Adaptive Optics Scanning Laser Ophthalmoscopy: A New Tool to Monitor Cones During Retinal Degeneration

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What Are Retinal Degenerations?

- Diverse group of inherited diseases, including Usher syndrome
- All associated with progressive loss of photoreceptors
- Today: update on new ways to study the vision cells (photoreceptors) in eyes with retinal degeneration
Scanning Laser Ophthalmoscopy (SLO)

- Confocal images of retinal planes
- Poor axial resolution (300 µm)
- Lateral resolution limited by optics of cornea/lens
Adaptive Optics Correct Aberrations

Increasing Pupil Size

Adding Adaptive Optics

- Overcomes blur from optical aberrations
- Shack-Hartmann wavefront sensor
- Deformable mirror
- Image individual photoreceptors with high resolution
Adaptive Optics Makes it Possible to See Microscopic Retinal Features in Living Eyes

No AO
(defocus and astigmatism corrected)

\[ \text{AO} + \text{SLO} = \text{AOSLO} \]
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Single frame with AO

AO + SLO = AOSLO
Adaptive Optics Makes it Possible to See Microscopic Retinal Features in Living Eyes

No AO
(defocus and astigmatism corrected)

Single frame with AO

Multiple frames with AO

AO + SLO = AOSLO
Adaptive Optics Scanning Laser Ophthalmoscope

Yuhua Zhang
Austin Roorda

2006 6/30
AOSLO in Usher Syndrome Type 3

• Can we image cones in patients with diseased photoreceptors?
3 Patients with Usher Syndrome Type 3

- Ages 20-32
- All with mutations in Clarin-1
- Range of visual field loss

Ratnam et al, JAMA Ophthalmol 2013; 131: 67-74
Patient 1: Vision 20/16

Ratnam et al, JAMA Ophthalmol 2013; 131: 67-74
Patient 2: Vision 20/20

Ratnam et al, JAMA Ophthalmol 2013; 131: 67-74
Patient 3: Vision 20/40

Ratnam et al, JAMA Ophthalmol 2013; 131: 67-74
Usher 3 Patients Show Normal Cone Spacing Where Cones are Clearly Seen

Ratnam et al, JAMA Ophthalmol 2013; 131: 67-74
How can we keep the vision cells alive longer?
Neurotrophic Factors

• CNTF: Ciliary NeuroTrophic Factor
  – Shown effective in at least 4 species with retinal degeneration
  – Encapsulated Cell Technology: ECT
    • Sustained delivery from transformed RPE cells
    • 6 month NEI study reported safety in patients with advanced RP and atrophic macular degeneration
As treatments are developed, how should we measure response?

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

Grover, Ophthalmology 1997
Iannaccone, IOVS 2004
Fishman, Retina 2007
Case Study: Neurotech CNTF3 and 4 Trials in RP Patients:
Outcomes over 12-24 months

• No adverse events
• Dose-dependent increase in retinal thickness in CNTF-treated eyes
• No significant changes in visual acuity
• Significant decline in central 30 degrees of visual field, reversible upon CNTF removal
• What happened to macular cones?

2007: 3 Multicenter Trials of CNTF

NT-501 Clinical Sites

- Richard Weleher
  Portland, OR
  CNTF3, CNTF4
- Jacque Duncan
  San Francisco, CA
  CNTF3, CNTF4
- David Telander
  Sacramento, CA
  CNTF3, CNTF4
- Kang Zhang
  Salt Lake City, UT
  All
- Jill Hopkins
  Los Angeles, CA
  All
- Tim Olsen
  Minneapolis, MN
  CNTF3, CNTF4
- John Heckenlively
  Ann Arbor, MI
  CNTF3, CNTF4
- George Williams
  Royal Oaks, MI
  CNTF2
- Jeffrey Heier
  Boston, MA
  All
- Ronald Carr
  New York, NY
  CNTF3, CNTF4
- Alessandro Inmacone
  Memphis, TN
  CNTF3, CNTF4
- Sundeep Grover
  Jacksonville, FL
  CNTF3, CNTF4
- Larry Halperin
  Ft. Lauderdale, FL
  All
- Albini/ Lam
  Miami, FL
  CNTF2, CNTF4
- David Brown
  Houston, TX
  CNTF2
CNTF3 and CNTF4 Trials: Outcomes

- No adverse events
- No significant changes in visual acuity
- No clinically significant changes in visual field
- Statistically significant increase in retinal thickness
Patient 1, Autosomal Dominant RP: Sham-treated eye

Baseline

2089 cones per deg\(^2\)

21 months later

1593 cones per deg\(^2\)

24% drop in cone density from baseline

Patient 1, Autosomal Dominant RP: CNTF-treated eye.

No change in cone density from baseline.

Baseline: 2131 c/deg²
15 months later: 2162 c/deg²
35 months later: 2225 c/deg²
Cone Density Decreased More in Sham-treated Eyes than CNTF-treated Eyes

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

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

Cone Density Analysis Results: CNTF vs Sham treatment over 30 months

- Cone density decreased by 9.3% per year more in sham-treated vs CNTF-treated eyes ($P = 0.002$)
- CNTF-treated eyes showed less cone loss
- AOSLO may be a sensitive way to measure disease progression and treatment response
- Larger studies using AOSLO are required to evaluate the effect of CNTF on cone structure

Talcott et al, IOVS 2011; 52: 2219-26
New CNTF Clinical Trials:

- Funding from FFB and USFDA supports 3 year study of in RP patients using AOSLO to measure cones over time

- Recruiting now to study how cones change over time
  - Vision must be better than 20/40, no cataract or edema
  - Email duncanj@vision.ucsf.edu for more information
Adaptive Optics in Retinal Degeneration Trials: Advantages

- Image photoreceptor structure with high resolution
- Retinal landmarks enable precise tracking over time
- Interocular symmetry makes it possible to use of contralateral eye as internal control
- AOSLO permits simultaneous high-resolution imaging and visual function testing

Tuten et al, OVS 2012; 89(5): 563-574
Adaptive Optics in Retinal Degeneration Trials: Challenges

- Difficult in patients with:
  - advanced disease
  - unstable fixation
  - nystagmus
  - media opacity
  - high refractive error
  - cystoid macular edema

- Image quality affects variability of measures
- Rods are small and hard to see
Adaptive Optics in Retinal Degeneration Trials: Challenges

- Few commercially-available, standard systems
- Each system needs normative data, information on repeatability, validation
- Labor intensive, time-consuming acquisition and analysis
- Natural history of retinal degeneration is not well-characterized
- Centralized interpretation by a Reading Center may reduce variability in measures to use AO metrics as clinical trial endpoints
Conclusions: Adaptive Optics Imaging for Clinical Trials in Retinal Degenerations

- Noninvasive, objective means of evaluating photoreceptors
- May provide sensitive outcome measures for treatment trials, in select patients with central cones
- Synergy: Combining different imaging approaches increases sensitivity of each imaging tool
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