Casey Scientists Tackle Stem Cell Therapy

When it comes to experimental treatments for age-related macular degeneration (AMD), stem cell transplantation continues to generate great interest. Patients are especially curious about its potential to restore vision lost to the advanced dry form of the disease, which currently is untreatable.

Although Casey Eye Institute researchers are not yet testing stem cell therapy in humans, they are collaborating with scientists at the National Eye Institute, biotechnology companies and other academic institutions to transform laboratory discoveries into new treatments.

On the way, however, they must overcome a number of hurdles, such as determining the best methods to increase the cells' survival and to know if they've survived after transplantation.

Stem cell research for AMD is still in the early phase and primarily evaluating its safety, says Casey director David Wilson, M.D.

“Although there are relatively effective treatments for wet AMD, we have not addressed vision loss from the advanced dry type. Stem cell therapy offers a promising approach,” Dr. Wilson says.

Trevor McGill, Ph.D., is studying ways to better identify stem cells once delivered to the eye and to improve their survival.

At Casey, researchers are focusing on the transplantation of retinal pigment epithelium (RPE) cells, one of the cell layers lining the back of the eye. The RPE performs crucial housekeeping duties, supporting and nourishing the retina's light-sensing photoreceptors. In early AMD, RPE cells begin to deteriorate and become less able to keep visual...
**Stem Cell Therapy** continued

cells healthy. By repopulating the retina with healthy RPE cells, the hope is to forestall the disease's progression.

Scientists are testing RPE cells produced through a cutting-edge technique called induced pluripotent stem (iPS) cell technology. With this method, cells from blood or skin are converted into undifferentiated cells and then reprogrammed to become specialized RPE cells for transplantation into the eye.

**Keeping cells alive**

One of the major challenges in stem cell transplantation is ensuring their survival in the eye, says Trevor McGill, Ph.D., research assistant professor at Casey and a leading expert in cell-based investigations for retinal disease. For more than a decade, Dr. McGill and his laboratory have been studying the immune response of cell transplantation in animal models. To prevent rejection, they must use high doses of steroids and other immunosuppressants, which can cause unpleasant side effects. “The question becomes, ‘how do you minimize rejection without high doses of these drugs?’” says Dr. McGill.

One possible answer may involve using the patient’s own cells, called autologous transplantation. “With the advent of new technologies, we can reprogram a patient’s blood cells to become stem cells and then coax them into becoming RPE cells for transplantation back into the patient,” he says. “Because the cells are derived from the same individual, theoretically, they should not be rejected,” he adds. So far, Dr. McGill and his team have tested autologous transplantation in several non-human primates and though it is early, they are seeing some improvement in cell survival. However, producing these tailor-made cell products on a commercial basis may also pose challenges, he says.

Casey researchers are also studying how best to deliver the cell therapies to the retina. Earlier this year, a team led by Dr. Wilson published a study in the medical journal *Retina* describing a new surgical approach that was highly successful in increasing cell survival. Other investigators were Dr. McGill, Martha Neuringer, Ph.D., Jonathan Stoddard, M.D., Lauren Renner, B.S., Steven Bailey, M.D., and Andreas Lauer, M.D.

**An ID for cells?**

Another challenge, says Dr. McGill, is that “we don’t have the ability to mark these cells and know if they are surviving in the eye, even with today’s sophisticated imaging technology.” What may look like RPE cells in imaging tests may actually be immune cells, he adds.

Dr. McGill’s group is collaborating with the laboratory of Casey ophthalmic imaging pioneer David Huang, M.D., Ph.D., to develop a contrast agent using gold nanoparticles that label the cells. “By incubating cells with this reflective substance, we hope to visualize them with optical coherence tomography,” he says. The project, supported by a grant from Research to Prevent Blindness, will also develop new ways to interpret the light that radiates from the transplanted cells.

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**Major Gift Bolsters Stem Cell Research**

For retired Oregon ophthalmologist Leigh Campbell, M.D., stem cell therapy represents a fascinating approach for the treatment of macular degeneration. “I want to support stem cell research in any way I can,” says Dr. Campbell, who trained at the University of Oregon Medical School (now OHSU) ophthalmology department in the 1950s.

In 2013, Dr. Campbell made a significant gift in honor of his late brother, Dr. Robert Campbell, to establish and maintain a research laboratory at Casey Eye Institute which combines the brothers' respective medical disciplines of ophthalmology and obstetrics. The lab is dedicated to stem cell research to advance eye care and health.

“Casey as a whole is doing a great job and its many achievements speak for itself,” he says. “Having this kind of institution in Oregon is a real plus.”

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**Stem Cell Therapy** continued
A Word of Caution about Stem Cell Treatments

In March, the New England Journal of Medicine reported that three women with macular degeneration suffered severe, permanent eye damage after undergoing a type of stem cell treatment at a private clinic in Florida. The patients received eye injections of stem cells derived from fat tissue extracted through liposuction.

These cases are a reminder that while stem cell therapy is being investigated at well-regulated research institutions like Casey, these treatments are not yet proven to be safe and effective, according to the American Academy of Ophthalmology.

On its website, the Food and Drug Administration cautions consumers to make sure that any stem cell treatment they are considering has been approved by the FDA or is being studied under a clinical investigation that has been submitted to and allowed to proceed by the FDA.

A Note from the Director

In this issue of Insight, we highlight two research projects that on their surface may seem very different. One, called CAREDS2, examines the connection between nutrition and macular degeneration while the other involves transplantation of healthy retinal cells to replace those lost to the disease.

Despite these different approaches in fighting macular degeneration, these and other investigations at the Macular Degeneration Center share some commonalities. Both are focused on the part of our retina that keeps light-sensing eye cells healthy and functioning, called the retinal pigment epithelium layer – or RPE. As we gain more understanding of the RPE's role, we can develop more effective methods of prevention and treatment, especially for the dry form of the disease.

Secondly, both efforts are the fruition of years of research by Casey scientists, often in collaboration with investigators at other institutions and government agencies. Although more work remains to unravel the puzzle of macular degeneration, the progress we are making in the lab and in clinical trials is heartening.

Finally and most importantly, these accomplishments would not be possible without your generous and enthusiastic support of our work, including the Center’s year-end appeal.

Thank you for helping our physicians, scientists and staff provide a brighter future for patients and families affected by this disease.

Christina J. Flaxel, M.D.
Director, Macular Degeneration Center

Participants Needed for Gut Microbiome and AMD Study

Are you over age 65? Please consider enrolling in Casey Eye Institute’s research study exploring the link between advanced macular degeneration and changes in gastrointestinal tract bacteria. The study is looking for people with advanced macular degeneration as well as those without the disease. Participants must be age 65 and older who:

- Have not had colon surgery, colon cancer, or inflammatory bowel disease (Crohn’s disease or ulcerative colitis)
- Are willing to come to Casey Eye Institute for one or two short visits

For more information about participating, contact Jennifer Maykoski, 503 494-3064.
Living with Vision Loss? Resources Help You Focus on Fun

Although declining eyesight can pose some challenges, it doesn’t mean enjoyable pastimes must end up on the sidelines.

Visual aids, assistive technology and community support can help you continue a favorite hobby or even discover new pursuits that will enrich your life and keep you engaged and active, says John Boyer, O.D., direction of Casey Eye Institute’s Vision Rehabilitation Center. Here are some resources to consider:

Casey’s Vision Rehabilitation Center

A good place to start is at Casey’s Vision Rehabilitation Center, where patients undergo vision evaluations and learn strategies for adapting to visual problems. Dr. Boyer and staff work with patients to meet their individual needs, and can recommend and dispense a wide range of vision aids for reading, playing cards and doing needlework and art projects. They can also give you advice on lighting and other simple adjustments to improve your vision, and refer you to other community resources.

Call 503-494-3098 or visit ohsucasey.com

Oregon Commission for the Blind

The commission’s independent living program provides training and resources to help Oregonians age 65 and older participate in leisure activities, volunteer, travel safely and maintain a greater level of independence. “For example, we teach clients how to access transportation services in order to attend activities, or teach cooking so they can entertain at home,” says Sarah Jo Chaplen, OCB’s director of Independent Living Services. In addition, “our mobility training enables clients to walk for exercise and fun, go hiking or visit a neighbor,” she says. The commission also hosts a weekly knitting group.

Call 888-202-5463 or visit oregon.gov/blind

Hull Park for the Blind

Sponsored by Oral Hull Foundation for the Blind, Hull Park provides year-round educational, recreational and social opportunities for blind and visually impaired people. Located in Sandy, Ore., the lush 22-acre property offers a wealth of camps and programs for all ages and physical abilities. It offers an “Enchantment Garden” that engages the five senses, recreation hall, walking paths with raised rails, dormitory, indoor swimming pool and hot tub. Activities range from the daring to tame, including zip lining, horseback riding, fishing, horseshoes and board games.

Seniors may be especially interested in the “Living with Vision Loss” seminars held throughout the year at the park. Each of the three-day sessions focuses on a particular topic, such as recreation and leisure, communication and technology and techniques of daily living.

A great introduction to the park are its “Low Vision Fun
Days,” which feature tours, use of the outdoor game court, watching a descriptive movie and hiking on secure trails. These events are open to the public, including sighted companions.

“Sight loss doesn’t have to result in dependency or isolation,” says Oral Hull director Sharon Elder. “At Oral Hull, you are surrounded by some great people with vision loss who can be wonderful role models,” she says.

The foundation also organizes a weekly lunch at a Portland restaurant. Transportation is not provided, but staff will happily help you figure out options. “We want to encourage independence,” says Elder.

Call 503-668-6195 or visit hullparkfortheblind.org

Portland Art Museum Tour for Blind or Partially-Sighted Visitors

The Portland Art Museum offers small, docent-led tours for blind and low vision visitors on the third Thursday of each month at 2:30 p.m. The tours feature extended verbal descriptions of works in the museum’s collection, and offer tactile examples when possible. For details on upcoming tours, visit the museum’s event calendar at portlandartmuseum.org

For more information or to arrange a special group tour, call 503-276-4290 and leave a message; a docent will return your call.

Northwest Association of Blind Athletes

If you’re keen to get back on a bike, go for a swim, or take a stroll in the park, the Northwest Association of Blind Athletes (NWABA) can get you up and moving. This organization, which serves blind and visually impaired people in Oregon, Washington, Idaho and Montana, has a number of programs and sports for all ages. “Many of our older athletes enjoy our partnership program, which pairs them with sighted volunteers for activities like running, walking, hiking, and tandem biking,” says Stacey Gibbons, program director.

NWABA provides transportation to events from the Oregon Commission for the Blind’s Portland office.

Call 360-448-7254 or visit nwaba.org

American Blind Bowling Association - Portland

Blind, visually impaired and sighted bowlers get together weekly for fun and exercise at a local Portland bowling alley, where metal rails are used to guide bowlers. Kyle Hanes, president of the eastside group, says bowling is a great way to lift your mood.

Contact Kyle at 503-408-6719
**Ocular implant for wet AMD (LADDER Study)**

**Purpose:** To compare the effects of an ocular implant that releases one of three different doses of ranibizumab (Lucentis) to injections of ranibizumab. The study implant releases the study drug continuously for a prolonged period of time and can be refilled by your doctor when needed. This approach may decrease the need for frequent injections into the eye. This Phase 2 study is recruiting newly diagnosed wet AMD patients age 50 or older who meet other eligibility criteria.

**Advanced imaging trials**

**Purpose:** To test the capabilities of high-speed optical coherence tomography (OCT) in patients with dry or wet AMD. Investigators are studying whether this non-invasive imaging technology can visualize and measure blood vessel growth as well as fluorescein angiography, which involves the injection of a contrasting agent to highlight the problem vessels. The team is also comparing how retinal anatomy and blood flow differ among study patients in early, intermediate and advanced dry AMD.

**Genetics of Age-Related Macular Degeneration Study**

**Purpose:** To find genetic mechanisms associated with AMD, which will lead to more accurate early detection and precise treatments. Researchers are using advanced whole genome sequencing technology to uncover gene variations in large families and other populations affected by AMD. The study is supported in part by a major grant from the National Eye Institute.

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**Study Explores Role of Macular Pigment**

Although it's only the size of a pencil point, the macula packs a powerful punch when it comes to our vision. The millions of light-sensing cells in the retina’s center allow us to see colors and fine details and provide the straight-ahead vision we need for reading, driving and other activities. The macula is also jam-packed with lutein and zeaxanthin — pigmented compounds only obtainable from dietary sources, such as green and yellow vegetables, or nutritional supplements. Called carotenoids, these nutrients are being studied for their potential in protecting against macular degeneration and other age-related eye diseases.

“Lutein and zeaxanthin are highly concentrated in the eye’s macula — about 10,000 times more than the amount in our blood serum,” says Steven Bailey, M.D., a retina specialist at OHSU Casey Eye Institute. Previous research suggests that macular pigments may lower inflammation, absorb harmful blue light and act as an antioxidant or “sun block” for the eye, he says.

*Study coordinator Jennifer Maykoski uses a special machine to measure the amount of pigment in Shelah Lompa’s macula.*

Continued
Studies with Completed Enrollment

Lampalizumab for advanced dry AMD

**Purpose:** To evaluate the effectiveness and safety of lampalizumab in patients with advanced dry AMD — also called geographic atrophy (GA). The study medication is given by injection into the eye and targets an enzyme that may encourage dry AMD to develop. The studies are examining changes in vision and the area of GA.

Enrollment in the parent studies are completed and patients are being followed. Those who complete all of their study visits can enroll into an extension, open-label study called OMASPECT.

Injectable medication for wet AMD (SEQUOIA Study)

**Purpose:** To compare the safety and effectiveness of the study drug abicipar pegol to ranibizumab (Lucentis) in patients in an eye with newly diagnosed wet AMD. Abicipar pegol is an anti-VEGF agent that may be more long lasting than some current therapies for wet AMD.

Gene therapy for wet AMD (GEM Study)

**Purpose:** To assess the safety and dosing levels of a gene-based treatment, RetinoStat, for wet AMD. In this Phase 1 study, two helpful genes are delivered directly to the retina, where they "turn on" proteins that block abnormal blood vessel growth in a sustained fashion.

Implantable medication for dry AMD

**Purpose:** To learn if an implantable medication, brimonidine, is safe and effective for treating advanced AMD (geographic atrophy). Brimonidine, used in eye drop form to treat glaucoma, has been shown to protect cells in the retina. In this Phase 2 study, a tiny pellet implanted in the eye releases the medication to the retina over a sustained period of time.

To better understand the link between diet and eye health, Dr. Bailey and his team are conducting a follow-up of the landmark Carotenoids in Age-Related Eye Disease Study (CAREDS), which tested hundreds of women with low and high levels of lutein and zeaxanthin between 2001 and 2004. The study is a component of the NIH’s Women’s Health Initiative Observational Study, which has tracked the health and lifestyle habits of post-menopausal women since the early 1990s. CAREDS has been a coordinated effort involving Casey Eye Institute and Kaiser Permanente in Portland, along with the University of Wisconsin-Madison and the University of Iowa.

In the initial study, researchers gathered information from hundreds of CAREDS participants about their diet, sunlight exposure and lifestyle habits, and took photos of their retinas. They measured the amount of these carotenoids in the blood as well as the macula using a test called heterochromatic flicker photometry.

The data collected and analyzed from CAREDS has yielded valuable insights, says Michael Klein, M.D., who was the principal investigator of CAREDS at Casey. "We’ve learned more about how dietary intake of these nutrients are manifested in the macula and blood stream, and how certain genes may influence the way the body processes them," he says.

With CAREDS2, scientists believe they have a unique opportunity to discover more about the impact of diet on macular degeneration as people age. The project involves bringing back the original CAREDS

*Continued on next page*
The Macular Pigment Study (continued)

participants for additional interviews and testing, including measuring macular pigment levels with a new and improved machine.

“The goal is to find out whether macular pigment levels have any bearing on the development of aging eye disease and its progression,” says Dr. Bailey. The study will also evaluate whether macular pigment changes with time, and how those changes may affect diseases like AMD.

“We hope to get a clearer picture about the connection between what we eat and our eye health, and to learn if measuring macular pigment provides useful clinical information for patients in the future,” says Dr. Bailey.

Macular Pigment Study

Save the Date!
Saturday, October 28, 2017
Doubletree-Lloyd Center

Macular Degeneration and Vision Expo
A free, daylong event featuring informative and inspiring talks and exhibits of community resources and visual aids. Visit our website at www.caseyamd.com this summer for more details.

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