A Vision for Gene Therapy

FFB Partnership Accelerates Advancement of Gene Therapies

A decade ago, five scientific leaders with expertise in gene therapy formed a company to commercialize their promising innovations for the treatment of incurable genetic diseases. They named the company Applied Genetic Technologies Corporation, with their acronym, AGTC, cleverly representing the four organic compounds — adenine, guanine, thymine, and cytosine — that make up the genetic code found in virtually every cell on the planet.

One of those founders was Bill Hauswirth, Ph.D., an FFB-funded researcher from the University of Florida, who at the time had just developed a gene therapy that would restore sight in more than 60 Briard dogs — including the world-famous Lancelot — born blind from Leber congenital amaurosis (LCA). Today, similar treatments in landmark Phase I clinical trials have restored some vision in 20 young adults and children who were virtually blind from LCA.

AGTC will soon be launching Phase I/II clinical trials of their LCA gene therapy at the University of Massachusetts and Oregon Health and Science University, where they will be treating younger participants with higher doses than those used previously. Both the concentration and volume of the injected solution will be increased as they attempt to treat a larger area of the retina with a more powerful therapy. The hope is that they can restore even more vision.

In partnership with the Foundation, AGTC is also developing gene therapies for X-linked retinoschisis (XLRS) and achromatopsia (day blindness), with the goal of bringing those to clinical trials shortly. FFB is currently funding preclinical studies for XLRS at the University of Florida, Oregon Health and Science University, and the University of British Columbia, as well as an achromatopsia study at the University of Pennsylvania.

“We are excited to see AGTC taking laboratory advancements funded by FFB and moving them into the clinic,” says Stephen Rose, Ph.D., chief research officer, Foundation Fighting Blindness. “It’s the quickest and most effective path to moving these treatments out to the people who need them, and it is opening the door to use gene therapies to treat a variety of retinal degenerative diseases.”

Jeffrey Chulay, M.D., chief medical officer at AGTC, says that many inherited retinal degenerative diseases are particularly amenable to gene therapy, because they are caused by a single genetic defect. He says, “We believe we have technology that can benefit patients with a variety of eye diseases. To treat the largest number of patients requires a commercial entity like AGTC, which has the production resources and expertise to obtain approval from the FDA.”

Chulay says that AGTC’s adeno-associated virus (AAV) technology, used to deliver the healthy gene to the retina, has a number of advantages, including an excellent safety track record and the ability to readily penetrate cells in the retina. Furthermore, the AAV treatments have demonstrated effectiveness over long periods of time. “We are excited for our technology’s potential to save and restore vision for people with a variety of retinal conditions,” he adds.

How Does Gene Therapy Work?

Virtually every cell in your body carries a complete set of an estimated 20,000 to 25,000 genes. Genes instruct cells which proteins to make, and these proteins are essential to the health and functioning of all your cells.

Most inherited retinal degenerative diseases are caused by a small variation (mutation) in a single gene.

These variations are like small misspellings in an instruction manual. Even a small misspelling can cause the wrong protein or wrong amount of protein to be made. That can lead to serious consequences like degeneration of the retinal cells that enable you to see.

Scientists are developing gene therapies to deliver a new, corrective gene to the retina, so cells make the right proteins, and stay healthy and functioning properly. Man-made therapeutic viruses are one way to deliver the corrective gene to the cells. The viruses are said to “transfect” — or penetrate — the cells with their healthy genetic cargo.

Gene therapy is administered by injecting a tiny drop of solution — which contains the virus and new gene — underneath the retina. The solution is absorbed into the retina over a period of hours.

The elegance of gene therapy is that one treatment can potentially be effective for several years or perhaps a lifetime.
MESSAGE FROM THE CEO

Blindness Can’t Wait

By William T. Schmidt, Chief Executive Officer

As the Foundation Fighting Blindness moves into Fiscal Year 2010 (beginning July 1, 2009), we are entering the most scientifically promising time in our 38-year history. From gene therapy to stem cells to pharmacological agents, never before have there been so many potential sight-saving treatments in, or moving toward, clinical trials.

When I joined the Foundation four years ago, much of our science news was about progress in preclinical studies; we reported on curing blindness in animal models of retinal disease. While funding these preclinical efforts was a critical step, and remains essential to the development of treatments and cures for all retinal degenerative diseases, reports on progress in human studies now dominate our headlines.

At the same time, the Foundation, like virtually all other nonprofits and commercial entities, has been impacted by the most difficult economic downturn in several decades. While we had been consistently achieving double-digit growth over the last few years leading into last July, our revenues actually declined by approximately 10 percent in Fiscal Year 2009.

Unfortunately, while our economy tries to regain momentum, vision loss from retinal degenerative diseases doesn’t take a respite. Blindness marches on. For those of you losing your vision, or with a loved one affected by a retinal disease, you know this reality all too well.

We now enter Fiscal Year 2010 with greater funding needs than ever before. There have never been so many research projects with such strong clinical potential presented to us by the retinal research community, and as clinical trials, they require significantly more funding than laboratory studies.

Please know that we at the Foundation are doing everything in our power to keep the research moving forward. We are working as urgently, resourcefully, and creatively as possible in our fundraising efforts. But we cannot do it alone.

Your sustained commitment is what has brought us to this hopeful point, and your continued generosity is what will keep us moving forward.

“We know that we at the Foundation are doing everything in our power to keep the research moving forward. We are working as urgently, resourcefully, and creatively as possible in our fundraising efforts. But we cannot do it alone. Your sustained commitment is what has brought us to this hopeful point, and your continued generosity is what will keep us moving forward.”

“Your sustained commitment is what has brought us to this hopeful point, and your continued generosity is what will keep us moving forward.”

Thanks for your dedication to being the light for more than 10 million Americans affected by retinal degenerative diseases. Thanks to your vision for a world without blindness, a cure is in sight.

William T. Schmidt
A PUBLICATION FOR MEMBERS OF THE FOUNDATION FIGHTING BLINDNESS

In the News

Capsule Slows Dry AMD

Neurotech Capsule Stabilizes Vision in Dry AMD, Shows Biological Effect for RP and Related Diseases

An innovative technology, employing a tiny capsule implanted in the eye, is stabilizing vision in people suffering from Geographic Atrophy (GA, also known as advanced dry age-related macular degeneration). The device is also showing a potentially beneficial effect for people with inherited retinal degenerative diseases such as retinitis pigmentosa (RP).

Encapsulated Cell Technology (ECT), developed by Rhode Island-based Neurotech, preserved vision in a majority of the 51 people with GA who participated in a Phase II clinical trial. Neurotech reported that 96.3 percent of participants receiving the high dose treatment had stable vision over a 12-month period. People with better visual acuity at the start of the treatment — 20/63 or better — appeared to benefit most. Neurotech is discussing a Phase III study of the ECT for GA with the FDA.

In two ongoing Phase II/III studies for people with inherited retinal degenerative diseases such as RP, Usher syndrome, and choroideremia, ECT demonstrated a biological effect after 12 months. Investigators reported that treated retinas were thicker, and therefore likely healthier, than those untreated, and the amount of thickening was dose dependent; the higher dose treatment appeared to result in greater thickening. Increased retinal thickening had not translated into better visual acuities or broader visual fields at the 12-month points in the studies.

One trial for inherited retinal conditions is an 18-month investigation for people with late-stage degeneration. The other study, which enrolled people with early-stage retinal degeneration, is a 30-month trial. Investigators will continue to monitor and report results as these two trials move forward.

“Neurotech’s Encapsulated Cell Technology has the potential to preserve the vision of millions of people with dry AMD,” says Stephen Rose, Ph.D., chief research officer, Foundation Fighting Blindness. “The results for people with RP and related diseases are encouraging. We hope retinal thickening translates into vision improvement as the studies progress.”

Introducing the NEER Network

 Contracts Inked for Five Clinical Trial Centers

The National Neurovision Research Institute, FFB’s clinical trials support organization, has concluded negotiations with five clinical trial and evaluation centers of the National Eye Evaluation Research (NEER) network. The centers form the nucleus of the NEER network, whose mission is to conduct natural history studies and clinical trials for emerging treatments and cures for retinal degenerative diseases, such as retinitis pigmentosa, Usher syndrome, age-related macular degeneration, Stargardt disease, and other related conditions. The five centers are: University of Medicine & Dentistry of New Jersey, University of Utah, The Children’s Hospital of Philadelphia, Wilmer Eye Institute at Johns Hopkins, and the Joan and Irwin Jacobs Retina Center in the Shiley Eye Center at the University of California, San Diego.

“The establishment of the NEER network positions us well to quickly launch clinical trials for promising treatments coming out of the laboratory,” says Stephen Rose, Ph.D., chief research officer, Foundation Fighting Blindness. “In fact, we are already considering the network for evaluating a potential drug to treat retinitis pigmentosa.”

DID YOU KNOW

The Foundation’s online message boards offer support and a sense of community for people living with retinal diseases.

Visit www.FightBlindness.org
A Career-long Quest

The Foundation Fighting Blindness has honored Dr. Dean Bok, of the Jules Stein Eye Institute of UCLA, with the prestigious Llura Liggett Gund Career Achievement Award. The highly coveted award was presented to Dr. Bok in recognition of his outstanding research achievements that are now leading to the development of promising preventions, treatments and cures for numerous retinal degenerative diseases. Dr. Bok received the award before an audience of his peers at a Foundation dinner following the Association for Research in Vision and Ophthalmology Annual Meeting in Ft. Lauderdale on May 7, 2009.

“The Llura Liggett Gund Award, which is named for a co-founder of the Foundation, is presented to a highly accomplished individual whose extraordinary research career has advanced the progress of retinal degenerative disease research in a uniquely significant way,” says Gordon Gund, chairman and co-founder of the Foundation Fighting Blindness. “For more than four decades, Dr. Dean Bok’s superlative research contributions to understanding the causes of these diseases, his mentorship of and collaboration with others, and his dedication to the development and oversight of the Foundation’s strategic research plan highly qualify him for this singular recognition.”

Dr. Bok has and continues to be a world-renowned expert in defining how vitamin A metabolism is essential to vision. His research led the way in establishing the gene defect in the vitamin A metabolic cycle that ultimately directed researchers toward recent successful gene therapy clinical trials for Leber congenital amaurosis.

“His research led the way in establishing the gene defect in the vitamin A metabolic cycle that ultimately directed researchers toward recent successful gene therapy clinical trials for Leber congenital amaurosis.”

Recipients of the Llura Liggett Gund Award are leading visionaries in the retinal research community and together have played significant roles in advancing the study of blinding diseases and the search for cures and treatments. The award has previously been presented to only four researchers throughout the Foundation’s 38-year history. Their combined efforts have led to breakthroughs that bring real hope to those affected by blindness. As the 2009 recipient, Dr. Bok joins this exclusive, unique group of researchers who together are bringing us closer to cures and treatments.

Strength in Numbers

New Partnerships Accelerate the Research Process

By Stephen Rose, Ph.D., Chief Research Officer, Foundation Fighting Blindness

I am very heartened to report that several pharmaceutical companies and venture capital firms have recently announced that they are making significant investments in retinal research, either through collaborations or direct funding.

These new partnerships not only strengthen the commitment toward moving potential treatments and cures for retinal degenerative diseases into the clinic, they should also accelerate the research process. Commercial investments and partnerships are occurring in part, because of the success in Foundation-funded research. Our investigators’ research efforts are demonstrating real potential for saving and restoring sight. Strong commercial backing to move them forward is affirmation that we are on the right track.

One notable announcement came from sanofi-aventis, which is making a $50 million investment in retinal gene therapy developer and FFB partner Oxford BioMedica. They are working toward launching clinical trials of their gene therapy product StarGen™ for people with Stargardt disease, UshStat™ for those with Usher syndrome, and RetinoStat® for people with age-related macular degeneration. Oxford’s lentiviral gene delivery technology has shown excellent results in late-stage preclinical studies, so the future for their treatments is very promising.

I was also pleased to learn that FFB partner Applied Genetic Technologies Corporation is receiving more than $11 million in venture capital. (Read more about their gene therapy development on page 1.)

In April, Pfizer announced a partnership with University College of London to develop embryonic stem cell treatments for age-related macular degeneration. This is a big step forward in advancing a treatment approach that holds extraordinary promise for treating a broad range of retinal degenerative diseases, and Pfizer brings valuable clinical trial expertise and resources to the collaboration.

It is imperative that the Foundation continue to fund more research to attract more outside capital. We can’t cure blindness alone; we need to leverage the support from our donor base into greater investments from our partners. I am excited by the progress we are making in developing these critical partnerships and collaborations. While we still have much more work ahead of us — there’s a lot of high-quality research that still goes unfunded — these moves from the commercial sector show that the Foundation is heading in the right direction.
Visionary Awards Dinner

Dining in the Dark Brings Light to Sight-Saving Cures

Eat dinner with the lights off. What better way to understand, if but for a moment, what it is like to be blind? And what better way to raise money for sight-saving treatments and cures?

In its third year, the dining in the dark theme, as part of the Foundation’s Visionary Awards Dinner, has left lasting impressions on thousands of guests around the country, who dared to eat in complete darkness. Most important, the unique event has raised millions of dollars to overcome blinding retinal degenerative diseases, which affect more than 10 million Americans and millions more around the world.

The dinners have also provided an opportunity for the Foundation to recognize philanthropists, business and community leaders, and renowned research professionals with Visionary Awards for their extraordinary efforts in saving and restoring vision. Six dinners were held in the first half of 2009. Pictured above are the individuals honored at those dinners.

Upcoming Dinners

September 29
Baltimore Dinner Gala

December 1
Northern Virginia Dining in the Dark

December 3
New York Dining in the Dark
these individual differences may suggest because understanding the reasons for an extremely important area of research. The reasons are not well known, but this is the same family? mutation — even people within the degeneration caused by the same genetic vary so much for people who have retinal Why can the severity of vision loss of Inherited Eye Diseases, the genes and related experts in identifying world-renowned Dr. Daiger is a Foundation Fighting Blindness. The support and generosity of their friends and family were awe inspiring. “Everyone rallied around us, and we raised almost $27,000,” Helaine says. The energy in the air, the laughter and spirit of all the participants helped turn her despair into hope, and the loneliness she felt just a few months ago was now replaced with a confident enthusiasm to do even more. Helaine also decided to take up an offer from Ron Kolber, a musician and family friend, who wanted to hold a benefit concert for Joshua. He and his band, The BBQ Boys, drew more than 200 people to Rock for Sight, and raised $5,000 for FFB’s mission.

Thanks to FFB and the promise of research, Helaine is now looking to the future with hope. She recalls, “After the diagnosis, I was just sad, sad, sad. A year later, I am back to my happy self. I’ll have a sad moment every once in a while, but it’s good to feel happy again. It’s good to be able to enjoy Joshua in the here and now and not worry too much of what the future holds. I don’t necessarily pray for a cure for RP as much as I pray for a way to stop the progression. I don’t want to be too greedy.” •

ASK THE DOC

Stephen Daiger, Ph.D. Director, Laboratory for Molecular Diagnosis of Inherited Eye Diseases, University of Texas—Houston

Funded by the Foundation Fighting Blindness since 1985, Dr. Daiger is a world-renowned expert in identifying and understanding the genes and related mutations that cause retinal degenerative diseases.

Why can the severity of vision loss vary so much for people who have retinal degeneration caused by the same genetic mutation — even people within the same family?
The reasons are not well known, but this is an extremely important area of research because understanding the reasons for these individual differences may suggest new ways to modify or slow the progression of vision loss.

Some people are “protected” from the bad effects of the disease and by understanding the protective factors, we may learn how to protect other people. Some modifying factors are probably environmental. For example, siblings exposed to different amounts of sunlight while growing up may have different vision loss.

However, some modifying factors are clearly inherited just as the original disease-causing mutation is inherited. But the inherited modifying factors are most likely in genes distinct from the original disease-causing gene. This is true for all forms of retinal disease, whether dominant, recessive or X-linked.

Have any researchers found modifier genes? FFB-funded researcher Dr. Hemant Khanna and his colleagues at the Kellogg Eye Center, University of Michigan, recently found one of the major genetic factors modifying Leber congenital amaurosis (LCA) and the severe complications that may be associated with this condition. What Dr. Khanna found is that a common, non-disease-causing variant in a gene with the symbol “RPGRI1P1” helps determine whether disease-causing mutations in other genes cause LCA alone or LCA with other disorders.

Are you and other researchers trying to find other modifier genes? Yes. In addition to the work of Dr. Khanna, FFB supports other studies to identify factors that modify the clinical results of mutations in retinal disease genes. For example, Dr. Eric Pierce, of the Scheie Eye Institute at the University of Pennsylvania, is studying genetic differences in mice that are partly protected from the effects of mutations that cause retinal diseases in humans. Also, we in Houston are studying factors that protect people who have autosomal dominant forms of retinitis pigmentosa. Finding the factors that protect some people with genetic mutations causing retinal degeneration is a major strategic goal of the Foundation Fighting Blindness, because they would likely have great potential as vision-saving treatments.
Since 2006, VisionWalk has raised more than $9 million dollars to help fund treatments and cures for blinding retinal degenerative diseases. Impressively, more than 28,000 walkers have participated in 90 walks across the country. VisionWalk is a great way to inspire and empower family, friends, and co-workers to get behind the Foundation's urgent mission to eradicate retinal degenerative diseases that affect more than 10 million Americans and millions more around the world.

This fall, 23 walks are scheduled around the country. So, form a team, register at www.VisionWalk.org, lace up your shoes, and join us in taking big steps for research.

Here's a list of walks scheduled for 2009:

- **September**
  - 19 Portland, OR
  - 26 Charlotte, NC
  - 27 St. Louis, MO
  - 28 Indianapolis, IN
  - 28 Minneapolis, MN

- **October**
  - 3 Denver, CO
  - 3 North Kentuck/ Cincinatti, OH
  - 10 Philadelphia, PA
  - 12 Des Moines, IA
  - 17 Memphis, TN
  - 24 Houston, TX
  - 26 Ft. Lauderdale, FL
  - 26 Boston, MA
  - 31 Long Island, NY
  - 31 Los Angeles, CA
  - 31 Louisville, KY

- **November**
  - 7 Tallahassee, FL
  - 8 San Diego, CA
  - 14 Westchester-Fairfield, NY
  - 15 Las Vegas, NV
  - 15 Tampa Bay, FL
  - 21 Birmingham, AL

For more information, visit www.VisionWalk.org

**Full Steam Ahead**

For Allison Libby, a Fateful Boat Trip Has Been an Apt Metaphor for Her Life's Journey

In January 2005, Allison Libby and hundreds of other college students were traveling the world on a “Semester at Sea” cruise when their ship got caught in a wicked winter storm and was struck by a 60-foot wave. For a while, it was touch and go as the boat sat dead in the water at a 45-degree angle in turbulent seas. The passengers donned life jackets, readying themselves in case they needed to abandon ship. But ultimately, the ship regained power, made some adjustments to its original itinerary, and resumed its journey to exotic destinations such as The Great Wall and the Taj Mahal.

For Allison, that nautical misadventure was just one of many big waves that have rocked her life. The first was congenital hearing loss. The second was a diagnosis of vision loss from retinitis pigmentosa when she was 13. And the third was the recent discovery that Usher syndrome 3 was at the root of her hearing and vision loss, and would continue to rob her of her ability to see and hear.

But Allison, now 24-years old, has continued her life's journey undeterred by the daunting prognosis that Usher syndrome holds for her. She graduated magna cum laude from the University of California, Los Angeles, and is pursuing a doctorate in clinical psychology from Pacific Graduate School of Psychology-Stanford Consortium. She loves to read, and continues to travel the world.

Understandably, her parents, Bonnie and Jeff, have at times struggled along with their daughter. Bonnie recalls some of the disheartening moments in Allison's young life: the time when she was 12 and couldn't see a beautiful meteor shower; the time the pediatrician first noticed something wrong with Allison's eyes; and the realization that she needed hearing aids. “The time she came to me and told me she needed to stop driving. I cried. She cried. It really hit home,” Bonnie says.

The Libbys became involved with the Foundation Fighting Blindness in the mid-1990s, shortly after Allison was first diagnosed with RP. Jeff created a database of people in Northern California who were affected with retinal degenerative diseases. They helped organize a small chapter and held a few local fundraising walks.

But VisionWalk has become an empowering force for the Libbys and the local chapter. Becky, Allison’s older sister, co-chaired the Inaugural Bay Area VisionWalk in 2007, and her mother, Bonnie, co-chaired the walk in 2008. Over the last three years, from 2007 through 2009, the region's walk has raised more than $300,000, and the Libby family alone raised $30,000 for the events.

Bonnie admits that fundraising wasn't something she looked forward to doing at first, but she's been surprised and pleased with the response from friends, family, and the community. “Now that the VisionWalk program has really blossomed, we are working as hard as we can. The Internet tools are also very helpful. It's easier to raise. And Golden Gate Park is a very scenic and visible venue,” she says. “I am not great at asking for money, but it is such a worthwhile cause. It's something important to millions of people, not just for our family.”

The Libbys are very excited about the progress of FFB-funded research in recent years. “The LCA gene therapy trials are really amazing as are the Neurotech studies,” says Bonnie. “Second Sight's retinal prosthesis is remarkable.”

In the meantime, Allison lives in Downtown San Francisco and continues to work, study, travel and take in as much of the world as she can. It's full steam ahead — just as it's always been.
Walmart Walks the Walk
Retailer Provides Strong and Growing Support for VisionWalk

As the nation’s largest retailer, Walmart likes to do things in big ways. So when the company began to support VisionWalk in 2006, it was only natural that they would emerge to become VisionWalk’s largest corporate sponsor, having raised nearly $73,000 through June 2009.

The retailer’s support for VisionWalk started as a grassroots effort in Colorado through Walmart Vision Centers at two stores. In 2008, 25 Colorado stores formed walk teams. In 2009, they plan to have all 48 Colorado stores on board. Also this year, the company is sponsoring 14 walks across the country.

Will Gould, who is manager of the Lakewood Walmart Vision Center and chair of the Colorado VisionWalk, says that working in an optical department and supporting FFB’s mission both bring him personal satisfaction. “When we fit customers and their children with new contacts or glasses, we receive instant gratification, because of the difference we have made in their lives. We often provide similar services for their family members, so it becomes a family affair. I especially enjoy helping the kids,” he notes. “FFB provides the same atmosphere at VisionWalk. Families come together to celebrate the drive to cure blindness. VisionWalk provides an opportunity for us to make a difference in people’s lives by raising money for this great cause, and at the same time, promoting good eye health.”

“We are delighted to have Walmart’s generous support. They have shown incredible enthusiasm and passion for our mission and a strong commitment to continually building support for it,” says William T. Schmidt, chief executive officer, Foundation Fighting Blindness.

The 2009 Colorado VisionWalk will be held on October 3 at City Park in Denver. More than 100 Walmart associates are expected to walk and help run the Walmart Food & Drink area and the Walmart Carnival Games for the kids.