OpRegen® engrafts within the retinal pigmented epithelium (RPE) of Gottingen mini-pigs by 4-weeks post-administration via subretinal delivery

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LAYMAN ABSTRACT

Geographic atrophy (GA) is a leading cause of blindness, with negative impacts on quality of life for affected patients. Although recently approved complement inhibitors delay the progression of GA, they have not shown improvement in vision. As such, there is still a high unmet medical need for therapies that can stop or reverse disease progression as well as improve visual function. OpRegen is an investigational cell therapy that contains human RPE cells, which are critical cells for supporting retinal health that become dysfunctional and are lost in GA. Here we show that OpRegen RPE cells successfully incorporate into the existing RPE layer in the eyes of healthy minipigs and that the OpRegen cells maintain markers of functional RPE cells. These data suggest that OpRegen RPE cells can be successfully delivered and incorporated into the retina. OpRegen is currently being evaluated in human clinical studies in patients with GA.

PURPOSE

To evaluate the survival and the distribution of OpRegen (a suspension of human embryonic stem cell-derived allogeneic RPE cells) 4 weeks post-administration via pars plana vitrectomy with subretinal delivery in Gottingen minipigs.

METHODS

5-6 month old, male, naive Gottingen minipigs (n=8, 11.2-14.6 kg) were subretinally administered 40-100 µL OpRegen suspension formulations (100,000-200,000 cells/eye) to both eyes via pars plana vitrectomy using varying surgical instrumentation and methodology as part of a surgical development study. One eye was not dosed due to a retinal detachment during vitrectomy. Animals were immunosuppressed to prevent rejection of xeno-transplanted cells, then monitored for 4 weeks after surgery. OpRegen was injected into the subretinal space without attempt to disrupt or ablate the native porcine RPE. OpRegen presence, survival, and differentiation were evaluated by a combination of histomorphological assessment [Hematoxylin and Eosin (H&E)] and immunohistochemistry (IHC) phenotyping [**ku80** (human origin) dual staining w/ **PMEL17** (differentiated RPE)]. Sections from 7-levels per eye were evaluated including the optic nerve, visual streak, and administration site. All slides were evaluated by board-certified veterinary pathologists.

RESULTS

Cases of OpRegen RPE cells integrated as a monolayer into native RPE were identified by IHC (**ku80+ cells**). OpRegen was observed in the subretinal space of 8/15 eyes and in 6 of these 8 eyes, OpRegen integrated into the minipig RPE as a monolayer. These cells were indistinguishable from the native RPE on H&E and were ku80+ (indicating human origin [e.g., OpRegen]) and **PMEL17+** (retention of RPE features).

Figure 1: Left: Procedure site, OpRegen administration. Note preservation of overlying retinal morphology (H&E). Right and Inset: IHC demonstrating integration of OpRegen as a monolayer within the procedure site (**purple; ku80 – human origin,** e.g., OpRegen).

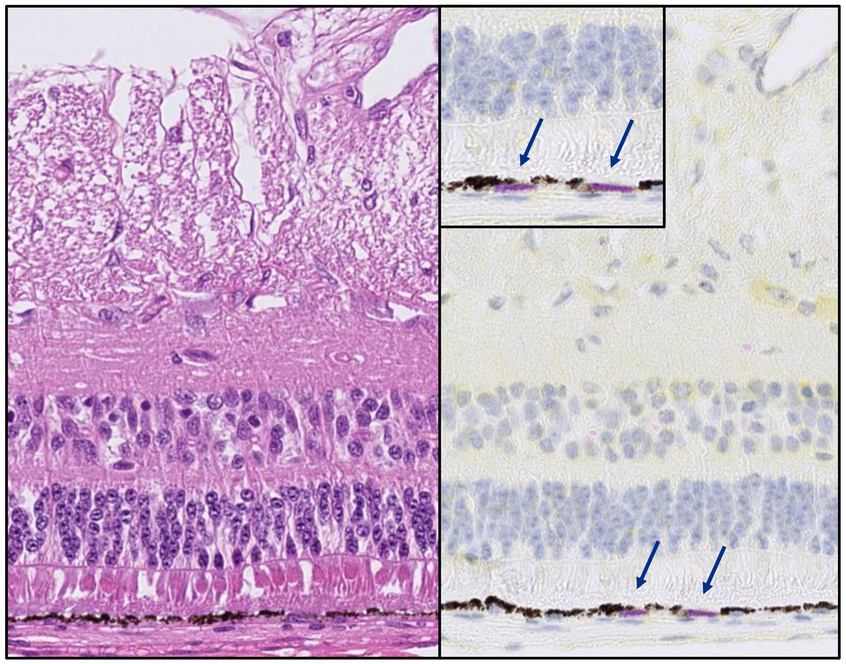
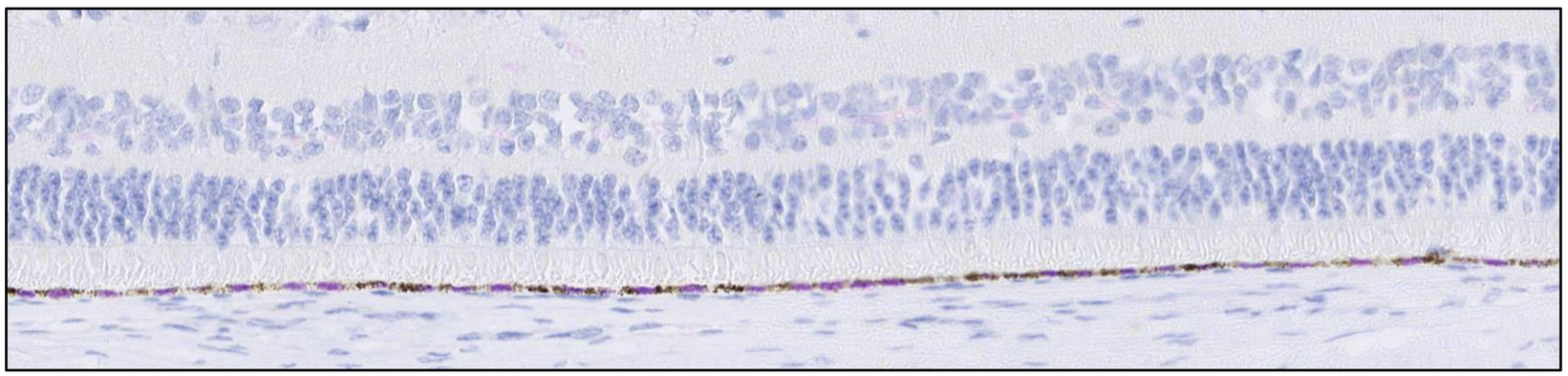


Figure 2: Regionally extensive integration of OpRegen cells (**purple: ku80 – human origin**; **yellow: PMEL17 – RPE differentiation**) as a monolayer within the RPE of a Gottingen minipig.



CONCLUSIONS

Engraftment of OpRegen was demonstrated in this large animal surgical model and was present at 4 weeks post-surgical administration. The similar size of the minipig eye compared to human eyes provides a useful model for evaluating surgical procedures intended for human use.

DISCLOSURES

Genentech, Inc., sponsored this study and provided support for the preparation of this poster. Authors RNA, HEW, YO, AS, TT, and VB were employed by Genentech, Inc. for this study. YO was a visiting professor from the Nagoya City University Graduate School of Medical Sciences. RB, VS, TC, CJ, and KD were employed by CRL-Mattawan during the completion of this study. OpRegen is being developed by Genentech in partnership with Lineage Cell Therapeutics.

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