

# Summary of Research & Developments, June 2010 Through May 2011

IMDSG Presentation

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## Introduction

Since 2006, I have done my best to condense the high points of the previous year's macular degeneration research into a single report that is concise and understandable for the layperson. I do so, because I understand first hand how important it is to be aware of everything being done on our behalf by the scientific community. Fear of the unknown is often the worst part of this disease. Information, therefore, is an effective weapon that we should all have access to.

Developments in the field of low vision treatment are occurring at an exponential rate. So fast that vision restoration and cures could conceivably become realities in some of our lifetimes. Through the years, we have seen impressive achievements in the areas of surgery, nutrition, and pharmacology. This past year, pharmacology has taken the lead, so most of this summary will discuss the drugs that are now under development and in clinical trials.

## PHARMACOLOGY

### Results From the Comparison of AMD Treatments Trial (CATT)

The most interesting development this past year was the findings from the Comparison of AMD Treatments Trial (CATT), sponsored by the National Eye Institute. This trial was designed to study the relative safety and efficacy of Genentech's Lucentis, the approved treatment for wet AMD, and off-label Avastin, a similar, but less expensive drug originally developed by the same company for treatment of colon cancer. At the end of the first year of the two-year trial, the two compounds have been found to be extremely similar in their improvement of mean visual acuity and in the occurrence of adverse events.

These are top line results, with more detail to come later. Meanwhile, the subjects will continue under observation as the trial proceeds through its second year. Five related trials are also underway in the UK and Europe, all of which deserve watching for potential new findings.

In addition to the general findings, the results also revealed surprisingly little difference in the efficacy of scheduled injections and the efficacy of injections delivered on an as-needed basis for both drugs.

The general consensus of opinion among doctors using Avastin is that they will continue using the drug off-label. At the same time, they will ensure that patients are fully aware of adverse events (SAE) that have been determined at this time to be neither significant nor insignificant to the end results. No discussions have yet been held with the Centers for Medicare and Medicaid Services (CMS) regarding changes in policy for reimbursement for Avastin as a treatment for wet AMD.

Another report will be published following conclusion of the trials next year. Meanwhile, it is important that patients discuss their treatment with their doctors for a full understand of the current findings.

## Fenretinide

ReVision Therapeutics' Phase 2 trials have been completed with a surprising outcome. In addition to expected positive results, researchers have found that the drug fenretinide, taken orally once a day, also reduces by 2.2-fold the rate of conversion to neovascularization (hemorrhaging) in patients with geographic atrophy (end stage dry AMD). This means that fenretinide, in addition to slowing the progression of dry AMD, could also become a pre-treatment for wet AMD, a condition that is responsible for 85-90% of AMD related vision loss.

As a result of these findings, the scientists hope to move forward to a larger phase 3 clinical trial to evaluate this therapeutic effect in a larger patient population.

### **Lucentis "Super Dose"**

Genentech's HARBOR trial has revealed that a higher dose of Lucentis (ranibizumab) for treatment of wet AMD has been found to be more effective in fifty "incomplete responders" over 24 months. "Incomplete responders" are individuals who have shown no appreciable response to the normal treatment. Intravitreal injection with 2.0 mg, however, rather than the current 0.5 mg, led to a significant decrease in retinal thickness (swelling) after the first 3 months, plus a 4-letter gain after 8 weeks. This improvement was maintained up to one year with no serious adverse events.

### **AL-8309**

Alcon Pharmaceuticals Company is developing a topical drug, AL-8309, which, when given one to two times daily has been shown to block the inflammatory response in rodent retinas exposed to blue light. Since inflammation is thought to be a contributor to development of AMD, and since AL-8309 inhibits the complement system that initiates inflammation, the drug is showing promise as a potentially effective treatment for dry AMD.

### **VEGF Trap-Eye**

Regeneron Pharmaceuticals, Inc. and Bayer Health Care, have entered phase 3 trials comparing the anti-angiogenic drug, VEGF Trap-Eye, with Lucentis for treatment of wet AMD, central retinal vein occlusion (CRVO), and diabetic macular edema (DME). The drug is expected to improve patients' visual acuity over time without the need for monthly intravitreal injections.

In the Phase 3 GALILEO study, patients with CRVO received six monthly injections of either VEGF Trap-Eye at a dose of 2mg or sham injections. At the primary endpoint patients gained 15 letters of vision from baseline. At a secondary endpoint they gained, on average, 18 letters of vision. These early findings showed that VEGF Trap-Eye has the potential to provide patients and physicians a new treatment option for central retinal vein occlusion.

Regeneron is now seeking marketing approval for treatment of CRVO in the United States. Bayer HealthCare is planning to submit regulatory applications in Europe in 2012.

### **Lucentis**

The current treatment protocol is recognized by the company as a burden on patients. Researchers are, therefore, working on ways to improve the delivery method. One possibility is reduction of frequency of injections.

Practitioners are finding that not all patients are responding as expected with Lucentis. About 10% of patients have actually lost 2-3 lines of acuity after treatment. To address this

issue, the new DAWN study will identify ahead of time, by means of a blood test, how well a patient will respond to the drug. Treatment could then be adjusted for best benefit. Genentech scientists are also looking at potential genetic causes for those patients who are not responsive to Lucentis.

As a side note, Novartis Pharmaceuticals Corporation is initiating a 5-year patient management study (LUMINOUS) to gain further understanding of long-term effectiveness of Lucentis, treatment patterns, long term safety, and health-related quality of life issues. The study was launched in 34 countries in March 2011.

## **NT-501**

Another drug, NT-501, developed by Neurotech, is a treatment designed to protect, and in some cases rescue, dying photoreceptors in the retina in order to preserve vision. This treatment relies on a growth factor produced by the human body called neurotrophic factor (CNTF). Human cells engineered to produce CNTF are implanted in the eye in a tiny specially designed capsule which protects these cells from the patient's immune system and continually releases a small amount of the growth factor. Neurotech has announced that this so-called encapsulated cell technology (ECT) has completed Phase 3 trials with good results.

There have been no serious ill effects associated with the treatment or with having the capsule implanted. NT-501 is also being tested as a treatment for other retinal degenerative disorders including retinitis pigmentosa.

## **New Treatment Possible for Dry AMD**

A new study published in the February 2011 journal Nature reports that dysfunction of an enzyme called DICER1 may be a cause of geographic atrophy (dry AMD). Researchers at the University of Kentucky found that levels of the enzyme are higher in healthy retinas than in eyes affected by AMD. They demonstrated that low DICER1 levels lead to buildup of a toxic genetic material called alu. This, in turn, causes geographic atrophy (dry AMD).

Two treatments may potentially halt the progression of the disease: one which boosts levels of the enzyme, and the other which breaks down the toxic Alu RNA. To test the hypothesis, the University of Kentucky is planning to start human trials by the end of 2011.

## **SURGERY**

### **Human Retinal Cells Developed From Non-embryonic Stem Cells**

On March 24, 2011, Georgetown University Medical Center reported in the journal "Stem Cells" that their researchers have, for the first time, produced retinal cells from human induced pluripotent stem (hiPS) cells, rather than embryonic stem cells. hiPS cells are derived from the patient's own body, thus bypassing the moral issue of using human embryos.

This is an important step in the research, but several viability and safety issues still need attention before hiPS cells can be introduced into humans.

### **Microplasmin for vitreal adhesion**

A single intravitreal injection of a new drug called microplasmin has been shown in Thrombogenics' Phase 3 trials to relieve adhesion of the vitreous (the gel that fills the inside

of the eye) to the inside of the retina. This reduces risk of damage from the tugging of the vitreous on the retina, which can lead to such conditions as diabetic vitreous hemorrhage and macular hole. It accomplishes this by inducing a gentle post vitreous detachment (PVD), and that can help eliminate the need for surgery to remove the vitreous from the eye.

### **Implantable Miniature Telescope Approved**

VisionCare Ophthalmic Technologies, Inc. announced on July 6 that the FDA approved the company's Implantable Miniature Telescope to improve vision in patients with end-stage AMD.

The telescope implant is designed to improve visual acuity. The magnification provided by the implant reduces the impact of the blind spot caused by end-stage AMD.

VisionCare will conduct a post-approval study to monitor patient outcomes under commercial conditions. A second smaller study will follow clinical trial patients for an additional two years.

VisionCare is submitting an application to the Centers of Medicare and Medicaid Services for a new code to establish Medicare beneficiary access to this implantation procedure. For more information about the telescope implant and related treatment program, see [www.centrasight.com](http://www.centrasight.com).

### **Radiation Therapy Continues To Show Promise**

In October, NeoVista made public the company's one-year results from the preliminary study MERITAGE-I. The study was designed to examine their radiation procedure (epimacular brachytherapy) for patients undergoing chronic therapy with anti-VEGF agents for wet AMD. Study results showed that a single radiation treatment stabilized visual acuity in 79% of this patient population, while decreasing the number of anti-VEGF injections required. Most importantly, 47% of patients enrolled in the study experienced some improvement in their visual acuity, while 10% of patients gained 15 or more letters of visual acuity at 12 months.

The study results also pointed to a favorable trend with respect to a reduced number of anti-VEGF injections following delivery of radiation versus the period of time leading up to the intervention. In addition, 25% of patients remained injection-free at 12 months following the procedure.

## **NUTRITION**

### **AREDS2**

The National Eye Institute's second Age-Related Eye Disease Study (AREDS2) is continuing. The original AREDS formula was approved in 1998. This time, subjects are being given a slightly altered formula containing the original vitamin dosages minus beta-carotene, a lower dosage of zinc, and addition of lutein, zeaxanthin and omega-3. The purpose is to see if the revised formula will help even more to slow the progression of AMD to the advanced stages. The new study began in June 2008, and results are expected in the year 2013. Meanwhile, many nutraceutical companies have gone ahead and updated their products to reflect the more current research. It is advisable to discuss with all of your professional care providers any additions or changes in your diet or supplementation.

## **TECHNOLOGY**

## **iPad2**

The most common complaint about low vision technology is the high price of assistive devices. With government assistance available only to veterans, many people simply cannot afford to purchase the products that can make their lives so much easier. With this year's introduction of Apple's new iPad 2, however, that has almost become a non-issue.

For less than half the cost of most electronic magnifiers, visually impaired people can now own virtually every low vision gadget all wrapped up in a device no larger than a thin book. The iPad2 can read to you in 21 languages, magnify images and text, tell you what color your shirt is, guide you across town, magnify the face of your grandchild, call a friend, shop online, manage your finances, identify currency, help you type a letter, read Braille, tell the date and time, and so much more. And it can all be done using tactile buttons or touch screen controls. Apple also offers a year of personal training on the iPad2 for \$99.

This has set the standard, and we can now expect more advances at even lower prices to come our way. And if that doesn't brighten your day, read on:

## **Driving Blind**

The National Federation of the Blind announced on January 29, 2011 that, for the first time, a blind individual has driven a street vehicle in public without the assistance of a sighted person.

The car was equipped with laser range-finding sensors that conveyed information to a computer inside the vehicle, allowing it to create and constantly update a three-dimensional map of the road environment. The computer sent directions to vibrating gloves on the driver's hands, indicating which way to steer, and to a vibrating strip on which he was seated, indicating when to speed up, slow down, or stop.

Also this past year, Google revealed it's own version of what they call an autonomous vehicle. The company has been working in secret on vehicles that can drive themselves.

According to the New York Times, seven Google test cars have driven 1,000 miles without human intervention and more than 140,000 miles with only occasional human control. One even drove itself down Lombard Street in San Francisco, one of the steepest and curviest streets in the nation. The only accident, engineers said, was when one Google car was rear-ended while stopped at a traffic light.

They say this technology may be available to the public in eight years. If that happens, one of the thorniest problems of low vision, transportation, will no longer be an issue.

## **AMD Numbers Continue to Fall**

"The number of Americans with macular degeneration fell 30 percent in about two decades," according to a study published in the January issue of the Archives of Ophthalmology, "reducing the threat from the leading cause of [visual impairment] among the elderly."

The study authors explained that "Reductions in smoking and blood pressure, key risks for the condition, and increased use of antioxidant vitamins that keep the disease at bay may account for the decline". The study also revealed that the rate of advanced AMD among all the participants was 0.8 percent, and that AMD affects approximately 6.5% of adults ages 40

and over, compared with the previous estimate of 9.4%.

Data was obtained from 7,081 people, aged 40 and older, who took part in the 2005 to 2008 National Health and Nutrition Examination Survey.

Other research has been confirming this trend. In 2007, a study found a lower 5-year incidence of early AMD in patients born or examined more recently, compared to similarly aged persons born or examined in an earlier period. 2,968 participants with early AMD and 3,588 participants with late stage AMD were examined at 5-year intervals between 1988 and 2005 as part of the Beaver Dam Eye Study.

Then, in 2010, a study reported to the Association for Research in Vision and Ophthalmology showed a 68% lower incidence of macular degeneration in the Baby Boom population. That research suggested that improvements in environment, behaviors, and other such modifiable factors may have contributed to the results. The "birth cohort" effect remained even after adjusting for AMD risk factors such as obesity, heavy drinking, and sunlight exposure.

The results of this research further emphasize the importance of environmental and lifestyle factors to retinal health.

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This wraps up my summary for this year. I hope you will share this information with your family, friends, and doctors. You are in a position to help others understand, and by doing so, you will be serving a valuable purpose. Thank you for your help!