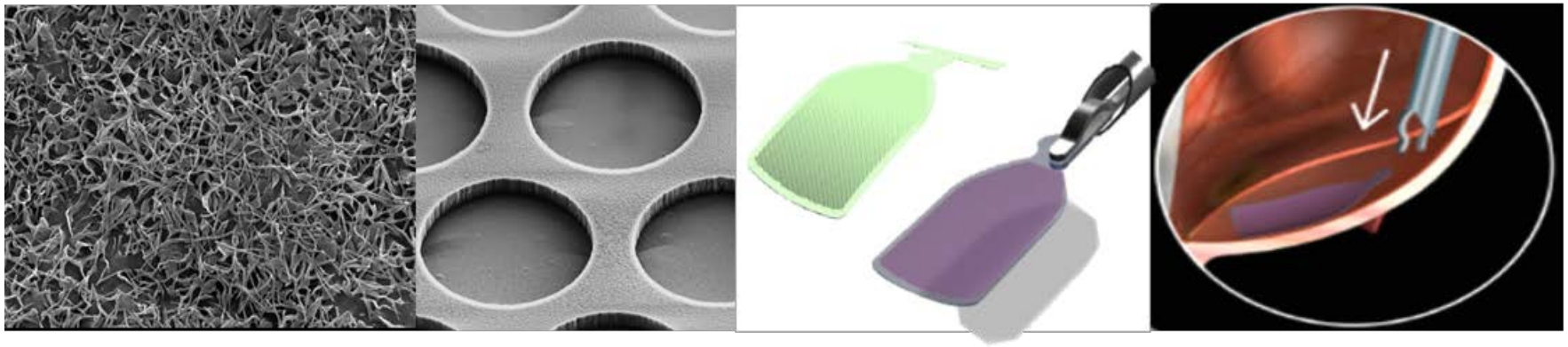

Long-term Follow-up of Subjects in a Phase 1/2a Clinical Trial of an Allogeneic, Bioengineered hESC-Derived RPE Implant for Advanced Dry Age-Related Macular Degeneration

ISSCR Annual Meeting June 2023

Jane S Lebkowski PhD

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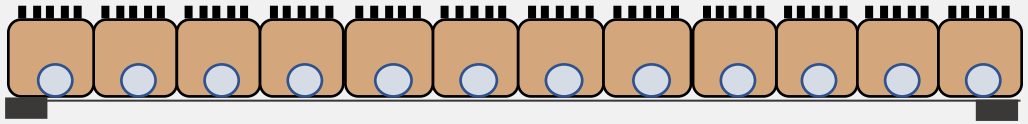
The CPCB-RPE1 Implant, Is Designed to Improve Vision in Patients with AMD

The Implant Design



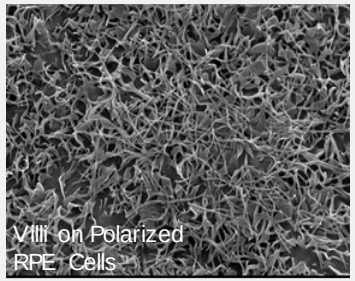
Polarized Healthy RPE Cells:
Replace Dysfunctional RPE Layer in AMD Retina

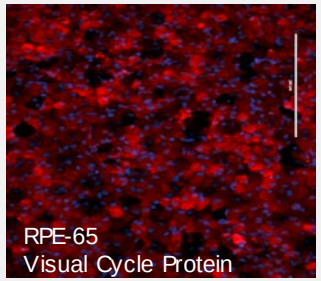
Ultrathin Diffusible Parylene Membrane:
Replace Degenerating Bruch's Membrane

The Critical Components

RPE Cells

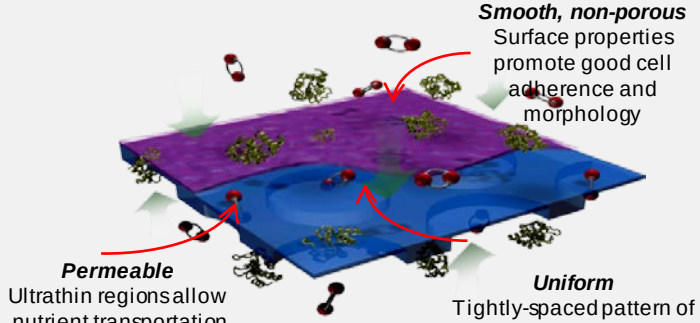
- Derived from pluripotent stem cells
- Polarized as in native retina
- Mature RPE cell function including visual cycle processing
- Integrate with photoreceptors to promote metabolic and growth factor support





Ultrathin Parylene Membrane

- Substrate for RPE cells to attach and polarize
- Uses USP Class VI biocompatible parylene monomer used >30 years in implantables
- Precise thickness to create diffusion properties similar to Bruch's membrane
- Provides flat surface without pores to limit cell penetration
- Foldable to reduce retinotomy size during implantation

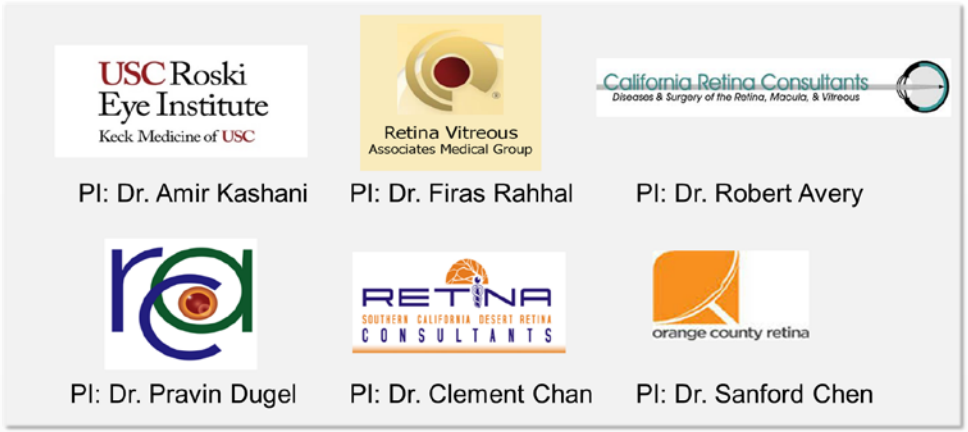


The CPCB-RPE1 Implant

Implant Body

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
Immunosuppression	68-Day Immunosuppression Protocol Using Tacrolimus



Phase 1/2a clinical trial designed to test:

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

Very late-stage, legally blind, subjects selected for first-in-human clinical trial due to novelty of product and approach

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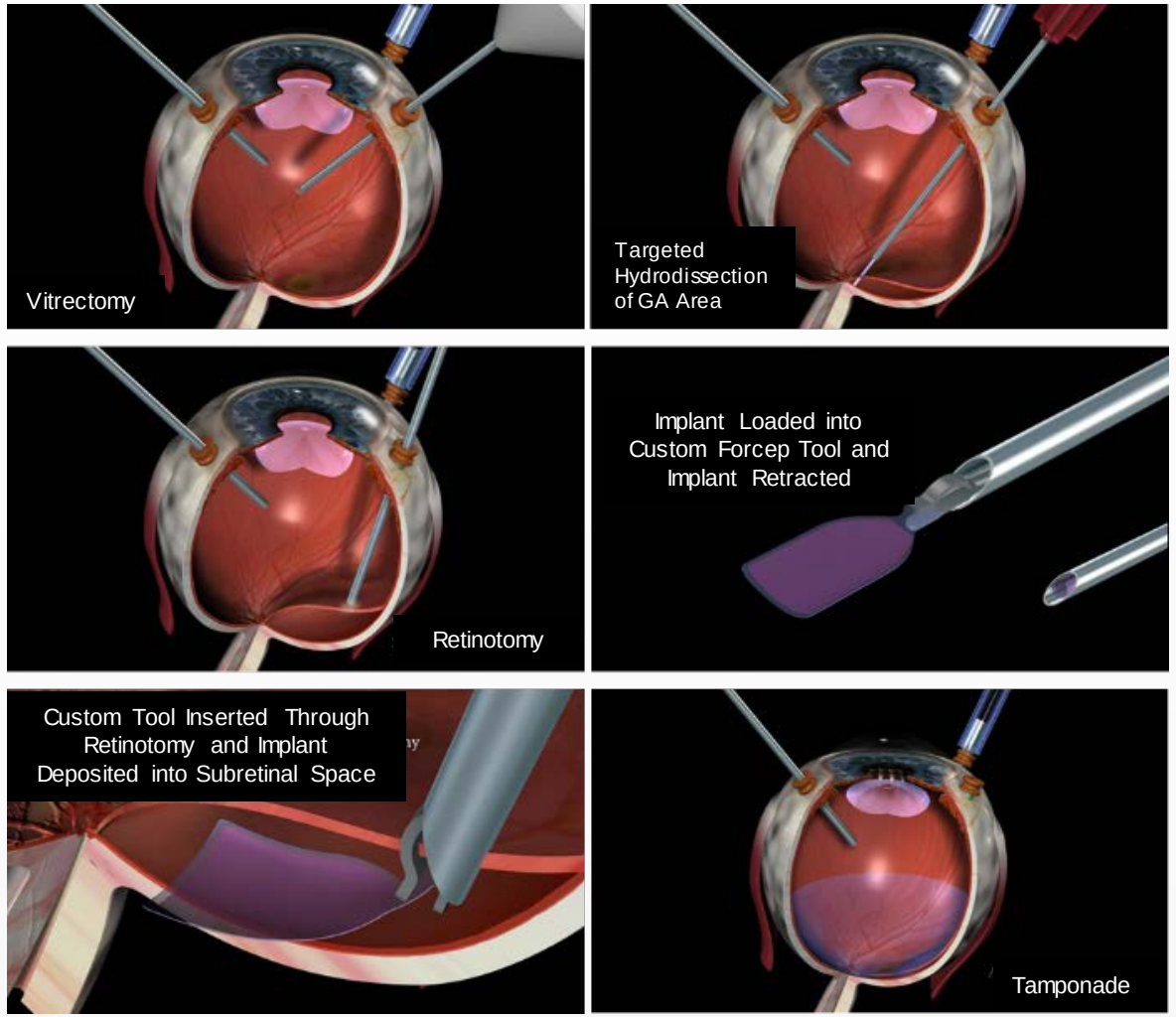
Implant Surgical Delivery: Uses Well-Established Retinal Surgery Procedures



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

- Uses Well-Established Retinal Surgery Procedures
- Administered as Outpatient Surgery

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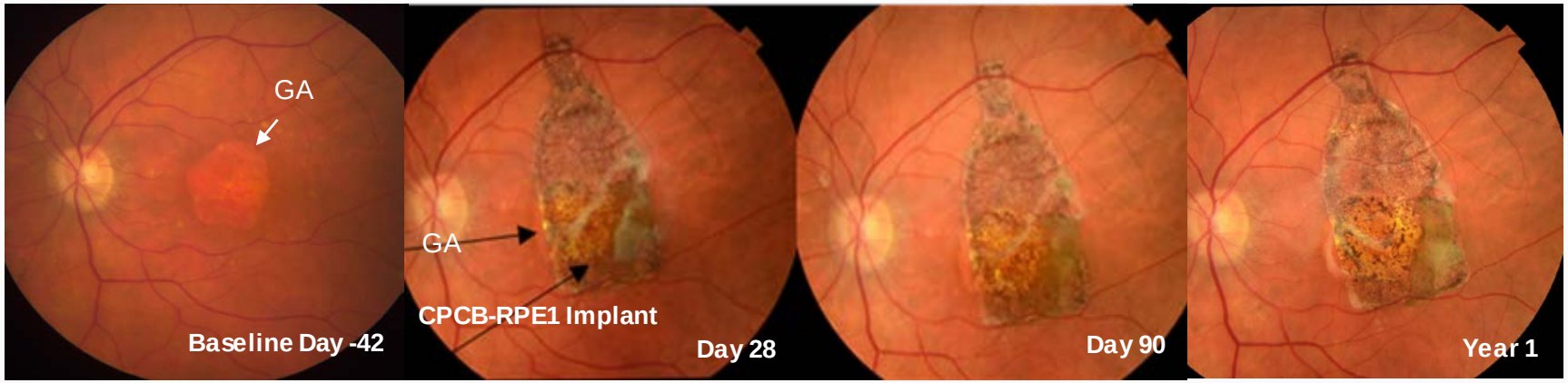
Imaging Shows Stable Placement of the CPCB-RPE1 Over the Area of GA Over Time

Subject 130



- Surgical Procedure Feasible and Safe
- Minimized Fibrinous Debris During Surgery
- Achieved Better Management of Hemorrhage
- Implant Stably Positioned Over Area of GA in All Subjects
- Stable Position of Implant Over Time

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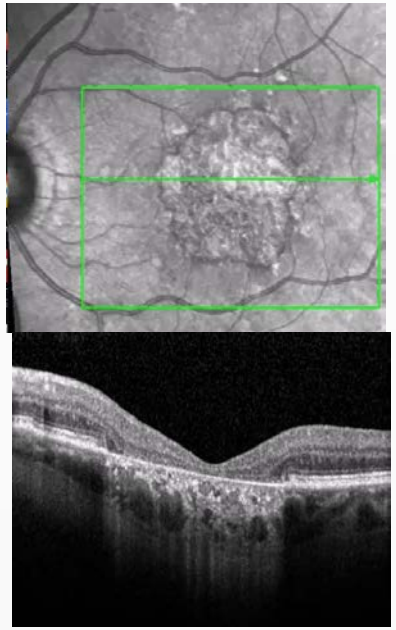
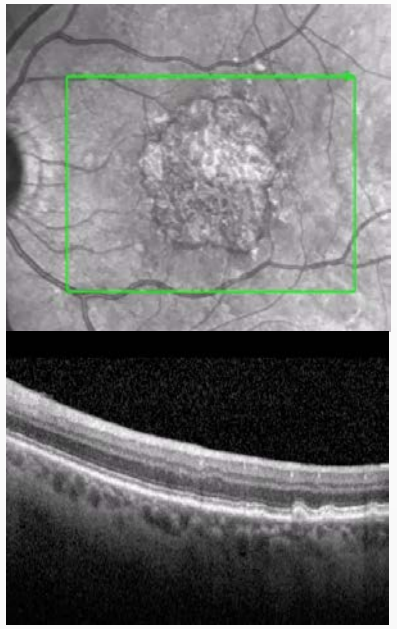
OCT Imaging Shows Good Preservation of Retinal Architecture Even When Implant Placed Over an Area with Intact Host RPE Cells.

Baseline Day -42

In Area of GA

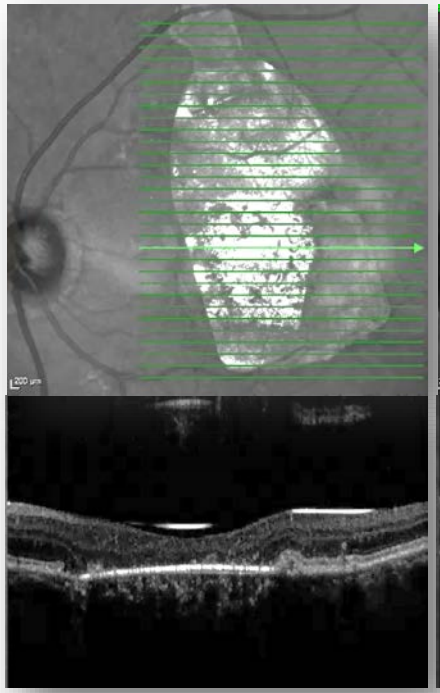


Outside Area of GA

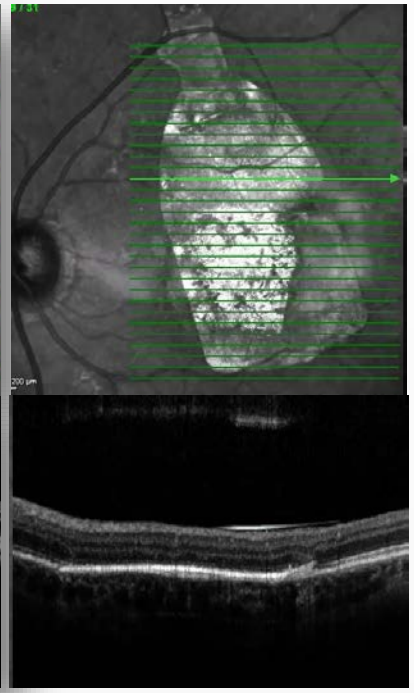


One Year Post-Implant

In Area of GA

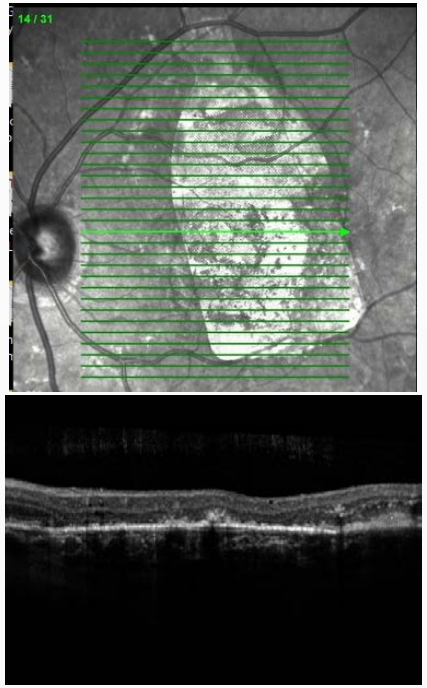


Outside Area of GA

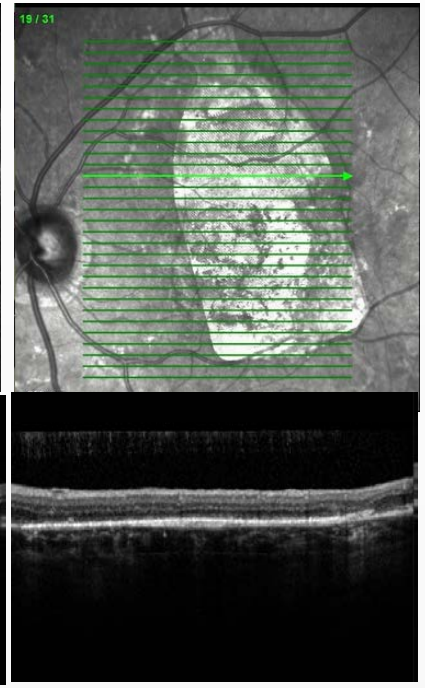


Three Years Post-Implant

In Area of GA



Outside Area of GA



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CPCB-RPE1: Ocular Serious Adverse Events Through Last- Follow-up

Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term and Treatment Group Through the End of the Study			
System Organ Class Preferred Term	**Cohort 1 (N=7)**	**Cohort 2 (N=9)**	**All Subjects (N=16)**
Number (%) of Subjects with Serious TEAEs	7 (100.0%)	5 (55.5%)	12 (75%)
Eye disorders	4 (57.1%)	1 (11.1%)	5 (31.0%)
Detachment of retinal pigment epithelium	1 (14.3%)	0 (0.0%)	1 (6.3%)
Retinal hemorrhage , edema, retinal deposits	3 (42.9%)	0 (0.0%)	3 (18.7%)
Macular edema	1 (14.3%)	0 (0.0%)	1 (6.3%)
Retinal detachment	1 (14.3%)	0 (0.0%)	1 (6.3%)
Vitreous hemorrhage	0 (0.0%)	1 (11.1%)	1 (6.3%)

Two SAE's Possibly Related to Immunosuppression: Pneumonia and Weight Loss Both of Which Resolved

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

- 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

Subject	# Mismatched HLA Alleles	Subject	# Mismatched HLA Alleles
204	9 of 12	401	≥9 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 at UCLA Immunogenetics Lab

No Robust Antibody Responses to Donor Cells as Measured in Peripheral Blood

- Antibodies to Single MHC Class I & II Molecules Assessed by Bead Flow Cytometry at UCLA Immunogenetics Lab.
- Assay Detects Antibodies to 97 MHC Class I & 99 Class II Antigens
- Antibody Responses to Individual MHC Class I and II Antigens Monitored at Baseline, 90,180, & 365-Days Post-Implantation.
- Baseline and Day 365 Day Data Available on 13/15 Subjects
- Only 1/13 Subject Had Weak Antibodies to a Single Donor HLA Antigen at Baseline day 180 and 365
- 12/13 Subjects Never Developed Antibodies to a Donor Antigen During the Year of Follow-up

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Change in Best Corrected Visual Acuity Over Time

One Year Post-Implantation | As of Last Follow-up

(mean 35.5 mos, range 12 to 54 mos, median 36 mos)

% Subjects With	Treated Eye % (n/15 Implanted Subjects)	Untreated Eye % (n/15 Implanted Subjects)	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)	27% (4/15)	7% (1/15)
% Subjects with Improved (>5 Letter Gain) or Stable BCVA (+/- 5 Letters from Baseline)	67% (10/15)	47% (7/15)	53% (8/15)	20% (3/15)
% Subjects with Worse BCVA (>5 Letter Loss)	33% (5/15)	53% (8/15)	47% (7/15)	80% (12/15)

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Change in Best Corrected Visual Acuity Over Time

One Year Post-Implantation — As of Last Follow-up

(mean 35.5 mos, range 12 to 54 mos, median 36 mos)

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Change in Best Corrected Visual Acuity Over Time

	One Year Post-Implantation		As of Last Follow-up (mean 35.5 mos, range 12 to 54 mos, median 36 mos)	
% Subjects With	**Treated Eye % (n/15 Implanted Subjects)**	**Untreated Eye % (n/15 Implanted Subjects)**	**Treated Eye % (n/15 Implanted Subjects)**	**Untreated Eye % (n/15 Implanted Subjects)**
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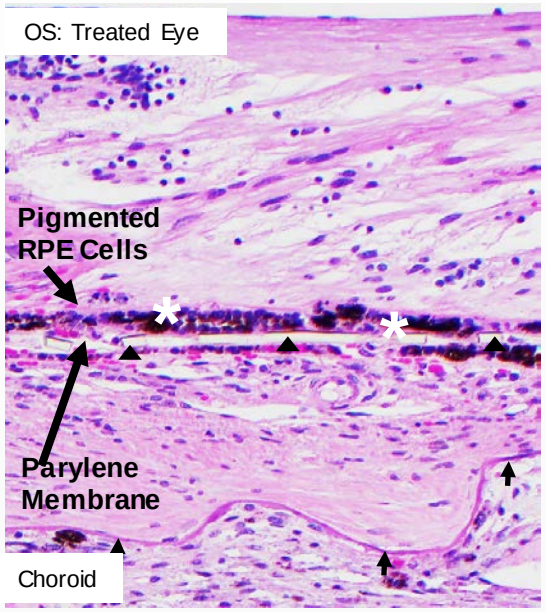
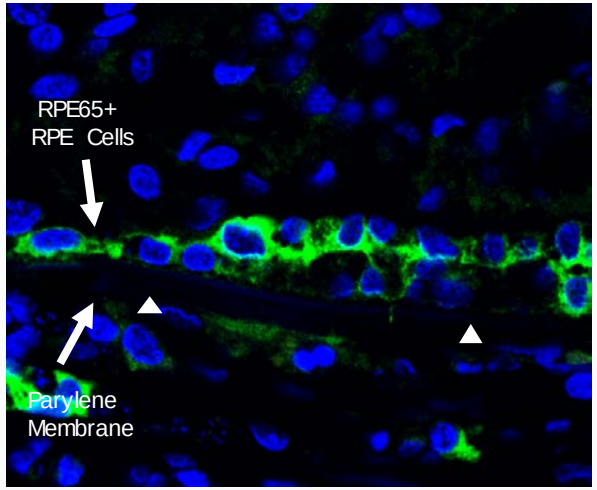
The Fully Allogeneic RPE Cells Survive at Least 2 Years with Only a Short Course of Immunosuppression

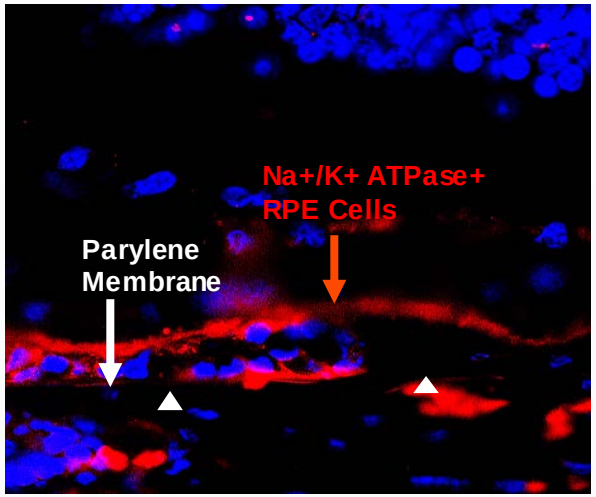
The RPE Cells are Polarized, Express Visual Function Proteins with Evidence of Phagocytic Activity



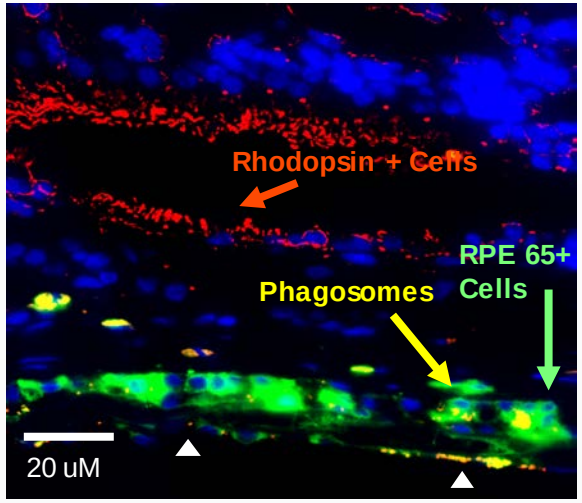
- Pigmented RPE Cells Survive on the Parylene Membrane at Least 2 Years



- 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.

Kashani et al. Stem Cell Reports 2022 17, 448-58

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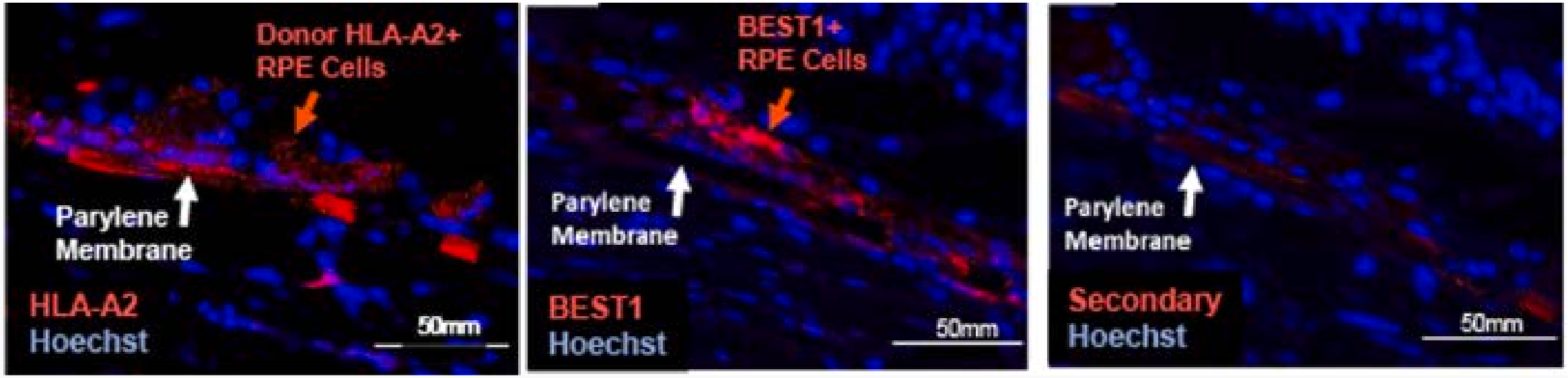
The Fully Allogeneic RPE Cells Survive at Least 2 Years with Only a Short Course of Immunosuppression



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Summary

- 27% of subjects in Phase 1/2a clinical trial had a >5 letter improvement in best corrected visual acuity as of last follow-up (mean 35.5 mos)
- Improvements ranged from 7-15 letters
- 53% of subjects were stable or improved as of last follow-up
- Such improvements exceedingly rare in natural course of the disease in such late-stage patients
- 80% of untreated eyes lost 8-21 letters over the same time period compared to only 47% in the treated eyes,
- Viable, functional, allogeneic implant cells survive >2 years after implantation
- Preparing for Phase 2b clinical trial.

Acknowledgements

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CIRM
CALIFORNIA'S STEM CELL AGENCY

Santen