

Stem Cell Therapy for Retinal Disease

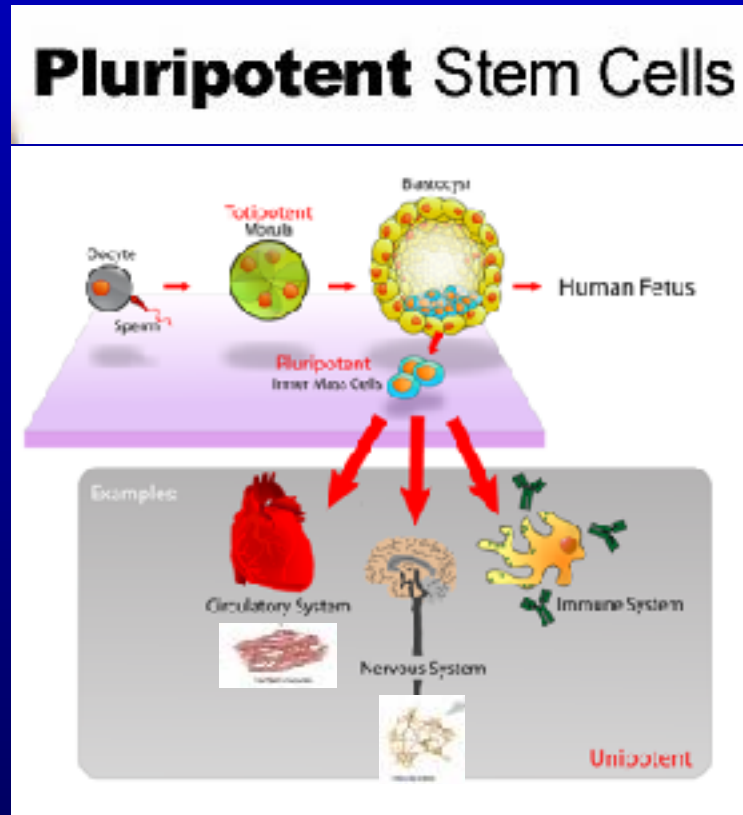
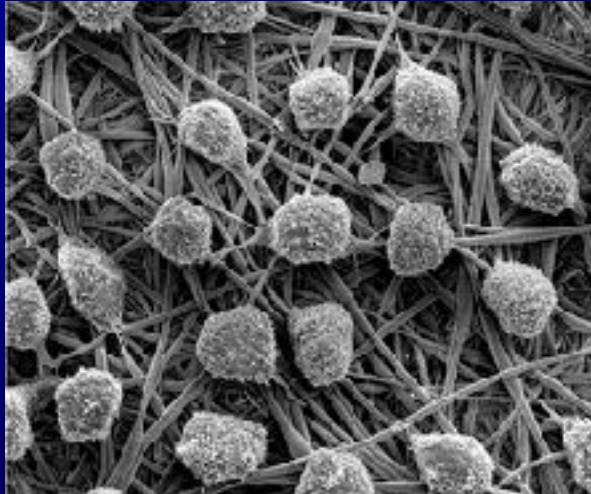


Dean Elliott
Associate Director, Retina Service
Massachusetts Eye & Ear Infirmary
Stelios Evangelos Gragoudas Associate Professor
Harvard Medical School
Boston, MA



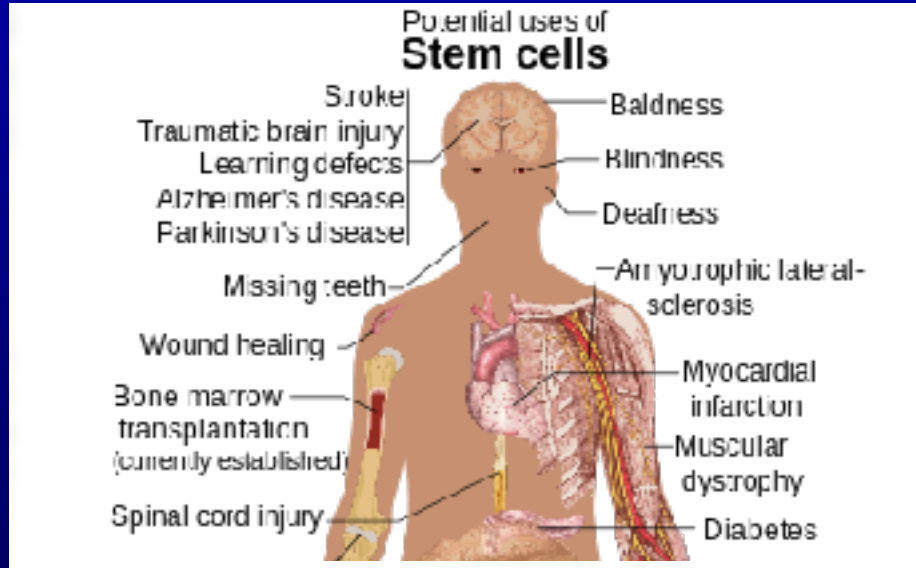
Stem Cells

- Discovered in 1998
 - Can develop into any cell type in the body



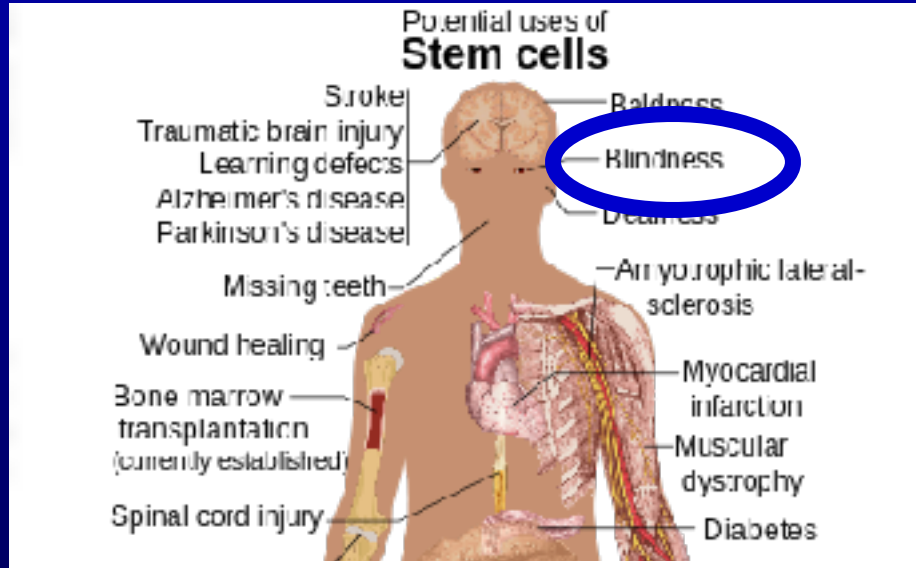
Stem Cell Treatment

- Regenerative Medicine
 - Using cell based therapies (stem cells) to treat human disease



Stem Cell Treatment

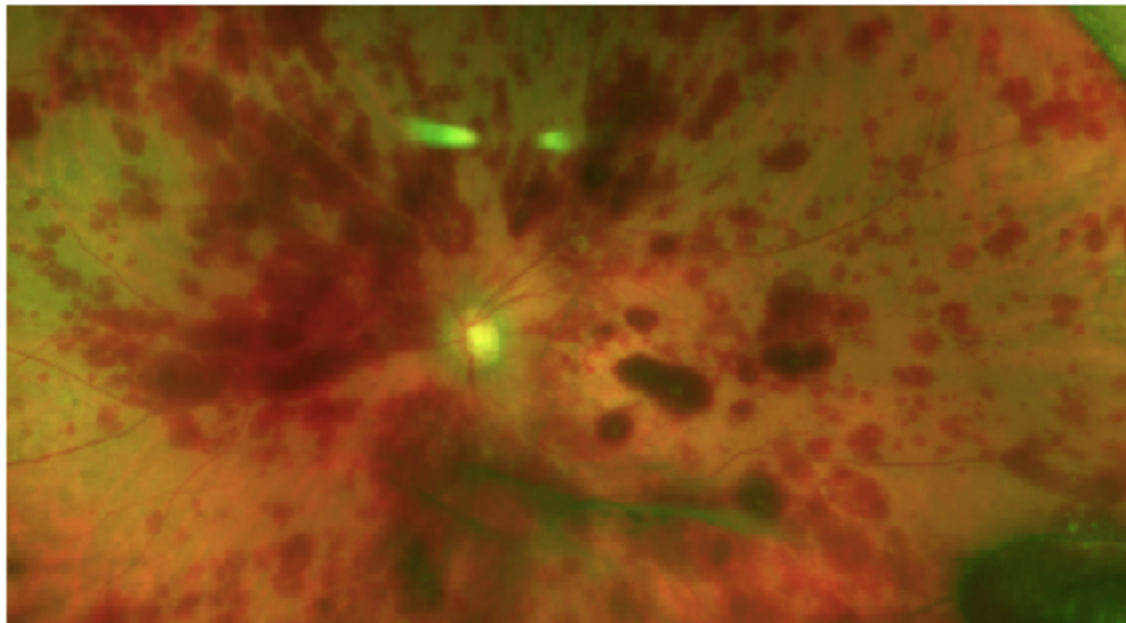
- Regenerative Medicine
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Stem Cells for Retinal Disease

Patients Lose Sight After Stem Cells Are Injected Into Their Eyes

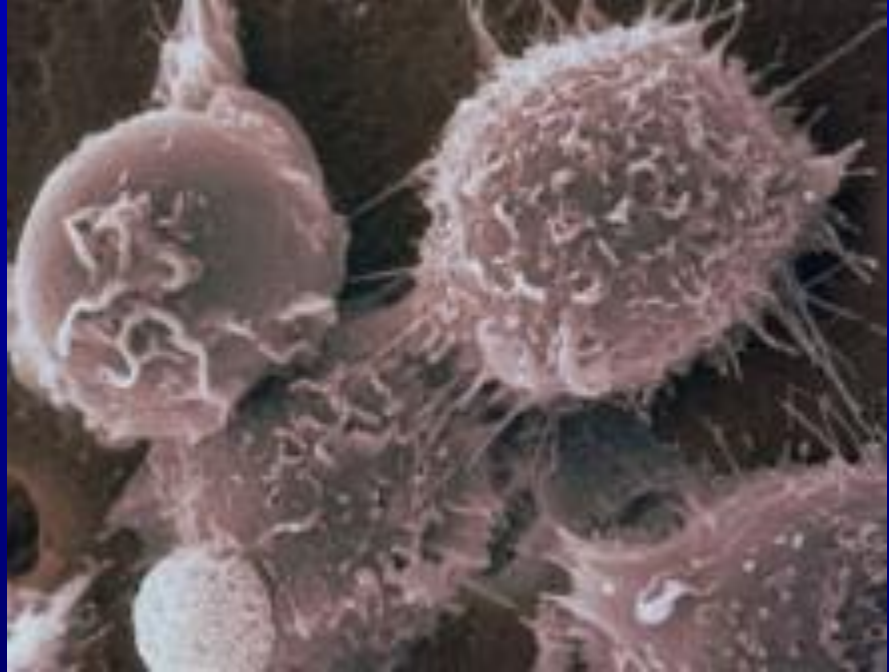
by DENISE GRADY MARCH 16, 2017



The left eye of a patient showing hemorrhages 13 days after stem-cell injection. Dr. Thomas Alizai

Stem Cells for Retinal Disease

- Cell replacement
- Trophic factors



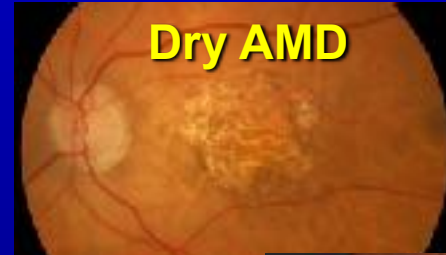
Summary – Stem Cells

- Cell replacement
 - RPE
 - Ocata Therapeutics



Summary – Stem Cells

- Cell replacement
 - RPE
 - Ocata Therapeutics
 - Photoreceptors
 - ReNeuron



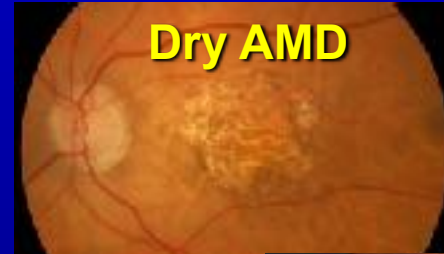
Summary – Stem Cells

- Cell replacement
 - RPE
 - Ocata Therapeutics
 - Photoreceptors
 - ReNeuron
- Trophic factors
 - Stem Cells, Inc



Summary – Stem Cells

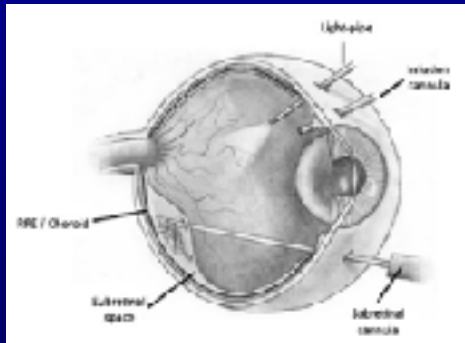
- Cell replacement
 - RPE
 - Ocata Therapeutics
 - Photoreceptors
 - ReNeuron
- Trophic factors
 - Stem Cells, Inc
 - Janssen (J&J)



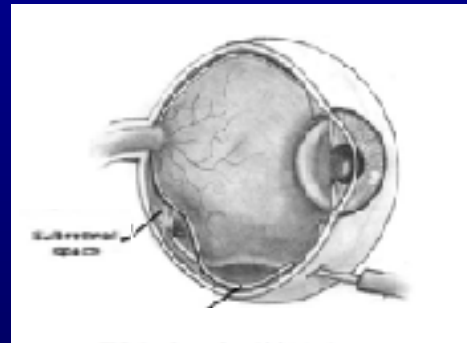
Stem Cells for Retinal Disease

- Subretinal administration
 - 2 approaches to administer stem cells in the **subretinal space**

Transvitreal delivery



Transscleral delivery



Stem Cells for Retinal Disease

- Cell replacement
 - **Transvitreal approach**
 - RPE
 - Ocata Therapeutics
 - Photoreceptors
 - ReNeuron
- Trophic factors
 - **Transvitreal approach**
 - Stem Cells, Inc
 - **Transscleral approach**
 - Janssen (J&J)

Cell Replacement - RPE

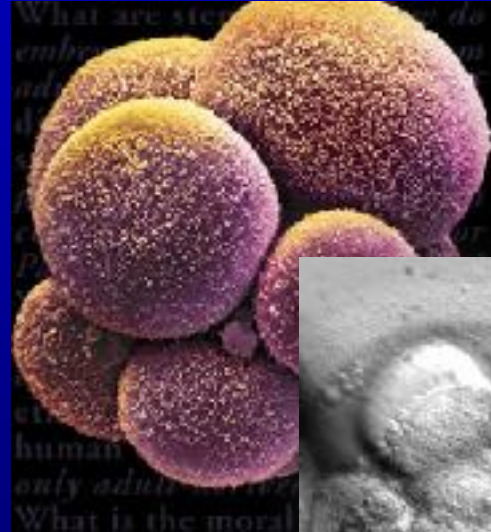
- **Ocata Therapeutics**

- Advanced Cell Technology

- phase 1 study

- Human embryonic stem cells

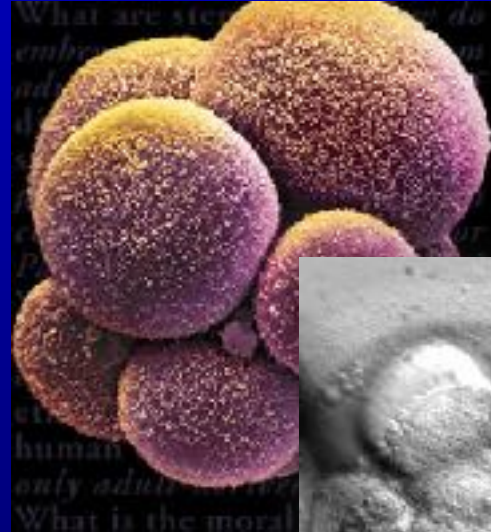
- Age-related Macular Degeneration
- Stargardt Disease



Cell Replacement - RPE

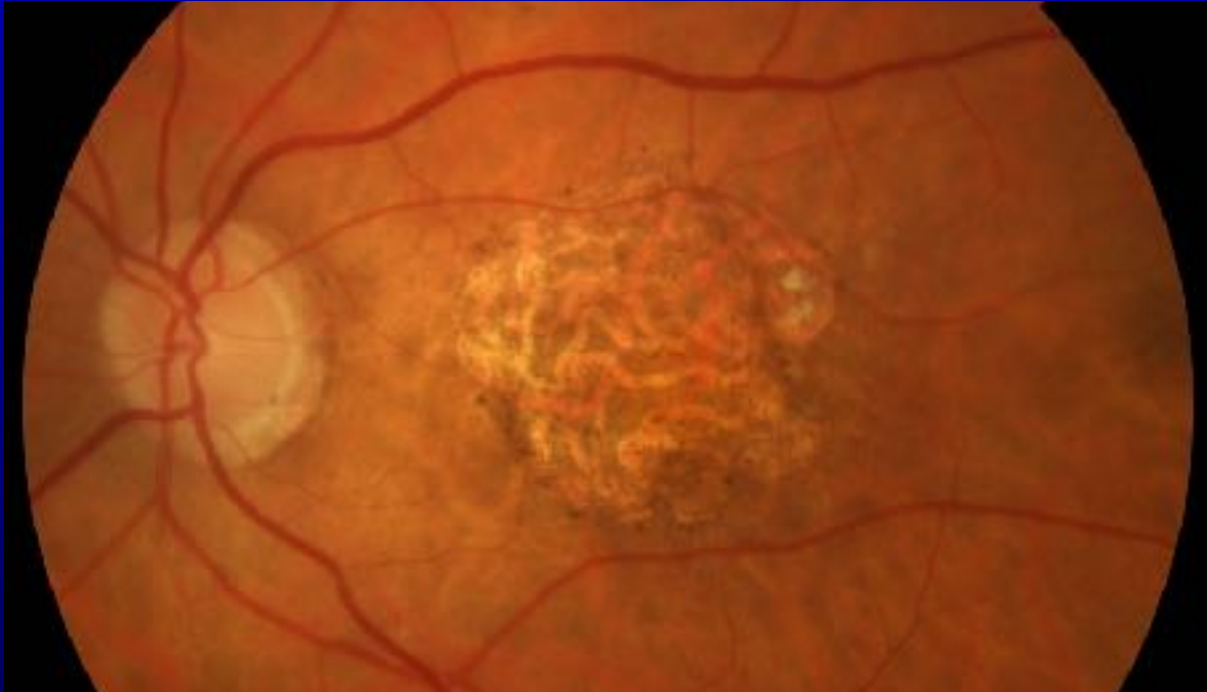
- **Ocata Therapeutics**

- Advanced Cell Technology
 - phase 1 study
- First human embryonic stem cell derived tissue trial



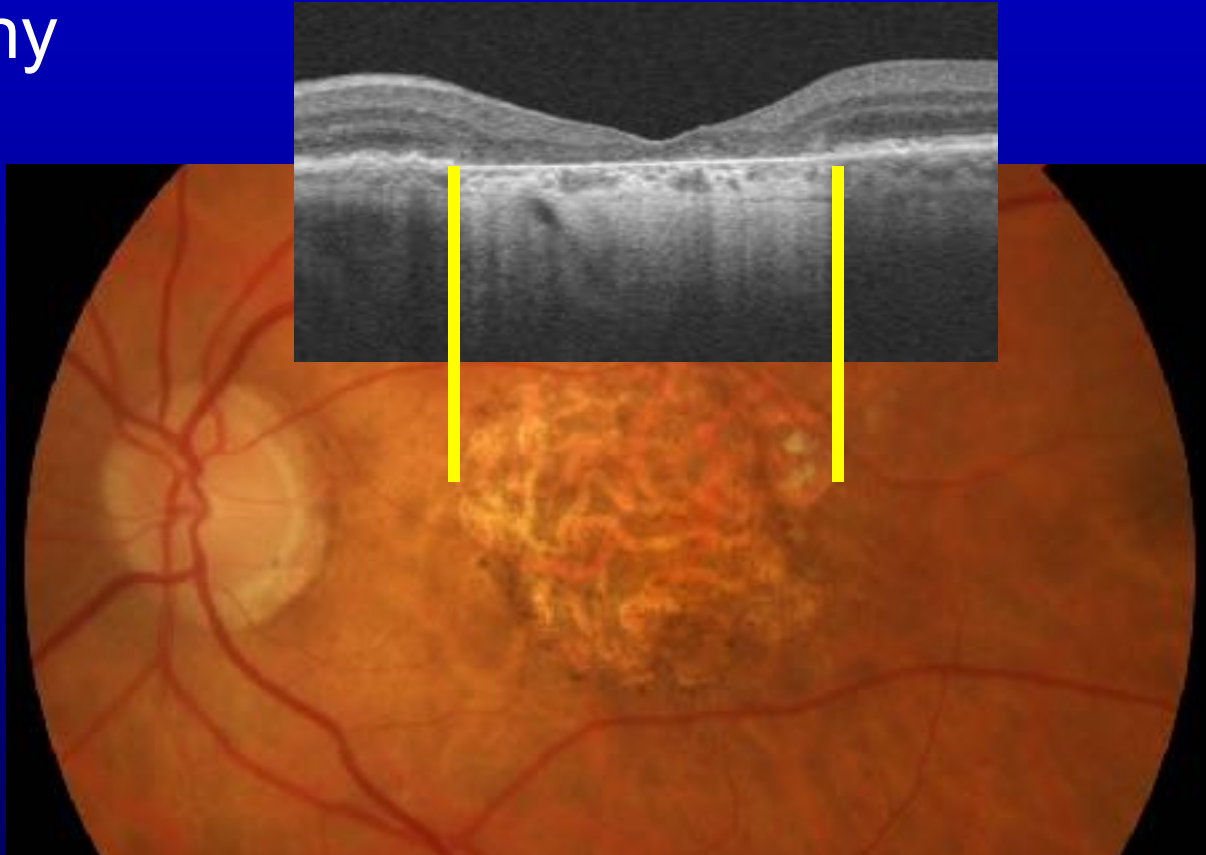
Dry AMD

- Atrophy



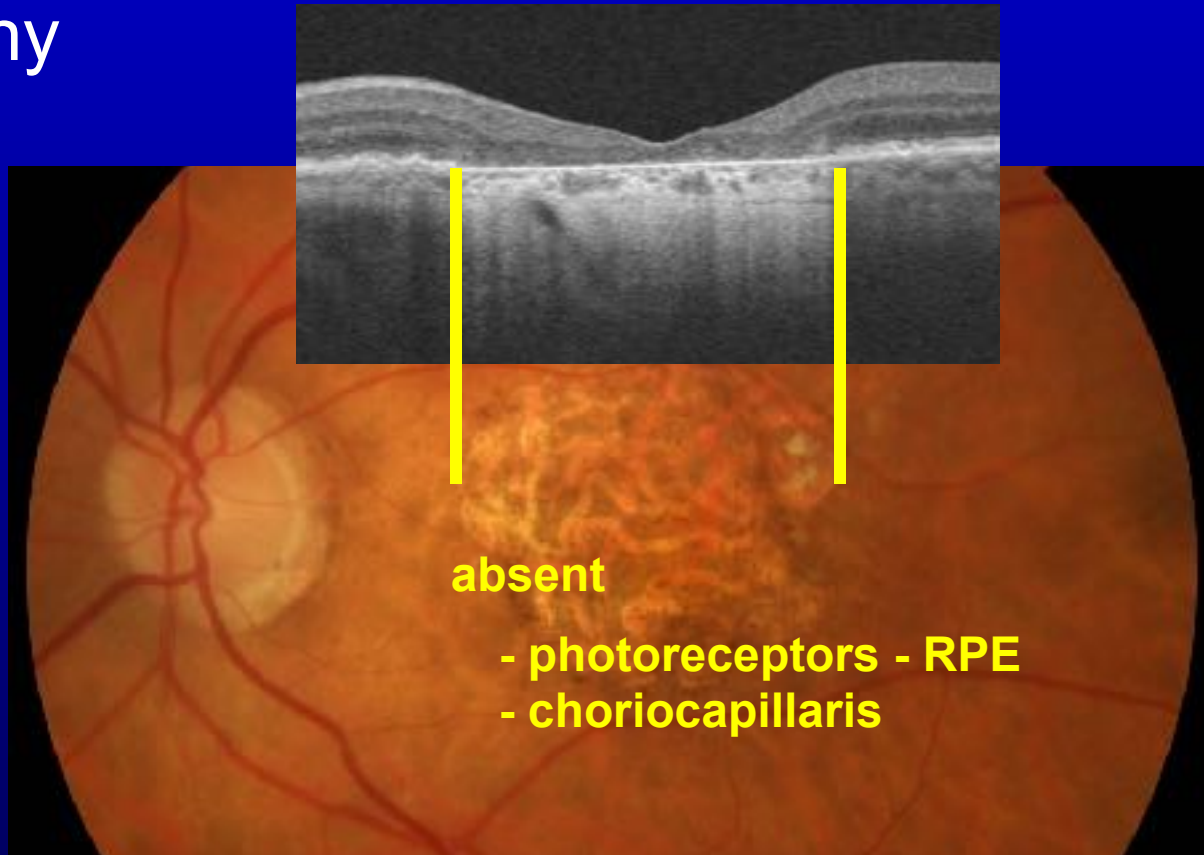
Dry AMD

- Atrophy

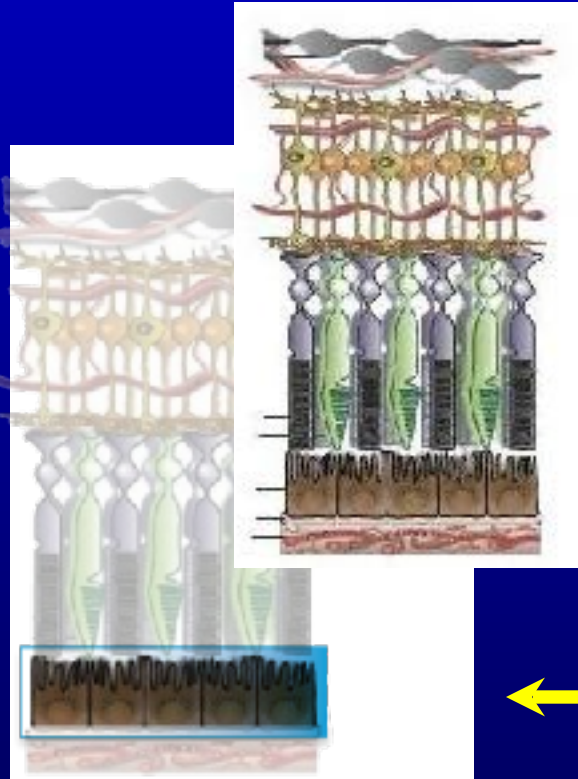


Dry AMD

- Atrophy



Retinal Pigment Epithelium



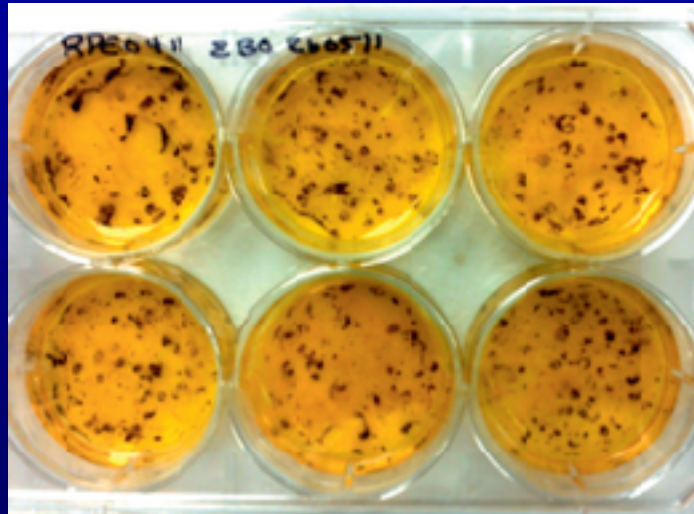
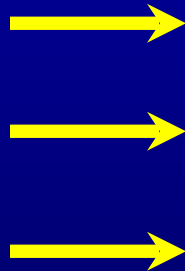
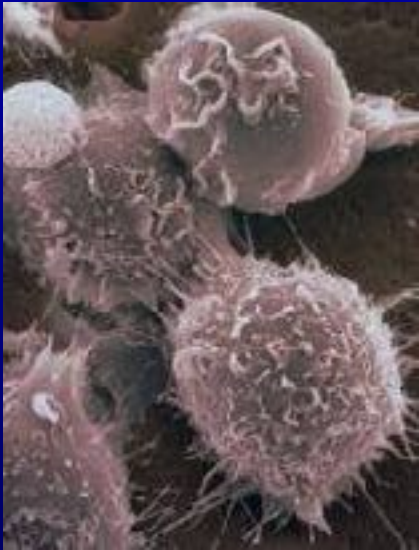
Phagocytose shed
photoreceptor outer
segments

Vitamin A metabolism

← **Can we replace lost RPE cells?**

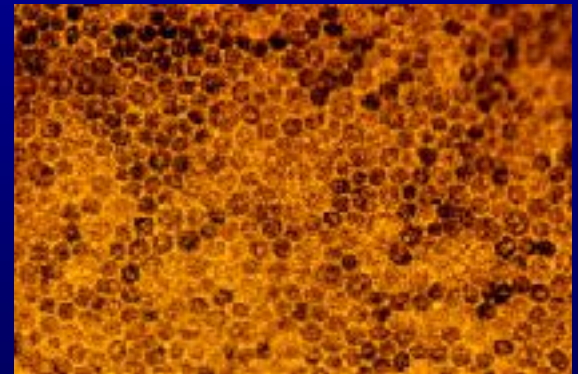
Stem Cells → RPE Cells

- Goal
 - To create immature RPE cells from stem cells



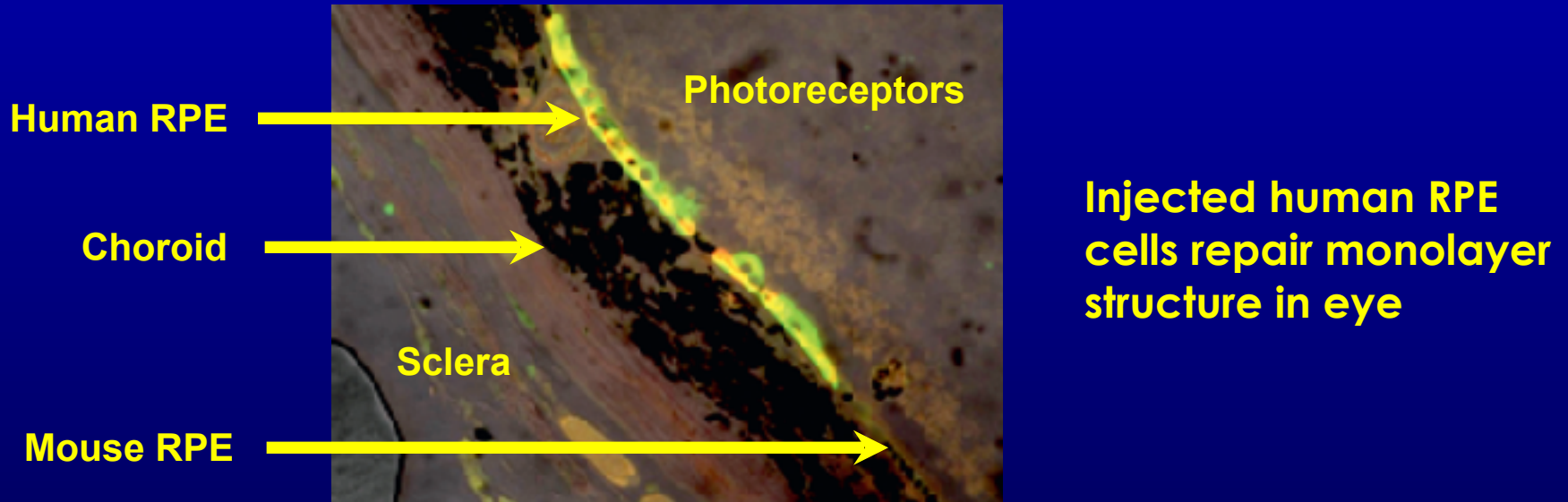
Stem Cells → RPE Cells

- Rationale for RPE cell therapy
 - Unique observational environment
 - Small dosage size
 - Immune-privileged site
 - Relative ease of administration



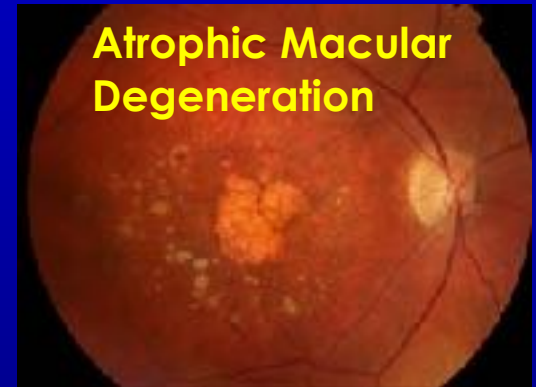
Preclinical Studies

- Retinal degeneration in mice
 - Subretinal transplantation of embryonic stem cells



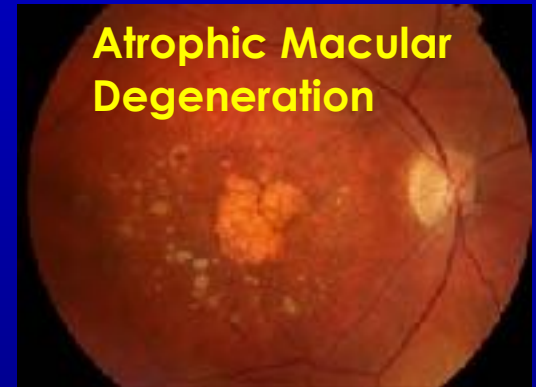
Phase 1 – Clinical Trial

- AMD and Stargardt
- 18 patients
 - 9 AMD, 9 Stargardt



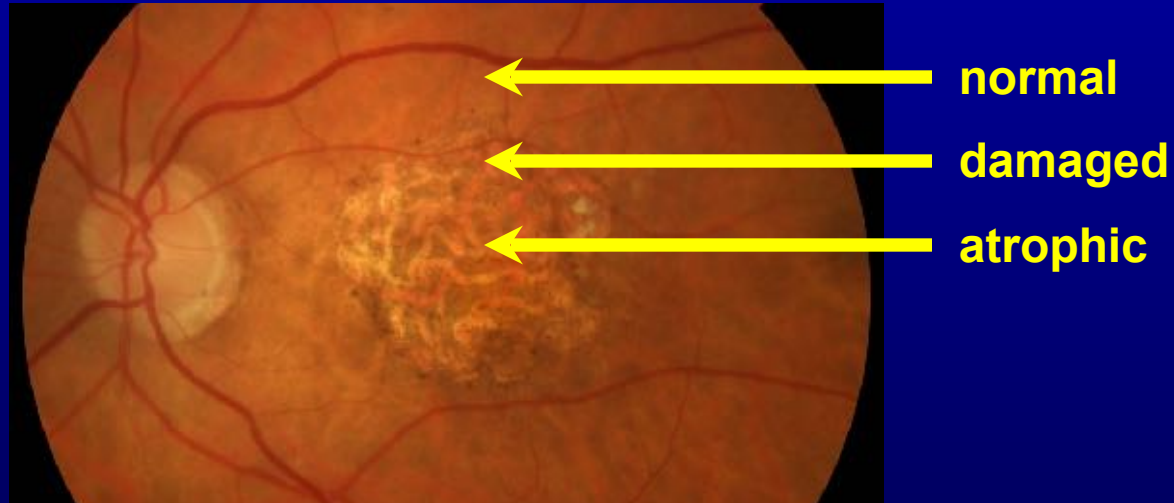
Phase 1 – Clinical Trial

- AMD and Stargardt
- 18 patients
 - 9 AMD, 9 Stargardt
 - Ascending doses
 - 50,000 cells
 - 100,000 cells
 - 150,000 cells



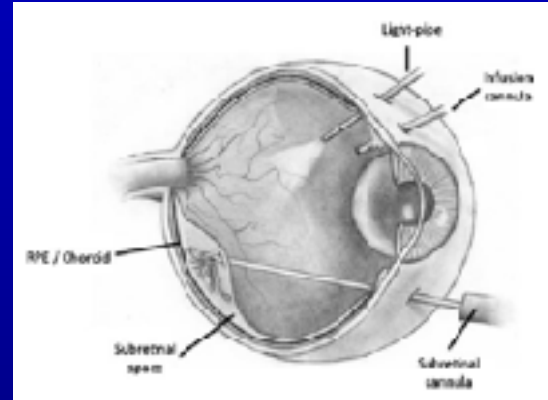
Subretinal Injection of Stem Cells

- Injection site preselected
 - to include normal, damaged, and atrophic RPE



Transvitreal Approach

- Complete vitrectomy
- Elevation of posterior hyaloid
- Subretinal injection of stem cells
 - injection site preselected
 - create access retinotomy
 - inject stem cells



Transvitreal Approach

- Subretinal injection
 - MedOne 38 gauge subretinal cannula



Atrophic AMD Case 1

- Selection of access retinotomy site

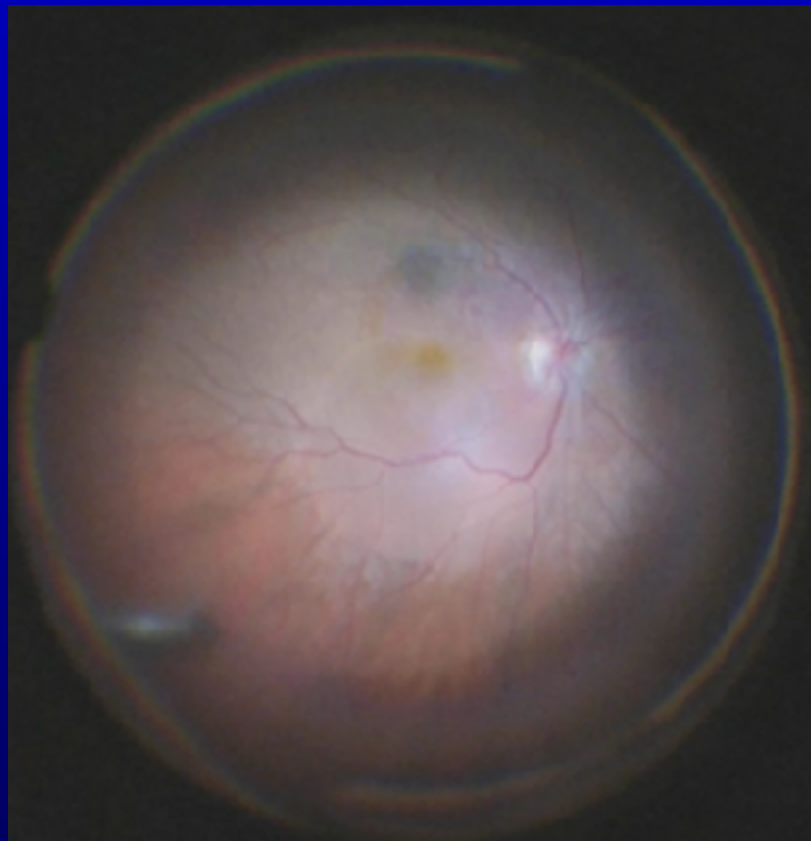


Atrophic AMD Case 1

- Ideal bleb location and extent



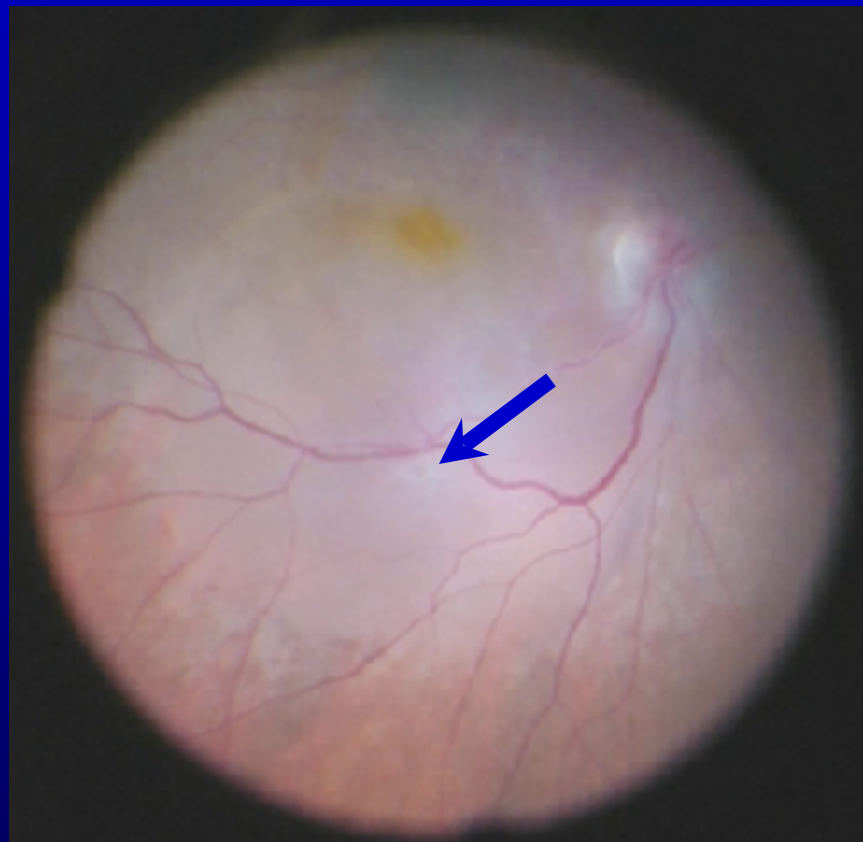
Intraoperative Photo



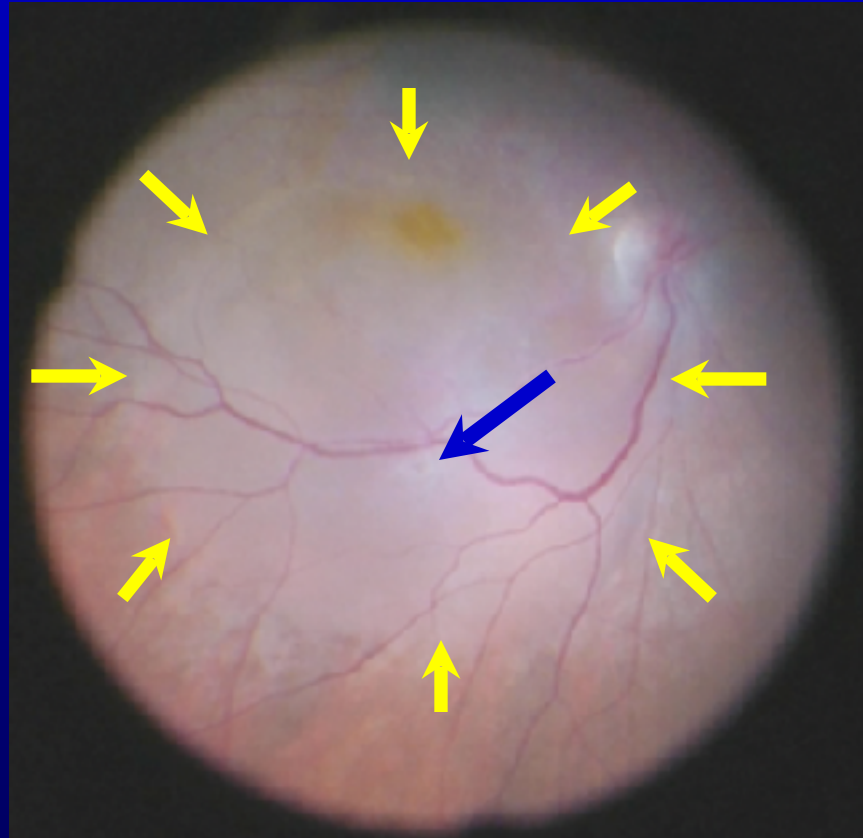
Intraoperative Photo



Intraoperative Photo

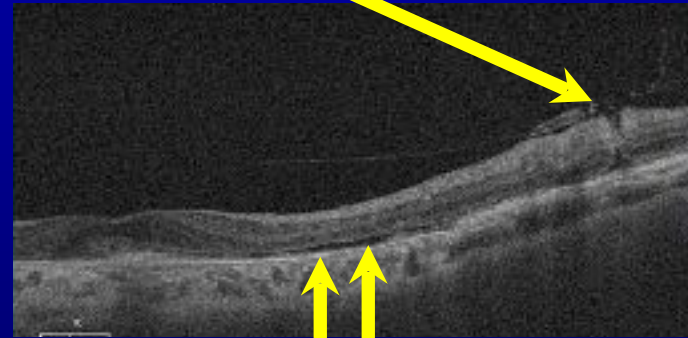
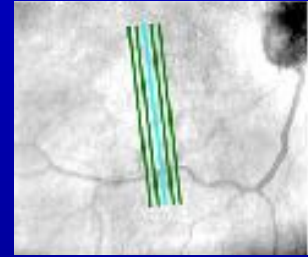


Intraoperative Photo



Retinotomy Site: Self-Sealing

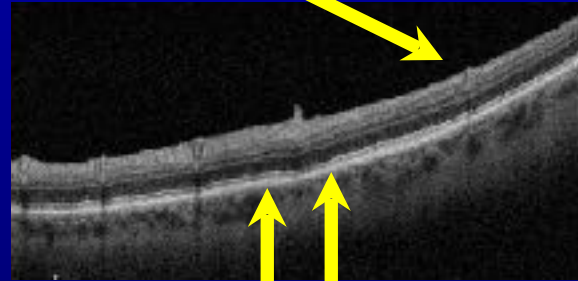
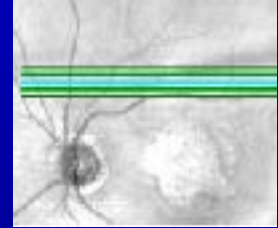
Retinotomy site
Postop day #1



Trace subretinal fluid
(bleb almost resolved)

Atrophic AMD Case 2

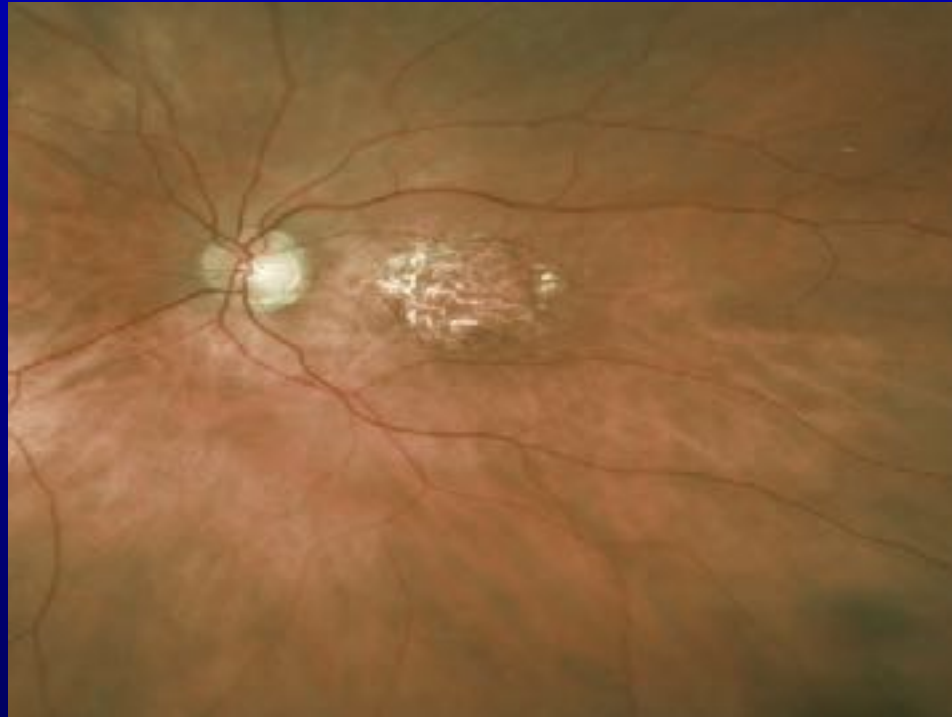
Retinotomy site
Postop day #1



No subretinal fluid
(bleb resolved)

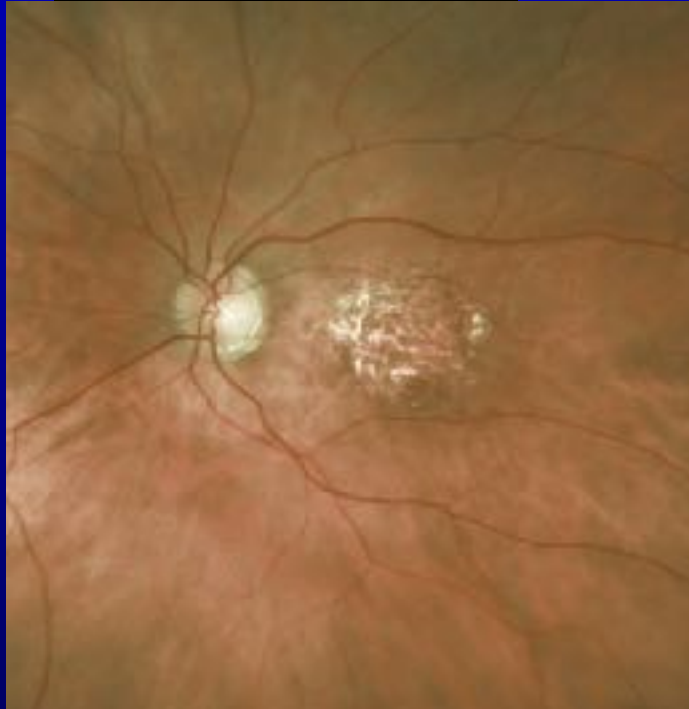
Atrophic AMD Case 2

Postop month 1



Atrophic AMD Case 2

Postop month 1

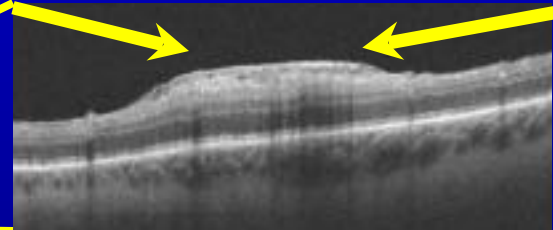
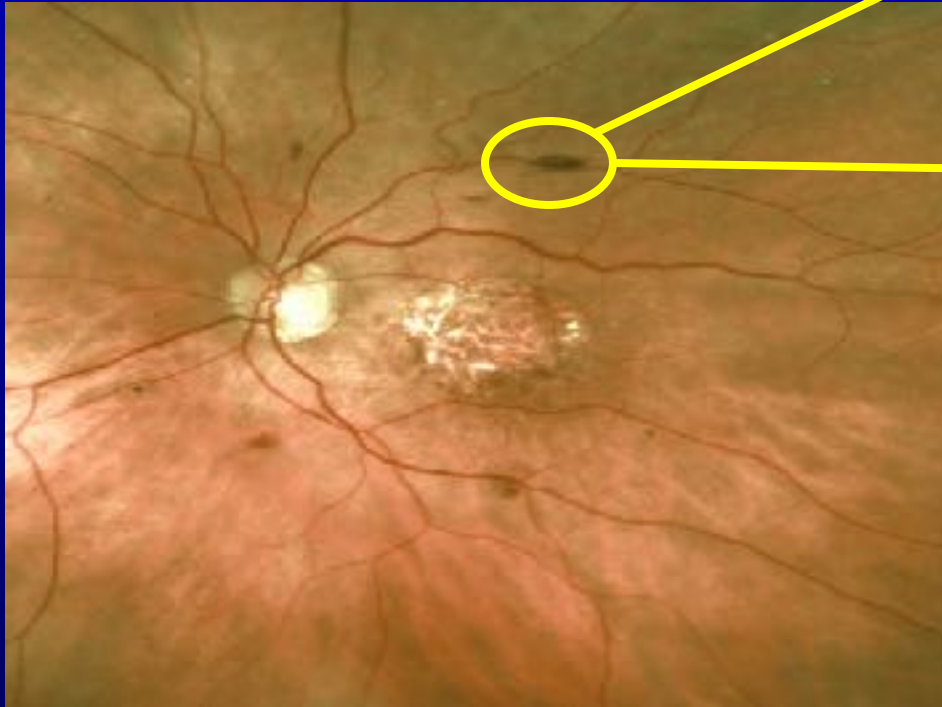


Postop month 4



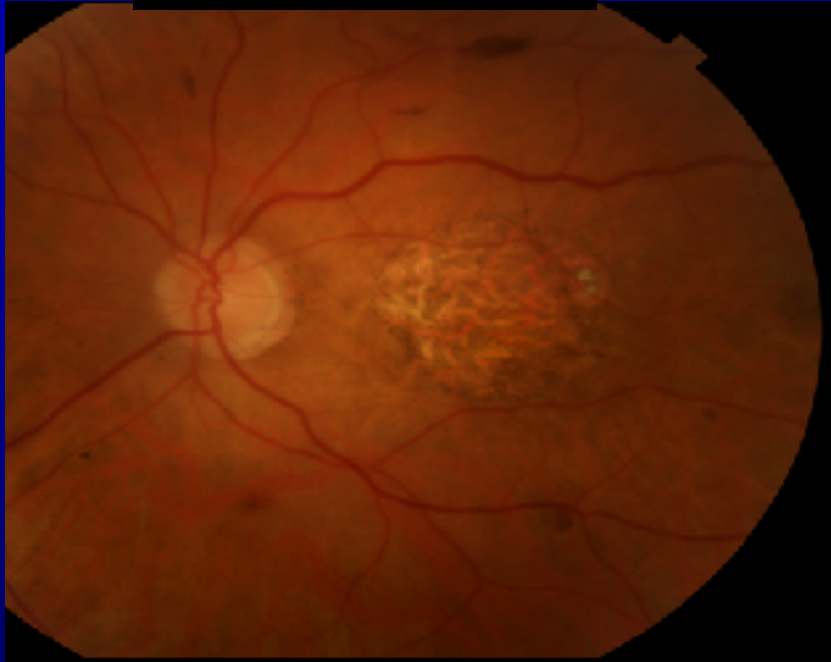
Atrophic AMD Case 2

Postop month 4

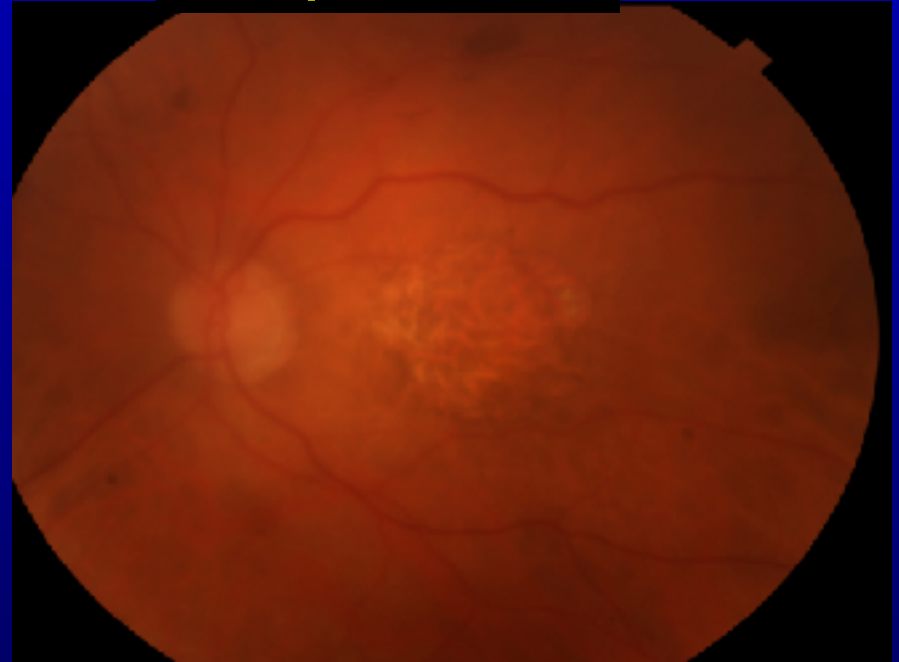


Atrophic AMD Case 2

Postop month 4

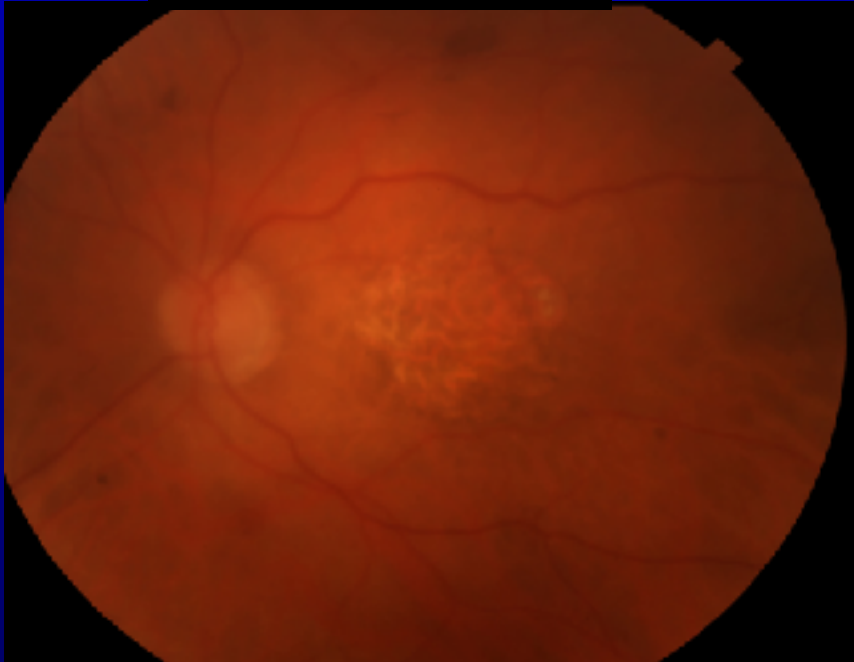


Postop month 6

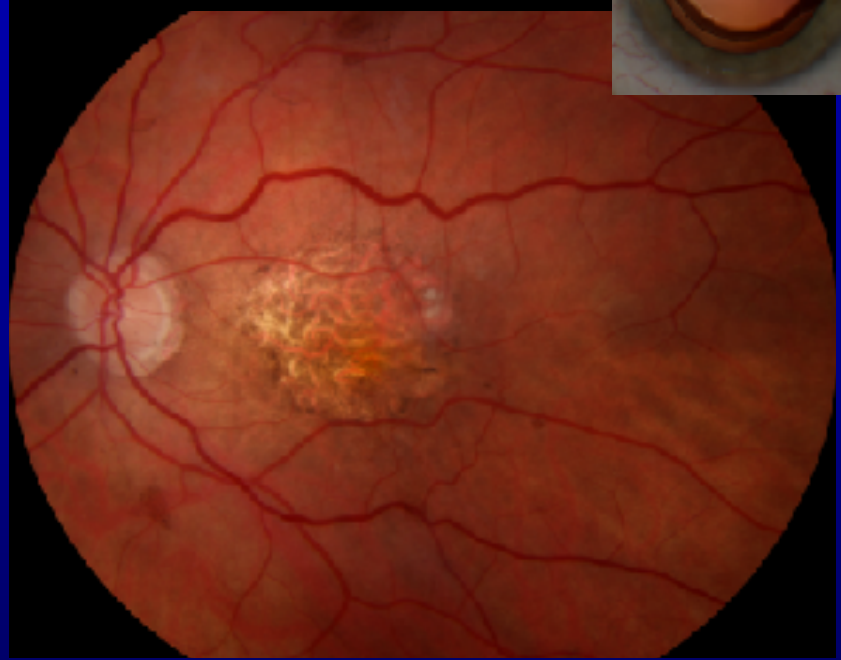


Atrophic AMD Case 2

Postop month 6



Postop month 12

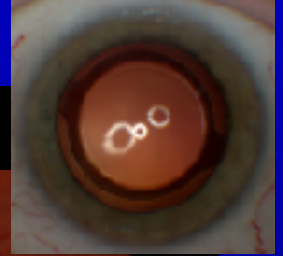
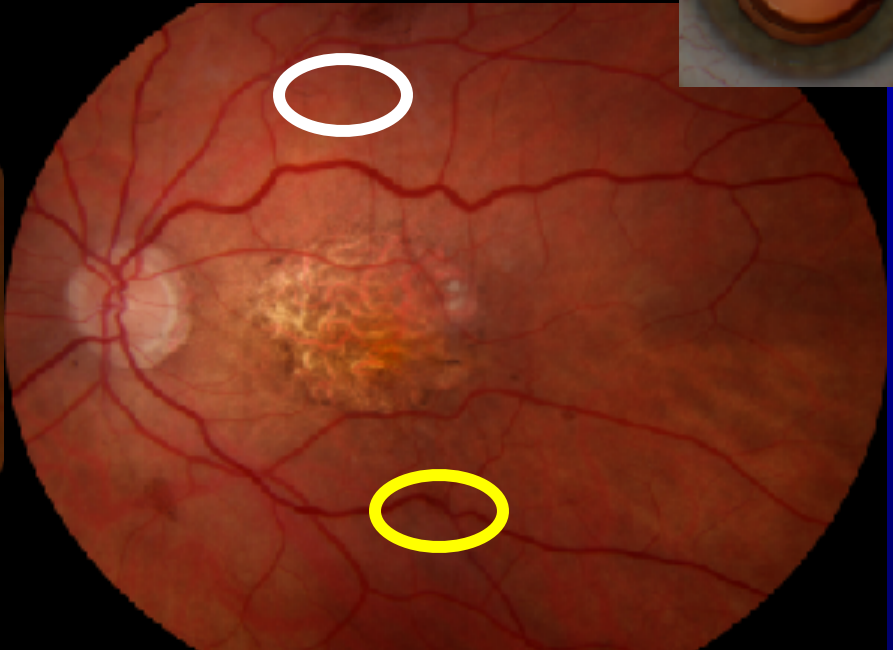


Atrophic AMD Case 2

Postop month 4



Postop month 12



AMD – Subretinal Pigment

Baseline



3 mos



6 mos



AMD – Subretinal Pigment

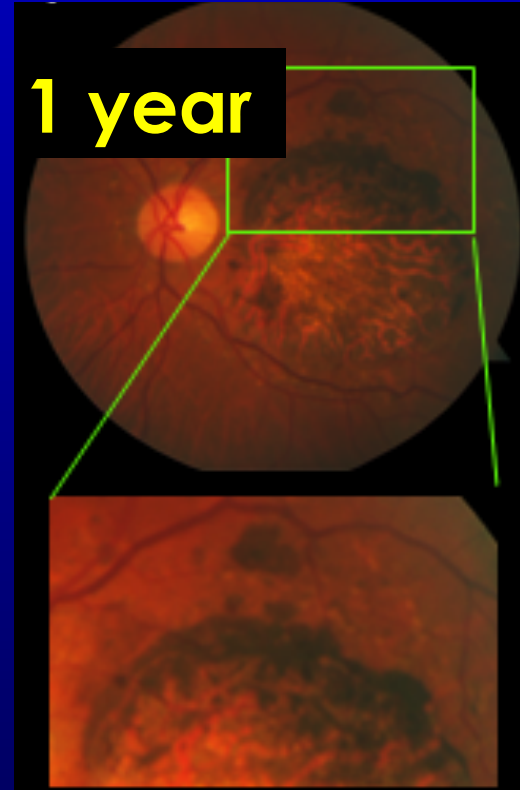
Baseline



6 months

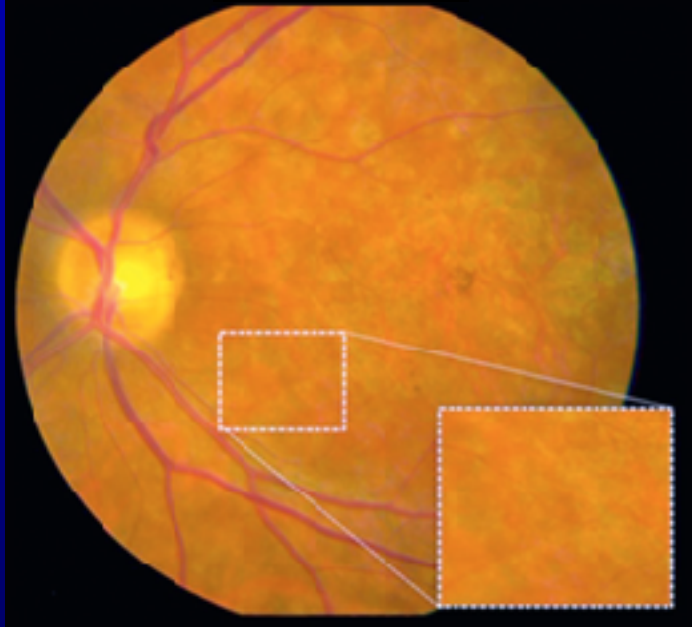


1 year

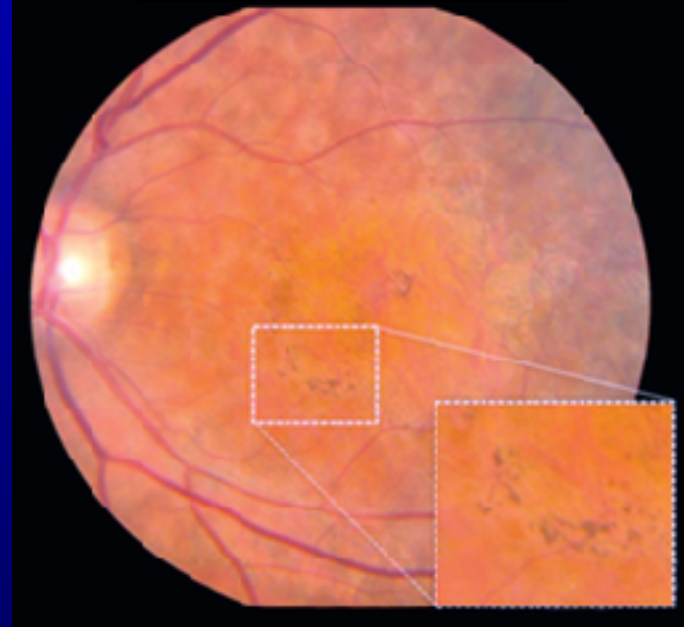


Stargardt – Subretinal Pigment

Baseline

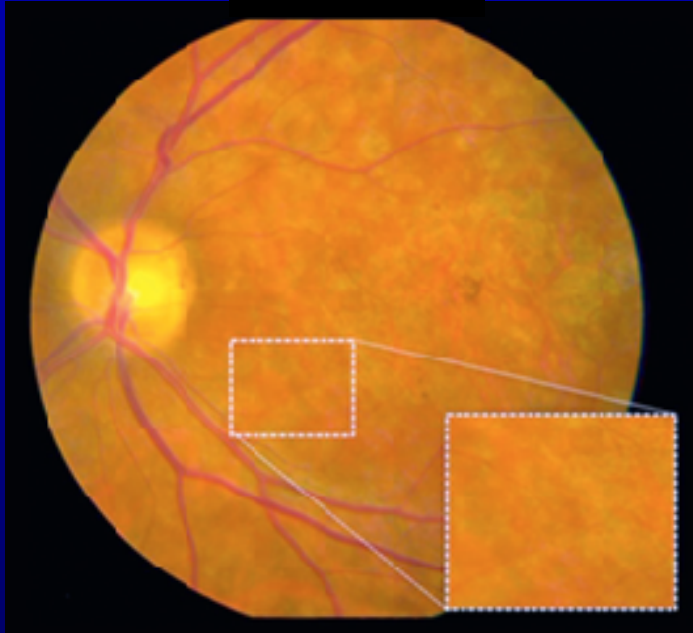


Postop week 1

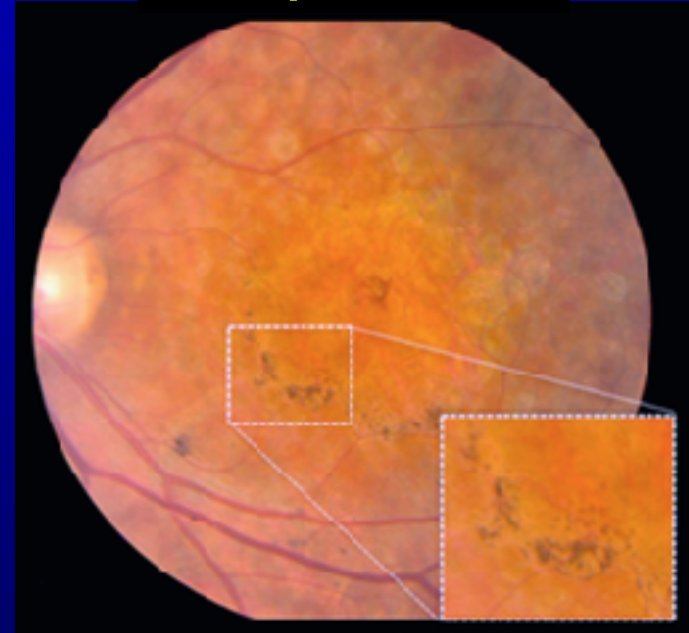


Stargardt – Subretinal Pigment

Baseline

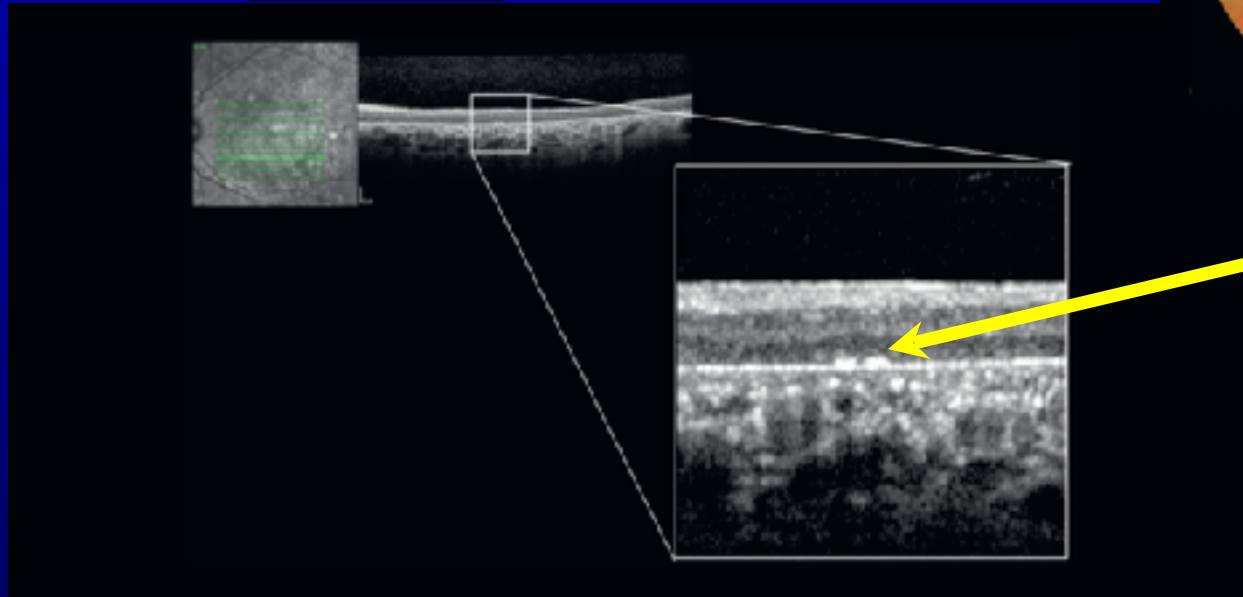
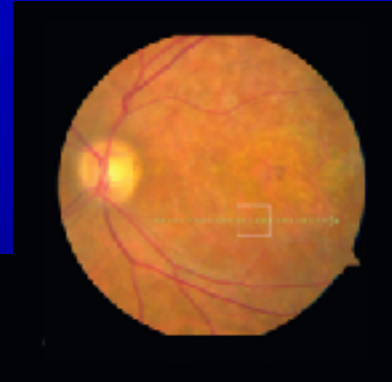


Postop week 6



Stargardt – Subretinal Pigment

Baseline



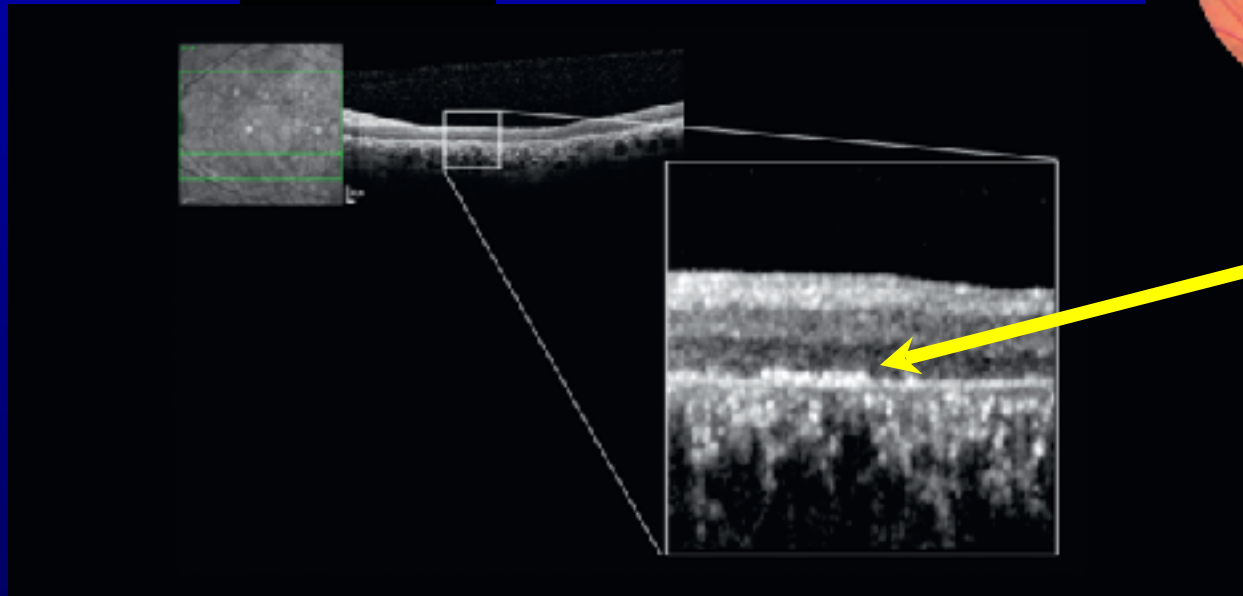
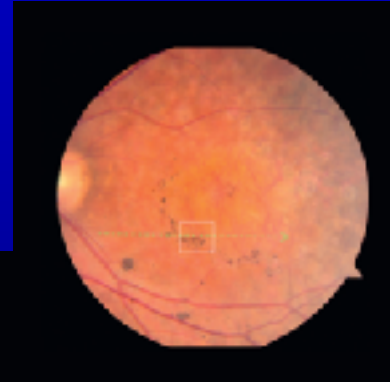
RPE



Stargardt – Subretinal Pigment

- Possible survival and engraftment of RPE

Month 3



Medium and Long-term Results

- 22 months median follow-up (up to 37 months)

THE LANCET

Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies

Shen D, Sivaloganathan S, D'Alagni G, et al. (2015) Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. *Lancet* 385:509-516.

Medium and Long-term Results

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Shen D, Sivalan L, Tai T, Hoggill S, Owen J, Sun C, Greenhalgh J, Philip Jackson H, Alford C, Gopal S, et al. *N Engl J Med*. 2015;373:1790-1801. doi:10.1056/NEJMoa1500312

- **No adverse events related to transplanted tissue**
 - No signs of:
 - Hyperproliferation
 - Rejection
 - Ocular adverse events
 - Systemic adverse events

Medium and Long-term Results

- 22 months median follow-up (up to 37 months)

THE LANCET

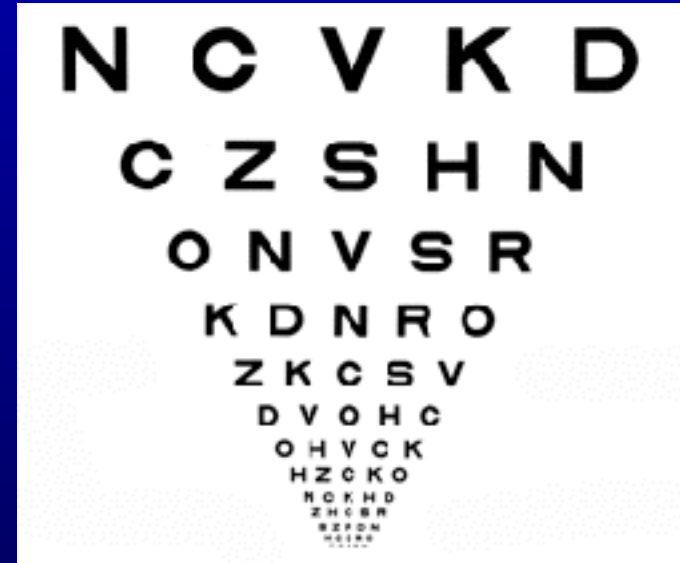
Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies

Shen D, Sivalanarayanan S, D'Amico DJ, et al. (2015) Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. *Lancet* 385:509-516.

- Anatomic results
 - 13 of 18 pts (72%) had patches of increasing subretinal pigmentation consistent with transplanted RPE

Medium and Long-term Results

- Visual results
 - Done as part of the safety evaluation
 - **No conclusions can be drawn**



Medium and Long-term Results

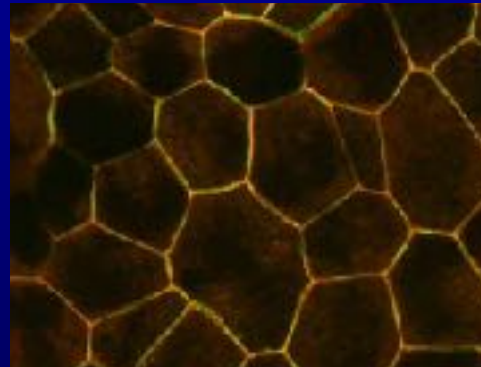
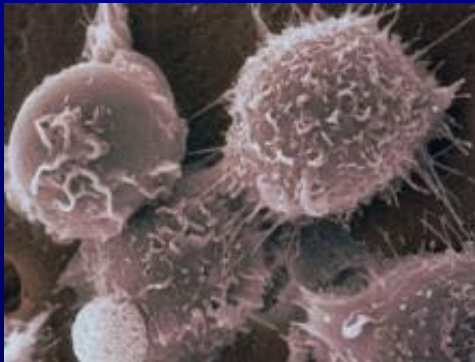
- Visual results
 - Study was not designed to evaluate vision

Medium and Long-term Results

- Visual results
 - Study was not designed to evaluate vision
 - Possible reasons for visual improvement
 - Examiner not masked (inherent bias)
 - Patient not masked (inherent bias)
 - Placebo effect (no control group)
 - Patient improvement due to repeat testing
 - Patient learning (eccentric fixation)

Conclusions

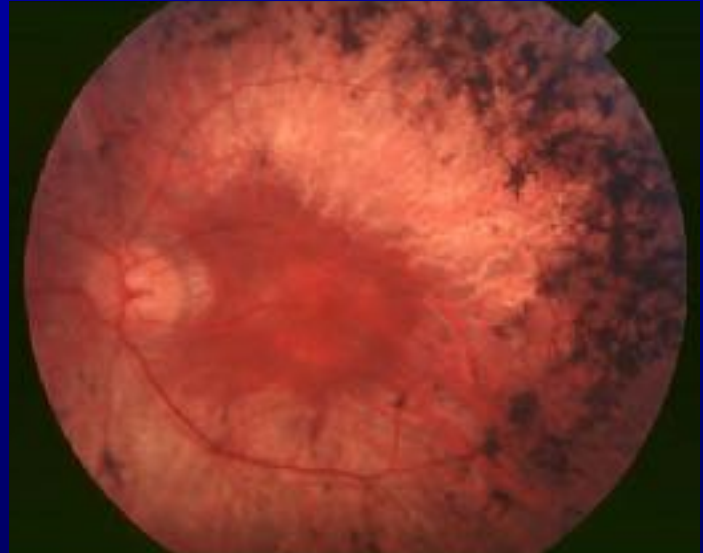
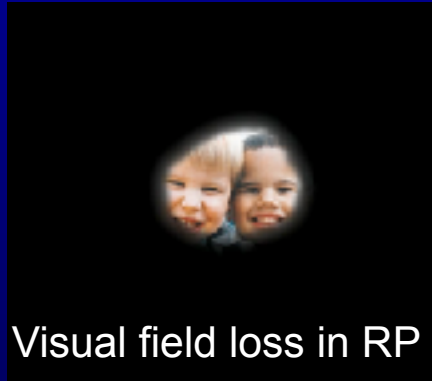
- Transplanted human embryonic stem cell-derived RPE
 - **No adverse events related to transplanted cells in 18 eyes**
 - **Well tolerated up to 37 months (median 22 months)**
 - **Approach appears safe**



Cell Replacement - Photoreceptors

- **ReNeuron**

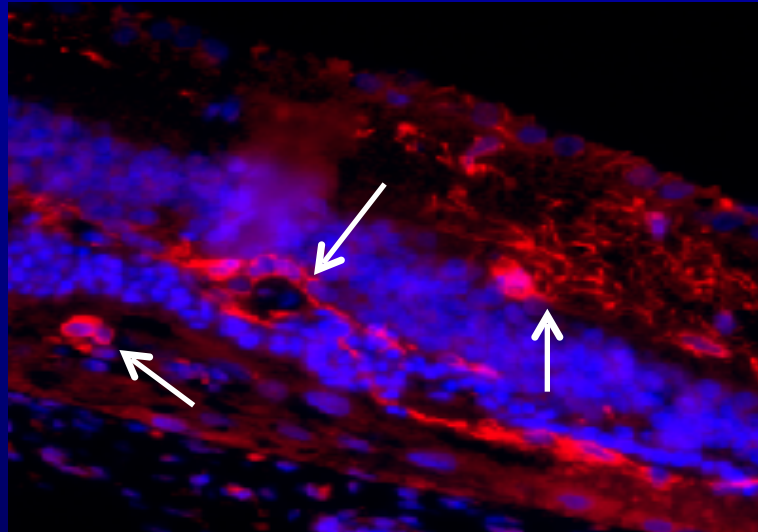
- Human embryonic retinal progenitor cells (hRPC)
 - differentiate into rods
- Retinitis pigmentosa
- Phase 1



Cell Replacement - Photoreceptors

- **ReNeuron**

hRPC survival at 12 weeks in RCS dystrophic rats



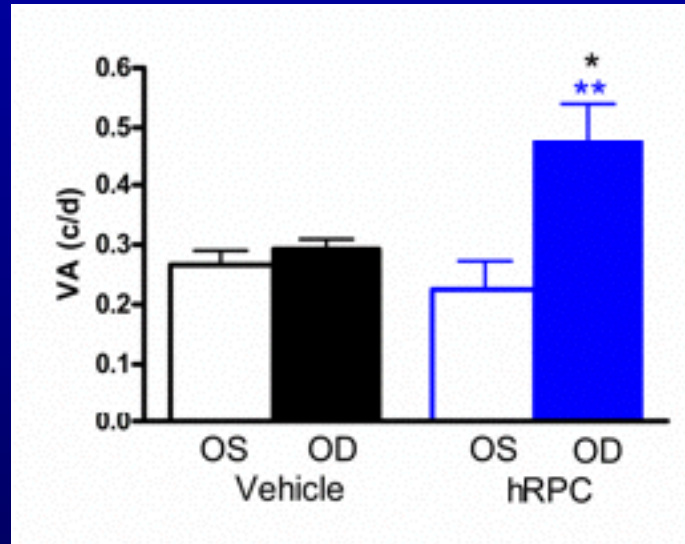
hRPC = red

photoreceptors = blue

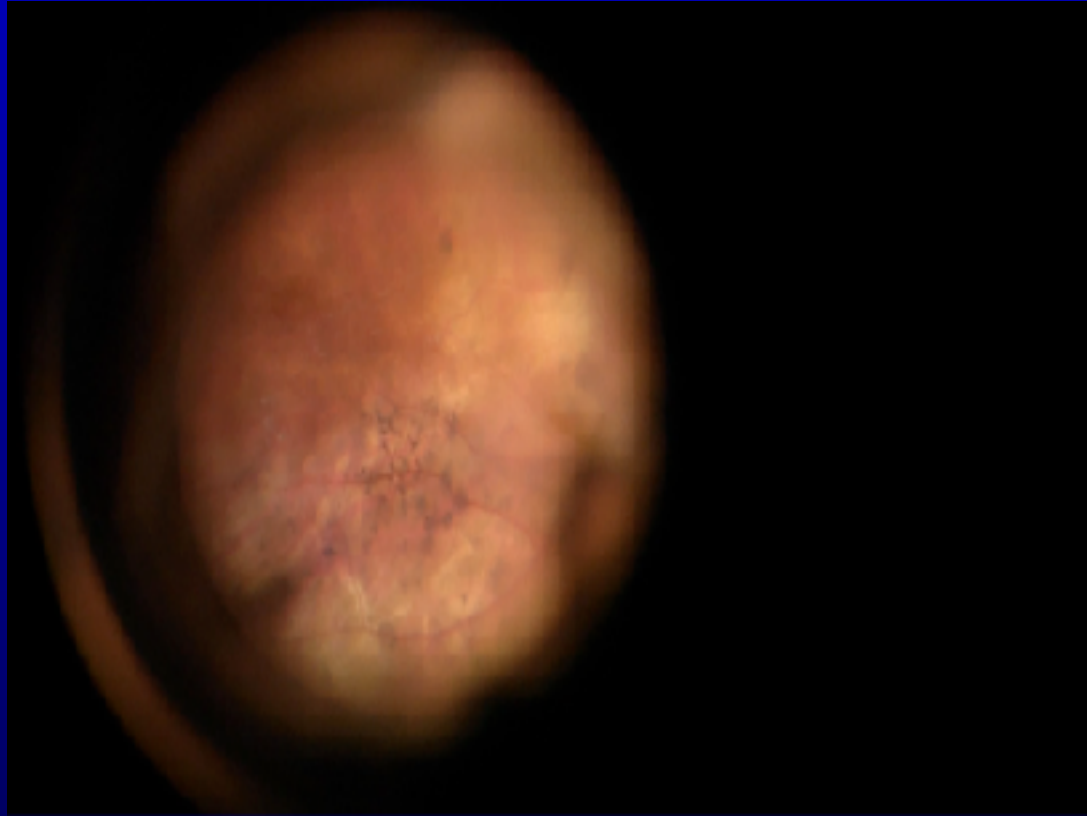
Cell Replacement - Photoreceptors

- ReNeuron

Visual acuity in RCS dystrophic rats



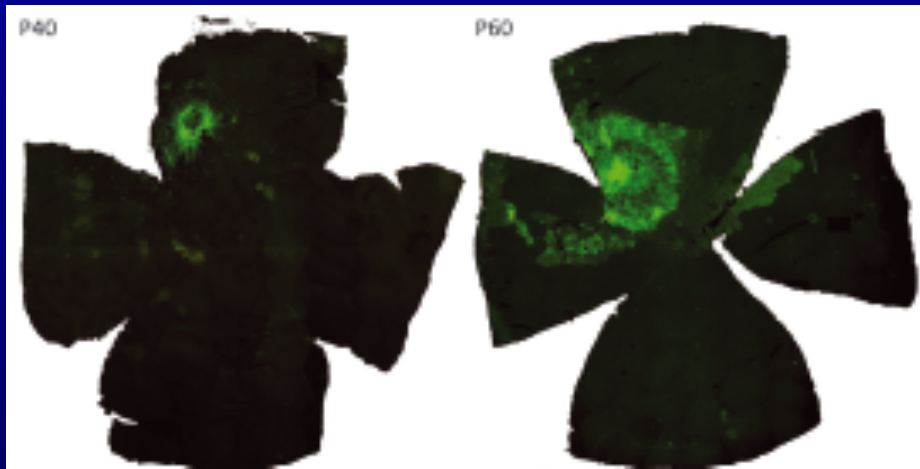
Cell Replacement - Photoreceptors



Trophic Factors

- **Stem Cells, Inc**

- Cells derived from fetal brain (HuCNS-SC)
- Preclinical studies (RCS rat): **outward migration of stem cells**



Transplantation of human central nervous system stem cells – neuroprotection in retinal degeneration

Trent J. McGill^{1,2}, Benjamin Collins^{1,2}, Bin Lu¹, Sharmal Wang¹, Sergei Gornov¹, Cheryl Tian¹, Stephen L. Hunt¹, Amy D. Lind^{1,2} and Melissa A. Garcia^{1,2*}
¹Department of Ophthalmology, Casey Eye Institute, Oregon Health and Science University, Portland, OR 97239, USA
²StemCells, Inc., Newark, CA 94560, USA

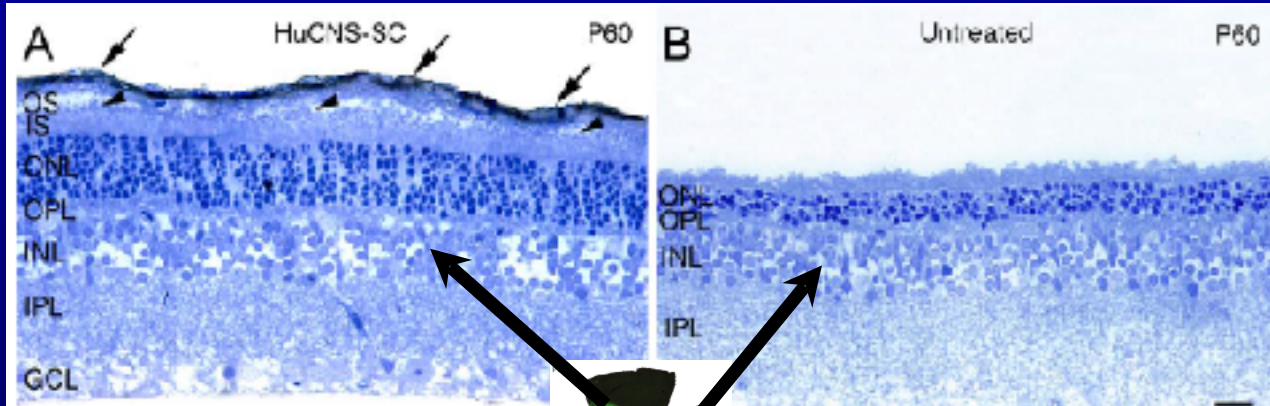
Trophic Factors

- **Stem Cells, Inc**

- Preclinical studies (RCS rat); **photoreceptors are preserved where HuCNS-stem cells have engrafted, but not elsewhere**

Phagocytosis of Photoreceptor Outer Segments by Transplanted Human Neural Stem Cells as a Neuroprotective Mechanism in Retinal Degeneration

Nicolas Garcia,¹ Laura Fernández-Sánchez,¹ Javier J. Morán,¹ Jie Lu,² Shaomei Wang,² Raymond Lu,² Stephen Stritt,² and Alexandra Caporaso¹



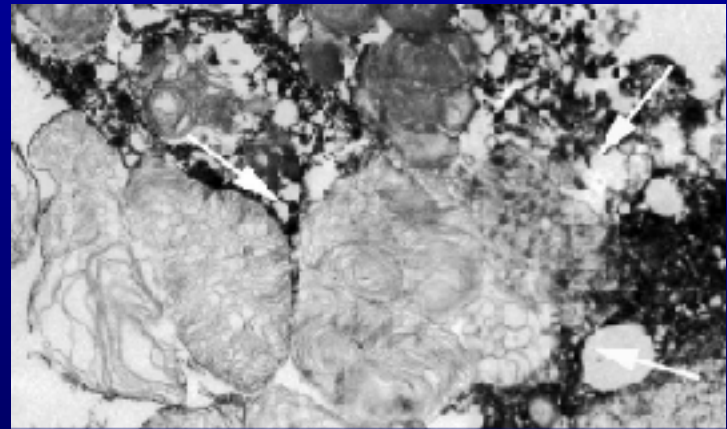
Trophic Factors

- **Stem Cells, Inc**

- Cells derived from fetal brain (HuCNS-SC)
- Preclinical studies (RCS rat): **outer segment discs phagocytosed by HuCNS-stem cells**

Phagocytosis of Photoreceptor Outer Segments by Transplanted Human Neural Stem Cells as a Neuroprotective Mechanism in Retinal Degeneration

Nicolis Cuenca,¹ Laura Fernández-Sánchez,¹ Trevor J. McGill,² Bin Lu,¹ Shaomei Wang,³ Raymond Linn,⁴ Stephen Huh,⁵ and Alexandra Capela⁷



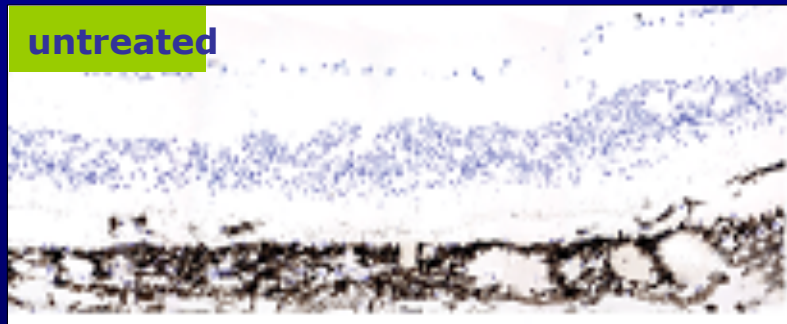
Trophic Factors

- **Stem Cells, Inc**
 - Phase 1/2 study completed
 - Dry AMD with GA, 15 patients
 - Safety established

 - Phase II pending

Trophic Factors

- **Janssen (division of Johnson & Johnson)**
 - human umbilical tissue-derived stem cells
 - preclinical studies
 - RCS rat



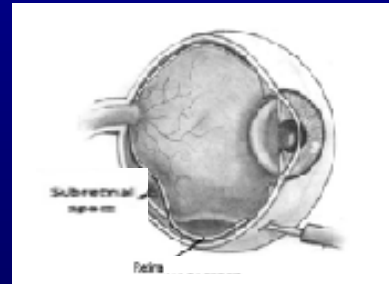
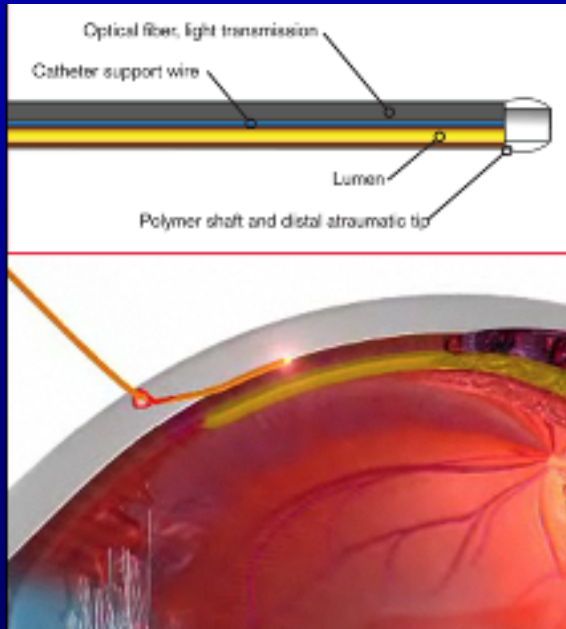
Trophic Factors

- **Janssen**

- human umbilical tissue-derived stem cells
- Phase 1 Clinical Trial (CNTO 2476)
 - AMD
- iScience microcatheter with fiberoptic illuminator and microcalibrated pump

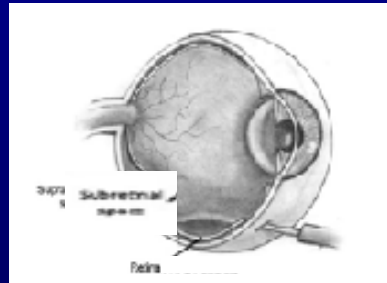
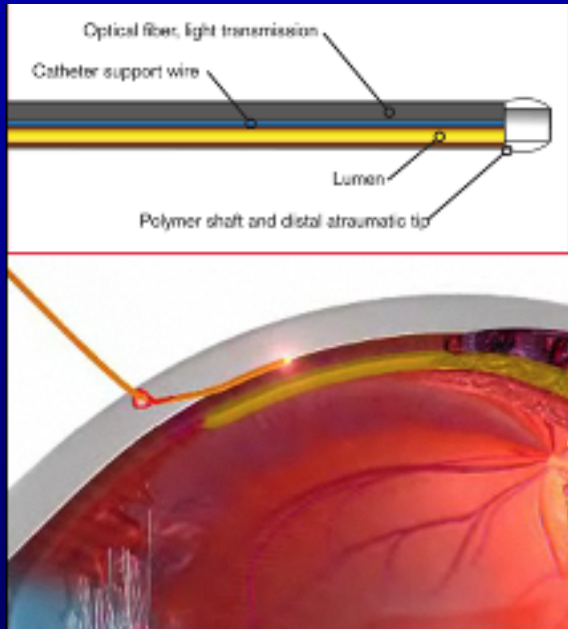
Transscleral Approach

- Transscleral delivery: catheter enters peripheral subretinal space



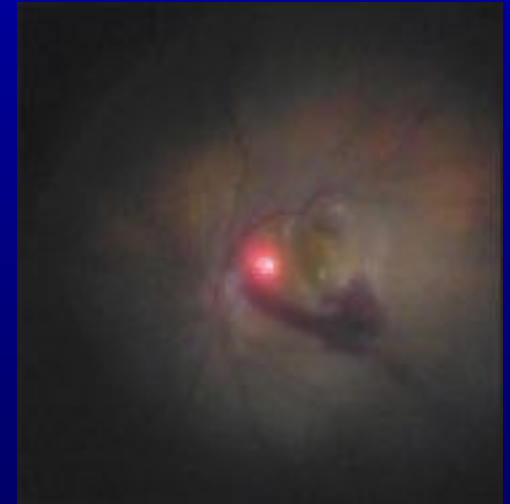
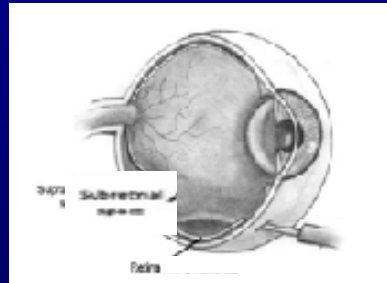
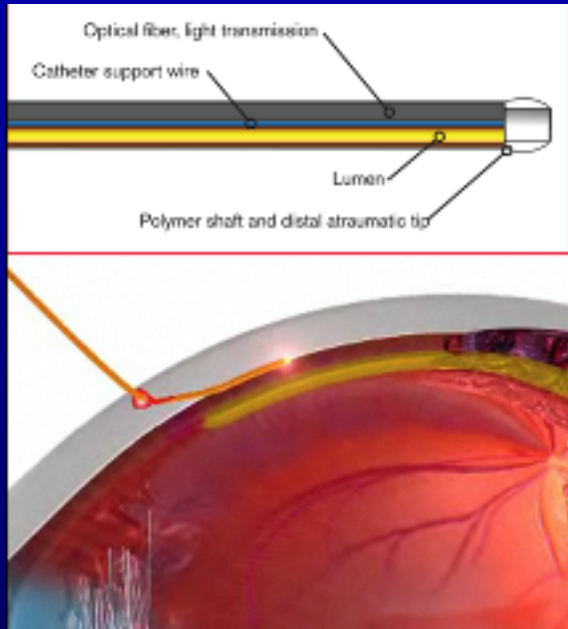
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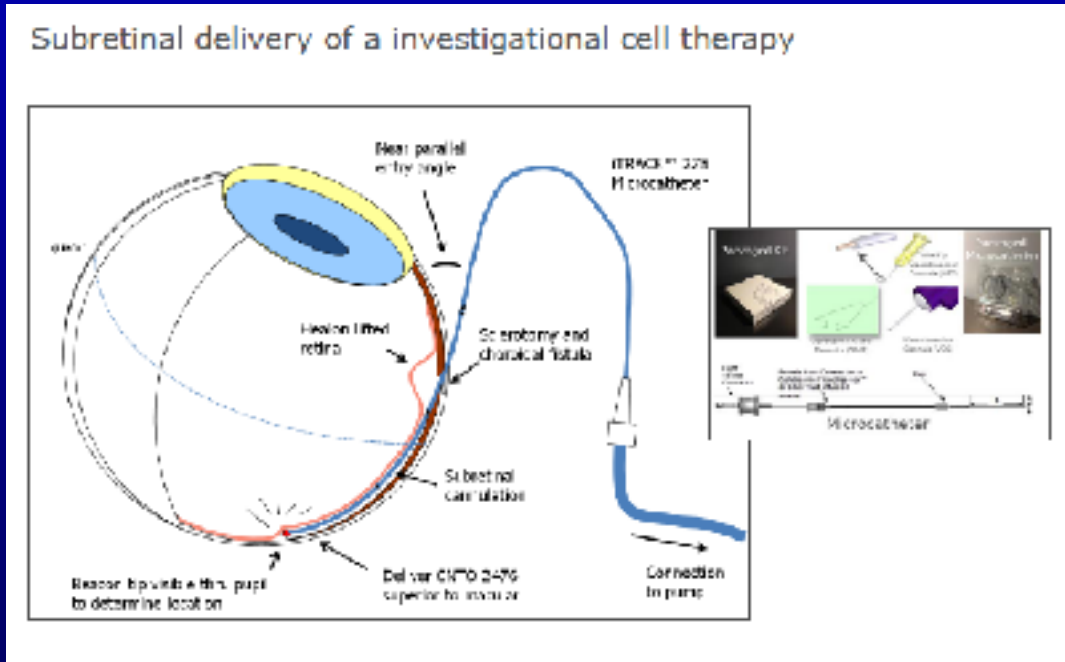
Transscleral Approach

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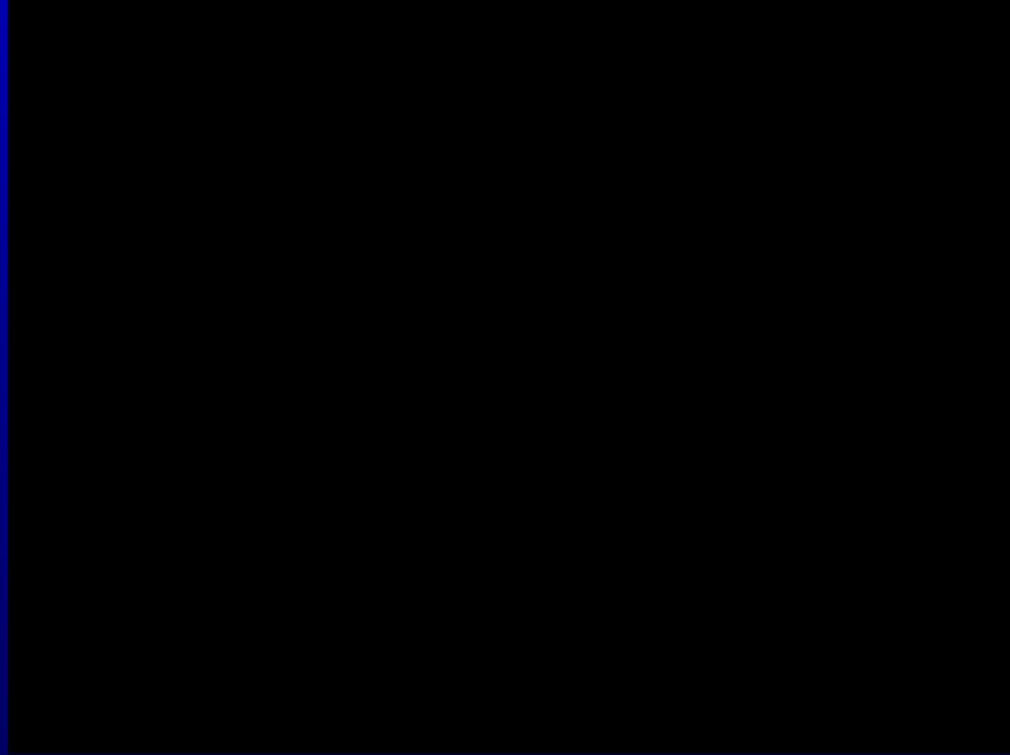
Transscleral Approach

- Transscleral delivery of stem cells: via peripheral subretinal space



Transscleral Approach

- Transscleral delivery of stem cells: via posterior subretinal space



**Courtesy of
Allen Ho,
Wills Eye
Hospital**

Stem Cells

- **Embryonic**
 - RPE (Ocata)
 - Photoreceptors (ReNeuron)
 - Trophic (Stem Cells, Inc)
- **Umbilical**
 - Trophic (Janssen)
- **Induced Pluripotent (iPS)**

Stem Cells

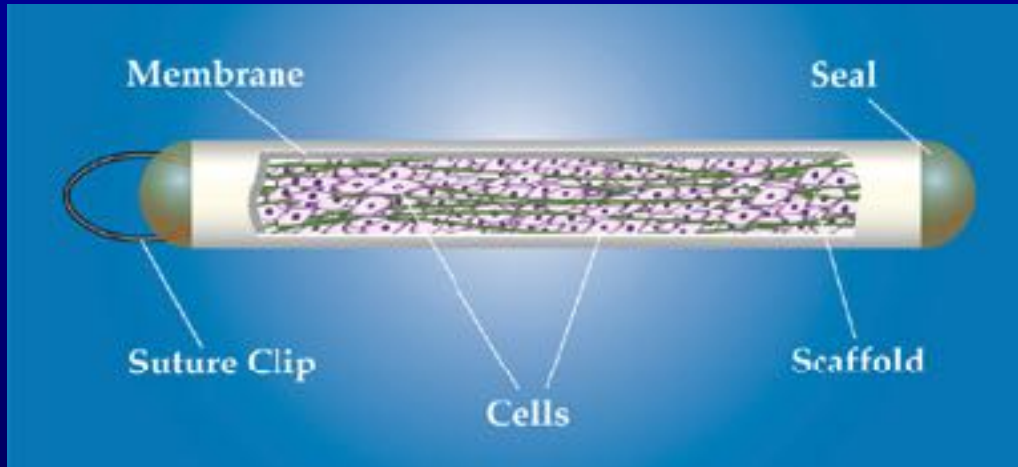
- **Induced Pluripotent (iPS)**

– Skin cells → Stem Cells → RPE (Riken Institute, Japan)

- Patient #1: doing well
- Patient #2: mutations identified prior to transplantation

Cell & Gene Therapy

- Neurotech
 - NT-501 implant
 - Cells encapsulated within a semi-permeable polymer membrane and supportive matrices in a hollow fiber configuration

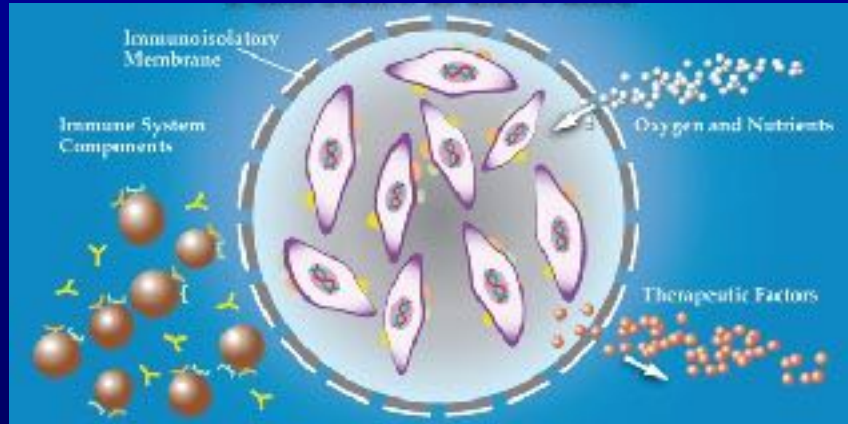


**Encapsulated Cell
Technology**

Cell & Gene Therapy

- Neurotech
 - NT-501 implant
 - Cells encapsulated within a semi-permeable polymer membrane and supportive matrices in a hollow fiber configuration

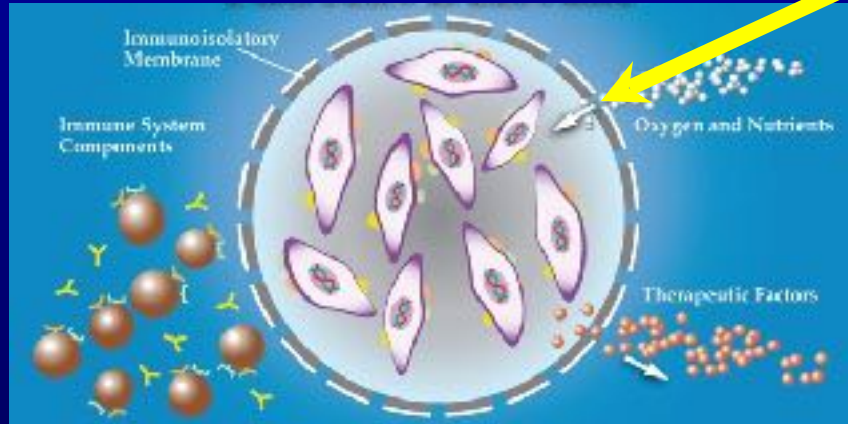
**human RPE cells
transfected with
CNTF gene**



Cell & Gene Therapy

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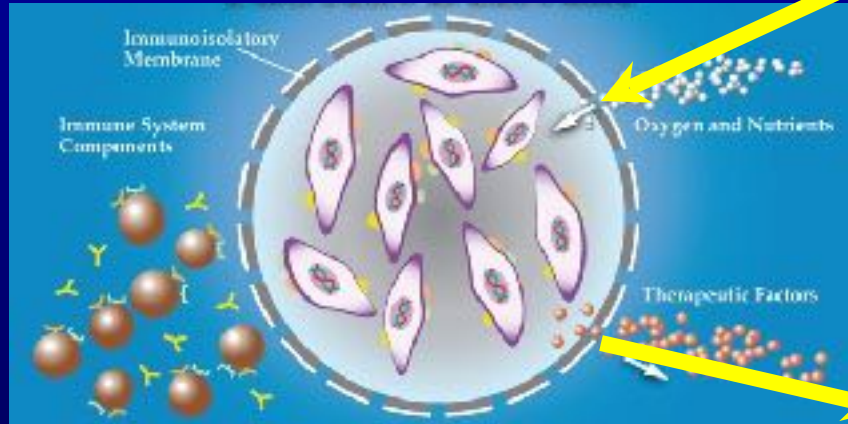
inward diffusion of oxygen and nutrients to support cell survival



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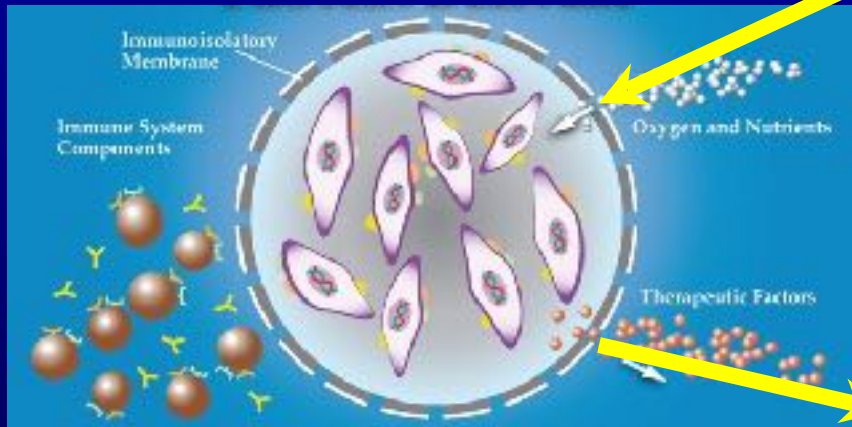
inward diffusion of oxygen and nutrients to support cell survival

outward diffusion of ciliary neurotrophic factor (CNTF)

human RPE cells transfected with CNTF gene

Cell & Gene Therapy

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inward diffusion of oxygen and nutrients to support cell survival

outward diffusion of ciliary neurotrophic factor (CNTF)

human RPE cells transfected with CNTF gene

both a device and a biologic

Cell & Gene Therapy

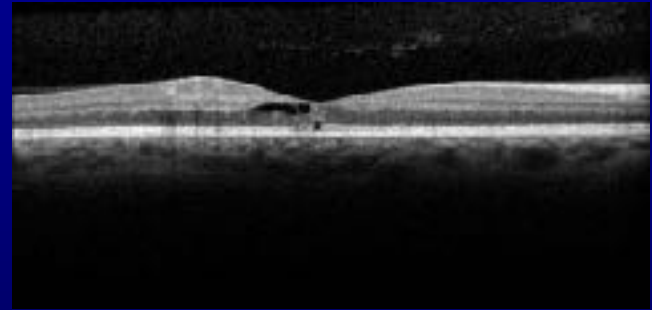
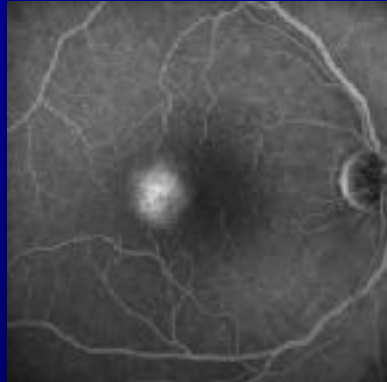
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6 mm x 1 mm



Cell & Gene Therapy

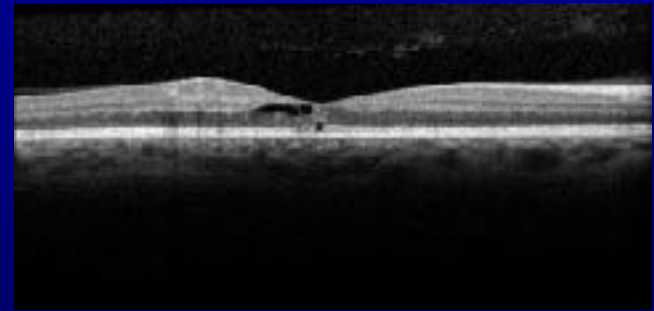
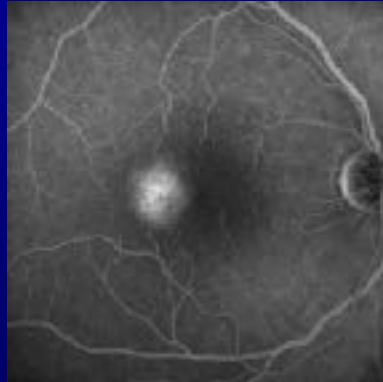
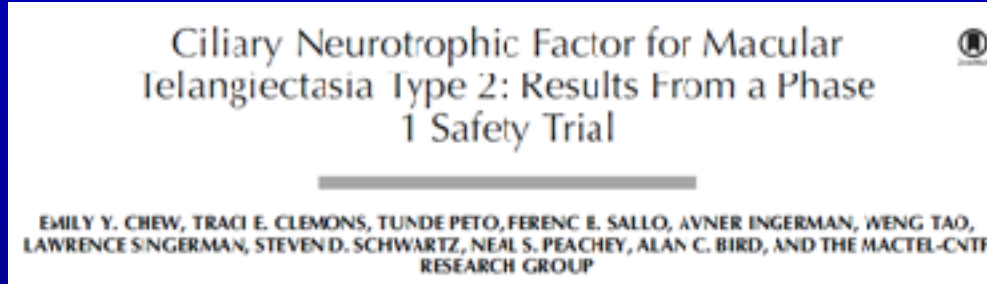
- Neurotech
 - CNTF: growth factor that preferentially stimulates and protects neural cells, including photoreceptors
 - slows photoreceptor cell death in animal models of retinal degeneration



Promising candidate for the treatment of Macular Telangiectasia

Cell & Gene Therapy

- Neurotech



Promising candidate for the treatment of Macular Telangiectasia

Cell & Gene Therapy

- Neurotech
 - Multi-center, masked, sham-controlled, phase 2 clinical trial
 - 68 patients with MacTel

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 - Primary outcome:
 - change in IS/OS at 24 months
 - Secondary outcomes:
 - change in BCVA
 - change in retinal sensitivity using microperimetry

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- Neurotech
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 - change in retinal sensitivity using microperimetry

Positive results

Summary – Stem Cells

- Cell replacement
 - RPE
 - Ocata Therapeutics
 - Photoreceptors
 - ReNeuron
- Trophic factors
 - Stem Cells, Inc
 - Janssen (J&J)



Summary – Combined Therapy

- Combined cell-based and gene therapy
 - **Neurotech**
 - Macular Telangiectasia

