# Saving Vision for People with Usher Syndrome

**By Ben Shaberman**

**Significant vision loss isn't easy for anyone, but it's especially challenging for people with hearing loss. It's no surprise that going blind is often a deaf person's biggest fear.**

Affecting as many as 50,000 people in the United States alone, Usher syndrome is the world's leading cause of combined hearing loss and blindness. While the one-two punch of the genetic disease places formidable challenges on those affected and their families, especially if vision loss becomes substantial, dozens of retinal researchers from around the world are making encouraging progress in developing preventions, treatments, and cures to save and restore vision.

Funded by biotechs, nonprofits such as the Foundation Fighting Blindness (FFB), and governmental organizations such as the National Eye Institute, many emerging therapies are, or will soon be, in human studies.

A review of many of these treatments is provided later in this article, but first, here's more information about Usher syndrome, including how and why it occurs, and how it is diagnosed.

## Inheritance, Diagnosis, and Symptoms

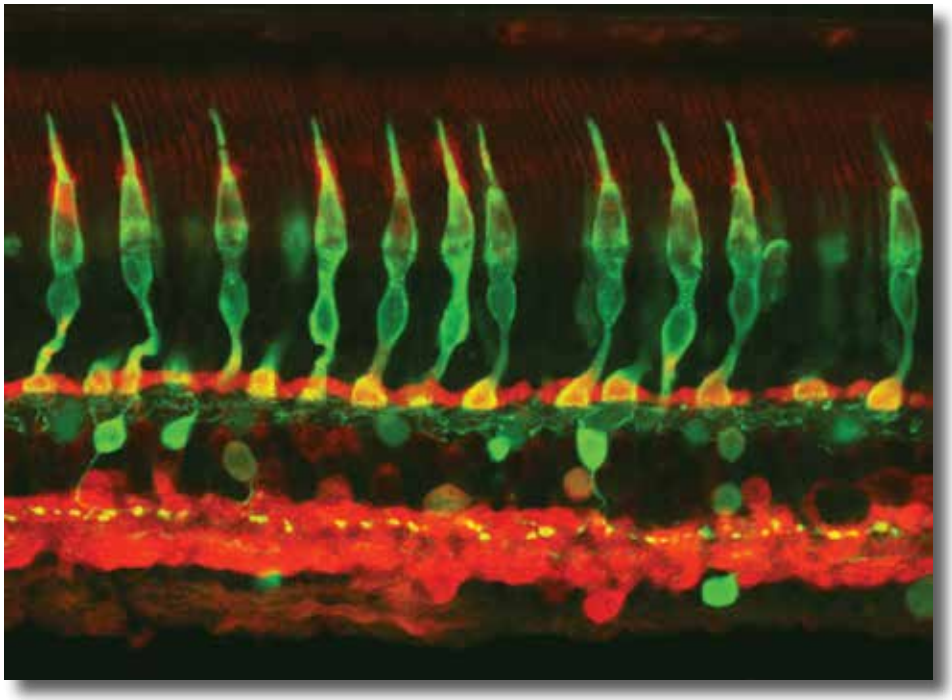
Usher syndrome usually comes as a surprise to a family. That's because it's inherited recessively meaning that both parents are likely to be unaware that they are unaffected carriers of the same mutated Usher syndrome gene. Each of their children has a one-in-four chance of inheriting a mutated copy of the gene from both parents, thereby getting the disease.

In many cases, infants and young children are first diagnosed with moderate or profound hearing loss. The diagnosis of Usher syndrome doesn't occur until later in childhood or early adolescence when an ophthalmologist or retinal specialist discovers during an exam that the patient has vision loss caused by a retinal degenerative disease known as retinitis pigmentosa. Also referred to as RP, the retinal condition can occur on its own or as a syndrome (e.g., Usher syndrome), meaning that it's part of a constellation of symptoms.

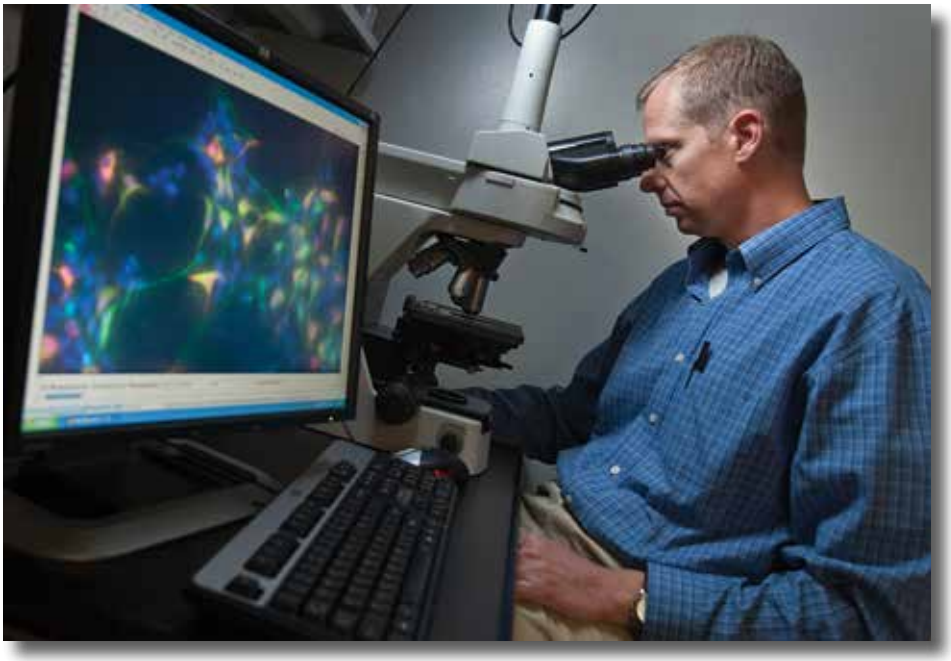
According to the National Institute on Deafness and other Communication Disorders, National Institutes of Health, approximately three to six percent of children who are deaf or hard of hearing have Usher syndrome.

The genetic mutations that cause Usher syndrome affect the development, health, and/or function of the retina, a thin layer of tissue which lines the back of the eye and gives us vision, as well the cochlea of the inner ear, which enables us to hear. These mutations can also affect the vestibular system of the inner ear causing balance problems.

More precisely, Usher syndrome affects cilia, tiny hair-like protrusions which provide sensory functions. In the retina, the sensory cilia are the outer segments of photoreceptors, which convert light into electrical signals that our brain interprets as vision. In the inner ear, they are known as stereocilia. In the cochlea, stereocilia process sound waves. In the vestibular system, they sense motion and gravity.



*Cross-section of the retina. Photo by Nicolás Cuenca, Ph.D., Universidad de Alicante, www.retinalmicroscopy.com.*



*David Gamm, M.D., Ph.D. (pictured here) at the University of Wisconsin-Madison, and Dennis Clegg, Ph.D., at the University of California, Santa Barbara, are collaborating to create a two-layer retinal patch, comprised of photoreceptors and supportive cells known as retinal pigment epithelium (RPE), both of which will be derived from iPSC. The patch is being designed to restore vision in people who have lost photoreceptors and RPE to advanced cases of retinal diseases such as RP.*

## More on RP Symptoms

Night blindness and loss of peripheral vision are usually the first signs of RP (and RP associated with Usher syndrome). As the disease progresses, the field of vision becomes more constricted. The visual field for some people can become as narrow as a straw or pinhole. In some advanced cases, people might only perceive light. The rate of progression can vary widely from person to person, even for people within the same family.

## Genetic Testing

Usher syndrome is designated as being type 1, 2, or 3 based on severity of symptoms with type 1 being the most severe. It can then be further categorized by letters, based on the mutated gene causing the condition. Thus far, 11 genes have been linked to Usher syndrome.

While audio and retinal sensitivity testing can help determine the type of Usher syndrome, genetic testing is ultimately the best way to get a definitive diagnosis for the type and determining which mutated gene is causing the symptoms. According to Radha Ayyagari, Ph.D., a genetic researcher from the University of California, San Diego, more than 70 percent of people with Usher syndrome are able to have their disease-causing gene identified through genetic testing.

The three Usher syndrome types, and the genes associated with them, are as follows:

## Type 1

Children with Usher syndrome Type 1 (USH1) are born profoundly deaf and with significant balance problems. Vision loss is progressive and usually diagnosed later in childhood.

Type 1 genes: MYO7A (USH1B), USH1C, CDH23 (USH1D), PCDH15 (USH1F), SANS (USH1G), CIB2 (USH1J)

## Type 2

Usher syndrome Type 2 (USH2) usually causes moderate-to-severe hearing loss which remains stable. Vision loss from USH2 is likely to be diagnosed in adolescence and progresses more slowly than in USH1. People with USH2 do not have balance problems.

Type 2 genes: USH2A, GPR98 (USH2C), WHRN (USH2D)

## Type 3

Usher syndrome Type 3 (USH3) is much rarer than the other types. Children with USH3 are usually born with normal hearing, vision, and balance. Loss of these sensory functions is progressive and varies significantly from person to person. Symptoms usually begin appearing in adolescence.

Type 3 genes: CLRN1 (USH3A), HARS (USH3B)

## Saving and Restoring Vision

Retinal scientists are developing a number of innovative approaches to treating the vision loss associated with Usher syndrome, including: gene therapies, cell replacement, neuroprotection, and artificial retinas. While some of these emerging therapies are directed toward a specific gene mutation, many are cross-cutting and have the potential to benefit people with many types of Usher syndrome, non-syndromic RP, and a wide range of other retinal degenerative diseases.

## Gene Therapy—Fixing the Genetic Defect

Vision restoration in groundbreaking human studies has paved the way for the development of gene therapies to treat Usher syndrome and a variety of other retinal degenerations. One nine-year-old boy, who was nearly blind from a retinal disease known as Leber congenital amaurosis (LCA), put away his navigational cane and played a full season of Little League Baseball after having just one eye treated in a clinical trial.

In a nutshell, gene therapy usually involves the delivery of copies of healthy genes to replace the defective copies. In most cases, scientists use a human-engineered virus, which can readily penetrate the cells, to deliver the therapeutic cargo to retinal cells. The treatment is contained in a drop of liquid

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that's injected underneath or near the retina. While researchers are still learning about gene therapy's long-term potential, they believe a single treatment might be effective for many years, perhaps a lifetime.

Oxford BioMedica, a biopharmaceutical company in the United Kingdom, and Sanofi, an international pharmaceutical company headquartered in France, are conducting an early-stage human study of a gene therapy for people with USH1B. The Phase I/II clinical trial is taking place at Oregon Health & Science University in Portland, Oregon, and Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts in Paris, France. The treatment has been deemed safe thus far. The companies will not report efficacy until the trial is completed in 2016.

Several other retinal gene therapies for Usher syndrome are being developed in the lab. For example, Muna Naash, Ph.D., at the University of Oklahoma, is working on a gene therapy for USH2A which uses nanoparticles—tiny man-made particles that are 1/10,000,000th of an inch or smaller—to deliver copies of therapeutic genes into retinal cells.

Retinal researchers are also developing drugs that can correct certain types of genetic defects.

In a study at the Johannes Gutenberg University in Mainz, Germany, Uwe Wolfrum, Ph.D., and his team are evaluating a drug that can "read through" defective genetic messages known as premature termination codons (PTCs) in models of USH1C. The drug enables the cell to read the complete message and make the right protein to keep it healthy and functional. A similar drug has already been used in clinical trials for Duchenne muscular dystrophy and cystic fibrosis, both of which are devastating conditions caused by PTCs.

### Stem Cells—Replacing Lost Retinal Cells to Restore Vision

Though stem cells are a relatively new, emerging treatment modality—embryonic stem cells weren't discovered until 1998—they're already in human studies for retinal diseases including age-related macular degeneration and Stargardt disease (juvenile macular degeneration). Stem cell clinical trials for RP should begin within the next year or two.

The power of stem cells lies in their ability to become virtually any cell type in the body, including retinal cells. By replacing retinal cells lost to disease, researchers believe vision can be restored for people with the most advanced retinal conditions. Also, stem cells are generally easy to replicate, so large quantities can be produced for therapeutic purposes.

Stem cells can be derived from a number of sources, including non-destructively from embryos. Researchers can also readily obtain them from other sources including a patient's skin or blood. Scientists are now able take a small skin sample and genetically tweak the cells so that they revert to a stem-cell-like state. Known as induced pluripotent stem cells, or iPSC, they can then be coaxed to become retinal cells (or any other cell type), which can be used to replace retinal tissue lost to disease, thereby restoring vision.

One of the first stem cell trials for RP is likely to be launched in 2015 by ReNeuron, a stem-cell development company in the United Kingdom. Its emerging therapy involves the transplantation of retinal progenitor cells, which are more mature than embryonic stem cells, but haven't completely developed into photo-receptors, the cells in the retina that make vision possible. Once the progenitor cells are transplanted, researchers believe they will mature into full-fledged photoreceptors and restore some of the patient's vision.

David Gamm, M.D., Ph.D., at the University of Wisconsin-Madison, and Dennis Clegg, Ph.D., at the University of California, Santa Barbara, are collaborating to create a two-layer retinal patch, comprised of photoreceptors and supportive cells known as retinal pigment epithelium (RPE), both of which will be derived from iPSC.

The patch is being designed to restore vision in people who have lost photoreceptors and RPE to advanced cases of retinal diseases such as RP. To optimize the patch's ability to integrate and survive in the recipient's retina, the cells are placed on a thin plastic scaffold and held together with a biodegradable gel. Drs. Gamm and Clegg are about three years away from launching a clinical trial for the patch.

### Neuroprotection—Keeping Retinal Cells Alive

Several research groups and companies are developing what are known as "neuroprotective" compounds and proteins which are designed to preserve vision by keeping retinal cells alive. A major advantage of the neuroprotective approach is that it has the potential to preserve vision in people with a wide range of retinal diseases including RP, Usher syndrome, and various forms of macular degeneration.

For example, MitoChem Therapeutics is developing a drug that works to keep retinal cells alive by boosting their mitochondrial function. Mitochondria operate like power plants for all the cells in our bodies including those of the retina. When mitochondrial capacity becomes diminished by diseases, cell survival is compromised. MitoChem is formulating their emerging drug as an eye drop and conducting preclinical studies in preparation for a future human trial. In lab studies thus far, the drug has done an outstanding job keeping retinal cells alive.

### Bionic Retina Receives FDA Approval

In one of the most exciting developments ever in vision restoration for retinal diseases, the Argus II Retinal Prosthesis System, also known as a bionic retina, recently received regulatory approval in the United States and Europe. Second Sight Medical Products, developer of the Argus II, is now implanting the device in patients at clinical centers around the United States.

The system consists of an external video camera mounted on a pair of sunglasses which sends visual images to a 60-electrode grid surgically implanted on the retina. The grid converts those images to electrical signals, which are sent back to the brain.

Users of the Argus II perceive

patterns of light, which the brain learns to interpret as vision. The device has enabled clinical trial participants who are profoundly blind from retinal degeneration to see shapes, recognize large letters and significantly improve mobility.

People with cochlear implants might not be eligible for the Argus II, though case-by-case exceptions are possible.

Second Sight and several other companies from around the world are developing next-generation artificial retinas to provide higher resolution vision restoration.

## More Research Information

**Foundation Fighting Blindness**
Much of the research discussed in this article was made possible by support from the Foundation Fighting Blindness (FFB), which is the world's leading non-governmental source of retinal degenerative disease research funding. FFB currently funds approximately 120 projects at prominent institutions around the world.

To learn more about the research under way for Usher syndrome and other retinal diseases, visit FightBlindness.org or call 800.683.5555.

**Coalition for Usher Syndrome Research**
This foundation helps families cope with the condition, while working to find a cure. www.usher-syndrome.org ***HLM***

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*Ben's book of essays,* The Vegan Monologues, *was published by Loyola University (Maryland) in 2009. His freelance essays and commentaries have been carried by the* Washington Post, Chicago Tribune, *National Public Radio, and a variety of other newspapers, magazines, and literary journals.*

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