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Subretinal implantation of human retinal progenitor stem cells (hRPC) for retinitis pigmentosa: Phase I/II interim safety update

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I have the following disclosures:

- **Consultant/advisor:** AGTC, Beam therapeutics, Blue Cross Blue Shield, Editas Medicine, Gensight, Sanofi
- **Principal Investigator / Investigator / or surgeon:** AGTC, MeiraGTX, ProQR, ReNeuron, Spark Therapeutics. Pending: NightStar
- Michael Young PhD and MEE have a direct financial interest in hRPC intellectual property. Clinical trial investigators do not.

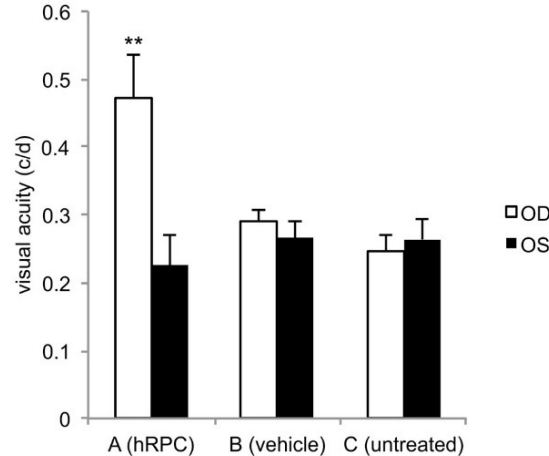
Human retinal progenitor cells for retinitis pigmentosa

hRPC is a cell-based retinal therapy

- Isolated from fetal retina
- Reproducibly expanded in culture in numbers needed for clinical application

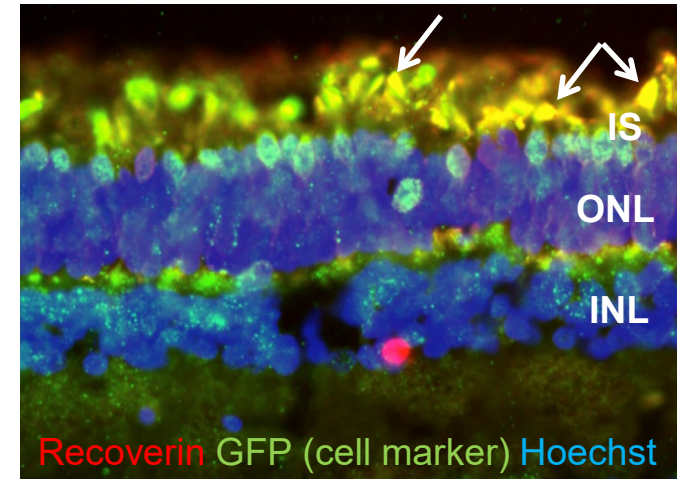
Baranov et al (2014)

Improved VA in hRPC-treated RCS rats 12 wks after transplantation



Luo et al (2014)

Allogeneic transplantation of pRPCs in pigs @ 4 weeks post-inj



Abud et al (2015)

- Potential mechanism(s) for hRPC effects: 1) Differentiation into retinal cells and integration into host retina; 2) Trophic support of host cells
- No immunosuppression required

Study Design

- Open label, single, ascending dose
(unilateral subretinal injection, worse-seeing eye)
- Treatment groups
 - Cohort 1: 250,000 cells, fresh formulation, n=3 subjects
 - Cohort 2: 500,000 cells, fresh formulation, n=3 subjects
 - Cohort 3-4: 1 million cells, cryopreserved, n=6 subjects
 - Cohort 5: 1 million cells, diluted cryopreserved, n=3 subjects
 - Cohort 6: still enrolling

Patient Characteristics – Study Eye

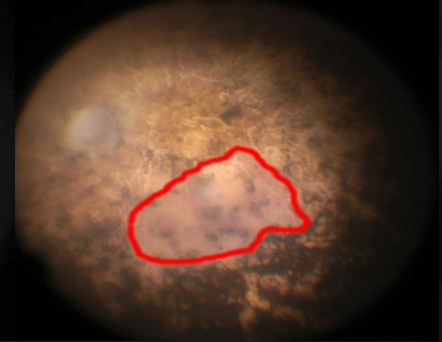
Baseline Test	Cohorts 1-4: Advanced RP (N = 12 subjects)	Cohort 5: Moderately advanced RP (N = 3 subjects)
Visual acuity- ETDRS letters (Snellen equivalent)	0-1 (LP to 20/800 ⁻³)	9-32 (20/230 to 20/600)
Visual field (Goldman V4e equivalent)	0-15 degrees	17-60 degrees
Cone flicker ERG (normal >50 microvolts)	0.1-2 microvolts	0-2.5 microvolts

Treated regions, examples

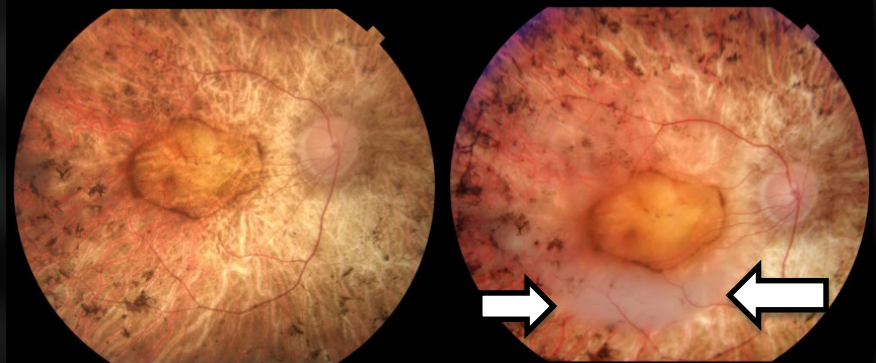
Intraoperative #1



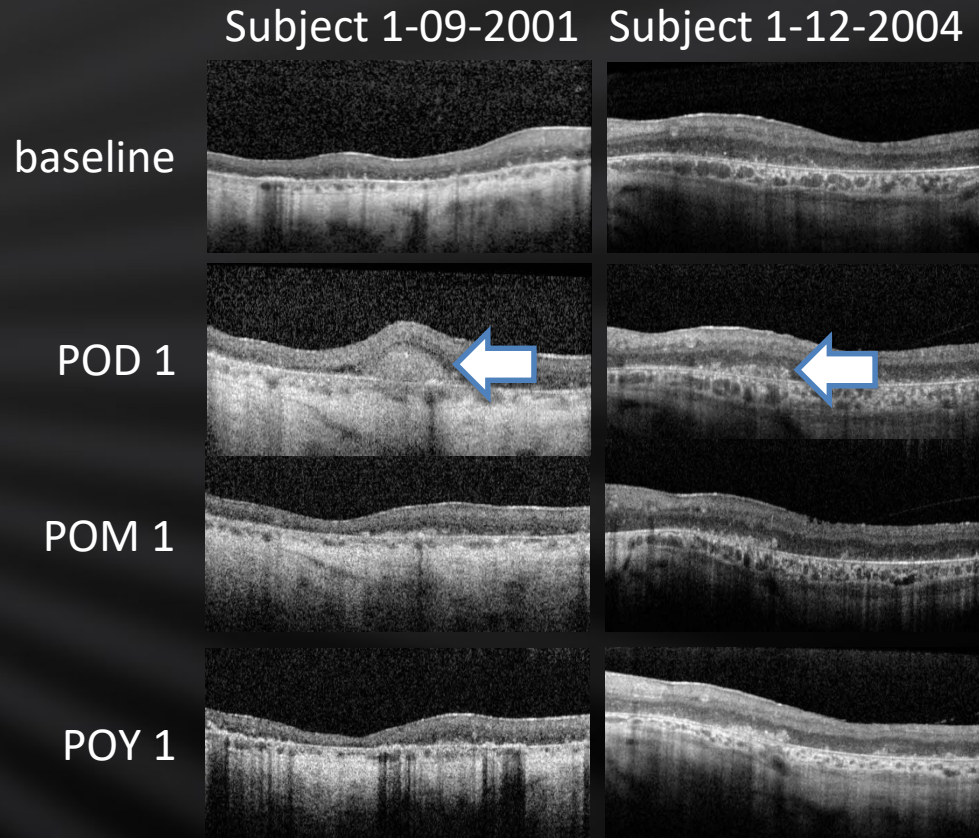
Intraoperative #2



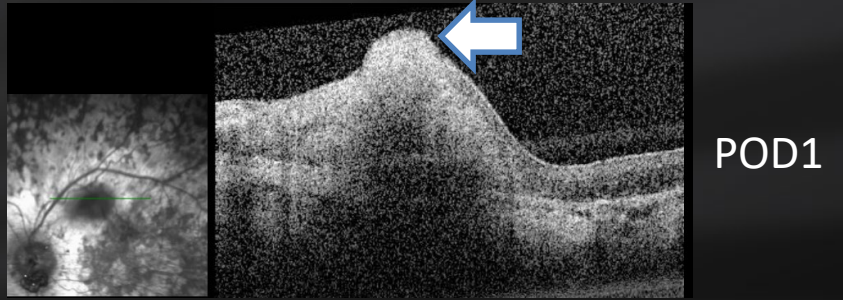
Pre-op → Postop Day 1



Imaging findings- thinning of subretinal material

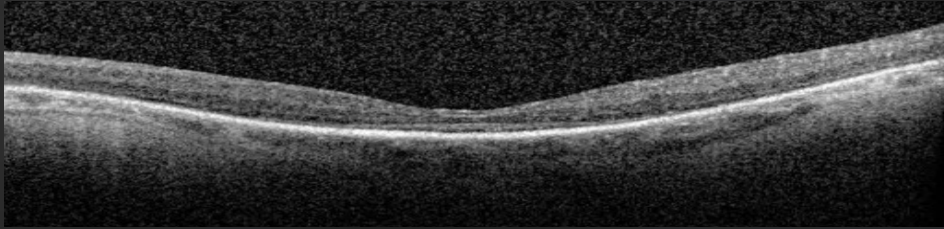


Imaging findings - Epiretinal deposit disappearing without ERM or PVR

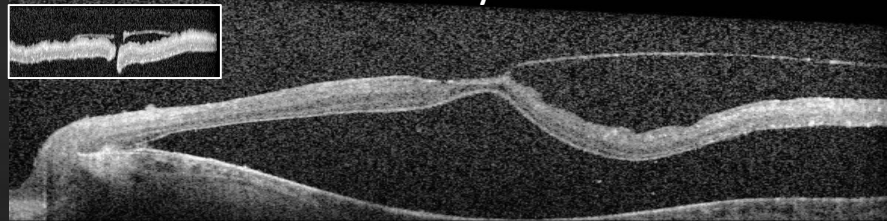


SAE – “worsening of epiretinal membrane requiring second surgery”
Retained thickened posterior hyaloid/ERM causing postop VMT / CME
Subjective persistent loss of vision

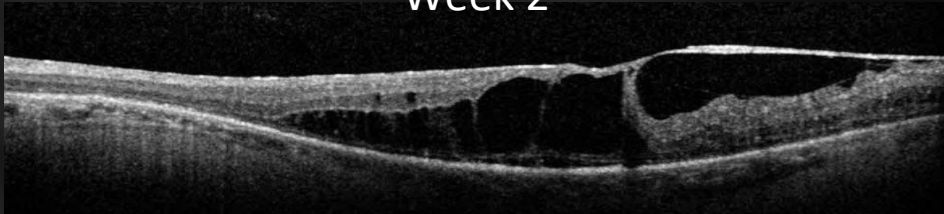
Baseline



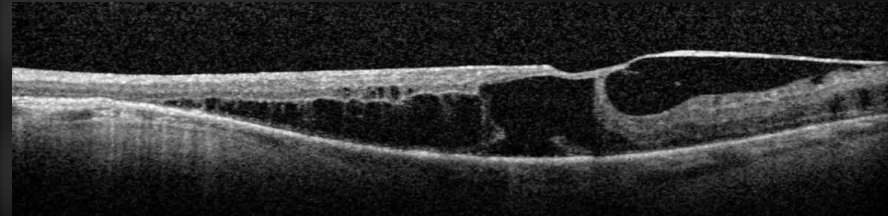
Day 1



Week 2

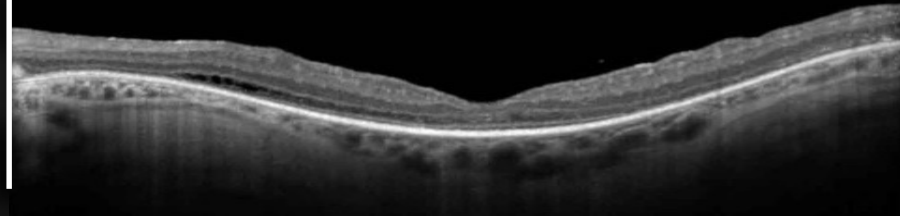


Month 1



Membrane peel

Month 2.5



Vitreoschisis (anomalous multilayered PVD) was typical during hyaloid detachment.

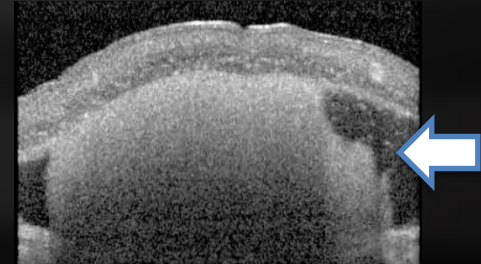
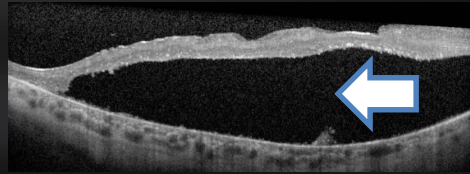
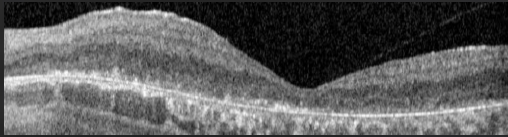
Subretinal bleb persistence with cryopreservative (HypoThermosol) improves with dilution

Fresh formulation
Fluid resolved by POD1

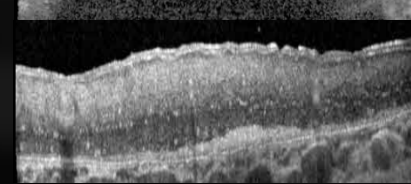
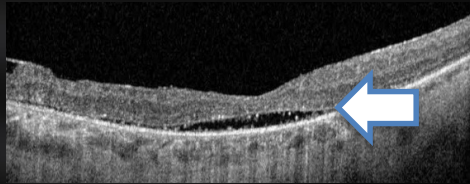
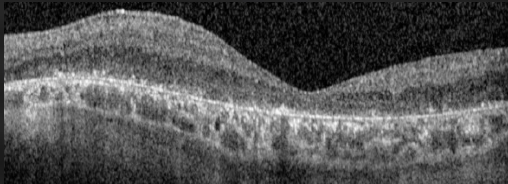
+ Cryopreservative
Present up to 2 weeks

+ Diluted
Cryopreservative
Present 4-7 days

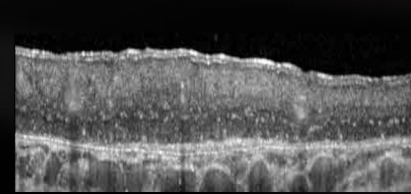
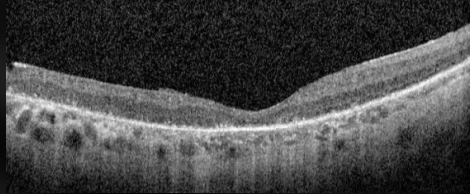
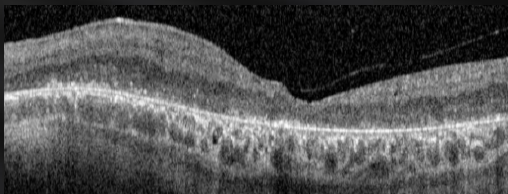
POD 1



POW2



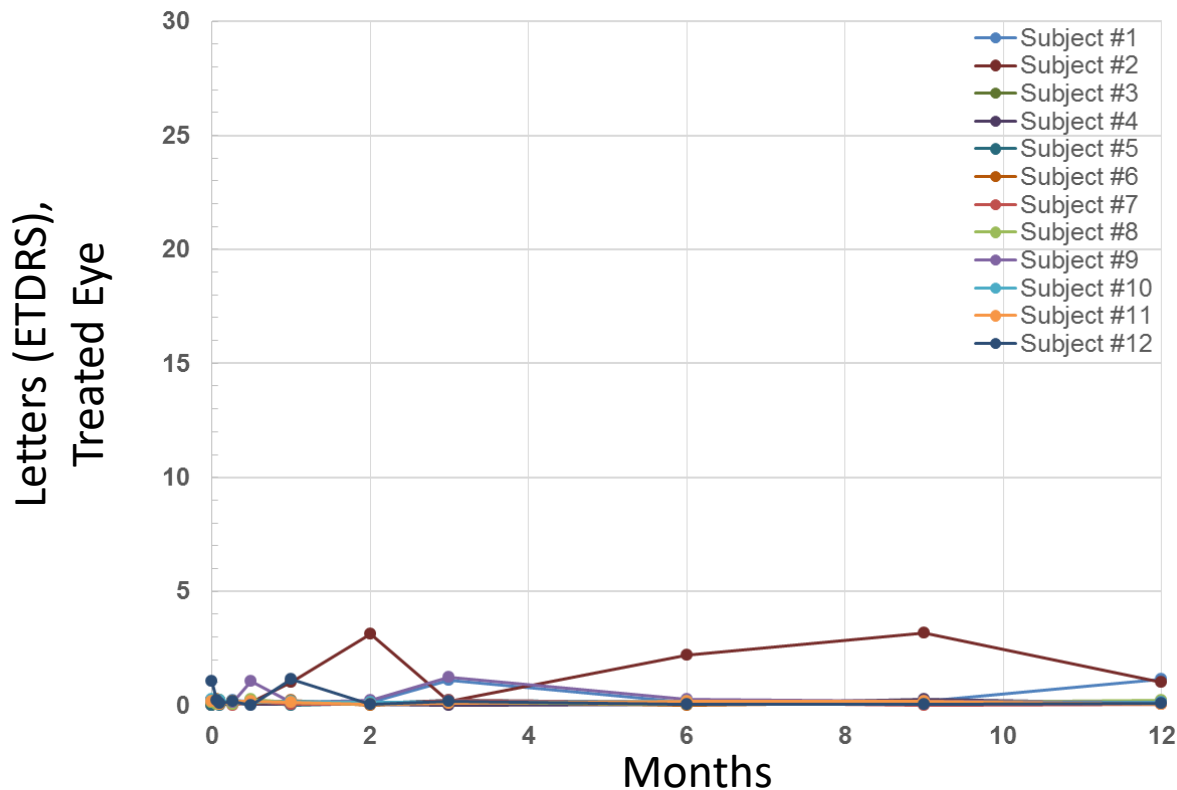
POM 1



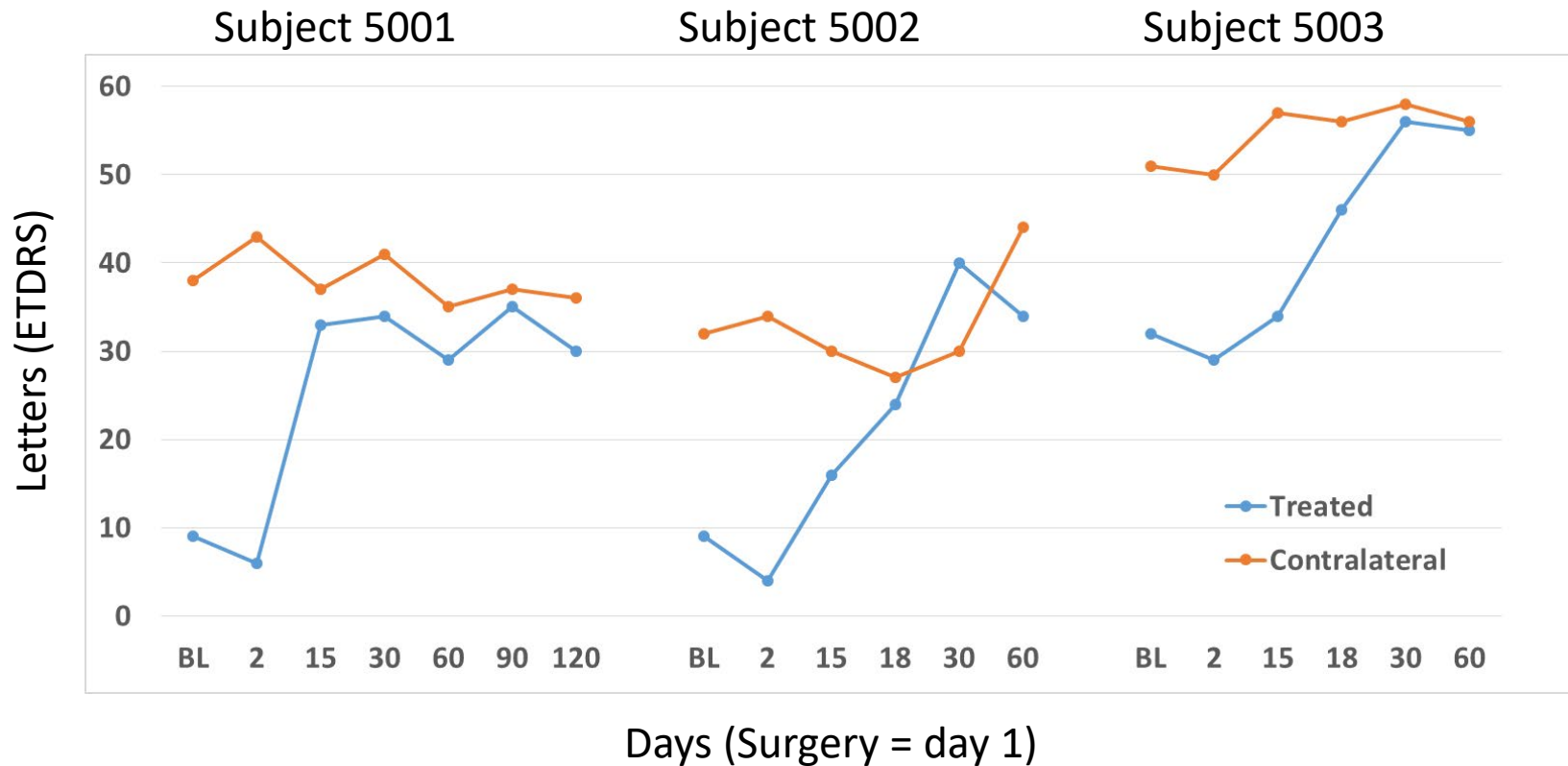
Summary: hRPC Interim Safety

- hRPC do not contribute to proliferative vitreoretinopathy (PVR)
 - Risks consistent with cell identity: mesenchymal > RPE > retinal progenitor cell
- hRPC do not cause significant inflammation
- Delayed bleb resorption with cryopreservative, believed to be due to increased osmolarity, improved with lower concentration
 - Potential risk to host retina, can exacerbate inferior settling of cells
 - Large animal model and additional subjects showed decreased bleb persistence with lower concentration of cryopreservative (decreased osmolarity); product has been reformulated
- Vitreoretinal observations
 - Advanced RP patients often have vitreoschisis / adherent posterior hyaloid which can contract – caused an SAE in one patient. Intraoperative triamcinolone needed.
- Other relevant ocular AEs:
 - subjective decrease in vision (some consistent with postop course)
 - dislocated/subluxed PCIOL in non-study eye then in study eye (1 subject)
 - flashes (1 subject)
 - Routine postop AEs

Best Corrected Visual Acuity: Cohorts 1-4 (Baseline: Light perception to 1 letter)



Best Corrected Visual Acuity: Cohort 5 (baseline 20/230-20/600)

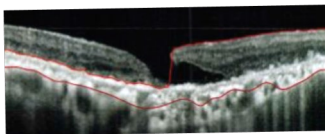
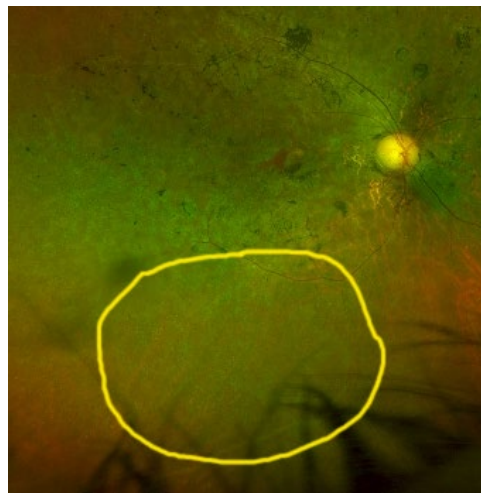


Cohort 5

Subject 5001



Subject 5002



Pre-existing lamellar hole:
eccentric treatment

Subject 5003



Cohort 5- Additional testing

- Subject 5001: No change on microperimetry, Goldmann visual field, imaging. FST 4 dB blue, 1 dB white more sensitivity
- Subject 5002: No change on Goldmann visual field, FST, imaging.
- Subject 5003: Eccentric Goldmann visual field increased more in treated eye (from 17° to 28° equivalent diameter) than contralateral eye (from 16° to 22°). No change on FST, imaging.

Conclusions

- hRPC safety profile
 - No clinically significant inflammation
 - No proliferative vitreoretinopathy (PVR)
 - One patient with traction from pre-existing ERM/thickened posterior hyaloid, subjective decreased vision
 - Extended bleb resorption times are improved with new formulation
- Visual acuity improvements noted in Cohort 5– additional cohorts enrolling now

Acknowledgments

- Research subjects and their families
- Michael Young, Petr Baranov, et al. for hRPC research
- ReNeuron for hRPC research and continued development
- Colleagues at the Retinal Consultants of Arizona site
- MEE clinical research department, study coordinators, and OR
- Co-authors

Sponsor:

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Site #2:



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in affiliation with
USC Roski Eye Institute
Keck Medicine of USC

Warning: In an open label study, subjective reports can be unreliable and should be treated with proper skepticism.

Cohort	Subject #	Subjective reports	Subjective summary
1	1-03-1001	Immediate vision loss centrally, Improved peripherally.	negative
1	1-06-1002	POM3 "something might have improved. picture looks richer." POM 9 no benefit. POM 12 feels color improved in study eye, but much less so by 2 yr visit.	positive, subtle
1	1-07-1003	Sees glimpses of color- subtle "tint" or "overlay".	positive, subtle
2	1-09-2001	No benefit. Both eyes getting worse slowly.	neutral
2	1-10-2003	No benefit.	neutral
2	1-12-2004	No benefit.	neutral
3	1-23-3001	Initially thought diplopia better and could see hand moving better but than not anymore.	positive, subtle
3	1-26-3002	Vision more vivid straight ahead and could see a light. Best vision used to be off to side but now center. "I'm still blind though"	positive
3	1-23-3003	Subjective loss of one area of upper-left vision since the surgery.	negative, subtle
4	1-32-4001*	Immediate central vision loss. not improving. Maybe some better colors at edge of central vision loss but overall much worse "like wearing sunglasses" *patient with SAE	negative*
4	1-29-4002	No significant change. Maybe intermittent improvement but "I wonder if placebo effect"	neutral
4	1-30-4003	I am definitely having more light in my right eye "The computer is definitely better" in high contrast.	positive
5	1-33-5001	"Can see food again" "Can see cell phone without magnifier - I can pick out a lot more than before", "I can see black font on a white background- before I couldn't see it" "sees more of the television without sweeping" "Peripheral vision is much crisper- notices when walking - lower left- pick up things." "I am not cured but it was worth it."	positive
5	2-01-5002	Field of vision is about the same but can see more clearly	positive
5	2-03-5003	Field of vision has gotten bigger and can see more clearly, increased light sensitivity	positive

Cohorts 1-4: range of advanced RP

