# Clinical Trials

## Offer New Hope for Treating Dry AMD

Three years ago, John McNamara, 73, was diagnosed with age-related macular degeneration (AMD), the most common cause of blindness in older adults in the United States. Fortunately, he qualified for a clinical trial at Bascom Palmer Eye Institute led by Philip J. Rosenfeld, M.D., Ph.D., professor of ophthalmology and one of the world's leading experts on this blinding disease.

**WHAT ARE THE RISK FACTORS FOR MACULAR DEGENERATION?**

- Age – Being 60 years of age and older
- Race – Whites are much more likely to lose vision from AMD than Blacks
- Gender – Women tend to be at greater risk for AMD than men
- Family history of AMD Smoking may increase the risk of AMD
- Obesity – Research studies suggest a link between obesity and the progression of early and intermediate stage AMD to advanced AMD

A Bascom Palmer surgical team, led by Ninel Z. Gregori, M.D., implanted embryonic stem cells into McNamara's left eye. "Since then, my macular degeneration has not progressed at all," said McNamara, a patient living in Plantation, Florida. "I'm now in a follow-up program so Dr. Rosenfeld and his team can keep track of my condition." McNamara's experience is particularly significant since he has the underlying "dry" form of AMD, rather than the more aggressive "wet" form. Although the dry form of AMD can convert to the wet form, which causes faster vision loss compared to the dry form, it only happens about 20 percent of the time. Most patients with dry AMD stay as dry AMD, but they lose their vision slowly over years rather than weeks, as with wet AMD. "Today, we have excellent treatments for wet AMD," said Rosenfeld, whose research has resulted in several important breakthroughs. "With our treatments for wet AMD, we can convert the wet AMD back to dry AMD; however, our patients with dry AMD still go on to lose a significant amount of vision from the dry AMD and become legally blind."

AMD typically causes the loss of central vision in both eyes, and usually affects people age 50 and above. Patients with AMD find it hard to see in dim light situations, and have difficulty driving. The symptoms of AMD can often resemble cataracts, and some patients may have both conditions.

Another patient, Marguerite Kuschner, 90, came to Bascom Palmer for cataract surgery by William Culbertson, M.D., the Lou Higgins Chair in Ophthalmology. "The surgery went fine, but afterwards I still wasn't seeing things very well," Kuschner said. "Dr. Culbertson referred me to Dr. Rosenfeld, who found I had the dry form of AMD. Since then, I've taken part in three research studies. My mother had AMD, too, and I don't want my children or grandchildren to suffer from this disease."

### Powerful therapies for wet AMD

In the early to mid 2000s, Rosenfeld discovered that injections of the cancer-fighting drug Avastin®, the brand name for Genentech's drug bevacizumab, halted wet AMD and actually improved vision. He was also the lead investigator in the clinical trials leading to the approval of Lucentis®, the brand name for ranibizumab, also developed by Genentech.

Since then, Rosenfeld has continued to study new medications as well as strategies for improving treatments for wet AMD and dry AMD. "Right now, patients with wet AMD typically require frequent injections for several years," he said. "We would like to reduce that burden on individuals by being able to tailor treatment more precisely."

Using Bascom Palmer's advanced optical coherence tomography (OCT) instruments to image the retina and its blood flow, Rosenfeld can see how well an AMD patient is responding to medical treatments. "Some patients do not need injections as frequently as others, depending on their individual conditions," he said.

(left) Right eye of a patient with intermediate dry AMD and large soft drusen in the macula

(below) Left eye of a patient with late dry AMD where the drusen have degenerated into geographic atrophy and loss of central vision

At the 2015 annual meeting of the Association for Research in Vision and Ophthalmology, Rosenfeld presented preliminary findings from a Phase 1 safety study of X-82, an oral medication by Tyrogenex, a biopharmaceutical company in Palm Beach, Florida. X-82 is a dual inhibitor of vascular endothelial growth factor and platelet-derived growth factor in development for treatment of wet AMD.

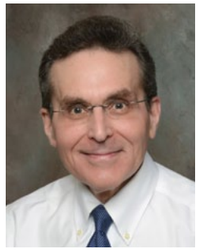
"Data from this study showed that the oral therapy X-82 may offer a strategy for non-invasive delivery of the necessary therapy to the eyes of patients with wet AMD without needing an injection," said Rosenfeld, noting that Bascom Palmer has been enrolling patients in a Phase 2 "APEX" trial of the drug. "An oral therapy is particularly useful for treating both eyes with a pill once a day. We look forward to further studies of this orally administered alternative."

### New trials for AMD

While advancing medical understanding of wet AMD, Rosenfeld has also been researching the genetic and metabolic factors that lead to the progressive loss of vision from dry AMD. A current Phase 2 clinical trial that is fully enrolled and should produce results in mid-2016 is a study sponsored by Acucela, a biotechnology company that investigates a visual cycle modulator known as emixustat hydrochloride.

"Emixustat is a once-a-day pill that slows the metabolic pathways in the retina, which should put the AMD disease process into hibernation and slow or stop disease progression," Rosenfeld said. "Since AMD is a disease that's always in both eyes, the idea of a pill once-a-day to treat both eyes is particularly attractive."

Another study that is fully enrolled and should produce results by mid-2016 is a trial investigating an intravenous inhibitor of beta-amyloid for dry AMD. This drug, which inhibits the same beta-amyloid protein that is implicated as a cause of Alzheimer's disease, is being studied in dry AMD by the pharmaceutical company GlaxoSmithKline. "Hopefully, one of these drugs will prove successful, but we can't wait for the results of these studies before beginning new clinical studies to test other promising strategies for stopping this disease. Since dry AMD progresses more slowly than wet AMD, we need to run these dry AMD studies for at least a year before we know if a treatment works. That's why we need to try different strategies at the same time to prevent blindness from AMD and hopefully one or more will succeed," Rosenfeld emphasized.



Dr. Philip J. Rosenfeld

He is also enrolling patients in clinical trials of medications that inhibit complement, a component of the immune system. "We know from genetic studies that complement activation plays a very important role in causing AMD, and by inhibiting complement activation, we hope to slow or stop the progression of this blinding disorder." One complement inhibitor being investigated is Lampalizumab®, developed by Genentech/Roche, and this drug is injected into the eye either every four weeks or every six weeks. "This complement inhibitor is the first drug for dry AMD that has shown promise in Phase 2 clinical trials," he said. "It's given us real hope that a treatment could preserve vision in patients with dry AMD." In addition, another drug known as APL-2, which is also a complement inhibitor from Apellis Pharmaceuticals, is currently being tested in patients with dry AMD, and this study is enrolling now as well.

**To schedule an appointment with a Bascom Palmer specialist, please call 1-888-845-0002 or visit bascompalmer.org.**

### WHAT ARE THE SYMPTOMS OF MACULAR DEGENERATION?

- Words appear blurry while reading, requiring greater illumination to see details
- Inability to recognize faces at a distance
- Blurred or blind spot in the center of vision
- Straight lines appear wavy or crooked
- Rapid loss of central vision

Vision with age-related macular degeneration

Normal vision

If you experience blurred or distorted central vision, you should visit your ophthalmologist immediately.
To schedule an appointment with a macular degeneration specialist, please call 1-888-845-0002.

"Generally, there is a long lead time between noticing a loss of vision due to dry AMD and having an impact on one's quality of life," added Rosenfeld. "Patients can take some common-sense steps to slow that progression, such as exercising regularly, taking AREDS 2 vitamins and eating a healthy diet that's rich in green leafy vegetables. If you smoke, you should stop immediately, because that makes your condition worse. It's like throwing gasoline on a fire."

To find better treatments for both dry and wet AMD, Rosenfeld and other Bascom Palmer ophthalmologists are studying new medications and stem cell therapies. "Usually, for wet AMD, we start patients on the established therapies, and then move on to the experimental treatments if the vision continues to deteriorate or the treatment burden becomes onerous," he said. "For dry AMD patients, there is no treatment besides vitamins and green leafy vegetables, so this population has so much to gain if a new treatment can be found."

Peter Mosheim, 86, has been going to Bascom Palmer for nearly 50 years, including nearly two decades of treatment for dry AMD. "I'm proud to say I've been Dr. Rosenfeld's guinea pig for several clinical studies," he said. "While there haven't been any miracles, I can still see pretty well."

### Offering varied clinical trials

Today, qualifying AMD patients can be enrolled in clinical trials at Bascom Palmer's eye centers in Miami and Palm Beach Gardens. Typically, two-thirds of patients in the trial will receive the real treatment, while one-third receive a placebo. As Rosenfeld says, "If I were a patient with dry AMD, I would like those odds – given the fact that if a patient doesn't participate, they'll never get any treatment, and currently we do not have any therapies that slow down the vision loss in dry AMD." ■



# What is a Clinical Study?

A clinical study involves research using human volunteers (also called participants) that is intended to add to medical knowledge. There are two main types of clinical studies: (1) clinical trials (also called interventional studies) and (2) observational studies.

Clinical trials apply the scientific method to human health. In observational studies, individuals are observed and their outcomes are measured by the investigators. In these studies the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured.

Almost 40 clinical trials, clinical outcomes and epidemiology studies are ongoing at Bascom Palmer Eye Institute, and most are national multicenter projects. These studies are funded by the National Eye Institute (NEI), private foundations and commercial organizations.

Ongoing studies at Bascom Palmer Eye Institute include studies on cataracts, corneal and external diseases, diabetic retinopathy, glaucoma, LASIK and laser vision correction, Leber's hereditary optic neuropathy, macular degeneration, macular telangiectasia, neuro-ophthalmology, strabismus and pediatric ophthalmology, and uveitis.

**For more information about Bascom Palmer's ongoing clinical trials, visit Bascompalmer.org or clinicaltrials.gov.**

**Thomas Albini, M.D.**, is enrolling patients for a randomized, masked multicenter study to assess the safety and efficacy of CLS-TA, triamcinolone acetonide injectable suspension, in the treatment of subjects with macular edema following uveitis.

**Jorge Fortun M.D.**, is the principal investigator of a two-year, randomized, double-masked, multicenter, three-arm study comparing the efficacy and safety of RTH258 versus Aflibercept in subjects with neovascular age-related macular degeneration.

**Arindel S. Maharaj, M.D., Ph.D.**, is the principal investigator of a study comparing ocular perfusion pressure and retinal blood flow in glaucomatous eyes with and without optic disc hemorrhage.

**Zohar Yehoshua, M.D., M.H.A.**, is the principal investigator for a randomized, double-masked, dose-ranging multicenter study comparing ACU-4429 with placebo in patients with age-related macular degeneration.

### Clinical Trials

In a clinical trial, participants receive specific interventions according to the research plan or protocol created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior, such as diet. Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo that contains no active ingredients, or to no intervention. Some clinical trials compare interventions that are already available to each other. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful, or no different than available alternatives (including no intervention). The investigators try to determine the safety and efficacy of the intervention by measuring certain outcomes in the participants.

### Who Conducts Clinical Studies?

Every clinical study is led by a principal investigator, who is often a medical doctor. Clinical studies also have a research team that may include doctors, nurses, social workers and other health care professionals.

Clinical studies can be sponsored, or funded, by pharmaceutical companies, academic medical centers, voluntary groups, and other organizations, in addition to Federal agencies, such as the National Institutes of Health, the U.S. Department of Defense, and the U.S. Department of Veterans Affairs. Doctors, other health care providers, and other individuals can also sponsor clinical research.

Clinical trials used in drug development are sometimes described by phase. These phases are defined by the Food and Drug Administration (FDA):

- Phase 0: Exploratory study involving very limited human exposure to the drug, with no therapeutic or diagnostic goals.
- Phase 1: Studies that are usually conducted with healthy volunteers and that emphasize safety. The goal is to find out what the drug's most frequent and serious adverse events are, and how the drug is metabolized and excreted.
- Phase 2: Studies that gather preliminary data on effectiveness (whether the drug works in people who have a certain disease or condition). For example, participants receiving the drug may be compared to similar participants receiving a different treatment, usually an inactive substance, called a placebo, or a different drug. Safety continues to be evaluated, and short-term adverse events are studied.
- Phase 3: Studies that gather more information about safety and effectiveness by studying different populations and different dosages, and by using the drug in combination with other drugs.
- Phase 4: Studies occurring after the FDA has approved a drug for marketing. These studies gather information about a drug's safety, efficacy or optimal use.

*Courtesy of clinical trials.gov*