Cone Structure in Eyes with RP treated with CNTF

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Retinal Degenerations: RP, Usher Syndrome

• Vision is lost when photoreceptors die
• No treatments or cures for inherited retinal diseases
• Development of a new treatment:
  – Ciliary NeuroTrophic Factor (CNTF)
  – A 2 decade journey

1990s: Matt LaVail and Roy Steinberg Describe Photoreceptor Rescue with CNTF

2000s: First Patients treated with CNTF

Retinal degenerations: Phase I trial of CNTF delivered by encapsulated cell intraocular implants

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As treatments are developed, how should we measure response?

- Can’t see photoreceptors
- Typically: Measure visual acuity, visual field sensitivity
- These take 7-10 years to change significantly
- New tools
  - AOSLO: image individual cone photoreceptors non-invasively in living eyes

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Neurotech CNTF4 Trial:
Outcomes over 24 months

- No adverse events
- No significant changes in visual acuity
- No significant changes in visual field
- Conclusion: CNTF doesn’t work in patients.....?
AO Ophthalmoscopes Have Cellular Level Resolution

AOSLO Analysis in 3 CNTF4 Study Patients

- Count the cones
- Measure changes in the cones over time
- Three metrics:
  - Average Cone Spacing
  - Cone Density
  - Individual Cone Tracking

Patient 1, Autosomal Dominant RP (Gly51Val rhodopsin):

- Sham-treated Eye
- CNTF-treated Eye
Patient 2, Usher Syndrome Type 2: 
  *Sham-treated Eye*

Patient 2, Usher Syndrome Type 2: 
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Patient 3, Simplex RP: 
  *Sham-treated Eye*

Patient 3, Simplex RP: 
  *CNTF-treated Eye*
Patient 1, Autosomal Dominant RP:
Sham-treated eye, superonasal to fixation

- Baseline: 2089 cones per deg
- 21 months later: 1593 cones per deg
- 24% drop in cone density from baseline

Patient 1, Autosomal Dominant RP:
CNTF-treated eye, inferotemporal to fixation

- Baseline: 15193 cones per deg
- 15 months later: 2131 cones per deg
- 3 months later: 2162 cones per deg
- 2329 cones per deg
- No change in cone density from baseline

Patient 2, Usher Syndrome Type 2:
Sham-treated eye, inferior to fixation

- Baseline: 2531 cones per deg
- 31 months later: 3206 cones per deg
- 21% drop in cone density after 31 months

Patient 2, Usher Syndrome Type 2:
CNTF-treated eye, temporal to fixation

- Baseline: 2329 cones per deg
- 20 months later: 2355 cones per deg
- 25 months later: 2329 cones per deg
- No change in cone density over 25 months
Patient 3, Simplex RP: CNTF-treated eye, inferotemporal to fixation

Baseline
20 months later
32 months later
No change in cone density in 32 months

Cone Density Decreased More in Sham-treated Eyes than CNTF-treated Eyes

Normal: gray region

Gray region: Estimated measurement error range (+6.3%)
CNTF Treated Eyes Showed Better Cone Survival

- Cone density decreased by 9.3% per year more in the sham-treated eyes compared to the CNTF-treated eyes ($P = 0.002$)
- Average cone density decreased by 222 cones/degree$^2$/year more in the sham-treated eyes compared to CNTF-treated eyes
- Cone spacing increased by 2.9% per year more in the sham-treated eyes compared to the CNTF-treated eyes ($P = 0.0001$)
- CNTF-treated eyes showed less cone loss

Individual Cone Tracking

- Identify and track individual cones from visit to visit
  - Brightness of each individual cone varies
  - Most accurate: provides evidence that cones are not being lost
  - Very demanding in terms of image quality, but can be done routinely on normal eyes

Patient 3: Individual Cone Tracking in the CNTF-Treated Eye
Conclusions:

- AOSLO demonstrated improved photoreceptor survival in eyes treated with CNTF
- CNTF may slow cone photoreceptor loss, despite non-significant changes in visual function
- AOSLO may be a sensitive way to measure disease progression and treatment response in patients with inherited retinal degeneration over 30 months

Acknowledgements

- Eugene de Juan, Jr., UCSF
- Matt LaVail, UCSF
- Arshia Mian, UCSF
- David Merino, UCSF
- Pavan Tiruveedula, UC Berkeley
Acknowledgements

• The National Eye Institute
• The Doris Duke Clinical Research Fellowship
• That Man May See, Inc.
• The Foundation Fighting Blindness
• Hope for Vision
• Research to Prevent Blindness
• Karl Kirchgessner Foundation
• NSF - Center for Adaptive Optics
• NIH – BRP Adaptive Optics Instrumentation for Advanced Ophthalmic Imaging (PI: David Williams)

References


Spectral-domain OCT: Patient #1
880 days s/p implantation

Sham-treated eye: 218 microns
CNTF-treated eye: 243 microns

Central foveal subfield thickness:
Averages of thickness values from center of 1-mm radius.
Normal is 270.2 microns (Grover S et al, 2009)

Longitudinal OCT Changes

Pt#1 Time-domain OCT
Pt#1 Spectral-domain OCT

OCT Conclusions

• Time-domain OCT showed greater central foveal thickness \( (P = 0.005) \) and larger foveal macular volume in CNTF-treated compared to sham-treated eyes \( (P = 0.009) \)

• Spectral-domain OCT showed greater central foveal thickness \( (P < 0.001) \) and larger foveal volume \( (P < 0.001) \) in CNTF-treated eyes than in sham-treated eyes

Average Cone Spacing

• Use local density histograms to determine the predominant distance between cones
  – Conservative and robust method for evaluating integrity of cone mosaic
  – Increased cone spacing corresponds to loss of cones
  – Advantages:
    • Reliable even when some of the cones are missed
    • Cone selections don’t have to be contiguous
    – Permits assessment of cone mosaic when image quality is more variable

Rodieck, Vision Neurosci 1991
Roorda et al, Vision Research 2003
Roorda et al, IOVS 2007
Duncan et al, IOVS 2007
Yoon et al, IOVS 2009
Normal Eyes Show Minimal Change in Cone Mosaic

- Cone-to-cone matching was done 4.5 years apart in normal subject
- 8/1906 cones (0.4%) were not seen at both sessions
- Cones in a healthy retina did not appear to degenerate appreciably over time
- High quality AOSLO images can be used to track individual cones reliably over long time spans

As treatments are developed, how should we measure response?

- Ideally: Evaluate disease progression and treatment response by imaging individual vision cells
- Study treatment response in less time
- Optical imperfections make individual photoreceptors hard to see in living eyes
- Adaptive Optics: compensates for optical imperfections in living eyes