Retinal Pigment Epithelium–Retina Transplantation for Retinal Degenerative Disease

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In this issue of the journal, Radtke and associates report on the results of a phase 2 clinical trial of fetal retinal pigment epithelium (RPE)–retina transplantations in patients with retinitis pigmentosa (RP) and age-related macular degeneration (AMD). Visual acuity (VA) improved in seven of 10 study eyes and in three of 10 fellow control eyes. Some issues that merit consideration are: the study design, the basis of the visual improvement, the potential immunogenicity of the transplantation, 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 VA was studied carefully before and after surgery. All patients underwent cataract extraction with intraocular lens placement and posterior capsulotomy before surgery 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 underwent cataract surgery before the transplantation; two subsequently underwent cataract surgery; and one did not have cataract surgery (Radtke N, personal communication). Thus, the visual loss in the fellow eyes probably was the result of progressive retinal degeneration. The use of experimental visual stimulation videos may be a confounding variable. Patients were instructed to cover the nontransplanted eye, but compliance was a concern (Radtke N, personal communication). If these videos have an effect, it may be masked by the way in which the stimulation was applied. Some of the diagnostic testing (e.g., optical coherence tomography, MP1, scanning laser ophthalmoscopy [SLO], and multifocal electroretinography) was not standardized. This limitation does not detract from the fundamental findings of the study. Some of these tests probably do not have the resolution needed to identify the portion of host retina that is revitalized by the graft. Evidence from Stargardt disease patients indicates that one can lose approximately 90% of the cones in the fovea and still retain 20/30 to 20/100 vision. Thus, the number of functioning photoreceptors mediating improved VA in the study patients may be so small that they cannot be visualized currently, even with high-resolution techniques such as adaptive optics, 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 entirely the result of the transplanted cells. In one animal model of RP, lensectomy and vitrectomy alone improved retinal survival. Retinal detachment (RD) seemed to have a neuroprotective effect on cones and rods in another animal model of RP. 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 the effect of surgery alone (vs the transplantation) is unlikely to account for the sustained improvement in vision based on the duration of the sham surgery effect in preclinical models. Nonetheless, because there is evidence that lensectomy, vitrectomy, and RD can improve photoreceptor survival in preclinical models and because the existence (and duration) of this effect in humans with RP, AMD, or both 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 the result of the transplantation, it seems likely to have been largely via a so-called rescue (vs a so-called replacement) mechanism, 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 transplantation is better, the same, or worse than that achieved by administration of specific neurotrophic factors is unknown. In principle, RPE–retina transplantations can produce more than one neurotrophic substance, which may be an advantage of this approach. The degree of visual improvement in the eyes receiving transplantations 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, based on the results of this study, to place fetal RPE–retina grafts under the fovea in patients with vision of 20/20 to 20/100. However, visual stabilization is highly desirable for patients with inexorably progressive disease. Assuming that the main benefit of the grafts is photore-
TABLE. Some Potential Sources of Cells for Photoreceptor Replacement*

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Developmental Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totipotent stem cell</td>
<td>Can form all lineages of the organism (including the placenta)</td>
</tr>
<tr>
<td>Pluripotent stem cell</td>
<td>Can form all lineages of the body (e.g., embryonic stem cell)</td>
</tr>
<tr>
<td>Multipotent stem cell</td>
<td>Can form multiple cell types of one lineage (e.g., retinal progenitor cell)</td>
</tr>
<tr>
<td>Reprogrammed cell</td>
<td>Nuclear transfer, cell fusion, or genetic manipulation to create a pluripotent cell</td>
</tr>
<tr>
<td>Immature postmitotic rod precursor</td>
<td>Can form rod photoreceptors</td>
</tr>
<tr>
<td>Fetal retina–retinal pigment epithelium sheets</td>
<td>Includes rods, cones, and other differentiated retinal neurons as well as Müller cells</td>
</tr>
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*Modified from Jaenisch and Young.15


