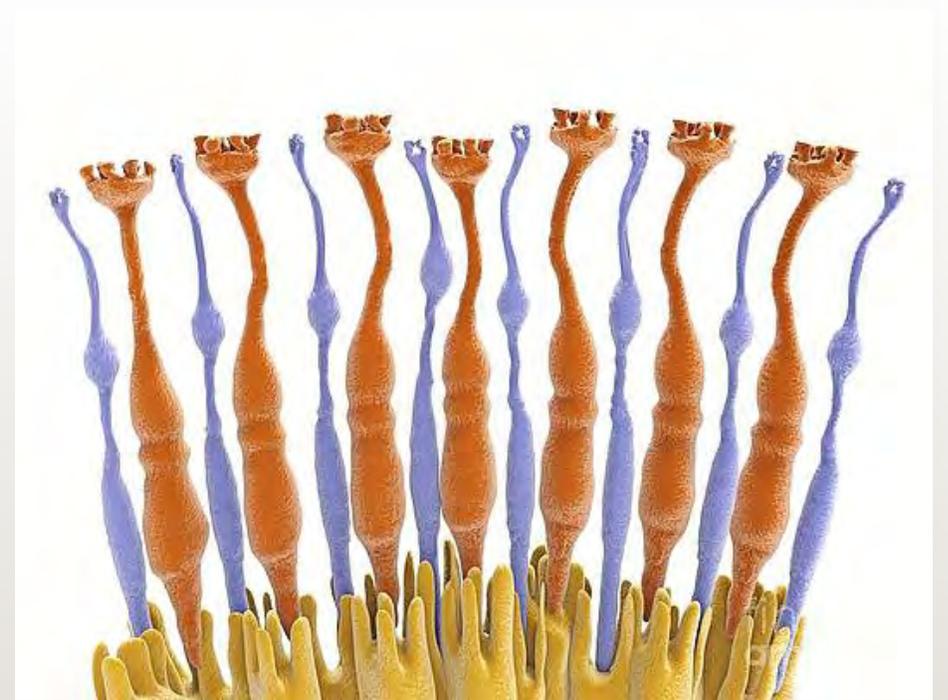


# UPDATE ON TREATMENT OPTIONS FOR DRY MACULAR DEGENERATION: CURRENT AND FUTURE

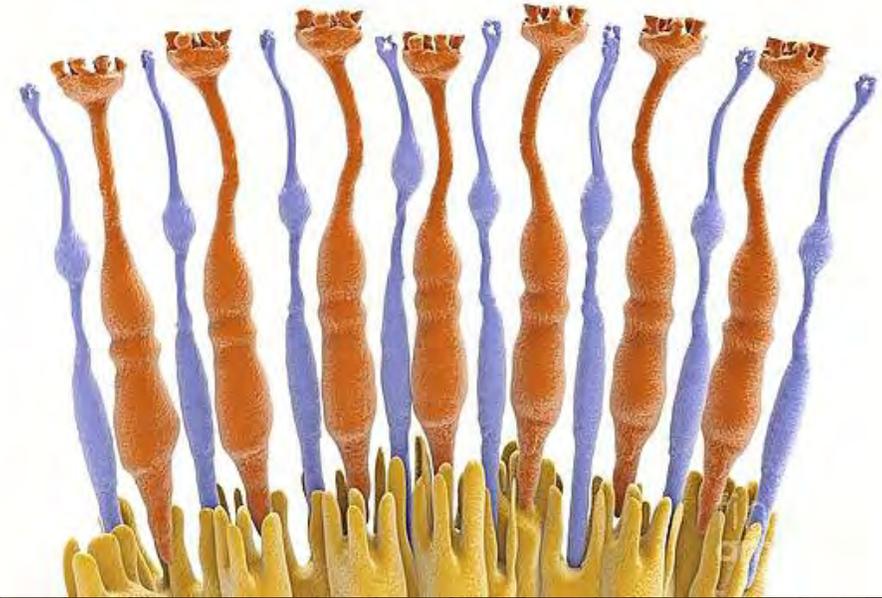
DIMITRI YELLACHICH  
VITREORETINAL SURGEON



## Age Related Macular Degeneration

- Wet AMD
- Dry AMD
- Dysregulation in the complement, lipid, angiogenic, inflammatory, and extracellular matrix pathways implicated AMD pathogenesis.
- 50 + genetic susceptibility loci (CFH and ARMS2)

0.2% of people aged 55-64  
13% of people aged over 85



*P Mitchell et al. Lancet 2018.*



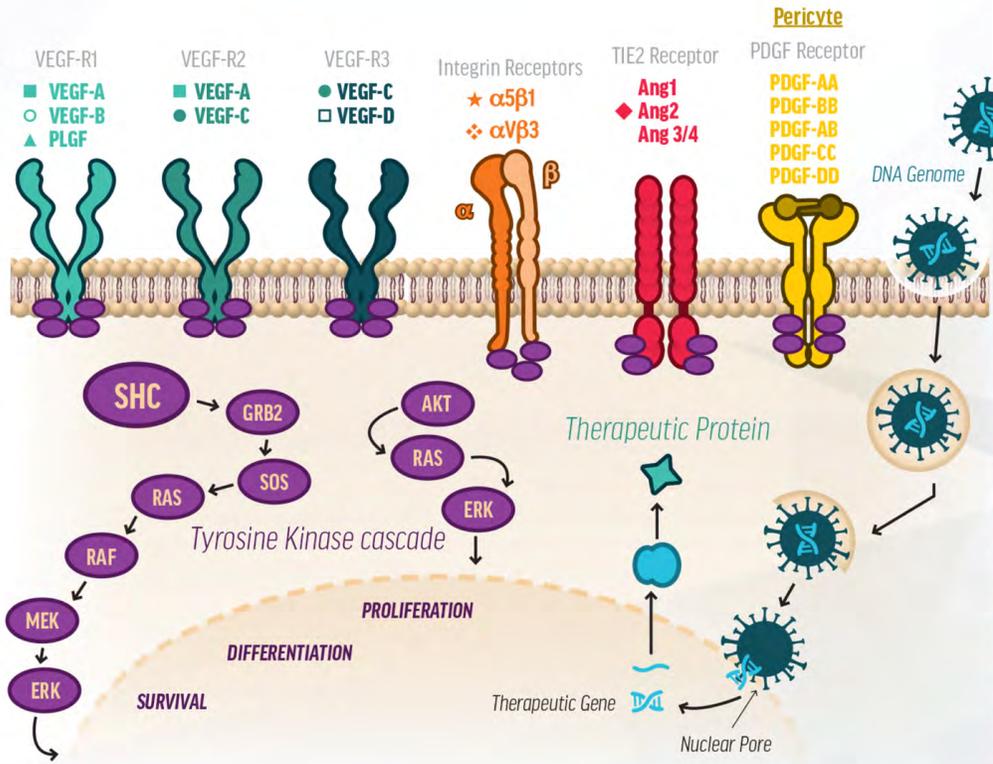
## Extracellular VEGF Pathways

| VEGF |   |  |
|------|---|--|
| PLGF | D C B A                                     |  |
| ■    | pegaptanib (Valeant) FDA-APPROVED           |  |
| ■    | ranibizumab (Genentech/Roche) FDA-APPROVED  |  |
| ■    | bevacizumab (Genentech/Roche) OFF-LABEL     |  |
| ■    | brolucizumab (Novartis) FDA-APPROVED        |  |
| ■    | abicipar pegol (Allergan)                   |  |
| ■    | KSI-301 (Kodiak Sciences)                   |  |
| ■    | FYB201 (biosimilar) (Formycon/Bioeq)        |  |
| ■    | PF582 (biosimilar) (Pfenex/Pfizer)          |  |
| ■    | razumab (biosimilar) (Iritas)               |  |
| ■    | CHS3551 (biosimilar) (Coherus Biosciences)  |  |
| ■    | SB-11 (biosimilar) (Samsung Bioepis)        |  |
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| ■    | ONS-510 (biosimilar) (Outlook Therapeutics) |  |
| ■    | Xiucane (biosimilar) (Xbrane)               |  |
| ■    | CHS3551 (biosimilar) (Coherus Biosciences)  |  |
| ■    | PD807 (biosimilar) (Biopharm)               |  |
| ■    | SBS7001 (biosimilar) (Siam Bioscience)      |  |
| ▲    | ○   | aflibercept (Regeneron/Bayer) FDA-APPROVED |
| ▲    | ○   | conbercept (Kanghong Biotech)              |
| ▲    | ○   | CHS-202 (biosimilar) (Coherus Biosciences) |
| ▲    | ○   | SOK583A1 (biosimilar) (Sandoz/Hexal)       |
| ▲    | ○   | MYL1710 (biosimilar) (Mylan/Momenta)       |
| ▲    | ○   | ALT-L9 (biosimilar) (Alteogen)             |
| □    | ●   | OPT-302 (Opthea)                           |

# Wet AMD Treatments

## Four agents currently available

### Over 40 in the pipeline



## Tyrosine Kinase inhibitor (TKi) Pathways

- OTX-TKi (Ocular Therapeutix)
- RTKi-MPP (Kala)
- GB-102 (Graybug)
- PAN 90806 (Panoptica)
- SK 1011 (Sanwa Kagaku)
- sutent (x-B2) (Tyrogenex)
- axitinib (Clearside Biomedical)
- AR-13503 (Aerie Pharmaceuticals)
- Caveolin subdomain downstream inhibitor
- CVX-51401 (CovtheRx)

## TIE2 Activation Pathways

- ◆ faricimab (Genentech/Roche)
- ◆ AXT107 (AsclepiX Therapeutics)

## Integrin Pathways

- |     |                             |                                  |
|-----|-----------------------------|----------------------------------|
| PAN | risuteganib (Allegra/Senju) | ★ volociximab (IVERIC bio)       |
|     | THR-687 (Oxurion)           | ◆ SF0166 drop (SciFluor)         |
|     |                             | ◆ AXT107 (AsclepiX Therapeutics) |

### Gene Therapy

- RGX-314 (RegenxBio)
- ▲ ○ ADVM-022 (Adverum)
- HMR59 (Hemera)

### Extended Duration Options

**Clearside Suprachoroidal Injection**  
axitinib (Clearside Biomedical)  
RGX-314 (RegenxBio)

**ranibizumab Port Delivery System (PDS)**  
Genentech

**Polymer Extended Release:**  
OTX-TKi (Ocular Therapeutix)  
GB-102 (Graybug Vision)  
KSI-301 (Kodiak Sciences)  
AR-13503 (Aerie Pharmaceuticals)

- Ranibizumab (Lucentis)
  - Aflibercept (Eylea)
  - Bevacizumab (Avastin)
  - Brolucizumab (Beovu!!!!)
- Phase 3
- DARPin abicipar pegol
  - Faricimab
  - Port Delivery System



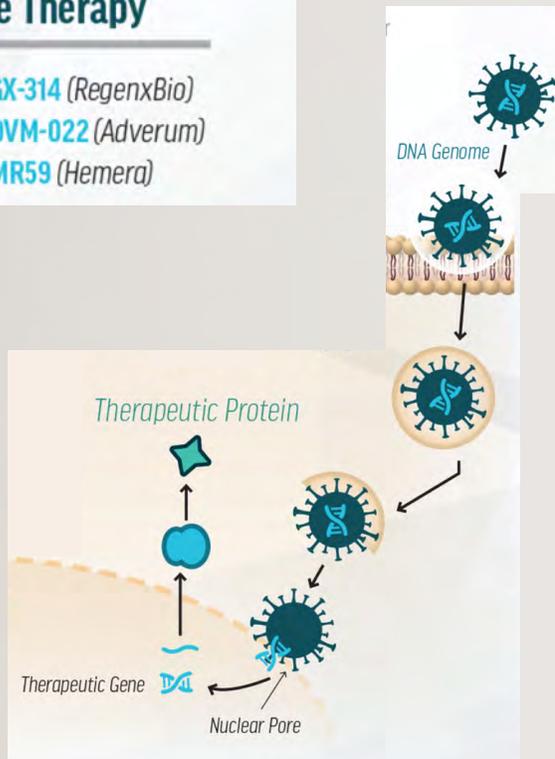
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- Phase 3 Port Delivery System



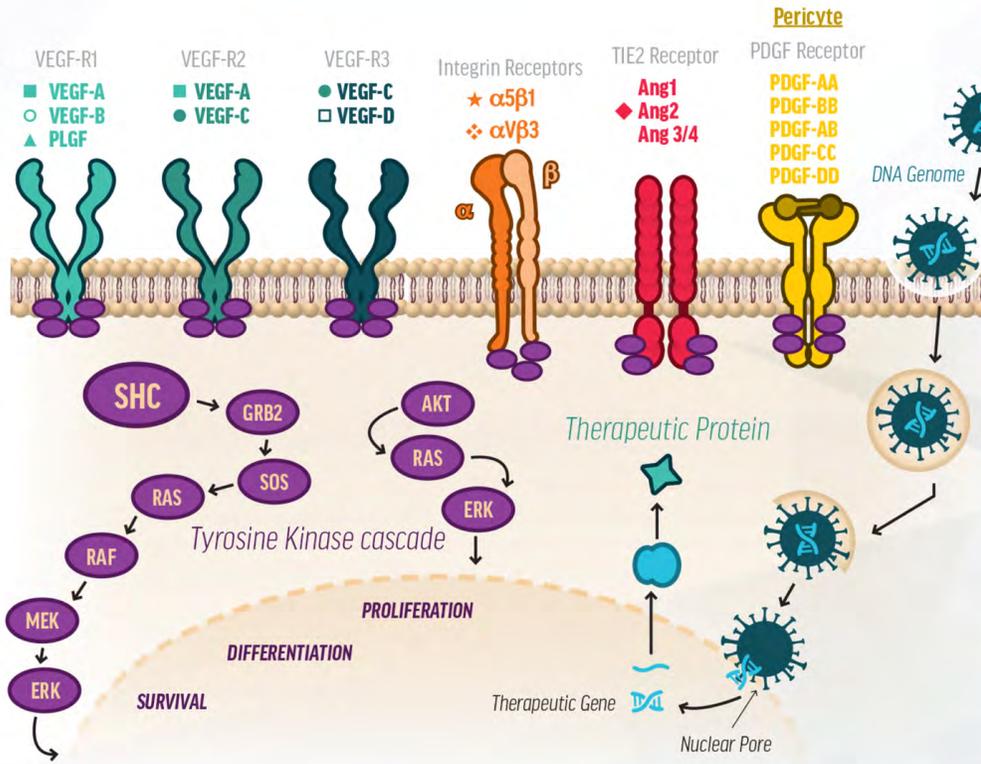
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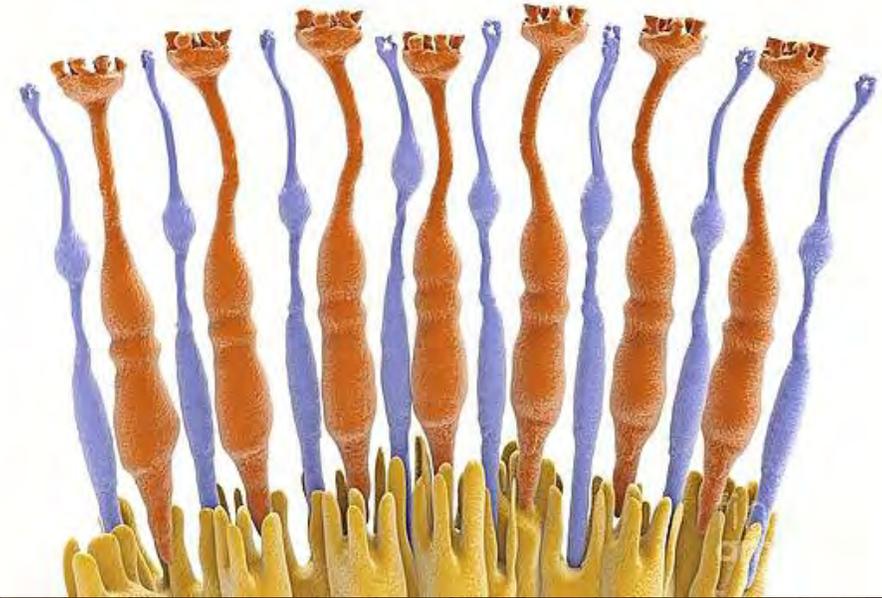
## Brolucizumab

- Rozimab
- RoziVu
- BuellerVu
- BlabZu
- MabMyVu



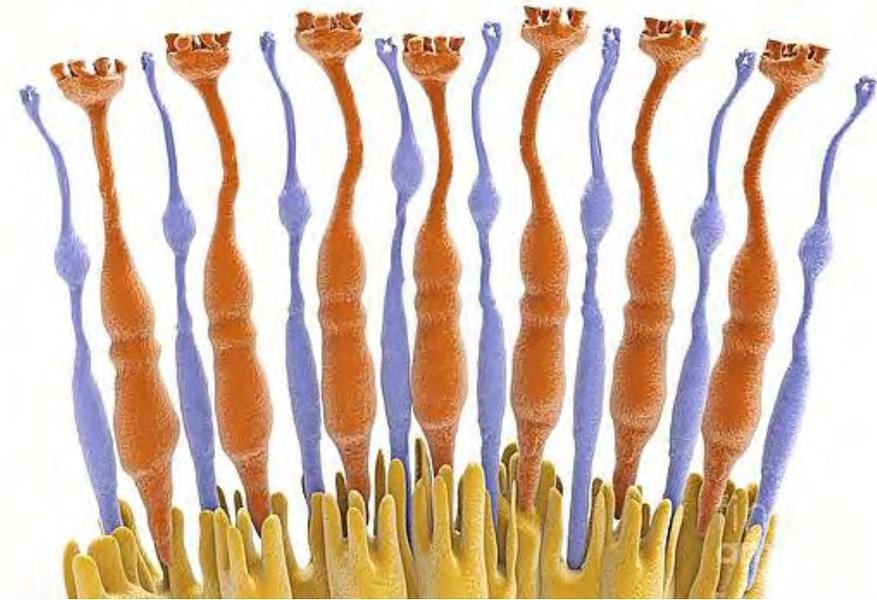
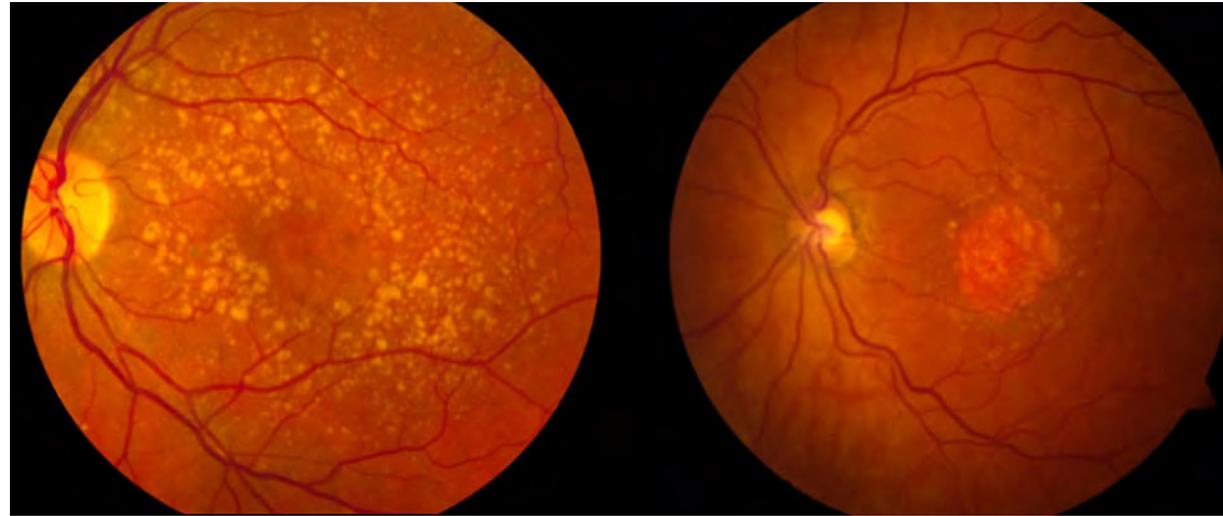
## Dry AMD Treatments

- Optical options
- Digital/Augmented Reality options
- Biological options
  - laser therapy
- Bionic Eye/Optogenetic
- Dietary/Environmental
  - Smoking
  - high-dose zinc and antioxidant vitamin supplements



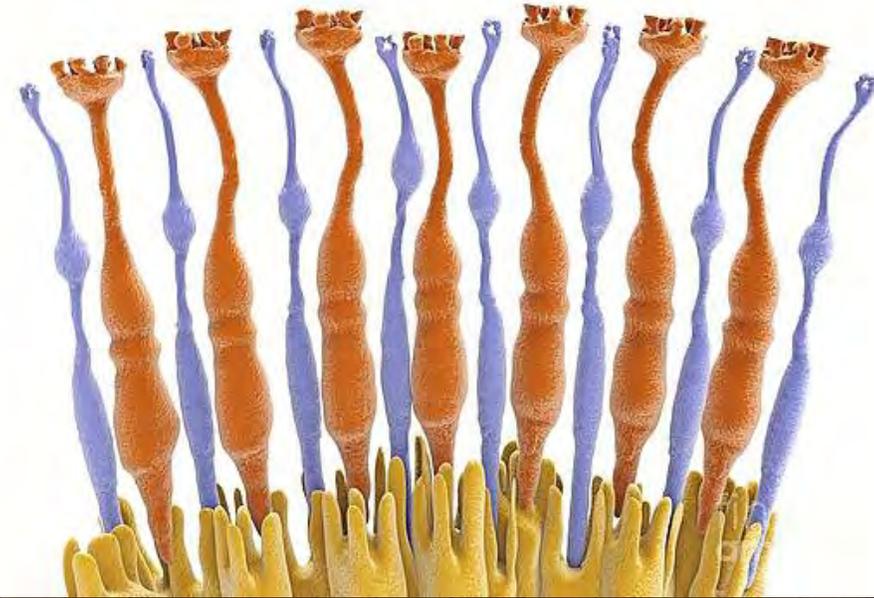
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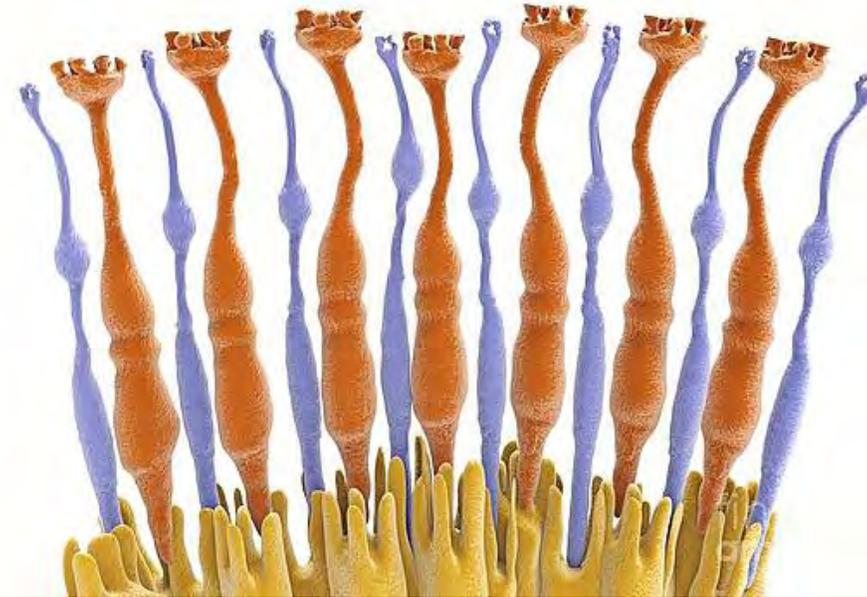
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## Dry AMD Treatments

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- Digital/Augmented Reality options
- **Biological options**
  - Cellular regeneration
- Bionic Eye/Optogenetic
- Dietary/Environmental
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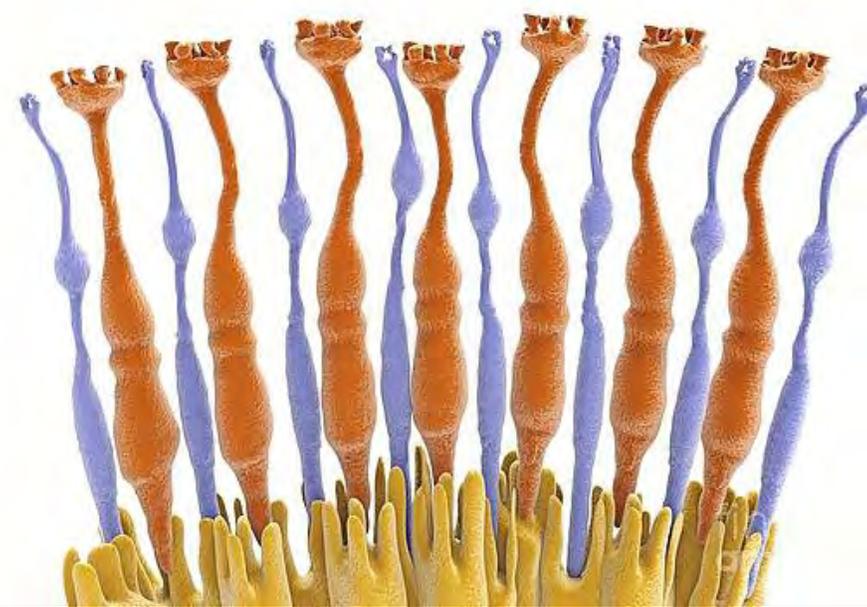
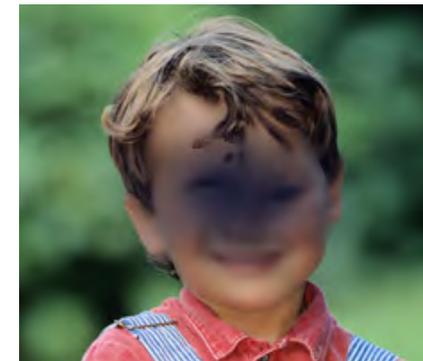


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- Biological options
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- Wet AMD
- Dry AMD

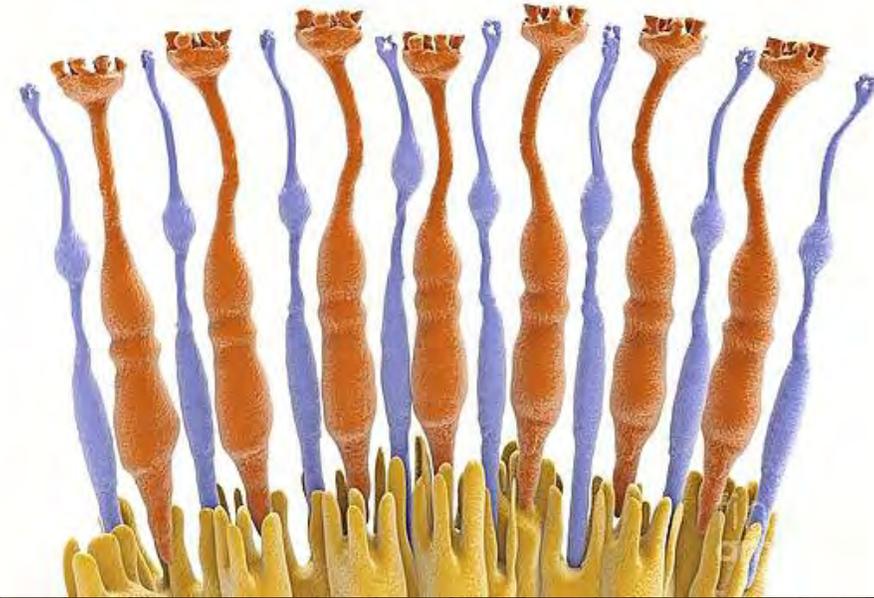


## AMD Treatments

## Neovascular Therapy

- Optical options
- Digital/Augmented Reality options
- Biological options
  - laser therapy
  - Cellular regeneration
- Bionic Eye/Optogenetic
- Dietary/Environmental
  - Smoking
  - high-dose zinc and antioxidant vitamin supplements

- Wet AMD
- Dry AMD



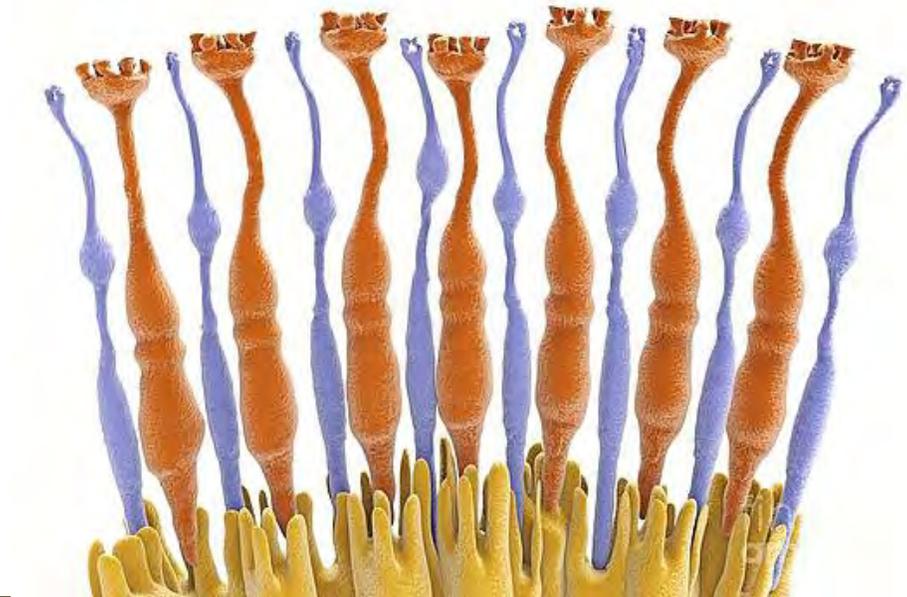
## Dry AMD Treatments

- Optical options
  - Low vision aids
  - Implantable miniature telescopes
- Digital/Augmented Reality options
- Biological options
  - laser therapy
- Bionic Eye/Optogenetic
- Dietary/Environmental



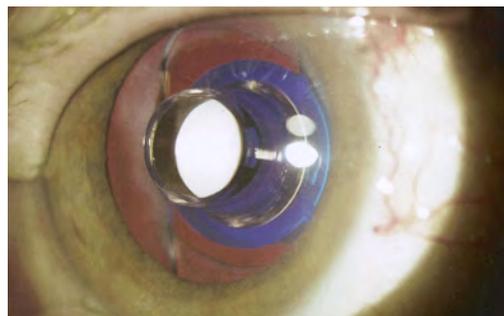
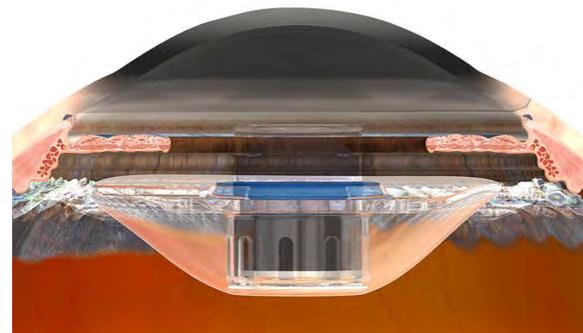
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- Optical options
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  - Implantable miniature telescopes
- Digital/Augmented Reality options
- Biological options
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- Dietary/Environmental



## Optical options

- Implantable miniature telescope (IMT)
  - Over 1000 papers on IMT
    - No RCT or quasi-RCT
      - One ongoing RCT
  - Magnification 2.2X, 3.0X
  - Monocular implantation
    - Peripheral vision lost in implanted eye
    - Patient preference to determine eye
  - Long term results limited
  - Uptake very low
  - More complex surgery and non reversible

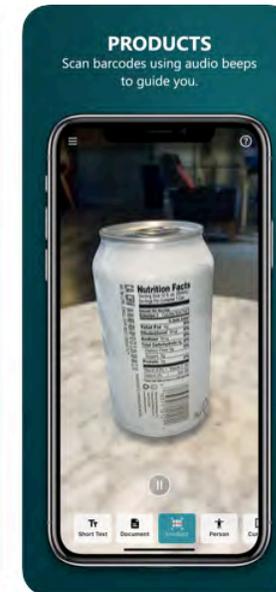


## Dry AMD Treatments

- Optical options
- Digital/Augmented Reality options
- Biological options
  - laser therapy
- Bionic Eye/Optogenetic



**Seeing AI** 4+  
Talking Camera for the Blind  
Microsoft Corporation  
★★★★★ 4.1, 36 Ratings  
Free



## Digital/Augmented Reality options

- Digital magnification up to 14X
- Contrast/colour enhancement
- Augmented reality overlay
- Text to speech
- Object/face recognition
- Price \$3000-6000



MyEye2: Orcam



NuEye Pro



AceSight



eSight



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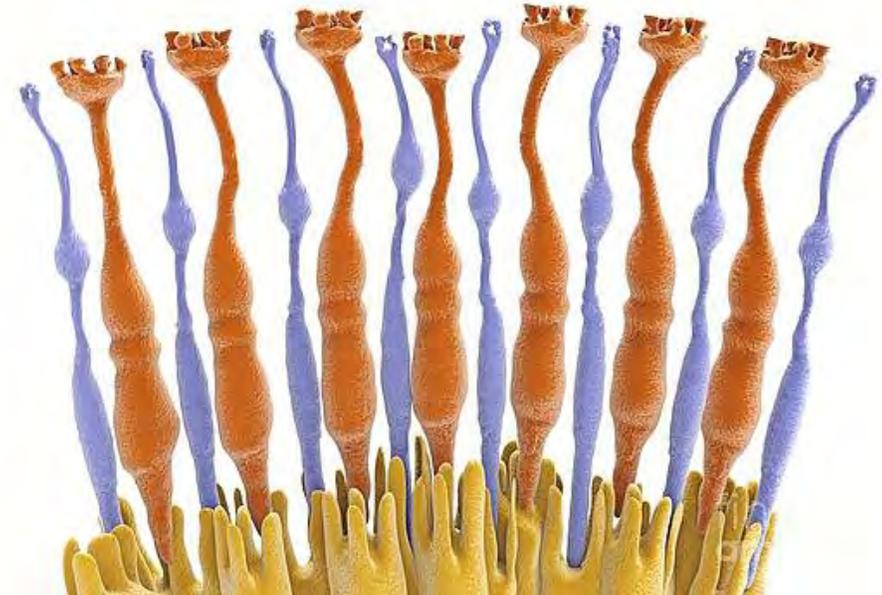


## Dry AMD Treatments

- Optical options
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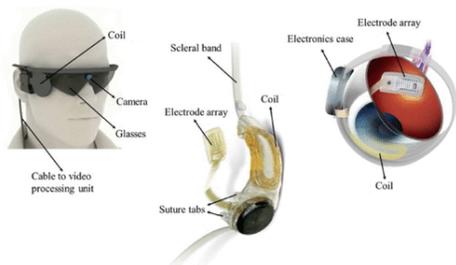
## Cortical Implants

- **Dobelle WH implanted various temporary designs in a series of experiments between 1970 and 1974**
- **In 1978 implanted a prototype still functioning in a now 62 year old man blind from trauma**

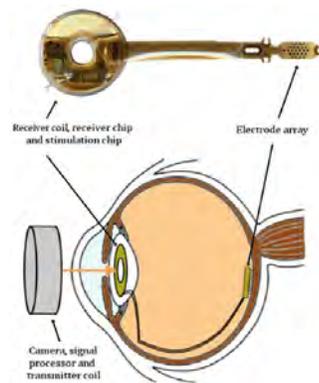


# Dry AMD Treatments

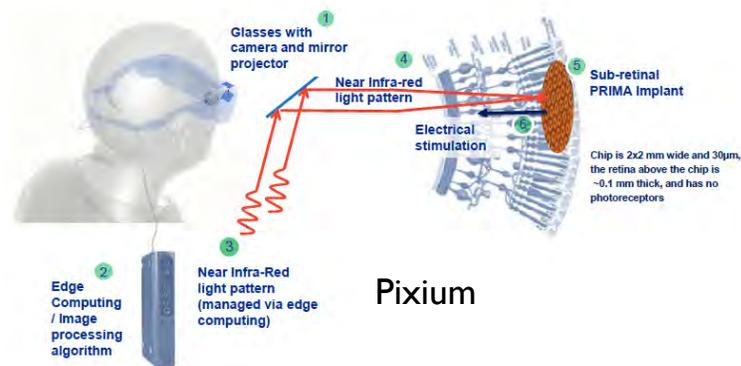
- Bionic Eye



Argus II



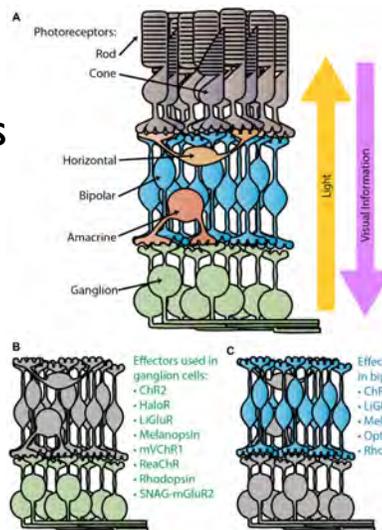
Epi-Ret III



Pixium

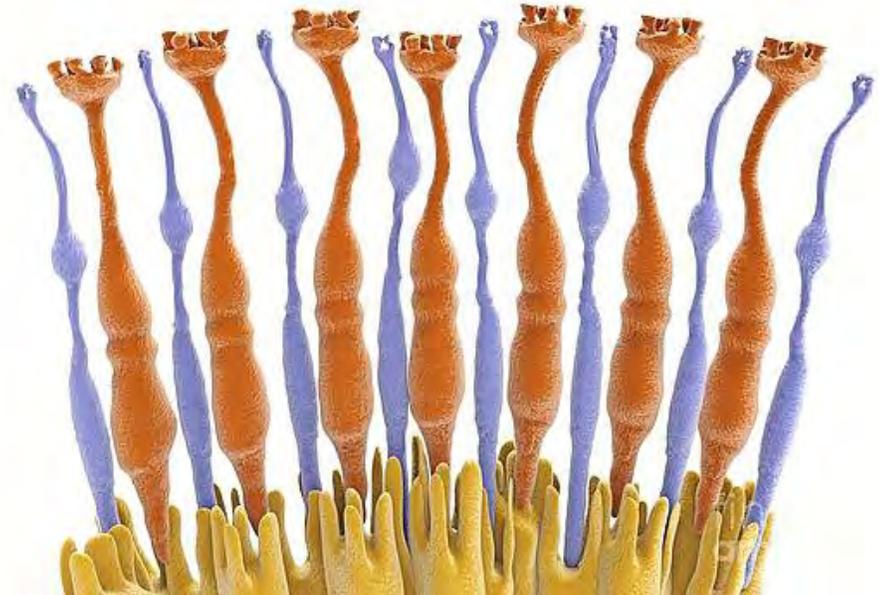
- Optogenetic

- bestowing light sensitivity to non-photoreceptor retinal cells



## Dry AMD Treatments

- Optical options
- Digital/Augmented Reality options
- **Biological options**
  - laser therapy



# Dry AMD Treatments

- Biological options

## 1 Neuroprotection

Repair mitochondrial dysfunction/ oxidative stress  
**elamipretide** (Stealth)  
**risuteganib** (Allegro)  
**photobiomodulation** (LumiThera)  
**brimonidine tartrate** (Allergan)

**FAILED**  
**NT-501 - ciliary neurotrophic factor** (Neurotech)  
**tandospirone** (Alcon)  
**OT-551** (Othera)

## 2 Reduce toxic by-product accumulation

Prevents Amyloid A $\beta$  oligomer assembly  
**GAL-101** (Galimedix)    **ALZ-801** (Alzheon)  
 Reduce DHA peroxidation  
**RT011** (Retrotape)

**FAILED**  
**Glatiramer acetate** (Copaxone, FDA approved, Teva)  
**RN6G** (Pfizer)  
**GSK933776** (GSK)

## 3 Visual cycle modulation

**ALK-001** (Alkeus)

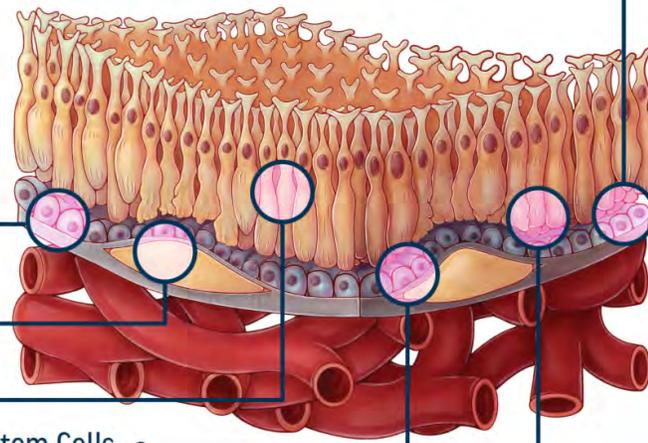
**FAILED**  
**fenretinide** (Sytera)  
**emixustat** (Acucela)  
**OT-551** (Othera)

## 4 Stem Cells

**Human embryonic stem cells (hESCs)**  
 (Lineage Cell Therapeutics)  
 (Regenerative Patch Technologies)  
**Umbilical stem cells (hUTCs)**  
**Human retinal progenitor cells** (iCyte)

## 6 Other approaches

**Inflammasome Inhibition**  
**kamuvudine** (Inflammasome Therapeutics)    **Xiflam** (OcuNexus)  
**Matrix Modulation**  
**doxycycline** (Oracea)    **HtrA1 inhibitor**  
**FHR2163** (Genentech/Roche)



- Chemotactic or anaphylactic peptides
- Convertases
- Alternative pathway
- Lectin pathway
- Classical pathways
- MAC proteins

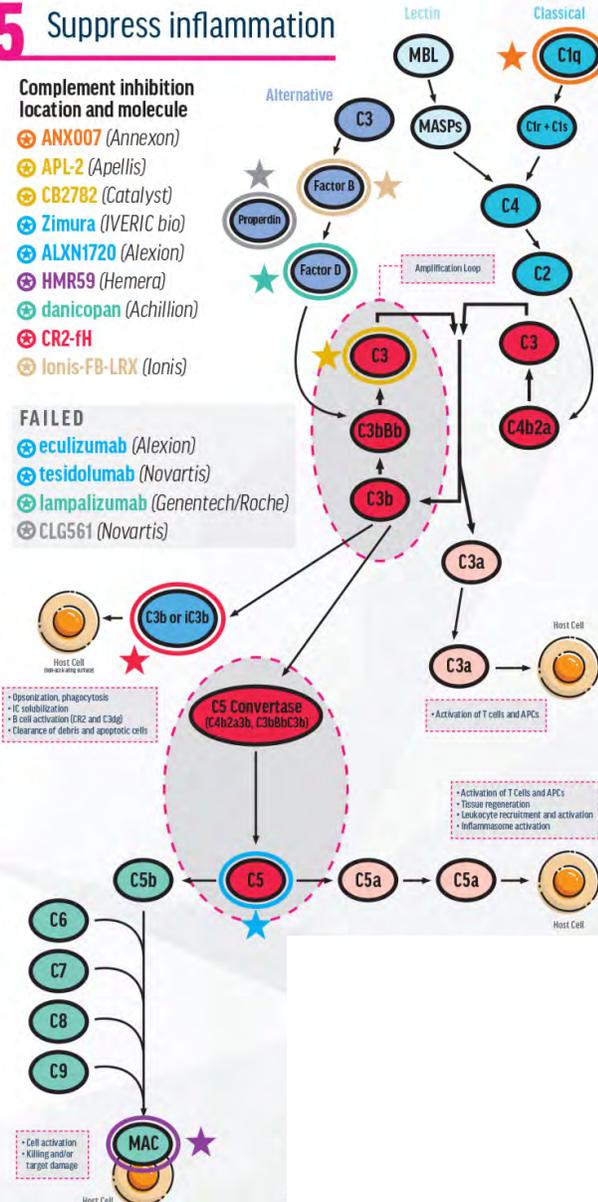
## 5 Suppress inflammation

### Complement inhibition location and molecule

- ANX007** (Annexon)
- APL-2** (Apellis)
- CB2782** (Catalyst)
- Zimura** (IVERIC bio)
- ALXN1720** (Alexion)
- HMR59** (Hemera)
- danicopan** (Achillion)
- CR2-FH**
- Ionis-FB-LRX** (Ionis)

### FAILED

- eculizumab** (Alexion)
- tesidolumab** (Novartis)
- lampalizumab** (Genentech/Roche)
- CLG561** (Novartis)



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**OT-551** (*Othera*)

Being trialed in mitochondrial diseases.  
Promotes mitochondrial function





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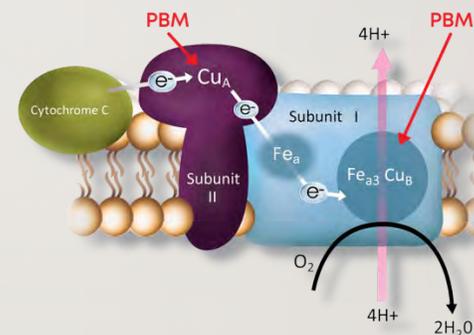
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Photomodulation 670nm light



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Currently running Phase III trial  
for Mac Tel



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**RN6G** (*Pfizer*)

**GSK933776** (*GSK*)

Decrease retinal amyloid and complement (C3) on photoreceptors and outer retinal layers



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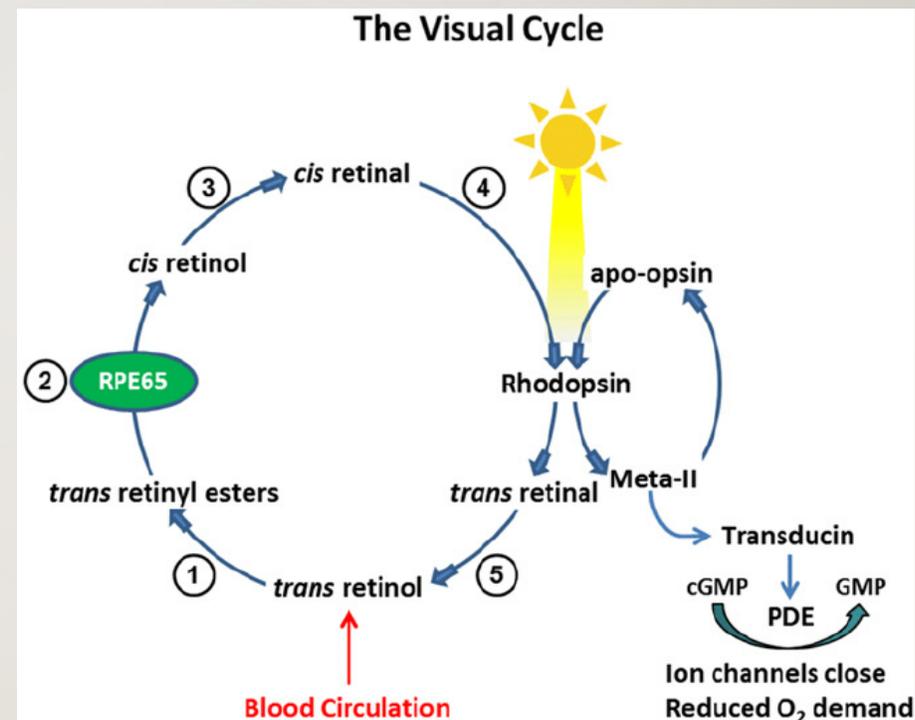
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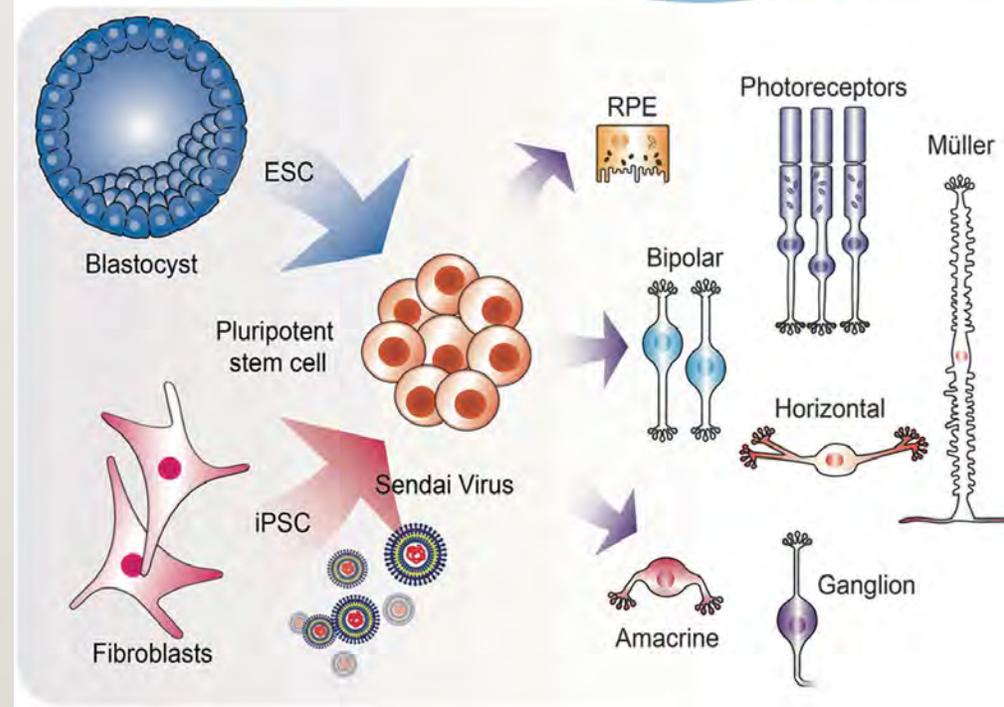
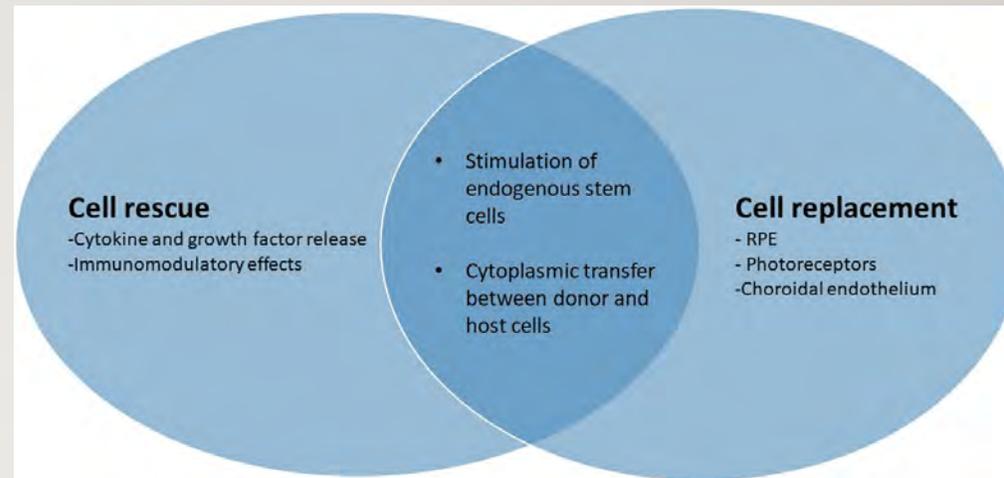
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- indefinite self-renewal ability
- capacity to give rise to any adult somatic cell type

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Chichagova et al. Eye 2018.



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# Dry AMD Treatments

## 4 Stem Cells

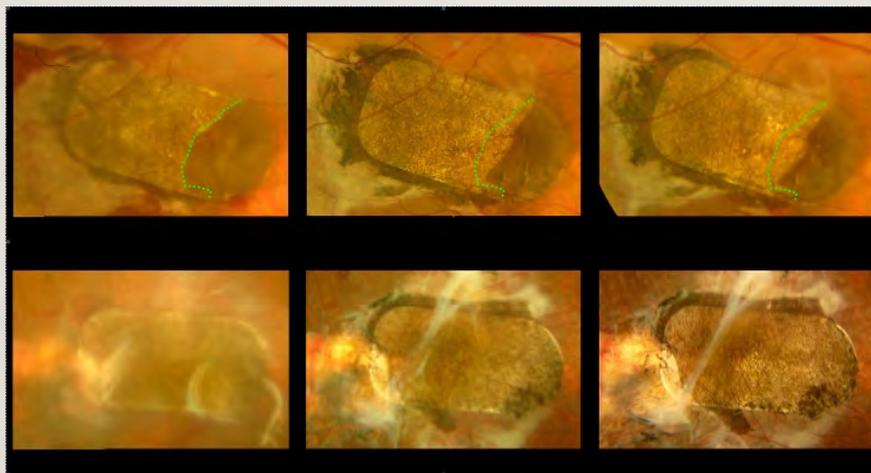
- indefinite self-renewal ability
- capacity to give rise to any adult somatic cell type

**Human embryonic stem cells (hESCs)**

*(Lineage Cell Therapeutics)  
(Regenerative Patch Technologies)*

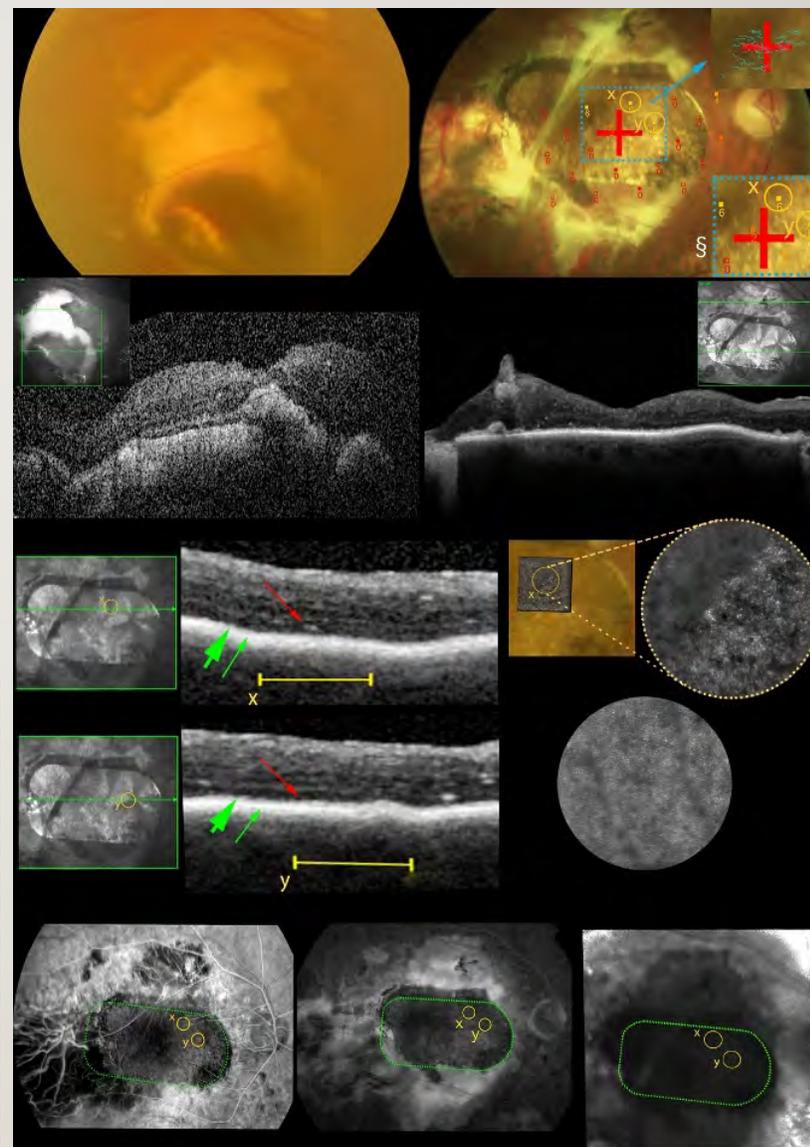
**Umbilical stem cells (hUTCs)**

**Human retinal progenitor cells (iCyte)**



Da Cruz et al. Nat Biotech 2016.

hESC-RPE monolayer on a synthetic basement membrane and delivering the patch into the subretinal space (zero age old cells)



# Dry AMD Treatments

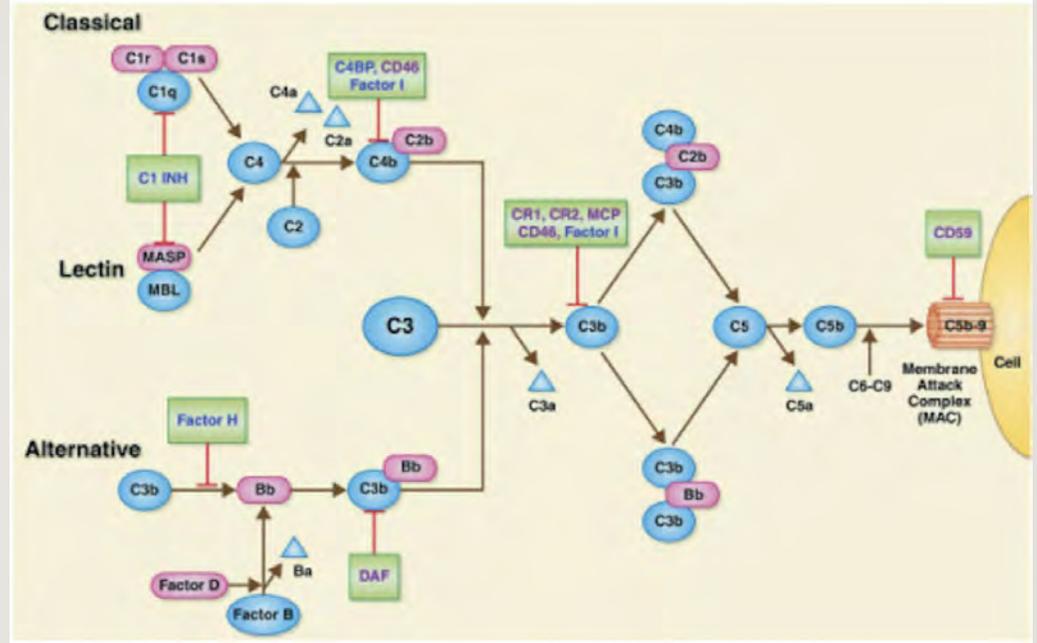
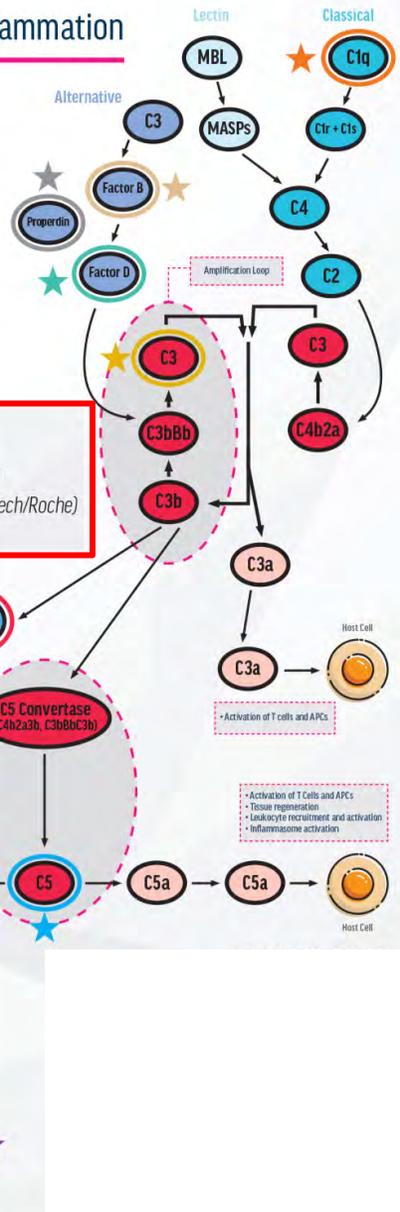
## 5 Suppress inflammation

### Complement inhibition location and molecule

- ⊕ ANX007 (Annxon)
- ⊕ APL-2 (Apellis)
- ⊕ CB2782 (Catalyst)
- ⊕ Zimura (IVERIC bio)
- ⊕ ALXN1720 (Alexion)
- ⊕ HMR59 (Hemera)
- ⊕ danicopan (Achillion)
- ⊕ CR2-FH
- ⊕ Ionis-FB-LRX (Ionis)

### FAILED

- ⊕ eculizumab (Alexion)
- ⊕ tesidolumab (Novartis)
- ⊕ lampalizumab (Genentech/Roche)
- ⊕ CLG561 (Novartis)



Dimitri Yellachich  
Vitreoretinal Surgeon



## Dry AMD Treatments

- Optical options
- Digital/Augmented Reality options
- Biological options
  - laser therapy





# Characteristics of 2RT<sup>®</sup> Retinal Rejuvenation

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Laser energy is confined to the RPE cell by targeting intracellular organelle melanosome.

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Creates microbubbles within the RPE cell which causes intracellular cavitation without collateral damage to surrounding cells.

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Non-thermal.

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532nm wavelength nanosecond laser pulse – completely different laser tissue interaction than retinal photocoagulation.

Roider J. *et al.* Response of the retinal pigment epithelium to selective photocoagulation. *Arch Ophthalmol.* 110:1786–1792 (1992).  
Roider J. *et al.* Therapeutical range of repetitive ns laser exposures in selective RPE photocoagulation. *Graefes Arch Clin Exp Ophthalmol.* 236:213–219 (1998).  
Brinkmann R. *et al.* Subthreshold (retinal pigment epithelium) photocoagulation in macular diseases; a pilot study *Lasers Surg. Med.* 27:451-464 (2000)

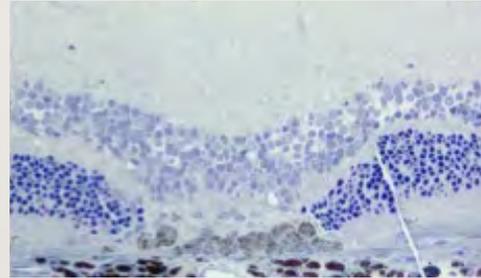
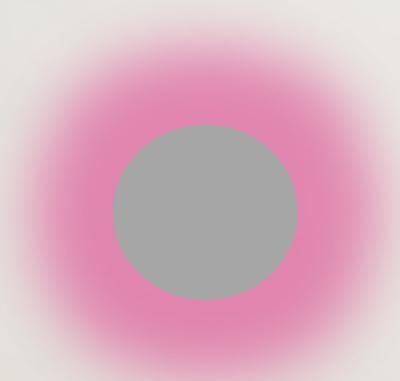
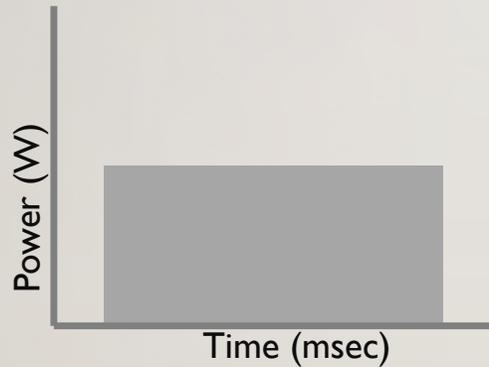
Dimitri Yellachich  
Vitreoretinal Surgeon





# 2RT<sup>®</sup> – A NOVEL LASER PROFILE

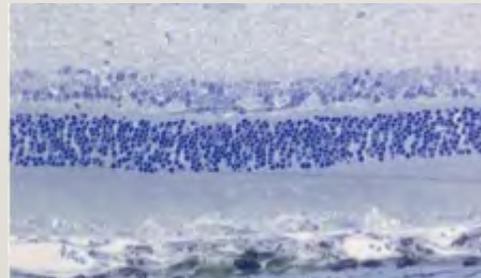
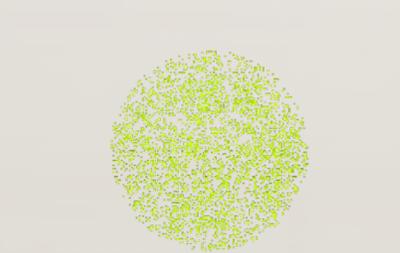
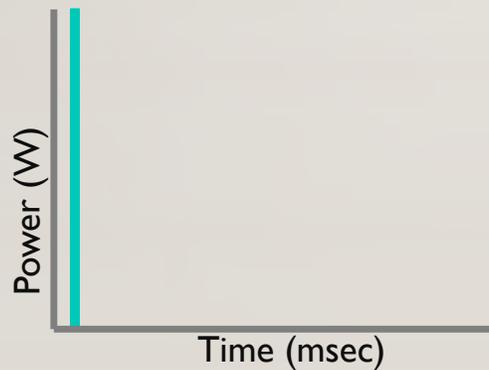
CW thermal photocoagulation has an extremely long duration and extremely high thermal exposure.



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## CW thermal photocoagulator

Destruction of the photoreceptor layer and collateral damage resulting from thermal laser exposure.



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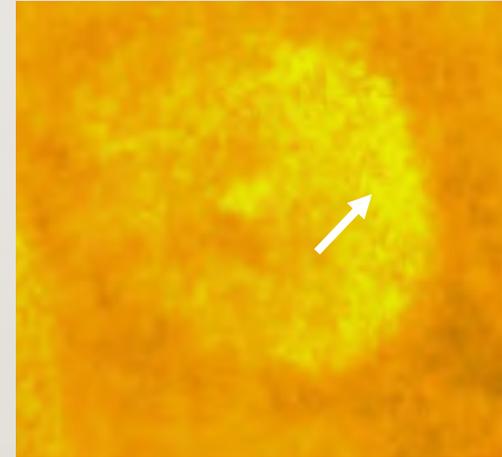
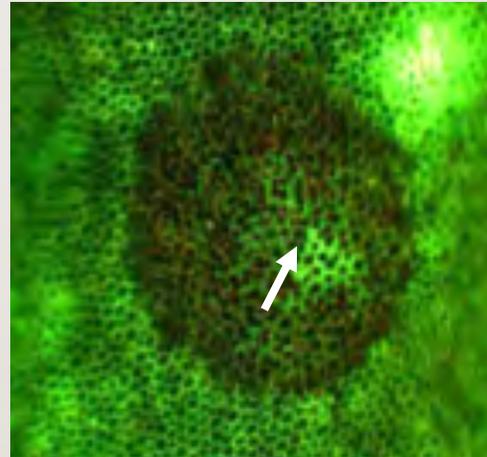
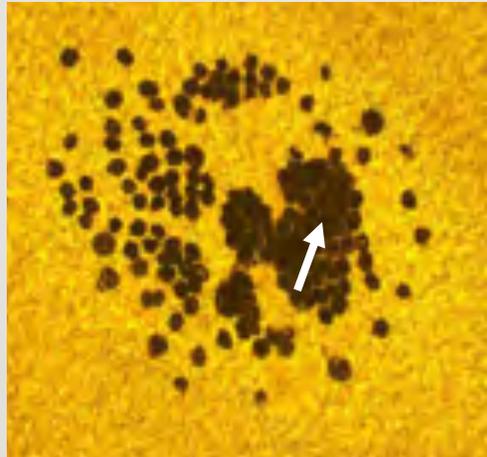
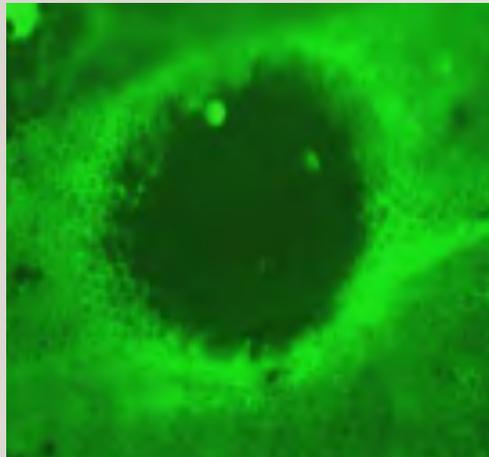
## 2RT<sup>®</sup>

Preservation of the photoreceptor layer at the clinical dose (0.3 mJ).



# 2RT<sup>®</sup> DOES NOT CAUSE THERMAL DAMAGE

2RT<sup>®</sup> selectively targets the RPE without resulting in the thermal damage inherent of conventional CW thermal photocoagulation.



## Photocoagulation

Porcine RPE

RPE cells are 'welded' onto neuroretina, with blanching point (visible effect threshold 13.0 mJ). Damage to sensory retina is apparent and as dose is increased, area of damage expands.

## Photocoagulation

Apposed neuroretina

## 2RT<sup>®</sup>

Porcine RPE

No ablation of surrounding RPE cells with no damage to photoreceptors. Blanching point (visible effect threshold 16.0 mJ) used as energy reference for clinical dose then stepped back

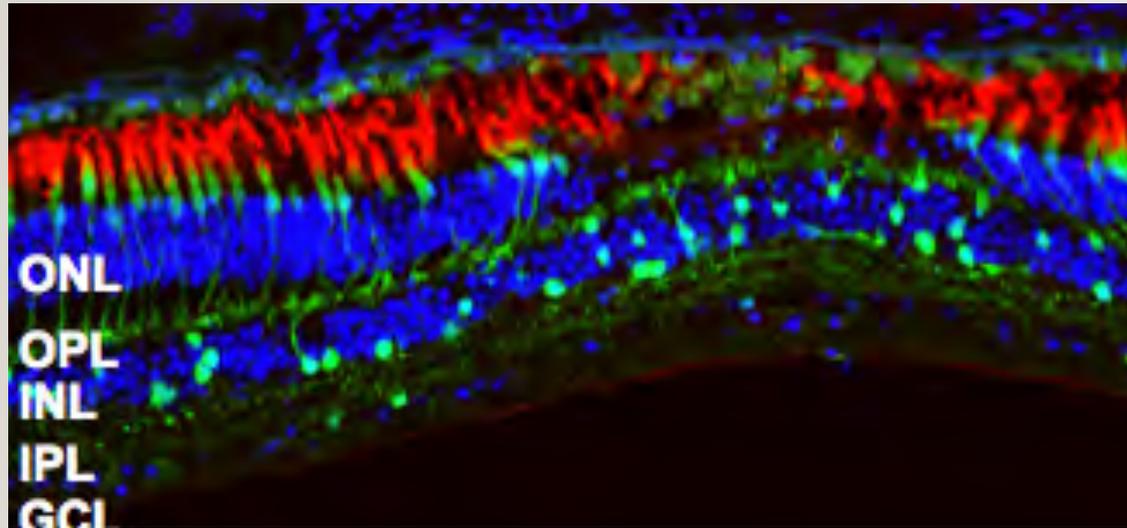
## 2RT<sup>®</sup>

Apposed neuroretina

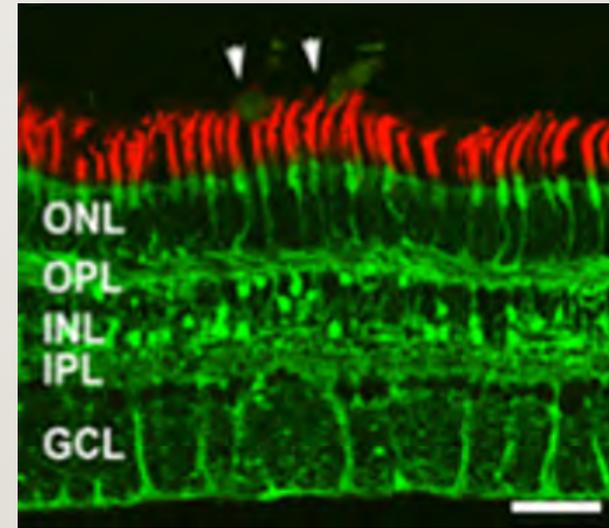


# RETINA INTEGRITY AFTER 2RT<sup>®</sup>

Transverse histology subsequent to thermal CW laser in human eye demonstrates destruction of the sensory layer overlying the RPE. In contrast, the integrity of the outer and inner retina remains intact following treatment with 2RT<sup>®</sup>.



CW thermal photocoagulation



2RT<sup>®</sup> at clinical dose (0.3 mJ)

# What is a nanosecond pulse?

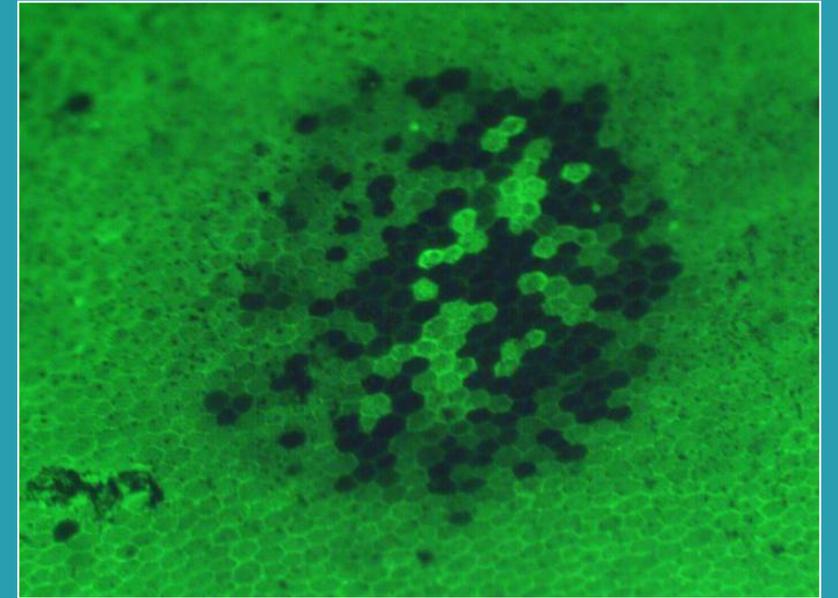
The nanosecond pulse enables it to achieve the desired therapeutic effect without causing collateral damage.

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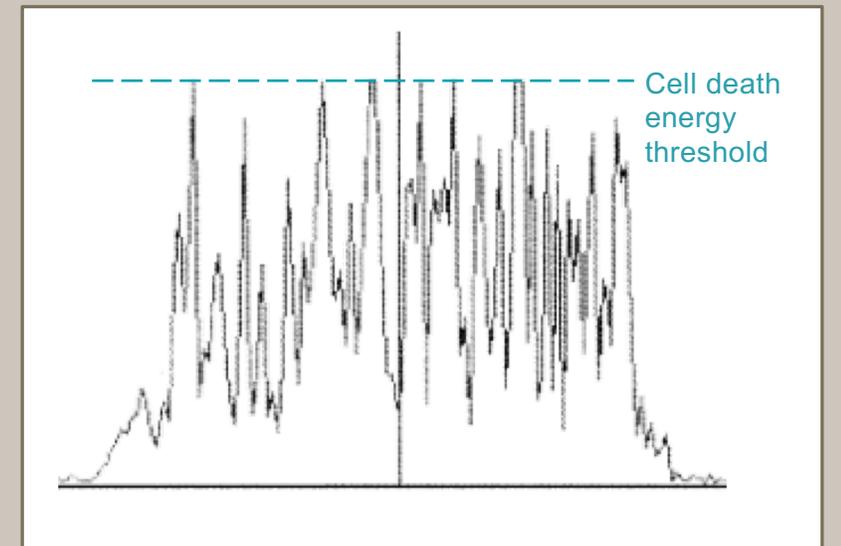
Only 10-40% of cells in the spot are randomly raised above damage threshold, causing them to degenerate.

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2RT<sup>®</sup> at 36mJ/cm<sup>2</sup>  
to ablate selective  
individual RPE cells.

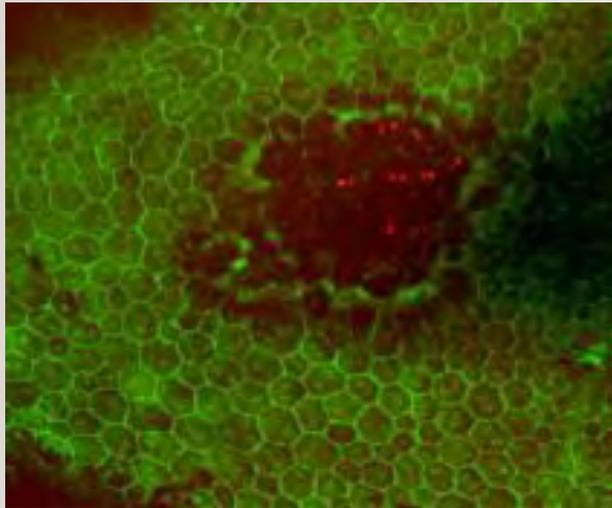


2RT<sup>®</sup> energy beam  
profile – a very  
specific proportion  
of RPE cells are  
subject to apoptotic  
energy threshold.



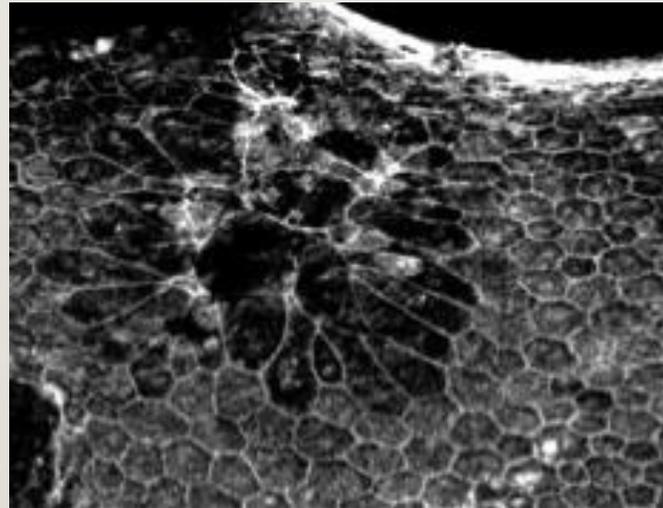
# 2RT<sup>®</sup> WOUND HEALING MECHANISM

wound healing mechanism without necrosis or injury. Live mouse cells



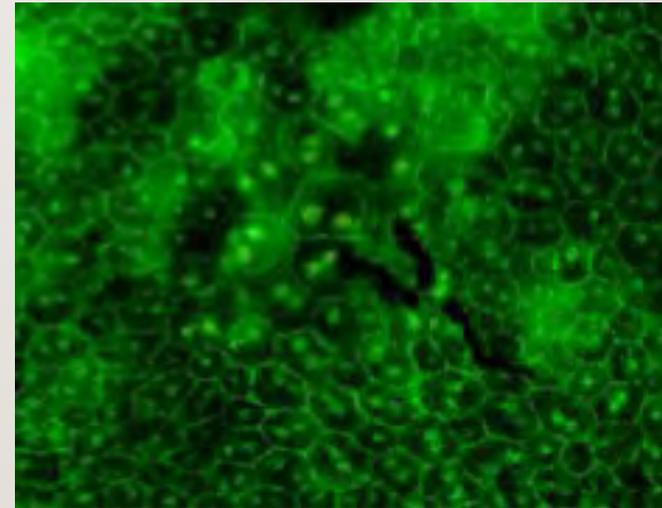
**5 hours post-treatment**

Selective cell death (TUNEL labelling-red) is noted.



**7 days post-treatment**

Increase in cell volume is clearly visible.



**1 month post-treatment**

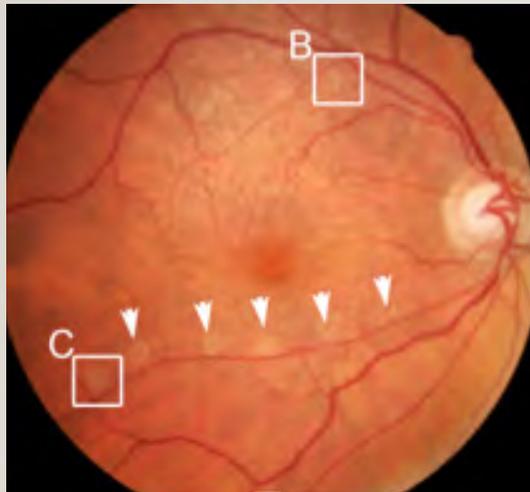
Almost complete healing of the RPE.



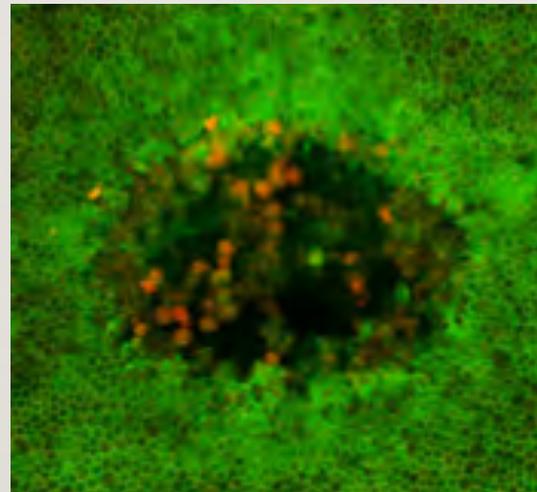
# 2RT<sup>®</sup> wound healing mechanism

2RT<sup>®</sup> has been shown to induce a positive wound healing effect in human histology.

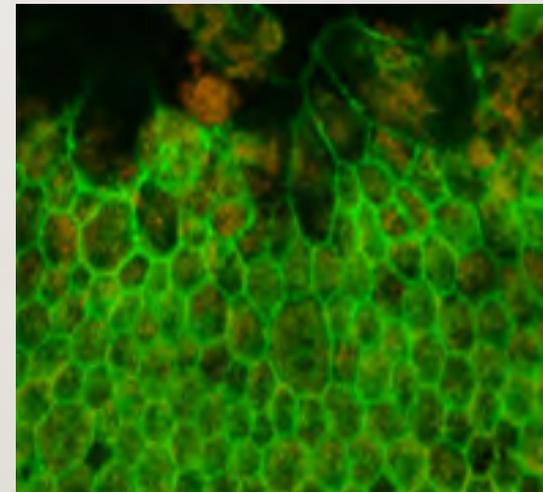
Six laser spots were applied superior to the macula at the clinical dose (0.3 mJ) (B); six laser spots were applied inferior to the macula at the suprathreshold dose (0.6 mJ) (C and corresponding arrows). One month following 2RT<sup>®</sup> the eye was exenterated eye (due to malignant lid cancer).



Treatment spot placement



1 month post treatment with 2RT<sup>®</sup>



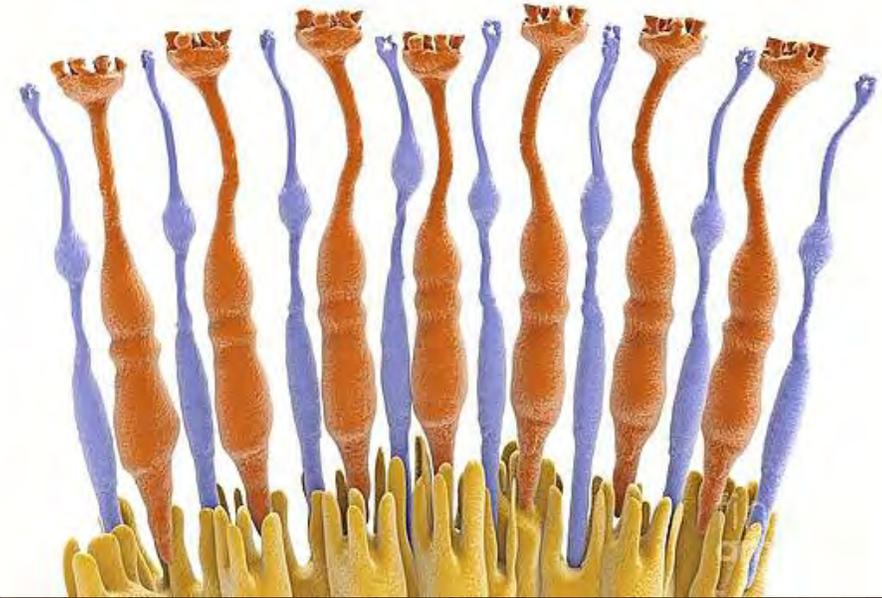
Proliferation of new RPE cells at the laser boundary.

## AMD Treatments

## Neovascular Therapy

- Optical options
- Digital/Augmented Reality options
- Biological options
  - laser therapy
  - Cellular regeneration
- Dietary/Environmental
  - Smoking
  - high-dose zinc and antioxidant vitamin supplements

- Wet AMD
- Dry AMD



## AMD Treatments

Brolucizumab (Beovu!!!!)

1. Rozimab
2. RoziVu
3. BuellerVu
4. BlabZu
5. MabMyVu

Thank You

