The Role of Phenotype in Selectively Enriching Patients for Clinical Studies

Developing Treatments for Dry Age-Related Macular Degeneration (AMD) Workshop
November 15, 2014
National Academy of Sciences Building, Lecture Room
2101 Constitution Ave., N.W., Washington, DC

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Healios K.K.: Consultant
Oraya: Consultant
Hoffman-La Roche: Study advisory board
Vision Medicines: Consultant
Xcovery Vision: Study advisory board
Dry AMD Treatments: Therapeutic Goals

- Prevent vision loss
- Slow the loss of vision
- Restore lost vision
Dry AMD Treatments: Visual Acuity as an Endpoint?

- Visual acuity
  - Vision loss takes years
  - Unrealistic short-term clinical trial endpoint
  - Vision loss may not correlate with disease progression
  - Surrogate outcome/endpoint needed for clinical trials
Growth of GA with **no** loss of vision

+2.4 mm²

Baseline 20/25

6 Months 20/25

Autofluorescence

OCT Fundus Image

3.0 mm²

5.4 mm²
Growth of GA with loss of vision
+2.4 mm²
Vision loss ≠ disease progression

Baseline 20/40 → Week 26 20/125

Baseline 20/25 → Week 26 20/25

+2.4 mm²
Central vision loss depends on proximity of GA to foveal center*
Phenotype Enrichment Depends on The Surrogate Endpoint

- Surrogate anatomic endpoints:
  - Growth of geographic atrophy (color, autofluorescence, or OCT en face imaging)
  - Progression to neovascular AMD
  - Change in drusen area and/or volume
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Growth of Geographic Atrophy

- Phenotype enrichment:
  - Autofluorescence patterns (e.g. banded)
  - Bilateral vs. unilateral GA
  - Disruption/atrophy of photoreceptors at margins of GA imaged by OCT
  - Decreased retinal sensitivity at margins of GA measured by microperimetry
  - Low luminance deficits
  - Presence/absence of reticular pseudodrusen (subretinal drusenoid deposits) or decreased choroidal thickness
  - Delayed dark adaptation
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Enlargement Rates of GA using Fundus Autofluorescence (FAF)

FAF Patterns

- 'None'
  - ER = 0.02 mm²/yr
- 'Focal'
  - ER = 0.36 mm²/yr
- 'Patchy'
  - ER = 1.84 mm²/yr
- 'Diffuse'
  - ER = 1.71 mm²/yr
- 'Banded'
  - ER = 2.52 mm²/yr
- 'Diffuse, Trickling'
  - ER = 3.78 mm²/yr

Example: Phase II and Phase III Lampalizumab Trials (Genentech/Roche)

Enrollment criteria:

• Bilateral GA
• Presence of hyperautofluorescence of either banded or diffuse patterns adjacent to the area of GA
• Area of GA: \( \geq 1 \text{ disc area} \) [DA] and \( \leq 7 \text{ DA} \) (if multifocal then 1 focal lesion \( \geq 0.5 \text{ DA} \))
Size vs. Unifocality vs. Multifocality

- Larger lesions appear to grow faster
- Multifocal lesions appear to grow faster
- Strategies to account for growth rate differences:
  - Square root transformation of area measurements
  - Correction for circularity index
AREDS Color Photo Measurements:
Change in area of GA over 4 years

Baseline Lesion Size
- LARGE >4 DA
- MEDIUM 0.75 - 4 DA
- SMALL 0.5 - 0.75 DA

Change in Area (mm²)

Growth rate depends on baseline lesion size

Geographic Atrophy: The Growth Rate Dilemma

- Growth rate increases with lesion size and multifocality
- As lesions grow larger, they grow faster
- Multifocality/multilobularity changes as lesions grow
- Variability in test-retest measurements increases as the area of GA increases
- What’s the solution for designing clinical trials?
Square Root Transformation Strategy: Difference in Areas = Difference in Radii

\[ \sqrt{\text{Area}} = \sqrt{\pi r^2} = r \sqrt{\pi} \]

\[ \Delta = r_2 \sqrt{\pi} - r_1 \sqrt{\pi} \]

\[ \Delta = (r_2 - r_1) \sqrt{\pi} \]

- Growth rate independent of baseline size
- Test-retest measurements independent of size

Yehoshua et al. Ophthalmology, April 2011; 118: 679-686
AREDS Database: Growth of GA over 4 Years (Courtesy of Emily Chew and Rick Ferris)

Growth rate no longer depends on size

Feuer et al., JAMA Ophthalmology, Jan. 2013
AREDS Color Fundus Database: Growth of GA over 4 Years
(Courtesy of Emily Chew and Rick Ferris)

Difference in Area Measurements

Difference in the Square Root Area Measurements

Confirms size range of GA for clinical trials
Non-Circularity Index (NCI) Helps Predict Progression of GA

Definition of NCI:

Actual Area
Perimeter Area

Actual perimeter = 2\pi r_p

r_p = radius of a circle with a perimeter equal to the perimeter from the actual GA

Perimeter Area = \pi r_p^2

If the GA lesion is a circle, then the NCI = 1

Circularity Index as a Risk Factor for Progression of Geographic Atrophy

Amita Domalpally, MD,¹ Ronald P. Danis, MD,¹ James White, BME,¹ Ashwini Narkar, MS,¹ Traci Clemons, PhD,³ Fredrick Ferris, MD,² Emily Chew, MD²

Ophthalmology 2013;120:2666-2671
Non-Circularity Index (NCI) Helps Predict Progression of GA

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Abnormal Anatomy and Visual Function Extends Beyond the Margin of GA

- **Histopathology:** Photoreceptor atrophy at variable distances from edge of GA


  Loss of photoreceptors 1400 μm from the edge of GA

  Intact RPE

- **Electrophysiology and microperimetry:** Photoreceptor dysfunction identified away from the edge of the GA

SD-OCT Imaging of the Outer Retina Can Show Disrupted Photoreceptors and Predict Progression of GA

- Ongoing prospective SD-OCT study
  - Eyes with GA secondary to AMD
  - Size of GA between 0.5 DA (1.8 mm²) and 7 DAs (18 mm²)
  - Followed for at least 1 year

Outer Retinal IS/OS/EZ Slab *En Face* Image

Bottom red line = 20 μm above RPE

Top red line = 40 μm above RPE
20μm thick slab containing the IS/OS/EZ boundary
20μm thick slab containing the IS/OS/EZ boundary
En Face Projection: IS/OS/EZ Region
IS/OS/EZ Slab *En Face* Image

Top red line = 40 μm above RPE

Black line = RPE

Bottom red line = 20 μm above RPE

Location of B-scan

B-scan through fovea
Case #1

Color Images

Heidelberg Autofluorescence Images

Sub-RPE Slab En Face Images (GA)

IS/OS/EZ Slab En Face Images (Focal Pattern)
Growth of GA Over 1 Year: Focal Pattern

Sub-RPE Slab
*En Face* Images (GA)

Baseline

6 Months

12 Months

Baseline GA

Baseline GA + Growth at 6 months

Baseline GA + Growth at 12 months
Correlation between B-Scan and Outer Retinal IS/OS/EZ Slab En Face Image

Location of B-scan

IS/OS/EZ Slab En Face Image (Focal Pattern)

B-scan Corresponding to Slab Image

Magnified IS/OS/EZ Slab En Face Image
Correlation between B-Scan and Outer Retinal IS/OS/EZ Slab En Face Image

A. Location of B-scan
B. B-scan Corresponding to Slab Image
C. Magnified IS/OS/EZ Slab En Face Image

IS/OS/EZ Slab En Face Image (Focal Pattern)
Correlation between B-Scan and Outer Retinal IS/OS/EZ Slab *En Face* Image

Location of B-scan

B-scan Corresponding to Slab Image

IS/OS/EZ Slab *En Face* Image (Focal Pattern)

Magnified IS/OS/EZ Slab *En Face* Image

Growth of IS/OS defect being used in ongoing CNTF trial in MacTel2
Loss of IS/OS/EZ Integrity Corresponds to Decreased Microperimetric Retinal Sensitivity

Loss of retinal sensitivity corresponds to perilesional area with increased autofluorescence

Growth of Geographic Atrophy

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Low Luminance Deficit Testing

Normal Luminance
ETDRS Acuity

Low Luminance
ETDRS Acuity

Low Luminance Deficit =
Normal Luminance VA score -
Low Luminance VA Score

Sunness JS, Rubin GS, Broman A, Applegate CA, Bressler NM, Hawkins BS. Ophthalmology. 2008 Sep;115(9):1480-8

2.0-log unit neutral density filter (filter lowers luminance by 100-fold), Kodak Wratten filter; Kodak, Rochester, NY
COMPLETE Study: Geographic atrophy
Low Luminance Deficit Predicts Growth Rate


Non-central GA with VA ≥ 20/60

(Pearson correlation r=0.38, p=0.007)
Growth of Geographic Atrophy

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Anecortave Acetate Risk Reduction Trial (Alcon Research. Ltd/Novartis)

- Prevent progression from high-risk intermediate AMD (soft drusen, pigment hyperplasia within 3000μm) to wet AMD
- Wet AMD in fellow eye
- Incidence of sight-threatening CNV in 4 years estimated at 33%

Anecortave Acetate Risk Reduction Trial
(Alcon Research. Ltd/Novartis)

• 2596 patients enrolled worldwide
• At Month 48:
  – Estimated 80% power to detect a 30% reduction in CNV
  – Estimated 92% power to detect a 35% reduction in CNV
• After interim analysis at 2 years, study stopped, never published
• Successful enrollment proves feasibility of this surrogate study design

Phenotype Enrichment Depends on The Surrogate Endpoint

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  - Changes in retinal/RPE/choroidal anatomy using a variety of imaging strategies
9 studies, 2216 subjects randomized
No evidence that disappearance of drusen reduced risk of developing CNV, GA or visual acuity loss
Cirrus SD-OCT Measurement of Drusen using the 200 X 200 Raster Scan Pattern: 6mm X 6mm

40,000 A-scans
Equal distances between A-scans and B-scans
Cirrus SD-OCT Fundus Scanning Pattern
200 X 200 A-scans (6mm X 6mm)

200 X 200 raster scan measures 6mm X 6 mm on the macula
Segmentation Algorithms
Segmentation Algorithms

Also available on the Topcon SDOCT instrument
Measuring RPE Elevations: Subtract “RPE Floor” from “RPE Elevations”
Drusen: Volume and Area Measurements

Area: 5.21 mm²
Volume: 0.899 mm³

RPE Segmentation

Zeiss Cirrus SDOCT, Ver. 6.0 software
Reproducibility of Drusen Measurements

- 103 eyes from 74 patient
- 5 separate SD-OCT scans at the same visit
- Highly reproducible


Mean Area = 3.49mm² (SD=0.04)  Mean Volume = 0.202mm³ (SD=0.002)
Natural History of Drusen in the Absence of Any Geographic Atrophy Using SDOCT Imaging

- 143 eyes
- Followed up to 24 months
- Different progression patterns observed
  - Increase: 48%/yr
  - Stable: 40%/yr
  - Decrease: 12%/yr

Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441
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Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441
Increase in Drusen Area and Volume: 48%/yr

Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441
Decrease in Drusen Area and Volume: 
3 Possible Outcomes

- Formation of geographic atrophy
- Formation of CNV
- No significant anatomic abnormality identified

Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441
Decrease in Drusen Area and Volume with Formation of GA: 4.5%/yr

<table>
<thead>
<tr>
<th>Color</th>
<th>Autofluorescence</th>
<th>OCT B-Scan</th>
<th>RPE Map</th>
<th>Hybrid Drusen Map</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><img src="image1" alt="Baseline Autofluorescence" /></td>
<td><img src="image2" alt="Baseline OCT B-Scan" /></td>
<td><img src="image3" alt="Baseline RPE Map" /></td>
<td><img src="image4" alt="Baseline Hybrid Drusen Map" /></td>
</tr>
<tr>
<td>Area: 3.75 mm²</td>
<td>Vol: 0.456 mm³</td>
<td>VA: 20/30</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Month 12</strong></td>
<td><img src="image5" alt="Month 12 Autofluorescence" /></td>
<td><img src="image6" alt="Month 12 OCT B-Scan" /></td>
<td><img src="image7" alt="Month 12 RPE Map" /></td>
<td><img src="image8" alt="Month 12 Hybrid Drusen Map" /></td>
</tr>
<tr>
<td>Area: 0.55 mm²</td>
<td>Vol: 0.016 mm³</td>
<td>VA: 20/63</td>
<td>GA Area: 1.28 mm²</td>
<td></td>
</tr>
</tbody>
</table>

Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441
**Decrease in Drusen Area and Volume with Formation of CNV: 3.5%/yr**

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<th>Color</th>
<th>OCT B-Scan</th>
<th>RPE Map</th>
<th>Hybrid Drusen Map</th>
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</thead>
</table>
| **Baseline**| ![OCT image](image1) | ![RPE image](image2) | ![Drusen map](image3) | Area: 2.56mm²  
Vol: 0.181mm³ |
| **Month 12**| ![OCT image](image4) | ![RPE image](image5) | ![Drusen map](image6) | Drusen & CNV  
Area: 2.41mm²  
Vol: 0.100mm³ |

Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441
Decrease in Drusen Volume > 50%
Without Formation of GA or CNV: 4%/yr

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<th>OCT B-Scan</th>
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</table>
| Baseline | ![Baseline OCT B-Scan](image1) | ![Baseline RPE Map](image2) | ![Baseline Hybrid Drusen Map](image3) | Area: 3.03mm²  
Vol: 0.222mm³ |
| Month 6 | ![Month 6 OCT B-Scan](image4) | ![Month 6 RPE Map](image5) | ![Month 6 Hybrid Drusen Map](image6) | Area: 0.032mm²  
Vol: 0 mm³ |
| Month 12 | ![Month 12 OCT B-Scan](image7) | ![Month 12 RPE Map](image8) | ![Month 12 Hybrid Drusen Map](image9) | Area: 0.03 mm²  
Vol: 0 mm³ |

Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441
Placement of 3 mm and 5 mm Diameter Circles Centered on the Fovea

Automatic algorithm registers the OCT fundus image with color fundus image

Placement of 3 mm and 5 mm Diameter Circles Centered on the Fovea

Automatic algorithm registers the OCT fundus image with color fundus image

Placement of 3 mm and 5 mm Diameter Circles Centered on the Fovea

Automatic algorithm registers the OCT fundus image with color fundus image

Quantification of Drusen with the 3 mm and 5 mm Diameter Circles Centered on the Fovea

Decrease in Drusen Volume > 50% Without Formation of GA or CNV as a Clinical Trial Endpoint

Natural History of Drusen Morphology in Age-Related Macular Degeneration Using Spectral Domain Optical Coherence Tomography

Yehoshua et al., 2011, Ophthalmology 118(12): 2434-2441

Table 7. Sample Size Table for Comparing Successful Outcomes in Treatment and Control Groups Depending on the Presumed Percent Treatment Success* and the Percent Power of a Study to Detect a Positive Outcome if One Exists

<table>
<thead>
<tr>
<th>Ratio of Experimental to Control Randomized Eyes</th>
<th>Percent with Successful Outcomes in Control Group</th>
<th>Number of Eyes Needed in Each Group Based on the Anticipated Percent with Successful Outcomes* and the Desired Power to Detect the Outcome†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>5%</td>
<td>80% Power 90% Power 18:18 23:23 59:59 75:75</td>
</tr>
<tr>
<td>2:1</td>
<td>5%</td>
<td>80% Power 90% Power 28:14 34:17 92:46 116:58</td>
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* A successful outcome was defined as shrinkage to <50% of baseline cube root volume without progression to geographic atrophy or neovascular disease.
† The number of eyes needed in each group was the same whether the follow-up interval was 6 or 12 months.
Phase II Eculizumab Study
Bascom Palmer Eye Institute

Inclusion:
High Risk Drusen
OR
Geographic Atrophy

Drusen Cohort
$N = 30$
2:1 Randomization

Eculizumab/Placebo
26 weeks

GA Cohort
$N = 30$
2:1 Randomization

Follow-up through one year

ClinicalTrials.gov Identifier: NCT0093588
Phase II Eculizumab Study: Bascom Palmer Eye Institute

Drusen Cohort
\( N = 30 \)

Visual Acuity: 20/63 or better
Drusen Volume \( \geq 0.030 \text{ mm}^3 \)
No evidence of GA
Can Eculizumab Decrease Drusen Volume > 50% Without Formation of GA or CNV as a Clinical Trial Endpoint?

Change in Drusen Volume as a Novel Clinical Trial Endpoint for the Study of Complement Inhibition in Age-related Macular Degeneration

Carlos Alexandre de Amorim Garcia Filho, MD; Zohar Yehoshua, MD, MHA; Giovanni Gregori, PhD; Renata Portella Nunes, MD; Fernando M. Penha, MD, PhD; Andrew A. Moshfeghi, MD, MBA; Kang Zhang, MD, PhD; William Feuer, MS; Philip J. Rosenfeld, MD, PhD

Garcia et al., 2014, OSLI-RETINA, January/February Vol.45, No. 1
COMPLETE Study: Drusen Outcomes

Drusen Volume Change at 26 Weeks

- Study + fellow eyes (n=37)
- Two eyes showing decreased volume were placebo treated
- Two eyes developing CNV were placebo treated
- Active vs placebo for drusen: p=0.15
- Outcome effectively ruled out a 22% or greater success rate for reducing drusen volume
  - based on the 95% confidence interval between treatment groups

50% decrease in drusen volume over 26 weeks
COMPLETE Study: Change in Drusen Volume Over 52 weeks

Week 26 Outcome

- Two eyes showing decreased volume were placebo treated
- Two eyes developing CNV were placebo treated

Week 52 Outcome

- 50% decrease in drusen volume over 26 weeks
- 50% decrease in drusen volume over 52 weeks

- Change in drusen volumes over 26 and 52 weeks consistent with natural history data
Increase in Drusen Volume

Baseline

Week 26

Week 52
COMPLETE Study: Drusen Examples

Decrease in Drusen Volume

Baseline: LLD 10
- VA 20/16 (92 letters)
- Vol = 0.2 mm³

Week 12: LLD 14
- VA 20/16 (90 letters)
- Vol = 0.009 mm³

Week 26: LLD 13
- VA 20/16 (94 letters)
- Vol = 0.005 mm³

Week 52: LLD 13
- VA 20/16 (91 letters)
- Vol = 0.006 mm³
COMPLETE Study: Drusen Examples

Conversion to CNV

Baseline
LLD 16
20/40 (72 letters)

Week 24
LLD 22
20/40 (69 letters)

Week 26
20/40 (73 letters)

Week 52
LLD 14
20/32 (75 letters)

2 placebo eyes developed CNV (p=0.13)
Drusen Cohort: Primary Study Question

- Drusen Cohort
  - Biostatistician: “Trial is a success”
  - But, drug failed to meet primary endpoint
• In drusen-only eyes:
  - Growth is more common than regression
  - Growth leads to GA
  - Growth leads to CNV
  - Perhaps, a composite endpoint is best
In drusen-only eyes, failure defined as:
- Growth of drusen volume/area
- Formation of CNV
- Conversion of drusen to GA
Goal of therapy = Prevent failure
- Prevent growth of drusen volume/area
- Prevent formation of CNV
- Prevent conversion of drusen to GA
Normal (placebo) failure rate is 60%
Based on natural history data, which was validated in the COMPLETE Study:
- For a study with 90% power
- to detect a 50% reduction in failure rate
- only 62 pts. needed per treatment arm

Why study drusen progression rather than enlargement of GA?
Drusen Progression as an Endpoint

- Earlier stage disease than GA
- Treat earlier and preserve more vision
- Better defined population than GA?
- May be at a stage influenced more broadly by therapies (e.g. complement inhibition)
- Could prevent progression to CNV
- If treatment slows growth of GA, would it necessarily be effective in slowing progression of drusen to GA?
- Could open possibility of treating even earlier based on genetics plus phenotype
Important Take-Home Messages

- Phenotype enrichment depends on endpoint
- Growth of GA is the most commonly used surrogate endpoint for dry AMD trials
- Enrichment strategies include hyper-AF patterns, size, complexity, and genetics
- Limitations of GA include analysis of growth rate and its late stage (too late?)
- Surrogate endpoints using earlier stages (e.g. drusen) attractive for Phase 2 studies
Possible Future Scenarios

• Treatment successfully slows or stops the progression of GA
  - What’s the labeled indication?
  - When will treatment be initiated?
  - Will early treatment prevent progression to GA or CNV?

• Treatment fails to slow or stop GA
  - Could treatment have prevented the progression to GA or formation of CNV?
  - If so, then goal would be to treat as early as possible