ACHROMATOPSIA

Clinical overview
and
updates on clinical trial

Christine Nichols Kay, M.D.

University of Florida

Gainesville, Florida

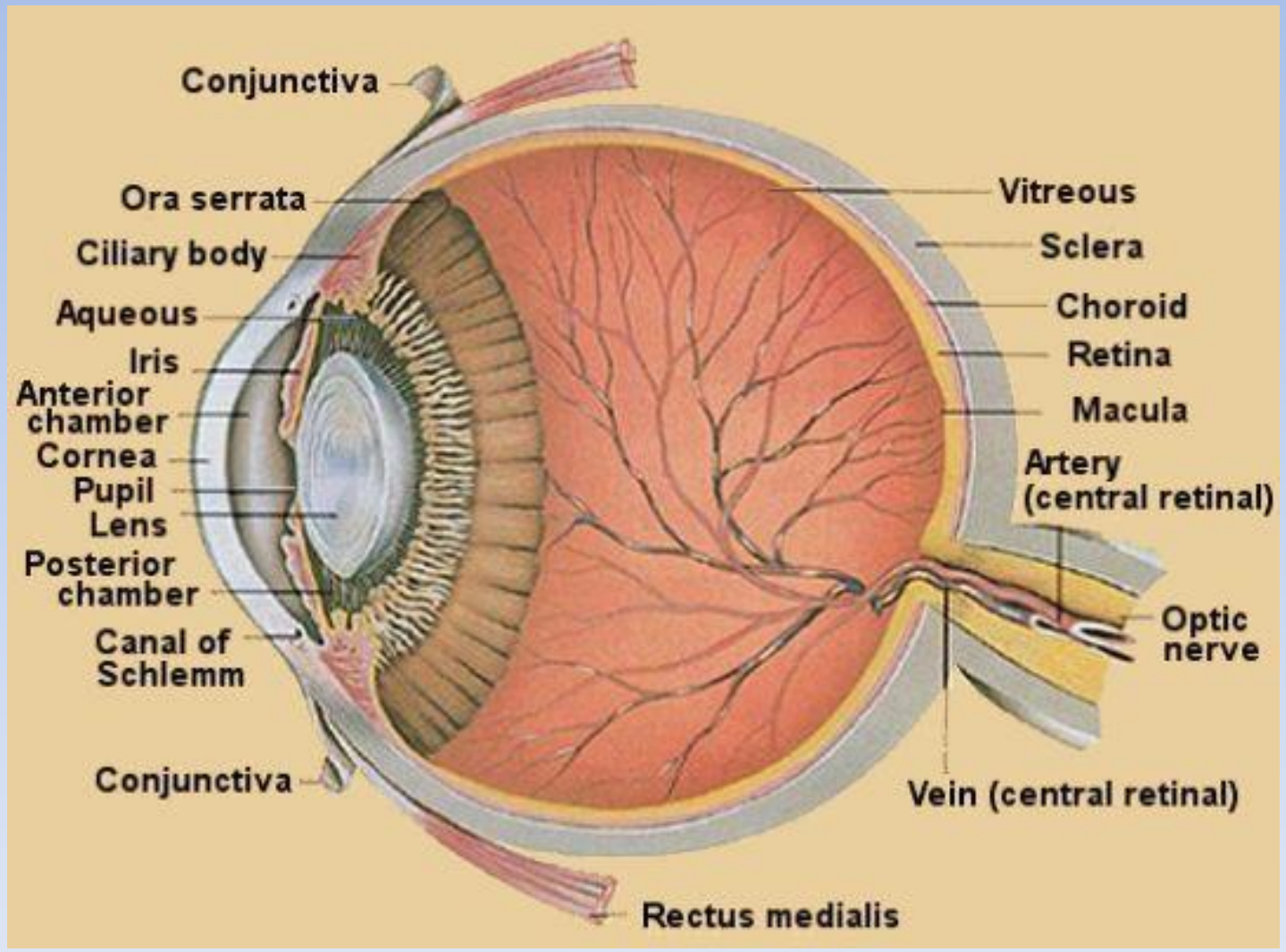
Foundation Fighting Blindness®
Driving research to save and restore sight

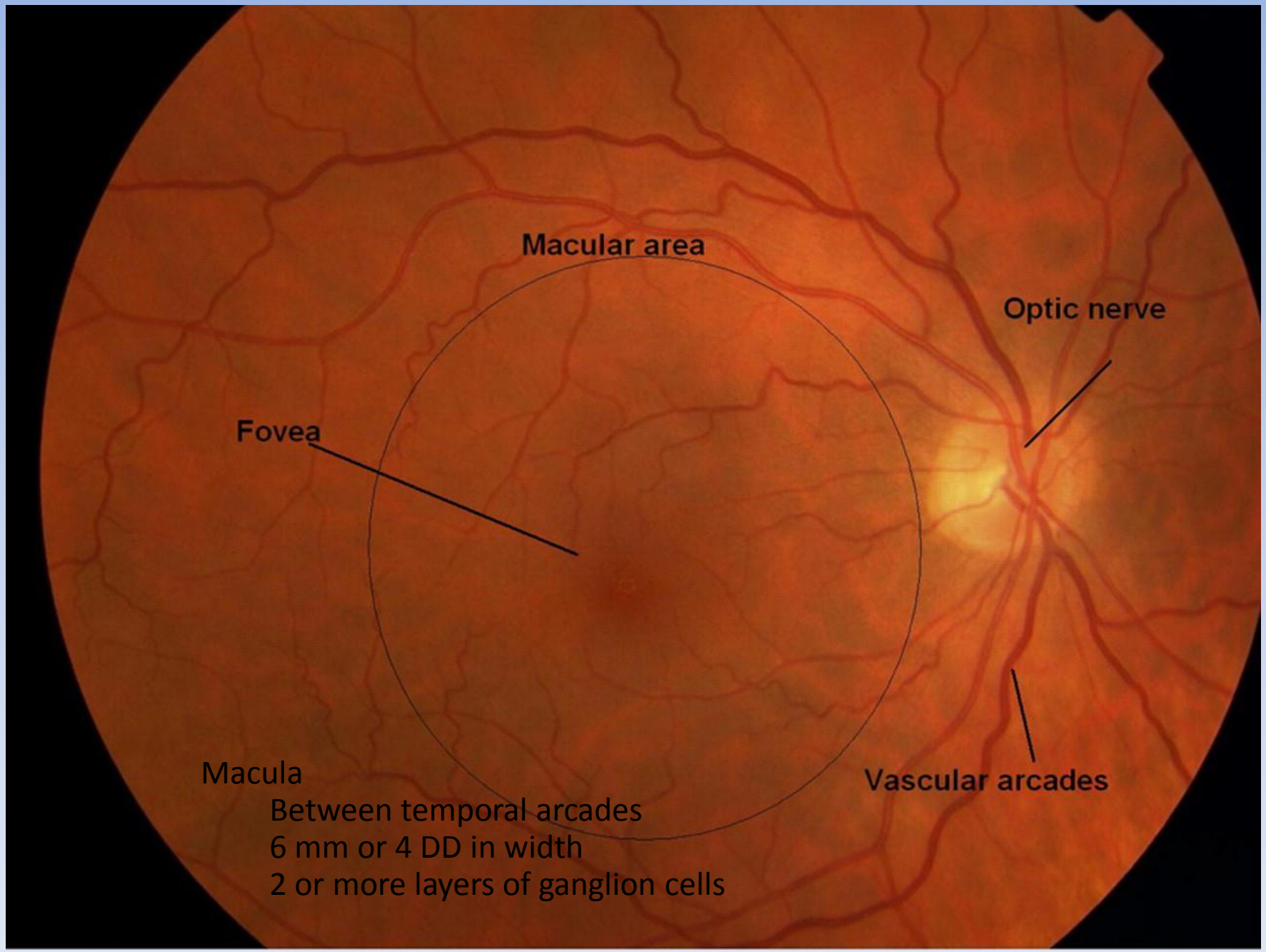
UF UNIVERSITY of FLORIDA
The Foundation for The Gator Nation

Achromatopsia

- Autosomal Recessive
- Prevalence of 1:30,000-50,000
- Mild congenital pendular nystagmus
- Protan (red), deutan (green), and tritan (blue) color defects
- Severe photophobia
- Decreased VA around 20/100-20/200
- ERG shows normal rod function and no cone function
- Can have normal fundus or classic foveal atrophy
- OCT with characteristic foveal photoreceptor atrophy

Anatomy overview



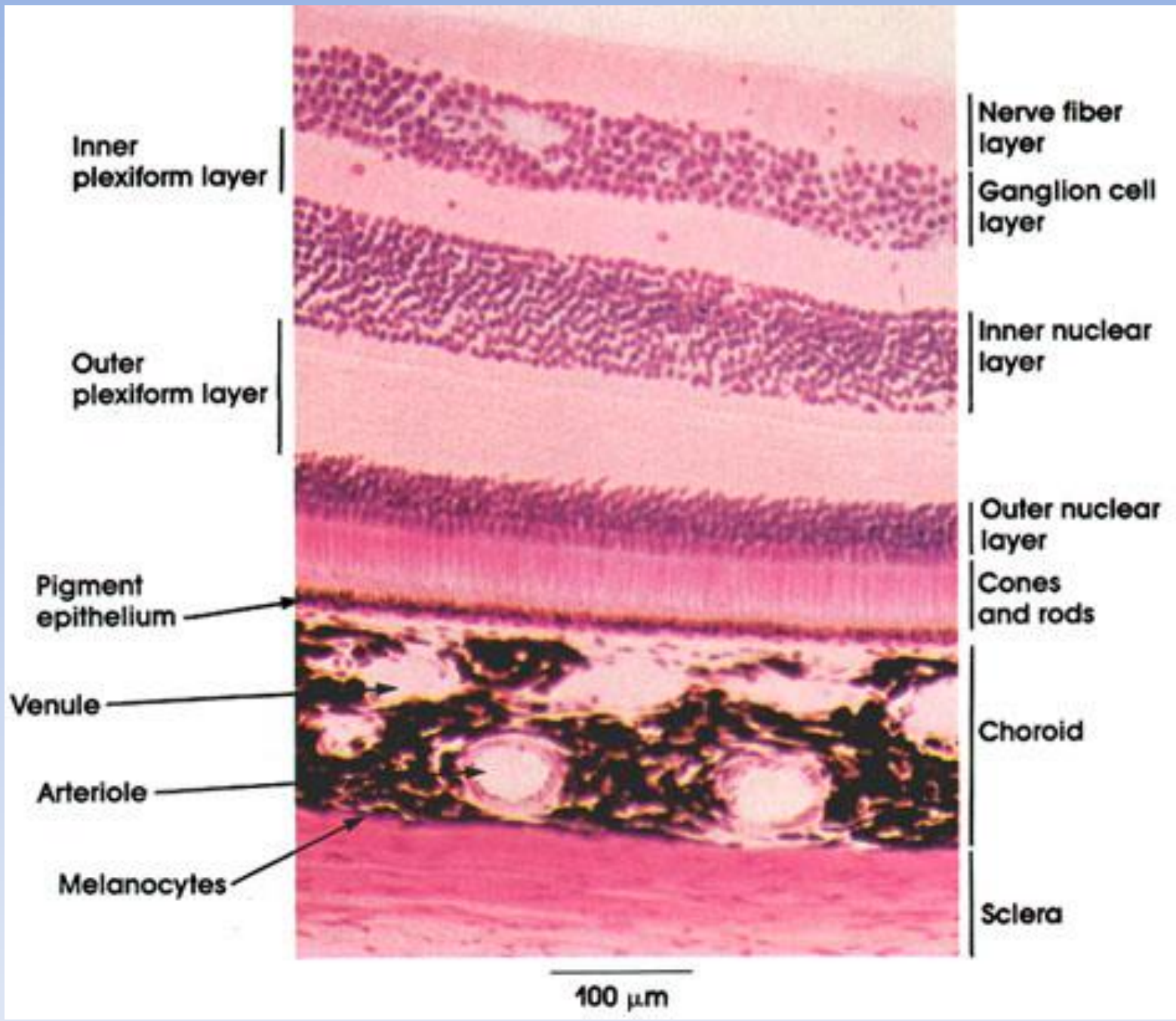


Macula

Between temporal arcades

6 mm or 4 DD in width

2 or more layers of ganglion cells


Inner plexiform layer
Outer plexiform layer
Pigment epithelium
Venule
Arteriole
Melanocytes
Nerve fiber layer
Ganglion cell layer
Inner nuclear layer
Outer nuclear layer
Cones and rods
Choroid
Sclera
100 μm

Photoreceptors

- Light sensitive cells found in the retina.
- Rods (93% of cells) and Cones (7%)
  - Rods: night vision, visual field
  - Cones: visual acuity, color vision

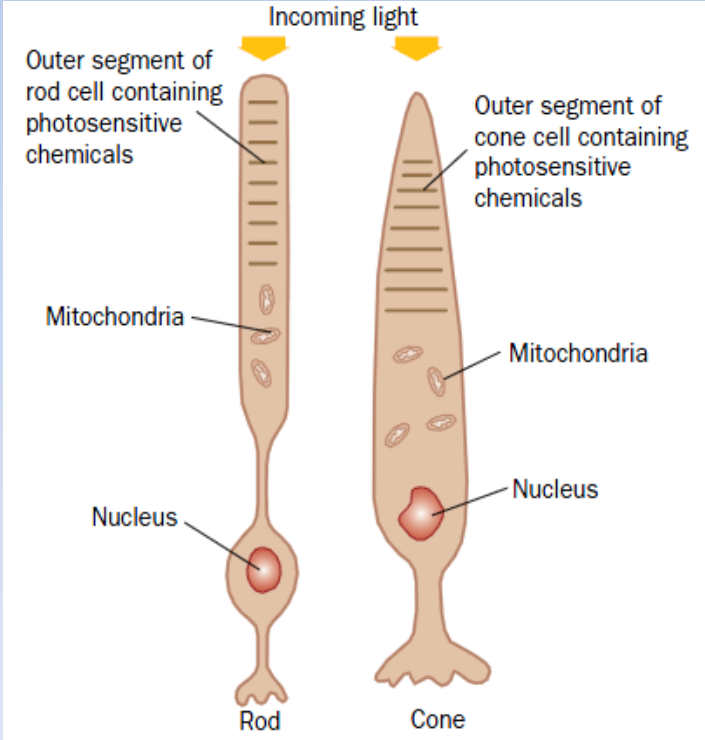
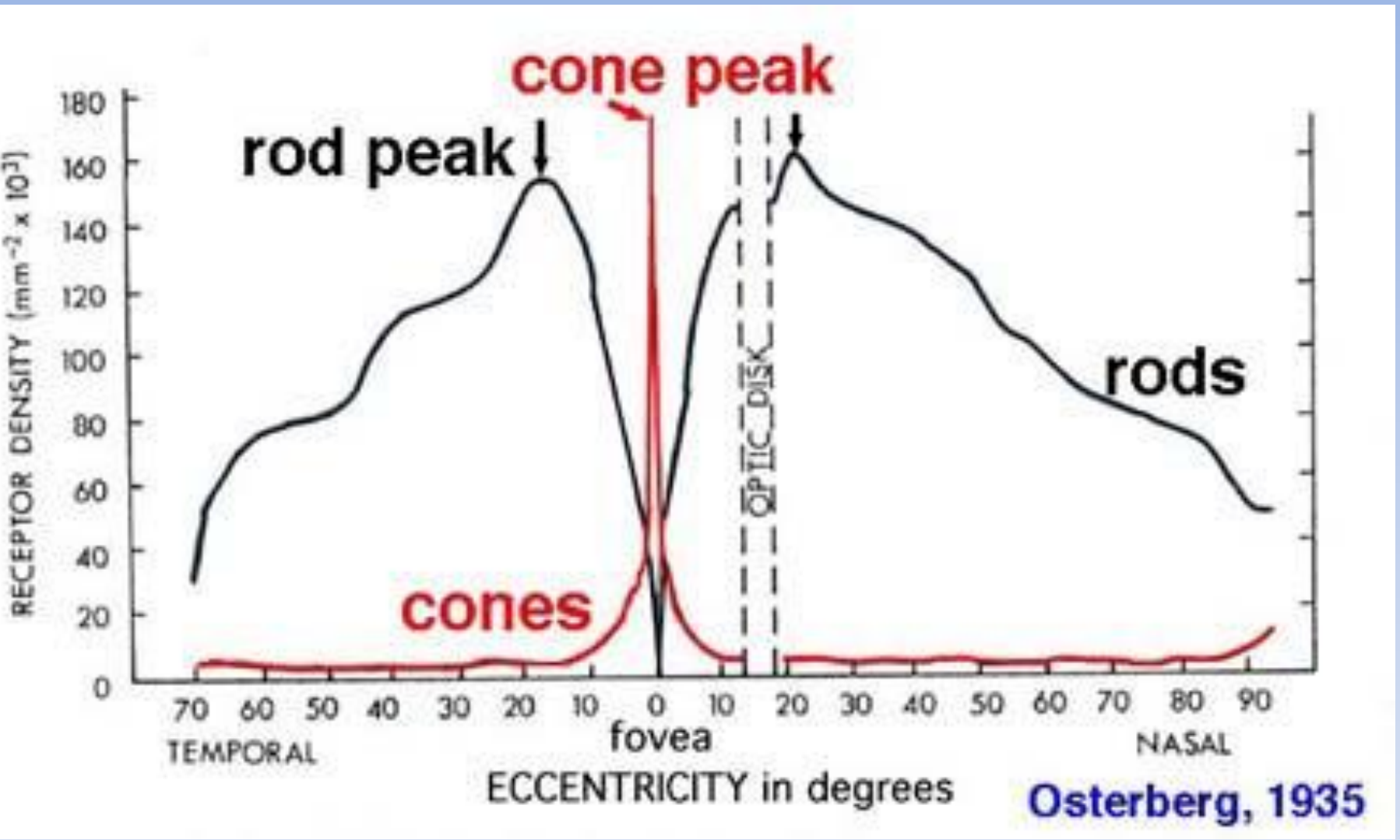


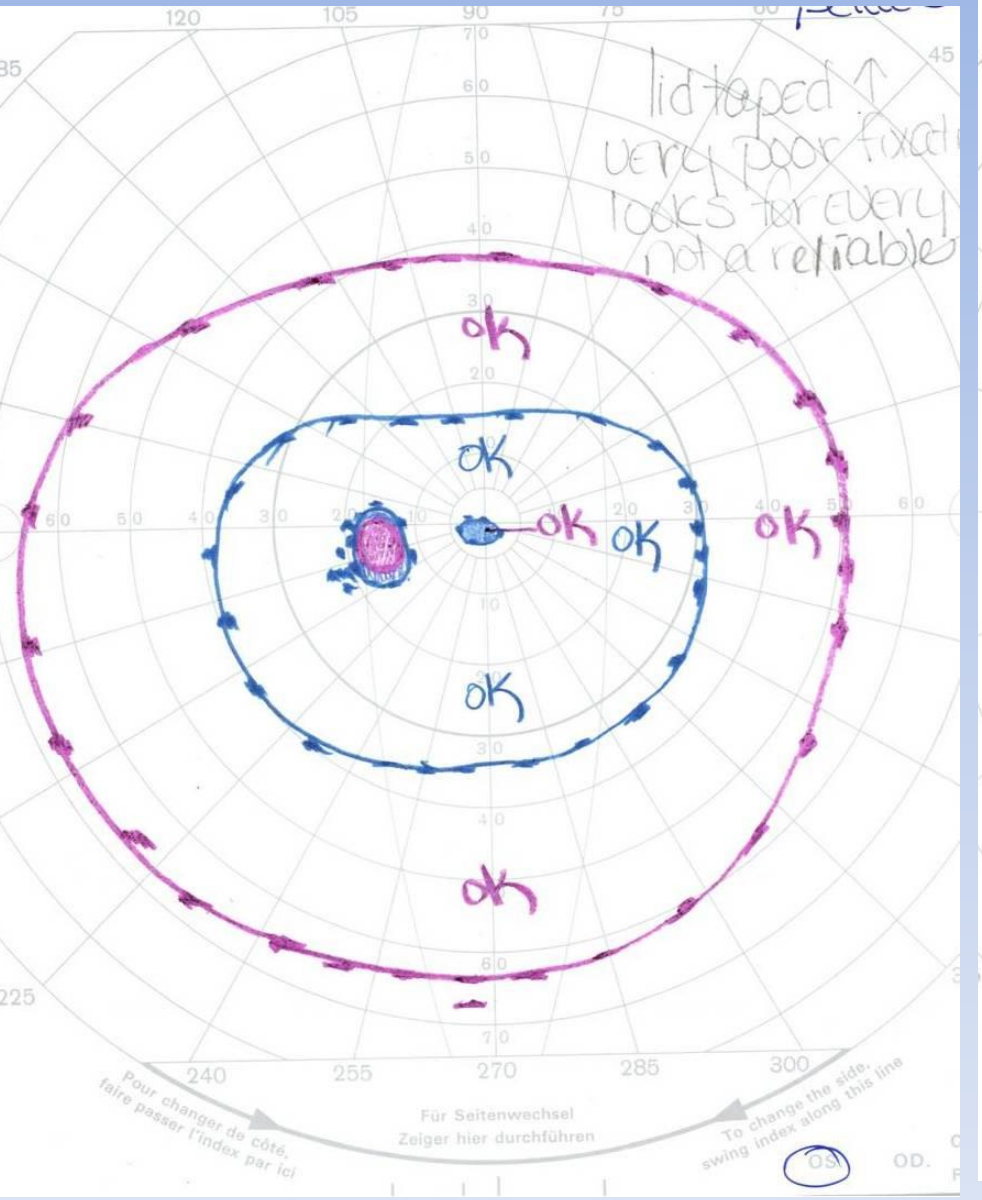
Figure 8.4.2 Basic structure of rods and cones


cone peak
rod peak
rods
cones
OPTIC DISK
RECEPTOR DENSITY (mm⁻² x 10³)
180
160
140
120
100
80
60
40
20
0
70 60 50 40 30 20 10 0 10 20 30 40 50 60 70 80 90
TEMPORAL
fovea
NASAL
ECCENTRICITY in degrees
Osterberg, 1935

Achromatopsia foveal atrophy

1

3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very poor fixat
looks for every
not a reliable
ok
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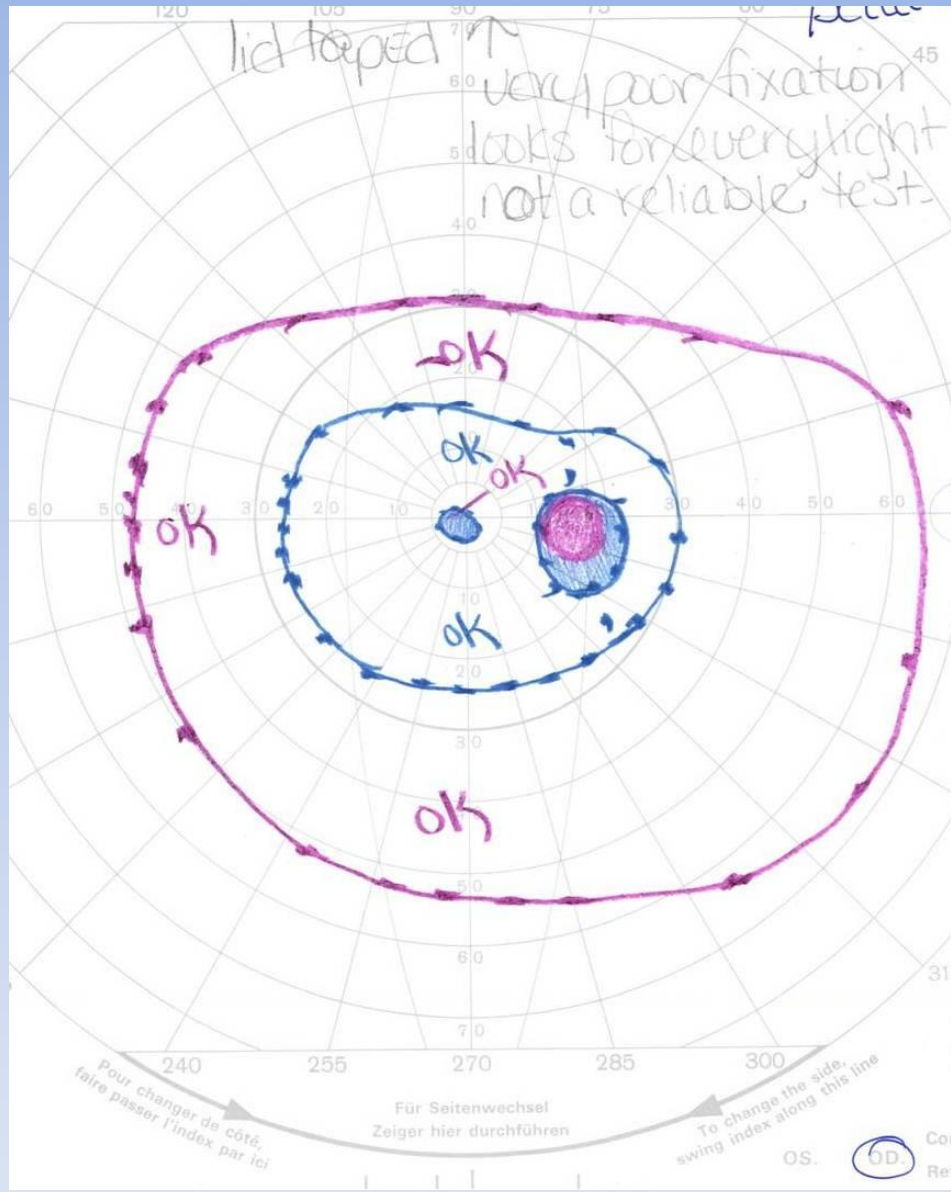
Für Seitenwechsel
Zeiger hier durchführen
Pour changer de côté,
faire passer l'index par ici
To change the side,
swing index along this line
OS.
OD.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very poor fixation
looks for every light
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Für Seitenwechsel
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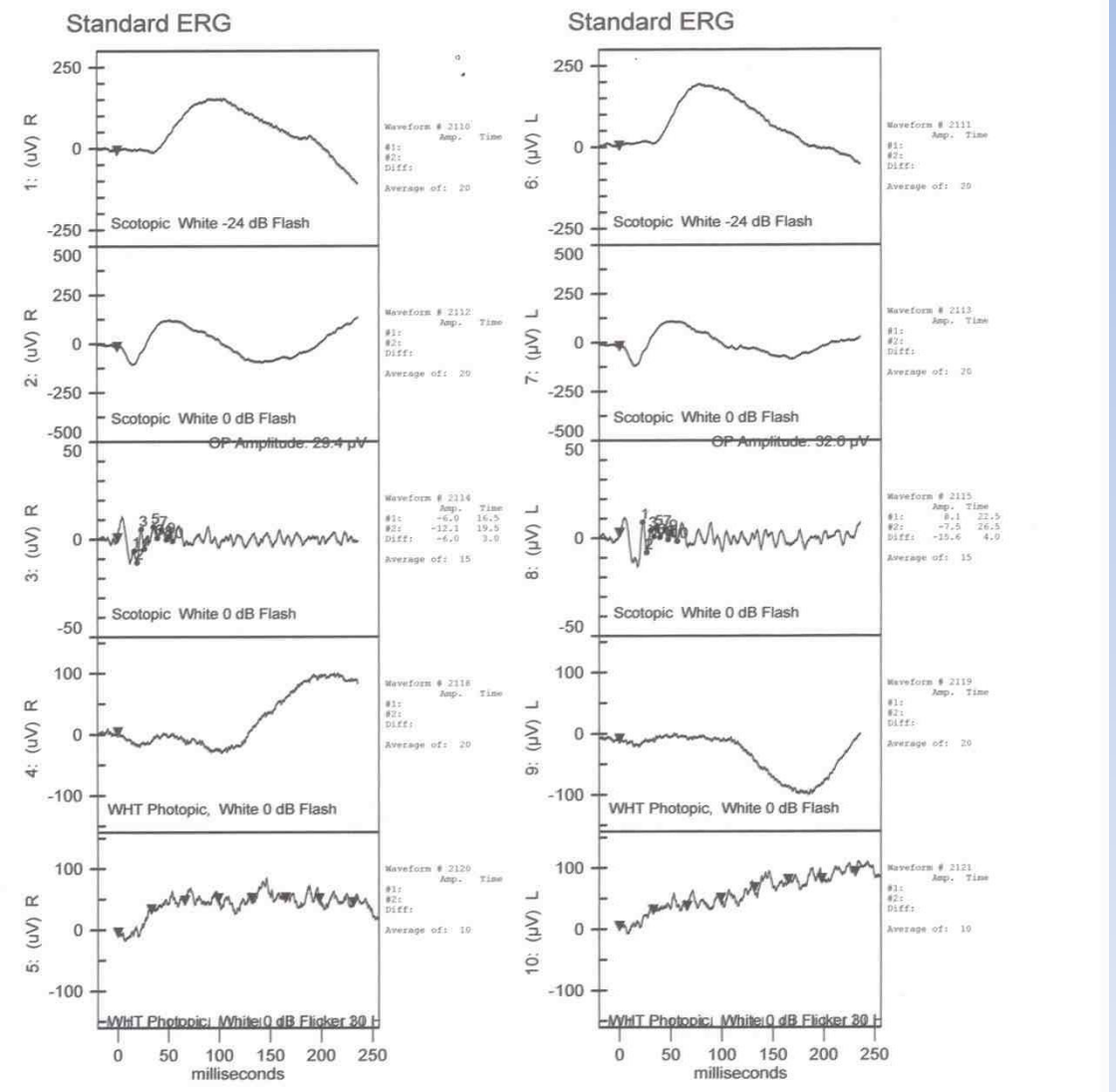
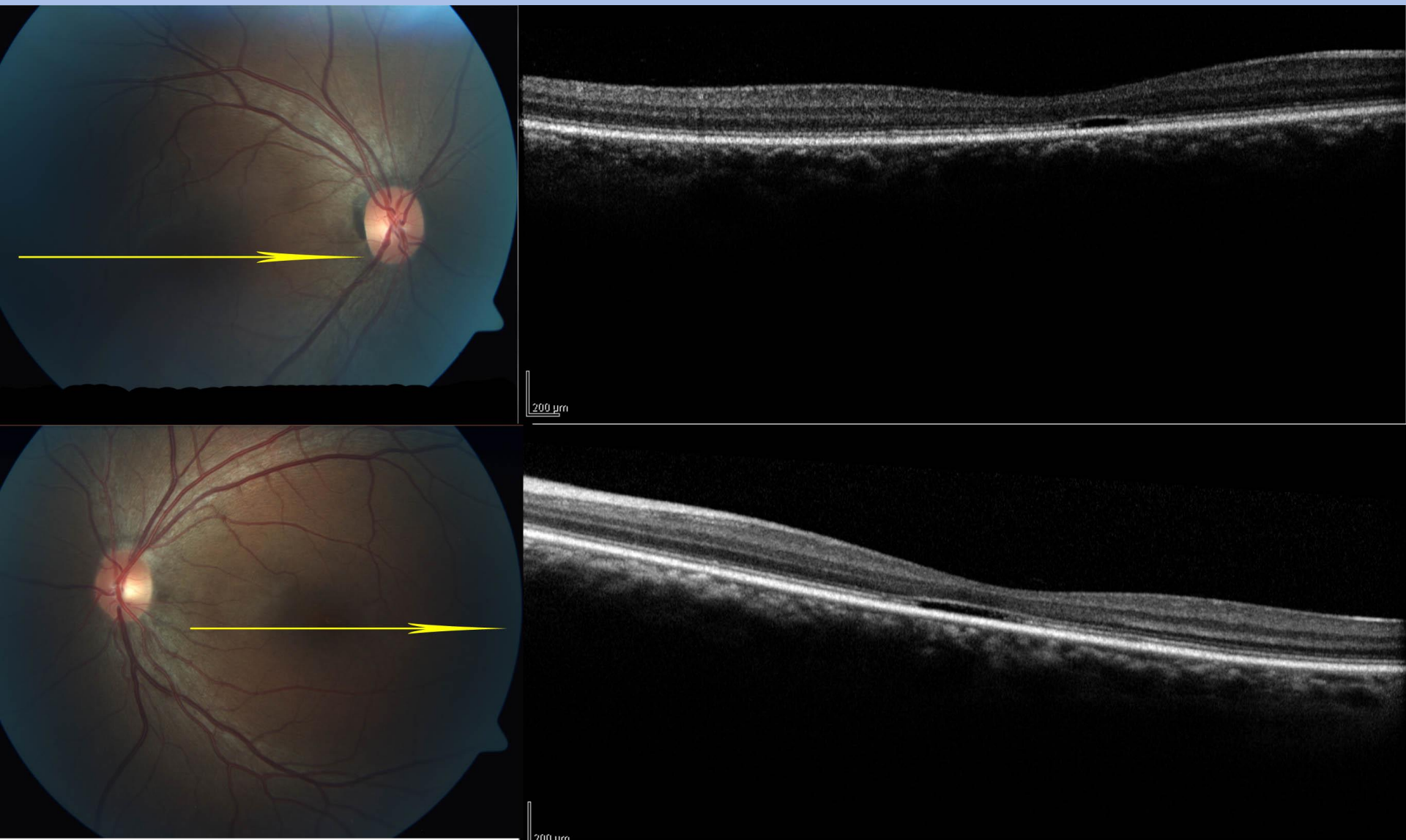
ERG


Standard ERG
1: (uV) R
Scotopic White -24 dB Flash
2: (uV) R
Scotopic White 0 dB Flash
OP Amplitude: 29.4 µV
3: (uV) R
Scotopic White 0 dB Flash
4: (uV) R
WHT Photopic, White 0 dB Flash
5: (uV) R
WHT Photopic, White 0 dB Flicker 30 Hz
milliseconds
Standard ERG
6: (uV) L
Scotopic White -24 dB Flash
7: (uV) L
Scotopic White 0 dB Flash
OP Amplitude: 32.6 µV
8: (uV) L
Scotopic White 0 dB Flash
9: (uV) L
WHT Photopic, White 0 dB Flash
10: (uV) L
WHT Photopic, White 0 dB Flicker 30 Hz
milliseconds

CNGB3-Achromatopsia OCT

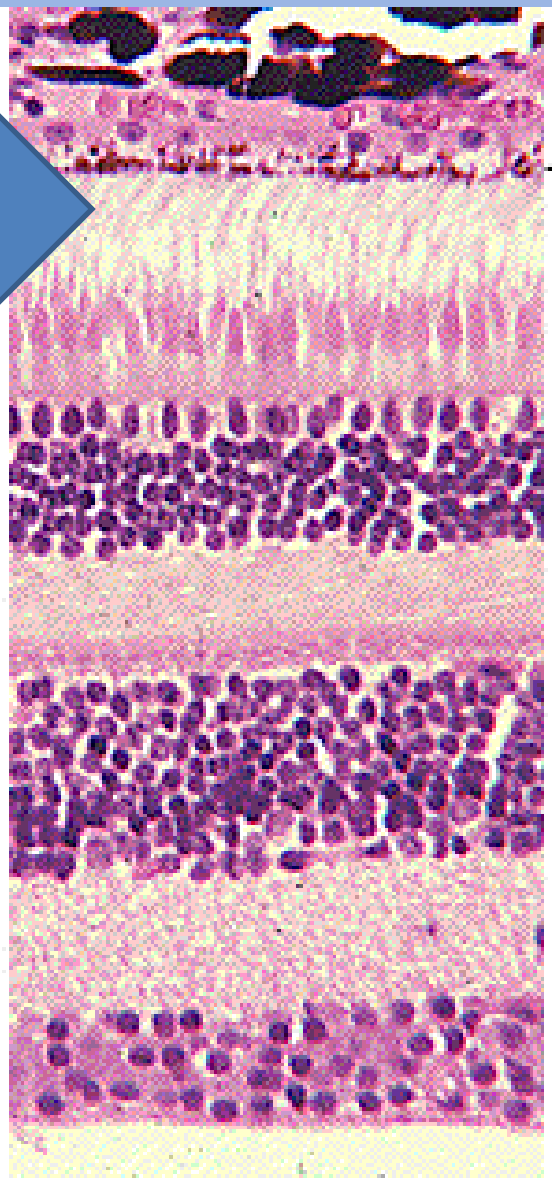


Genetics of Achromatopsia

- CNGA3 or CNGB3, **C**yclic **N**ucleotide **G**ated **C**hannel (Subtype A or Subtype B)
  - CNGA3 (25%)
  - CNGB3 (50%):
    - Most frequent mutation is Thr383fsx mutation (80%) – this frameshift mutation causes truncation of pore-forming loop and C-terminal cytoplasmic domain, and no intact CNGB3 is formed.
- GNAT2 (1%)
- PDE6C (1%)

Retinal Physiology

- Quick overview…



choroid

pigment epithelium

outer segments

inner segments

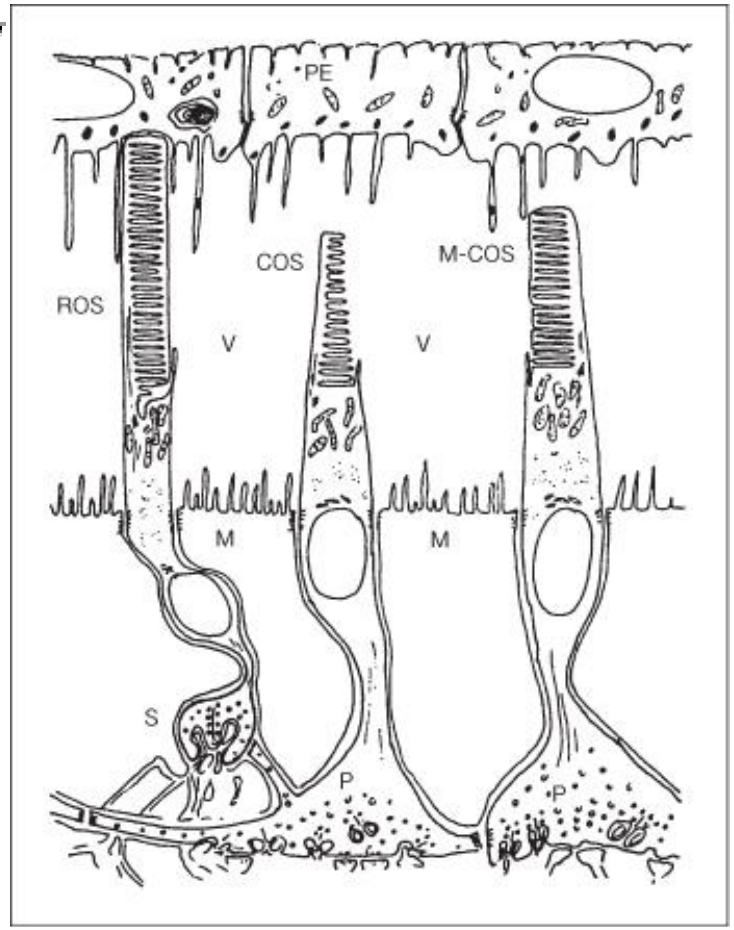
outer nuclear layer (ONL)

outer plexiform layer (OPL)

inner nuclear layer (INL)

inner plexiform layer (IPL)

ganglion cell layer (GCL)

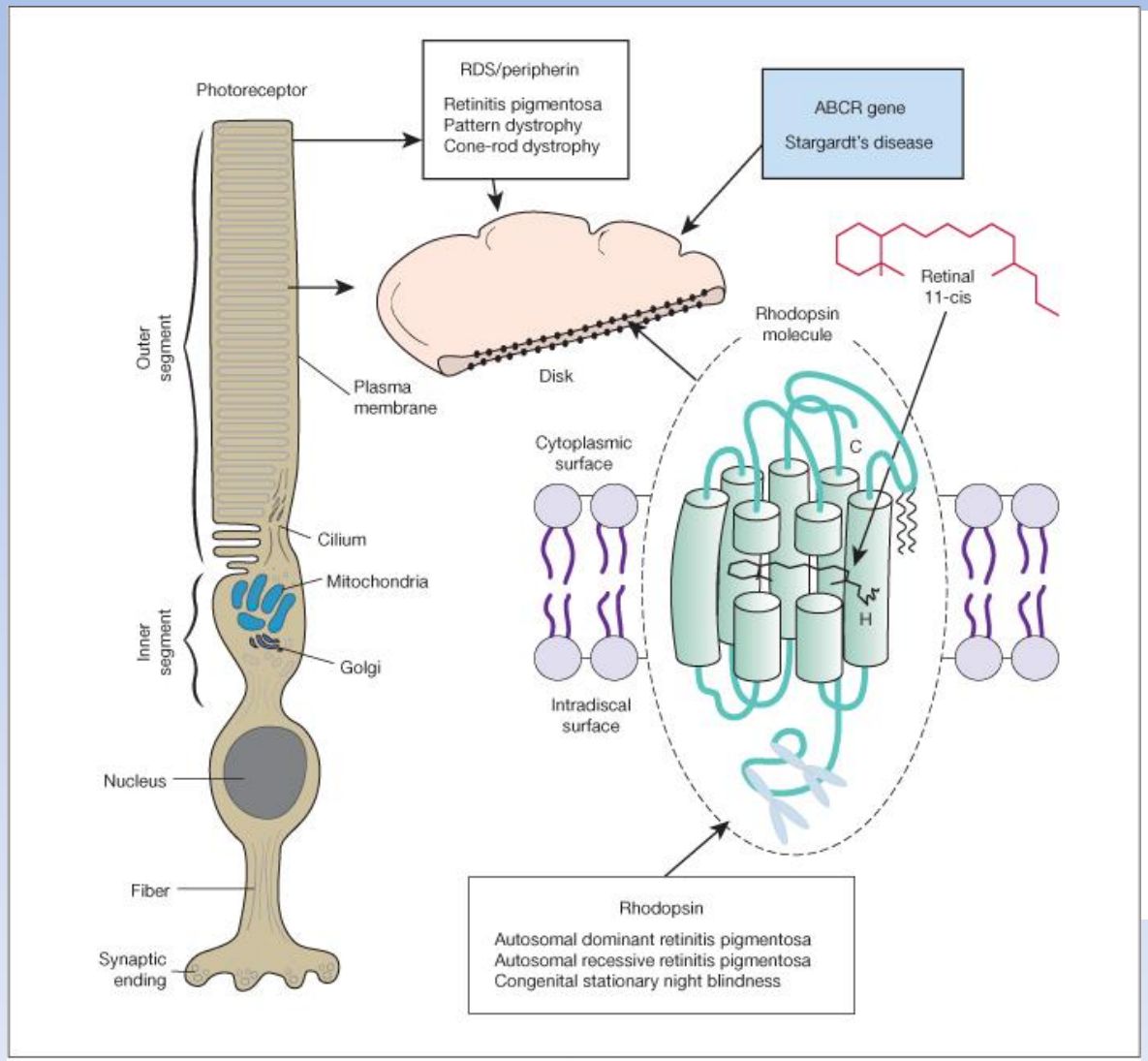


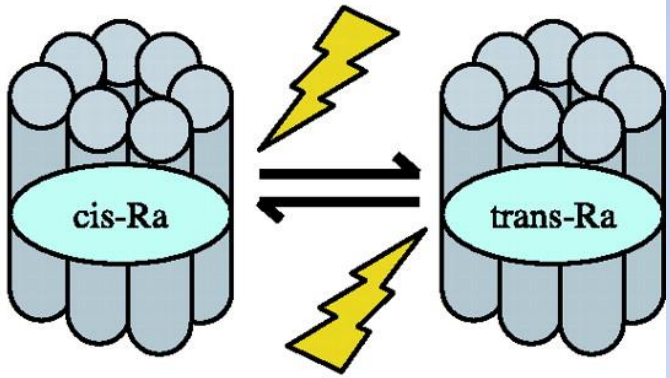
Physiology of Photoreception: THE MAJOR PLAYERS

- **Photoreceptor outer segment:**
  - –Phototransduction
- **RPE cell:**
  - –Visual cycle

The Outer Segment:

the light sensitive part of a photoreceptor





First step in phototransduction is activation of rhodopsin by light causes isomerization of 11-cis to all-trans

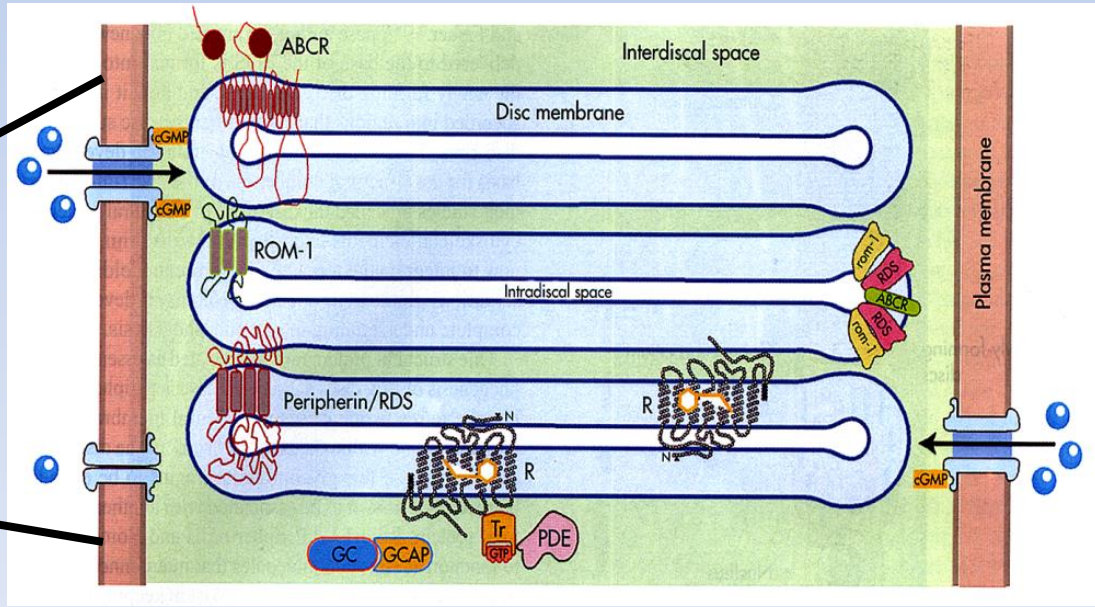
Cyclic Nucleotide Gated Channels

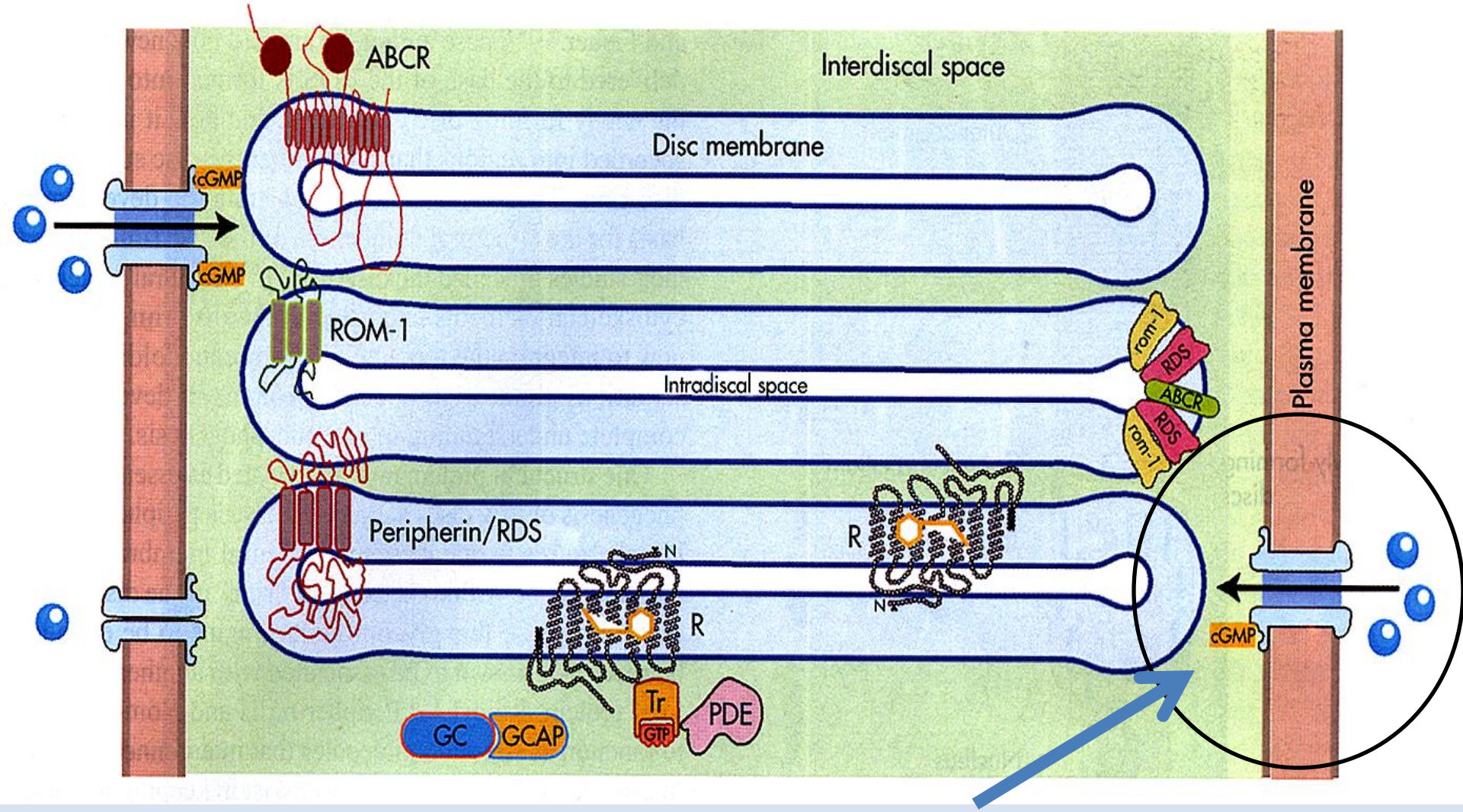
- CNG channels are localized to **plasma membrane of outer segment**
- Belong to superfamily of voltage-gated ion channels
- Play **pivotal role in phototransduction**:
  - CNGA1/B1: in rods
  - CNGA3/B3: in cones

CNGA3 versus CNGB3

- Two channel subunits, alpha and beta
- Alpha subunits are ion transporting structures
- Beta subunits modulate the behavior of alphas but do not function as channels by themselves
- CNGA3 and CNGB3 mutations involve inability to properly control or respond to altered levels of cGMP.
- cGMP level controls the opening of cyclic nucleotide gated-ion channels.

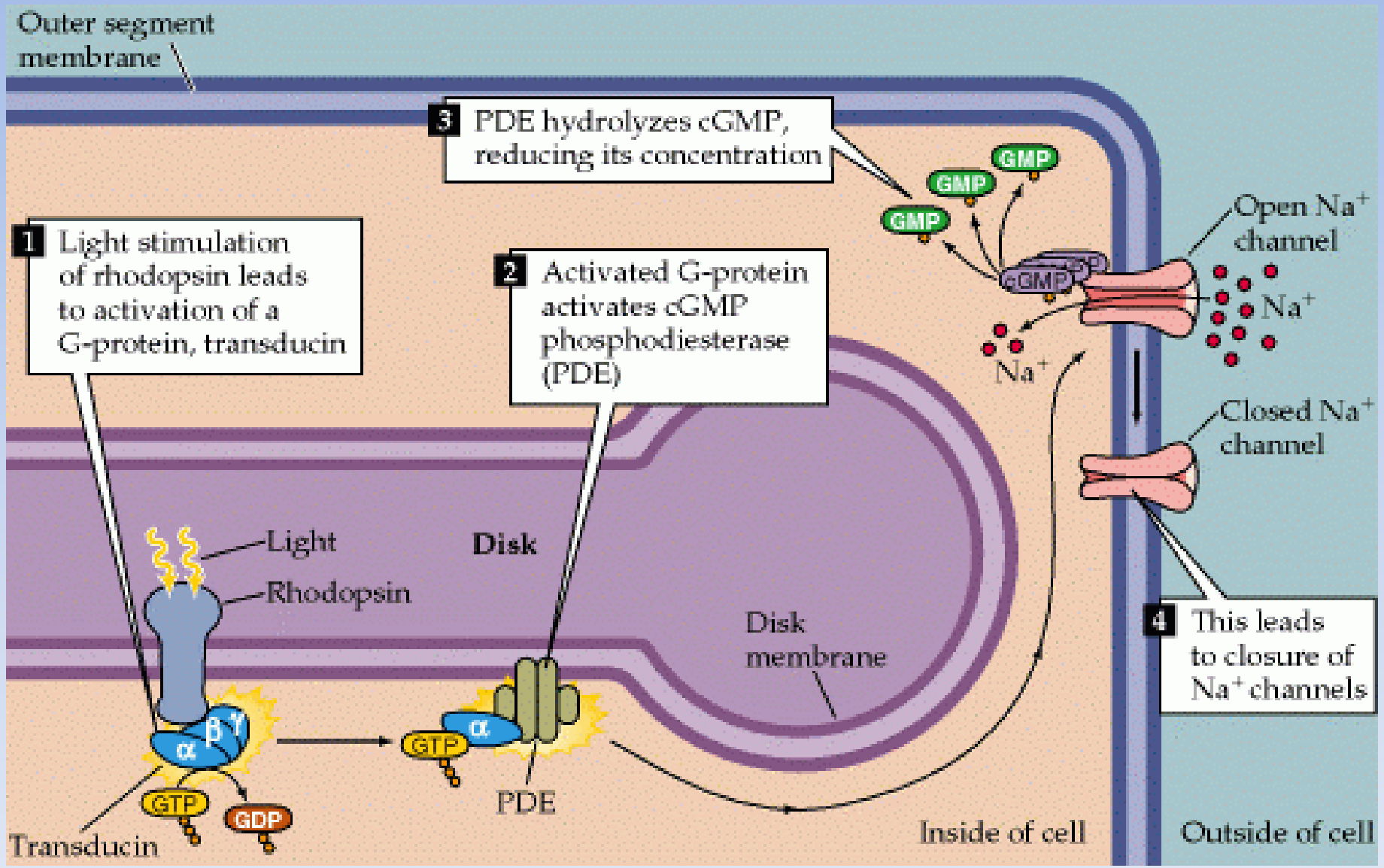
CNG channels localized to photoreceptor outer segment





Cyclic nucleotide gated channel

Light stimulation leads to hydrolysis of cGMP → CNG channel closure → reduction of inward Na+ and Ca2+ currents → membrane hyperpolarization



Physiology summary

- Achromatopsia involves mutations in genes that play critical roles in the way the retina electrically responds to light (PHOTOTRANSDUCTION)
- Achromatopsia involves mutations in CONE cells, which are clustered in the fovea, and are responsible for visual acuity and color vision.

Current management of achromatopsia in humans

- Tinted glasses (to minimize severe photosensitivity).
- Currently no approved treatment.
- Gene therapy studies underway…

CLINICAL TRIAL UPDATE

- **Clinical and Genetic Characterization of Individuals With Achromatopsia**
- **NATURAL HISTORY TRIAL**
- NIH grant (R24) to University of Florida and AGTC to co-sponsor a clinical trial on Achromatopsia
  - PI: Bill Hauswirth
  - Clinical PI's:
    - Casey Eye Institute: Dick Weleber
    - Chicago, Lighthouse: Gerald Fishman
    - University of Florida: Christine Kay
    - Bascom Palmer: Byron Lam
    - Wisconsin: Joe Carroll (Adaptive Optics)
- Actively recruiting patients.

Population

- The study population will consist of up to 150 individuals at least 6 years of age with a clinical diagnosis of achromatopsia.

Protocol

Study Duration: Approximately 1.5 years per participant

Objectives

Clinically characterize and genotype individuals with CNGB3-achromatopsia.

Determine progression and stability of clinical measures

Determine a subset of reliable endpoints and identify inclusion/exclusion criteria for future clinical trials

Study Design: Patients with mutations in both alleles of the *CNGB3* gene will be evaluated twice a year for up to 1.5 years by using a variety of non-invasive visual function tests to more fully characterize their clinical condition.

TESTING

- Genetic testing to confirm 2 CNGB3 mutations at Casey.
- Routine ophthalmic examination and visual acuity
- Color vision
- Reading speed (MNREAD)
- Microperimetry
- Two color dark adapted static perimetry (Octopus)
- Nystagmus testing on MP1S
- Light sensitivity testing (Octopus)
- Optical coherence tomography
- Fullfield and Multifocal Electroretinography
- Fundus photography
- Quality of life questionnaire
- Adaptive optics retinal imaging (Wisconsin)

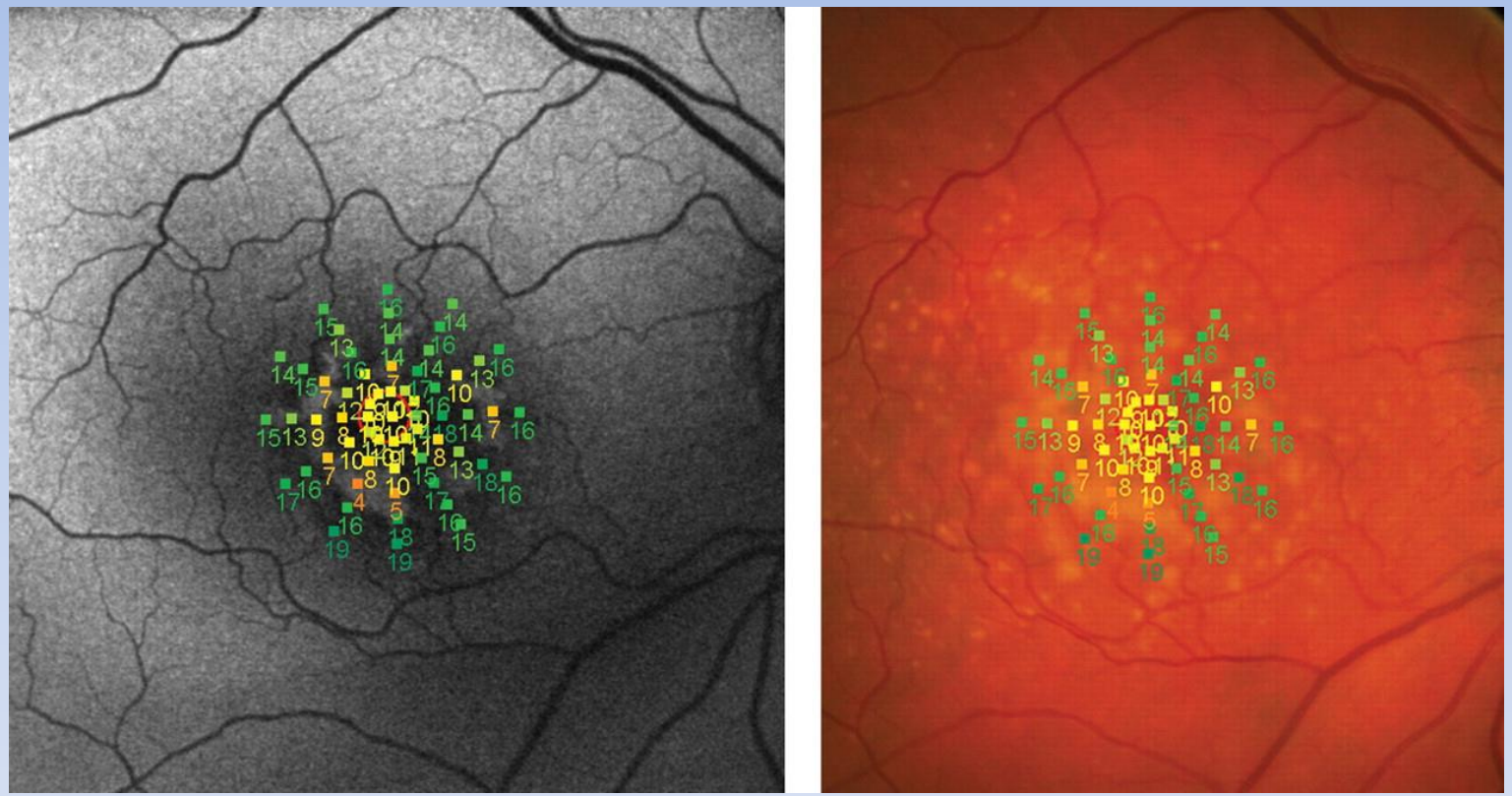
Visual acuity

Figure 1 Electronic Visual Acuity Tester (EVA)

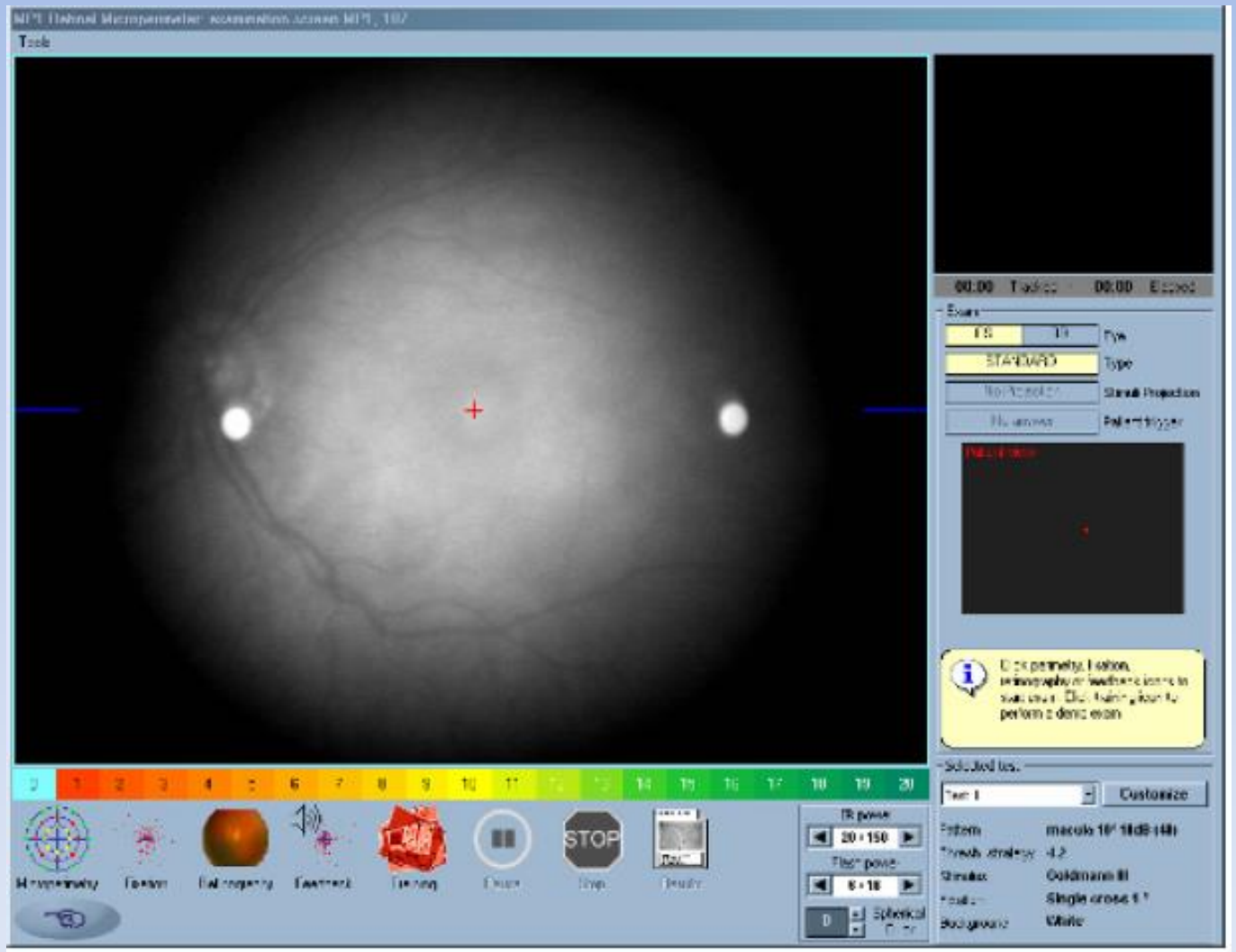
Figure 6 Example of an MNREAD chart. Actual charts are 11 by 14 inches.

Farnsworth color testing

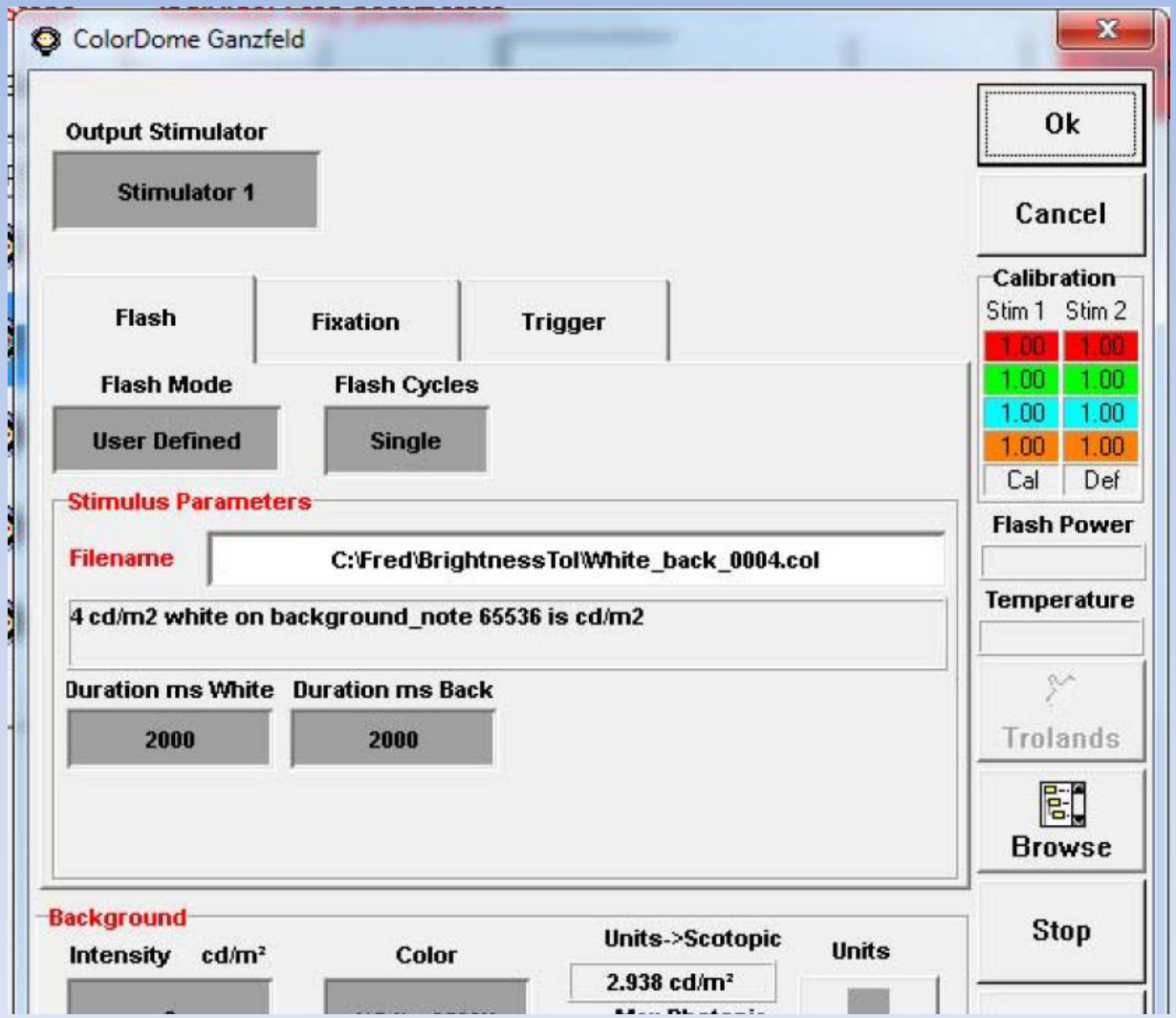
Microperimetry – assess function at particular anatomical location



Nystagmus testing on MP1S



LIGHT SENSITIVITY TESTING ON ESPION



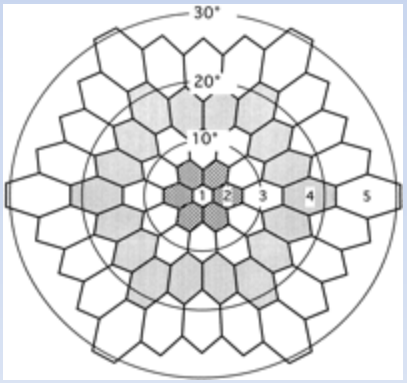
Ganzfeld Electroretinogram

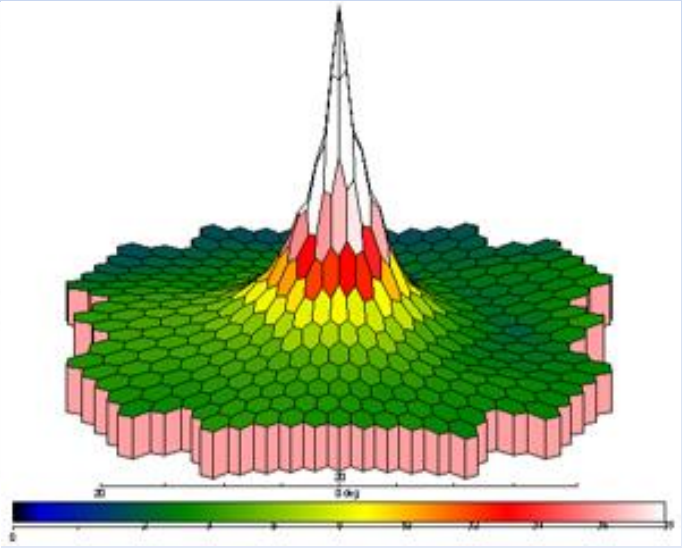
Burian-Allen contact lens electrode

DTL electrode

Multifocal ERG

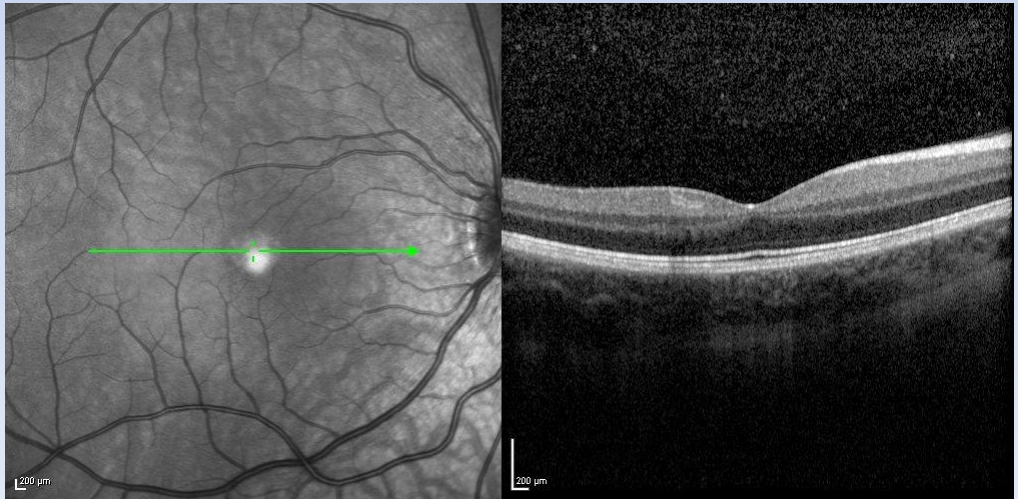
- In 1990s Dr. Sutter created program to extract hundreds focal ERGs from 1 electrical signal
- ERG activity in central 30 degrees tested
- Subject fixates on stimulus of hexagon pattern
- ERG tracings recorded



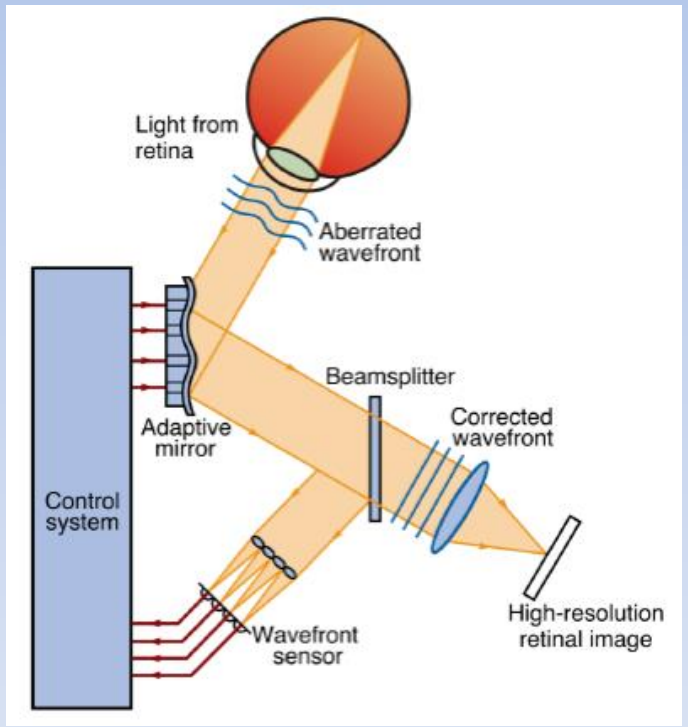


Imaging

- Spectral domain OCT

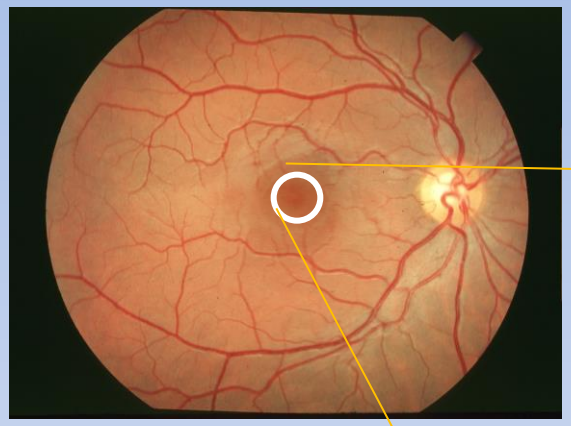


- Adaptive Optics

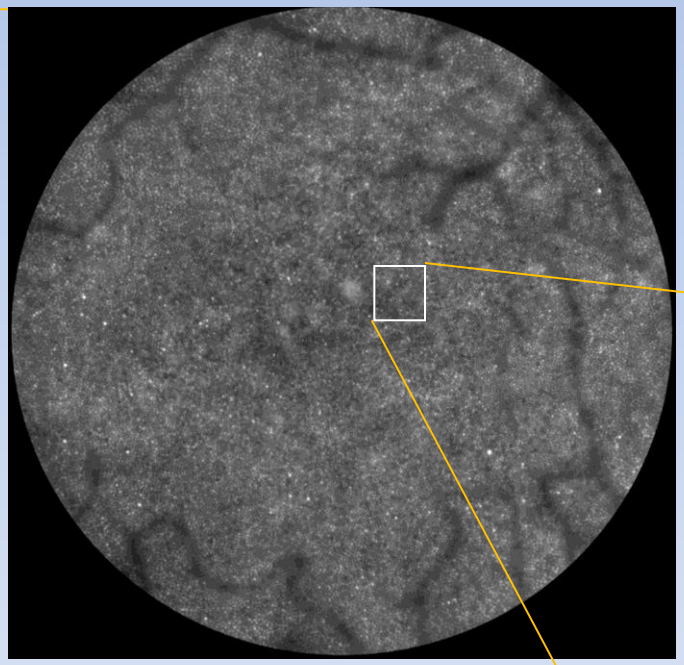


Carroll, Gray, Williams 2005

Retinal imaging with adaptive optics

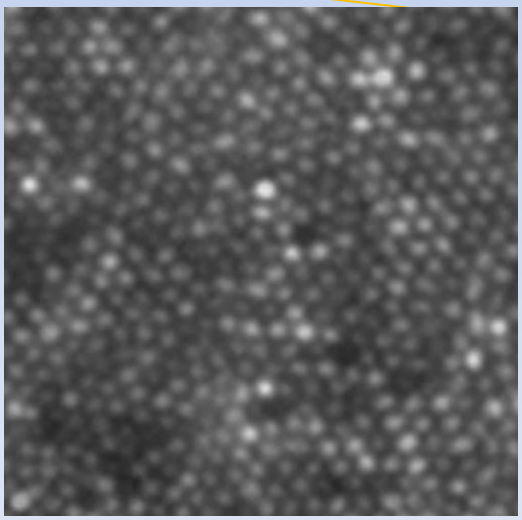


30 degrees



3 degrees

2 μm resolution



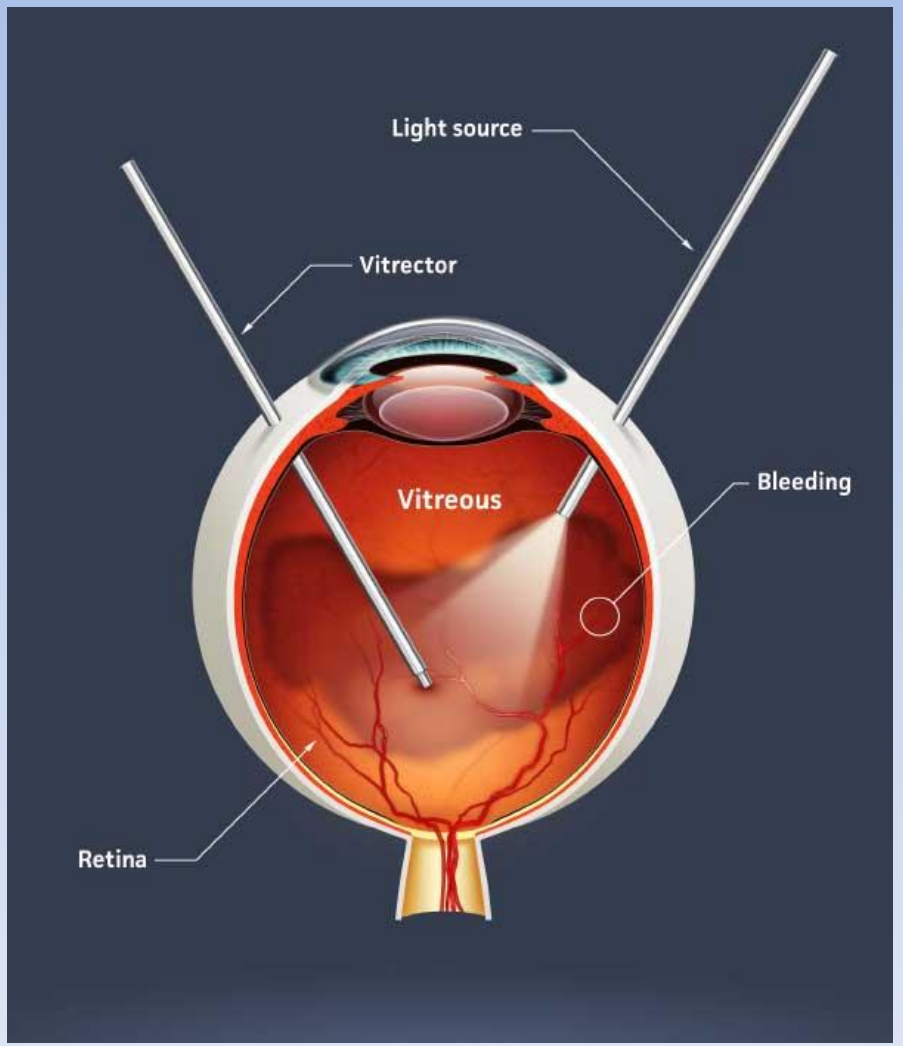
Mina Chung, University of Rochestor, Flaum Eye

Gene therapy for CNGB3 achromatopsia

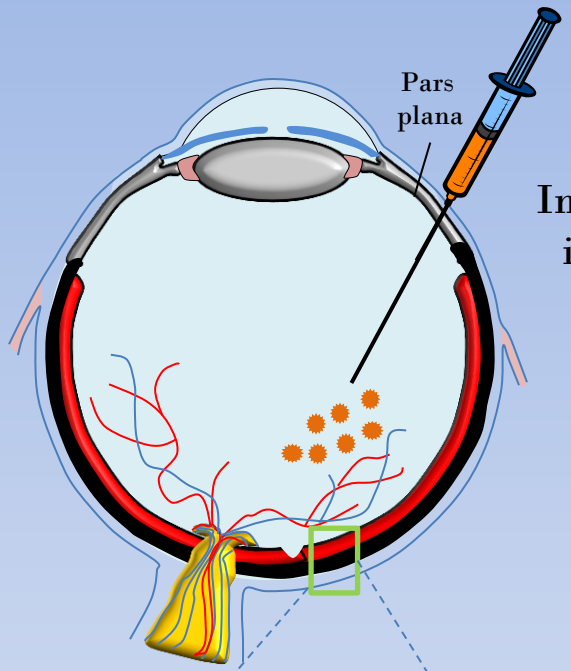
- Plan to submit IND to FDA for gene therapy trial.
- Vector being chosen/optimized for preclinical testing.

- *Shannon Boye to talk much more about Gene Therapy in next talk!*

Surgical approach for gene therapy: VITRECTOMY



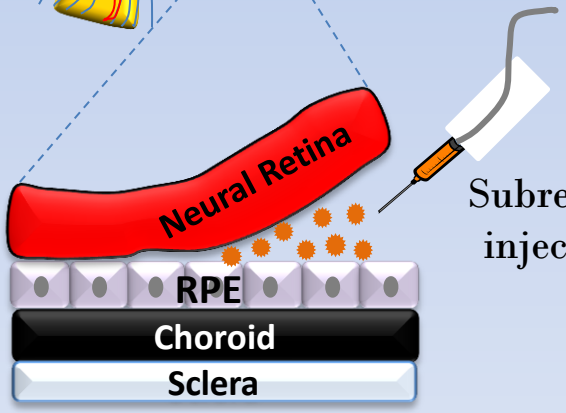
Vector delivery considerations



Intravitreal injection

Can we get the vector to the cells we intend?

Will the immune system cooperate with us?



Subretinal injection

Is injecting under the retina ("subretinal injection") causing tissue damage?

Current gene therapy clinical trials

- Phase 1 trials:
  - Choroideremia: Oxford/Moorfields, (AAV2)
  - AMD: Genzyme (AAV2-sFLT01; intravitreal)
  - Stargardt: StarGen (Lentivirus)
  - Usher 1B: UshStat (Lentivirus)

- Phase 3: FIRST PHASE 3 trial for gene therapy:
  - RPE65-LCA: Ongoing at Iowa/Penn, (AAV2)