CIRM DISEASE TEAM GRANT - MACULAR DEGENERATION

USC Doheny Eye Institute
- Mark Humayun, PI
- David Hinton Co-PI

UCSB Macular Degeneration and Stem Cell Centers
- Dennis Clegg, Co-PI
- Lincoln Johnson

Caltech Biology and Chemistry
- Scott Fraser
- Bob Grubbs
- Yu-Chong Tai

City of Hope Center for Biomedicine and Genetics GMP Facility
- Larry Couture

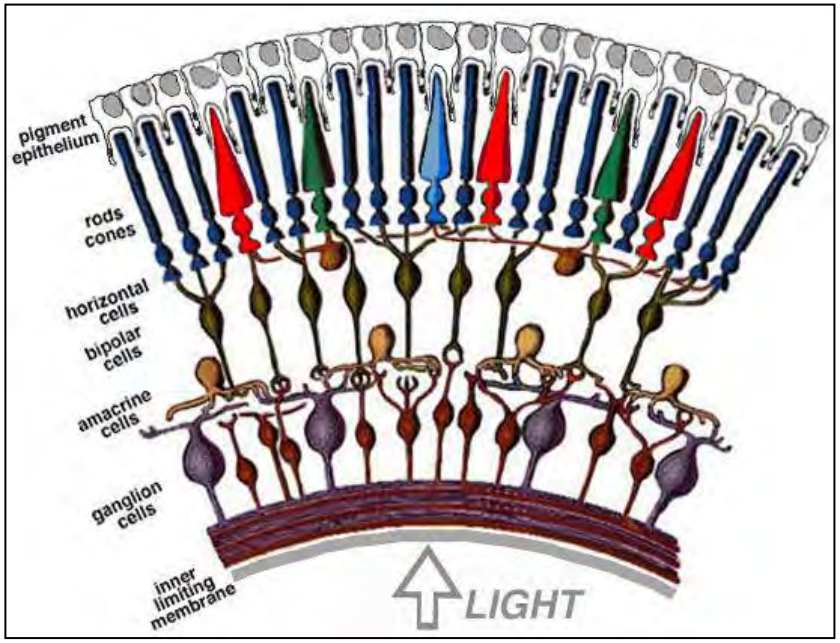
THE CALIFORNIA PROJECT to cure blindness

Regenerative Patch Technologies™

Jane Lebkowski, PhD
Katy Spenk, PhD

Univ College of London; Pete Coffey; MRC Partnership

Age Related Macular Degeneration

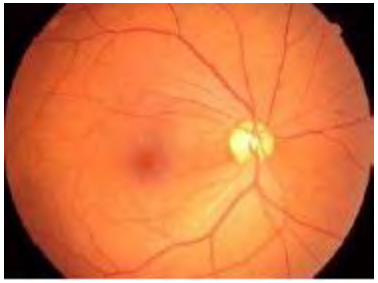


- AMD is a leading cause of blindness in people over the age of 55.
- Responsible for approximately 20% blindness in the U.S.
- Responsible for approximately $250B healthcare costs in U.S. annually

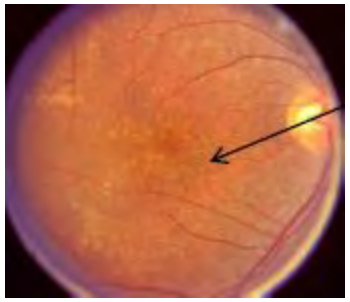
- Characterized by progressive loss of fine acuity vision in central portion of the visual field.
- Loss of vision is due to dysfunction of retinal pigment epithelium (RPE) and eventual death of RPE and photoreceptors in the macula.
- Good candidate disease for cell-based therapeutics.

Proposed Treatment Addresses Disease Pathology

Normal

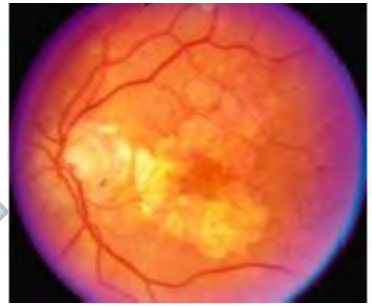


Early AMD

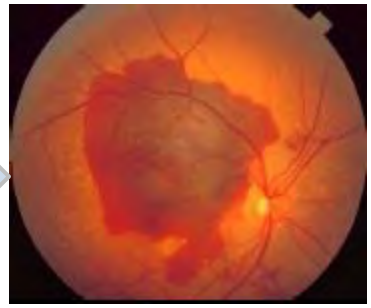


- Dysfunction of retinal pigmented epithelium (RPE)
- Degeneration of Bruch's membrane
- Accumulation of drusen

Advanced AMD



Dry (atrophic) AMD
80-90%



Wet (exudative) AMD
10-20%

- Loss of photoreceptors
- Vision loss

Treatment Hypothesis: Replace damaged RPE on synthetic Bruch's membrane to prevent vision loss

Dry AMD: Current Standards of Care

- Multivitamins (ARED Preservision) only slow the progression in early AMD.
- Macular translocation has improved vision in some patients but has many clinical complications.
- Other approaches for transplanting autologous or fetal RPE have high retinal detachment risks and/or are limited by availability of tissue.

Dry AMD: Competitive Landscape

Approach:	Company:
› **Pharmacological:**	ReVision Fenretinide (phase IIb)
	Acucela ACU-4429 (phase II)
	Psivida Illuvien (phase II)
	Genentech Anti-Factor D (phase I/II)
	MacuCLEAR (phase I)
	Ophthotec ARC 1905 (phase I)

Advanced surgical methods, non-invasive imaging, excellent endpoint parameters, and small numbers of cells needed make dry AMD an excellent candidate for cellular therapy.

› **Stem Cell**:	Advanced Cell Technologies (phase I)
	StemCells, Inc. (phase I)
	UCL/Pfizer (preclinical)
	Cell Cure (preclinical)

Sources:
ClinicalData.gov,
Company Websites

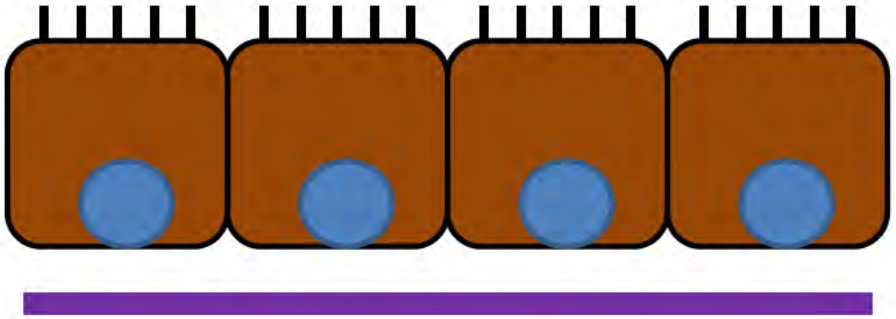
Key Attributes for Ideal Cell Based Product

Important Target Attributes:

- Provide Functional Support for Photoreceptors
- Provide Improvement in Visual Acuity
- Implanted Using Simple Procedures Developed for the Retina
- Safe and Efficacious with No or Localized Immunosuppression
- “Off-the Shelf” Product Readily Available for Patient Use
- Manufacturing Process Needs to Supply Doses Compatible with a High Demand Therapeutic
- Stable Shelf Life for At Least One Year
- No Complex Processing by Health Care Providers
- Have COGs Compatible with Reimbursement Policies

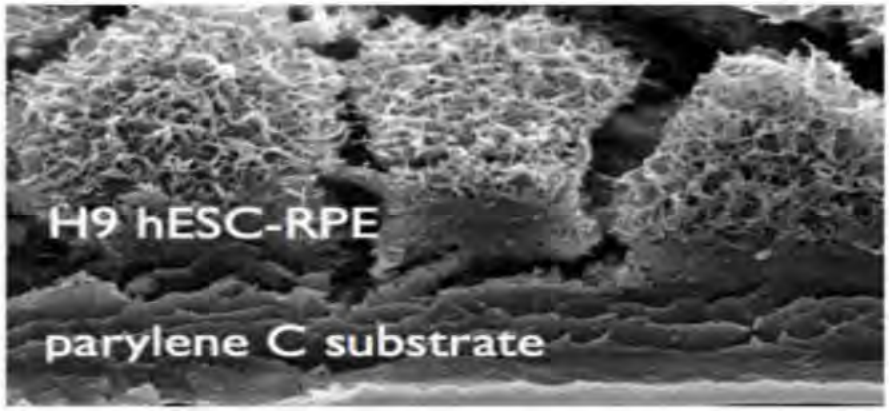
hESC-RPE Synthetic Substrate Patch

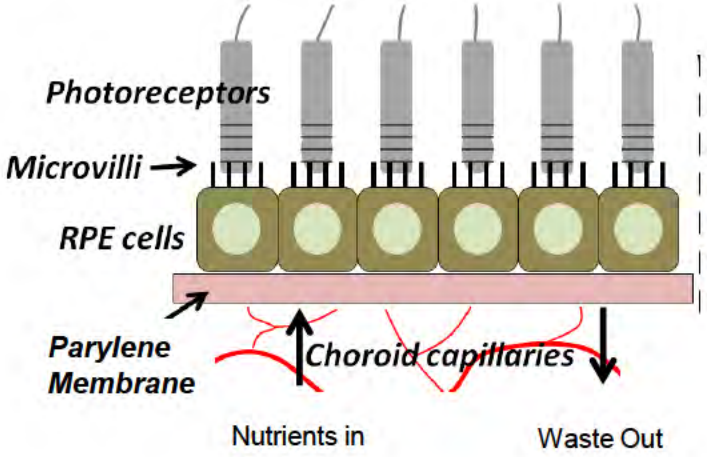
The hESC-RPE /synthetic substrate patch differs from current therapeutics



RPE Cells

Parylene Substrate





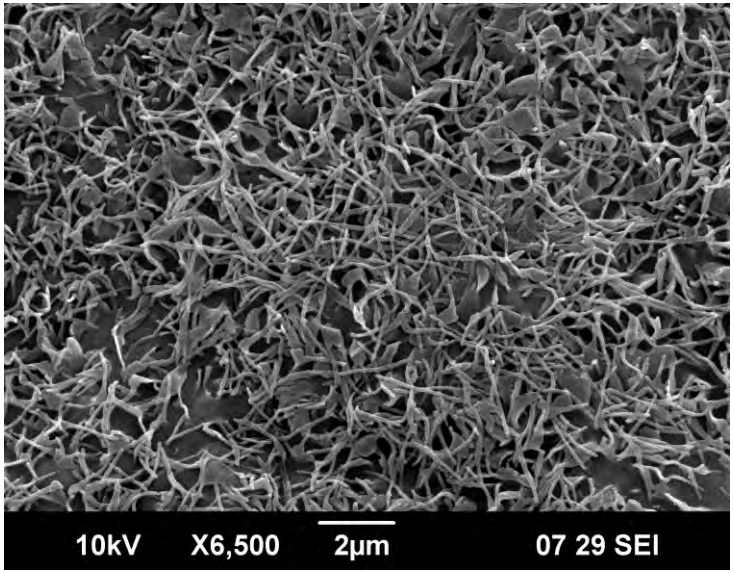
CPCB-RPE1

CPCB-RPE1: Why Polarized RPE on a Membrane Instead of Suspension RPE cells

Advantage Over Competitors Using Suspension Cells

Polarized RPE Cells

- Are non-proliferative
- Do not migrate and remain at the site of implantation
- Show increased neurotrophic growth factor (PEDF) secretion from the apical surface
- Secrete VEGF specifically from the basal surface to promote choriocapillaris survival
- Can integrate with PR outer segments thus promoting efficient phagocytosis of ROS
- Are more resistant to stress
- Have apical and basal domains that promote appropriate transport functions.

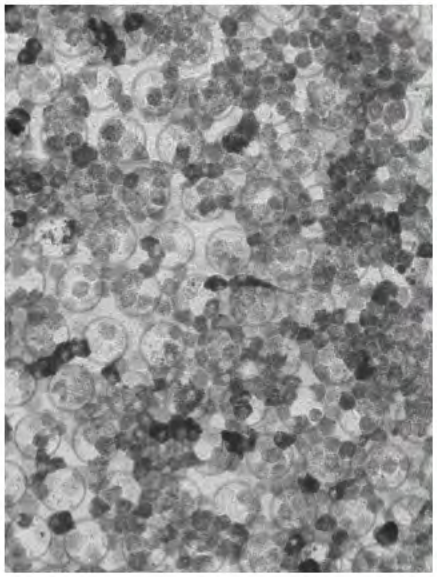


Polarized RPE on Parylene Membrane (4 mos)

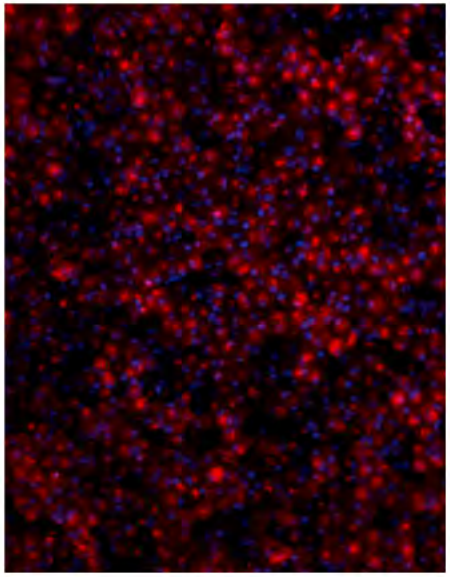
CPCB-RPE1: RPE Cell Phenotype

>99% RPE Cells as measured by Flow, ICC, qPCR

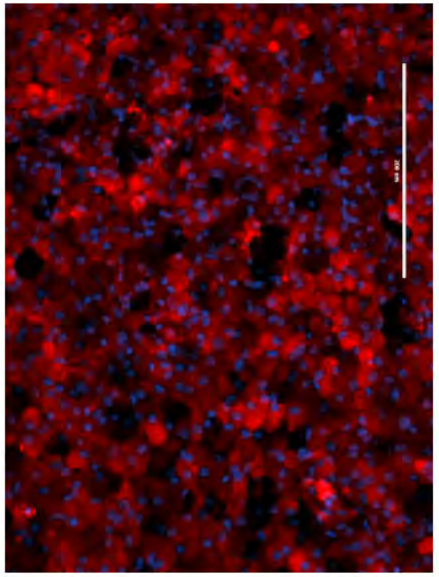
Morphology



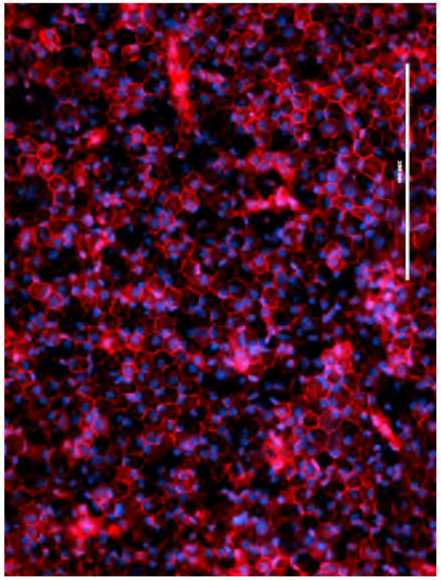
PMEL



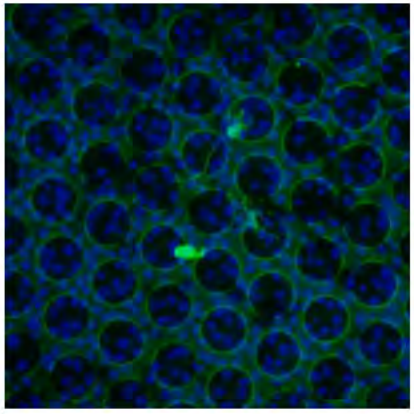
RPE-65



ZO-1

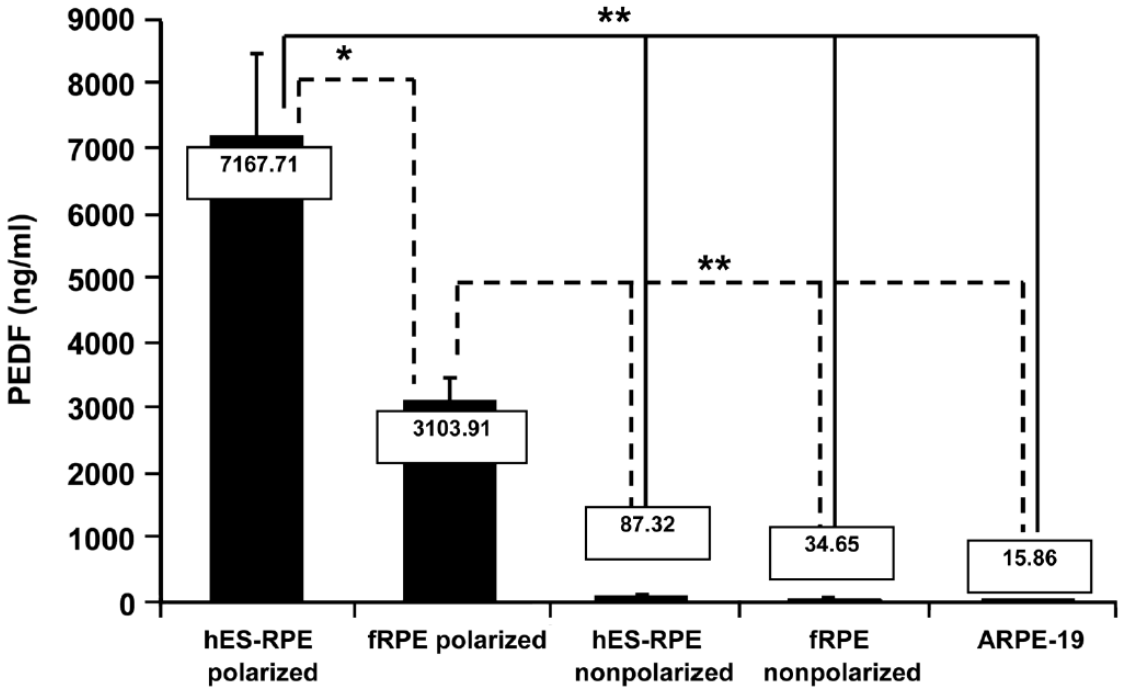


MAP2



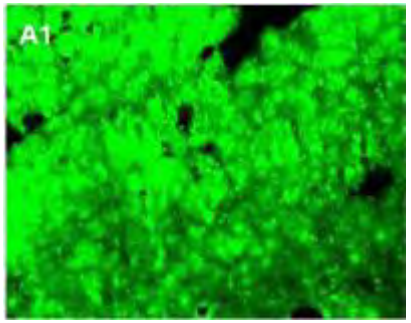
∴ (3) MAP2 (+) cells, with neuronal morphology were observed in a field of approximately 37,500 cells → ~0.008% incidence of MAP2 (+) cells

Polarized RPE Secrete More PEDF

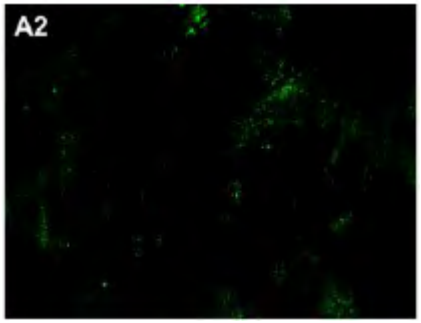


PEDF

Polarized RPE

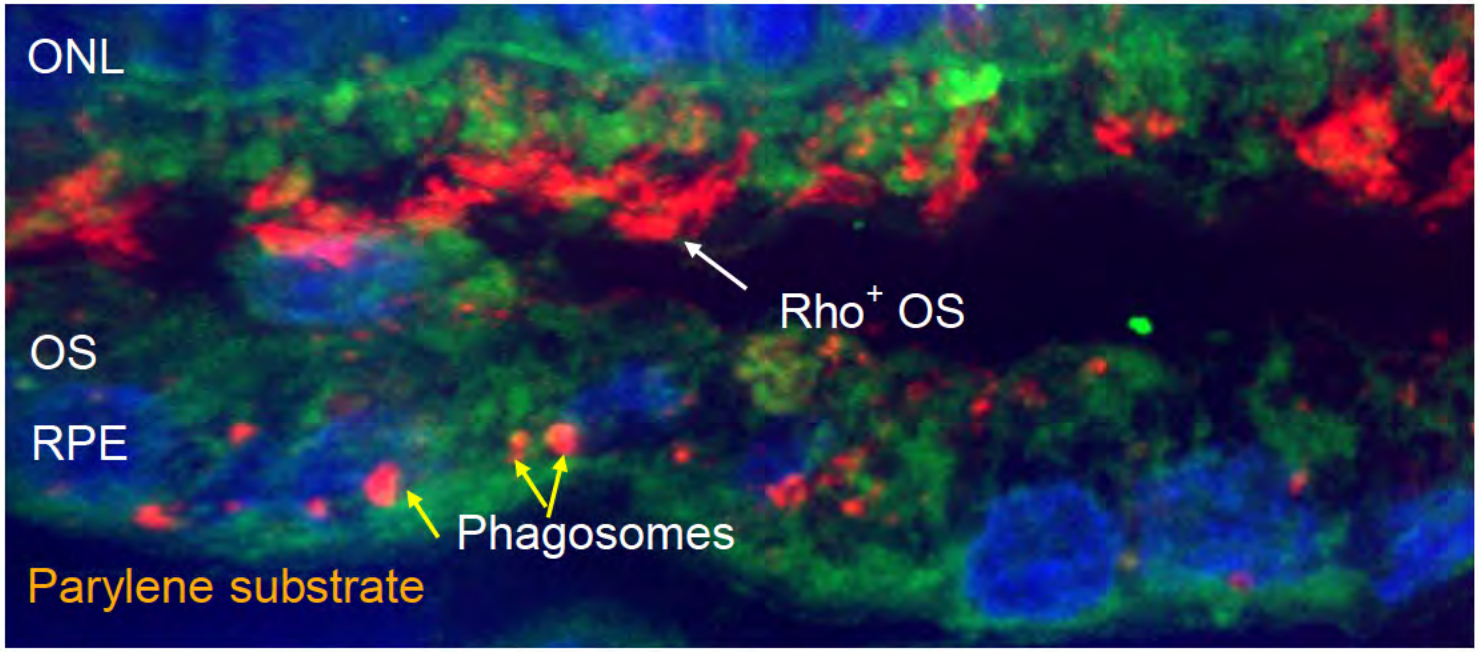


Non-Polarized RPE

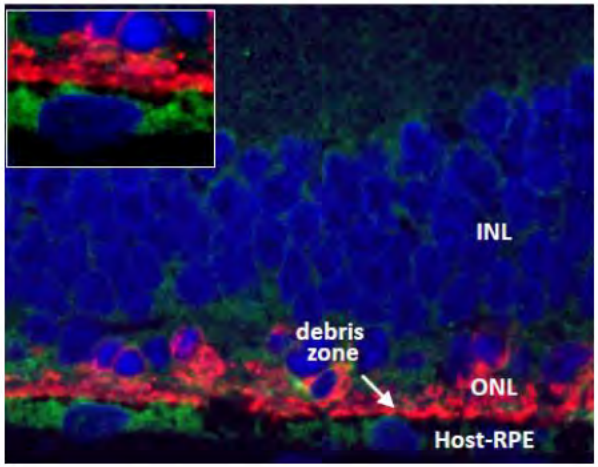


CPBE-RPE1 Phagocytoses Photoreceptor Outer Segments in the Host Retina

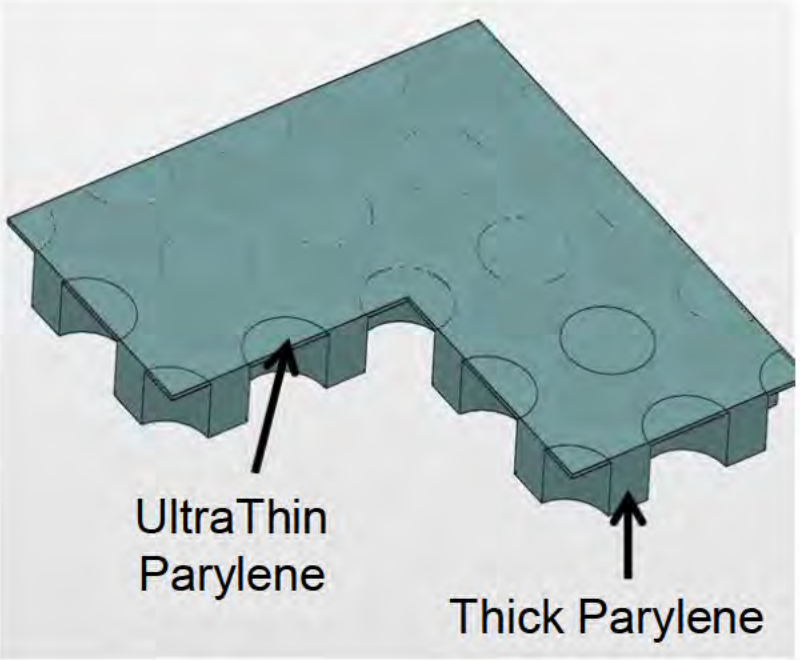
60 days after implantation



Phagocytosis not observed in native RCS retina



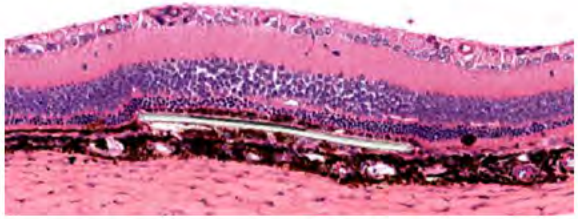
Design of Parylene Membrane Supports Nutrient Exchange and Mechanical Strength



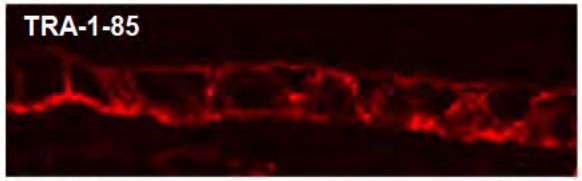
- Parylene is a biocompatible material with a proven medical track record
  - USP Class VI
  - Used for more than 3 decades for implant leads
- Thick parylene mesh (6µm) provides mechanical support
- Ultrathin parylene membrane (0.3µm) provides nutrition diffusion zone (>1000kD)

CPCB-RPE1 Cells Survive Post Transplant

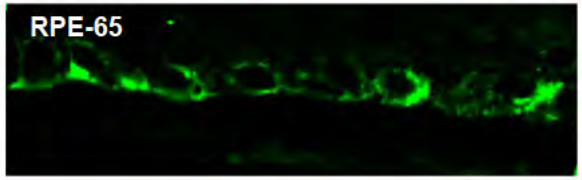
RCS rat retina with CPCB-RPE1 : good RPE survival along the implant



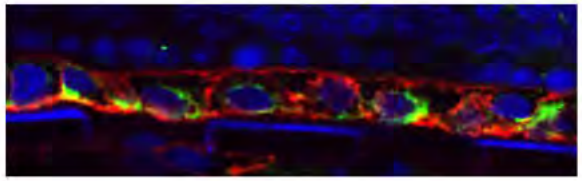
60 days post implantation



Human



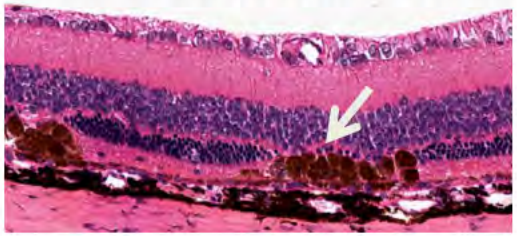
RPE

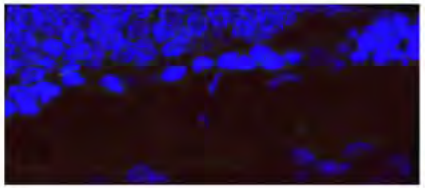


DAPI

Human RPE Cell Survival Observed for at Least 6 Mos.

RCS rat retina with hESC-RPE cell suspension : Poor (10%) RPE Cell Survival



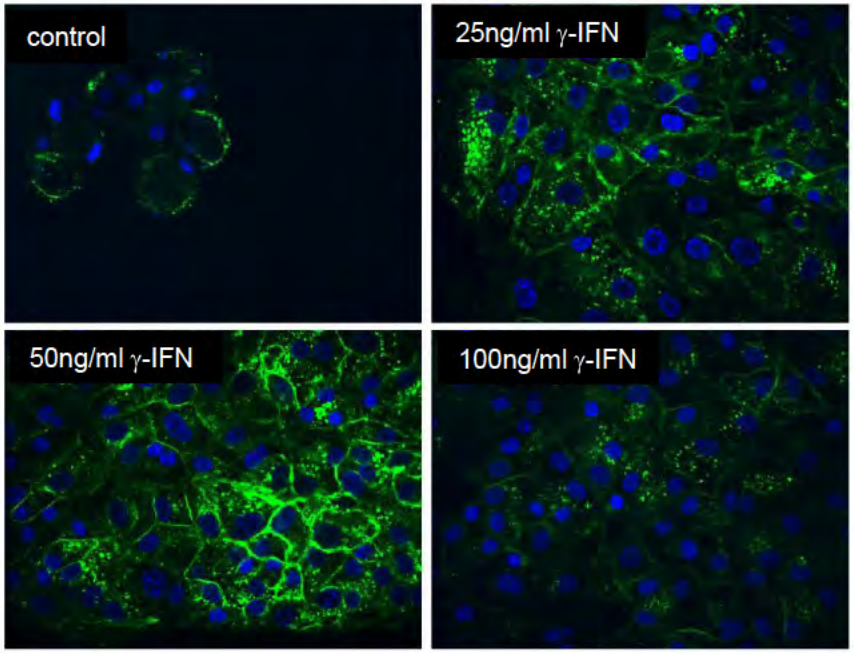


TRA-1-85 and RPE-65 were not expressed in the cell clumps (arrow) found in rat's subretinal space

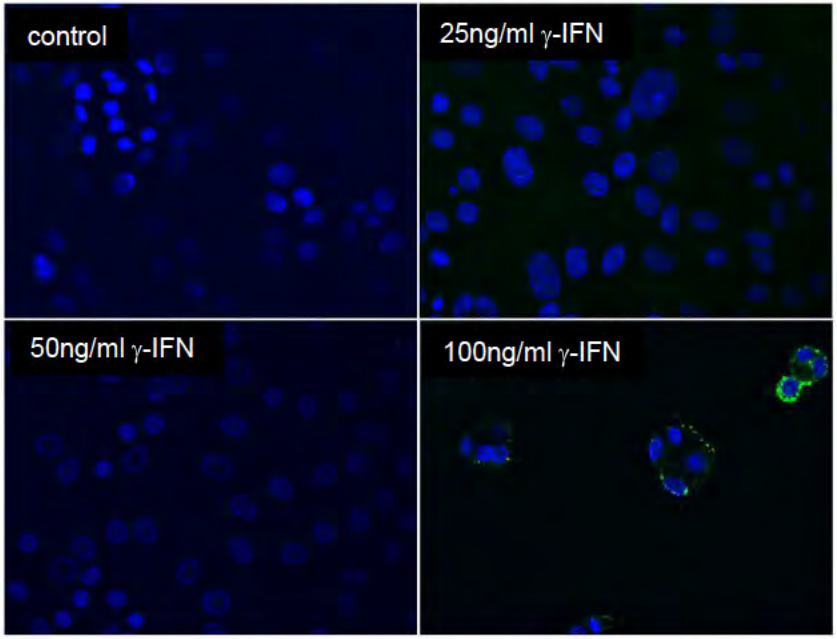
CPCB-RPE1 Cells Express MHC Class I and Not Class II

In Vitro

MHC Class I

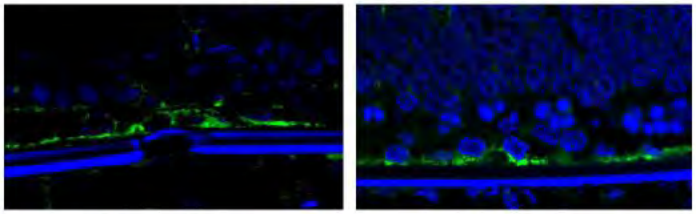


MHC Class II



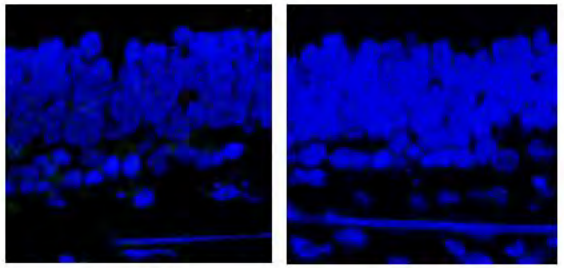
In Vivo

MHC Class I



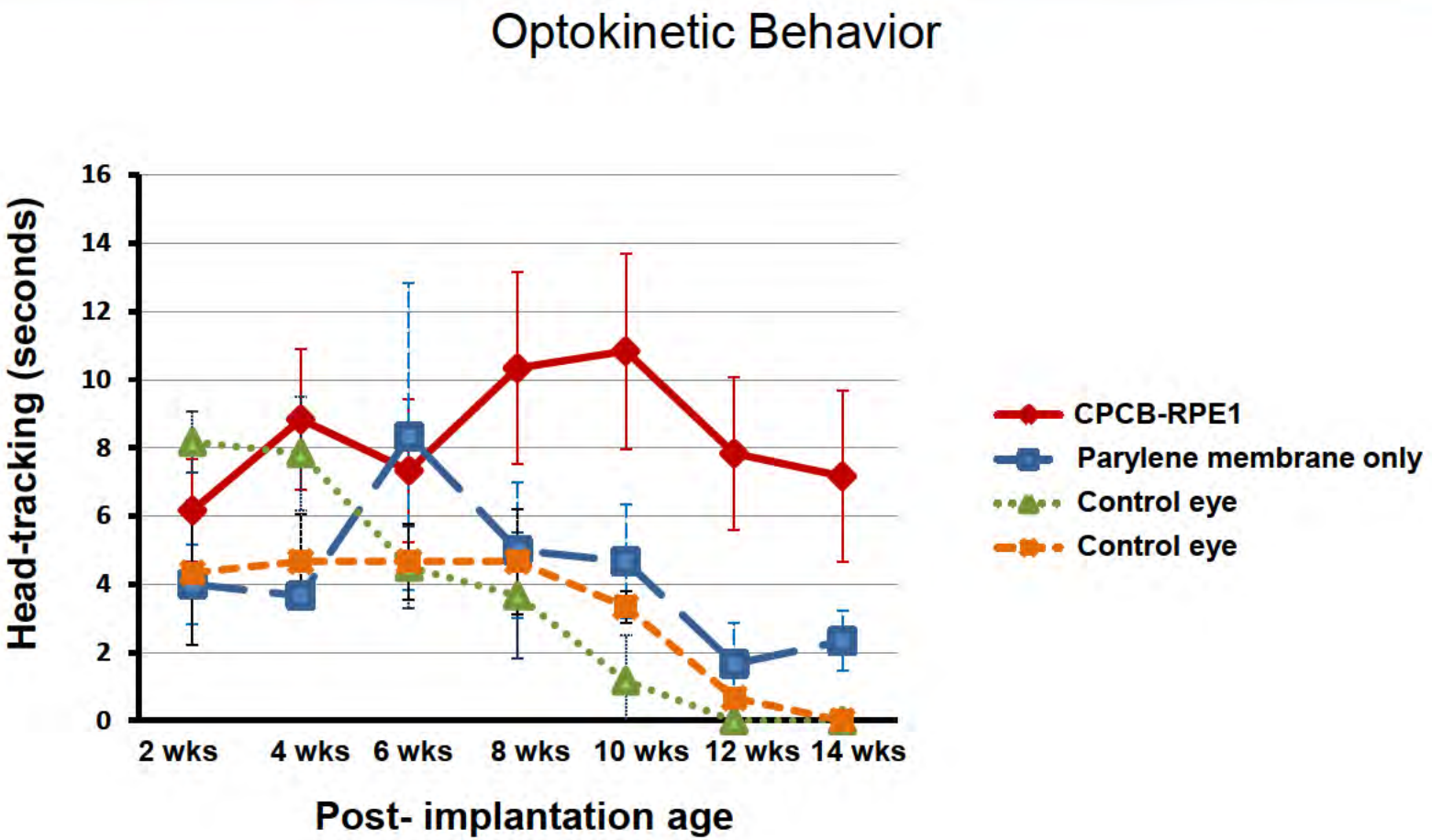
2 months 5 months

MHC Class II



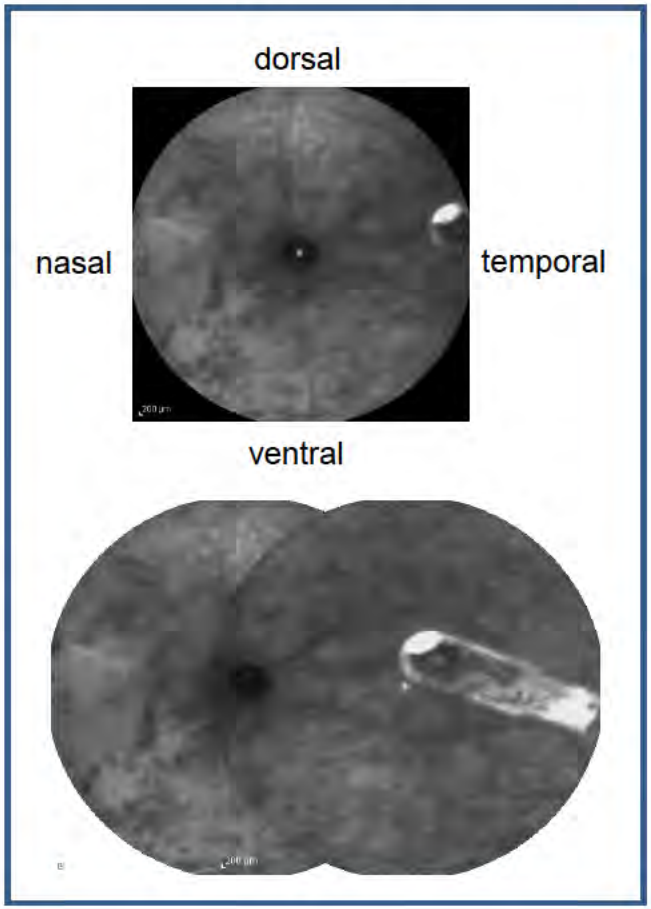
2 months 5 months

CPBE-RPE1 Prolongs Visual Acuity in the RCS Rat

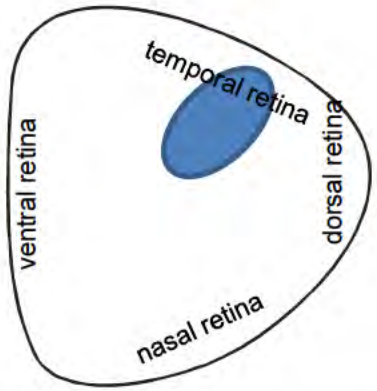


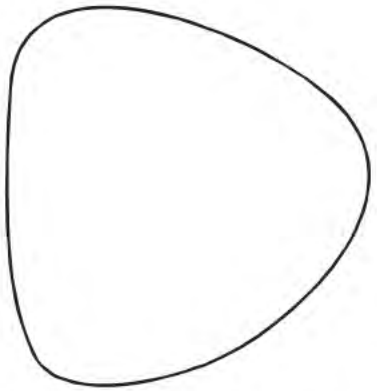
Superior Colliculus Electrophysiology Shows Positive Effects of CPCB-RPE1

CBCP-RPE1 implanted RCS rat
(6 months post-implantation)



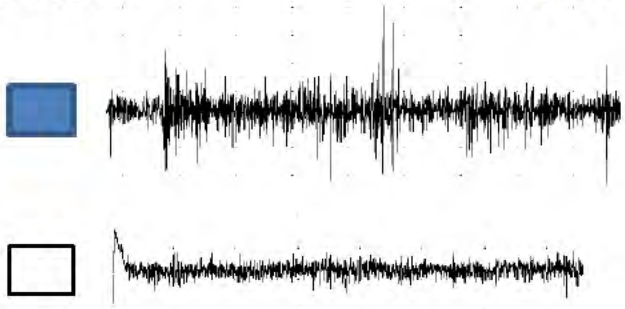
At Threshold Stimuli Responses Recorded in Area of Implant





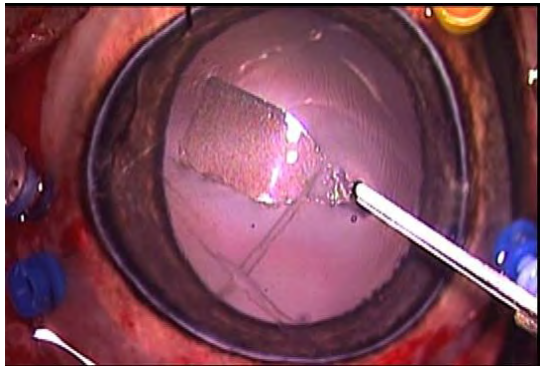
hESC RPE implanted RCS rat SC

Age-matched non-implanted RCS rat SC

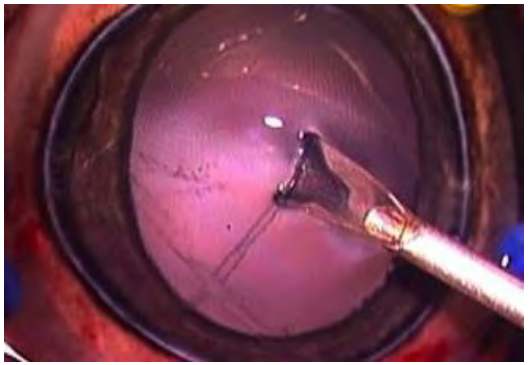


Delivery of CPCB-RPE1
Pars Plana Approach; Custom Implantation System

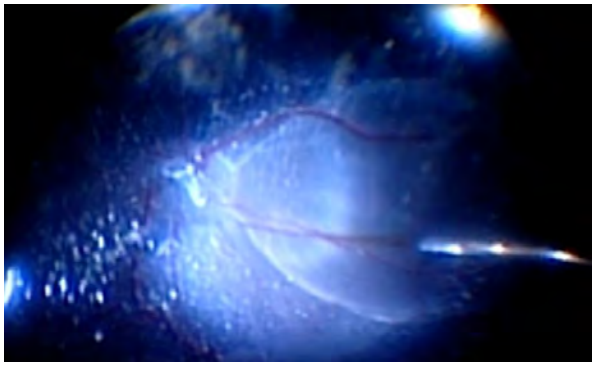
Delivery in the Yucatan Pig



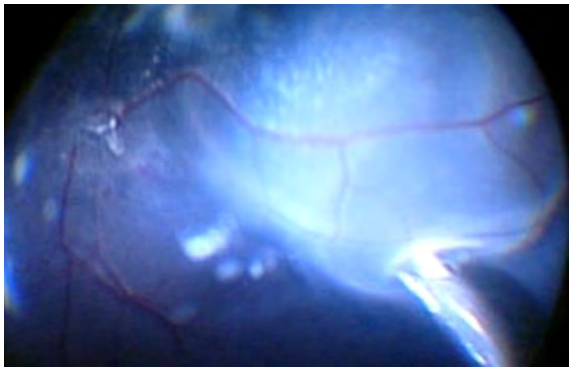
Complete Pars Plana Vitrectomy
Substrate on the corneal surface



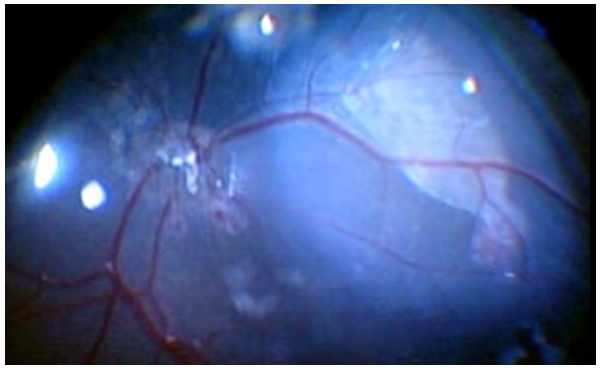
Folding with the tissue injector



Cannula Used to Inflate Blister
Between Retina and Choroid
Peripheral Retinotomy 1.5 mm



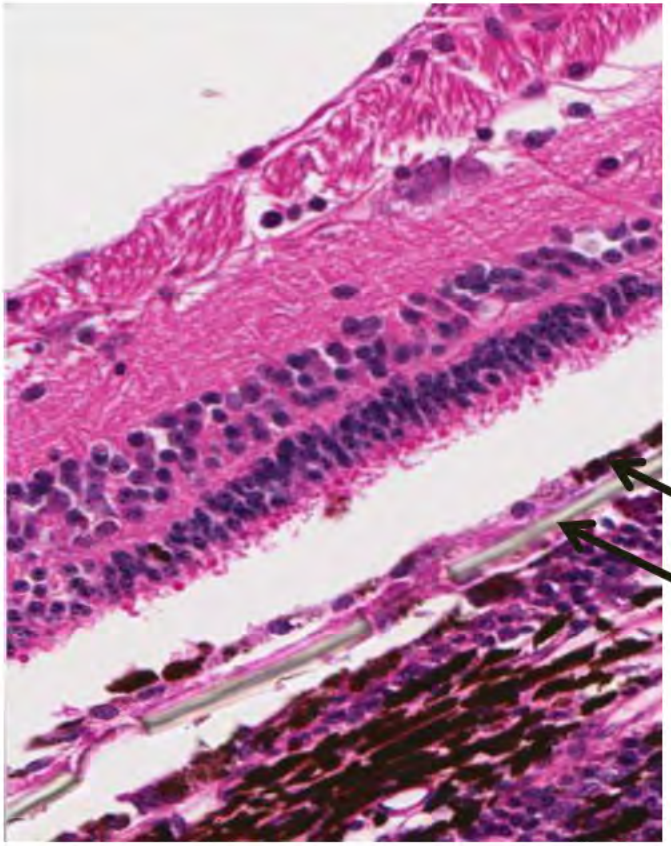
Subretinal implantation with the tissue injector



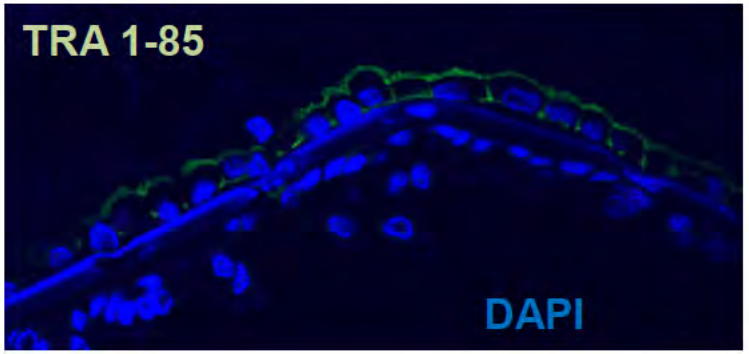
Blister Evacuated. Perfluorocarbon liquid
and laser retinopexy. Air-Oil exchange

CPCB-RPE1 Survives in the Yucatan Pig Subretinal Space

3 Months after Surgical Implantation



hESC-RPE



Release of CPCB-RPE1 Product

COMBINATION PRODUCT; PMOA is biologic/cell based

Final Release of CPCB-RPE1 Will Assess

- CELLS
  - Morphology
  - Viability
  - % Membrane Coverage
  - Targeted Cell Compositional Analysis
  - Non-targeted Cell Compositional Analysis
  - Candidate Potency Markers
  - Sterility
  - Mycoplasma
  - Endotoxin
- SUBSTRATE
  - Toxicity/Sterility

CPCB-RPE1: Phase 1 Manufacturing Site and Process

City of Hope

Center for Applied Technology Development

cGMP Compliant Production of Cells, Vectors and Protein for Academia and Industry

- Manufacturing Process: Defined
- Technology Transfer and SOP Generation for ICB Production: Complete
- Manufacturing Protocols Transferred from UCSB to COH
- Production of 2 cGMP-compliant H9 MCBs Completed
- Raw Material Sourcing for ICB Production Complete
- Performance Testing of the MCB Underway to Produce ICBs
- MCB Adventitious Agent Testing to be Completed After Successful ICB Production
- Assay Transfer/Qualification: Underway
- Final Process for Membrane Plating, Culture, Release and Transport of CPCB-RPE1 Under Development.

FDA Pre-IND Meeting Outcome

Briefing Package Supplied to Office of Cell, Tissue and Gene Therapy of CBER

- Preclinical POC Studies
- IND Enabling Safety/Toxicology Studies
- Manufacturing Qualification Studies
- Clinical Study Details

Pathway to IND

Conclusions

COMBINATION PRODUCT

PMOA is biologic/cell based

Proof of Principle from pre-clinical studies

Manufacturing plan and site established

Pathway to IND defined- IND to be filed