A Customized Vision for the Future: Personalized Medicine in Ophthalmology

Every year, more than 40,000 corneal transplants are performed in the United States. They help to restore vision to thousands of people who have sustained damage to their corneas as a result of disease or trauma. But corneal transplantation has its limitations. There is only so much donor tissue available, and it often comes from older individuals who may have had deteriorating eye function of their own. And although rejection of foreign tissue is not as common a problem as with solid organ transplants, some transplanted corneas do get rejected by the patient’s body.

But what if you could generate your own new cornea or retina with just a few cells taken from your own skin? That’s the ultimate goal of ongoing research being conducted at Columbia’s Department of Ophthalmology, and it’s just one way in which personalized medicine is transforming vision care.

When the human genome was finally sequenced in 2003, the project had taken 15 years and cost approximately $3 billion. Today, any individual can have his genome sequenced within two months at a cost of $1,000. Within five years, experts predict, whole-genome sequencing for an individual will cost just $1,000.

The rapid explosion of new knowledge about genetics (and associated fields like proteomics) has ushered in a new age of personalized medicine. Instead of treating everyone with a certain disease with the exact same therapy, physicians can analyze individual genetic and molecular variations to help determine how a patient will respond to a particular medication. Individuals with a family history of breast cancer or Huntington’s disease can have their own genetic code deciphered to determine if they carry disease-causing mutations.

“It’s a big new catchphrase that everyone is using in science, but in ophthalmology, I think there will be two major categories where personalized medicine will be applied,” says Lucian Del Priore, M.D., Ph.D., Professor of Clinical Ophthalmology and Robert L. Burch III Scholar. “The first is to determine the individual’s genetic profile and to...

A Visionary Partnership: Low Vision Rehabilitation Clinic Gives Columbia Patients a New Focus

When individuals with cataracts, glaucoma, retinal disease, or another major eye problem come to the Department of Ophthalmology, they often will leave with vision that is nearly normal. State-of-the-art diagnostic techniques, surgical advances, and medical therapies enable our ophthalmologists to restore eyesight to people who thought they might never see again.

It doesn’t always work that way, however. For some people, their vision has been so damaged, or the disease process is so intractable, that they will always struggle to see. For these people, there is nothing an ophthalmologist can do to give them back the sight they have lost, or are continuing to lose.

But that doesn’t mean that there is nothing anyone can do for them. At the Low Vision Rehabilitation Clinic of The Jewish Guild for the Blind, people with limited vision receive comprehensive evaluations of their vision and an in-depth, personal assessment for the kind of tools that they will need to help them navigate life with vision loss. Columbia’s Department of Ophthalmology routinely refers patients to The Guild’s twelve-story West 65th Street, a true one-stop shop for people with blindness or extremely limited vision.

“For these people, normal eyeglasses aren’t going to meet their needs,” says Laura Sperazza, O.D., The Guild’s Director of Low Vision Rehabilitation Services. “They’ve exhausted medical and surgical correction. They’re not coming to us because they have a diagnosis of glaucoma or age-related macular degeneration (AMD)—they’re coming to us because they can’t see. Their goal isn’t visual correction anymore; it’s functional. They want to shop for their groceries, pay their bills, and read their newspapers.”

On a recent blustery winter morning, a woman in her 60s named Lydia Garcia arrives for a follow-up visit at The Guild. She has myopic degeneration, with 20/100 vision in her right eye and 20/800 vision in the left. “My right eye was the better one, but now there have been changes and I can hardly see,” she reports. Mrs. Garcia’s ophthalmologist has identified macular elevation and will send her for further testing to determine if there is a retinal detachment.

But in the meantime, Mrs. Garcia wants to be able to read the newspaper. The Low Vision Rehabilitation

continued on page 2
Dear Friends,

Glaucoma. Keratoconus. Leber’s congenital amaurosis. Age-related macular degeneration. Fuchs’ corneal dystrophy. What do all these eye diseases have in common? They all have an identified genetic component. Over the past two decades, nearly 500 genes that contribute to inherited eye diseases have been identified. As our understanding of the genetic basis of eye diseases continues to grow, so will our capacity to treat these diseases. In this issue of Viewpoint, we examine some of the exciting research initiatives now taking place at Columbia that will develop the field of personalized medicine to bring customized therapies to future generations of people with eye disease.

Deciphering the mysteries of the connections between the brain and the eye, and what happens when those connections go awry, is the job of the neuro-ophthalmologist. Each patient presents a new and often complex diagnostic challenge. The profile of the department’s Neuro-ophthalmology service highlights the dedication of these specialists, and the unique nature of their partnership with researchers at Columbia’s main campus.

This year, we are excited to welcome to our department a highly experienced vitreoretinal surgeon Jason Horowitz, M.D., who brings to our team a high degree of skill in all adult surgical procedures. You can learn more about Dr. Horowitz’s passion for his work on page 4.

Sometimes, even the finest diagnostic techniques, the latest treatment options and the finest surgeons cannot restore a person’s sight. But that’s not the end of the story. Columbia’s partnership with The Jewish Guild for the Blind and its extraordinary Low Vision Clinic, which is featured on page 1, through vision rehabilitation gives patients with uncorrectable vision problems a host of technological tools and options for living a full and active life.

In this issue, we also feature several other remarkable organizations, whose generous support helps to make possible all of the work that we do here in the Department of Ophthalmology. These organizations, along with the long list of individual supporters and friends of the department, leave me feeling both proud and humbled as I reflect on your dedication to our shared mission of understanding and treating eye disease. As always, I am privileged to work with you, and thank you for your commitment to our work.

With all best wishes,

Stanley Chang, M.D.
K.K. Tse and Ku Tei Ying Professor
Edward S. Harkness Professor
Chairman, Department of Ophthalmology

Low Vision Rehabilitation Clinic

Clinic had previously prescribed a set of magnifiers for reading that boosted her vision by a factor of 3, but now they are no longer strong enough.

Dr. Sperazza runs through a series of tests with Mrs. Garcia. At the Low Vision Rehabilitation Clinic, standard eye charts, such as the Snellen, have been left far behind. Instead, the clinic’s specialists use an illuminated Ferris-Bailey ETDRS visual acuity chart, mounted on wheels so that it can be brought as close to the patient as possible—even just one meter away (about three feet). If the patient can’t see the top line (which means her vision is worse than 20/800), the doctor brings out “Designs for Vision” number cards, which are held very close to the patient’s face and moved to different positions to assess not just the range, but also the field of vision. “These charts can measure visual acuity down to 20/1500 or even worse,” says Dr. Sperazza.

Working with Mrs. Garcia, Dr. Sperazza quickly finds that she can barely read the illuminated chart at two meters (just over six feet) away with her right eye, and sees nothing with her left. The card isn’t much better. The doctor replaces her right eye, and sees nothing with her left. The clinic also offers clip-on magnifiers; a wide range of hand and stand magnifiers with differing powers and some with illumination; magnifiers for people who want to pursue hobbies like reading the mail, a photograph and sometimes reading material. In addition, the clinic also offers clip-on magnifiers; a wide range of hand and stand magnifiers with differing powers and some with illumination; magnifiers for people who want to pursue hobbies like reading the mail, a photograph and sometimes reading material. In addition, the clinic also offers clip-on magnifiers; a wide range of hand and stand magnifiers with differing powers and some with illumination; magnifiers for people who want to pursue hobbies like reading the mail, a photograph and sometimes reading material.

The magnifiers prescribed for Mrs. Garcia are just one of the many vision tools the Low Vision Rehabilitation Clinic offers. The clinic also stocks specialized glasses which magnify up to 12X. These sit on the nose like regular glasses and require objects to be held very close to the eyes, allowing people to see money, the mail, a photograph and sometimes reading material. In addition, the clinic also offers clip-on magnifiers; a wide range of hand and stand magnifiers with differing powers and some with illumination; magnifiers for people who want to pursue hobbies like reading the mail, a photograph and sometimes reading material.

Second-year Columbia ophthalmology residents train at The Guild every year, participating in clinical sessions. Dr. Sperazza comments, “With this partnership, we hope to create new generations of ophthalmologists who realize that just because there are no more medical or surgical options, that doesn’t mean there’s nothing to be done for their patient. The Columbia residents are eager to learn and they want to do as much as possible for their patients, so it’s a great fit,” concludes Dr. Sperazza. “Our goal in having the residents participate in the program is not to make all ophthalmologists vision rehabilitation specialists,” says Guild Director of Vision Program Development Roy G. Cole, O.D.

“Rather, to have them understand what can be done for their patients.”

The collaboration between Columbia and The Guild has existed on a formal basis for six years, but informally, for a much longer period, according to
Clinical Spotlight: Neuro-Ophthalmologists: Detectives of the Eye

A New York woman in her eighties had a cataract removed from her left eye. Instead of finding relief from her vision problems, she felt that something still seemed wrong with the newly corrected eye, although upon testing it appeared to have perfect 20/20 vision. She preferred to continue using her right eye, which still had a cataract and tested at 20/200.

The woman visited several ophthalmologists in New York and Los Angeles, as well as others in London, Paris, Hong Kong and Japan. None of them could figure out what was wrong. At last, she was referred to the Neuro-ophthalmology service within Columbia’s Department of Ophthalmology.

“We asked her what it was that bothered her about the vision in that left eye,” recalls Jeffrey G. Odel, M.D., Associate Clinical Professor of Ophthalmology. “She said ‘I don’t like the light. I don’t mind the dimness in the unoperated eye, but I keep seeing all these twinkling lights.’”

That was the clue Dr. Odel needed. He reviewed the patient’s chart and saw that she was taking the cardiac drug digoxin, a form of digitalis. “This drug can cause a person to perceive photopsias—little twinkling lights in the periphery of her vision—and may make everything appear to have yellowish or greenish hues,” he says. “The brighter the light a person is exposed to, the more symptomatic she is. Once the cataract was removed from the patient’s left eye, the brightness of her restored vision activated the digoxin side effect. But on the right eye, the dark yellow cataract was acting as a sunglasses and blocking the digoxin-induced photopsias.”

Dr. Odel consulted with the patient’s internist, who switched her to another heart medication. Within the week, the vision in her left eye returned to normal.

Neuro-ophthalmologists might be called the detectives of the eye. “We deal in complex disorders of vision for which even the language may not have yet developed to help patients describe their experiences,” Dr. Odel explains. “How do you know that you see the same color that I do? Or that you perceive motion or the form of an object in the same way? If that sense gets disturbed, how do you express that? We are primarily seeing patients who have perceived ‘something different,’ but sometimes they don’t even realize that it’s about their vision.”

Recently, for example, Dr. Odel saw a patient who had fainted and fallen. “She kept on expressing her problem as a tightness around the eye,” he says. “It turns out that she had damaged her optic nerve in the fall and her side vision was constricted, but she didn’t have the language to describe it.”

A patient’s first visit to Columbia’s Neuro-ophthalmology service (most are referred by other specialists) usually takes an intense two to three hours, during which Dr. Odel and his colleagues concentrate on the person’s history and physical exam.

Sometimes, as with the digoxin patient, the history yields all the clues the doctors need. But in many other cases, a detailed history must be combined with extensive physical examination and special testing. “We at Columbia have the most sophisticated capabilities for distinguishing whether a complex condition involves the retina, the optic nerve or the brain,” Dr. Odel says. “There are many diseases that affect the optic nerve, but not the retina, and vice versa, and a few that affect both.”

Columbia’s Neuro-ophthalmologists have a longstanding partnership with Donald Hood, Ph.D., James F. Bender Professor of Psychology and Professor of Ophthamlic Science (in Ophthalmology), whose laboratory on the main campus focuses on the biological bases of vision and the assessment of normal and diseseed visual systems. “They send at least three a week to our lab—the most challenging ones that they need help in differentiating,” says Vivienne Greenstein, Ph.D., Professor of Clinical Ophthalmology, who works with Dr. Hood.

Their tools include:
- Behavioral visual fields. Dr. Hood’s visual field testing involves techniques that can assess how sensitive someone is to light and determine precisely the spatial pattern of that person’s visual problem.
- Electroretinograms (ERG). Much like an electrocardiogram, the ERG uses a sensor placed on the surface of the eye to record electrical potentials within that eye.
- We’re experts on a form of ERG called the multifocal ERG that allows us to get spatially tuned local electrical activity from the retina, says Dr. Odel.

“Often if a patient complains about an area of blindness in his upper left field of vision, this technique will tell us if the blindness is due to a problem in the retina or not.” If the multifocal ERG is normal, the defect lies outside the retina.

- Multifocal visually evoked potentials (VEP). These tests involve electrodes placed on the back of the skull over the primary visual area in the brain, again, much like an electrocardiogram. “If the problem shows up in the VEP but not in the ERG, the visual defect is located somewhere between the retina and the brain,” says Dr. Hood. “If it appears on both, it’s the retina.” This tool is particularly effective not only for ruling out an organic cause of vision loss, but also for diagnosing and following patients who have optic neuritis, as with multiple sclerosis, says Dr. Greenstein. “It’s a very helpful tool if the patient has a questionable or unreliable visual field, because it gives us an objective measure.”
- Optical coherence tomography (OCT). This noninvasive test provides structural information on the retina and optic nerve in a matter of minutes, developing an anatomical picture of the layers of the retina, including the optic nerve.

“If the optic nerve scan is normal and the multifocal VEP is abnormal, then we have to start considering a problem in the brain itself,” says Dr. Hood. “One possibility is that the VEP has big delays in it, in which case the problem is likely to be multiple sclerosis. There are other cases where the potentials are virtually imperceptible, and then we would send the patient for an MRI scan, which might indicate something like a stroke.”
Foundation Fighting Blindness Honors Stanley Chang, M.D.

Stanley Chang, M.D. was honored by the Foundation Fighting Blindness (FFB) at its 2011 Banking on a Cure Dinner, held Wednesday, January 19th at the Plaza Hotel’s Grand Ballroom. The Foundation presented Dr. Chang with its Outstanding Research Award in recognition of his revolutionary work in the development of new surgical approaches to treat complicated forms of retinal detachment, including the use of perfluoropropane gas and perfluorocarbon liquids and related surgical techniques. Dr. Chang was introduced at the dinner by Department of Ophthalmology Vice Chair John Flynn, M.D., who declared himself “humbled by the sheer size of the task itself, for Stanley Chang is no ordinary man. I have known few men who match him, and none who surpass him. Without exception, he said, patients love Dr. Chang... "whether or not he can perform the surgical near-miracles so routine in his practice to restore their vision.”

"He never leaves an eye or a room until he is satisfied that everything in it is as close to perfect as he can make it.” Dr. Chang thanked the FFB and its leaders for their creative support of the exciting research that is bringing hope to people with retinal disease. Also feted at the dinner for his outstanding work in the development of these new molecular therapies gives us limitless potential for innovative ways of treating diseases of the eye. I don't think we have yet come close to fully integrating all the new capabilities we now have. It's a very exciting environment to work in.”

Retinal Surgeon Joins Columbia Faculty

If Jason Horowitz, M.D. had listened to his father, he wouldn’t have followed in his footsteps by becoming an ophthalmologist. “He didn’t encourage me to choose this career pathway,” says Dr. Horowitz. “He used to joke that you can’t fool someone by performing an operation, and then telling them that they can see when they cannot!”

Entering medical school at Yale University, Dr. Horowitz expected that he would pursue another medical specialty. “But the more I learned about ophthalmology, the more I became attracted to it. Physics and optics, sciences which have always fascinated me, are an essential part of ophthalmology, the more I became interested in understanding eye mechanisms and eye diseases.”

The newly minted physician was also fascinated with the concept of deciphering how the eye works. “I particularly loved how physics was integrated into an understanding of eye mechanisms and eye diseases.”

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"Returning to New York and having the opportunity to work anywhere within the influence of Dr. Chang was too good to pass up,” Dr. Horowitz explains.

Dr. Horowitz’s fascination with the retina stems from its close connection to the brain. “It has that element of complexity, carrying the promise that if you can understand the retina, you can perhaps understand more of how the brain works—the end goal of what all scientists would love to know,” he says. “The retina itself is complicated enough, but it also gives you that intellectual window into the brain, as well as an actual physical one. When you look at the retina, you’re looking directly into the optic nerve, which is an outcropping of the brain.”

His practice at Columbia will encompass all retinal procedures in adult patients. “I really enjoy the surgical repair of retinal detachment and diseases of the macula, and rehabilitating eyes that have been ravaged by diabetic retinopathy,” he says. “Even the approaches that allow us to treat a lot of age-related diseases with the new injectable pharmaceuticals are very satisfying. The newer treatment paradigms, which have only been around for five or six years, have radical implications for improved vision.”

Anti-angiogenesis drugs and their application to a condition such as age-related macular degeneration could dramatically alter ocular pharmacology in general, Dr. Horowitz suggests. “The fact that you can create such a revolution with the development of these new molecular therapies gives us limitless potential for innovative ways of treating diseases of the eye. I don't think we have yet come close to fully integrating all the new capabilities we now have. It’s a very exciting environment to work in.”
outstanding generosity and commitment to the retinal disease community was Arvy B. Bourkoff, Vice Chairman, Global Head of Telecom, Media, and Technology Investment Banking at UBS Investment Bank. “We’re thrilled to recognize two visionary leaders in the banking and retinal research fields with the Foundation Fighting Blindness’ signature award,” said Bill Schmidt, CEO of the Foundation Fighting Blindness. “Their commitment to driving sight-saving research will help lead to brighter futures for the more than 10 million Americans affected by vision-robbing retinal diseases.” The dinner, with over 350 guests in attendance, raised $1 million for retinal disease research.

Neuro-Ophthalmologists continued from page 3

Although Columbia’s researchers did not invent these techniques, Dr. Hood says, they have combined them in innovative ways to give ophthalmologists the information they need to best diagnose and treat their patients. “We’re also involved in trying to better understand how various diseases affect the retina and the brain by combining these techniques in different ways,” he explains. “At the moment, we’re developing better ways to detect diseases of the optic nerve like glaucoma by combining optical coherence tomography with the behavioral visual field.”

Sometimes, patients have visited literally dozens of doctors by the time they get to the Neuro-ophthalmologists at Columbia, Dr. Odel says. “For example, there is a group of patients who have what we call Occult Macular Dystrophy. They have difficulty with central visual acuity, but can see fine in the periphery of their vision. They don’t have a cataract or a refractive error, the cornea is clear, the retina looks normal and the nerve looks normal.”

It’s little wonder, then, that these patients have often lost track of the number of puzzled doctors they have seen before reaching Columbia. Then they are tested in Dr. Hood’s lab. “The multifocal ERG can analyze an isolated defect in the cones in the absolute center of the retina,” says Dr. Odel. “We couldn’t make this diagnosis before the onset of multifocal ERG. Right now we don’t have a treatment to offer these patients, but at least we can prevent them from getting their wallet biopsied and undergoing unnecessary MRI scans.”

One of the founders of the Neuro-ophthalmology program at Columbia is Myles Behrens, M.D., Professor of Clinical Ophthalmology and Co-Chief of the Neuro-ophthalmology Clinic, who some 40 years ago returned to the medical school from a fellowship with the renowned William F. Hoyt at the University of California, San Francisco, intent on shaping a program similar to Dr. Hoyt’s.

“Over the years, we’ve had about 40 fellows in the program, one or two at a time,” says Dr. Behrens. “But the specialty is shrinking, largely because of the financial aspect. Here, we only work with fellows who are very much interested in pursuing the field as we do, practicing and teaching in a major academic medical center, or in pursuing the neuro-scientific aspects of the field.”

Some solution should be found to help appropriately compensate neuro-ophthalmologists for the time and expertise they put into their practice and attract more young ophthalmologists into the field, Dr. Odel says. “We are the interface between ophthalmology, general medicine and neurology, for complex patients who do not fit easily into a standard eye exam,” he explains. “For these patients, the story is king. If the doctor doesn’t take a medical history in laborious detail and starts with his tools instead, and makes the wrong assumption about what should be imaged, he may go off on the wrong track.”

Neuro-ophthalmologists also recognize a patient’s psychological needs. “Even if we can’t cure a patient, we can at least tell that person what they have and give them support to cope better,” Dr. Odel says. “That’s the primary job of the physician, to educate and comfort. We make ourselves available 24-7. Since I’ve been here, I’ve never once gone off call. When my patients call me, I answer instantly. If the patient doesn’t feel I’m in his corner, I have lost one of my most valuable therapeutic tools.”
Science Insight: Partners in Treating and Curing Blindness

Every day, scientists in the Department of Ophthalmology are engaged in an extraordinary range of research efforts aimed at deciphering the root causes of many diseases and disorders that damage and destroy vision and at developing treatments and cures to save and restore sight.

And every day, those scientists are supported by an extraordinary group of organizations that are as equally committed to ending blindness. When the Viewpoint features a new discovery about the genetics of an eye disorder, or highlights the innovative ways we are using new technologies to diagnose vision-ravaging conditions at earlier stages, there is almost always an outside organization that has helped to make it possible for that work to move forward.

At present, five external foundations support the programs of the Department of Ophthalmology with more than $2 million in ongoing funding.

Chief among these organizations is the Foundation Fighting Blindness (FFB), a public charity that, over its 40-year history, has raised some $400 million to combat the full spectrum of retinal degenerative diseases.

The department has a five-year Center Research Grant from FFB, which underwrites five separate projects. Module 1 focuses on assessing the severity, progression, and prognosis of various retinopathies including ABCA4-related retinopathy and retinitis pigmentosa (RP). Module 2, a collaboration with the University of Medicine and Dentistry of New Jersey, aims to develop cell-based therapy as a treatment for age-related macular degeneration (AMD). Module 3 is a regenerative medicine study. It seeks to determine if reengineering a part of the retina called Bruch’s membrane can reverse the effects of aging and disease, including atrophy involved in advanced AMD. Module 4 involves gene therapy approaches for treating diseases of the retina caused by mutations in the ABCA4 gene, such as Stargardt disease, cone-rod dystrophy, RP, and possibly AMD. And Module 5 involves developing effective measures for the outcome of new therapies for eye disease that can be effectively used in clinical trials.

Research to Prevent Blindness (RPB) has a broad mandate: the prevention, treatment or eradication of all diseases that threaten vision. Over its 50-year history, it has awarded nearly $300 million in grants to researchers in the U.S. and overseas. Through a current unrestricted Challenge Grant, the foundation is enhancing the faculty’s efforts to develop and plan a wide range of eye research programs.

Macular degeneration research is a leading focus of the American Health Assistance Foundation (AHAF), which sponsors research aimed at curing age-related diseases. AHAF currently funds a two-year project investigating the role of vitamin A in slowing the accumulation of a cellular byproduct called lipofuscin, which in excess quantities has been implicated in the pathology of AMD.

Treatments and cures for macular degeneration and diabetic retinopathy are the particular goal of the International Retinal Research Foundation (IRRF). The IRRF is currently financing a project to evaluate a new small molecule therapy aimed at protecting photoreceptor cells, which may prove to be an effective treatment for atrophic AMD, also known as “dry” AMD.

Friends of the Congressional Glaucoma Caucus Foundation takes a community outreach approach to combat eye disease, educating people about the risks of developing glaucoma and what they can do to seek early diagnosis and treatment. Partnering with the foundation since 2006, the Department of Ophthalmology has created a screening program for high-risk individuals, such as African-Americans and Hispanics over the age of 40, in our local community of Washington Heights-Inwood. Weekly screenings at both community sites including churches and banks, and neighborhood events such as street fairs help our faculty diagnose at-risk individuals early on in their disease, after which they are referred to the Harkness Eye Clinic or to community ophthalmologists to ensure that they get the necessary treatment.

“It would be impossible for us to pursue the innovative research and comprehensive community outreach that are hallmarks of our department without the continuing support of these essential organizations,” says Department Chair Stanley Chang, M.D.

Personalized Medicine

continued from page 1
develop patient-specific cell lines to treat various disorders. The second is to test the efficacy of a therapeutic agent based on his genetic makeup.

Creating patient-specific cell lines that can be used to treat eye disease is the goal of Stephen H. Tsang, M.D., Ph.D., Assistant Professor of Ophthalmology, Pathology and Cell Biology, and interim Associate Director of the Bernard and Shirlee Brown Glaucoma Laboratory.

Dr. Tsang is now taking cells from skin biopsies of patients who have retinal degeneration, growing them in culture, and inducing them to become “pluripotent”—that is, cells that have the potential to become almost any part of the body. Dr. Tsang has been able to coax these cells to differentiate into the cells of the retinal pigment epithelium—the layer of the eye directly beneath the retina.

“The technology is most advanced with corneal epithelial stem cells,” he says. “For people who have had a bad alkaline burn to the cornea or another trauma, we will soon be able to take stem cells from the good eye and help generate a new corneal surface for the other eye.”

But what if the person’s eye damage comes from a disease, such as diabetic retinopathy? If the disease is part of the patient’s own genetic code, transplanting new corneal or retinal cells with the patient’s existing genetic programming could just reintroduce the same disease. With a condition such as age-related macular degeneration (AMD), that might not be so bad, says Dr. Del Priore. “Newly-generated retinal cells might behave as if they are brand new, which should give the patient another 55 or so years before AMD sets in.”

Other diseases, however, aren’t age-related. Leber’s congenital amaurosis, for example, is an inherited eye defect that appears early in life and causes severe loss of vision by childhood or late adolescence. “Transplanting newly generated cells with the exact same genetic defect would make very little difference,” says Dr. Del Priore.

To use cell-based therapy for patients with such diseases, ophthalmologists will need to correct the “mistake” in the original genetic code. Each step in that process can now be done, says Dr. Tsang—and each step has involved contributions by scientists at Columbia—but the pieces haven’t yet been put together to go full circle, from a skin biopsy to making the patient see again.

“Using high-throughput, next-generation DNA sequencing technology applied by Rando Allikmets [Ph.D.,] here at Columbia, we can identify what gene to correct. With a combination of technology developed in Japan and the work of Elizabeth Robertson [M.D.,] formerly at Columbia’s Department of Genetics and Development, we can make stem cells,” Dr. Tsang enumerates. “Then, we can repair the genetic...
defect discovered by Dr. Allikmets, using gene replacement techniques pioneered at Columbia and can reimplant the cells with surgical techniques."

Before clinical trials of this approach can start at Columbia, says Dr. Tsang, more safety data is needed. In January, a company recently received FDA approval to conduct a Phase III clinical trial of human embryonic stem cell therapy in 12 patients with dry-type AMD. Patients will receive implants with RPE cells derived from the company’s embryonic stem cell lines.

"We may have safety data from this trial in two years, at which point we could apply to the FDA for a trial involving human skin cells," says Dr. Tsang. "As long as this approach is shown to be safe, we will then test stem cells from the skin of patients with the most severe macular degeneration, correct the genetic defect, and reimplant them."

The other side of personalized medicine involves using genetic information to select the perfect drug for an individual patient—and to develop new drugs that target individual mutations. Medication called valproic acid," says Dr. Del Priore. "The researchers had screened hundreds of drugs to get this finding. In a small clinical trial, they then showed that patients with retinitis pigmentosa had a slowing of vision loss when placed on valproic acid. Now they’re expanding that finding to a larger study involving hundreds of patients. Even if we can’t totally stop the rate of retinal degeneration, could we design or find a drug that will slow it down by a factor of three or four so that vision loss happens when the patient is 90 instead of at 30?"

To determine if new genetic approaches to eye disease are truly effective, new methods of following their outcomes in patients must also be developed. Leading-edge imaging technologies that are now being investigated in the Department of Ophthalmology are likely to play a key role.

"Imaging of the eye allows us to understand if the expression of a disease is different in one individual than in another, which might indicate a certain therapeutic course," says Janet Sparrow, Ph.D., Anthony Donn Professor of Ophthalmic Science, who is studying the use of a light-imaging technique called fundus autofluorescence. Her laboratory has also led the field in understanding the material in the retina that is the source of fundus autofluorescence.

"When we use certain instruments, we can see that the surface of the retina exhibits fluorescence, and with some retinal diseases, the amount of fluorescence in the individual can vary," Dr. Sparrow explains. "Working with Francois Delori, Ph.D. at the Schepps Eye Research Institute in Boston, we are developing approaches that will quantify the brightness of the fluorescence in one individual vs. another, and are attempting to understand what different autofluorescence patterns mean. They might tell us that the course of the disease is more advanced, or that it’s a more severe form of the disease. Ultimately, as new therapies become available, fundus autofluorescence may help us follow the efficacy of a treatment. It’s a way of screening drugs that is not possible in other systems, but we can do so noninvasively in the eye because of this kind of imaging."

Dr. Del Priore compares the changes going on now in personalized medicine to the shift from pencil and paper to the computer. "There’s a convergence of techniques that are rapidly changing the way things are done. I think we’ll look back in 10 years and realize that this was a crucial time in medicine, and in ophthalmology specifically. The growth of personalized medicine is not linear, but exponential, and I think it will change the way we practice. Hundreds of disorders will fall, one at a time."

The Genetics of AMD

One of the best-understood diseases of the eye, genetically speaking, is age-related macular degeneration (AMD). That’s due in large part to the study of research developed by Rando Allikmets, Ph.D., (William and Donna Acquavella Professor in the Department of Ophthalmology and Pathology and Cell Biology and Research Director of the Edward S. Harkness Eye Institute, whose lab, in collaboration with many clinical faculty members (Drs. R. Theodore Smith, Gaetano Barile, Stanley Chang, John Merriam, etc.), has collected blood samples and clinical information from more than 3,000 AMD patients and people without the condition. Their work has been seminal to the identification of more than half of the genetic variations that underlie AMD.

"Since 2005, when we found that complement genes and complement pathways are involved in AMD, many companies have rushed in to pursue complement-based therapeutics," he says. "The market is enormous, as the disease is growing in prevalence given our aging population."

At this point, the only available therapy for AMD is the use of anti-angiogenesis drugs (known as anti-VEGF agents, because they suppress vascular endothelial growth factor). In some 10% of patients, an abnormal growth of blood vessels in the macula can be halted back by these therapies. "But we’re still fighting the symptom and not the cause," says Dr. Allikmets. "What’s most important is to understand the gene variants that underlie the disease, the causality and the progression—which probably have nothing to do with variations in VEGF receptors. We are trying to find out what the genetic markers are that we must screen for therapeutic applications, in order to determine if the therapy will be efficient or not. Once we know that, then that is personalized medicine."

But even before the development of new therapies, the genetic understanding of AMD made possible by the research of Dr. Allikmets and colleagues is making a difference in the lives of people with the disease. "Vitamin A supplements have long been offered to people with AMD because it is believed that they can delay the progression of the disease," he says. "But our research has shown that in some patients with AMD, their genetic defect involves the removal of vitamin A. For those patients, additional vitamin A can be detrimental rather than beneficial. We need to know the genetic basis of a particular case to determine who should take vitamin A and who should not."

Fine-tuning which patients should take a certain vitamin might seem simple, but it’s anything but—and it’s an early frontier in personalized medicine. "We don’t have true personalized treatments for any eye disease yet, but some are coming," Dr. Allikmets says. "We’re at the beginning of figuring them out right now."
Will you have to take a distribution from your Individual Retirement Account (IRA) during this tax year? If you’re over the age of 70.5, then the law mandates that you take a certain amount from your IRA every year—whether you want to or not. This “minimum required distribution” is calculated by the IRA custodian, based on your age and the total funds that you have in the account. And because the money went into your IRA tax-free, now that it’s coming out, it’s taxable as income.

But a new law allows you to save on these taxes by making a gift to a charitable organization such as the Department of Ophthalmology at Columbia University. The Tax Relief, Unemployment Insurance Reauthorization and Job Creation Act of 2010 extended a law allowing individuals to distribute up to $100,000 of their minimum required distribution directly from their IRA to charities, without including that amount in their gross income for tax purposes.

“You can make a charitable gift directly from your IRA to the organization of your choice, and it will count as part of your minimum required distribution,” says Laura Tenenbaum, Columbia’s director of development, gift planning. “The money is not included in your income for this year, and you also do not take a tax deduction for your charitable donation.”

Choosing to manage your minimum required distribution this way could result in significant tax savings, Tenenbaum says. “Imagine that you need to take a minimum of $50,000 from one or more IRAs. That may well put you into a higher tax bracket. But this year, you can take that whole amount, or anything up to $100,000, and make a gift to offset that requirement.”

The gift must come directly from the IRA itself, not via the taxpayer, so that there is no question about its provenance. “You cannot hold that check. You cannot have it first,” Tenenbaum says. “Instead, you simply contact Merrill Lynch or Vanguard or whatever your custodian is, and request that they send your minimum required distribution, or whatever portion of it you choose, up to the maximum $100,000, to the charitable organization of your choice.

The process is simple:
• When you are ready to take the Required Minimum Distribution for 2011, contact your plan administrator to ask if it has a specific form for you to use.
• To make a gift to Columbia, you will need to provide the plan administrator the following information:
  • the official name of the University: The Trustees of Columbia University in the City of New York, and
  • the address to mail the check. Please direct the plan administrator to mail the check to: Department of Ophthalmology Attn: Jane Heffner 635 West 165th Street, Box 13 New York, NY 10032
• If there are any questions, please contact Laura Tenenbaum in the Office of Gift Planning at 212-342-2108.
• You will also want to write a letter to Columbia to tell us how you want us to use your gift. For example, you might wish to support fellowships that train the next generation of physicians in an area of ophthalmology that has been important to you or your family, or to fund important new research into conditions like age-related macular degeneration or Stargardt macular dystrophy.

“Many people have very large IRAs, and the required minimum distribution can be a substantial amount of money,” Tenenbaum notes. “This offers them an opportunity to reduce their tax burden while at the same time doing something charitable that they may not have been able to do in the past.”