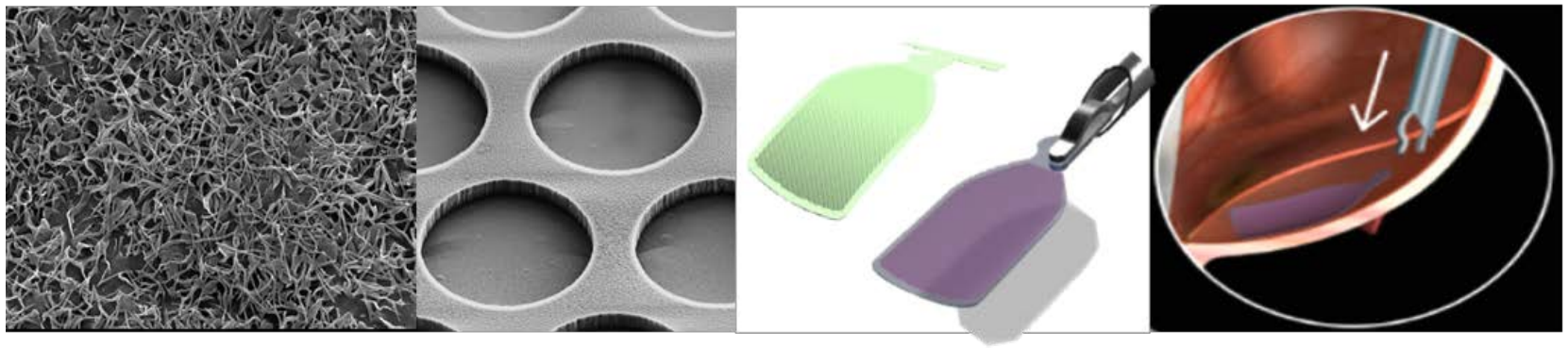

Phase 1/2a Clinical Assessment of a Bio-engineered RPE Cell-Based Implant for the Treatment of Advanced Dry-Age-Related Macular Degeneration

ISSCR Annual Meeting 2021
June 26, 2021
Jane S. Lebkowski Ph.D. , President

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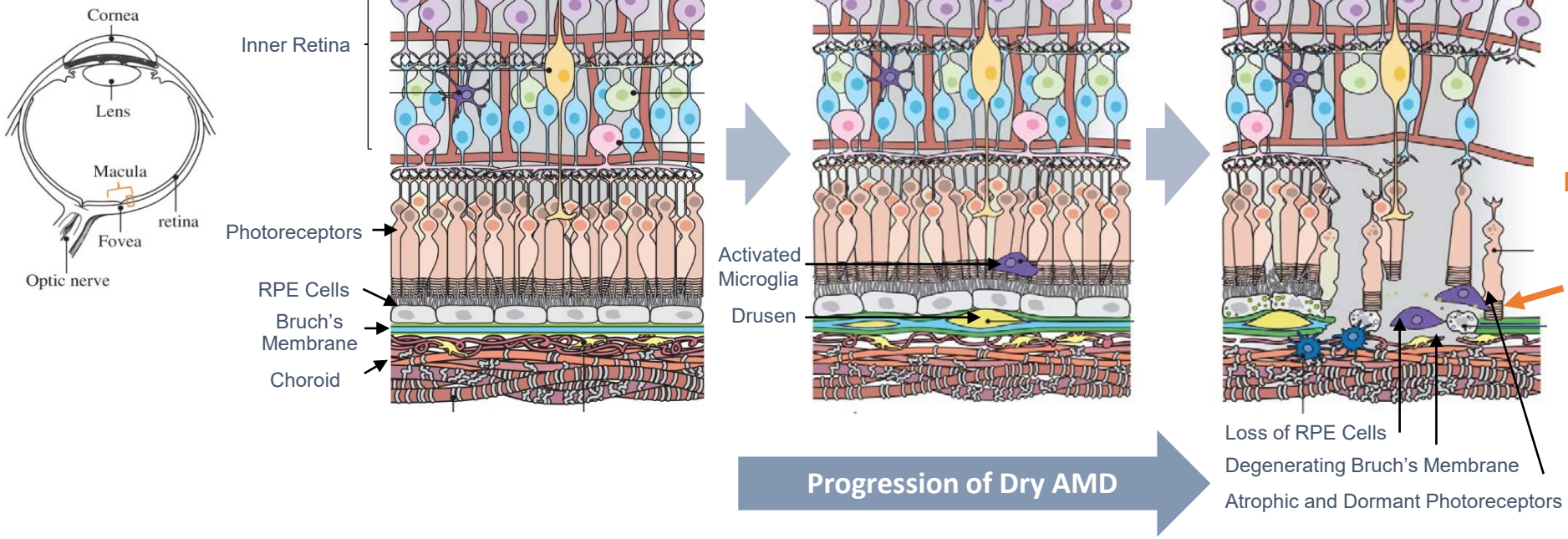
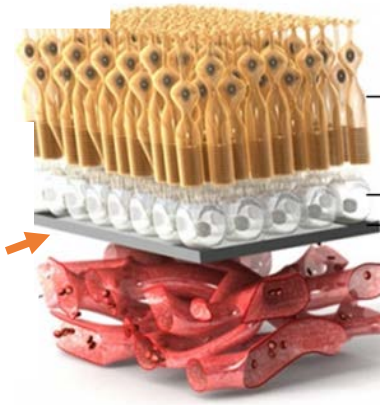
Implant Designed to Address the Disease Pathology in Geographic Atrophy

CPCB-RPE1 Implant



Treatment Hypothesis:
Insert Implant of RPE Cells on a Synthetic Bruch's Membrane to Preserve of Improve Visual Function

Insert RPE Cells on a Synthetic Bruch's Membrane



Implant Provides Metabolic and Structural Support for Photoreceptors

van Lookeren Campagne et al., J Pathol 2014; 232: 151–164

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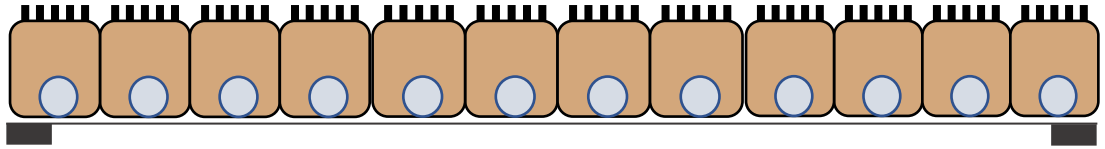
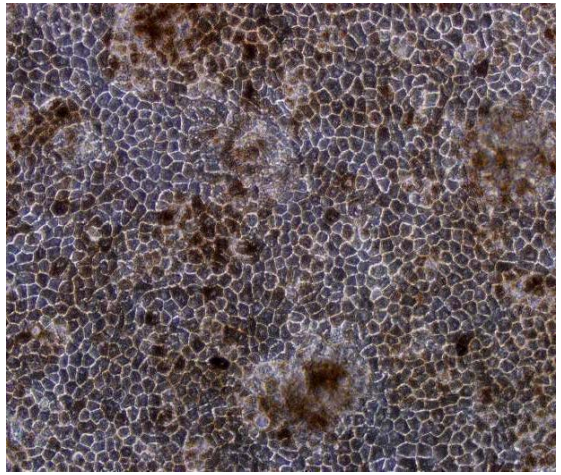
CPCB-RPE1: A Composite RPE Cell-Parylene Membrane Implant



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

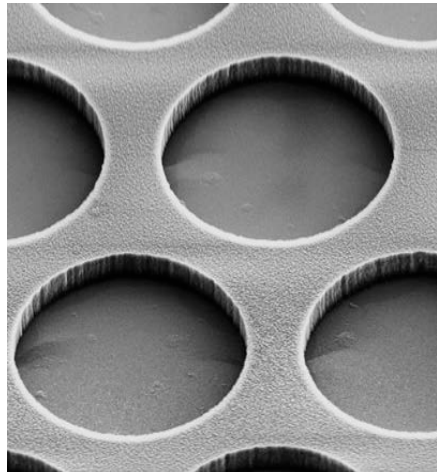
Ultrathin Diffusible Parylene Membrane:
Replace Degenerating Bruch's Membrane

RPE Cells Produced from Pluripotent Stem Cells



+

Ultrathin Parylene Membrane



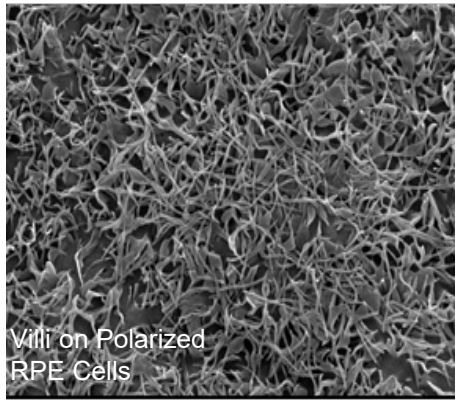
CPCB-RPE1 Implant

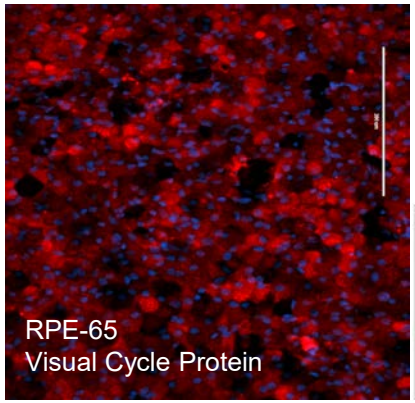
Implant Body

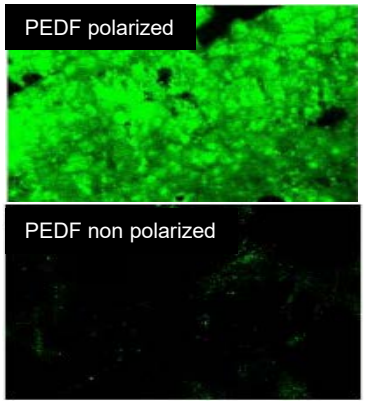
The CPCB-RPE1 Implant Has Two Key Components: RPE Cells and a Parylene Membrane

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
- When polarized have increased neurotrophic growth factor (PEDF) secretion from the apical surface
- Secrete VEGF specifically from the basal surface to promote choriocapillaris survival
- Integrate with photoreceptors to promote metabolic and growth factor support

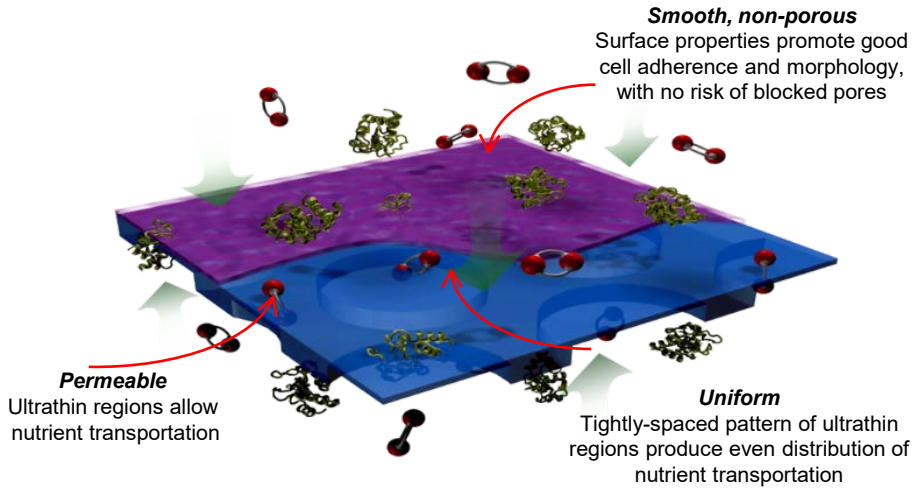






Ultrathin Parylene Membrane

- 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 recreate diffusion properties of Bruch's membrane
- Provides flat surface without pores to limit cell penetration
- Is foldable to reduce retinotomy size for implantation



Objectives of the Phase 1/2a Clinical Trial

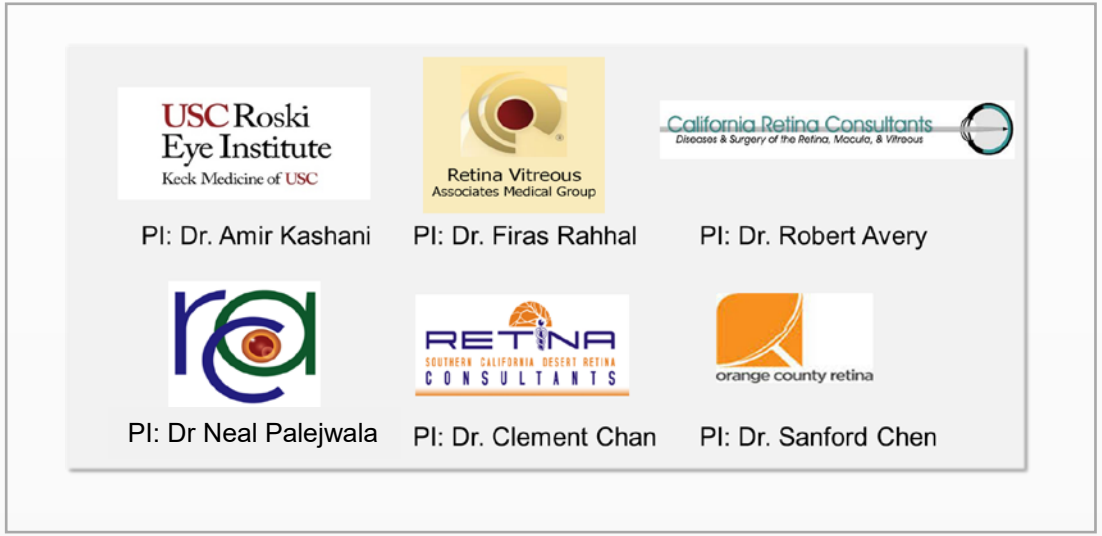
Assess:

- The safety and feasibility of administration of the implant
- The safety of the implant
- The immunosuppression regimen
- Possible signals of efficacy

Initiated clinical studies in subjects with late-stage advanced geographic atrophy who are legally blind.

Phase 1/2a Clinical Trial Designed to Establish Safety and Potential Activity of the Implant in Patients with Advanced Disease

Study Design and Population	
Design	Single Arm Open Label Study
Indication	Advanced, Dry Age-Related Macular Degeneration with Significant Geographic Atrophy Involving the Central Fovea
Number of Subjects	16 Subjects
Visual Acuity of Treated Subjects	BCVA ≤20/200; Worst Eye Treated; All Treated Eyes Legally Blind
Dose	One Implant
Primary Endpoint	Test the Safety and Tolerability of CPCB-RPE1 at 1 Year Post Implantation
Secondary Endpoint	Assess Visual Acuity Retinal Function After CPCB-RPE1 Administration



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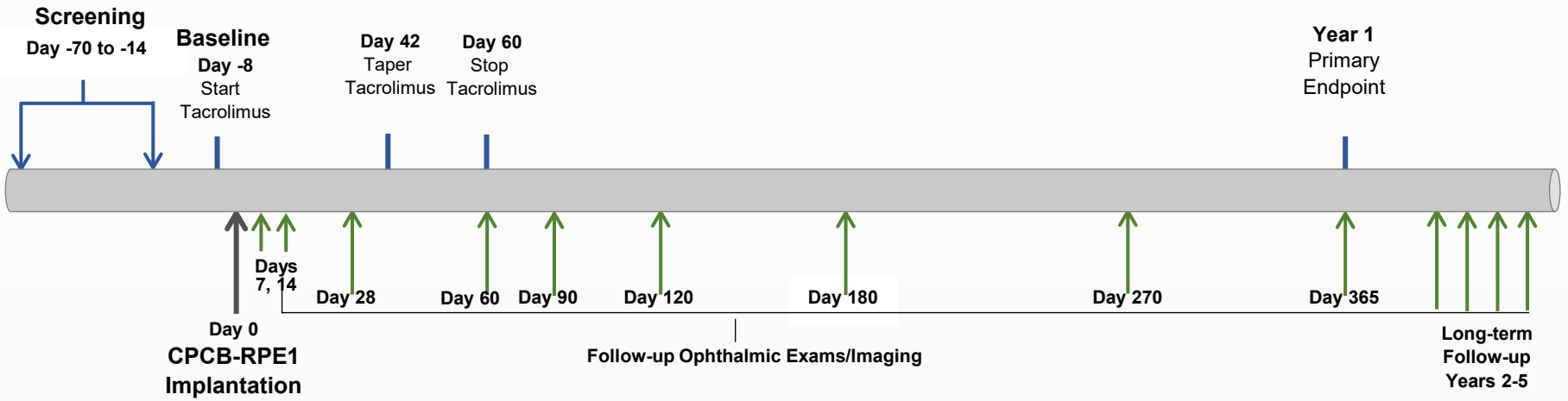
Phase 1/2a Clinical Trial Schema



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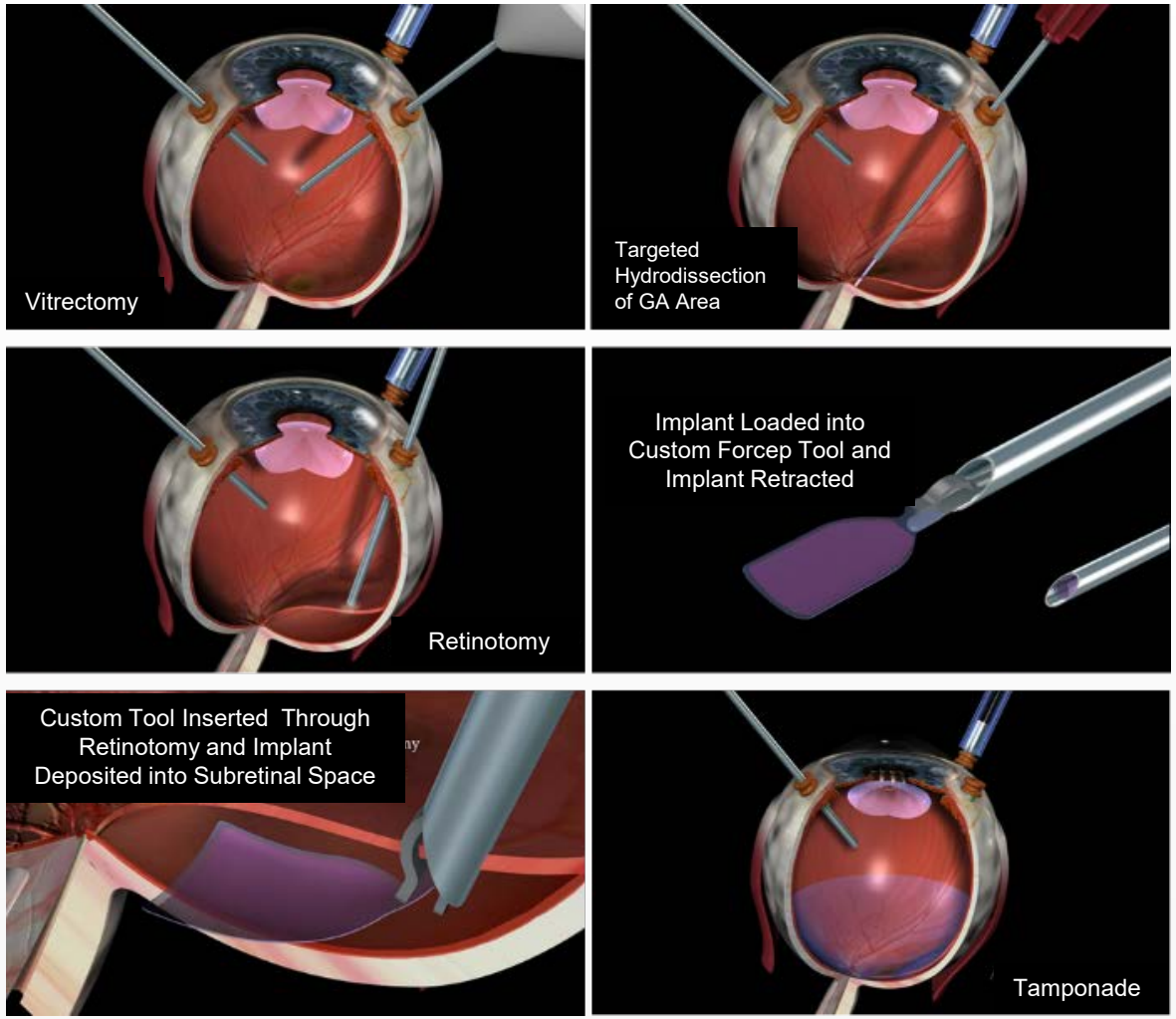
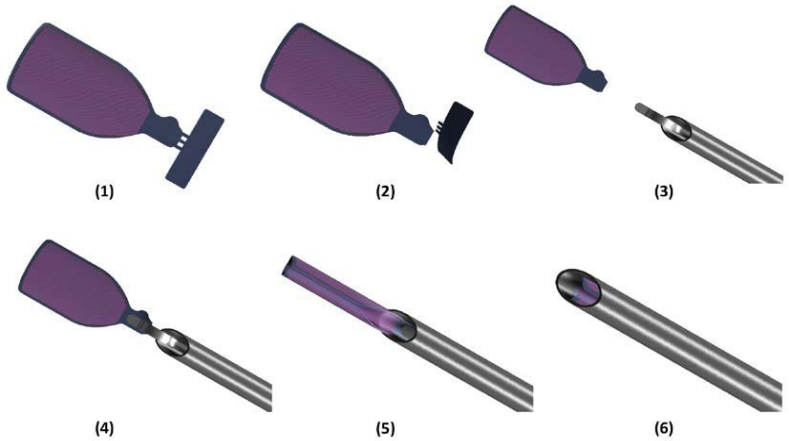
Implant Surgical Delivery: Uses Established Retinal Surgery Procedures





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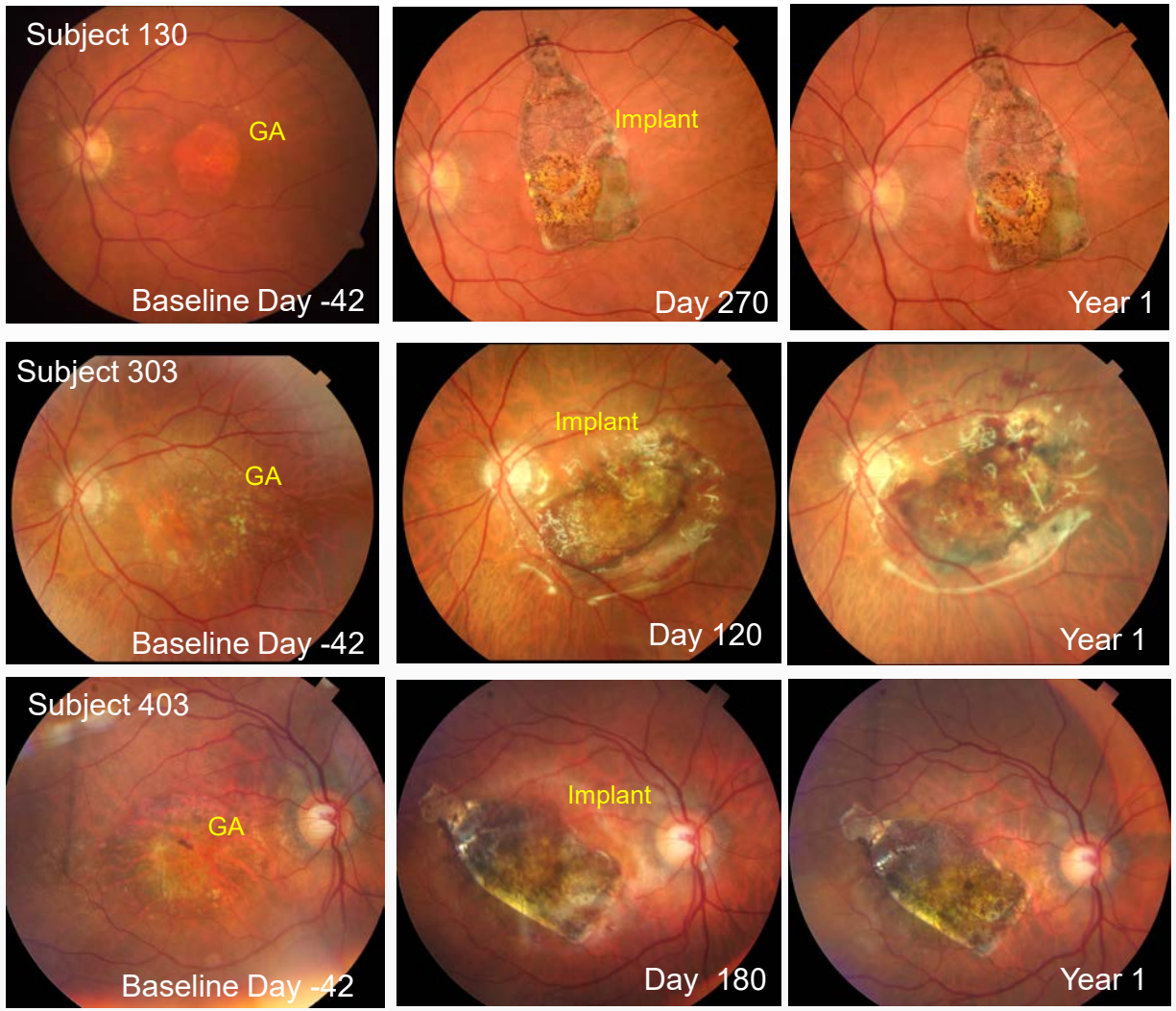
CPCB-RPE1 Implant Delivery Safe and Positioned Over Area of Geographic Atrophy



- 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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A Low Dose, Short-Duration Immunosuppression Course Was Used for the Phase 1/2a Clinical Trial

No Class I or Class II HLA Matching Performed Between Donor RPE Cells and Recipient Subject

Subject	# Mismatched HLA Alleles	Subject	# Mismatched HLA Alleles
204	9 of 12	401	13 of 16
125	14 of 16	216	12 of 16
128	9 of 16	403	12 of 16
303	11 of 16	404	13 of 16
304	10 of 16	606	13 of 16
305	12 of 16	502	13 of 16
130	11 of 16	607	12 of 16
501	13 of 16		

- Genotyping Performed On 16 HLA Class I and Class II Alleles to Determine Extent of Mismatches
- All Subjects Have More than 50% of Alleles Mismatched
- Best Match is 7 of 16 HLA Alleles

The Immunosuppression Regimen

- Subjects receiving CPCB-RPE1 were started on oral tacrolimus at Day -8 before implantation (Day 0).
- On Day 42 post-implantation, tacrolimus tapering was initiated and then dosing was terminated at Day 60. Tacrolimus dosing was at approximately 0.075 mg/kg/day to achieve target blood concentrations of 3-10 ng/ml.
- Tacrolimus doses were adjusted as required to achieve this target trough level.

*Genotyping performed at UCLA Immunogenetics Lab

No Robust Antibody Responses to Donor HLA Antigens as Measured in Peripheral Blood

The Assay

- Antibodies to single Class I and Class II molecules assessed by bead flow cytometry at UCLA Immunogenetics Lab.
- Assay detects antibodies to 97 HLA Class I antigens and 99 HLA Class II antigens

- 1/13 subject developed weak antibodies to a single donor HLA antigen (DQB1)
- 12/13 subjects never developed antibodies to a donor antigen during one year of follow-up

Subject	# Mismatched Subject HLA Alleles with CPCB-RPE1	Detection of Antibodies to Donor HLA Antigens			
		Baseline	Day 90 of follow-up	Day 180 of follow-up	Day 365 of follow-up
128	9 of 16	-	-	not done	-
303	11 of 16	-*	-*	not done	-*
304	10 of 16	-	-	not done	-
305	12 of 16	-	-	-	-
130	11 of 16	-	-	-	-
501	13 of 16	-*	-*	-*	-*
401	13 of 16	-*	-*	-*	-*
216	12 of 16	-*	-*	-	-
403	12 of 16	-	-	-	-
404	13 of 16	-*	-	+* (weak Ab to donor DQB1)	+* (weak Ab to donor DQB1)
606	13 of 16	-	-	-	-*
502	13 of 16	+* (moderate Ab to donor DQB1)	+* (moderate Ab to donor DQB1)	+* (moderate Ab to donor DQB1)	+* (moderate Ab to donor DQB1)
607	12 of 16	-	-*	-*	-*

(-) No antibodies to donor HLA antigens detected; (+) Antibodies to donor HLA antigens detected. Mean fluorescence intensity (MFI) was used to classify the antibodies as not present, weak, moderate, or strong. The definitions of those classifications were: 1) not present MFI < 1000; 2) weak, MFI 1000-3000; 3) moderate, MFI 3000-5000; and 4) strong, MFI >5000.

*Subject had antibodies to non-donor HLA molecules the identity of which were consistent across timepoints tested. The majority (61%) of these were characterized as weak binding antibodies with 26% classified as moderate and 13% classified as strong.
It is of interest that subject 502 which had pre-existing antibodies to donor HLA antigen DQB1 showed survival of the RPE cells as assessed by fundus photography.

No Clinical Evidence in Any Subject of Inflammatory Responses Including Cell, Flare, Vascular Staining, Retinitis, Vitritis, Vasculitis or Choroiditis

Subject 125: Characteristics

- Female, Age 84 at time of implantation.
- Subject treated eye had largest area of geographic atrophy and worst BCVA (Hand Motion) of any subject in the clinical trial
- Subject treated eye had the biggest difference in BCVA between the treated (Hand Motion) and untreated eye (20/50)
- Neither the treated nor untreated eye showed a change in BCVA after implantation
- Follow-up continued for 2 years until patient succumbed to pneumonia (unrelated)
- Treated and untreated eyes collected for histological analysis

HLA Molecular Typing Analysis from Subject 125 Receiving CPCB-RPE1 and the Donor H9 hESC line

HLA Locus	Subject 125		H9 Cell Line Source of CPCB-RPE1	
	Allele 1	Allele 2	Allele 1	Allele 2
A	01:01:01	11:01:01	02:01:01	03:01:01
B	07:02:01	35:01:01	35:03:01	44:27:01
C	**04:01:01**	07:02:01	04:01:01	07:04:01
DRB1	04:07:01	11:01:01	15:01:01	16:01:01
DQB1	03:01:01	03:01:01	05:02:01	06:02:01
DQA1	03:03:01	05:05:01	01:02:01	01:02:02
DPB1	02:01:02	02:01:02	04:01:01	10:01:01
DPA1	**01:03:01**	01:03:01	01:03:01	02:01:01
#Mis-matched Alleles with H9	14/16			

Bolded alleles are a match with an HLA allele expressed in H9 cells

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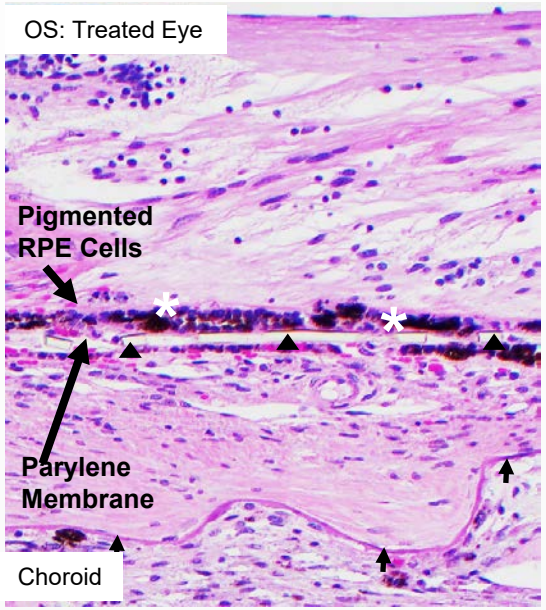
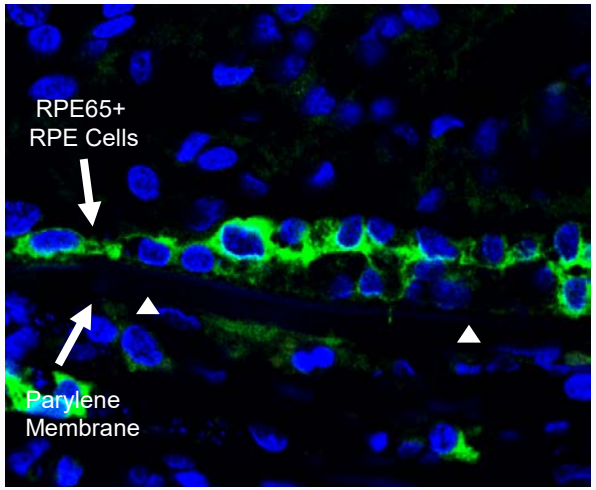
The Fully Allogeneic RPE Cells Survive at Least 2 Years with Only a Short Course of Immunosuppression

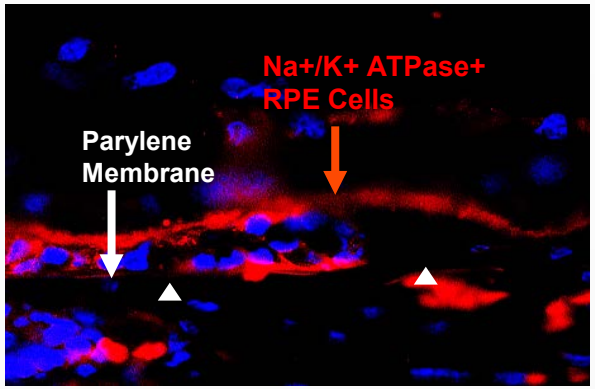
The RPE Cells are Polarized, Express Visual Function Proteins with Evidence of Phagocytic Activity



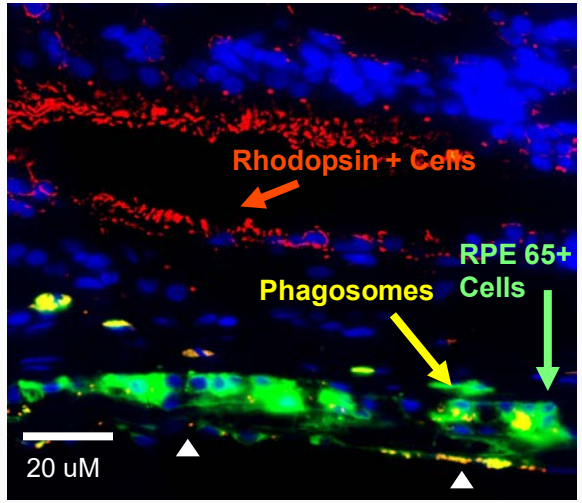
- Pigmented RPE Cells Survive on the Parylene Membrane at Least 2 Years



- 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

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

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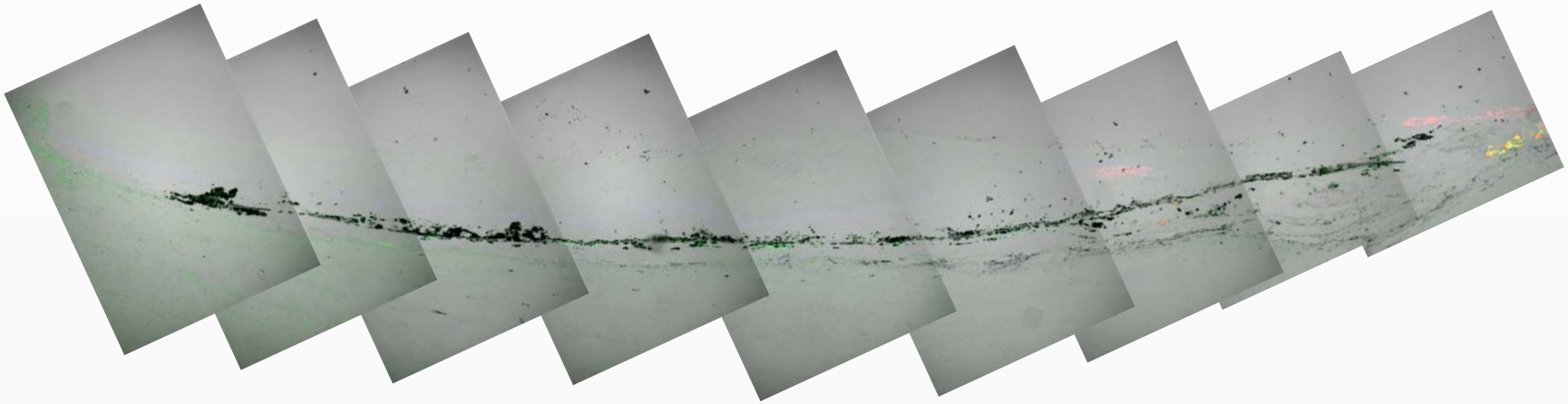
Pigmented, RPE-65+ RPE Cells Are Observed Along the Entire Length of the Implant

RPE65+ Cells
RPE Cell Pigmentation



- Allogeneic RPE Cells Survive at Least 2 Years with Only a Short Course of Immunosuppression
- The RPE Cells are Polarized, Express Visual Function Proteins with Some Evidence of Phagocytic Activity

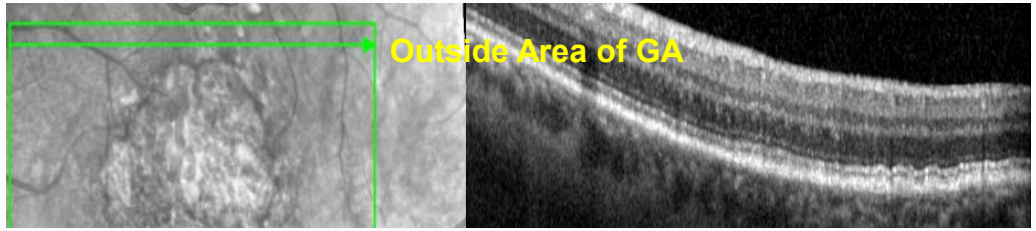
Serious Adverse Events In First Year of Follow-up: Number and Frequency of Subjects in Which the Event Occurred

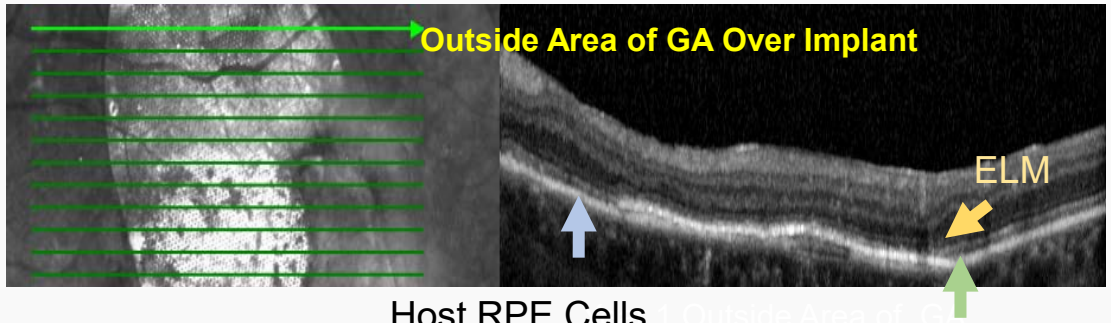
Specific Organ Class	Subjects 1-7	Subjects 8-16	Total (n=16)	Relatedness
#Subjects Reporting at Least One SAE**	6 (85.7%)	2 (22.2%)	8 (50.0%)	-
# Subjects Reporting Ocular SAEs⁺	4 (57.1%)	0 (0.0%)	4 (25.0%)	-
Retinal deposits, hemorrhage, edema*	3 (42.9%)	0 (0.0%)	3 (18.8%)	Possibly Related to Implant or Procedure
Macular edema and focal retina detachment	1 (14.3%)	0 (0.0%)	1 (6.3%)	Possibly Related to Implant or Procedure
# Subjects Reporting Gastrointestinal Disorder SAEs	2 (28.6%)	1 (11.1%)	3 (18.8%)	
Colitis ischemic	0 (0.0%)	1 (11.1%)	1 (6.3%)	Possibly Related to Immunosuppression
Rectal prolapse	1 (14.3%)	0 (0.0%)	1 (6.3%)	Unrelated
Small intestinal obstruction	1 (14.3%)	0 (0.0%)	1 (6.3%)	Unrelated
# Subjects Reporting Infection Related SAEs	1 (14.3%)	1 (11.1%)	2 (12.5%)	
Pneumonia	0 (0.0%)	1 (11.1%)	1 (6.3%)	Possibly Related to Immunosuppression
# Subjects Reporting Cardiac Related SAEs	1 (14.3%)	0 (0.0%)	1 (6.3%)	
Cardiac failure	1 (14.3%)	0 (0.0%)	1 (6.3%)	Unrelated
# Subjects Reporting Other SAEs	1 (14.3%)	0 (0.0%)	1 (6.3%)	
Weight decreased	1 (14.3%)	0 (0.0%)	1 (6.3%)	Unrelated
# Subjects Reporting Neoplasms (benign, malignant and unspecified) Related SAEs	1 (14.3%)	0 (0.0%)	1 (6.3%)	
Esophageal adenocarcinoma	1 (14.3%)	0 (0.0%)	1 (6.3%)	Unrelated

* One subject with focal detachment of retinal pigmented epithelium and resolved;
** Comparison between Subjects 1-7 and Subjects 8-16 for all SAE: p= 0.0401 Fisher's exact 2-sided test
⁺ Comparison between Subjects 1-7 and Subjects 8-16 for all ocular SAEs ; p= 0.0192 Fisher's exact 2-sided test

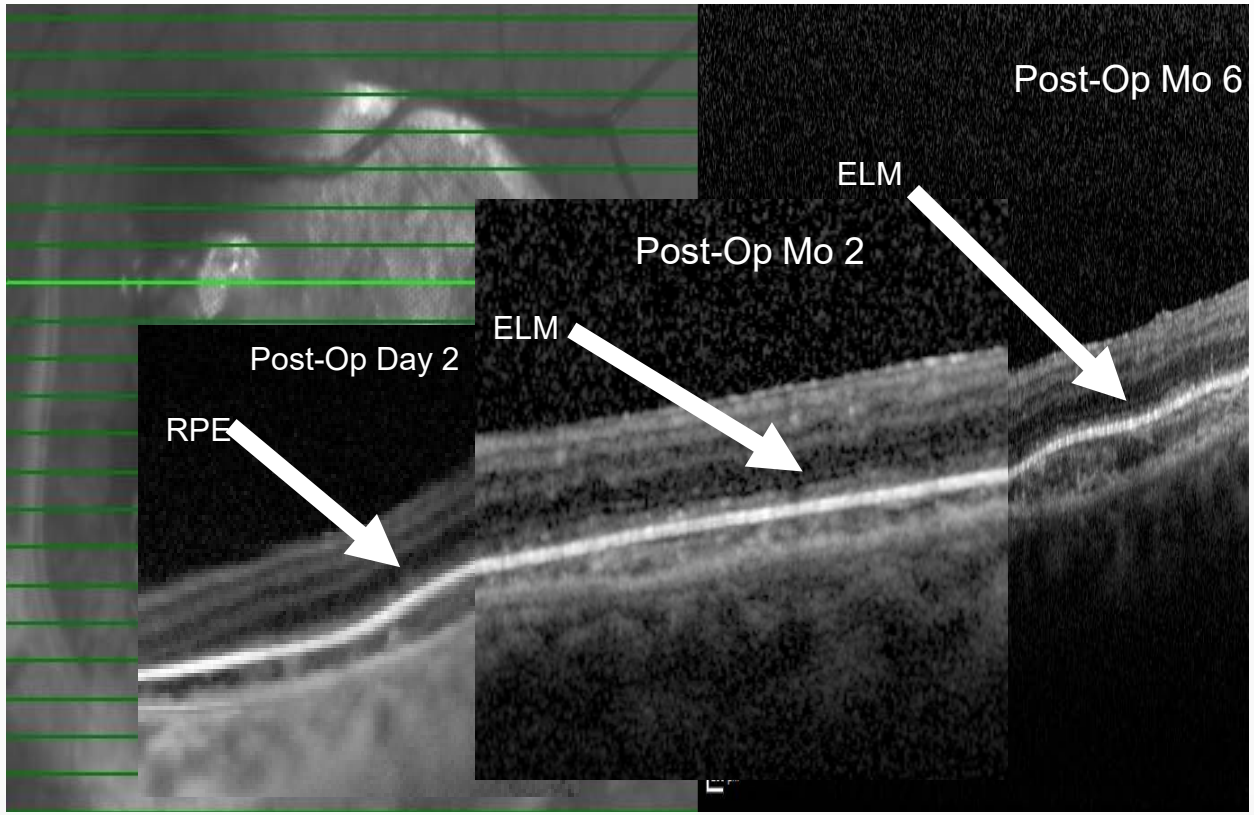
Good Preservation of Retinal Architecture with Reappearance of External Limiting Membrane

Preservation of Retinal Architecture Even Outside Areas of GA





Reappearance of External Limiting Membrane in Some Patients



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Change in Best Corrected Visual Acuity: One Year Post- Implantation

Overall Improvement in Visual Acuity Outcome Compared to Fellow Eye

	Treated Eye % (n/15 Implanted Subjects)	**Untreated Eye % (n/15 Implanted Subjects)**
% Subjects with **Improved** BCVA (>5 Letter Gain)	27% (4/15)	7% (1/15)
% Subjects with **Improved** (>5 Letter Gain) or **Stable** BCVA (+/- 5 Letters from Baseline)	67% (10/15)	53% (8/15)
% Subjects with **Worse** BCVA (>5 Letter Loss)	33% (5/15)	47% (7/15)

Improvements 6-13 Letters

Change in Best Corrected Visual Acuity as of Last Follow-up

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

Regenerative Patch Technologies™

Acknowledgements

Patients and Caregivers

CPCB-RPE1 Team

Mark Humayun, USC
David Hinton, USC
Dennis Clegg, UCSB
Biju Thomas, USC
DanHong Zhu, USC
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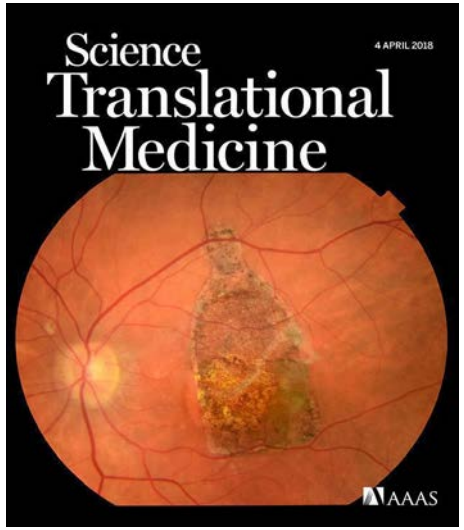
CIRM
CALIFORNIA'S STEM CELL AGENCY

Santen



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

RETINAL DISEASE

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

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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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