Scatter laser surgery helps diabetic retinopathy but can’t restore vision already lost, something our scientists are working on doing.

A “neurosphere” isolated from eyes with advanced retinopathy of prematurity, a disease that blinds 400 to 600 babies each year.
Vision for the future

Fighting blindness by developing new technologies, therapies and knowledge to retain and restore vision

An affiliate of Harvard Medical School

The Schepens Eye Research Institute
The Schepens Eye Research Institute was founded in 1950 as the Retina Foundation by renowned retinal surgeon Charles L. Schepens, MD.

Across our 55-year history, there are many examples of innovation—from devising new surgical techniques to innovative instruments to examine the eye; from the first therapeutic eye drop for dry eye, to the first fiber-optic magnifier; from discovering that stem cells from the retina can be used to repair damaged retinas, to regenerating a damaged optic nerve.

Equally important are the surgeons and researchers who have trained here and the scientific articles that continue to increase the knowledge that will lead to new treatments and cures.

Since our inception, we also have trained more than 600 postdoctoral fellows in various disciplines of eye research; trained more than 500 eye surgeons, who now practice around the world; and published more than 4,600 scientific papers and books about eye health and disease.
Setting new sights

Picture Monet’s haystacks, their blur of colors, their increasing darkness at day’s end. Imagine if this was the only way you saw the world, blurred and out of focus. Then squint, close your eyes, and experience what’s it’s like to perceive the world in partial, then total, darkness.

Limited vision or total blindness is a reality for 1 out of every 28 Americans over the age of 40.

At the Schepens Eye Research Institute, our goal is to reverse what is now irreversible, and prevent what has been unpreventable. Unfortunately, right now, there are treatments but no cures for most eye diseases. Our research strives to change that—and has already led to new drugs, technologies and knowledge. With faculty appointments at Harvard Medical School and access to its intellectual resources, Schepens Eye Research Institute scientists are the best in their field.

By age 75, 1 out of 4 of us have experienced significant vision loss.

Our motivation? Premature infants whose retinopathy leads to a life of blindness. Soldiers in Iraq or the children in America who suffer eye injuries. Adults who struggle with diabetic retinopathy, macular degeneration and glaucoma—and gradually lose their independence.

As baby boomers age in the coming decade, we are facing an epidemic of blindness.

The needs are pressing. We are moving as quickly as possible to illuminate the causes and mechanisms of eye diseases—and to discover and make available new, innovative treatments and cures.

14 million Americans have visual impairments significant enough to limit their enjoyment of everyday activities.

We are seeking partners in this journey of discovery. We have the highest level of NIH funding of any independent eye research institute, but federal funding for all academic research has leveled off. Current funding allows us to apply over $25 million to our research. The costs of advancing our work, however, will only increase.

We are currently applying $25 million per year toward research.

With your support, we can help people with eye diseases today—and keep others from getting them tomorrow.

Michael S. Gilmore, PhD
President, CEO and Dewalt and Marie Ankeny Director of Research
Looking across

Within the newly renovated laboratories of the Schepens Eye Research Institute, science is proceeding across the entire bench-to-bedside continuum: from projects with an immediate practical application today to work that elucidates the genetics and molecular pathways that may lead to cures tomorrow.

We straddle two worlds. We reside within the academic world of Harvard Medical School and the international eye research community, with many active research collaborations. But we also team up with partners in the corporate world, who can help us deliver the ultimate prize—new diagnostics, treatments and cures.

By a combination of visionary research that brings new knowledge and understanding, and research focused on translating this vision into cures and treatments, we hope to benefit those who suffer from blinding eye diseases and injuries—now and into the future.

Here’s a sampling of recent discoveries and devices made in our eye research laboratories:

• **Damaged retinas can be repaired using stem cells.** This approach has worked in two animal models and is a promising sight-saver for those with macular degeneration and diabetic retinopathy. The retina is the tissue at the back of the eye that senses light and sends images to the brain.

• **Sight nerves lost may now be found.** Damaged optic nerves that carry images to the brain, like other central nervous system nerves, cannot naturally repair themselves. For the first time, by manipulating genes that block regrowth, our scientists have regrown damaged optic nerves in mice. This has huge implications for people with glaucoma, which in late stages damages the optic nerve, as well as for people paralyzed by spinal cord injuries, and those with Parkinson’s and Alzheimer’s diseases.

• **Stopping “growth factor” may stop blindness.** A growth factor called VEGF, identified by one of our scientists as a culprit behind the abnormal blood vessel formation and leakage in diabetic retinopathy and macular degeneration, can be blocked to prevent sight-losing damage. Genentech—the company that pioneered the first successful VEGF-blocking drug for cancer—is testing a variation of this drug in patients with age-related macular degeneration.

• **Low-vision devices extend years of independence and enjoyment.** For most eye diseases, sight is lost gradually. Until we can stop this loss, our scientists are inventing better technologies to take advantage of limited sight so that those with sight loss can read, drive a car, watch television, and be able to enjoy life.
New directions

With new leadership comes an enthusiasm for new possibilities. Change came unexpectedly in 2004 with the death of our president of ten years, J. Wayne Streilein, MD. But Michael S. Gilmore, PhD—an outstanding scientist and administrator—took the helm, and renewed our focus on innovation and discovery. Dr. Gilmore was previously vice president for research at Oklahoma University Health Science Center, where under his purview their $100 million annual research portfolio grew 40 percent.

We’ve also launched a new Corporate Alliances program, directed by Mary M. Chatterton, MBA, JD. This program augments the research funding that the National Institutes of Health provides our researchers. Corporations are keenly interested in the newest research that is percolating in our labs and they have the wherewithal to help bring new products to the marketplace—and to people.

We are carefully choosing partners who respect the traditional freedoms and rights of academic scientists. In return, an affiliation with us permits companies to greatly expand their research and development capabilities, and to collaborate with the world’s leading vision researchers. Johnson & Johnson Vision Care is one of our founding sponsors. They are providing support to fund young scientists and create new faculty positions.

“The Founding Sponsors Program is a successful relationship between Vistakon, a division of Johnson & Johnson Vision Care, Inc. and Schepens Eye Research Institute. The access to distinguished researchers and doctors allows us to investigate a wide variety of areas through in vitro and in vivo studies.”

Craig Walker
Director Materials Research & Development
Johnson & Johnson Vision Care
Scientific collaborations

Fresh insights about some of our most puzzling diseases may come from putting people trained in different disciplines together to tackle the same problem. The Schepens Eye Research Institute is involved in many of these kinds of collaborations, locally with other Harvard-affiliated researchers, and nationally and internationally with researchers throughout the world:

• **Roadmap to Curing Blindness.** The Schepens Eye Research Institute was chosen from among 300 organizations to receive a $2.2 million grant from the National Institutes of Health as part of their NIH Roadmap initiative. Our role in this NIH effort to promote new ways to approach biomedical dilemmas is to design an interdisciplinary center for research in blinding eye diseases. By including scientists from other research disciplines in tackling vision problems, this collaboration may also generate benefits that extend to other diseases.

• **Joint Clinical Research Center.** This collaboration between Schepens Eye Research Institute and Massachusetts Eye and Ear Infirmary provides fellowships and seed money to scientists and clinicians working together on research that will directly improve treatments and outcomes for patients.
The Schepens Eye Research Institute is an affiliate of Harvard Medical School: all of our research faculty have Harvard appointments.

Replacing cells destroyed by disease. Our scientists who are exploring the exciting potential of stem cells in curing eye disease are also collaborating with other Harvard scientists on how best to advance stem cell science.

When my triplets were born prematurely, I had so much to worry about. On top of all their other medical problems, I learned that my daughter might go blind. I hope the research our retina specialist does at the Schepens Eye Research Institute comes in time to help Sinead. But even if it doesn’t, it will help others; these children are so sick.

Annette Hynes, mother of Sinead, who has advanced retinopathy of prematurity, now age 4.
As a Schepens Eye Research Institute researcher for 20 years, and the Director of Scientific Affairs for 5 years, I have come to think of the Institute as a family. The halls are full of familiar faces, and there is a level of cooperation and responsiveness not always possible in larger and more bureaucratic university settings. As a result, we have been able to support an unusually wide spectrum of research spanning all across the eye. This allows for cross-fertilization of discoveries in different areas, encouraged by our collegial atmosphere. It’s no wonder that Schepens Eye Research Institute is a hotbed of innovation.

Darlene A. Dartt, PhD
Director of Scientific Affairs

Preventing, diagnosing, treating and rehabilitating vision problems

Diseases of the eye surface

The cornea is the transparent outer cover of the eye and can be damaged by conditions such as dry eye, ocular allergy, corneal dystrophy, myopia or by infection or injury. The leading cause of patient visits to an eye care professional is for treatment of dry eye symptoms.

Diseases of the back of the eye

The retina and optic nerve are susceptible to diseases such as macular degeneration, diabetic retinopathy and glaucoma that are associated with aging or other systemic diseases like diabetes.
Ocular injuries

Eye injuries can affect the cornea, retina and other ocular tissues. They may result from accidents that occur in the workplace, home, sports or battlefield through blunt trauma or through damage by exposure to chemicals, lasers or heat. Non-healing eye wounds present special problems and may result in infection, ulceration or scarring.

Vision and visual optics

Vision can be affected by numerous diseases including age-related macular degeneration, retinitis pigmentosa, glaucoma, diabetes, brain injury or stroke. Diagnostic devices developed at Schepens Eye Research Institute help practitioners diagnose the cause of vision loss and technologies are developed to assist patients living with low vision.
For over 50 years, the Schepens Eye Research Institute has been a pioneer in discovering the causes of eye disease and developing treatments and cures for vision loss. Its research not only benefits those suffering from eye ailments, but also has far reaching applications in other areas of medicine. I’m particularly proud of the work by Schepens’ researchers on stem cells, which will benefit everyone suffering from neurological disease. I look forward to your future accomplishments, and I know that Schepens’ success will continue to improve the quality of life for millions of Americans with vision problems.

Senator Edward M. Kennedy

Working to retain and restore vision—today, tomorrow, and into the future

The Schepens Eye Research Institute’s $37 million expansion and renovation project was completed in early 2005. Now our 41 scientists, 32 affiliated clinical scientists, 65 post-doctoral fellows, and technical staff work in bright, state-of-the-art laboratories—with plenty of room for future growth. R&D Magazine awarded our new facilities “Lab of the Year” for 2005, commending their “inspirational environment” and “breath-taking transformation of what was once routine, anonymous space.”
Today’s solutions

There is an urgency to find ways to retain and restore vision lost to eye disease and trauma. Right now, there are millions who are facing darkness due to debilitating eye conditions—and the number is expected to increase as more of us age. Research done in our laboratories has directly led to new therapies and devices that are helping patients today.

When tears aren’t enough

Dry eye can feel like you just walked through a sandstorm in the Sahara desert—with your eyes open. Tears bathe and nourish the surface of the eye. If not enough tears are produced, or they evaporate, the eye feels gritty, irritated or painfully inflamed. For the more than 10 million Americans who have dry eye, most of them women, dry eye ranges from merely annoying to so painful and debilitating that it can destroy the quality of one’s life. It’s also a major reason why people stop wearing contact lenses as they get older.

An effective relief for dry eye came out of the laboratories of the Schepens Eye Research Institute. Jeffrey Gilbard, MD, developed an artificial tear in the form of eye drops that are now marketed as TheraTears.

As understanding about tears and dry eye has increased through research, we are closer to a true cure. David A. Sullivan, PhD, an Associate Professor at Harvard Medical School, found evidence that the hormone androgen has a role in preventing inflammation and the evaporation of tears. An androgen eyedrop that he developed in his laboratory at the Schepens Eye Research Institute, backed by funding from the NIH and Allergan, Inc., is now in clinical trials.

Tears are not simply water. The tear film consists of three layers, one of which is the mucin layer. Mucin serves as a barrier, like soldiers standing side by side, tethered to the surface of the eye. If the eye is injured, say by a mascara wand, or altered by dry eye, the barrier is broken and the eye is left susceptible to inflammation. Our Ocular Surface Scholar, Ilene K. Gipson, PhD, has pharmaceutical funding to assess drugs that might help dry eye by enhancing mucin action. Dr. Gipson is also a Professor of Ophthalmology at Harvard Medical School.

“Particularly in a ground war such as we’re engaged in Iraq, where ambushes and explosives pose an ongoing threat, being able to deliver fast, efficient, efficacious care to soldiers who’ve suffered eye wounds and trauma can make the difference between saving a young person’s sight, or not. Advances pioneered at the Schepens Eye Research Institute will significantly advance the care we’re able to provide in the field and improve subsequent hospital care and outcomes. This ground-breaking work will, no doubt, soon benefit all those who suffer eye wounds and trauma.”

Col. Thomas P. Ward, USA, MC
Consultant to The Surgeon General in Ophthalmology
Vision lost may now be found

Detailed vision needed for reading and driving is the job of the millions of cells in the macula, a tiny area in the middle of the retina. Usually related to the aging process, there is sometimes a slow breakdown of the cells in the macula. In about 10 percent of cases, this “dry” form of age-related macular degeneration (AMD) worsens and becomes “wet,” that is, new but fragile blood vessels grow and leak blood under the macula, rapidly damaging it. AMD is the leading cause of blindness, and it is feared that as more of our population ages, it will become epidemic. Current treatments can sometimes stop the destruction of sight in the wet form, but can’t restore lost vision. Preliminary results of a drug that blocks the growth factor called VEGF, however, are extremely exciting. After one year, almost half of the patients randomized to receive Genetech’s anti-VEGF drug called Lucentis had enough visual improvement to drive or read.

This potential sight-saving treatment is a direct outgrowth of research by Patricia D’Amore, PhD and others who identified VEGF as the cause of abnormal blood vessel growth, first in a model of diabetic retinopathy. Dr. D’Amore, who is the Ankeny Scholar of Retinal Molecular Biology at the Schepens Eye Research Institute and Professor at Harvard Medical School, and her group have recently uncovered evidence that VEGF is also likely to be important in the development of AMD.

Age-related macular degeneration, the leading cause of blindness, blurs the central area of vision necessary for reading and driving.
Seeing with assistance

There are a whole array of devices available now or in development that will help those with diminishing vision to enjoy life with what vision they have left. Many of such devices have been developed or evaluated by Eli Peli, MSc, OD, the Schepens Eye Research Institute Moakley Scholar in Aging Eye Research and world-renowned low-vision expert.

One product that recently went on the market, for example, is a lens he designed for people with hemianopia, left-side blindness, a condition caused by stroke, head injury or brain tumors. Chadwick Optical, Inc.—a small Vermont company that specializes in customizing ophthalmic lenses for the visually impaired—is producing them. The resulting product, the EP lens, stands for Expansion Prism but was also named in honor of Eli Peli.

Eye support for the troops

The Schepens Eye Research Institute is actively engaged in a partnership with the United States Army Medical Research & Materiel Command (a medical research division of the Department of Defense) to solve critical vision problems encountered by our troops. They have pressing needs today—and the solutions we find will also benefit civilians with eye injury and disease.

In modern-day warfare, eye injuries have increased dramatically. Soldiers’ body armor saves lives but it doesn’t protect their faces from injury. Lasers used as detection devices can burn holes in the retina, if aimed at the eye accidentally, or used as a weapon—a future anticipated use in combat. And dry eye is a frequent side effect of corrective refractive surgery, which the Department of Defense encourages troops to undergo to eliminate the need for glasses or contacts, as they can be broken or lost in the field.

One of our many research initiatives with the military is to develop a “living bandage” for the eye. It can take days to weeks to get someone with an injured eye to a hospital for comprehensive treatment. If living tissue were applied right on the battlefield as a temporary bandage, there would be fewer complications or infections. Three of our scientists who have been working on creating an artificial cornea for corneal transplantation—James Zieske, PhD, Nancy Joyce, PhD and Jeffrey Ruberti, PhD—are adapting their work to this important application.
The joy of seeing

Eli Peli helps people make the most of limited vision

“Every week I have someone in my office who is crying with joy,” says Eli Peli, MSc, OD. One-half day a week, he helps match patients who have limited vision with innovative low-vision devices that enable them to read, drive, work, watch television and enjoy life in a way they no longer thought possible. In these few hours of his busy week, Dr. Peli can vividly see the fruits of 20 years of his labor.

The focus of his research at the Schepens Eye Research Institute is on the way the eye and brain process images as visual function is lost. He starts with a particular problem caused by an eye disease, delves into the visual perception and limitations imposed by it, and strategizes ways and devices to enhance the visual function that remains. Dr. Peli, who is a Professor of Ophthalmology at Harvard Medical School, is virtually the only one in the world doing this kind of practical, low-vision research.

The problems and solutions differ according to the disease. For example, with age-related macular degeneration, people lose their central vision. They have only their side, or peripheral vision left. In other eye diseases, like the inherited retinitis pigmentosa, there is first night blindness followed by loss of peripheral vision, then, in advanced stages of this devastating eye disease, the entire retina is destroyed, leaving only a pinpoint of vision in the center. As diabetic retinopathy advances, there is blurring and an increasing darkening of the visual field.

For these and other eye diseases, Dr. Peli has developed specially adapted lenses—fiber optic reading magnifiers, telescopic lenses built into glasses for driving, prism glasses for people who lose vision due to strokes, and electronic devices for night vision. He tries to make each as cosmetically appealing as possible, so people won’t feel so self-conscious about using them.

“With the devices available today, I can get most everybody reading, so I concentrate on enhancements that will increase people’s mobility through driving or walking, or enjoyment through watching television,” he says.

One project in the works, for example, is a system his team is developing that would magnify images on the new digital televisions. He envisions a system that, similar to captioning for the deaf, embeds information in each frame of the video signal about what part of each frame is the essential point-of-interest. A person at home could then use a remote control to adjust the magnification and maintain the point of interest in view.

From his scientific investigations emerge inventions that help thousands hold on to some of the joys of sighted life.
Tomorrow’s treatments

The path to discovering new cures and therapies is rarely straightforward. Often, it’s like a treasure hunt: a scientist finds clues, these pose other questions, and the path turns. Something is learned each time. And that something just might mean a better therapy—or cure.

Outsmarting “thinking” bacteria

Tens of thousands of deaths occur each year in the United States due to bacteria that are resistant to the antibiotics in our arsenal. Even some strains that once responded are now resistant to current treatments. Michael Gilmore, PhD, the President, CEO and Ankeny Director of Research of Schepens Eye Research Institute, recently reported on how one particularly ferocious strain of enterococcus bacteria wreaks destruction—a crucial step in learning how to prevent and treat these infections.

This type of enterococcus causes its damage by producing a toxin that will destroy the eye or, if in the bloodstream, kill the patient. Dr. Gilmore’s team discovered how this bacterium “decides” when to make the toxin and attack. It sends out a tag team of two molecules. One molecule probes for human cells, such as blood cells, and sticks to one if it finds it. If that happens, the second molecule reports back to the enterococcus to make the toxin. But if no cell is found, the first molecule sticks instead to its partner, preventing it from reporting back—and no toxin is made. This is an important clue to developing drugs to block the release of toxin.

Infections can occur in the eye after an eye laceration, or anywhere in the body after surgery or a stay in a hospital intensive care unit. Finding a solution in the eye is applicable to anywhere in the body these infections attack.

Building better vaccines

Certain areas of the body enjoy a special immune-privilege—the eye is one such area, as is the brain, ovary and testis. The eye doesn’t mount the normal immune response to foreign invaders because it could be irreparably damaged by inflammation in the process. The knowledge about how the eye molecularly stops the immune response could be applicable to preventing rejection after organ transplantations or quelling diseases where the body’s immune system goes awry and attacks itself (autoimmune diseases).
Andrew W. Taylor, PhD, an Assistant Professor at Harvard Medical School, found another application. His research group at the Schepens Eye Research Institute identified several proteins associated with the nervous system that control immune privilege in the eye. They combined one of these neuropeptides with an antigen that a particular vaccine is designed to target. They found that adding this neuropeptide to the vaccine stopped the inflammatory response without affecting the vaccine’s effectiveness. This could have the important result of reducing the incidence of vaccine side effects, a reason some people avoid disease-preventing vaccines.

Diabetes can damage the tiny blood vessels inside the retina, the light-sensitive tissue at the back of the eye. Over time, diabetic retinopathy can get worse and cause vision loss such as shown here.

Inflammation disrupts the smooth layers of the retina (left), leading to loss of vision and blindness. Eyes treated with alpha-MSH gene therapy are protected and vision is maintained (right).
Cells dying as part of the destructive process triggered by high glucose levels in diabetes—a process our scientists have found a way to stop.

**Advances in preventing rejection**

Corneal transplants are by far the most common form of transplantation, with nearly 40,000 cases performed annually in the United States alone. The cornea is the transparent outermost layer of the eye, the point of entry for light. When damaged by injury, infection or disease, the cornea needs to be replaced to restore vision.

Rejection of a foreign cornea is less of a problem because the eye is an immune-privileged site, but it still happens. This is particularly true if there is already inflammation due to the original injury or disease. Patients who get corneal transplants need to take steroid drops to prevent rejection, but the drops themselves can cause infections, glaucoma or cataracts.

Reza Dana, MD, MSc, MPH, an Associate Professor at Harvard Medical School, and his group at the Schepens Eye Research Institute have found a new strategy to prevent corneal graft rejection. They identified the role of a growth factor called VEGFR-3 in activating the immune response. The group demonstrated in a mouse model that the rejection process could be stopped by blocking VEGFR-3.

Our scientists have found a growth factor that, if blocked, may improve the success rates of corneal transplants.
Watchful waiting

Mara Lorenzi works to stave off diabetic retinopathy

People with diabetes live with years of anxious, watchful waiting. Over time, unless kept in very tight control, their high blood glucose (sugar) levels damage blood vessels and nerves throughout their bodies. Potentially blinding diabetic retinopathy is one of the most feared complications that can happen. Finding a way to prevent it would be a major breakthrough.

The research of Mara Lorenzi, MD at the Schepens Eye Research Institute is dedicated to reaching this goal. “As a physician I want to be able to do something to keep people healthy,” says Dr. Lorenzi, who is a Professor at Harvard Medical School. “Good glucose control is a tremendous weapon, but if I could offer patients another barrier against the terrifying possibility of losing sight, a great burden would be lifted.”

Diabetes is epidemic in this country, affecting 18 million people. Another 41 million have pre-diabetes and are at risk for the disease, which is increasingly striking children and adolescents as well as older adults.

“I see a big role for additional drugs,” says Dr. Lorenzi, who is investigating several that might prevent or halt the molecular sequence of events that leads to diabetic retinopathy.

One destructive process that is activated when glucose is high, for example, is the “polyol pathway.” Aldose reductase inhibitors can block this pathway, but when one of them was tested in clinical trials in the 1980s, results were disappointing. It caused skin toxicity and its effect didn’t even reach the retina. Suspecting that the dose was inadequate, Dr. Lorenzi’s group upped the dosage 20 times and demonstrated its preventive powers against all the abnormal processes at work in the retina in diabetic rats. She is looking at other drugs in the same family that might work as well, but without the side effects.

Currently, diabetic retinopathy is not diagnosable until an eye exam reveals abnormal vessels. “By this point, there is quite of bit of damage that’s irreversible,” she points out. “To test the use of drugs for prevention, we need a marker that’s much earlier in the disease process.” The thickness of the retina is a possible marker that her research team is investigating.

Dr. Lorenzi is convinced she made the right choice when she came to the Schepens Eye Research Institute 18 years ago. Most of her time is devoted to eye research, reserving one day a week to seeing patients at Massachusetts General Hospital’s Diabetes Clinic. “To make this a bearable disease, I must devote time to finding answers.”
Future promise

Sometimes an idea seems more like science fiction than real science at first. People say it can’t be done. But the right people at the right time take a hunch and doggedly pursue it.

Regenerative medicine—such as using stem cells to repair damage from a disease—is a prime example of breakthrough thinking. Scientists at the Schepens Eye Research Institute are at the forefront of proving its future promise. That promise is a cure for blinding diseases.

Getting the nerve to see

Nerves of the central nervous system once destroyed cannot repair themselves. The research of Dong Feng Chen, MD, PhD flies in the face of that truism. Her Schepens Eye Research laboratory team has found a way, using a mouse model, to regenerate a damaged optic nerve, the first time anyone has been able to do that.

The optic nerve transmits the impulses for sight from the retina to the brain. If it is damaged, as happens in advanced cases of glaucoma, sight is irretrievably lost. Or is it?

Central nervous system nerves like the optic nerve have the ability to regenerate before birth while a baby is developing. At some point this ability shuts off. Dr. Chen, who is also an Assistant Professor of Ophthalmology at Harvard Medical School, and her colleagues have found a way to wake up this dormant ability, at least temporarily, using a mouse model.

They discovered two major “brakes” to the regeneration process and devised ways to circumvent them. Their manipulations restored at least half, and probably more, of the damaged optic nerve. But after two weeks, regeneration stopped again.

Three views of an optic nerve regenerating, the first time anyone has been able to accomplish this.
They now suspect there’s a third brake that kicks in at two weeks in mice (the timing may be different in humans). They have a clue: myelin—the sheath that encloses nerve fibers—matures at two weeks. They are collaborating with researchers at Children’s Hospital and elsewhere to see if myelin is the third brake.

It could be more than a decade before this work translates into helping people. Just to find that third brake could take five years, if it isn’t myelin. But searching the medical literature, they have identified drugs that regulate the two pathways to regeneration that they already know about. There may be a medical solution. And if this approach works, the pay-offs here could be big: for those with glaucoma, spinal cord injury, Parkinson’s and Alzheimer’s diseases.

Side vision is the first to fail as a result of glaucoma, which can lead to optic nerve damage and complete loss of vision.

**Not too late for infants born early**

Progress has come with a cost to infants born significantly premature. Infants weighing less than 2 3/4 pounds—so tiny they can be cupped in two hands—can survive, only to face a host of potential problems. One problem is retinopathy of prematurity, which in advanced forms can leave a baby blind for life. This happens to 400 to 600 babies each year.

Kameran Lashkari, MD, in his laboratory at the Schepens Eye Research Institute, is pursuing two scientific routes to help these babies and their desperate parents. One is to see if stem cells might be useful. The other is to investigate a mutation in a protein that appears to be more prevalent in babies with severe retinopathy of prematurity. Either approach could be a key to restoring sight.
In babies born early, the blood vessel network of the retina is not finished forming, and when the babies are put on oxygen to survive, normal vessel growth stops. Once weaned off oxygen, the signal is sent to restart, but the blood vessels formed are abnormal and fragile. For most babies, the disease either regresses at this point or laser or cryo (freezing) surgery will take care of the problem. But in a small percentage of cases, the disease rapidly progresses. There is bleeding, scarring, and the retina is pulled off the back of the eye and detached.

Dr. Lashkari, a vitreoretinal specialist at Massachusetts Eye and Ear Infirmary and an Instructor at Harvard Medical School, has identified stem cells in the scar tissue, and used them to isolate and propagate retinal progenitor cells. To test if these progenitor cells are useful for retina transplantation, they are transplanting them into chick eyes and, in collaboration with Dr. Chen’s laboratory, into mice—with promising results. Now he has to prove the stem cells can integrate into the circuitry of the retina and survive. They have a long way to go to clinical application, but the potential is exciting.

Green fluorescent protein tracks transplanted retinal stem cells as they repair photoreceptor cells, resulting in mice that can see better.

As the baby boom population ages, eye diseases and impairments of all sorts will be increasingly common. While not fatal, loss or reduction of vision takes a huge toll: on one’s independence, finances, self-respect. Of the five senses we possess, I believe that sight is the most precious. Research advances made in the Schepens Eye Research Institute’s labs have always made a big difference, but going forward, their potential to improve the quality of life for huge numbers of people will be dramatic. As someone who has benefited directly from the Institute’s innovations, and who understands how investment by individuals is critical to advance the pace of progress, I can think of few organizations more worthy of enthusiastic support.

Charles de Gunzburg
Trustee
Stem cells to rescue the retina

Michael Young is using stem cells to repair retinas

People kept telling Michael Young, PhD that retinal transplantation wouldn’t work. And at first nothing he tried did work. Then, recognizing the potential of stem cells when they were discovered in 1998, he was the first to transplant specialized stem cells called progenitor cells into a mature retina.

Ever since, he has worked toward the goal of getting these cells to repair retinas damaged by such diseases as macular degeneration and retinitis pigmentosa. Unlike other approaches that cannot bring back cells and sight already lost, stem cells can replace lost cells, and are capable of reclaiming connections to the brain so sight can be restored.

His work has moved way beyond “the potential is there” to “I am very hopeful.”

It was a big decision for him to come to the Schepens Eye Research Institute seven years ago. He was finishing his post-doctoral work at MIT, studying the retina as a model for how the brain develops its plasticity—constantly changing its nerve pathways based on experience, learning, and new stimulations. Transplantation intrigued him as a way to study plasticity.

But the goal of the Minda de Gunzburg Research Center for Retinal Transplantation here at the Schepens Eye Research Institute is nothing short of restoring sight to the blinded eye. “I had to ask myself before coming here if this was doable,” recalls Dr. Young, who is now director of this research center as well as an Assistant Professor at Harvard Medical School. “Were the problems solvable? I finally decided that even if the problems weren’t solvable, we would learn things from the effort.”

Dr. Young surmounted the hurdles of transplantation in ways he couldn’t have dreamed of when he first came here. Using mice bred so that all their tissue is fluorescent green and then similarly bred pigs, he has been able to track transplanted stem cells. In both animal models, the stem cells find the retinal injury and repair it. They have shown that mice after such a transplant actually can see better.

Dr. Young’s group is now perfecting a more exact way to deliver the stem cells to where they are needed. They devised a hair-thin polymer scaffold on which stem cells grow in an orderly layer of retinal tissue, which can then be implanted. They’ve been getting great results with this approach.

There are issues to work out in their animal models, which will probably take a minimum of three years. But then the next step is a clinical trial using their stem cell techniques on the eyes of people with devastating retinal diseases. By employing stem cells, Dr. Young is now more certain that the problems of retinal transplantation are solvable.
Future promise

Treatments

- Methods to prevent mucin shedding to treat dry eye and affect fertility
- Telescopic eyeglasses for low vision patients
- Molecular probes to interfere with genes promoting unwanted immune reactions
- Anti-infectious corneal bandage for use in trauma
- Barriers to prevent viral or bacterial infection of mucosal surfaces
- Gene therapy to stimulate tear secretion
- Gene therapy to reduce inflammation
- Artificial cornea for human transplantation
- Gene therapy to increase corneal endothelial cell density
- Drugs to promote wound repair in the eye, brain and skin
- New approaches to prevent progression of atherosclerosis in diabetes
- Immunotherapy for eye and brain tumors to protect against recurrence
- New uses for existing drugs to treat glaucoma, multiple sclerosis, spinal cord injury

Tools

- Retinal tissue engineering using stem cells and polymer substrates to construct CNS tissue equivalents for transplant
- Compounds to pretreat the brain or retina to enhance success of retinal or stem cell transplantation
- Method of removing mucins on mucosal surfaces to allow gene transfer and enhance fertility
- Determination of cornea’s role in expressing proteins that regulate inflammation and antigen-specific immunity
- Ways to prevent corneal cell death to promote the success of corneal transplantation
- Screening methods to identify drugs for treatment of nerve injuries
- Mechanism of regulating blood vs. lymphatic vessel growth developed to control their contribution to inflammation and immunity

Diagnostics

- Identification of biomarkers to diagnose evaporative dry eye syndromes and to predict contact lens intolerance

Targets + Models

- Identification of a novel form of heat shock protein that when prevented from cleaving, protects the retina from endophthalmitis
- Mechanisms for “metabolic memory” — hidden marks that diabetes leaves on tissues — to determine the progression of diabetic complications, and reveal processes to target with new drugs
- Manipulation of inflammatory cytokines in diabetic retinopathy to discover new therapeutics for prevention
- Chromatin-associated abnormalities targeted in diabetic vascular disease

The Schepens Eye Research Institute
**Tomorrow’s treatments**

- Drugs to induce nerve growth to treat retinal and central nervous system damage and neurodegenerative diseases
- Drugs to prevent antibiotic-resistant infections
- Vaccine to prevent spread of cancer in patients with metastatic melanoma
- Pharmaceuticals to stimulate meibomian gland function and treat evaporative dry eye due to menopause, aging, contact lens intolerance and autoimmune disease
- Device for enhancing TV image for low vision viewers
- Drugs to prohibit colonization of bacteria that promote corneal and other infections
- Synthetic hormones to suppress inflammation and autoimmune diseases
- Day or night image enhancement devices for military application

**Today’s solutions**

- Mediators of inflammation for use in transplant, allergy, arthritis, asthma and autoimmune diseases
- Unique eyeglasses to expand vision in patients with optic nerve disorders, stroke or brain tumor
- New uses for inexpensive drugs like aspirin to prevent diabetic retinopathy
- Vitamins to minimize eye inflammation and treat dry eye

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Picking up the pace

Just the other day I saw a television segment about a little girl with an incurable cancer of the eye, which had spread to her brain. Her wish had been granted and she was on her way to visit Mickey Mouse at Disneyland. It was a powerful reminder of the urgency of the work at the Schepens Eye Research Institute.

The retinoblastoma from which this girl suffered can be treated if discovered early enough. And this critical early diagnosis is only possible because of an instrument developed here by the Institute’s founder, Dr. Charles Schepens. Prior to that invention, virtually all children diagnosed with this disease died from it.

Unfortunately it isn’t always caught early. In the story I saw, her mother expresses the hope that more research might help others, even if it’s too late for her daughter. Dr. Bruce Ksander, a scientist at the Schepens Eye Research Institute, is hard at work on just such a treatment.

As the new Chairman of the Board of the Schepens Eye Research Institute, I am in constant contact with the exceptional scientists who work at the Schepens. These wonderful people are doing excellent work and are always developing new ideas to retain or restore vision.

The work here is a long-term investment, but every year we see pay-offs. Magnifying lenses that allow people with diminishing vision to drive their cars, drugs that prevent eye infections, strategies to regenerate cells to cure blinding diseases that are plaguing our aging population. The results coming from our labs make a real difference in people’s lives.

Excellent scientists, visionary leaders, laboratories that facilitate collaboration and discovery, and a proven track record—the ingredients for success are all in place. If we can increase our financial support, we can accelerate the pace of discovery.

We probably all know people with glaucoma, macular degeneration or diabetic eye disease—frightened about losing their sight. There is an urgency to come up with better solutions. In addition to the funding we receive from the government, our partnerships with individuals, corporations, and foundations are essential. Together, we all play a critical role. Together, we can re-write the ending to many stories—including that of the little girl.

Kennett F. Burnes
Chairman of the Board, Schepens Eye Research Institute
President and Chief Executive Officer, Cabot Corporation