

Session 3

**Imaging endpoints, current methods,
relationship with
histology and retinal function**

GA Histology / imaging overlays

Christine A. Curcio, PhD

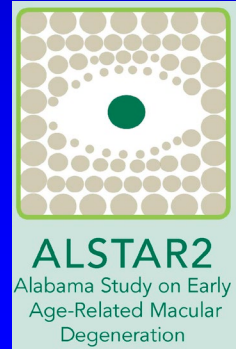
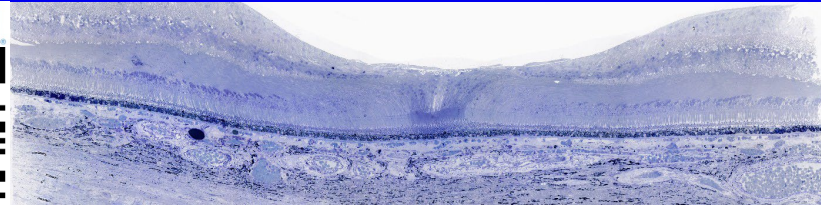
Department of Ophthalmology and Visual Sciences

Heersink School of Medicine

University of Alabama at Birmingham

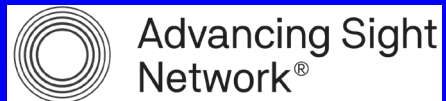


<http://projectmacula>



Support

- National Eye Institute: R01EY029595, P30EY03039, R01EY027948
- Institutional: Research to Prevent Blindness, Inc; EyeSight Foundation of Alabama
- Private: Dorsett Davis Discovery Fund; Anonymous donor
- Past: R01EY06109, R01EY024378, R01028282; RPB AMD Catalyst; Thome Foundation, International retinal Research Foundation, Macula Society, Macula Foundation (NY); NEI P30 EY003039; Genentech



Disclosures

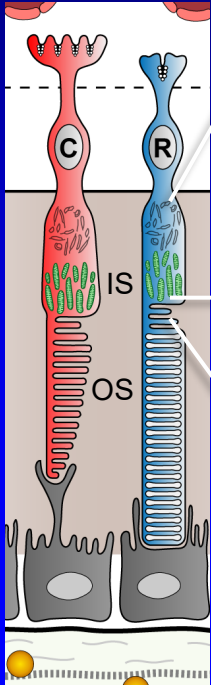
- Research support: Heidelberg Engineering, Genentech/ Roche
- Consult: Osanni, Genentech/ Roche, Boehringer-Ingelheim, Annexon, Mobius, Ripple, Sparing Vision, Roche, Heidelberg Engineering, Octant, Merck, Espansione, Sanofi, Topcon

Takeaway messages

- Inner segments are light-catching funnels
 - Morphology and high refractive index
- Anatomic correlate of EZ: outer 1/3 of inner segment ellipsoid
- Deposits perturb photoreceptor segments, EZ
- At GA border, photoreceptors die back from OS, translocate cell bodies inwardly, drop out
- Much histologic detail is visible in good SDOCT

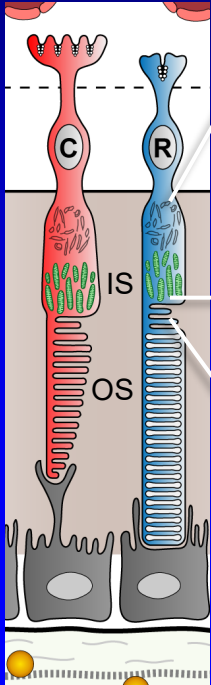
Inner segments are funnels that catch light for outer segments

- Refractive index inside cells exceeds that of interstitial space



Hoang, Linsenmeier, Chung, Curcio, 2002. Visual Neuroscience 19: 395
Harosi, Novales Flamarique, 2012. J Gen Physiol 139: 159.

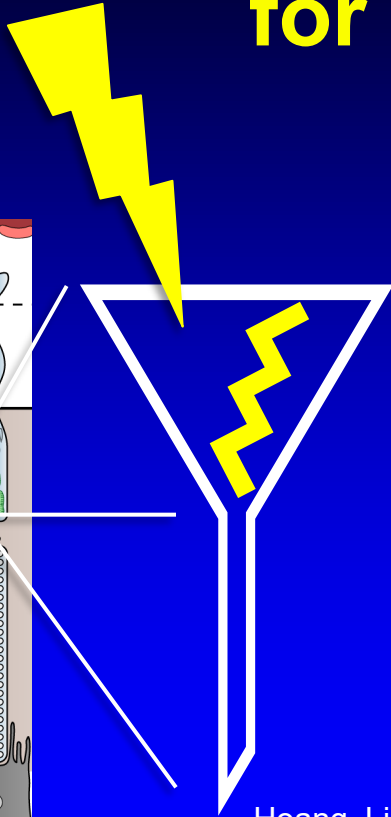
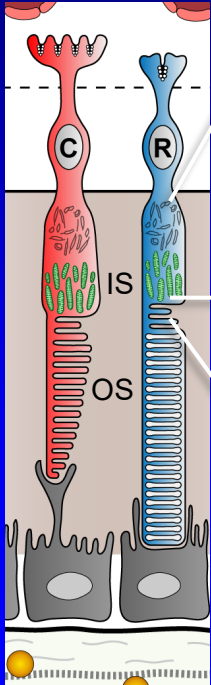
Inner segments are funnels that catch light for outer segments



- Refractive index inside cells exceeds that of interstitial space
- Total internal reflection confines light inside photoreceptor (waveguiding)

Hoang, Linsenmeier, Chung, Curcio, 2002. Visual Neuroscience 19: 395
Harosi, Novales Flamarique, 2012. J Gen Physiol 139: 159.

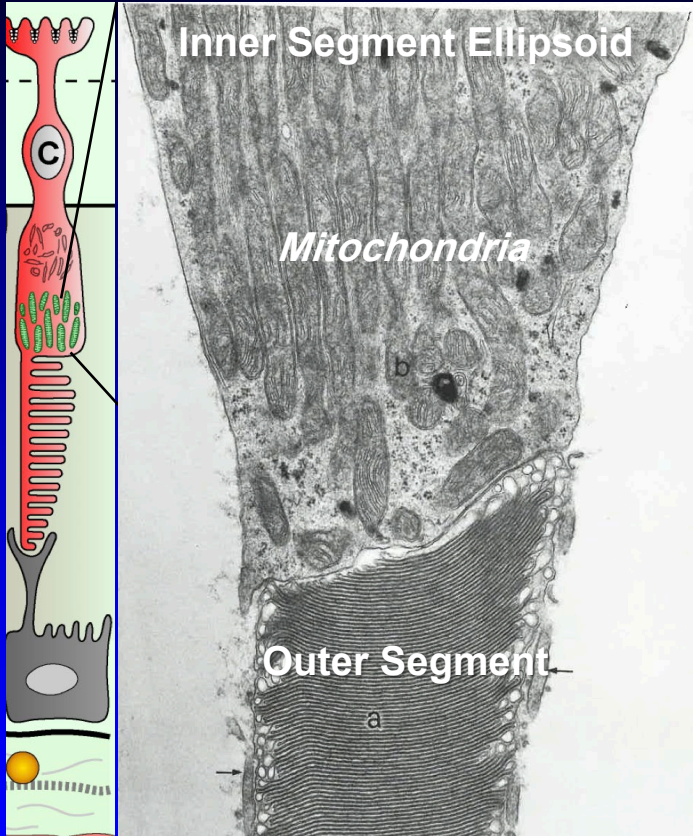
Inner segments are funnels that catch light for outer segments



- Refractive index inside cells exceeds that of interstitial space
- Total internal reflection confines light inside photoreceptor (waveguiding)
- Mitochondria contribute with high refractive index

Hoang, Linsenmeier, Chung, Curcio, 2002. Visual Neuroscience 19: 395
Harosi, Novales Flamarique, 2012. J Gen Physiol 139: 159.

Mitochondria are tightly packed, full of membranes



Hogan, Alvarado, Weddell.
Ocular Histology. 1971.

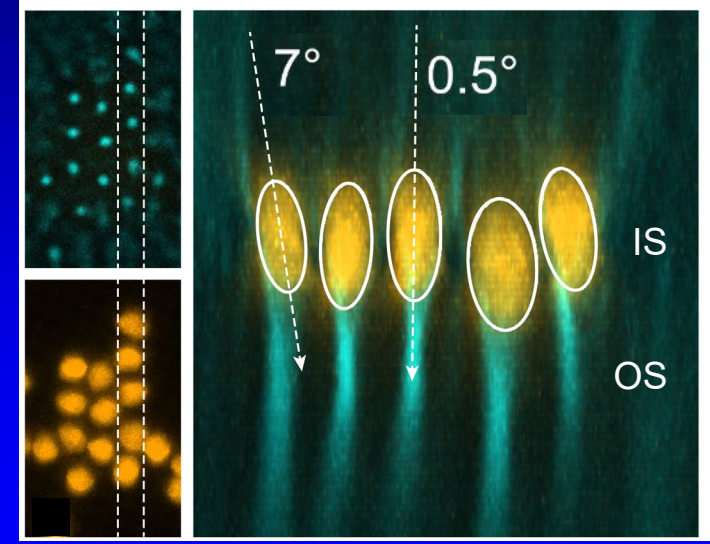
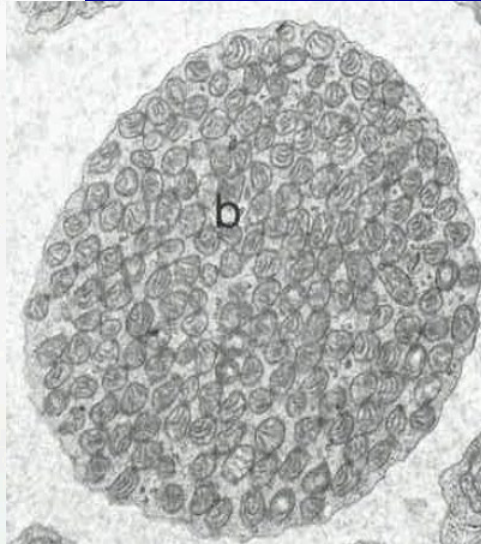
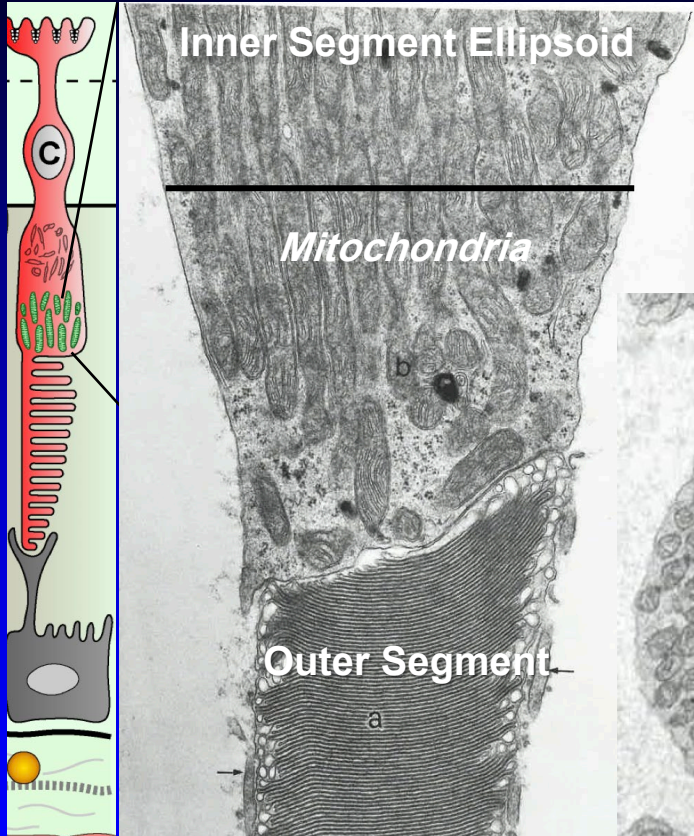
Mitochondria are tightly packed, full of membranes



Hogan, Alvarado, Weddell.
Ocular Histology. 1971.

Mitochondria are tightly packed, full of membranes

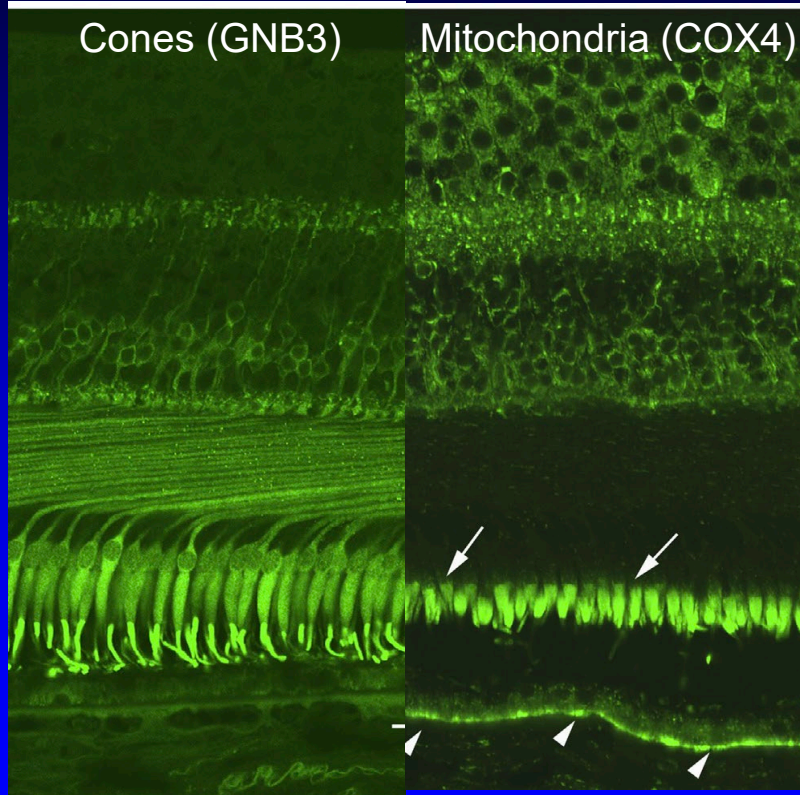
*Isolated inner segments –
act as lenses*



Hogan, Alvarado, Weddell.
Ocular Histology. 1971.

Ball, Chen, Li, 2022. Sci Adv 8: eabn2070

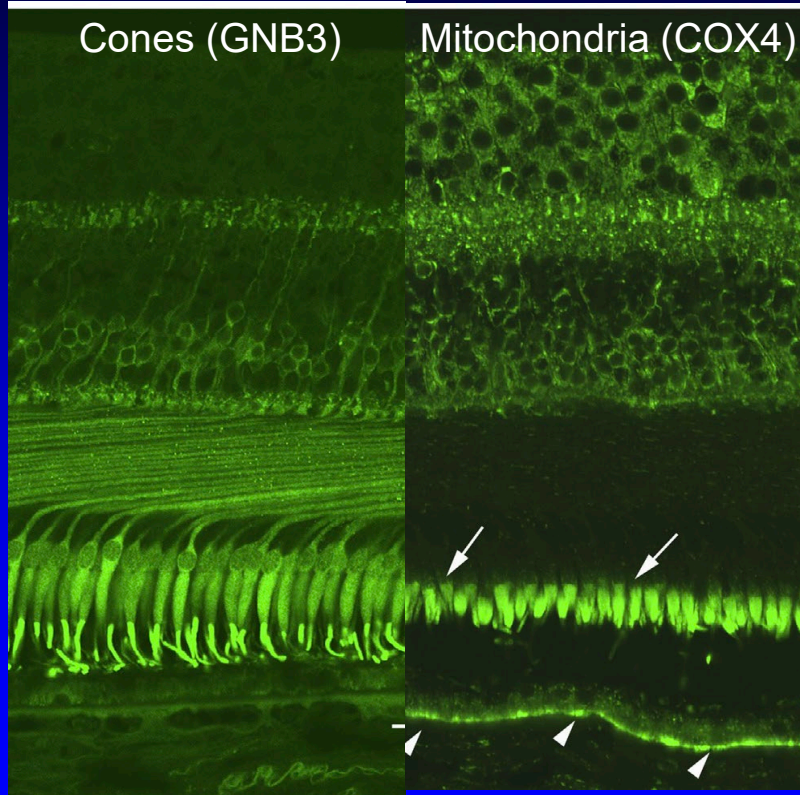
Histologic ISeI contains mitochondria



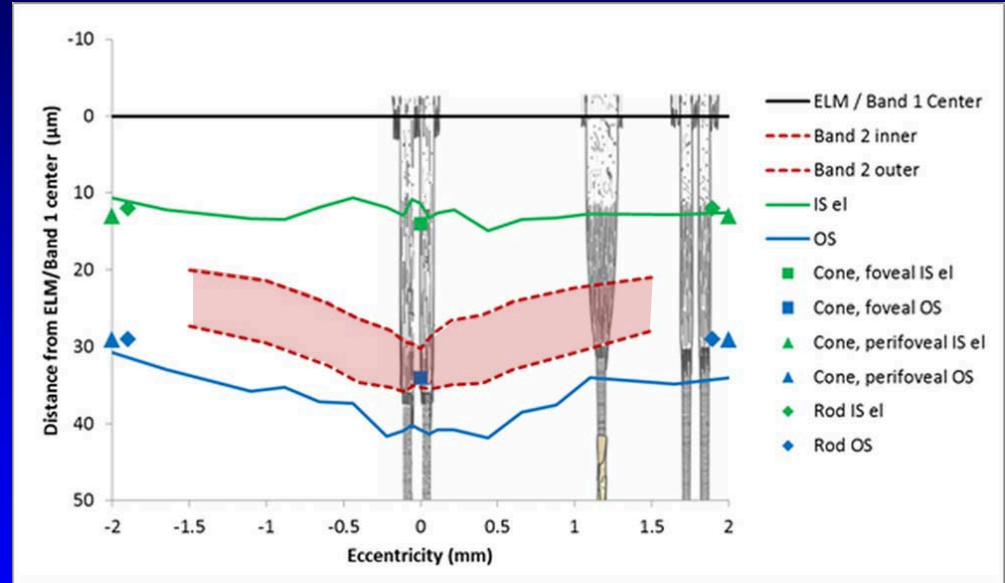
Cuenca, Ortuno-Lizaran, Pinilla, 2018.
Ophthalmology 125: 407.

Classified as public by the European Medicines Agency

EZ overlays outer 1/3 of histologic ISel

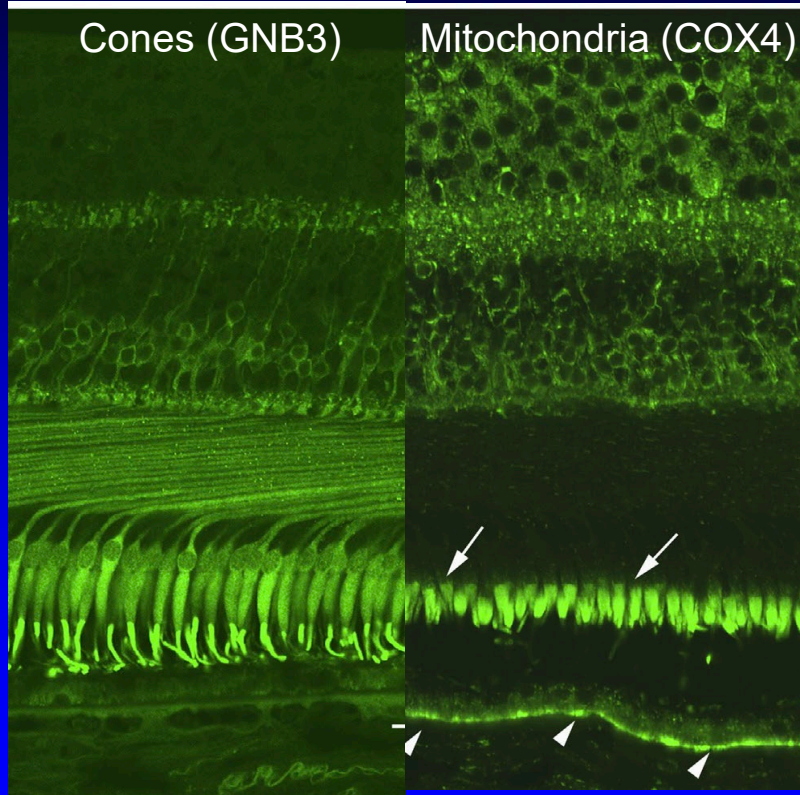


Cuenca, Ortuno-Lizaran, Pinilla, 2018.
Ophthalmology 125: 407.

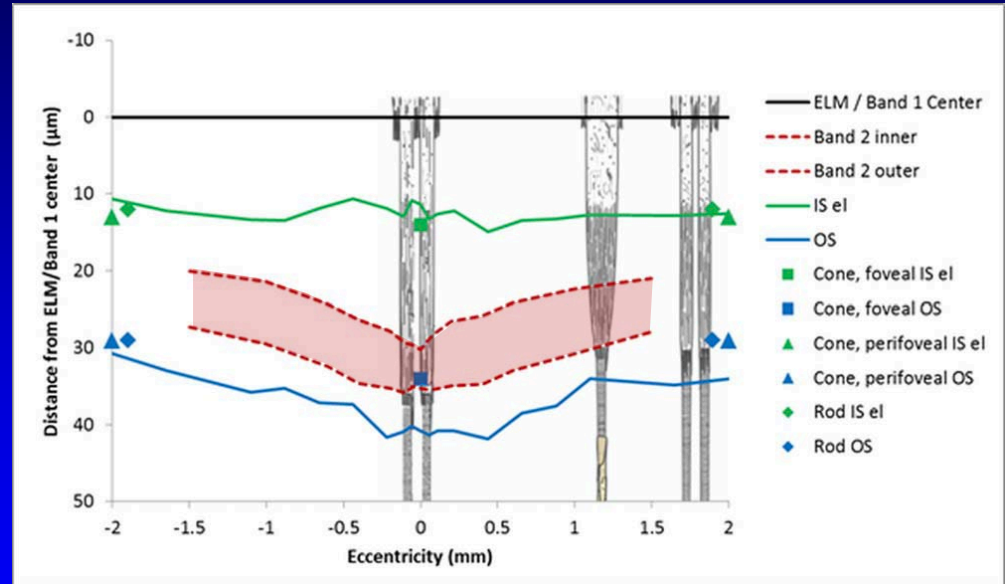


Outer bands fit to Gaussian curves
Ross ... Spaide, Sloan, Curcio, 2015. IOVS 56: 4166.
Measurements from high-res histology, n=18
Curcio, Messinger ... Spaide, 2011. IOVS 52: 3943.

EZ overlays outer 1/3 of histologic ISel



Tapered shape of inner segment?



Outer bands fit to Gaussian curves

Ross ... Spaide, Sloan, Curcio, 2015. IOVS 56: 4166.

Measurements from high-res histology, n=18

Curcio, Messinger ... Spaide, 2011. IOVS 52: 3943.

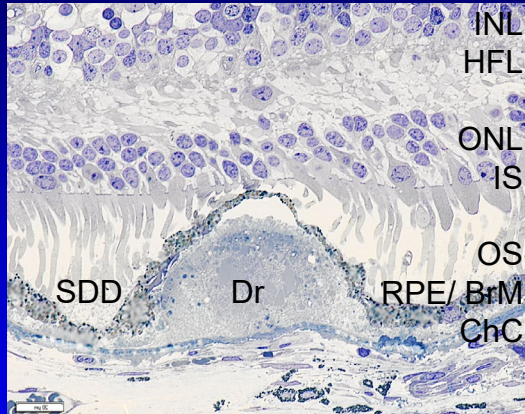
Cuenca, Ortuno-Lizaran, Pinilla, 2018.

Ophthalmology 125: 407.

Photoreceptors in AMD – from early AMD to geographic atrophy

Over drusen

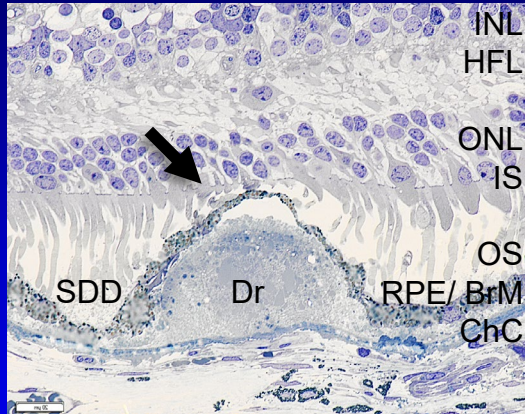
Short/ missing OS, IS



<http://projectmacula>

Over drusen

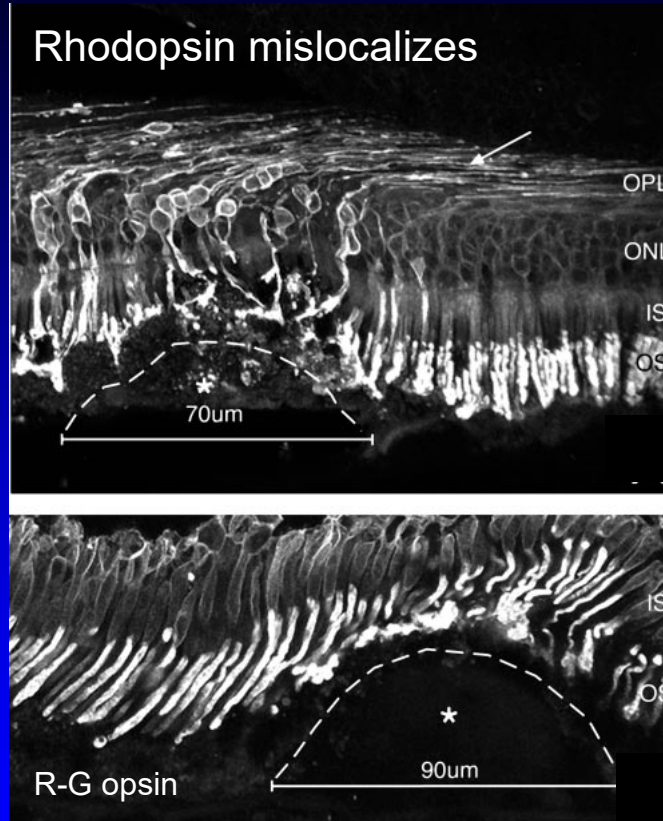
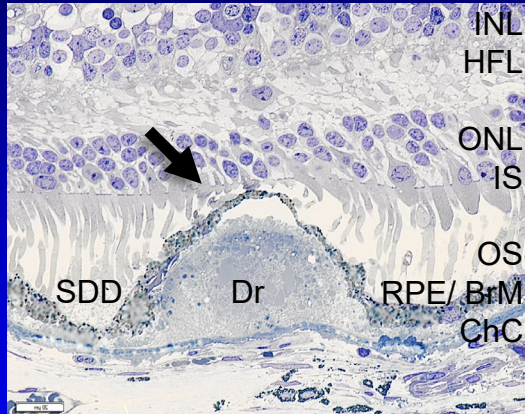
Short/ missing OS, IS



<http://projectmacula>

Over drusen

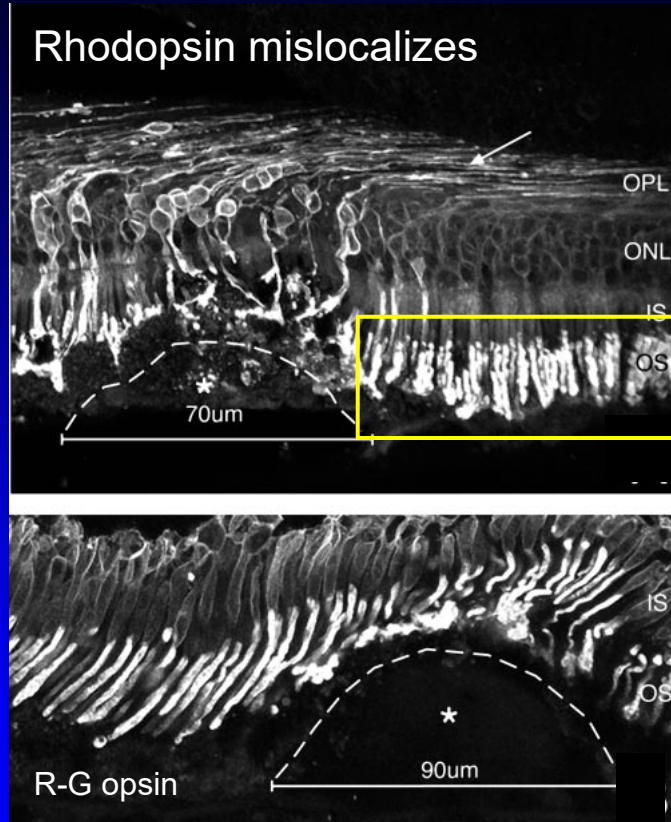
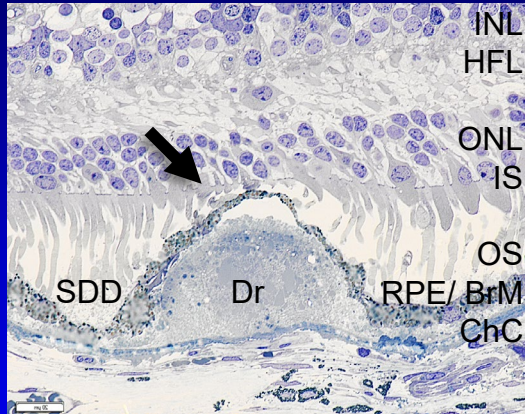
Short/ missing OS, IS



P. Johnson ...Fisher, Anderson, L.
Johnson, 2003 IOVS 44: 4481.

Over drusen

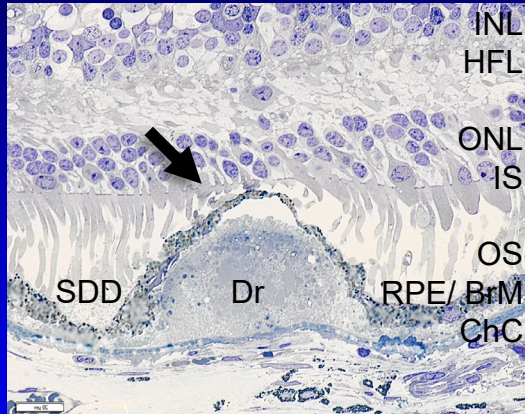
Short/ missing OS, IS



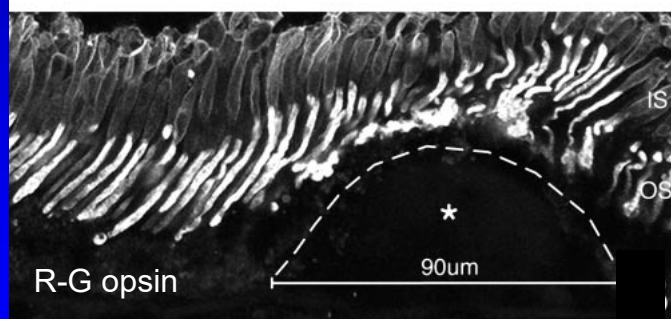
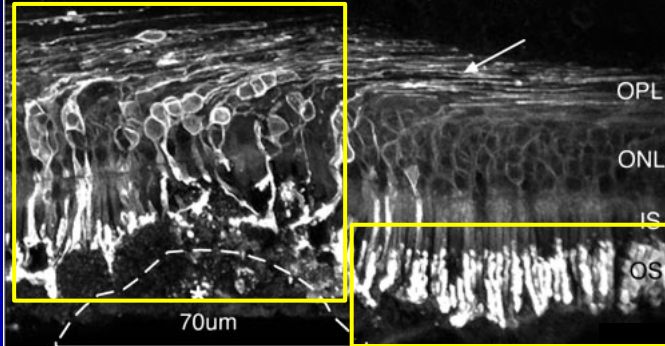
P. Johnson ...Fisher, Anderson, L.
Johnson, 2003 IOVS 44: 4481.

Over drusen

Short/ missing OS, IS



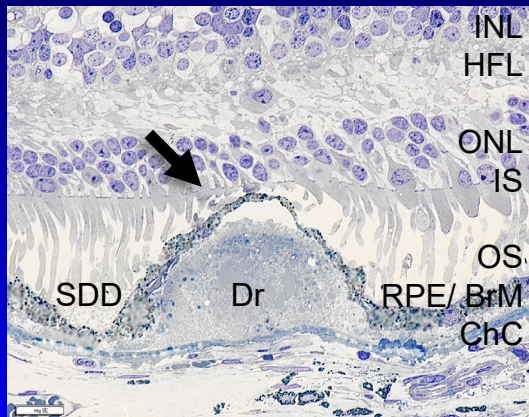
Rhodopsin mislocalizes



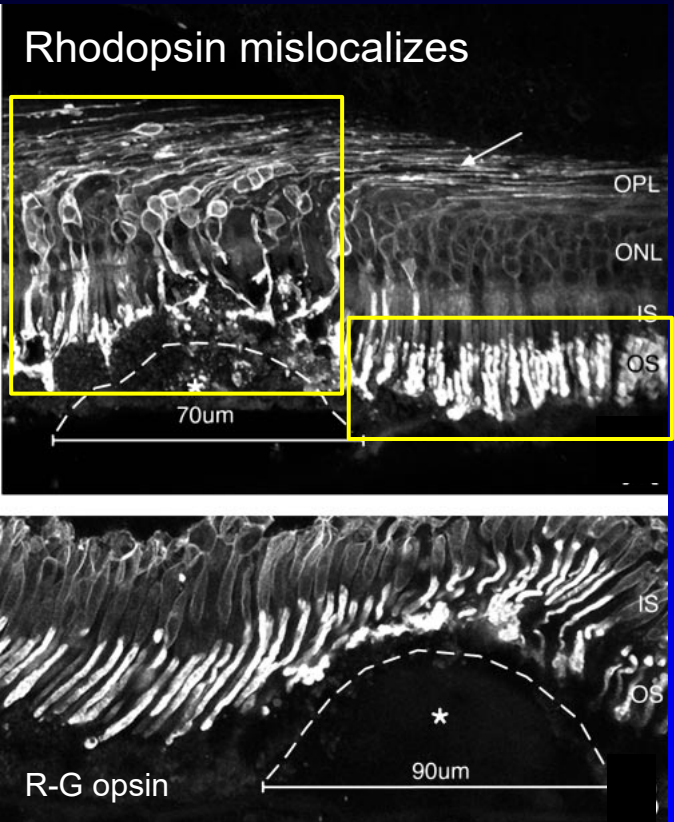
P. Johnson ...Fisher, Anderson, L.
Johnson, 2003 IOVS 44: 4481.

Over drusen

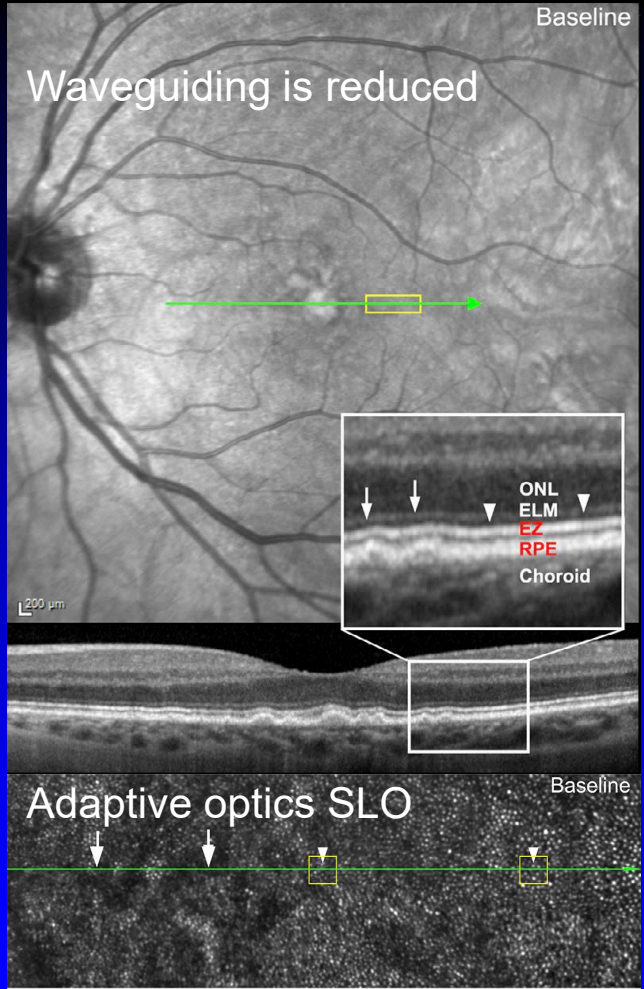
Short/ missing OS, IS



<http://projectmacula>

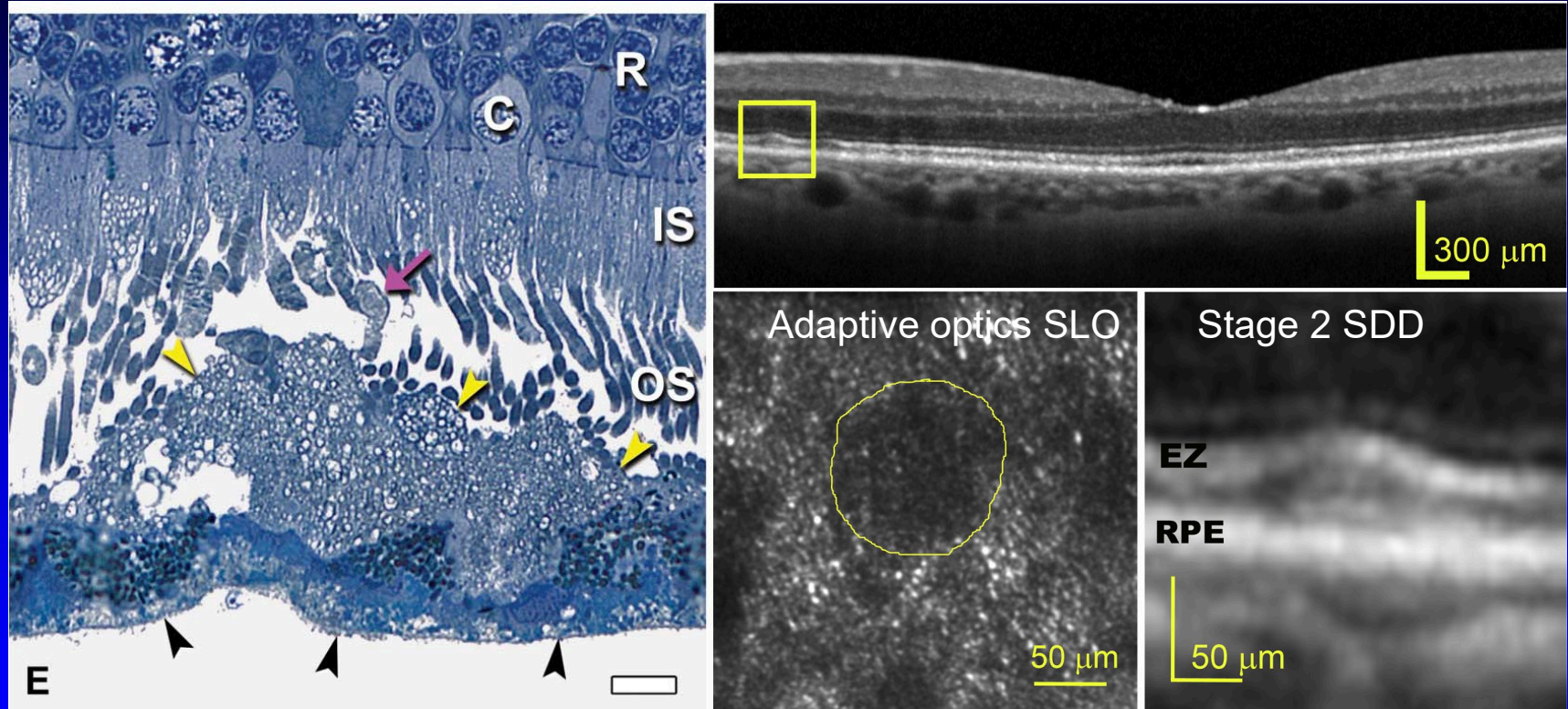


P. Johnson ...Fisher, Anderson, L. Johnson, 2003 IOVS 44: 4481.



Wang ...Zhang, 2022. 20
Am J Ophthalmol 248: 60.

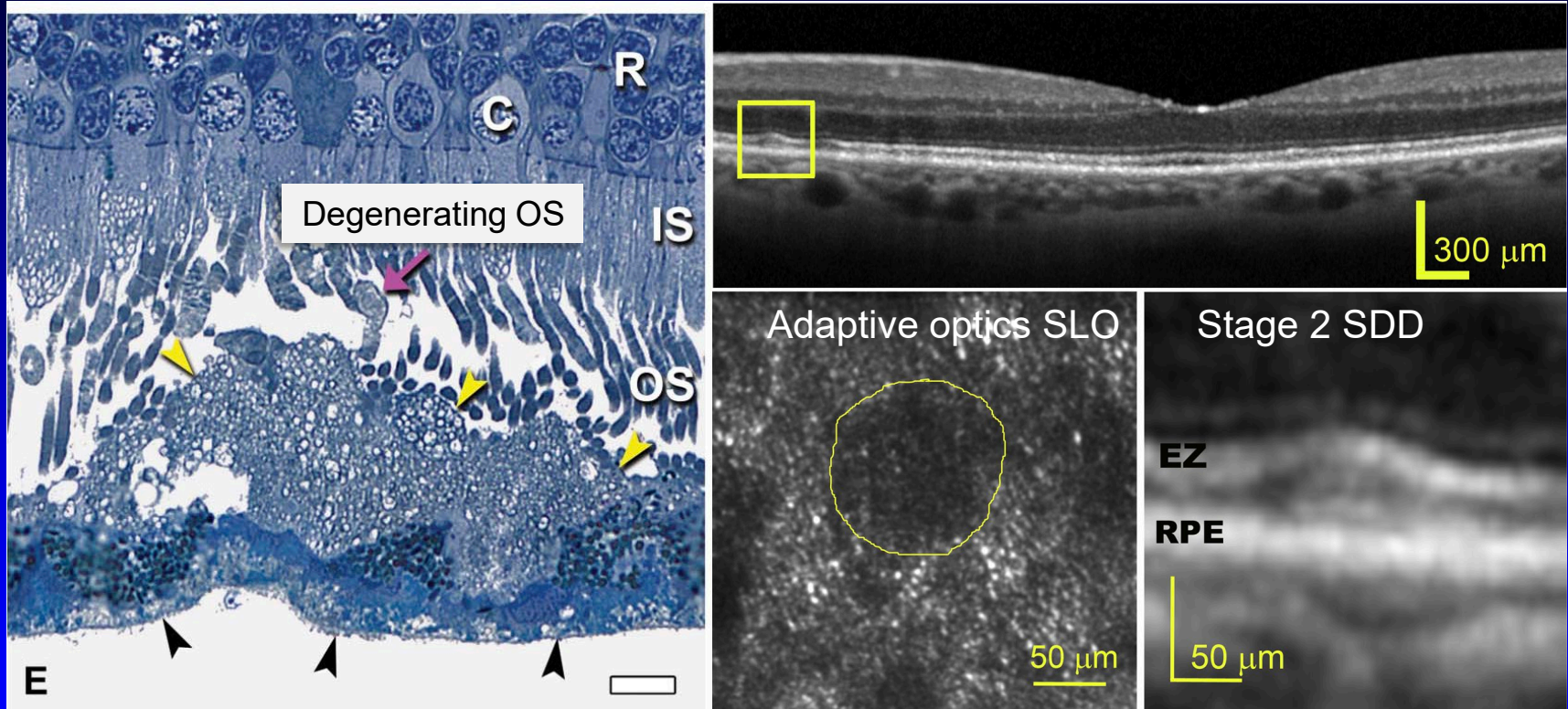
Over subretinal drusenoid deposits



Curcio, Messinger, Sloan, McGwin, Medeiros, Spaide, 2013. Retina 33: 265.

Zhang, Wang, Blanco, Clark, Witherspoon, Spaide, Girkin, Owsley, Curcio, 2014. Am J Ophthalmol 158: 584.

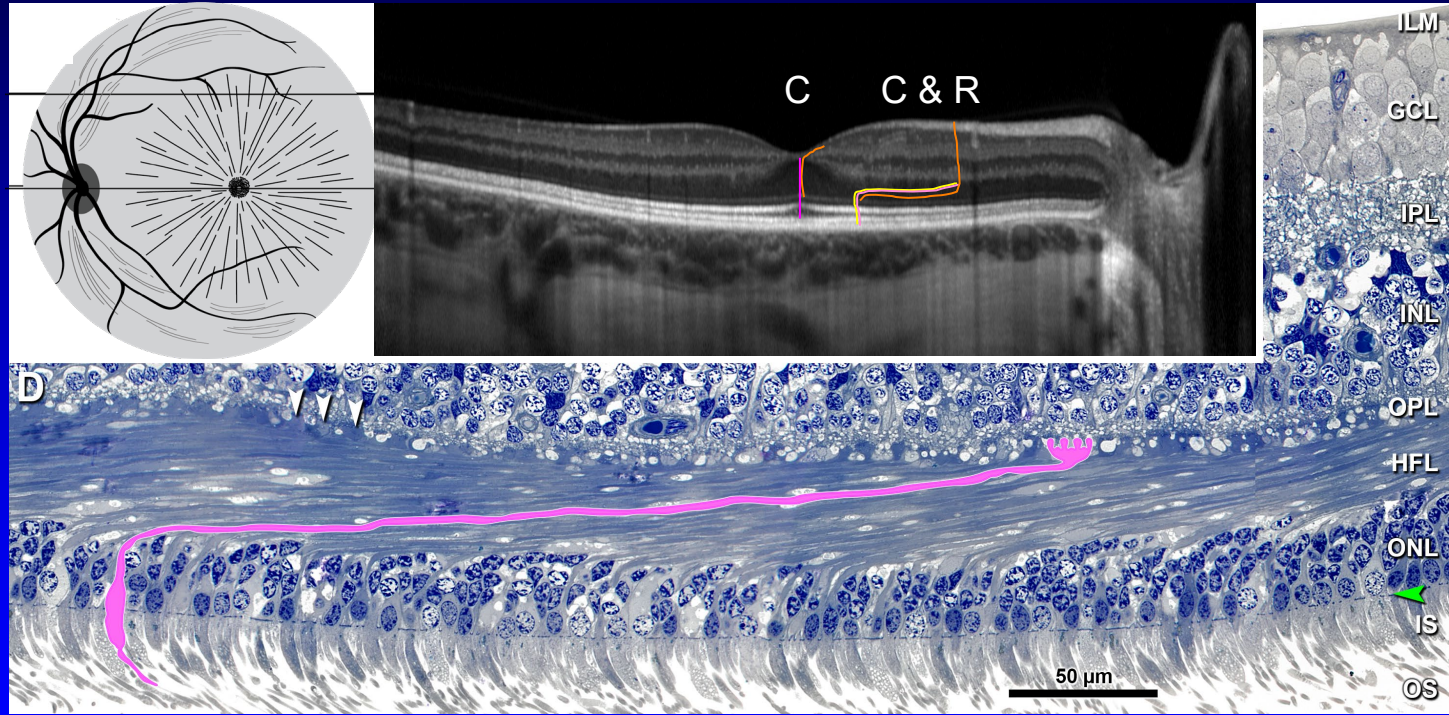
Over subretinal drusenoid deposits



Curcio, Messinger, Sloan, McGwin, Medeiros, Spaide, 2013. Retina 33: 265.

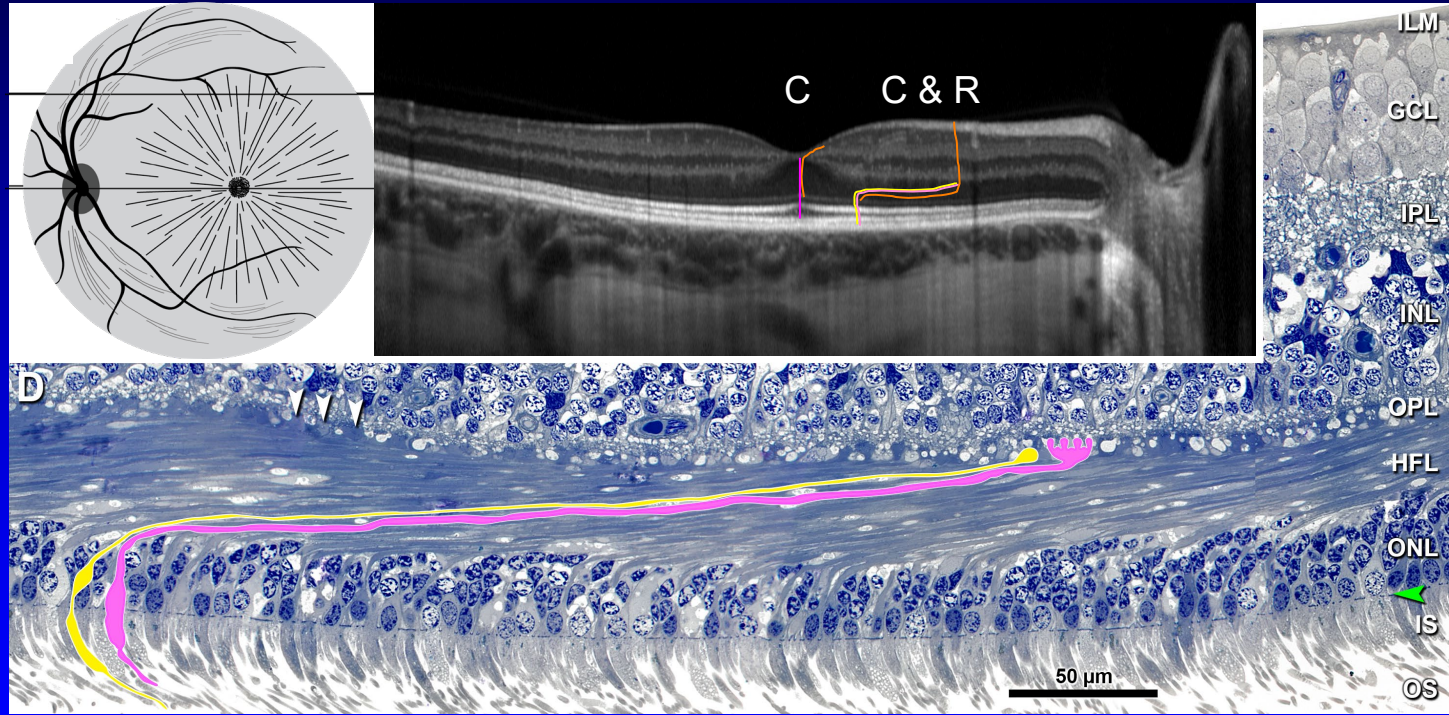
Zhang, Wang, Blanco, Clark, Witherspoon, Spaide, Girkin, Owsley, Curcio, 2014. Am J Ophthalmol 158: 584.

Photoreceptors: cones



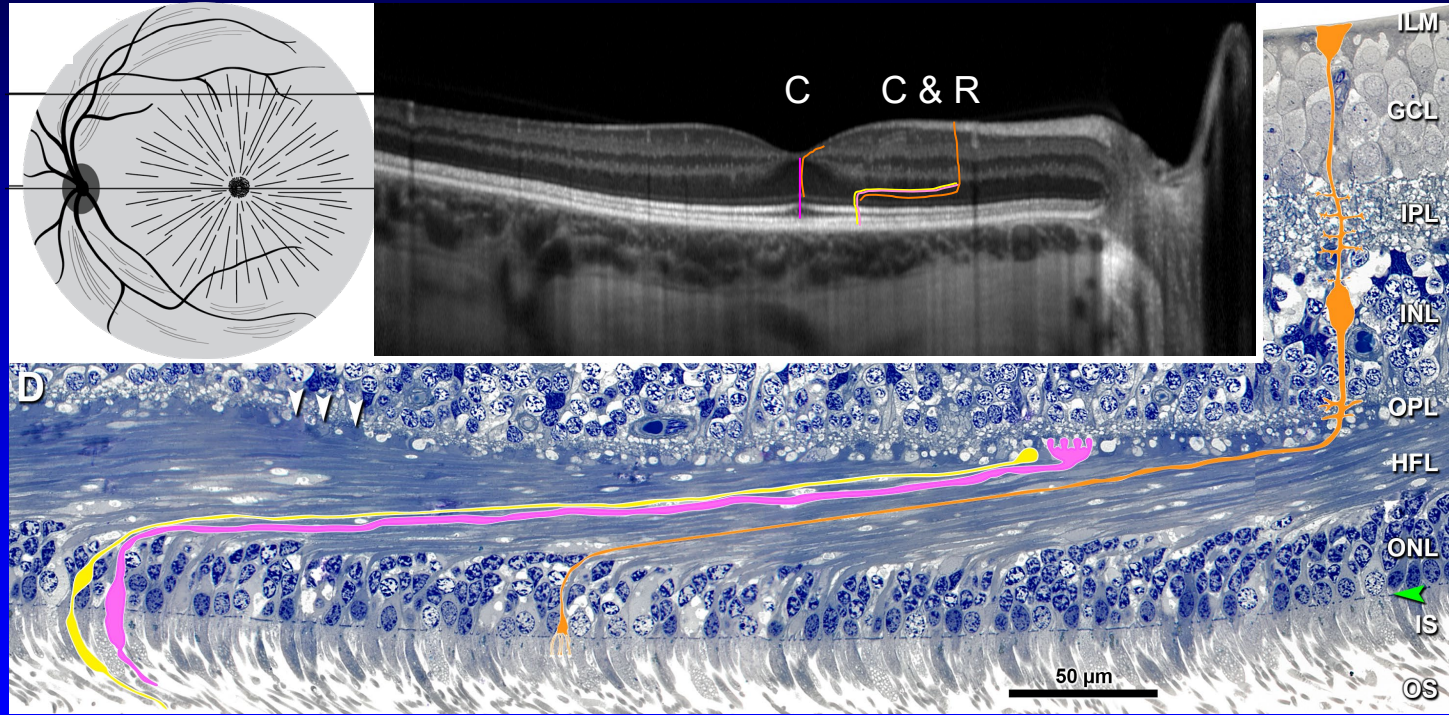
Original: Li, Huisin, Messinger, Dolz-Marco, Ferrara, Freund, Curcio. 2018. Retina 38:1937

Photoreceptors: rods



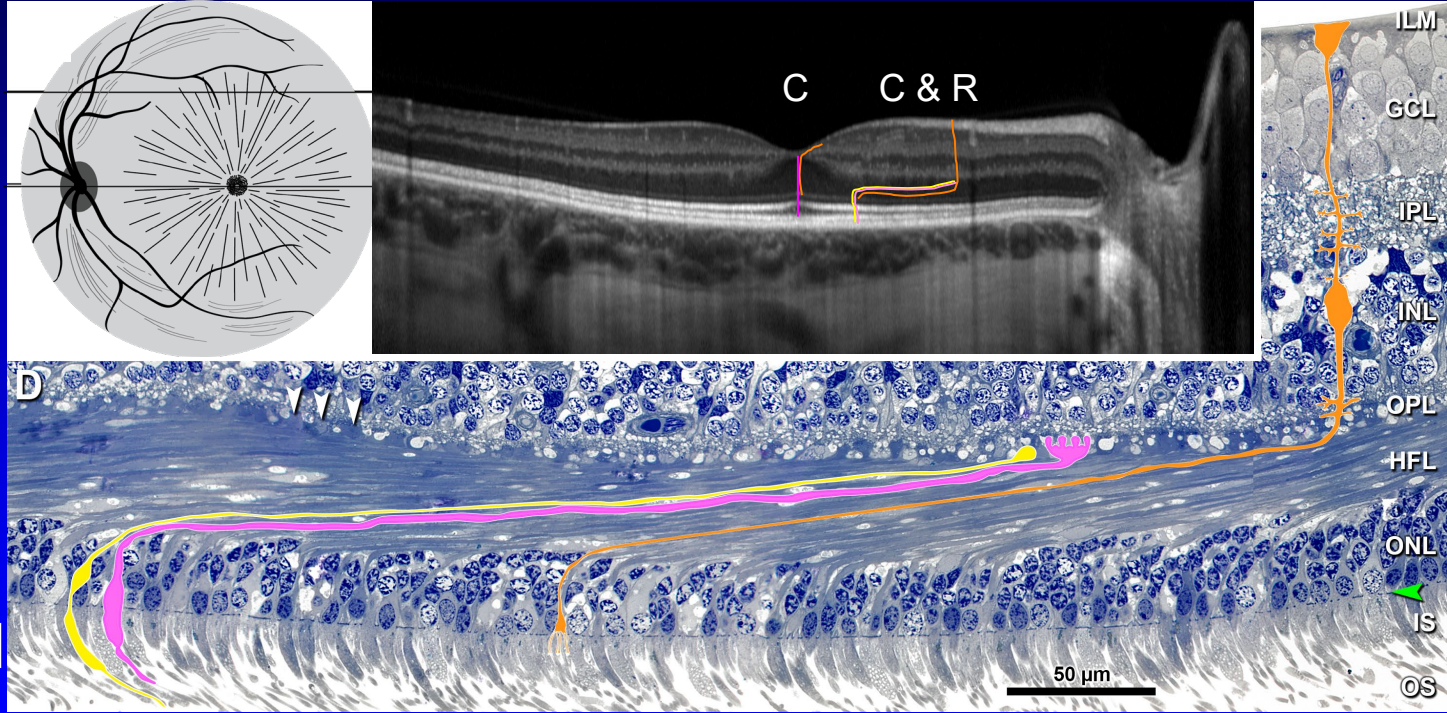
Original: Li, Huisinigh, Messinger, Dolz-Marco, Ferrara, Freund, Curcio. 2018. Retina 38:1937

Support cells: Müller glia



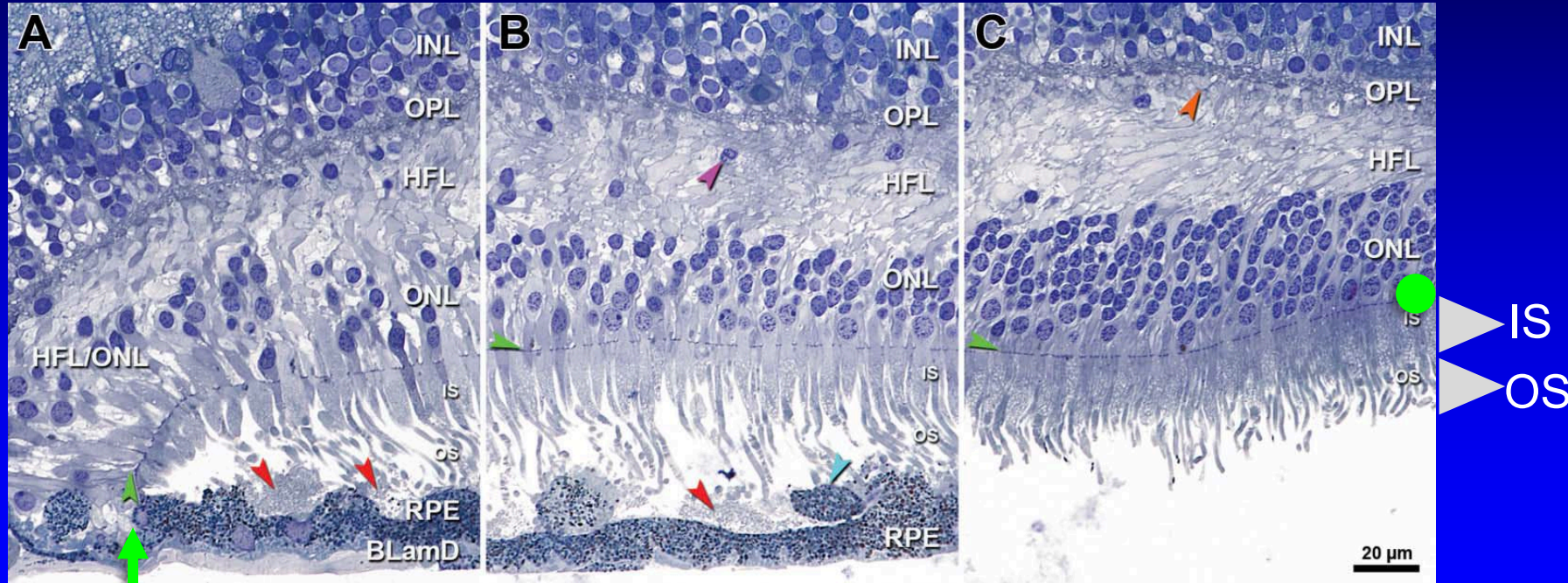
Original: Li, Huisinigh, Messinger, Dolz-Marco, Ferrara, Freund, Curcio. 2018. Retina 38:1937

Support cells: Müller glia



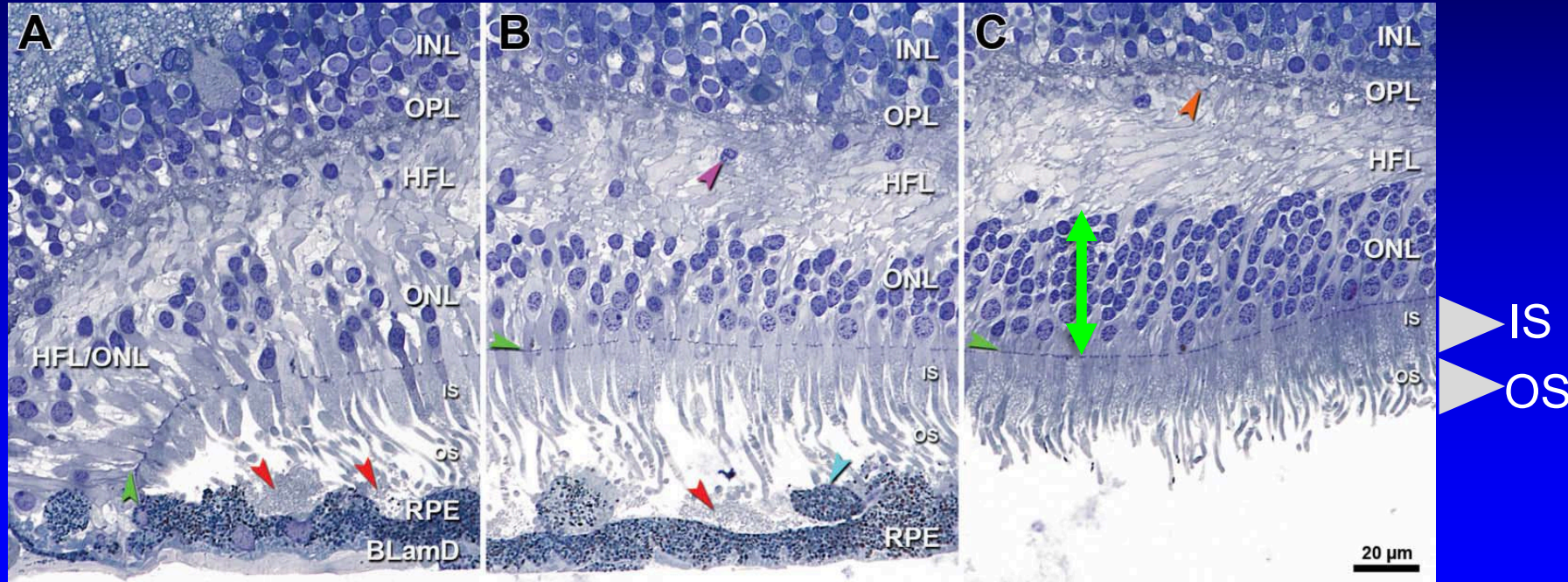
Original: Li, Huisinigh, Messinger, Dolz-Marco, Ferrara, Freund, Curcio. 2018. Retina 38:1937

Dyslaminations, photoreceptor degeneration & loss in GA



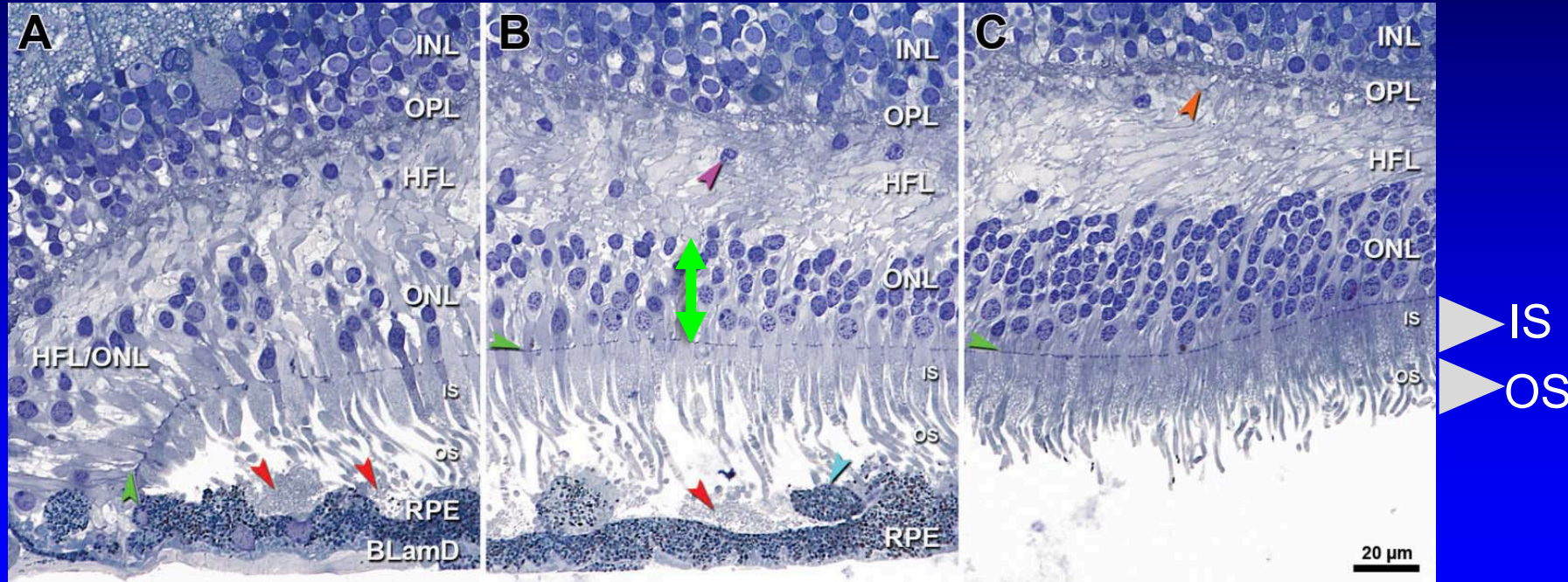
Chen, Messinger, Zhang, Spaide, Freund, Curcio, 2020. Retina 40: 618.

Dyslaminations, photoreceptor degeneration & loss in GA



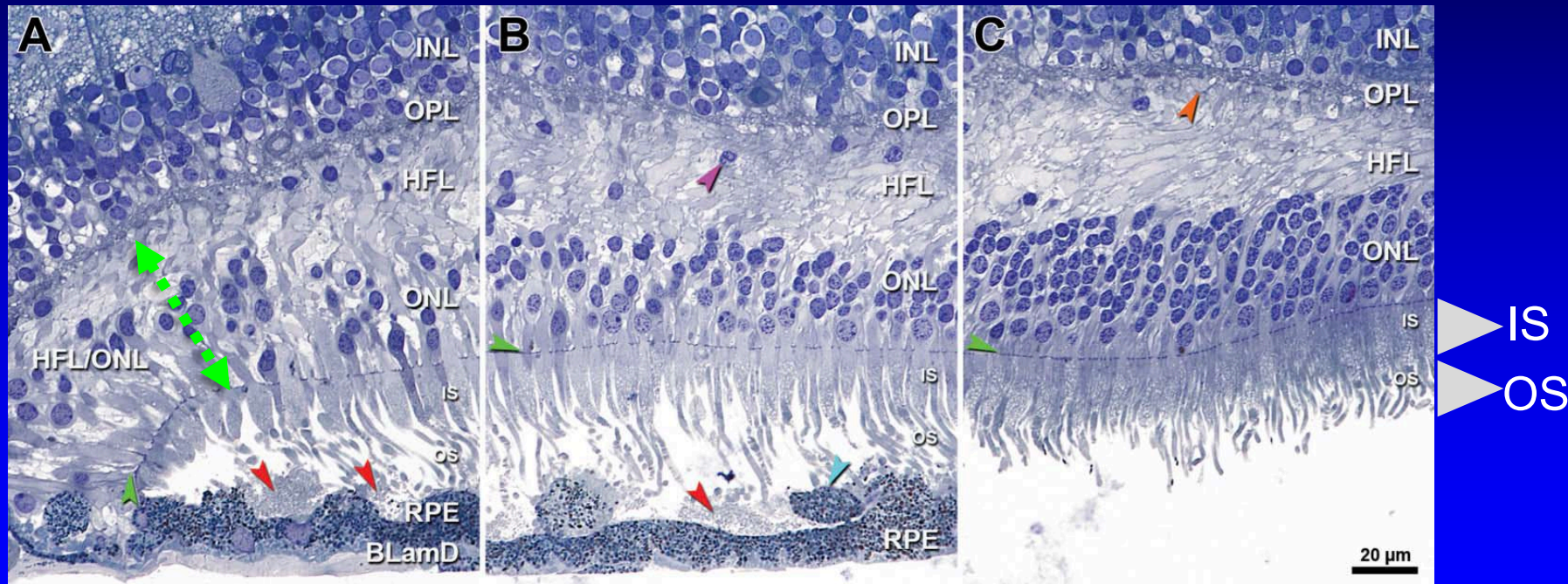
Chen, Messinger, Zhang, Spaide, Freund, Curcio, 2020. Retina 40: 618.

Dyslaminations, photoreceptor degeneration & loss in GA



Chen, Messinger, Zhang, Spaide, Freund, Curcio, 2020. Retina 40: 618.

Dyslaminations, photoreceptor degeneration & loss in GA

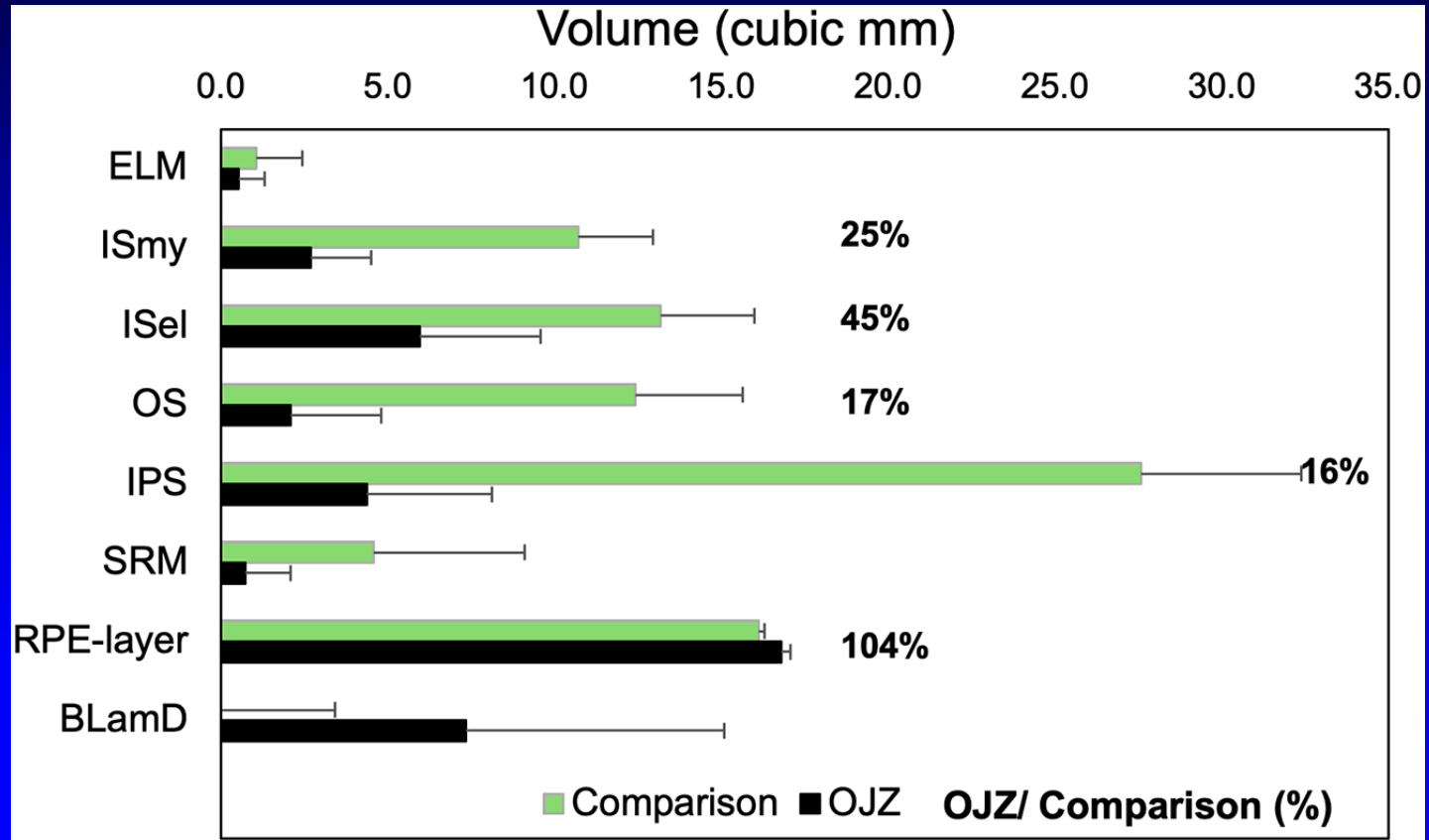


Chen, Messinger, Zhang, Spaide, Freund, Curcio, 2020. Retina 40: 618.

OJZ of GA: Photoreceptors die back from OS

93-year-old white woman, multifocal GA, observed for 5 years, 6 years before death

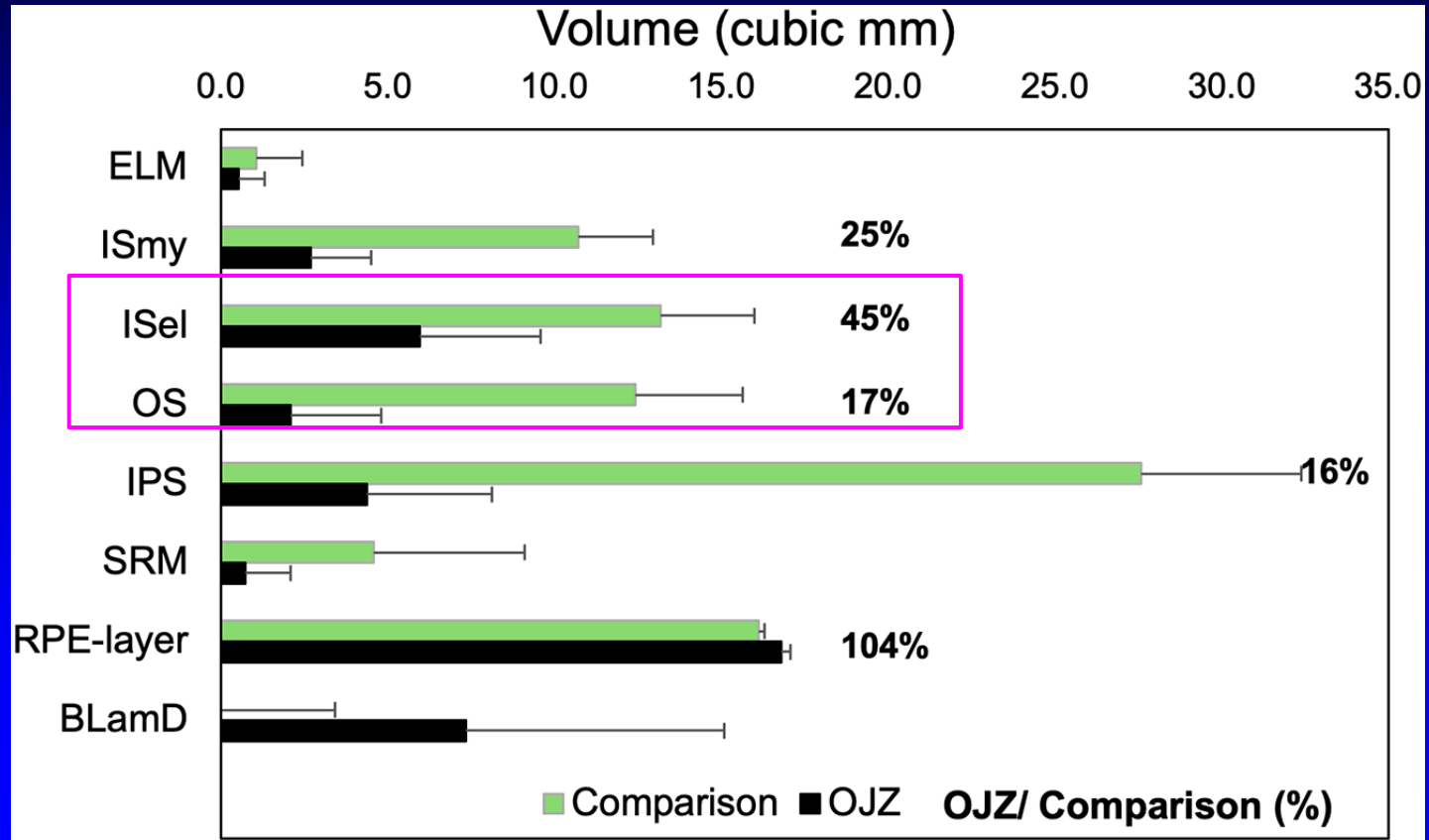
Curcio, Messinger, Sloan, Edwards, Bijon, Huemer, Leingang, Freund, Berlin, 2026. IOVS 67: 12



OJZ of GA: Photoreceptors die back from OS

93-year-old white woman, multifocal GA, observed for 5 years, 6 years before death

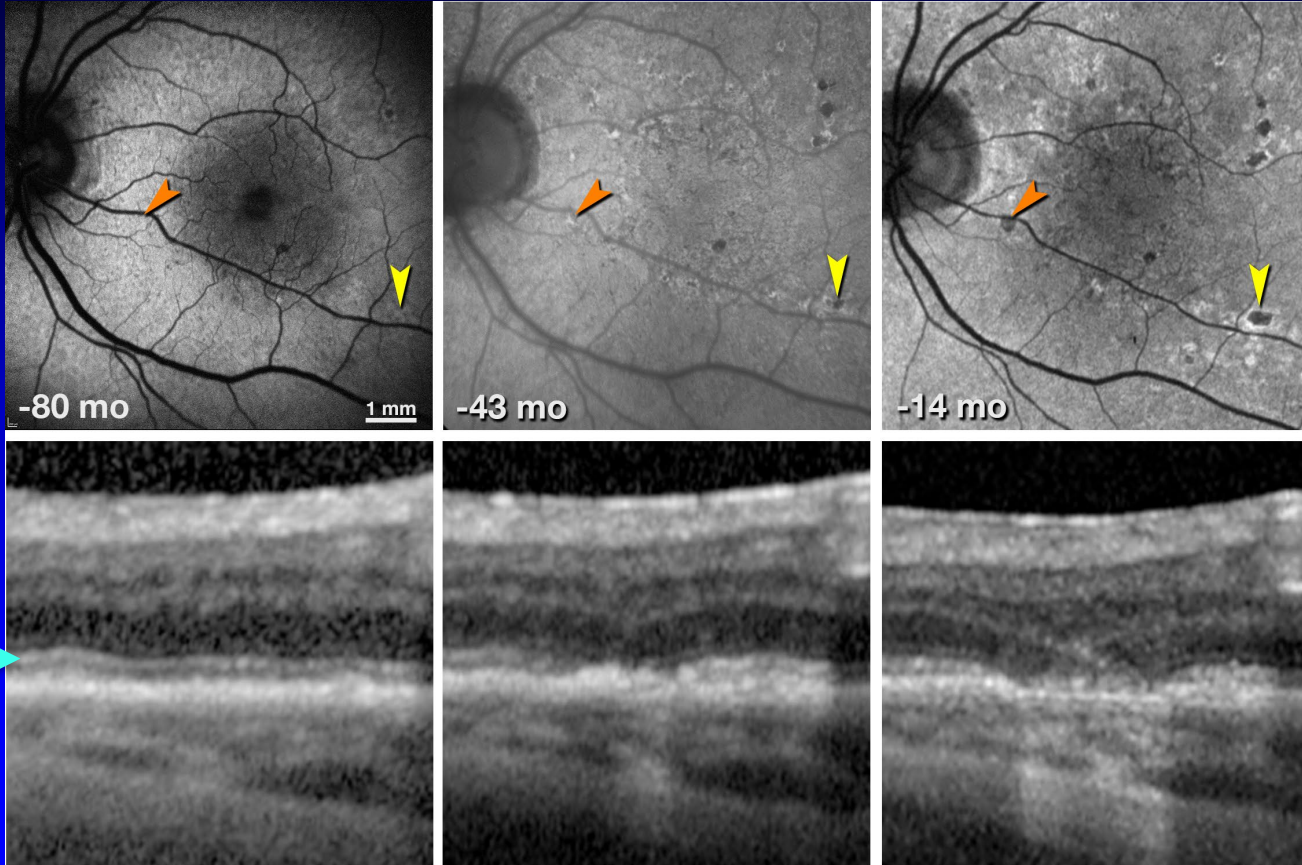
Curcio, Messinger, Sloan, Edwards, Bijon, Huemer, Leingang, Freund, Berlin, 2026. IOVS 67: 12



Photoreceptor demise at one atrophic spot

White woman, bilateral AMD, 9 years' multimodal imaging before death at age 90 years

FAF
SDOCT

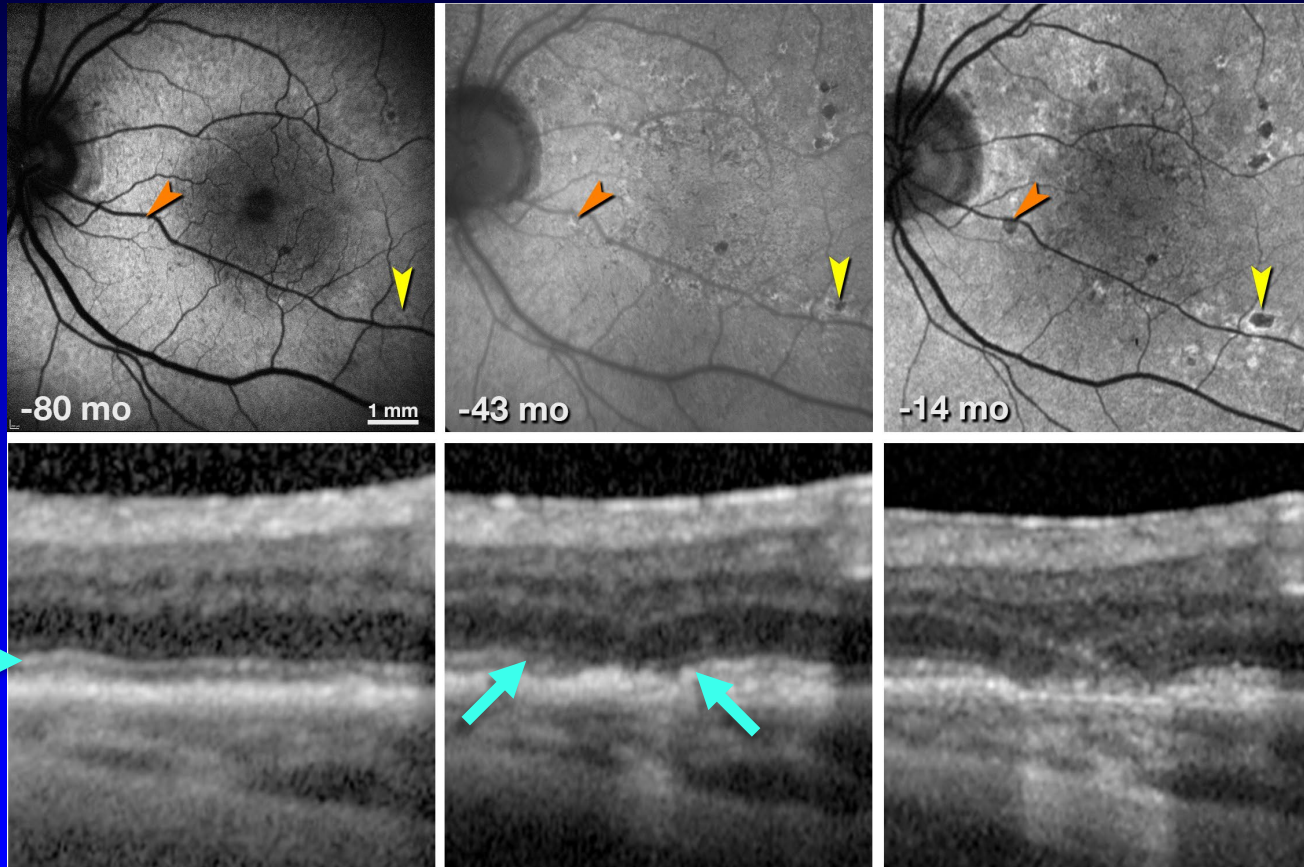


CAM4: Guymer, Rosenfeld, Curcio ... Sadda, 2020. Ophthalmology 127: 394.

Photoreceptor demise at one atrophic spot

White woman, bilateral AMD, 9 years' multimodal imaging before death at age 90 years

FAF
SDOCT

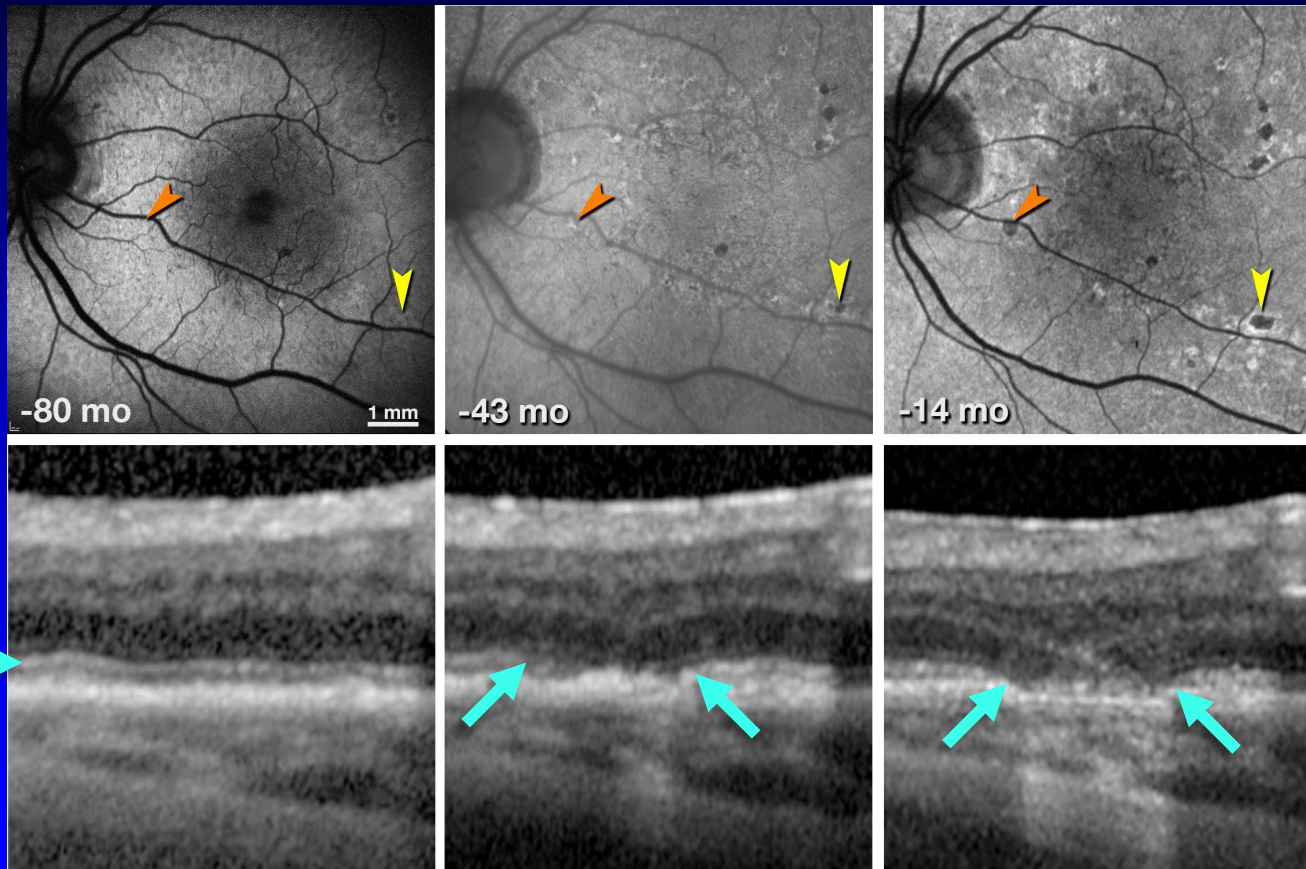


CAM4: Guymer, Rosenfeld, Curcio ... Sadda, 2020. Ophthalmology 127: 394.

Photoreceptor demise at one atrophic spot

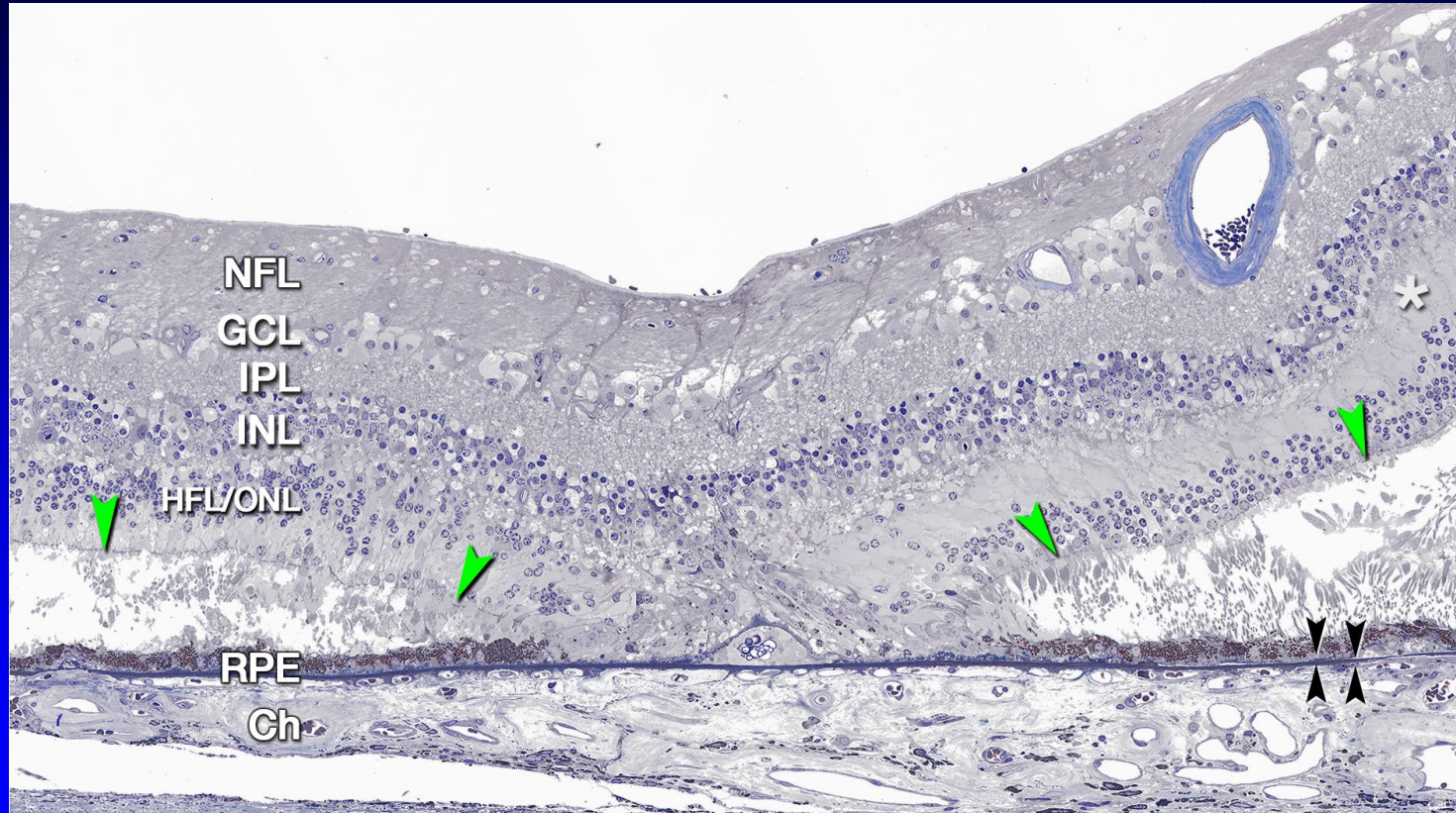
White woman, bilateral AMD, 9 years' multimodal imaging before death at age 90 years

FAF
SDOCT



CAM4: Guymer, Rosenfeld, Curcio ... Sadda, 2020. Ophthalmology 127: 394.

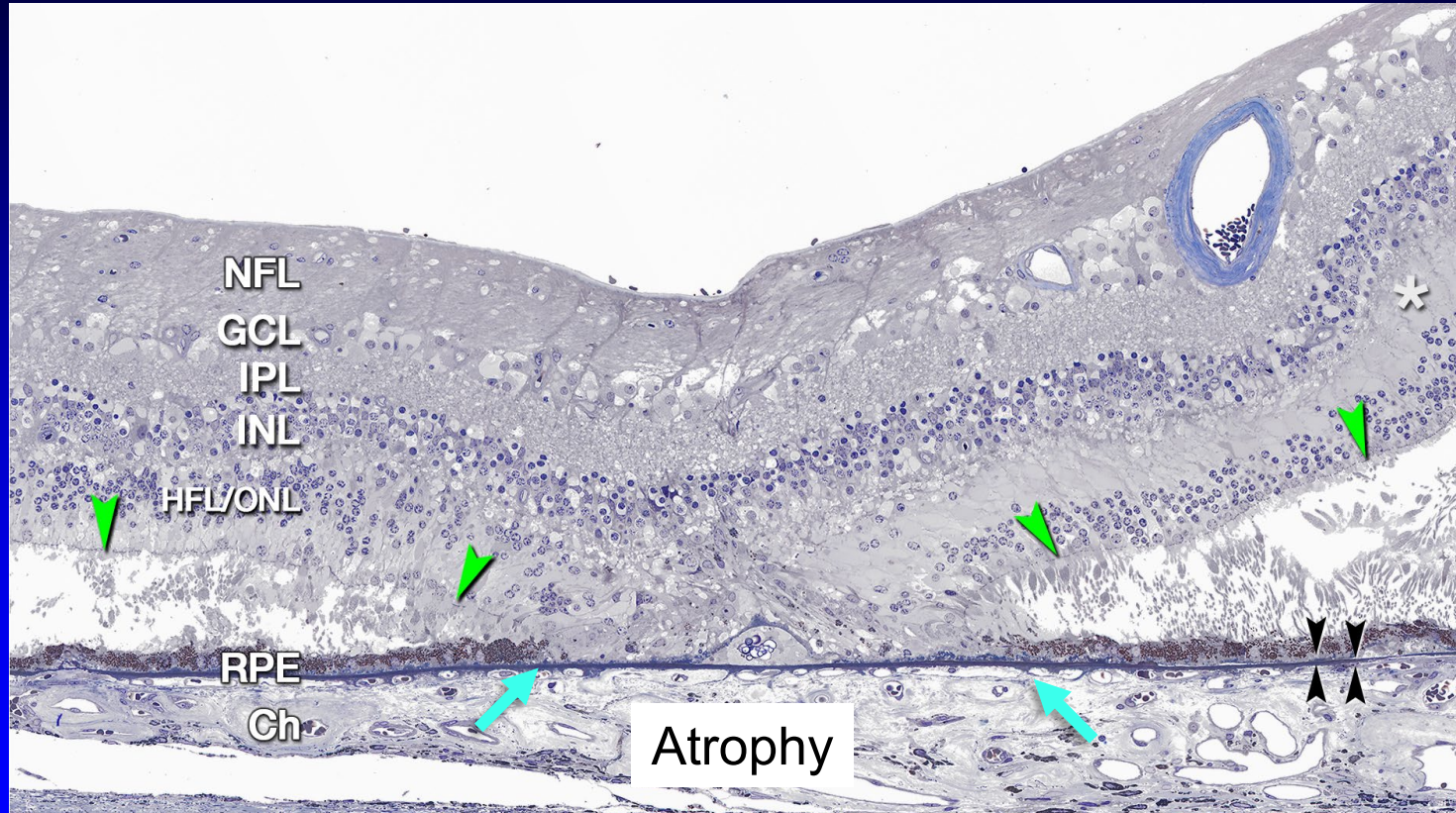
Photoreceptor demise at one atrophic spot



CAM4: Guymer, Rosenfeld, Curcio ... Sadda, 2020. Ophthalmology 127: 394.

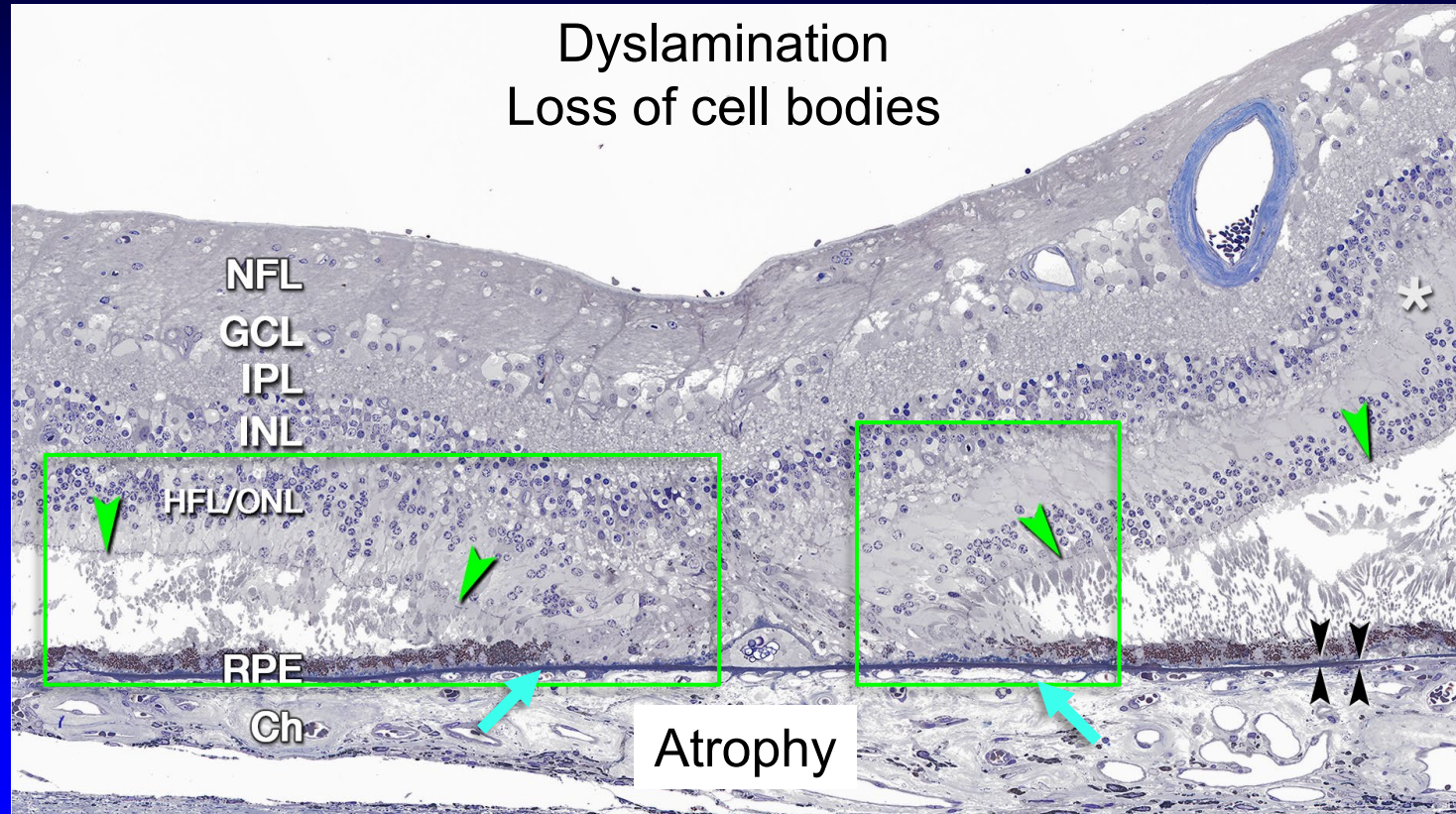
Classified as public by the European Medicines Agency

Photoreceptor demise at one atrophic spot



CAM4: Guymer, Rosenfeld, Curcio ... Sadda, 2020. Ophthalmology 127: 394.

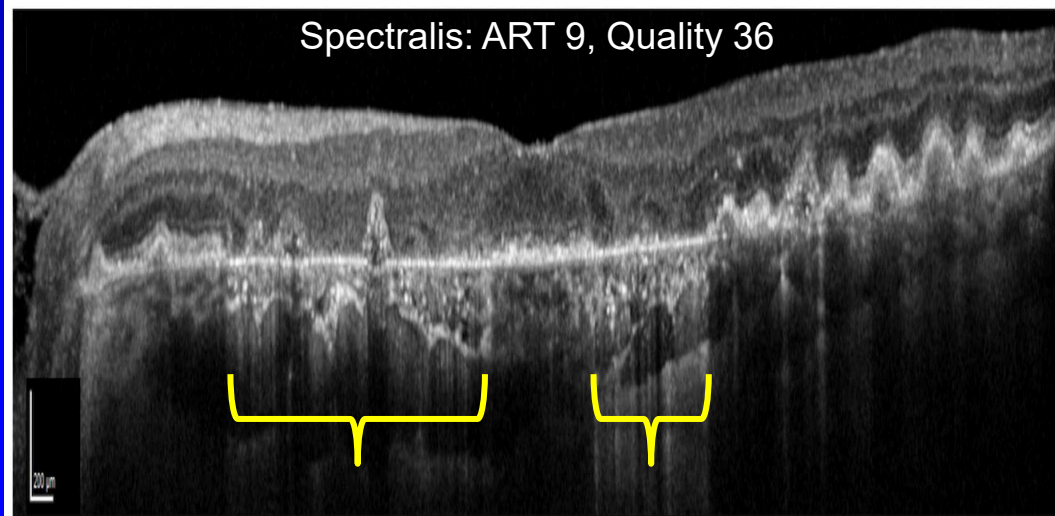
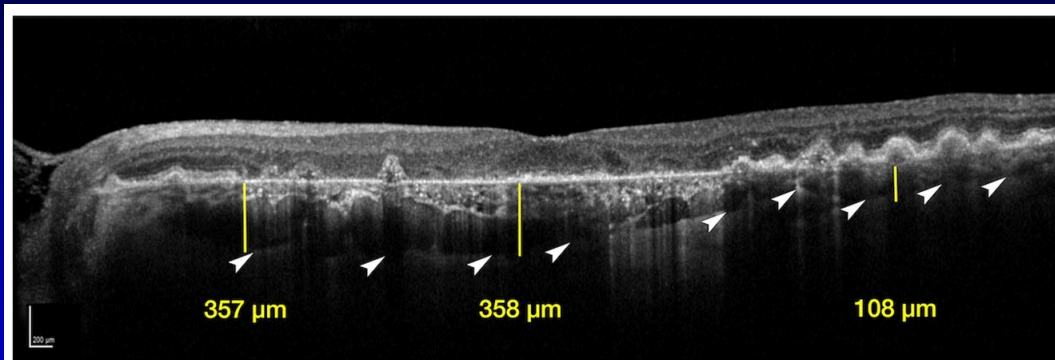
Photoreceptor demise at one atrophic spot



CAM4: Guymer, Rosenfeld, Curcio ... Sadda, 2020. Ophthalmology 127: 394.

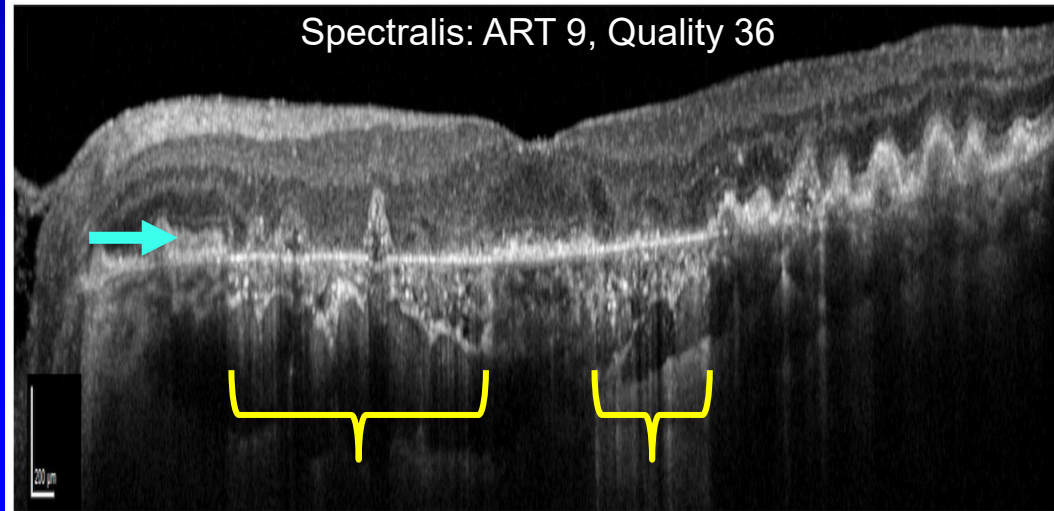
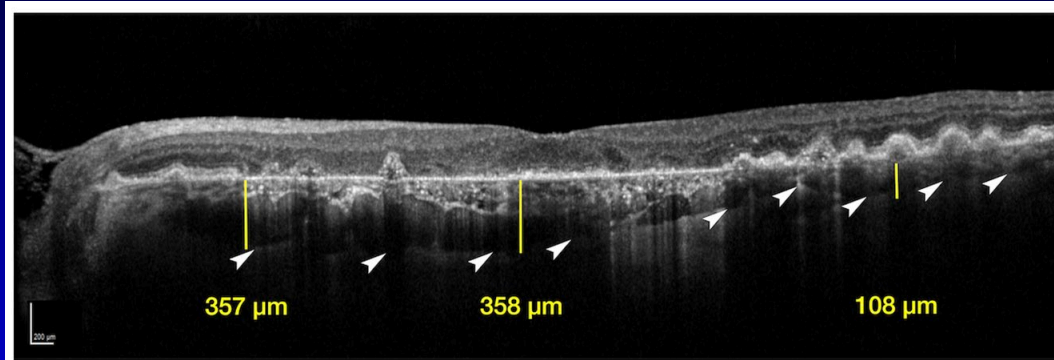
Microscopic detail is visible in high-quality SDOCT

Curcio, Messinger, Sloan, Edwards, Bijon, Huemer, Leingang, Freund, Berlin, 2026. IOVS 67: 12



Microscopic detail is visible in high-quality SDOCT

Curcio, Messinger, Sloan, Edwards, Bijon, Huemer, Leingang, Freund, Berlin, 2026. IOVS 67: 12



Takeaway messages

- Inner segments are light-catching funnels
 - Morphology and high refractive index
- Anatomic correlate of EZ: outer 1/3 of inner segment ellipsoid
- Deposits perturb photoreceptor segments, EZ
- At GA border, photoreceptors die back from OS, translocate cell bodies inwardly, drop out
- Much histologic detail is visible in good SDOCT

*Preventing atrophy from starting will also prevent its expansion
Preventing neovascularization will also prevent fluid and fibrosis*

Thanks for your attention!



cacurcio@gmail.com

2025 Proctor Medal
Association for Research in
Vision and Ophthalmology

Jointly awarded with
Cynthia Owsley PhD