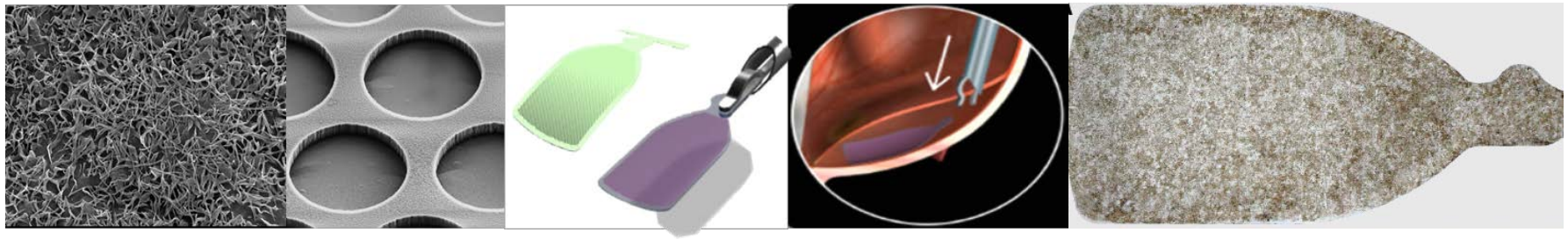
Advancing A Bio-Engineered Implant for Improvement of Vision in Dry-Age Related Macular Degeneration



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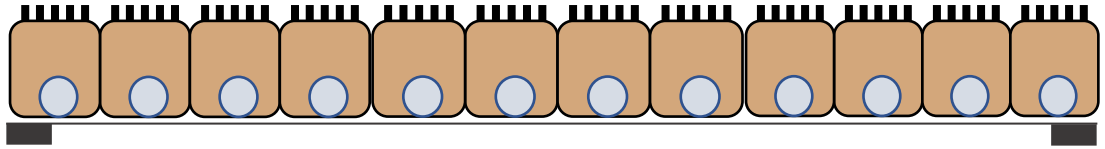
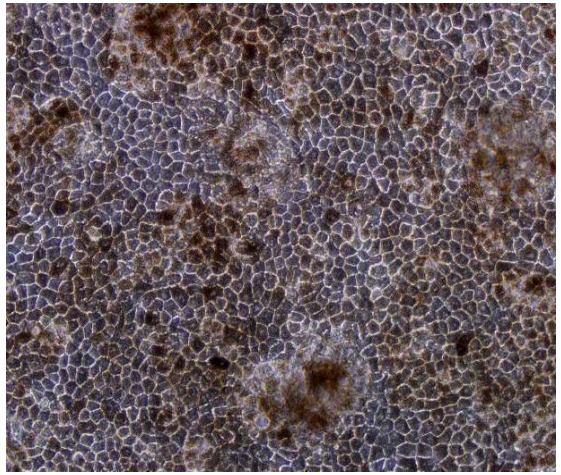
CPCB-RPE1: A Composite RPE Cell-Parylene Membrane Implant



Polarized Healthy RPE Cells:
Replace Dysfunctional RPE Layer in AMD Retina

Ultrathin Diffusible Parylene Membrane:
Replace Degenerating Bruch's Membrane

RPE Cells Produced from Pluripotent Stem Cells



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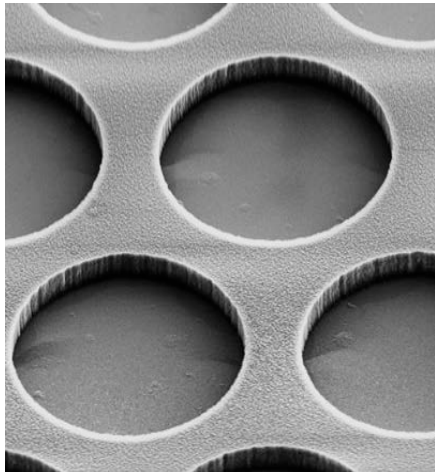
Ultrathin Parylene Membrane



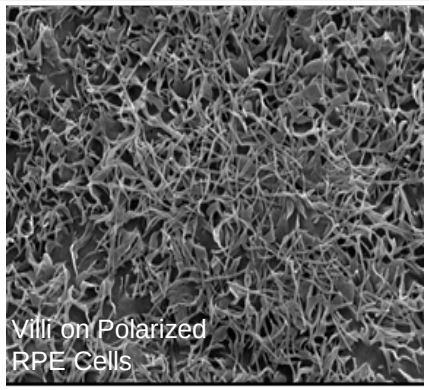
CPCB-RPE1 Implant

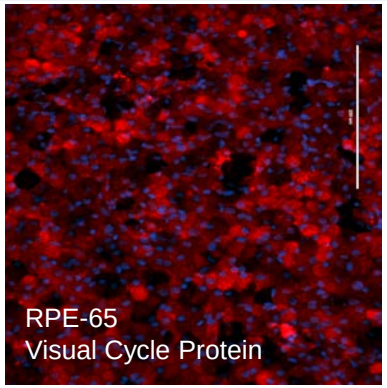
Implant Body

The CPCB-RPE1 Implant Has Two Key Components: RPE Cells and an Ultrathin Parylene Membrane

RPE Cells

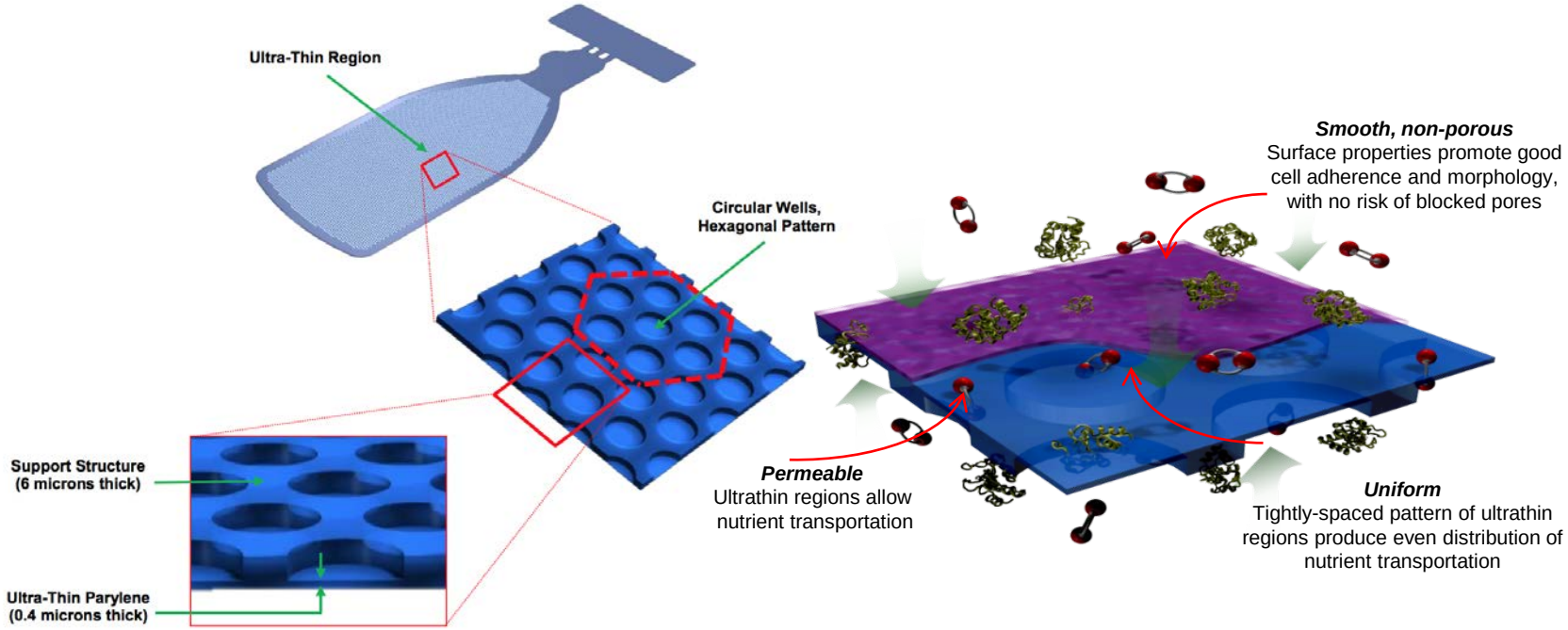
- Derived from pluripotent stem cells
- Polarize to have functional apical and basal surfaces as in native RPE cells in the retina
- Execute mature RPE cell function including visual cycle processing
- Integrate with photoreceptors to promote metabolic and growth factor support



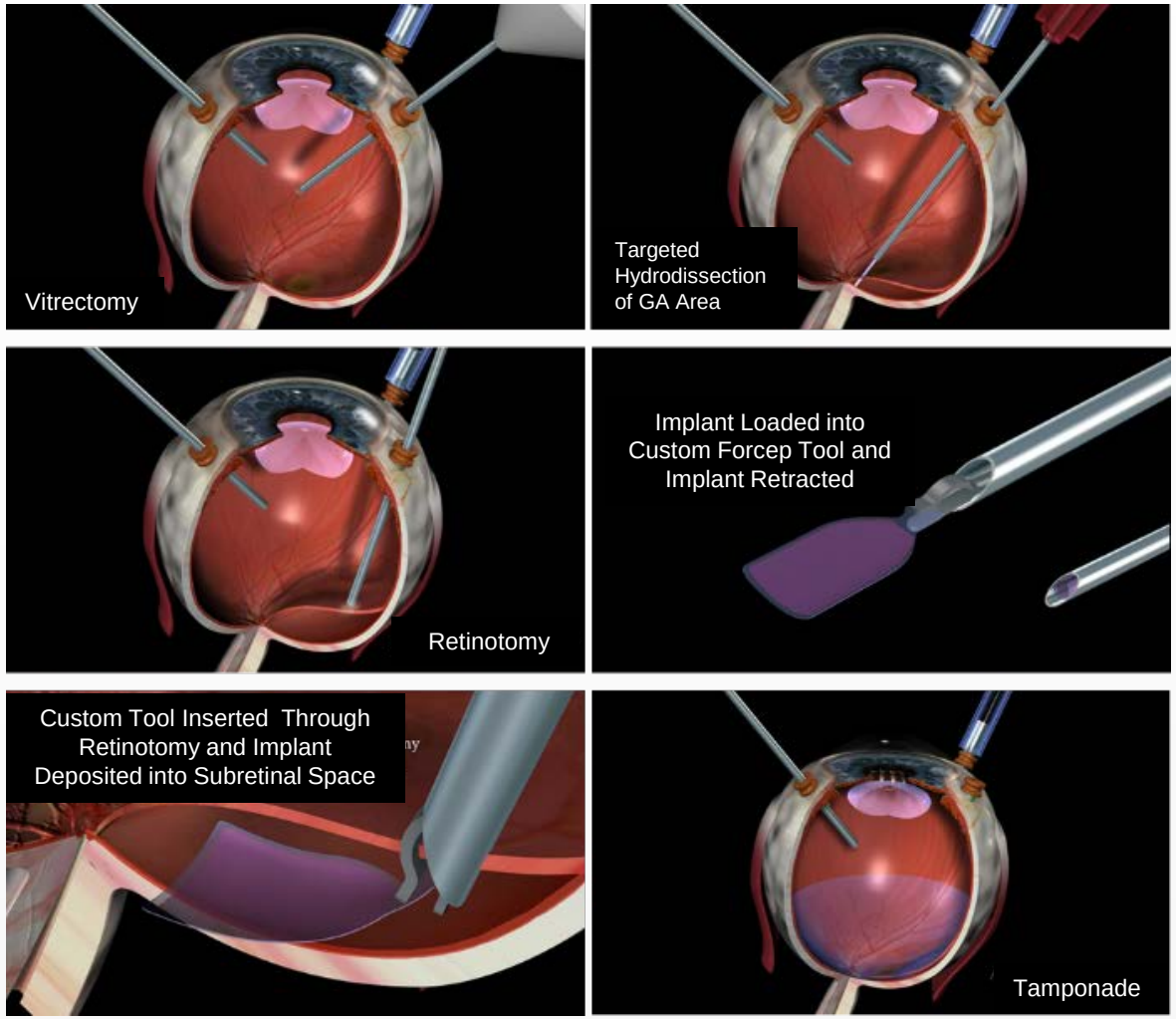


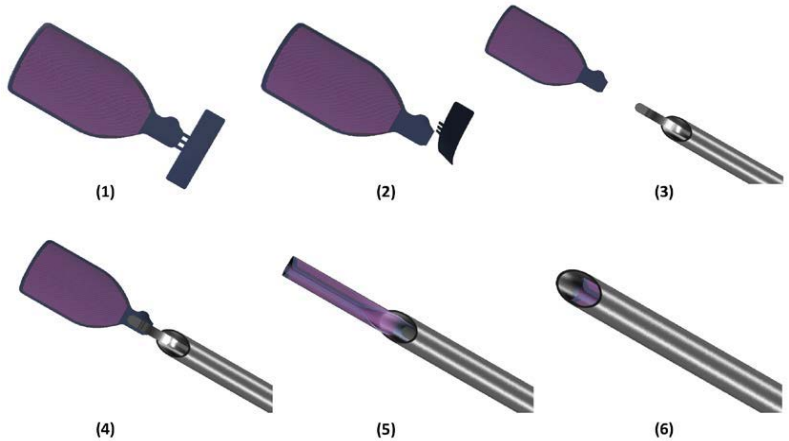
Ultrathin Parylene Membrane

- Healthy substrate for RPE cells to attach and polarize
- Fabricated with USP Class VI biocompatible parylene monomer
- Used >30 years in implantables
- Machined to precise thickness to create required diffusion properties similar to Bruch's membrane
- Provides flat surface without pores to limit cell penetration
- Is foldable to reduce retinotomy size during implantation



Implant Surgical Delivery: Uses Established Retinal Surgery Procedures





Custom surgical tool and ability to fold membrane enables delivery through 1.5mm Peripheral Retinopathy

- Uses Established Retinal Surgery Procedures
- Administered as Outpatient Surgery

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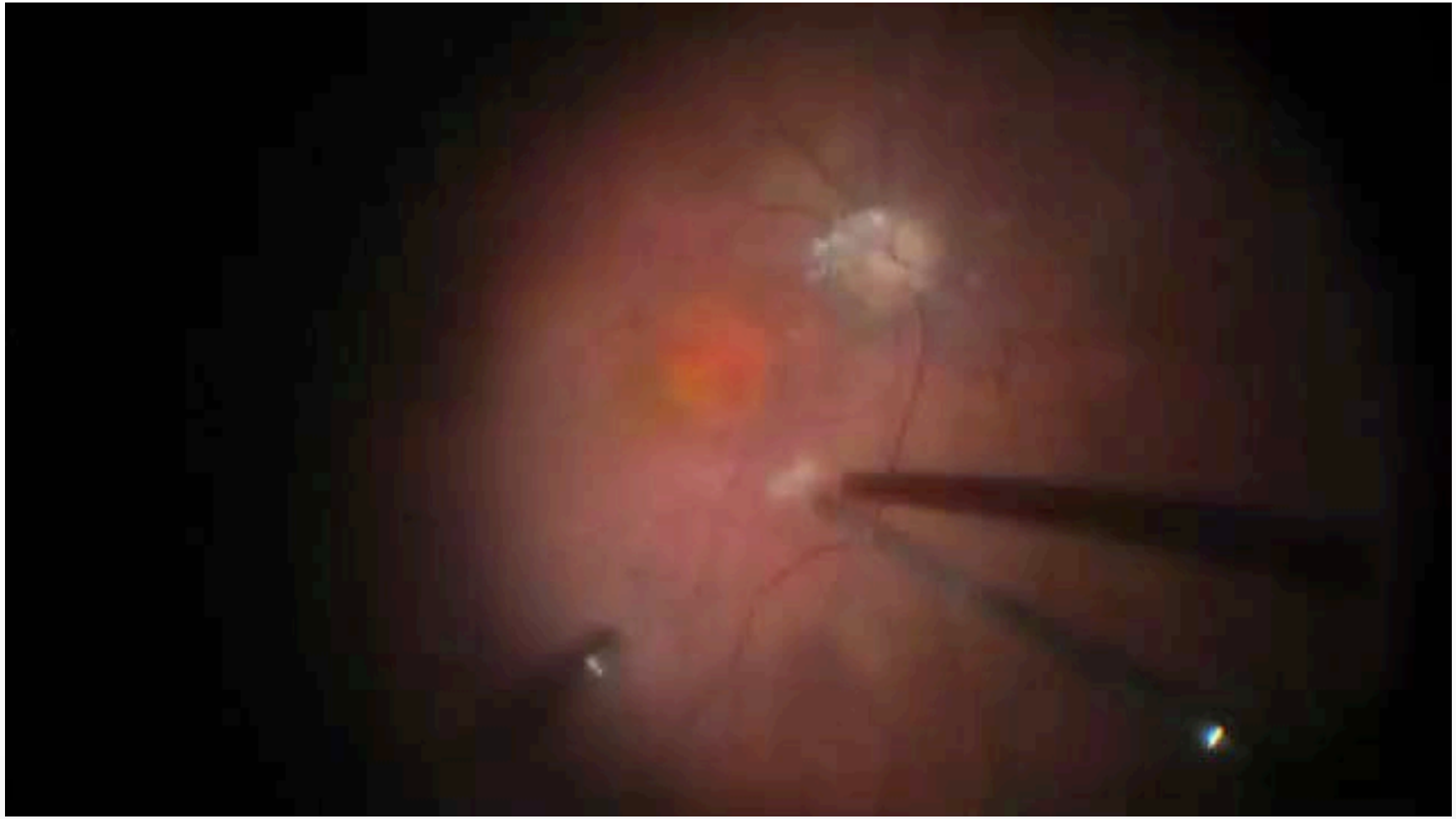
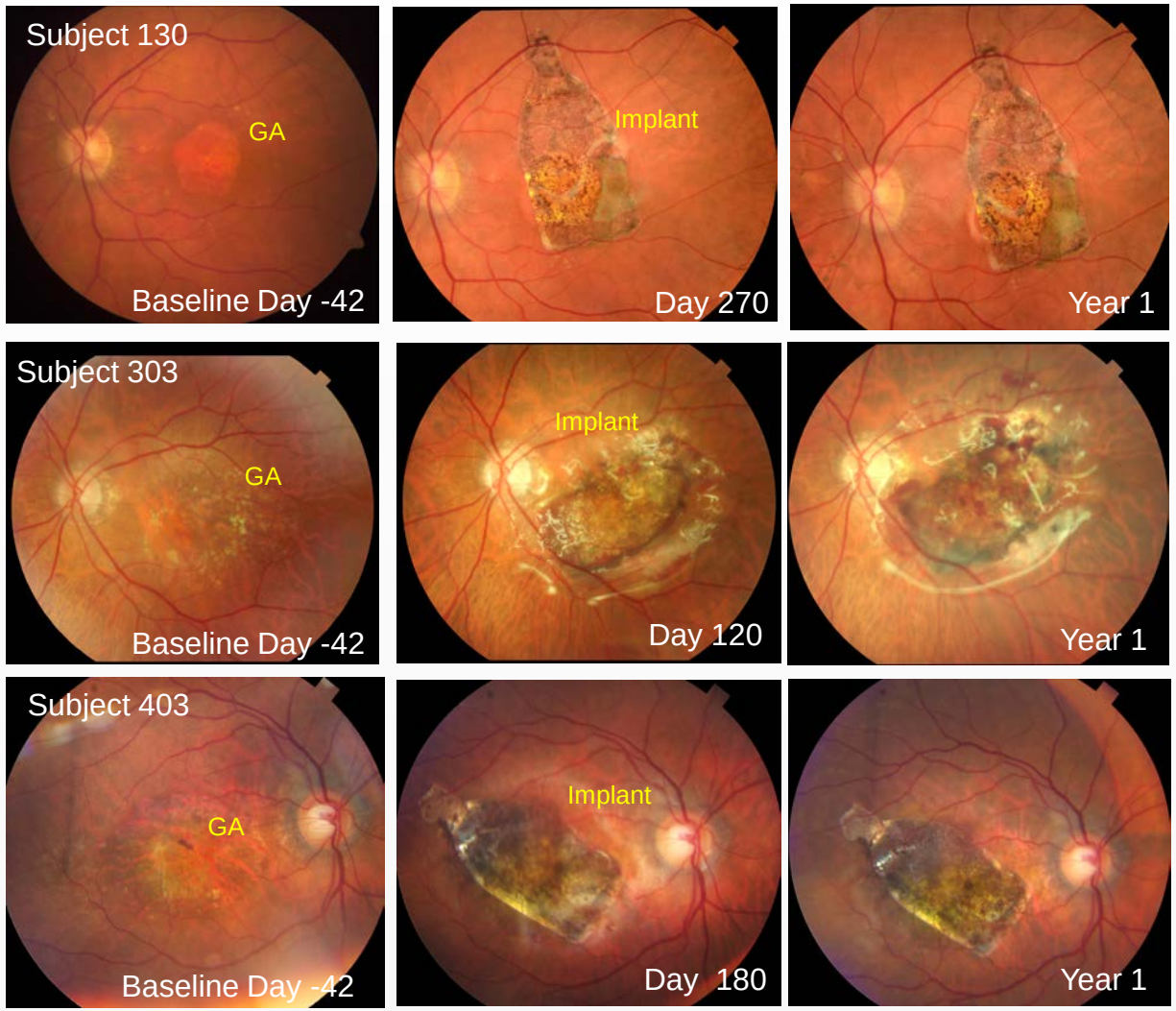
The Surgical Procedure: Subject 130



CPCB-RPE1 Implant Delivery Safe and Positioned Over Area of Geographic Atrophy



- The Surgical Procedure is Feasible and Safe in the Outpatient Setting
- Refined Implantation Procedure to Minimize Hemorrhage and Fibrinous Debris
- Implant Stably Positioned Over Area of GA in All Subjects
- Stable Position of Implant Over Time
- No Evidence of Implant Degeneration
- Implant Covers 100% of Fovea/Central Macular a Median 87% (30.5-100%) of the Area of GA.
- Percent Coverage Inversely Associated with Size of GA, Median 13.8mm^2 (6.0-46.4mm^2) in this Advanced Patient Population

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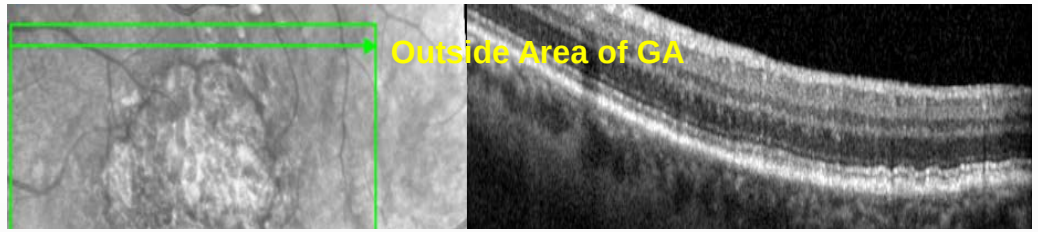
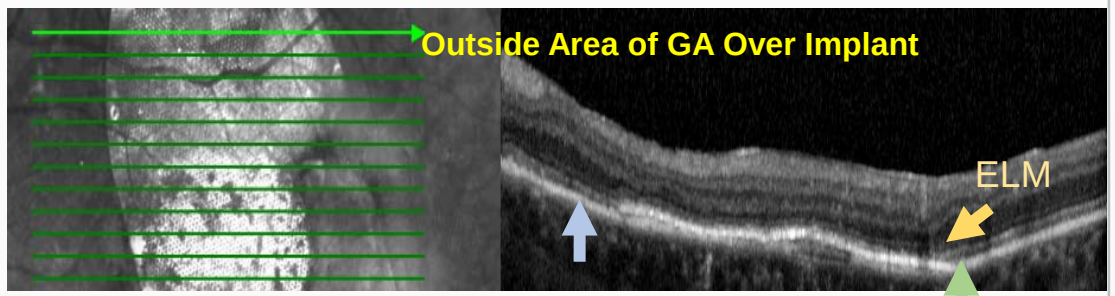
Safety Profile Through One Year of Follow-up





Host RPE Cells

CPCB-RPE1 Implant

- No unanticipated serious adverse events due to surgery or implant
- Ocular SAEs related to hemorrhage and edema confined to 4 of first 7 subjects in study. No ocular SAEs reported in first year of follow-up in subsequent 8 subjects due to better hemorrhage prevention
- 68-day tacrolimus immunosuppression regimen well tolerated in most subjects.
- No evidence of rejection of allogeneic RPE cells even with short immunosuppression course**.**
- RPE cells observed in histology specimens from subject who passed away due to unrelated causes 2 years after implantation.
- Good preservation and retinal architecture even when implant placed over an area with intact host RPE cells.

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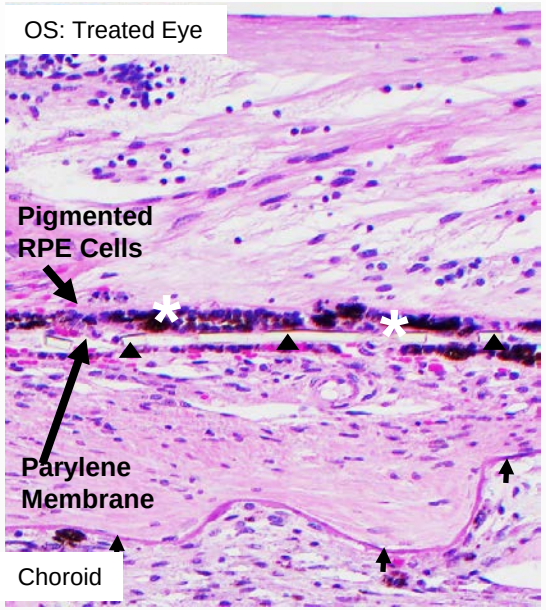
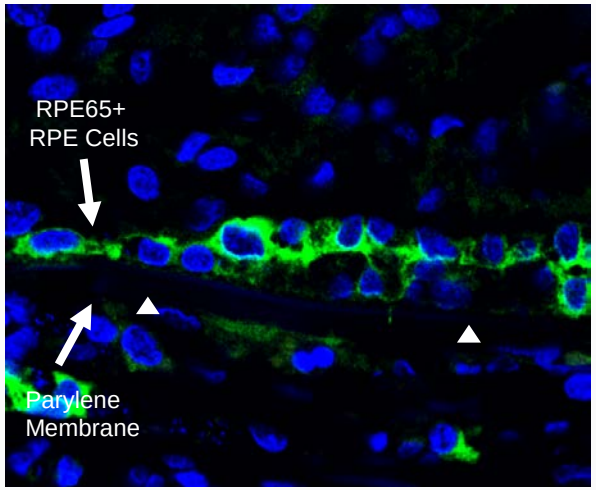
The Fully Allogeneic RPE Cells Survive at Least 2 Years with Only a Short Course of Immunosuppression

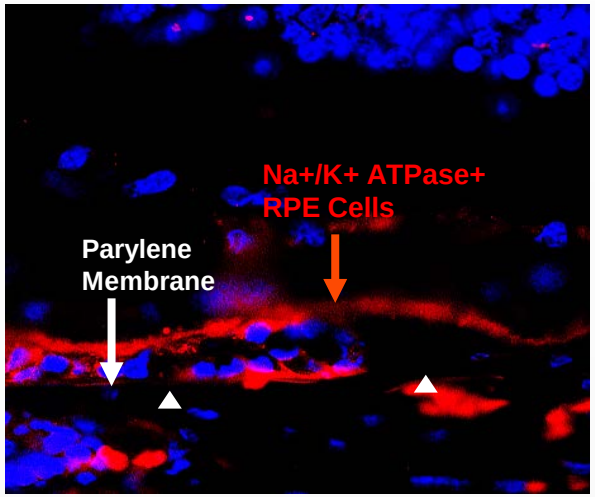
Histological sections through the implant at >2 Years post-administration in deceased subject 125



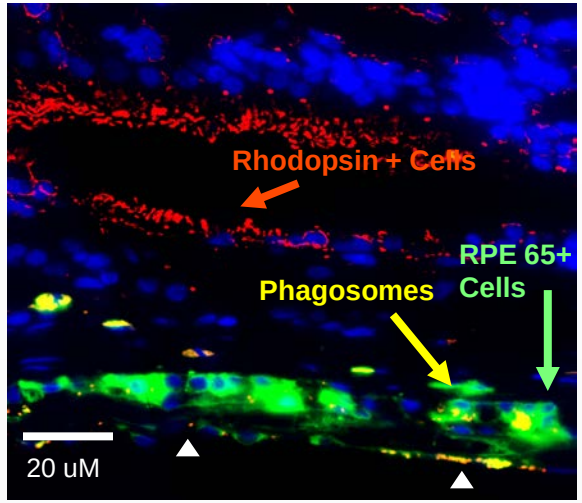
- Pigmented RPE Cells Survive on the Parylene Membrane at Least 2 Years



- Implanted RPE Cells Express RPE65, a Visual Function Protein



- Implanted RPE Cells Have Apical Expression of Na+/K+ATPase, Suggesting Polarized Mature Function.



- Spared Rhodopsin + Rosettes Over Implant
- Presence of Phagosomes Suggests Functional Integration of Implant RPE Cells

The RPE Cells are Polarized, Express Visual Function Proteins with Evidence of Phagocytic Activity

OS: Implanted eye; White Stars: Implanted HESC-RPE; White or Black Triangles: Parylene Membrane; Black Arrows Bruch's Membrane.

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Phase 1/2a Trial Shows Encouraging Signals of Activity in Legally- Blind Eyes

Background Context

- Reformation of the external limiting membrane associated with better vision in repair of macular holes*
- Improvement in BCVA in patients with advanced GA is exceedingly rare**
- Drugs in development now only strive to slow progression.

Signals of Activity at One Year Post- Implant

- Reappearance of external limiting membrane over the implant in some patients
- 27% (4/15) subjects showed >5 letter improvement in BCVA. Improvements range from 6-13 letters at 1 year.
- Best corrected visual acuity stable or improved in 67% (10/15) of subjects
- BCVA outcomes superior to that of the fellow untreated eye in majority of subjects

* Landa G et al 2012; 26, 61-69.
** Sunness JS et al Ophthalmology 1997; 104(10) 1677-1691

Implanted Eyes Show Superior Outcome Compared to Untreated Eyes Even Upon Long-term Follow-up

Changes in BCVA as of Latest Follow-up (mean 34, median 36, range 12-48 mos)

Improvements 7-15 Letters

% Subjects With	**Treated Eye % (n/15 Implanted Subjects)**	**Untreated Eye % (n/15 Implanted Subjects)**
% Subjects with **Improved** BCVA (>5 Letter Gain)	27% (4/15)	0% (0/15)
% Subjects with **Improved** (>5 Letter Gain) or Stable BCVA (+/- 5 Letters from Baseline)	60% (9/15)	20% (3/15)
% Subjects with **Worse** BCVA (>5 Letter Loss)	40% (6/15)	80% (12/15)

Losses of 8-21 Letters

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Objectives of the Phase 1/2a Clinical Trial Met

Assess:

- The Safety and Feasibility of Administration of the Implant
- The Safety of the Implant
- The Immunosuppression Regimen
- The Feasibility of Possible Outcome Measures and Endpoint
- Possible Signals of Efficacy

- Showed Safety & Feasibility of CPCB-RPE1 Administration
- Refined the Surgical Procedure
- Demonstrated No Major Immune Responses to the Implant
- Evidence of Activity

Preparing for Phase 2b Clinical Trial Designed to Be Part of Registration Package

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CALIFORNIA'S STEM CELL AGENCY

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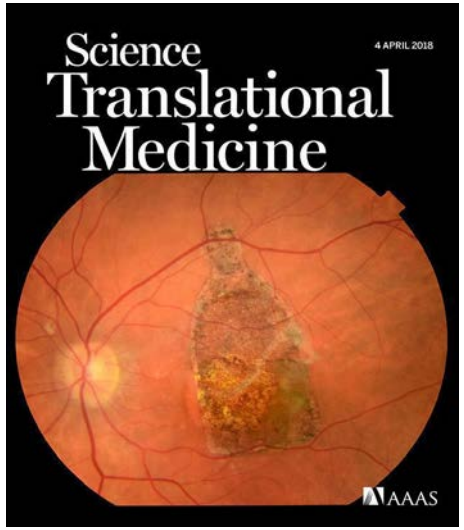

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

RETINAL DISEASE

A bioengineered retinal pigment epithelial monolayer for advanced, dry age-related macular degeneration

Amir H. Kashani,[1]* Jane S. Lebkowski,[2] Firas M. Rahhal,[3] Robert L. Avery,[4] Hani Salehi-Had,[5] Wei Dang,[6] Chih-Min Lin,[6] Debbie Mitra,[1] Danhong Zhu,[7] Biju B. Thomas,[1] Sherry T. Hikita,[8] Britney O. Pennington,[8] Lincoln V. Johnson,[2,8] Dennis O. Clegg,[8] David R. Hinton,[1,7] Mark S. Humayun[1,9]*

Retinal pigment epithelium (RPE) dysfunction and loss are a hallmark of non-neovascular age-related macular degeneration (NNAMD). Without the RPE, a majority of overlying photoreceptors ultimately degenerate, leading to severe, progressive vision loss. Clinical and histological studies suggest that RPE replacement strategies may delay disease progression or restore vision. A prospective, interventional, U.S. Food and Drug Administration–cleared, phase 1/2a study is being conducted to assess the safety and efficacy of a composite subretinal implant in subjects with advanced NNAMD. The composite implant, termed the California Project to Cure Blindness–Retinal Pigment Epithelium 1 (CPCB-RPE1), consists of a polarized monolayer of human embryonic stem cell–derived RPE (hESC-RPE) on an ultrathin, synthetic parylene substrate designed to mimic Bruch's membrane. We report an interim analysis of the phase 1 cohort consisting of five subjects. Four of five subjects enrolled in the study successfully received the composite implant. In all implanted subjects, optical coherence tomography imaging showed changes consistent with hESC-RPE and host photoreceptor integration. None of the implanted eyes showed progression of vision loss, one eye improved by 17 letters and two eyes demonstrated improved fixation. The concurrent structural and functional findings suggest that CPCB-RPE1 may improve visual function, at least in the short term, in some patients with severe vision loss from advanced NNAMD.

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