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Transplantation of Intact Sheets of Fetal Neural Retina With its Retinal Pigment Epithelium in Retinitis Pigmentosa Patients

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- **PURPOSE:** To show the safety of transplanting sheets of fetal neural retina together with its retinal pigment epithelium (RPE) to patients with retinitis pigmentosa.
- **DESIGN:** Interventional case series.
- **METHODS:** Sheets of fetal neural retina and RPE were transplanted together into the subretinal space near the fovea unilaterally in the eyes of five patients with retinitis pigmentosa who had only light perception in both eyes. The patients were followed for 6 months. The main outcome measures were tissue typing of both donors and recipients, fluorescein angiography, multifocal electroretinogram (mfERG) testing, and clinical examination. No immunosuppressive medications were given.
- **RESULTS:** No evidence of rejection was observed. Up to 6 months there was no evidence of tissue disintegration, retinal edema, or scarring. There was no change in vision both by Snellen acuity and with mfERGs. Growth of the transplant was noted in two of five patients at 6 months vs. 2 weeks. All patients typed were HLA mismatched with donor tissue.
- **CONCLUSIONS:** This study indicates that fetal retina can be transplanted together with its RPE and survive for at least 6 months without evidence of rejection. However, no improvements in vision were observed, possibly due to the severe retinal degeneration of the patients. (*Am J Ophthalmol* 2002;133:544–550. © 2002 by Elsevier Science Inc. All rights reserved.)

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N. D. Radtke, M. J. Seiler, and R. B. Aramant have a proprietary interest in the implantation instrument and procedure.

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RETINITIS PIGMENTOSA (RP) IS A GROUP OF INHERITED diseases with mutations in photoreceptor or retinal pigment epithelium (RPE) genes. In these diseases, blindness is due to specific degeneration of photoreceptors and/or RPE even though the inner retina that connects to the brain may still remain relatively intact.^{1–3} If the diseased photoreceptors and/or RPE can be replaced by transplantation of retinal tissue and if the new cells can connect to the functioning part of the host retina, a degenerated retina might be repaired and eyesight might be improved.

Retinal transplantation studies in animals have involved either RPE cells^{4–6} or cells of the neural retina.^{7–12} Transplantation of RPE cells has aimed at delaying retinal degeneration. Several groups have shown that transplantation of healthy RPE cells in an animal model of RPE dystrophy can rescue photoreceptors that would otherwise degenerate.^{4,5} The rescue effect is related to the age of the donor cells: only young, not adult RPE cells support long-term survival.^{13,14} However, RPE cell transplants have not been shown to have any effect on retinal degeneration in the rds mouse, a model of photoreceptor degeneration.¹⁵

The success of RPE transplants in RCS rats has led to clinical trials in age-related macular degeneration (ARMD) patients. Approximately 14 ARMD patients received fetal RPE transplants in Sweden^{16–18} and one patient received adult RPE transplants in the United States.¹⁹ The first transplants performed on patients with “wet” ARMD showed signs of rejection at 3 months.¹⁷ In wet ARMD, the Bruch membrane and the RPE have been compromised, permitting leukocyte and humoral access to the grafts. However, in another study, patients with the “dry” form of ARMD where the blood retinal barrier remains intact demonstrated less rejection and RPE patch transplants also fared better than the transplants of dissociated cells in the same type of dry ARMD patient.^{16,18}

RPE transplantation can rescue existing photoreceptor cells.^{4,5} However, when photoreceptors are irreversibly lost, transplantation of RPE cells is not enough; photore-

ceptors will also need to be replaced. This has been investigated by relatively few research groups.^{8-12,20,21} Fourteen RP patients in India,²² eight patients with RP, and one patient with ARMD in the U.S.²³ received aggregate retinal transplants and eight patients received adult photoreceptor sheet transplants in the United States.^{24,25} So far, these clinical trials have shown no rejection, but also no improvement in vision. However, since there was only histology in two cases, the presence of a more subtle graft rejection cannot be excluded.

Using rats with retinal degeneration, Seiler and Aramant have shown that an area of damaged retina can be morphologically repaired by a sheet of fetal retina.^{10,11,26} The technique is extensively described.²⁷ Such transplants can develop layers as in a normal retina^{10,11,26} and phototransduction processes occur in transplanted retinal sheets similar to normal retina.²⁶ In RCS rats and transgenic rats with retinal degeneration, transplants of fetal retinal sheets can restore visual responses in an area of the superior colliculus that topographically corresponds to the placement of the transplants in the retina.^{28,29} Preliminary studies suggest synaptic connections between subretinal transplants and host retina by trans-synaptic virus tracing from the host brain to the transplant.³⁰

At the present time, however, there is no published convincing experimental evidence that transplanted fetal neurosensory retina can reestablish connections with the residual neural network. Even if this is not the case, the transplanted tissues might exert a positive rescue effect through the production of neurotrophic factors on the recipients' remaining photoreceptors, as has been shown in animal experiments *in vitro* and *in vivo*.^{31,32}

The uniqueness of the approach presented in this paper is the ability to transplant intact sheets of human fetal neural retina and RPE together. Fetal donor tissue has many advantages over adult tissue. Fetal cells have a high capacity to sprout processes, to produce trophic substances, and can overcome the trauma of transplantation much easier than adult cells, because they do not depend so heavily on oxygen as adult cells.³³ Fetal retinal tissue is less likely to be immunogenic than adult tissue.^{34,35}

The purpose of the study was to evaluate the safety of transplanting fetal neural retina and RPE together in humans. The hypotheses were that the tissues would survive in the subretinal space, that they would not pose any toxic effect to the retina, nor would there be any rejection. Measures of visual function were employed to assess whether this technique could be explored in humans as a therapeutic strategy in some diseases of retinal degeneration.

METHODS

THE STUDY WAS AN INTERVENTIONAL CASE SERIES WHERE five patients with retinitis pigmentosa and a vision of light

perception in both eyes were studied without a control group for comparison. Five patients from a clinical retinal practice received transplants of intact sheets of human fetal neural retina and RPE. Appropriate institutional review board approvals were obtained from Norton Audubon Hospital and from the University of Louisville Human Studies Committee and were conducted under the FDA IND number BB-INDD 8354. Each patient who received a transplant had given an informed consent after extensive counseling regarding the realistic expectations of the procedure.

Patients included in the study had light perception (LP) vision in each eye for at least 1 year with a diagnosis of retinitis pigmentosa, were 21 years of age or older, not pregnant, had signed the consent form for retinal transplantation, and were willing to return for follow-up visits.

Criteria for exclusion from the study included any significant ocular disease that compromised or could compromise vision in the eye to be studied and thus confound the analysis, participation in another ophthalmic clinical trial or use of any other investigational new drugs within 12 weeks before the start of the study treatment, intraocular surgery within the last 2 months, capsulotomy within the last month in the study eye, a history of uveitis, Coats' disease, or diabetic retinopathy, glaucoma, or a cataract that prevents visualization of the posterior pole.

Eyes of fetuses ranging from 11 to 16 weeks gestational age were obtained by informed consent. Donor consent was completed by a team independent from the surgical team. Donors were not compensated and had agreed to a termination of pregnancy before being approached to donate tissue for research. The tissue was kept cold in Hibernate E medium with B27 supplements (Gibco BRL, Rockville, Maryland) after harvesting until it was transplanted from 4.5 to 7.5 hours later (see Table 1). Donor eyes, dissected free of ocular muscles and connective tissue, were incubated for 30 minutes at 37 C in dispase (Collaborative Biomedical Products, Bedford, Massachusetts). This made it possible to dissect sclera and choroid away from the RPE. Dissection of the choroid was done in the surgery room. After dissection of the fetal retina with its RPE and the removal of the vitreous, pieces of 1.5 × 2.0–3.0 mm were cut out (see Table 1) and implanted subretinally near the fovea. A standard vitrectomy surgical procedure was performed and a 3 mm retinotomy was made approximately 5 mm away from the planned implantation site horizontally and parallel to the horizontal raphe of the nerve fiber layer. A custom-made implantation instrument was used.^{10,27,36} The tissue was loaded into a flat plastic nozzle (inner lumen at tip 0.3 mm × 2.0 mm) that was curved at a 130-degree angle. The tissue was loaded inside the tip and oriented with the RPE sheet towards the convex side. The loaded instrument was inserted under the retina through the retinotomy site and the tissue was placed into the target area with the right orientation.

Donor tissue that was dissected away was used for the tissue typing of the donor. Tissue typing of three donors

TABLE 1. Overview of Patients and Procedures

Patient #	1	2	3	4	5
Age	45	68	25	39	48
Sex	M	M	M	M	F
Fetal tissue gestational age (weeks)	16	15.5	13.5	11	13
Time from abortion to implantation (hrs:min)	6:07	7:13	5:18	4:30	4:57
Size of tissue (mm)	1.5 × 1.9	1.5 × 2.5	1.5 × 2.5	1.5 × 3.5	1.5 × 3.0
Observation time after transplantation (months)	11.75	11.25	10.25	10.0	9.75

TABLE 2. Tissue Typing of Donor and Recipient

Marker	Donor #3	Rec. #3	Donor #4	Rec. #4	Donor #5	Rec. #5
HLA-A	2	29	2	11	2	3
HLA-A	26	Ax	Ax	32	32	23
HLA-B	18	8	44	7	51	70
HLA-B	60	57	49	8	61	By (poss. 67)
Bw4		Bw4	Bw4		Bw4	
Bw6	Bw6	Bw6		Bw6	Bw6	Bw6
HLA-DR	4	4	4	15	1	7
HLA-DR	14	7	11	17	14	13
DR51,52,53	52,53	53	52,53	52	52	52,53
HLA-DQ	5	2	7	2	5	2
HLA-DQ	8	3	8	6	-	5

Rec. = recipient.

and their recipients was done. Two patients received six antigen-mismatched grafts (HLA-A, -B, -DR mismatch). One patient received a 5-antigen mismatch graft (match at a single HLA-DR antigen) (see Table 2).

The donor DNA was extracted using a DNA tissue extraction kit (QIAGEN, Valencia, California) and typed for HLA-A, -B, and -DR antigens by PCR amplification using sequence specific primers (Pel Freeze, Deer Brown, Wisconsin).

Complete preoperative assessments (ocular examination, fluorescein angiography, and mfERG) were repeated after surgery at 1 week, 6 weeks, 3 months, and 6 months (see Table 1). Multifocal electroretinography was repeated three times before surgery and has applications for diagnosis in patients with retinal disorders (see³⁷ for review). To assess potentially corresponding physiologic changes in the region of the transplant, photopic mfERGs (mean luminance, 200 cd/m², 75 Hz frame rate) were recorded using a Burian–Allen electrode (Hansen Ophthalmic Development Library, Iowa City, Iowa) and a VERIS Science 3 system (EDI, Inc., San Mateo, California). A 42 × 38-degree field of 103 hexagons was used with the hexagons flashing on or off according to a pseudorandom binary m-sequence. A cross-correlation technique was used to extract local responses from the continuous electroretinography.

RESULTS

THE TRANSPLANT COULD EASILY BE OBSERVED AFTER SURGERY by indirect ophthalmoscopy, because of its heavy pigmentation (Figure 1, left). In two of the patients, this pigmented area of the transplant area increased in size, whereas the remaining three had pigment loss (Table 3). The pigment loss might have been due to separation of the RPE cells or to the fact that the pigment production of the cells could not keep up with the growth of the cells. Figure 1 shows the growth of the RPE at 2 weeks (Figure 1, left) vs. 3 months (Figure 1, right). Fluorescein angiography showed no leakage in the area of the transplant at 6 months in any patient (Figure 2, left and right). Although the clinical appearance of rejection in the retina is still somewhat unclear, no evidence of tissue destruction, as evidenced by leaking on fluorescein, scarring of the retina, or necrosis of the retina was seen at 6 months in all five patients. No systemic or intraocular immunosuppressive medications were used in any patient. Tests of the medium surrounding the tissue before implantation for sterility and endotoxin levels were all within normal limits (Table 3). Patient's vision, as assessed both with Snellen acuity and with mfERG, showed no change.

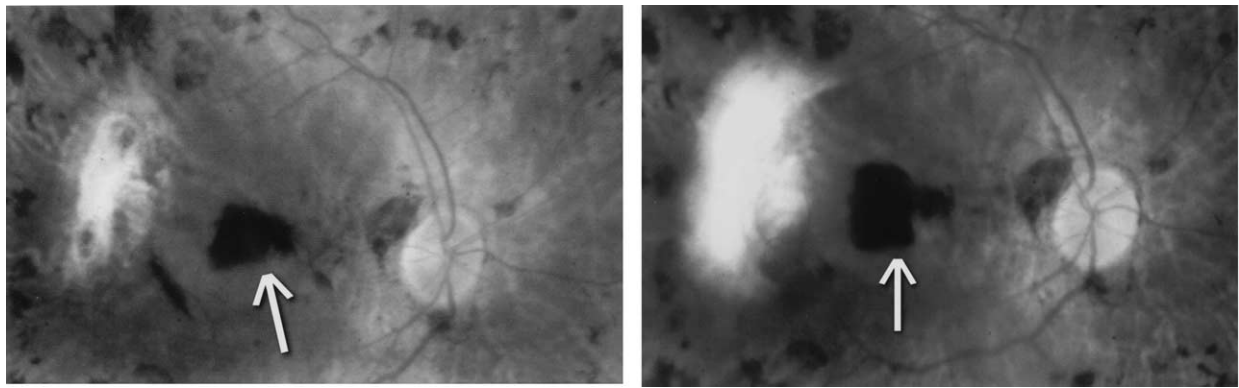


FIGURE 1. (Left) RP patient with light perception (LP) vision 2 weeks after implantation of sheet of fetal neural retina with retinal pigment epithelium (RPE) (arrow) 0.1. (Right) RP patient with LP vision 3 months after implantation. Note growth of transplanted sheet of fetal neural retina and RPE (arrow) as compared with same area in the left frame.

TABLE 3. Results

Patient #	1	2	3	4	5
Fundus	Pigment growth, scar	Pigment loss	Pigment growth, scar	Pigment loss	Pigment loss
Preoperative vision	LP	LP	LP	LP	LP
Postoperative vision	LP	LP	LP	LP	LP
Fluorescein			no leakage		
Multifocal ERG			no change		
Tissue fluid testing/sterility			no organisms seen		
Endotoxin normal < 1.00 ng/ml	0.04 ng/ml	0.11 ng/ml	0.2 ng/ml	0.11 ng/ml	0.03 ng/ml

ERG = electroretinogram; LP = light perception.

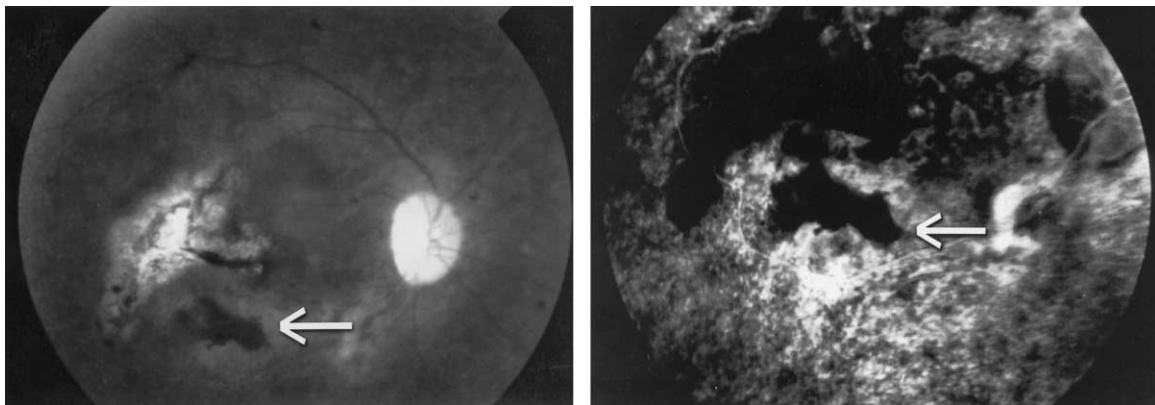


FIGURE 2. (Left) Retinitis pigmentosa (RP) patient with light perception (LP) vision 6 months after transplantation of fetal neural retina and retinal pigment epithelium (RPE) (arrow). No immunosuppression was used. (Right) RP patient with LP vision 6 months after transplantation of fetal neural retina and RPE with no leak on fluorescein (arrow). No immunosuppression was used.

DISCUSSION

THE APPROACH USED IN THIS TRIAL WAS TO TRANSPLANT intact sheets of fetal neural retina and RPE. In RCS rats, it has been shown that freshly harvested intact sheets of fetal RPE and retina transplanted together into the subretinal space can develop approximately normal morphol-

ogy.¹¹ Recently, it has been shown that co-grafts of human fetal retina with RPE can develop normally in athymic nude rats.³⁸ Such transplants have the potential to benefit retinal diseases with dysfunctional RPE and photoreceptors such as human RP. A unique instrument and method have been developed to transplant sheets of fetal neural retina and RPE into the subretinal space between the neurosen-

sory retina and RPE. This approach has significant advantages over other techniques. This technique maintains the correct orientation of the retinal sheets.^{10,27} The minimal trauma associated with the procedure reduces the possibility of rosette formation or rupture of the Bruch membrane.

In this study, by 6 months postoperatively there was no rejection seen clinically or with fluorescein angiography. It is true that graft rejection may be accompanied by graft encapsulation, tissue destruction, and macular edema on fluorescein angiography. However, one cannot exclude the presence of more subtle graft rejection without histology. Previous reports of human transplantation have varied in the incidence of rejection depending on whether the transplantation was patches of RPE cells or dissociated cells and whether the patients had wet or dry macular degeneration.¹⁶⁻¹⁸

The co-grafting of fetal neural retina with RPE is difficult. The fetal RPE can easily loosen from the retina during removal of the choroids, because the photoreceptor outer segments have not yet developed. Partially dissected retina-RPE sheets cannot be stored for a long period or the RPE start to contract and roll up. When the RPE sheets roll up during or after transplantation, the transplants will contain RPE clusters that usually interfere with the ordered organization of the retinal transplant. Sometimes, the RPE sheet falls apart and dispersed RPE cells can be seen migrating through the retinal transplant.^{11,27} Nevertheless, transplants can be achieved in which the co-transplanted RPE stays as a monolayer with tight junctions between the RPE cells that support the development and maintenance of the photoreceptors of the transplant.¹¹

In the three tested donor and recipient pairs, all were mismatched for class I and class II major histocompatibility complex (MHC) antigens. The absence of rejection likely reflects the immunologically privileged site of the subretinal space.³⁹⁻⁴¹ In addition, the transplantation of sheets of fetal RPE and neural retina together (instead of patches of RPE, dissociated RPE cells, adult sheets of RPE, or fetal retinal cell aggregates) might be important for the lack of rejection, despite the potential for rejection based on the microglia in the donor retina.^{42,43}

Many studies indicate that transplants of dissociated RPE cells to the subretinal space undergo chronic rejection¹⁸ and express MHC class I and II antigens after transplantation.⁴⁴ However, transplantation of intact sheets might have immunologic advantages: Allografted sheets of RPE, in contrast to dissociated cells, have been shown to be immunologically privileged—they are not rejected when transplanted to the kidney capsule.⁴⁵ Postnatal retinal tissue, however, was rejected.

The neural retina itself is not immunogenic, but the RPE and microglial cells in the donor retina are immunogenic.^{42,45} Most microglial cells are associated with blood vessels. These cells migrate into the retina postnatally in the rat³⁴ and beginning at 16 weeks gestation in the human.³⁵ Since the number of microglial cells in fetal rat

retina is much lower than in postnatal retina,³⁴ it is likely that fetal retina is less immunogenic than postnatal retina in that species, because fetal retina still lacks inner retinal vessels. However, no one has tested this hypothesis in other animals or humans. In our model, using allografts of Long-Evans or ACI rat donors into Sprague-Dawley or RCS recipients, stable transplants were seen in rats 6–10 months after surgery.^{10,27,46} This indicates that allogeneic retinal sheet transplants can be tolerated in the subretinal space of rats with retinal degeneration.

Tissue typing of donor and recipient in three cases show a single HLA-A match in one patient, indicating that the lack of rejection in our cases was not due to HLA matching. In the next planned clinical trials, the donor tissue and the recipients will be tissue typed for class I and class II MHCs. Furthermore, recipient blood will be tested for antibodies to donor MHC antigens to monitor immunologic reactivity of these grafts. Further immunologic studies will include monitoring of the systemic immunologic responses, although these efforts are complicated by the lack of donor lymphoid tissue.

Our patients had nystagmus and lack of fixation, therefore making mfERG testing difficult. The approval of the Food and Drug Administration (FDA) to perform this procedure in patients with better vision (up to 20/800) and less nystagmus will provide our future studies with greater potential for showing improved function with mfERG and mfVEP testing. Improved vision will allow for better fixation and more accurate determination of local response which may explain why the less severely affected patients described in our previous report³⁶ showed a transient second order mfERG response.

Diseases that affect the RPE and photoreceptor cells of the retina, for example, RP, ARMD, rod-cone dystrophy, and Stargardt's, could benefit from this type of transplantation. Laboratory research to improve connectivity of donor to host should enhance the potential for a functional success of this procedure.

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REFERENCES

1. Santos A, Humayun MS, de Juan E Jr, Greenburg RJ, Marsh MJ, Klock IB, Milam AH. Preservation of the inner retina in retinitis pigmentosa. A morphometric analysis. *Arch Ophthalmol* 1997;115:511-515.

2. Milam AH, Li ZY, Fariss RN. Histopathology of the human retina in retinitis pigmentosa. *Prog Retin Eye Res* 1998;17:175–205.
3. Humayun MS, Prince M, de Juan E Jr, Barron Y, Moskowitz M, Klock IB, Milam AH. Morphometric analysis of the extramacular retina from postmortem eyes with retinitis pigmentosa. *Invest Ophthalmol Vis Sci* 1999;40:143–148.
4. Li L, Turner JE. Inherited retinal dystrophy in the RCS rat: prevention of photoreceptor degeneration by pigment epithelial cell transplantation. *Exp Eye Res* 1988;47:911–917.
5. Lopez R, Gouras P, Kjeldbye H, Sullivan B, Reppucci V, Brittis M, Wapner F, Goluboff E. Transplanted retinal pigment epithelium modifies the retinal degeneration in the RCS rat. *Invest Ophthalmol Vis Sci* 1989;30:586–588.
6. Little CW, Cox C, Wyatt J, del Cerro C, del Cerro M. Correlates of photoreceptor rescue by transplantation of human fetal RPE in the RCS rat. *Exp Neurol* 1998;149:151–160.
7. Silverman MS, Hughes SE. Transplantation of photoreceptors to light-damaged retina. *Invest Ophthalmol Vis Sci* 1989;30:1684–1690.
8. Del Cerro M, Ison JR, Bowen GP, Lazar E, Del Cerro C. Intraretinal grafting restores function in light-blinded rats. *NeuroReport* 1991;2:529–532.
9. Gouras P, Du J, Kjeldbye H, Yamamoto S, Zack DJ. Long-term photoreceptor transplants in dystrophic and normal mouse retina. *Invest Ophthalmol Vis Sci* 1994;35:3145–3153.
10. Seiler MJ, Aramant RB. Intact sheets of fetal retina transplanted to restore damaged rat retinas. *Invest Ophthalmol Vis Sci* 1998;39:2121–2131.
11. Aramant RB, Seiler MJ, Ball SL. Successful co-transplantation of intact sheets of fetal retinal pigment epithelium with retina. *Invest Ophthalmol Vis Sci* 1999;40:1557–1564.
12. Kwan AS, Wang S, Lund RD. Photoreceptor layer reconstruction in a rodent model of retinal degeneration. *Exp Neurol* 1999;159:21–33.
13. Li L, Turner JE. Optimal conditions for long-term photoreceptor cell rescue in RCS rats: The necessity for healthy RPE transplants. *Exp Eye Res* 1991;52:669–679.
14. Sheedlo HJ, Li L, Turner JE. Effects of RPE age and culture conditions on support of photoreceptor cell survival in transplanted RCS dystrophic rats. *Exp Eye Res* 1993;57:753–761.
15. Li L, Sheedlo HJ, Turner JE. Retinal pigment epithelial cell transplants in retinal degeneration slow mice do not rescue photoreceptor cells. *Invest Ophthalmol Vis Sci* 1993;34:2141–2145.
16. Algvere PV, Berglin L, Gouras P, Sheng Y, Kopp ED. Transplantation of RPE in age-related macular degeneration: observations in disciform lesions and dry RPE atrophy. *Graefes Arch Clin Exp Ophthalmol* 1997;235:149–158.
17. Algvere P, Berglin L, Gouras P, Sheng Y. Transplantation of fetal retinal pigment epithelium in age-related macular degeneration with subfoveal neovascularization (see comments). Comment in: *Graefes Arch Clin Exp Ophthalmol* 1994;232:706. *Graefes Arch Clin Exp Ophthalmol* 1994;232:707–716.
18. Algvere PV, Gouras P, Dørgard Kopp E. Long-term outcome of RPE allografts in non-immunosuppressed patients with AMD. *Eur J Ophthalmol* 1999;9:217–230.
19. Weisz JM, Humayun MS, De Juan E Jr, et al. Allogenic fetal retinal pigment epithelial cell transplant in a patient with geographic atrophy. *Retina* 1999;19:540–545.
20. Aramant R, Seiler M, Turner JE. Donor age influences on the success of retinal transplants to adult rat retina. *Invest Ophthalmol Vis Sci* 1988;29:498–503.
21. Silverman MS, Hughes SE, Valentino T, Liu Y. Photoreceptor transplantation: Anatomic, electrophysiologic, and behavioral evidence for the functional reconstruction of retinas lacking photoreceptors. *Exp Neurol* 1992;115:87–94.
22. Das T, del Cerro M, Jalali S, et al. The transplantation of human fetal neuroretinal cells in advanced retinitis pigmentosa patients: results of a long-term safety study. *Exp Neurol* 1999;157:58–68.
23. Humayun MS, de Juan E Jr, del Cerro M, et al. Human neural retinal transplantation. *Invest Ophthalmol Vis Sci* 2000;41:3100–3106.
24. Kaplan HJ, Tezel TH, Berger AS, Wolf ML, Del Priore LV. Human photoreceptor transplantation in retinitis pigmentosa. A safety study. *Arch Ophthalmol* 1997;115:1168–1172.
25. Kaplan HJ, Tezel TH, Berger AS, Del Priore LV. Retinal transplantation. *Chem Immunol* 1999;73:207–219.
26. Seiler MJ, Aramant RB, Ball SL. Photoreceptor function of retinal transplants implicated by light-dark shift of S-antigen and rod transducin. *Vision Res* 1999;39:2589–2596.
27. Aramant RB, Seiler MJ. Retinal transplantation—advantages of intact fetal sheets. *Prog Ret Eye Res* 2002;21:57–73.
28. Woch G, Aramant R, Seiler M, Sagdullaev B, McCall M. Retinal transplants restore visually evoked responses in rats with photoreceptor degeneration. *Invest Ophthalmol Vis Sci* 2001;42:1669–1676.
29. Sagdullaev BT, Aramant RB, Seiler MJ, Woch G, McCall MA. Retinal transplantation restores visual responses in a transgenic rat model of retinal degeneration [Abstract]. *Soc Neurosci Abstr* 2000;26:1099.
30. Aramant RB, Seiler MJ, Woch G. Retinal transplants form synaptic connections with host retinas with photoreceptor degeneration—demonstrated by trans-synaptic tracing from host brain (ARVO abstract). *Invest Ophthalmol Vis Sci* 2000;41 (suppl):S101.
31. Mohand-Said S, Hicks D, Simonutti M, Tran-Minh D, Deudon-Combe A, Dreyfus H, Silverman MS, Ogilvie JM, Tenkova T, Sahel J. Photoreceptor transplants increase host cone survival in the retinal degeneration (rd) mouse. *Ophthalmic Res* 1997;29:290–297.
32. Mohand-Said S, Deudon-Combe A, Hicks D, Simonutti M, Forster V, Fintz AC, Leveillard T, Dreyfus H, Sahel JA. Normal retina releases a diffusible factor stimulating cone survival in the retinal degeneration mouse. *Proc Natl Acad Sci* 1998;95:8357–8362.
33. Wasselius J, Ghosh F. Adult rabbit retinal transplants. *Invest Ophthalmol Vis Sci* 2001;42:2632–2638.
34. Ashwell KW, Hollander H, Streit W, Stone J. The appearance and distribution of microglia in the developing retina of the rat. *Vis Neurosci* 1989;2:437–448.
35. Provis JM, Leech J, Diaz CM, Penfold PL, Stone J, Keshet E. Development of the human retinal vasculature: cellular relations and VEGF expression. *Exp Eye Res* 1997;65:555–568.
36. Radtke ND, Aramant RB, Seiler MJ, Petry HM. Preliminary report: indications of improved visual function following retina sheet transplantation to retinitis pigmentosa patients. *Am J Ophthalmol* 1999;128:384–387.
37. Hood DC. Assessing retinal function with the multifocal technique. *Prog Retin Eye Res* 2000;19:607–646.
38. Seiler M, Aramant R. Intact-sheet transplants of human fetal retina with pigment epithelium develop normal lamination and survive long-term in nude rats. *Exp Eye Res* 2000;71 (suppl 1 ICER Abstracts):S60.
39. Jiang LQ, Jorquera M, Streilein JW. Subretinal space and vitreous cavity as immunologically privileged sites for retinal allografts. *Invest Ophthalmol Vis Sci* 1993;34:3347–3354.
40. Grisanti S, Ishioka M, Kosiewicz M, Jiang LQ. Immunity and immune privilege elicited by cultured retinal pigment epi-

- thelial cell transplants. *Invest Ophthalmol Vis Sci* 1997;38:1619–1626.
41. Wenkel H, Streilein JW. Analysis of immune deviation elicited by antigens injected into the subretinal space. *Invest Ophthalmol Vis Sci* 1998;39:1823–1834.
 42. Ma N, Streilein JW. Contribution of microglia as passenger leukocytes to the fate of intraocular neuronal retinal grafts. *Invest Ophthalmol Vis Sci* 1998;39:2384–2393.
 43. Larsson J, Juliusson B, Holmdahl R, Ehinger B. MHC expression in syngeneic and allogeneic retinal cell transplants in the rat. *Graefes Arch Clin Exp Ophthalmol* 1999;237:82–85.
 44. Zhang X, Bok D. Transplantation of retinal pigment epithelial cells and immune response in the subretinal space. *Invest Ophthalmol Vis Sci* 1998;39:1021–1027.
 45. Wenkel H, Streilein JW. Evidence that retinal pigment epithelium functions as an immune-privileged tissue. *Invest Ophthalmol Vis Sci* 2000;41:3467–3473.
 46. Aramant R, Seiler M. Retinal transplantation. *Sci Medicine* 2000;7:20–29.