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RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: SAFETY STUDY IN RETINAL TRANSPLANTATION FOR AGE RELATED MACULAR DEGENERATION

PROTOCOL NO.: None
WIRB® Protocol #20050380

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502-636-2823 (24-Hour Pager)
800-643-8197

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

You have been invited to participate in an investigational retinal transplantation study because you have 20/200 vision in one eye or worse, due to dry age related macular degeneration. Investigational means that this procedure has not been approved by the Federal Drug Administration (FDA). "Retinal transplantation" means to place new healthy fetal retinal cells into the lining of the back of the eye. Subjects who have a vision of 20/800 or worse in one eye will have new fetal retinal cells transplanted under the retina. This investigational research is being sponsored by the University of Louisville Department of Ophthalmology and Visual Sciences and the Vitreoretinal Research Foundation. The Vitreoretinal Research Foundation is a non-profit health organization that supports retinal research. Norton Audubon Hospital and Jewish Hospital in Louisville are the primary sites for this study.

EXPLANATIONS OF SOME WORDS IN THIS CONSENT FORM:

Retinal tissues, the layers in the back of the eye, consist of neural retina and retinal pigment epithelium. *Neural retina* is the nerve cell layer that processes light into vision.

The *photoreceptor cells* in the neural retina detect the light and change it into electrical signals, which are then transferred to the brain by other retinal cells. *Retinal pigment epithelium (RPE)* is the layer behind the neural retina which helps both to feed the cells of the neural retina and also to get rid of waste products.

The *fetal tissue* is derived from dead fetuses at the first 8 to 16 weeks of pregnancy obtained from elective induced abortions. *Elective induced abortion* means that a woman decides herself to end her pregnancy.

Fetal retinal cell transplantation includes transplantation of fetal RPE cells and/or fetal neural retina. *Retinal pigment cell transplantation* means only transplantation of RPE cells. RPE can be *co-grafted* with retina, the RPE and the retina are not separated.

PURPOSE:

The purpose of the study is:

1. To test safety and effectiveness of the procedure (transplanting human fetal retinal tissue into the human eye).

2. To determine that the donor tissue transplanted will not cause harm to the host eye.
3. To confirm that the donor tissue will not provoke a rejection response in the host eye.

EXPLANATION OF OUR STUDY:

This is not the first time fetal RPE or retinal cells have been transplanted in humans. To date, most of the available information in humans is from work using techniques different from ours. So far, work of others has not shown that vision improves after such transplants.

Approximately 14 subjects have had fetal RPE transplants in Sweden with 12 subjects having had adult RPE transplants in the United States for age-related macular degeneration. Fourteen subjects have had fetal retinal transplants in India for retinitis pigmentosa, with eight subjects having adult photoreceptor transplants in the United States. No objective functional benefit has been observed or documented in any of these subjects. As of January 2005, our group has had done transplants in 14 subjects.

There will be 10 subjects in this study per year. It is expected that the length of the study will be two years.

Before surgery, two complete exams will be done at least 30 days apart to confirm visual acuity. You will be required to stay in the hospital 23 hours for a transplantation operation. You will be asked to sign a separate consent form for this procedure. For seven days you will receive oxygen through a nasal tube from a portable tank and have a device to measure the oxygen in your blood. After the operation, you will be examined at one week, one month, three, six, nine, twelve, and twenty-four months. During the postoperative period, which may be up to three months, travel by air would be strictly prohibited. After the first 12 months, you will be examined once a year. These visits will include a variety of eye exams. Including, but not limited to: complete examinations of the front and back of the eye, tests for eye pressure, visual acuity as well as an fluorescein angiography (test which takes pictures of a blood vessel after injection of a kind of dye). The non-operated eye will also be thoroughly examined. The amount of time required for follow-up visits will be approximately three hours.

Advantages of fetal donor tissue

There are many reasons why we have chosen to use fetal donor cells -- and not adult donor cells -- for this study.

The fetal cells have a better ability to grow and connect the transplant cells with the cells of the subject. Fetal cells do not depend as heavily on oxygen as adult cells. However, there is a chance that your immune system, the body's infection fighting mechanism, could reject the transplant at a later time. However, the subretinal space into which the cells are placed is called an immune privileged site. This means there is a higher probability that the transplant is not rejected.

Animal studies

Retinal transplantation studies have involved either RPE cells or cells of the neural retina.

Transplantation of RPE cells intends to stop continued damage to the retina. In an animal study model, the RCS rat, that has defective RPE cells, photoreceptor damage can be halted by transplantation of healthy RPE cells. Only young, not adult, RPE cells can support long-term survival of the host photoreceptor cells.

RPE transplantation can rescue existing photoreceptor cells. However, when photoreceptors are irreversibly lost, they need to be replaced. To bring back vision would require, in addition, successful transplantation of photoreceptors.

Our group has focused on transplantation of fetal retinal cells. We have shown that human fetal retinal transplants in rat subjects develop all cell types and that the transplanted photoreceptors produce several substances that are important for sensing light. In addition, we have indications that human and rat fetal retinal transplants grow processes and make synapses (nerve contact points) with the recipient's retina. The functional significance of such contacts has not been demonstrated and the contacts represent host graft contacts that are still under investigation. We have shown in experimental animals that pieces of fetal retina can be transplanted as an intact sheet with very little disturbance to that tissue and develop layers as in a normal retina.

Fetal tissue transplanted in humans

This field of research has developed so rapidly in the last few years that it is impossible to give an approximate number of subjects involved. Human fetal tissue transplantation has been used in many areas of medicine, including liver, and neurological disorders, such as Parkinson's disease.

In clinical studies with Parkinson's subjects, fetal dopaminergic transplants have been able to reduce the symptoms of this incurable disease in some studies, whereas there were no effects in other studies. One study has shown severe side effects in 15% of the subjects.

The eye is another area of research where fetal tissue transplantation has been used. Two kinds of fetal retinal cells have been transplanted in subjects. Several studies have been published about clinical studies with transplantation of one of these types of fetal retinal cells. These transplants were done first to five subjects with severe macular degeneration with bleeding vessels.

Although the transplants survived in the beginning, the disease process of macular degeneration could not be stopped and continued to get worse. However, the authors of this study reported better graft survival when they tried transplantation on nine more subjects who had a less severe stage of macular degeneration without bleeding vessels. A different group has done another study with transplantation of fetal retinal cells at John Hopkins University and in India. Six subjects with retinitis pigmentosa were transplanted with fetal retinal grafts at Beijing Friendship Hospital in China as a safety study. No adverse (bad or harmful) effects from the transplantation of fetal tissue were observed. Subjects have reported subjective, but not objective improvements after transplantation of retinal or iris cells from the subjects' own eyes into the center of the eye. All these attempts have shown no objective visual benefits and are difficult to evaluate for their real success. Our technique is different than techniques used in other studies. While separated fetal retinal cells were injected in most of the other studies and some had sheets of adult RPE transplants or sheets of adult photoreceptors, our transplantation is different in that with our studies we are using co-grafts of double sheets of fetal neural retina and fetal retinal pigment epithelium.

<u>POSSIBLE RISKS:</u>

This research procedure might have unwanted side effects for different reasons.

Adverse effects related to the "experimental pilot study" surgery are: (1) A retinal detachment where the neural retina may become separated from the cells that nourish it (retinal pigment epithelium) may occur; this may make an extra operation necessary. (2) There may be bleeding in the fluid-filled part of the eye. (3) Hemorrhaging in the eye and scar tissue formation under the retina. (4) An infection may occur. (5) The normal pressure in the eye may increase and cause a disease called glaucoma which destroys the nerves and causes blindness. (6) The top layer of the eye, the cornea, is very soft. It may become damaged and not heal as it should. (7) Cataracts may form. This means that the lens in the eye becomes cloudy. Then the lens might have to be removed. (8) Double vision may occur; the eyelid can droop or hang down. (9) There may be a change in the way the eye looks or the eye may be so damaged that it has to be removed. (10) There may be complications due to anesthesia, allergic reactions or complications from the use of certain medicines. There is a possible risk of complete loss of vision in the operated eye.

The adverse effects related to transplantation include: (1) The knowledge that the tissue was obtained from an induced abortion may cause psychological stress. (2) There is a possible risk of transmission of viral infection, such as AIDS or hepatitis, from the transplanted tissue. However, blood of the woman having the abortion that has donated the fetal tissue will have been tested for the presence of antibodies against human immunodeficiency virus (HIV, the virus that causes AIDS) and hepatitis (HAV, HBV, HCV). To reduce the risk for virus transmission, aborted tissue from women positive for the above-mentioned viruses is excluded. (3) There is a possibility of an immunological reaction to the transplanted tissue. That means that the immune system, the body's infection fighting mechanism of the subject, could reject the transplant at a later time.

There is a rare chance of a severe inflammatory reaction that may adversely affect your vision. This type of reaction is called sympathetic ophthalmia.

This is a possibility but the prevalence of sympathetic ophthalmia is difficult to measure because it has always been a relatively rare disease; as a result of improvements in modern surgical and medical treatment, it has become even more uncommon.

Pregnant and nursing women are excluded as subjects from the study. Pregnancy testing will be done in women of childbearing potential.

It is necessary to be aware that there may be additional risks in this procedure that are currently unknown.

Your condition may not get better or may become worse while you are in this study.

Should an injury occur from this research effort, Dr. Norman D. Radtke may be contacted at 502-636-2823 (24-Hour Pager) or 800-643-8197 where further information may be obtained.

ANTICIPATED BENEFITS:

This is a safety study and there is no anticipated visual benefit to these subjects with wet or dry macular degeneration. In dry age-related macular degeneration, we may heal the damage to the retina with growth factors produced by the transplanted tissue. RPE helps to feed and get rid of unwanted waste from the photoreceptor cells in the neural retina. Placing new healthy co-grafted RPE and retinal tissue back in place may improve vision.

COSTS:

The cost of the examination to determine if you qualify as a candidate is $481.00. Travel costs to Louisville and accommodations while in Louisville are your responsibility. All costs of the other preop tests, surgery, and postop follow-up will be at no charge to you.

PAYMENT FOR PARTICIPATION:

There will be no payment for being a part of this research study.

ALTERNATE TREATMENT:

You do not have to participate in this study to receive treatment for your condition. You can discuss these options with the study doctor. Another option would be to do nothing.

Dry age-related macular degeneration therapies have used medical therapies, principally vitamin and antioxidant treatment. To date, the research is still ongoing with the National Eye Institute sponsoring AREDS (The Age Related Eye Disease Study) to test the effect of such substances. Experimental work on blood filtering, diode grid photocoagulation, for treatment of drusen and artificial retinas is ongoing.

Wet age-related macular degeneration has many experimental surgical approaches. Photodynamic therapy, submacular surgery, translocation surgery, and Argon laser treatment are the most common.

Other approaches include radiation therapy anti-angiogenesis research, and transpupillary thermotherapy (TTT). Less than 50% of subjects with these experimental surgical approaches have been documented to have any significant improvement in vision.

Use of low vision aids is also an alternative.

Dr. Norman D. Radtke, the study doctor, will discuss these other options with you.

VOLUNTARY PARTICIPATION/WITHDRAWAL:

Your participation in this research study is voluntary. You may refuse to participate or you may stop your participation in the study at any time without penalty or loss of any benefits to which you are otherwise entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent.

NEW FINDINGS:

You will be informed of any new findings that might change your decision to be in this study. This would apply to findings that have become available after you have signed the consent form, but before transplantation.

COMPENSATION FOR INJURY:

In case of an unexpected event or injury during this study, you will receive immediate care. The cost of postoperative complications, if determined by the investigators to be due to the experimental surgery and not the natural course of age-related macular degeneration, will be covered by the study. No compensation for loss of wages or injury will be routinely provided.

SOURCE OF FUNDING:

Funding for this research study will be provided by Norman D. Radtke, M.D., PSC.

FINANCIAL DISCLOSURE:

Dr. Radke is part owner or the company developing this product. Please feel free to ask any questions you might have about this matter.

CONFIDENTIALITY:

Your medical research records from this study will be kept in a locked cabinet in the office of Dr. Norman D. Radtke, Suite 240, 3 Audubon Medical Plaza, Louisville, Kentucky. This information will be held in confidence to the extent permitted by law. No one will have access to your name if your research records are used for newspapers, articles, teaching, etc.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES:

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you.

What information may be used and given to others?

If you choose to be in this study, the study doctor will get personal information about you. This may include information that might identify you. The study doctor may also get information about your health including:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research about
  - Physical exams
  - Laboratory, x-ray, and other test results
- Records about any drug you received
- Records about the study device

Who may use and give out information about you?

Information about your health may be used and given to others by the study doctor and staff. They might see the research information during and after the study.

Who might get this information?
Your information may be given to the sponsor of this research. "Sponsor" includes any persons or companies that are working for or with the sponsor, or are owned by the sponsor.

Information about you and your health which might identify you may be given to:

- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Human Subjects Protection Program (HSPPO)
- The University of Louisville Department of Ophthalmology and Visual Sciences
- Vitreoretinal Research Foundation
- Governmental agencies in other countries
- The Western Institutional Review Board® (WIRB®)

Why will this information be used and/or given to others?
Information about you and your health that might identify you may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose.

The information may be given to the FDA. It may also be given to governmental agencies in other countries. This is done so the sponsor can receive marketing approval for new products resulting from this research. The information may also be used to meet the reporting requirements of governmental agencies.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

The information may be reviewed by WIRB®. WIRB is a group of people who perform independent review of research as required by regulations.

What if I decide not to give permission to use and give out my health information?
By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research.

May I review or copy the information obtained from me or created about me?
You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your information until after the research is completed.

May I withdraw or revoke (cancel) my permission?
Yes, but this permission will not stop automatically.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is my health information protected after it has been given to others?
If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others without your permission.

QUESTIONS:

If you have questions about this study and your rights of being part of a scientific study, or if at any time you feel you have experienced a research-related injury, can be obtained from the office of Dr. Norman D. Radtke, Suite 240, 3 Audubon Medical Plaza, Louisville, Kentucky, 502-636-2823 (24-Hour Pager) or 800-643-8197.

If you have any questions about your rights as a research subject, you may contact:

Western Institutional Review Board® (WIRB®)
3535 Seventh Avenue, SW
Olympia, Washington 98502
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: ClientServices@wirb.com.

You will be given the opportunity to discuss any questions about your rights as a research subject, in confidence, with a member of the IRB.

WIRB is a group of people who perform independent review of research.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to participate in this study, you will be given a signed and dated copy of this consent form.

CONSENT:

I have read or had read to me this consent form and have been given the chance to talk about it and ask questions. All my questions about the study and my participation in it have been answered. I may call Dr. Norman D. Radtke at 502-636-2823 (24-Hour Pager) or 800-643-8197 to answer any questions I may have while I am in this study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form, I have not waived any of the legal rights which I otherwise would have as a subject in a research study.

_____
SUBJECT NAME (PRINTED)

_____ _____
SIGNATURE OF SUBJECT DATE SIGNED

_____ _____
N. D. RADTKE, M.D. DATE SIGNED
SIGNATURE OF INVESTIGATOR

_____ _____
SIGNATURE OF PERSON CONDUCTING DATE SIGNED
INFORMED CONSENT DISCUSSION
(IF OTHER THAN THE INVESTIGATOR)

---------- Use the following only if applicable ----------

If this consent form is read to the subject because the subject is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject. The subject freely consented to participate in the research study.

_____ _____
Signature of Impartial Witness Date

Note: This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling subjects who do not speak English.