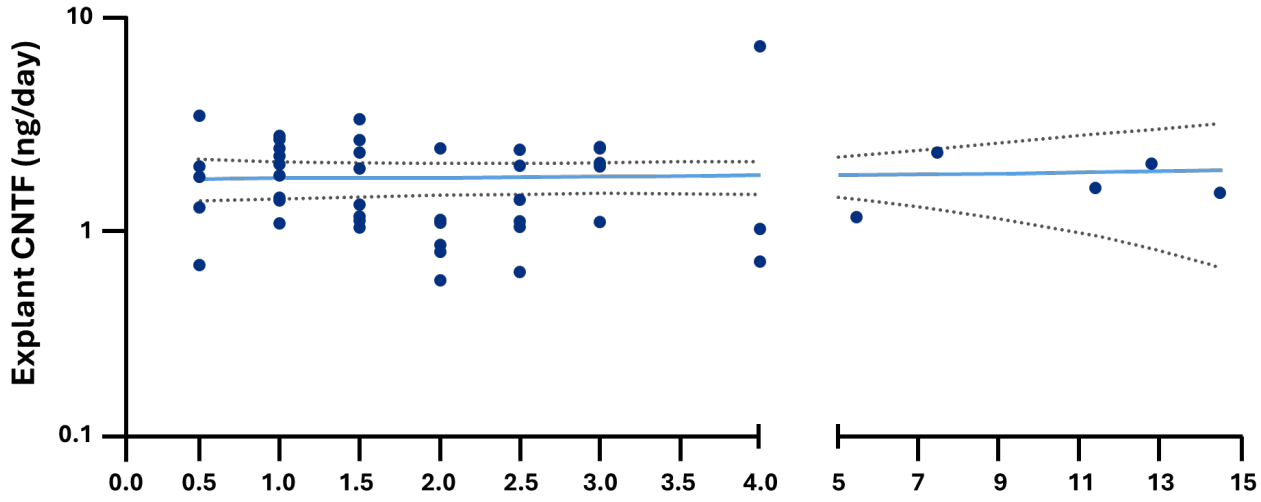
- Revakinagene taroretcel-lwey explants were collected and assessed for:
  - Rate and potency of CNTF produced[a]
  - Histology of the encapsulated cells producing CNTF[b]
    - Samples were scored by three independent analysts on cell morphology and cell density
- Serum from select patients were evaluated 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 cell density.

# Long-term CNTF Release[a] After Revakinagene Taroretcel-lwey Implantation

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

**Secretion of CNTF by duration that revakinagene taroretcel-lwey was implanted[b]**



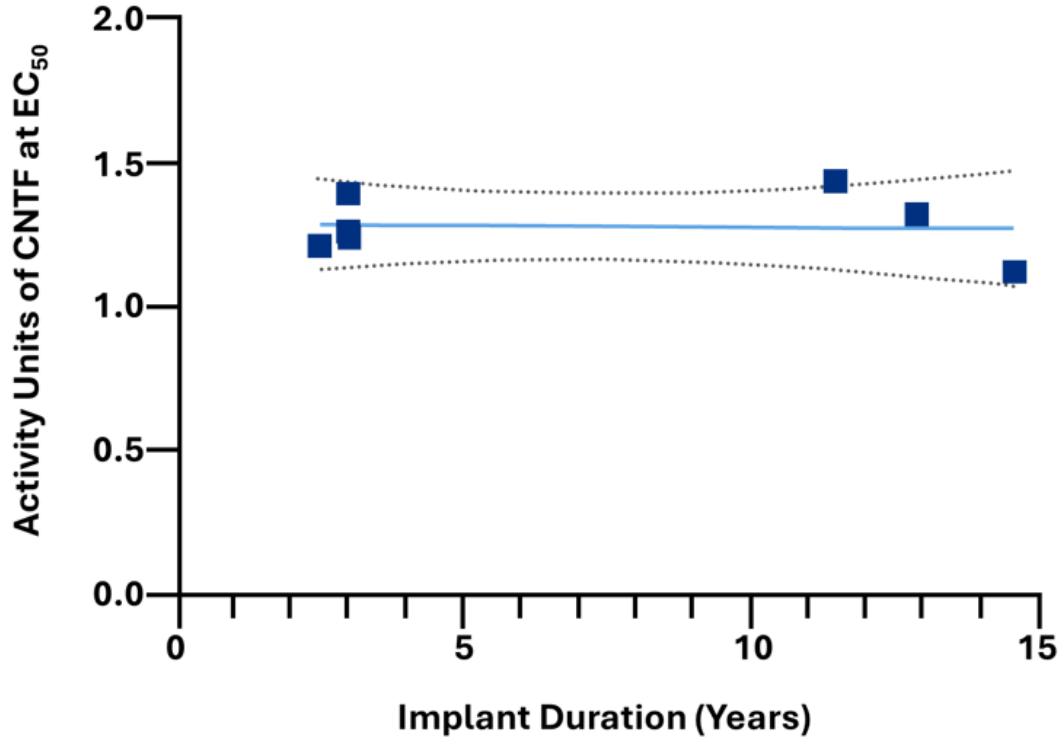

| Time | 0.5 | 1 | 1.5 | 2 | 2.5 | 3 | 4 | 5.47 | 7.49 | 11.42 | 12.82 | 14.52 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| n | 5 | 10 | 8 | 6 | 6 | 6 | 3 | 1 | 1 | 1 | 1 | 1 |

CI, confidence interval; CNTF, ciliary neurotrophic factor; ELISA, enzyme-linked immunosorbent assay; n, number of explants; ng, nanogram.
[a]As measured by an ELISA (Quantikine ELISA, R&D Systems). [b]Samples were grouped by the nearest half year for implant durations <3 years. The solid line indicates the mean CNTF level, and the dotted lines indicates the range of the 95% CI.

# CNTF From Revakinagene Taroretcel-lwey Explants Compared With Reference

- Explant release of CNTF was tested for bioactivity relative to a reference protein using a modification of the CNTF bioassay
- Specific activity of the samples averaged 1.26 activity units over that of the reference protein, indicating bioactivity
- Samples were not significantly different from each other over the duration of the implant period

**Units of activity of CNTF produced by revakinagene taroretcel-lwey explants over 14.5 years of implant duration (n=7)[a]**




CI, confidence interval; CNTF, ciliary neurotrophic factor; $EC_{50}$, half-maximal effective concentration.
[a]Seven samples were analyzed, two of which were analyzed twice, and the results were averaged. 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.

# Revakinagene Taroretcel-lwey Explant Histology Over Time

- Cell morphology from 48[a] revakinagene taroretcel-lwey explants was similar across explant times, up to 14.5 years
- Cell density from explants was also similar
  - This was true even for the explants with the longest implant duration

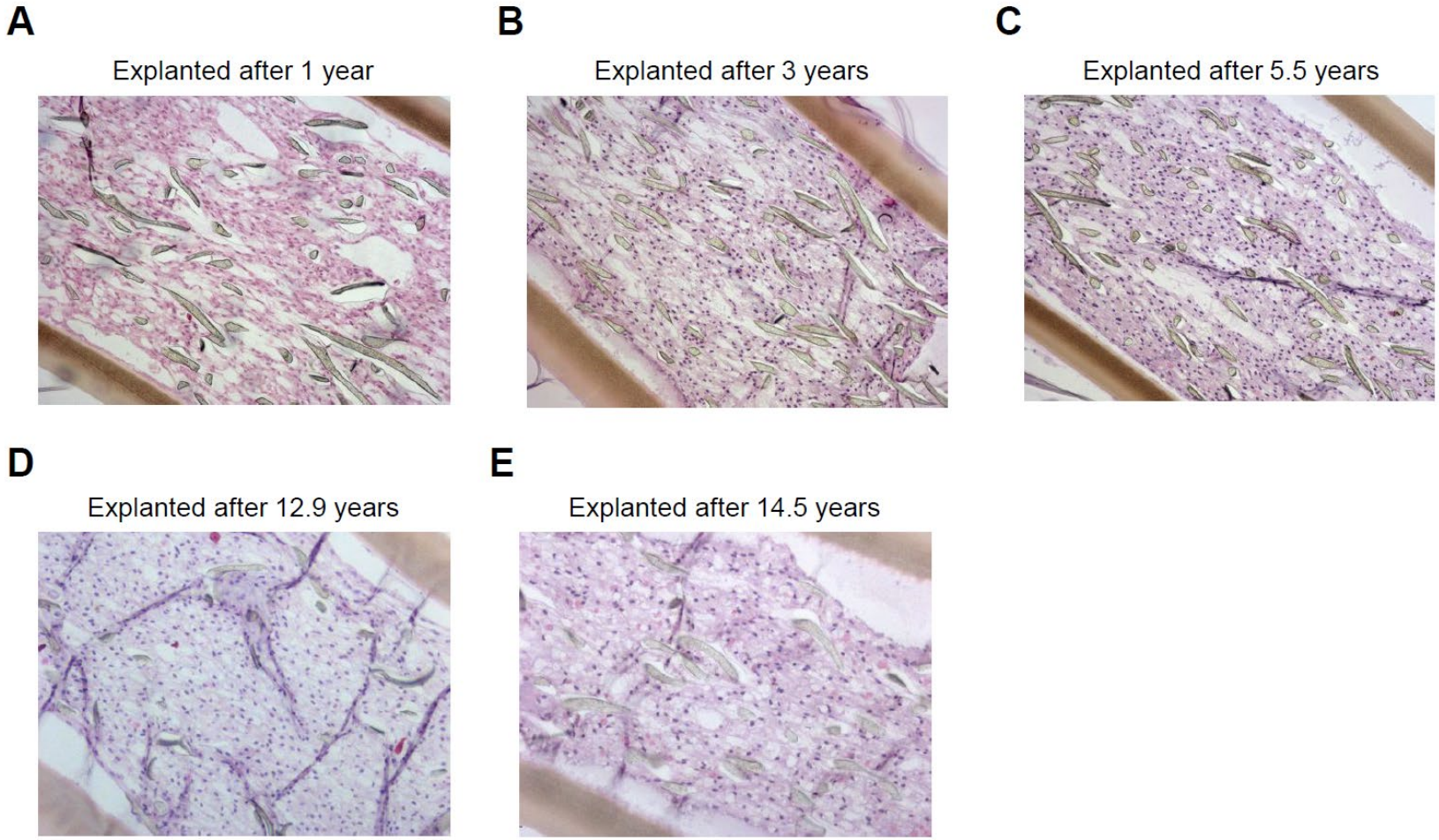



Figure shows representative histologic (hematoxylin and eosin–stained) sections of encapsulated NTC-201-6A cells from revakinagene taroretcel-lwey explants that had been inserted in patients for 1 to 14.5 years (A–E). [a]One explant did not have a sample evaluable for histological analysis.

# 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 revakinagene taroretcel-lwey released **consistent levels** of **bioactive CNTF** at time points as long as **14.5 years**
- Histological evaluation determined that cells from revakinagene taroretcel-lwey explants that had been implanted for up to 14.5 years were **similar in cell density and morphology**
- 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]
- These findings suggest that revakinagene taroretcel-lwey has the potential to be a long-term **therapeutic option for chronic retinal degenerative diseases**

CNTF, ciliary neurotrophic factor; ng, nanogram.

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

# Acknowledgements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