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EXPERIMENTAL TREATMENTS RESTORE PARTIAL VISION TO BLIND PEOPLE

Retinal prosthesis and fetal tissue transplant show promise in human studies

CHICAGO — Two experimental treatments, a retinal prosthesis and fetal tissue transplant, restored some vision to people with blinding eye diseases. The findings, presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news on brain science and health, may lead to new treatments for the blind. Researchers also reported that an engineered protein restored vision in an animal model and identified ways to improve stem cell treatments.

The new studies tested both people and animals with two degenerative eye diseases: retinitis pigmentosa and age-related macular degeneration. These diseases destroy the light-sensitive nerve cells in the retina, leading to blindness. In all, vision loss and eye disease affect 3.6 million Americans and cost the United States $68 billion each year.

Research released today shows that:

- A retinal prosthesis restores partial vision to people who are totally blind. The prosthesis, made of an array of electrodes, transmits visual information captured by a video camera (Jessy Dorn, PhD, abstract 216.6, see attached summary).
- Transplanted "sheets" of fetal retinal cells improve visual acuity in several people with retinitis pigmentosa and age-related macular degeneration (Robert B. Aramant, PhD, abstract 837.12, see attached summary).
- Engineered, light-sensitive proteins restore vision in a mouse study of retinitis pigmentosa. The findings could lead to new treatments for people with degenerative retinal diseases (Natalia Caporale, PhD, abstract 806.10, see attached summary).
- As researchers strive to develop stem cell therapies for eye disease, a new method increases the yield of retinal cells from human stem cells derived from both embryonic and adult tissue (Jason S. Meyer, PhD, abstract 113.1, see attached summary).

"Basic neuroscience research has formed the basis for significant progress in treating eye disease," said press conference moderator Rachel O. L. Wong, PhD, of the University of Washington, an expert on visual system development. "These studies would not be possible without technological advances and basic science research that continues to explain the normal function and development of the visual system," Wong said.

This research was supported by national funding agencies, such as the National Institutes of Health, and by private and philanthropic organizations.

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Abstract 216.6 Summary

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"Bionic Eye" May Help the Blind to See

Retinal prosthesis shown to restore partial vision

A new artificial retina, an array of electrodes implanted on the back of the eye, has been found to restore partial vision to totally blind people. In a study focused on 15 blind participants who had the implant for at least three months, 10 of the patients subsequently tested were able to identify the direction of moving objects. The research was presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"These results give new hope to the many people with degenerative retinal diseases," said Jessy Dorn, PhD, of Second Sight Medical Products, Inc., lead author of the study. More than two million Americans suffer from eye diseases such as retinitis pigmentosa and age-related macular degeneration, slowly losing their vision as the nerve cells that detect light are destroyed, due to either age or illness. There is no known cure.

In this case, the researchers worked around the destroyed cells. Each participant was given a pair of glasses with a small video camera mounted on it, and a belt with a tiny computer attached. The computer processed video images from the camera and transmitted the data to the implanted electrodes on the retina. When the users "looked" at a monitor with a white bar sweeping across a black screen, the electrodes that corresponded with the moving bar stimulated cells in the eye, creating spots of light in their fields of vision.

"We found that most of the study participants were better able to determine the direction of the bar when using the prosthesis system than without it, or with a scrambled video input," Dorn said. "In other words, this new system gave most blind people the ability to identify an object's direction of motion — something they could not do without it."

An international clinical trial is now testing the prosthesis system. To date, 32 blind people have received the implant.

Research was supported by the National Eye Institute.

Scientific Presentation: Sunday, Oct. 18, 2:15–2:30 p.m., Room N228

216.6, The Argus™ II retinal prosthesis improves the ability of subjects to perform a spatial task
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TECHNICAL ABSTRACT: Purpose: The feasibility of the Argus™ II 60 electrode epi-retinal system to partially restore vision to subjects blinded by Retinitis Pigmentosa is currently under investigation in several clinical centers worldwide. The purpose of this work was to test whether the system provided spatially distinct information through multi-electrode stimulation, allowing subjects to determine the direction of motion of an object in the visual field. Methods: The Argus™ II retinal prosthesis consists of an array of 60 independent electrodes. The stimulation current of each electrode is determined by the brightness at the corresponding area of the scene captured in real-time by a camera mounted on the subjects' glasses. Subjects maintained eye and head fixation on the center of a 19" touchscreen monitor placed 12" in front of them. After an audio prompt, a 1.4" wide white line swept across the black monitor screen at a randomly chosen angle (0-360°). The speed of the motion was fixed throughout the experiment but varied across subjects. After each trial, the subjects drew the direction of motion they perceived on the touchscreen. An experiment consisted of 80 trials with automated verbal feedback. The experiment was run in three conditions: with the subjects' native vision alone (system off), with the system on and normal spatial mapping of the video image to the electrodes, and with the system on and scrambled spatial mapping between the image and the electrodes (as a control condition, Caspi et al., 2009). Results: The error (difference between the direction of the moving line and the direction drawn) was calculated for each trial. Ten out of 15 subjects had smaller average error with the system on than with their native vision alone (t-test, $p<0.05$). Of these, 7 of the 8 subjects that were available for further testing had significantly smaller average error with a normal spatial mapping than with a scrambled spatial mapping. Four subjects showed no difference in the results when performing the task with the system on (and normal spatial mapping) compared to performing the task with their native vision alone (system off), and one subject had better performance when the system was off, due to residual native vision. Conclusions: The Argus™ II retinal prosthesis improved the ability of most blind subjects (10 out of 15) to identify the direction of a moving object. This work demonstrates that the system provides spatio-temporal information from multiple stimulating electrodes that can be used to perform perceptual tasks.

Abstract 113.1 Summary

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New Method to Coax Retinal Cells from Stem Cells

Findings could lead to more effective treatments for eye disorders

Researchers have developed a new method for identifying retinal precursor cells derived from human embryonic stem cells (those from embryonic tissue) and induced pluripotent stem cells (those from adult skin cells). These precursor cells represent the earliest stages of retinal development. The new method results in a greater yield of retinal cells from stem cells and could be used to better understand disease processes and realize effective treatments for eye disorders. The findings were presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Problems associated with retinal degenerative diseases are due to the injury and death of neurons, or support cells that can't regenerate. The cell types primarily affected are the light-sensing rod and cone photoreceptors and the adjacent retinal pigment epithelium, which maintains proper photoreceptor health and function. If these cells could be replaced or bypassed, sight could be restored.

"So far, a number of human cell sources have been examined to see if they produce multiple retinal cell types, but most candidates have proven inadequate," said Jason S. Meyer, PhD, at University of Wisconsin, the study's lead author. "In comparison, human stem cells have produced cells that are clearly of a retinal nature."

When the stem cells were isolated and matured, specific retinal cell types could be identified, including photoreceptors and retinal pigment epithelium. Using this new system, the authors could regulate the production of certain cell types by adding or removing particular compounds to the cells. "This ability could aid in the discovery of new therapeutic approaches to a variety of disorders affecting the retina," Meyer said. "These findings could lead to treatments for other neurological disorders, in addition to eye diseases."

Research was supported by the National Eye Institute, the Foundation Fighting Blindness, the Lincy Foundation, and the Retina Research Foundation.

Scientific Presentation: Sunday, Oct. 18, 8–8:15 a.m., Room S100A

113.1, Development of a model system for retinogenesis from a highly enriched population of human embryonic stem cell-derived retinal progenitors
J. S. MEYER[1], E. E. CAPOWSKI[1], R. L. SHEARER[1], K. A. WALLACE[1], L. S. WRIGHT[1], D. M. GAMM[2]; [1]Waisman Ctr., [2]Waisman Center, Dept. of Ophthalmology and Visual Sci., Univ. Wisconsin, Madison, WI

TECHNICAL ABSTRACT: Human embryonic stem cells (hESCs) have the potential to provide comprehensive model systems for the earliest stages of human ontogenesis. To serve in this capacity, hESCs must undergo a targeted, stepwise differentiation process that follows a normal developmental timeline. We have previously demonstrated that hESCs could be guided to differentiate in a manner that meets each of the major developmental stages of human retinogenesis. However, this differentiation occurred within a mixed neural population that made it difficult to distinguish developmental events that were specific to the retinal population. In order for hESCs to effectively serve as a model system, it would be important to isolate these hESC-derived retinal progenitors from the remaining anterior neural population. In the current study, we describe a method for identifying hESC-derived neurospheres that are highly enriched for retinal progenitor cells. Upon the isolation of these retinal neurospheres, greater than 90 percent of all cells expressed the definitive neural retinal progenitor marker Vsx2 (also called Chx10). Upon further maturation of this population of cells, major classes of differentiated retinal cell types were identified. Furthermore, production of retinal cells at various stages of differentiation was influenced by the addition of specific factors at defined times in culture. Thus, this study demonstrates that, under appropriate conditions, hESCs possess the potential to serve as a reliable, comprehensive and specific model system for human retinogenesis.

Abstract 837.12 Summary

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Transplanted Tissue Improves Vision

Study shows enhanced visual acuity

A clinical study is the first to show that advanced stages of incurable retinal diseases can be stopped and improved by a cell replacement technique. The researchers transplanted intact "sheets" of fetal retinal cells that develop into light-sensitive nerve cells, along with a supporting layer of tissue, into damaged human eyes. The findings were presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

To date, most clinical studies have targeted the early stages of retinal disease in attempts to rescue photoreceptors, the light-sensitive nerve cells. But once photoreceptors have died, they cannot be regenerated. Animal studies have shown that transplanted donor cells and nearby sustaining tissue grow into healthy cells and integrate with the recipient's own damaged retina. The researchers created a special instrument to transplant these extremely fragile sheets of young retinal cells.

Of the 10 patients who received the transplants (four with age-related macular degeneration and six with retinitis pigmentosa), seven improved, one remained the same, and two continued to deteriorate. The individuals were assessed using different methods. The main test was to read letters on a chart to check visual acuity, and follow-up time was between one and six years.

Although most tissue donors and recipients were tested for compatibility, no immunological match was seen. "Despite this limitation, it was encouraging that no rejection was seen clinically and the surgery had no negative side effects," said Robert Aramant, PhD, visiting scientist at the University of California, Irvine, and lead author.

The authors suggest that these results — along with previous positive results in animal retinal degeneration studies — are evidence of the safety and benefits of retinal transplantation in humans. Widespread application, however, would be limited by the restricted access to donor tissue. "These results indicate that this is a viable technique, but more patients are needed to confirm these results," Aramant said. The clinical study was performed in Louisville, Ky.

Research was supported by an anonymous donor, the Foundation Fighting Blindness, the Kentucky Lions Eye Foundation, the Murray Foundation Inc., Research to Prevent Blindness, and the Vitreoretinal Research Foundation. Drs. Aramant and Seiler have a proprietary interest in the implantation instrument and procedure.

Scientific Presentation: Wednesday, Oct. 21, 4–5 p.m., South Hall A

837.12, Retinal transplantation improves vision in macular degeneration and retinitis pigmentosa patients
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TECHNICAL ABSTRACT: Purpose: In a Phase II clinical trial, the efficacy and safety of transplantation of sheets of fetal retina together with its retinal pigment epithelium (RPE) was investigated in age-related macular degeneration (AMD) and retinitis pigmentosa (RP) patients. Methods: In a nonrandomized trial, four AMD and six RP patients (vision: light perception to 20/320) were transplanted in one eye with a sheet of freshly dissected fetal retina together with its RPE. Patients were clinically observed for signs of rejection by fundus exams and fluorescein angiograms. Visual acuity testing by Early Treatment Diabetic Retinopathy Study (EDTRS) was the main outcome measurement method. Several patients were tested by a Scanning Laser Ophthalmoscope, multifocal ERG or Microperimetry. Most tissue donors and recipients were tissue typed for MHC antigens. The follow-up time was one year. Seven of the patients were continually followed up between 2 and 6 years. Results: None of the patients had electrophysiologically measurable responses. At one year after transplantation, three RP and four AMD patients showed improved EDTRS visual scores; one RP patient remained the same and two decreased. One RP patient's vision improved from 20/800 to 20/160 and was maintained at 20/200 for 5 years. At six years, the patient had 20/320 in the surgery eye, but the non-surgery eye had deteriorated to hand motion vision. No immunological match was seen between donor and host but no rejection was observed clinically. Conclusion: Seven patients showed improved visual acuity at one year. Several patients maintained improved vision for several years. These results give evidence of the safety and beneficial effects of retinal transplantation and are supported by the many positive research results in animal retinal degeneration models.

Abstract 806.10 Summary

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Engineered Proteins Restore Light Sensitivity to Animals

Vision shown in both eye and brain response

Engineered, light-sensitive molecules introduced into a blind rodent's eye resulted in vision, according to results from an interdisciplinary collaboration between numerous labs. The findings were presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The results could lead to treatments for people with inherited, blinding eye diseases such as retinitis pigmentosa, which affects one in every 3,000 individuals.

In past studies, researchers made a blind animal's visual cells respond to light by introducing a light-sensitive algae protein into the eye. This new study manipulates existing proteins that our brains normally use to transmit information between neurons, and makes them light sensitive.

The researchers focused on several light-sensitive proteins, each with its own unique properties that could be fine-tuned to meet researchers' specific needs. One such engineered protein, LiGluR (Light Activated Glutamate Receptor), can turn neuronal activity on and off upon illumination with specific wavelengths of light. There are many glutamate receptors in the human brain, but they are not normally light sensitive.

"Our approach was to build on these initial studies, to 're-engineer nature,' by solving a deficit with engineered light-sensitive proteins," said Natalia Caporale, PhD, at the University of California Berkeley, the study's first author. "This approach could prove to be a viable therapeutic option for people who have lost significant vision and are in the late stages of retinal degeneration," she said.

Compared with naturally occurring photosensitive proteins, LiGluR can initiate larger and longer-lasting responses in neurons, making it a promising candidate for treatments intended to restore vision.

Research was supported by the Nanomedicine Development Center for the Optical Control of Biological Function and the Foundation Fighting Blindness.

Scientific Presentation: Wednesday, Oct. 21, 3:15–3:30 p.m., Room N426

806.10, LigluR-mediated visual cortical responses in the rd1 mouse model of retinitis pigmentosa
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TECHNICAL ABSTRACT: Retinitis pigmentosa refers to a heterogeneous group of inherited diseases in which genetic mutations result in progressive photoreceptor degeneration. Without photoreceptor activity, visual processing cannot take place, despite the fact that second and third order retinal neurons remain functional. These diseases currently cause severe visual deficits in one of every 3,000 individuals. Currently, there are no approved therapies to slow the progression of this disease, or stop photoreceptor cell death. An alternative therapy is to restore light responsiveness to a retina devoid of photoreceptors by expressing light-activated channels in surviving neurons. We used intravitreal injection of adeno-associated virus serotype 2 (AAV2) to deliver the engineered light activated glutamate receptor, LiGluR, to retinal ganglion cells (RGCs) in the *rd1* mouse model of blinding retinal degeneration, which lacks photoreceptors at the late stages of the disease.
Single-unit recordings from retinal wholemounts show that LiGluR successfully imparts light sensitivity onto RGCs, allowing for precise and reversible light-mediated control of spiking activity. Local field recordings in anesthetized mice were used to characterize LiGluR-mediated visual responses at the cortical level in response to brief (50ms) and long (300ms) pulses of full-field illumination. Visual responses were maximal at ~380nm (corresponding to the peak wavelength sensitivity of LiGluR), and could be obtained even 48 hours post-injection of the photoswitch. Peak LiGluR-mediated cortical field potentials in response to a 300ms full-field flash (-371.5 ± 36 μV, n=13) were significantly larger ($p<0.0001$, Wilcoxon sign rank test) than those mediated by Channelrhodopsin2 (-61.7 ± 12.3 μV,n=6). These results suggest that LiGluR is a promising candidate for therapeutics aimed at restoring visual function to patients in late stage retinal degeneration.