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RPE-Retina Transplantation for Retinal Degenerative Disease

Marco Attilio Zarbin¹

¹ *Institute of Ophthalmology and Visual Science, New Jersey Medical School, Newark, NJ*

In this issue of the *American Journal of Ophthalmology*, Dr. Radtke and his colleagues report on the results of a phase 2 clinical trial of fetal retinal pigment epithelium (RPE)-retina transplants in patients with retinitis pigmentosa (RP) and age-related macular degeneration (AMD).¹ Visual acuity improved in 7 of 10 study eyes and in 3 of 10 control fellow eyes. Some issues that merit consideration are: the study design, the basis of the visual improvement, the potential immunogenicity of the transplant, alternative approaches to retinal transplantation, and current challenges to further progress. Each of these issues is considered below.

Regarding methodology, a strength of the trial is that visual acuity was studied carefully before and after surgery. All patients underwent cataract extraction with intraocular lens placement and posterior capsulotomy pre-operatively in the study eye. Because fellow eyes did not, as a matter of protocol, undergo this procedure, there is a potential source of bias in the study design. Among the fellow eyes, seven had undergone cataract surgery before the transplant; two had subsequent cataract surgery; and one did not have cataract surgery (Norman Radtke, personal communication). Thus, the visual loss in the fellow eyes probably was due largely to progressive retinal degeneration. The use of experimental visual stimulation videos might be a confounding variable. Patients were instructed to cover the non-transplanted eye, but compliance was a concern (Norman Radtke, personal communication). If these videos have an effect, it might be masked by the way in which the stimulation was applied. Some of the diagnostic testing (e.g., OCT, MP1, SLO, multifocal ERG) was not standardized. This limitation does not detract from the fundamental finding of the study. Some of these tests probably do not have the resolution needed to identify the portion of host retina re-vitalized by the graft. Evidence from Stargardt disease patients indicates that one can lose ~90% of the cones in the fovea and still retain 20/30–20/100 vision.² Thus, the number of functioning photoreceptors mediating improved visual acuity in the study patients might be so small that they cannot be visualized currently, even with high-resolution techniques such as adaptive optics.³ SLO and MP1 testing, however, are valuable, as they permit identification of the preferred fixation locus(i) with respect to the graft.

It is possible that visual improvement in the study eyes is not due entirely to the transplanted cells. In one animal model of RP, lensectomy and vitrectomy alone improves retinal survival.⁴ Retinal detachment seems to have a neuroprotective effect on cones and rods in another animal model of RP.⁵ Furthermore, as the authors note, inserting a needle into the subretinal space without injecting cells can result in improved vision in animal models of retinal degeneration. The authors posit that effect of surgery alone (vs. the transplant) is unlikely to account for the sustained improvement in vision, based on the duration of the sham surgery effect in preclinical models. Nonetheless, since there is evidence that lensectomy, vitrectomy,

Address: Room 6155, Doctors Office Center, 90 Bergen Street, Newark, NJ, 07103, Phone: 973-972-2038, Email: zarbin@umdnj.edu.

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and retinal detachment can improve photoreceptor survival in preclinical models and since the existence (and duration) of this effect in humans with RP and/or AMD is unknown, there may be limitations in using “unoperated” fellow eyes as controls. Ideally, a fellow eye with a similar degree of disease severity at the start of the study that undergoes the same surgery as the study eye except for the receipt of the retinal graft is the best control for the sight-restoring effect of the transplanted cells. This approach poses ethical dilemmas, but they may not be insurmountable.

If visual improvement was due to the transplant, it seems likely to have been largely via a “rescue” (vs. “replacement”) mechanism,⁶ which is consistent with the MP1 findings in patient 1 showing increased sensitivity in an area adjacent to but not overlying the graft. Whether visual recovery mediated by a retinal transplant is better/same/worse than that achieved by administration of a specific neurotrophic factor(s) is unknown. In principle, RPE-retina transplants can produce more than one neurotrophic substance, which might be an advantage of this approach. The degree of visual improvement in the eyes receiving transplants was quite modest. Perhaps visual recovery would have been better if patients had undergone surgery earlier in the course of their disease. At this time, it may not be wise to place fetal RPE-retina grafts *under* the fovea in patients with vision of 20/20–20/100 based on the results of this study. However, visual stabilization is highly desirable for patients with inexorably progressive disease. Assuming that the main benefit of the grafts is photoreceptor rescue, one might consider placing the tissue *adjacent* to the fovea in patients with relatively good visual acuity.

Dr. Radtke and his colleagues assessed immune surveillance of the transplants carefully. As they note, the HLA antibody studies do not rule out the possibility that the donor tissue was recognized. The absence of inflammation on fluorescein angiography is encouraging in this regard, but recent results in AMD indicate that chronic inflammation can occur at the level of RPE-Bruch’s membrane with no signs of inflammation on angiography. The loss of RPE pigmentation in 8 of 10 patients may be innocuous. In some cases, it may signify RPE death, which would be consistent with the progressive choriocapillaris atrophy seen in patient 7.⁷

It seems unlikely that, if effective, fetal RPE-retina transplants can be provided on a large scale. Different approaches merit consideration, depending on whether one is attempting rescue or replacement. RPE cells and photoreceptors can produce substances that have a rescue effect on host photoreceptors.^{8, 9} Thus, one might be able to transplant adult RPE-photoreceptor sheets to stabilize vision. (It is possible that fetal tissue is less likely to undergo immune rejection.) In some cases, gene therapy probably will be more effective for photoreceptor rescue than cell-based therapy.^{10, 11} Different types of cells might be used to achieve photoreceptor replacement (Table). Multipotent retinal progenitor cells,¹² immature post-mitotic rod precursors,¹³ and fetal RPE-retina sheets¹⁴ all have been transplanted in preclinical retinal degeneration models and have shown evidence of synapse formation with host retina and some improvement in visual behavior. At this time, however, the process is extremely inefficient. In one study, less than 0.5% of transplanted cells integrated with the host retina.¹³

Significant challenges for foveal reconstruction by replacement therapy include: efficient tissue delivery,¹⁶ integration of the transplant with the host and re-establishment of functional synaptic circuitry,¹⁷ maintenance of an appropriate state of differentiation by the transplanted tissue,¹⁵ and immune surveillance.¹⁸ Solutions to these challenges may depend on the specific retinal degenerative disease in question, the duration of the disease, and the type of cell one is transplanting. Restoration of precision vision for patients with advanced disease seems more likely to be achieved by a replacement strategy than by rescue, so these obstacles are worth addressing. The work of Dr. Radtke, his colleagues, and many other investigators is bringing us closer to the resolution of these issues and the establishment of sight-restoring therapy for retinal degenerative disease.

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Table

Some potential sources of cells for photoreceptor replacement.*

Cell type	Developmental Capacity
Totipotent stem cell	Can form all lineages of the organism (including the placenta)
Pluripotent stem cell	Can form all lineages of the body (e.g., embryonic stem cell)
Multipotent stem cell	Can form multiple cell types of one lineage (e.g., retinal progenitor cell)
Reprogrammed cell	Nuclear transfer, cell fusion, or genetic manipulation to create a pluripotent cell
Immature post-mitotic rod precursor	Can form rod photoreceptors
Fetal retina-RPE sheets	Includes rods, cones, and other differentiated retinal neurons as well as Muller cells

* Adapted from Jaenisch and Young.¹⁵