



## Bright Spot on Geographic Atrophy Map

**O**VER 200,000 PEOPLE in the U.S. each year develop the “wet” or neovascular form of AMD in which growth factors cause scar tissue to replace the center of the retina, the light-sensitive tissue lining the inside back of the eye. Unlike their wet AMD counterparts, whose vision loss often can be stopped with periodic injections of anti-growth factor agents into the middle cavity of the eye, patients with geographic atrophy, the “dry” form of AMD associated with vision loss, traditionally have been left without any treatment options.

With geographic atrophy, patients may lose vision when abnormal yellowish material, termed drusen, accumulates below the center of the retina for years if not decades, ultimately causing the overlying retina to disintegrate. Since retina tissue does not replace itself once lost, dry AMD can cause irreversible blank spots in the vision to interfere with reading, driving, and recognizing faces.

This blinding condition can cause substantial vision loss for at least 20,000 additional people each year, according to **Neil Bressler, MD**, the James P. Gills Professor of Ophthalmology and Chief of the Retina Division. Now, with Dr. Bressler chairing the Executive Advisory Committee of two studies



**Dr. Bressler, left, and Dr. Campochiaro**

involving over 300 sites worldwide including Johns Hopkins University, investigators at Wilmer are taking part in a landmark trial with a treatment that appears promising for slowing the worsening of geographic atrophy.

“One of theories behind the degeneration is that it’s related to an inflammatory pathway in the body known as the complement pathway,” Dr. Bressler says. So, the hope is that an anti-complement factor, injected periodically into the middle cavity of the eye might slow down this rate of atrophy, he explains.

While the pace of atrophy

worsening can be different among individuals, in a preliminary, company-conducted study of this agent known as lomalizumab (Roche/Genentech), investigators found that this agent, compared with no treatment, slowed visual loss more often than might be expected by chance variation among individuals. “The average deterioration that occurred in the people who received the injection of the anti-complement factor, their loss of tissue, was slower than in those who got no treatment at all,” Dr. Bressler says. “However, the study was not designed to be definitive, and it’s still possible that the difference noted was due to chance alone.”

Now, Wilmer investigators are collaborating with Roche/Genentech on a definitive study to determine if the lomalizumab is really effective and safe to warrant its use as part of standard care for this dry form of AMD. The study will also tap the expertise of, **Peter Campochiaro, MD**, the George S. and Dolores Dor Eccles Professor of Ophthalmology, who will be the principal investigator of the clinical site at Wilmer, one of the sites worldwide participating in the study.

After the lomalizumab has been injected into the eye, much of it may be gone in about 30 days. It

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## Eye Tumors May Hold a Key to Better Understanding Cancer



Each year, patients travel from all over the world to be treated at Wilmer for vision-threatening and life-threatening forms of eye cancer. **Mary Beth Aronow, MD**, Assistant Professor of Ophthalmology, has been interested in the field of ophthalmic oncology since attending

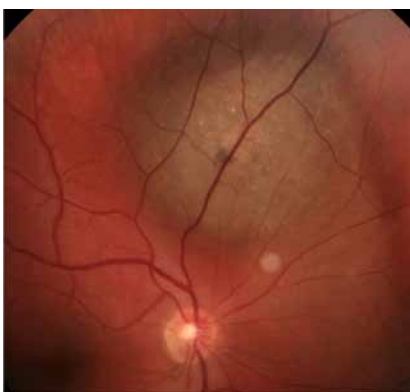
medical school at Yale University. “The eye is one of the only places where you can see a tumor in its near entirety,” she says. “This provides a unique opportunity to visualize tumors as they are responding to therapy.” Eye tumors are an excellent model for studying the clinical behavior of cancer and for developing improved treatment strategies for patients.

Dr. Aronow came to Wilmer from the Cleveland Clinic where she trained in ophthalmic oncology and most recently from the National Eye Institute, National Institutes of Health, where she pursued fellowship training in medical retina.

At Wilmer, Dr. Aronow is treating the spectrum of intraocular tumors. She has instituted a research program to advance our understanding of uveal melanoma. “Once this tumor metastasizes outside of the

eye, we do not have good therapies,” she says, adding that better adjuvant therapies for individuals with high risk uveal melanoma are needed. In recent years, many centers have implemented adjuvant treatment trials. “I would like to see Johns Hopkins be among these,” Dr. Aronow says.

Retinoblastoma is the most common primary intraocular tumor in children. Johns Hopkins is one of just a few institutions worldwide that offers intra-arterial chemotherapy, a highly localized form of treatment, to



**Choroidal melanoma with characteristic orange pigment and subretinal fluid.**

children with this life-threatening condition. Dr. Aronow is pleased to have access to this approach. With excellent available therapies, nearly all children in the US with retinoblastoma survive and retain good vision in many cases. ■

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## Dry AMD under the Microscope



While there’s currently no way to head off dry AMD, a common cause of blindness in Western cultures, **James T. Handa, MD**, Robert Bond Welch Professor of Ophthalmology, is hard at work trying to understand how the disease develops.

His team is studying how

oxidative stress magnifies the immune response and leads to macular deterioration. “When there’s too much oxidative stress in the eye or in other areas of the body, the immune response converts from a protective one to being overactive,” Dr. Handa says. Or, this response can fail altogether, causing tissue injury and leading to macular degeneration, he explains.

Also, he is examining how the Nrf2 system, which is a factor in our cells (a “transcription” factor) that protects cells and in this case turns on a system of antioxidant genes, may be involved. “In our macular degeneration samples, as well as in our animal model, we find that the Nrf2 response gets blunted with too much oxygen or with aging,” Dr.

Handa says. If this Nrf2 system fails, too great an immune response may create some tissue damage.

So, he is trying to determine where in the cell the damage is arising by comparing tissue damage in genetically-modified mice with Nrf2 to those without this. After exposing the mice to a cigarette-smoke stressor, he will determine if macular degeneration is magnified when the Nrf2 system is failing and test whether some drugs can rejuvenate the system.

In other work, he is considering whether complement, which is part of the immune system, when genetically impaired, may be contributing to AMD. Complement-factor H is known to help regulate

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# Home-field Advantage Found for Monitoring Patients with AMD

**F**OR THOSE OVER AGE 50, THE “wet” or choroidal neovascular form of age-related macular degeneration is the leading cause of blindness throughout most of the developed world. If this disease is left untreated, the vast majority of eyes will become legally blind. Yet, when appropriate treatment is given, vision can be maintained at the presenting level in 90% of cases for at least several years, with about 30% of these patients even able to improve somewhat from the level of vision at which they present to the eye doctor.

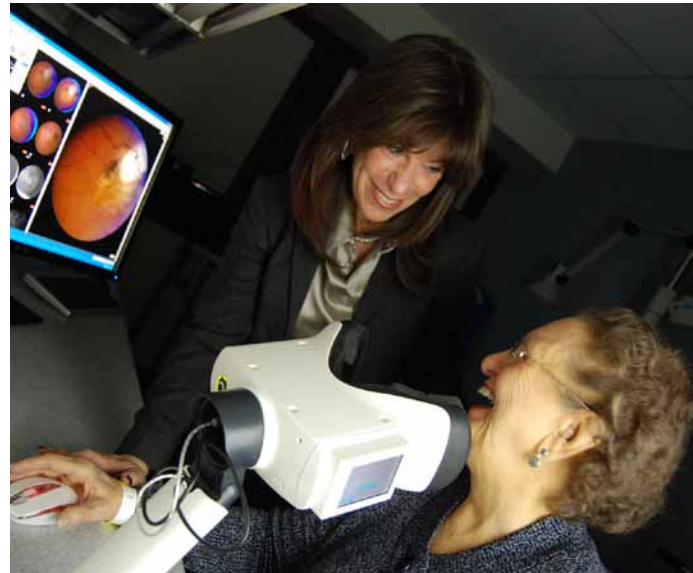
“Since we have a therapy that can maintain vision in 90% of people affected by neovascular (wet) AMD, the critical issue shifts to early diagnosis of this aspect of the disease,” stresses **Susan B. Bressler, MD**, the Julia G. Levy PhD Professor of Ophthalmology at Wilmer.

Dr. Bressler has been one of the leaders in a clinical trial evaluating the efficacy of a home monitoring strategy that uses the ForeseeHome (Notal Vision, Inc.) device, which was developed with initial tests at Wilmer several years ago to try to identify when eyes with AMD have progressed to wet macular degeneration as early as possible.

This device can monitor the central field of vision in each patient’s eyes and transmit these results via tele-monitoring to a remote monitoring center. Regular test results are monitored for changes that may signify the start of wet AMD. In a recent study of the ForeseeHome strategy, half of the trial participants chosen

by the process of randomization, like a flip of the coin, were asked to use the device daily in conjunction with traditional monocular vision function testing, such as use of an Amsler grid, while the other half used traditional testing alone. Both groups also received pre-scheduled office visits to monitor for AMD progression following the usual practice recommendations of their individual physician.

“When study participants developed wet macular degeneration, the event, worsening of their AMD, appeared to be picked up earlier if they were using the device plus standard care as compared to standard care alone,” Dr. Bressler says. Those assigned to the device group had a median loss of 4 letters on the eye chart when their AMD progressed to the neovascular phase as compared with a median loss of 9 letters for those individuals using traditional monitoring without the



**A patient is pleased with the ease of monitoring her own vision from home using the ForeseeHome device (pictured with Dr. Susan Bressler, left).**

home device, a substantial difference. Dr. Bressler terms this difference clinically meaningful since the device allowed most patients to maintain vision of 20/40 or better at the time their neovascular AMD was diagnosed, a level that is not associated with driving restrictions and is consistent with the absence of any substantial visual impairment. With prompt initiation of wet AMD treatment in these eyes, there is a high probability these patients will avoid meaningful compromise in their everyday life functions.

Dr. Bressler views the results here as having great import. “This is the only home monitoring system that really has been demonstrated to make a difference in picking up neovascular AMD early,” she says. The ForeseeHome system is already FDA-approved and Dr. Bressler is hopeful that it ultimately will be covered by all medical insurance companies. ■

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# Fluid Treatment Boundaries for Central Serous Chorioretinopathy



Deciding when to initiate treatment for patients with central serous chorioretinopathy is a vexing issue. With this condition, subretinal fluid collects and stresses the photoreceptor cells, the rods and cones, in the retina lining the inside back of the eye and which are critical to creating the image which we see. Patients typically have some decreased visual acuity. But even when this is not compromised, they may experience distortion and have reduced retinal sensitivity making dark objects look somewhat faded or gray. Indeed, some such eyes have been shown to have decreased cone density. Since most episodes resolve within 6 months, the standard care is to wait up to 6 months before

treating these patients.

**Catherine B. Meyerle, MD**, Assistant Professor of Ophthalmology at Wilmer, is now investigating the ideal timing of photodynamic therapy (PDT) here. PDT targets the increased choroidal hyper-permeability that can allow fluid to collect, she explains. The original PDT parameters were adapted from studies in age-related macular degeneration. “There have been multiple central serous chorioretinopathy studies refining these parameters, looking at reduced dose and reduced fluence. However, the ideal time to treat is still not known,” Dr. Meyerle says. “Perhaps earlier intervention would be more appropriate for these people.”

Dr. Meyerle is also looking into possible new treatments. Most novel treatments today focus on targeting the choroid, the layer of tissue that

provides blood vessel support to the rods and cones, but the retinal pigment epithelium, a layer of cells supporting the rods and cones, plays an important role too, she points out. “Treatment designed to promote better retinal pigment epithelial function also might be valuable,” she says.

In Dr. Meyerle’s view, central serous chorioretinopathy remains undertreated. In 30% to 50% of cases, fluid recurs and may lead to damage with every episode, she points out. “While patient’s visual acuity may be reasonable on standard testing with a high contrast eye chart, I think these people have issues with sensitivity to subtle changes in contrast and distortion of vision, where images have a wavy appearance,” she says. “I think earlier intervention would help these patients.” ■

## Part of the new crowd: Christopher J. Brady



For **Christopher J. Brady, MD**, a new face on the Wilmer faculty as of August 1st, but returning to Hopkins where he received his M.D. degree, the idea of bringing the wisdom of many to interpretation of potential diabetic retinopathy fundus photos is appealing. Dr. Brady, who recently finished his retina fellowship including state-of-the-art retinal surgical training at Wills Eye Hospital in Philadelphia, worked on a pilot telemedicine project there involving “crowdsourcing.” This screening project is one he hopes to expand on at the two clinics where he will be working, Wilmer within the Johns Hopkins Hospital and the Wilmer Bethesda satellite office.

The premise of his research is to try to figure out within mass public screening whether it’s possible to decentralize the interpretation of photographs of the retina, the light-sensitive tissue of the back of the eye, and harness the power of many through the Internet.

With this, he explains, individuals do small Internet-based tasks for minimal compensation, making it affordable to communities world-wide to have screening for damage to the retina from diabetes.

Dr. Brady started out by recruiting 10 anonymous people per selected fundus photograph to render their interpretation and compared this to an expert’s findings. “People did much better than I expected,” he says. “If they made a mistake, typically it was that they overestimated level of retinopathy.” Later, with a larger, more subtle data set, the crowd still reliably detected higher levels of disease, but did struggle with more subtle diabetic retinopathy cases. His work already has been recognized as award-winning research within the specialty society of retina physicians in the U.S. and published in the peer-reviewed literature.

Now at Wilmer, Dr. Brady would like to broaden the scope of this work. He hopes to get access to additional data sets which allow him to try out this approach on real patients

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## Sights on New Diabetic Treatment Target



For patients with diabetic eye disease, the threat of blindness is ever present. However, research being conducted by **Akrit Sodhi, MD, PhD**, Assistant Professor of Ophthalmology, seeks to change this. One of the major focuses of Dr. Sodhi's work at the Wilmer Eye

Institute is on looking for novel treatment targets for patients with diabetic eye disease.

Already he has helped identify an important new gene known as Angiopoietin-like 4 (ANGPTL4). Dr. Sodhi and fellow investigators are honing in on this factor, which is increased in diabetic ocular conditions. "We're currently looking at the possibility of inhibiting this target to treat both diabetic macular edema and diabetic retinopathy," Dr. Sodhi says.

Findings have shown that expression of the ANGPTL4 gene increases for the same reason that VEGF (Vascular Endothelial Growth Factor) becomes elevated. Both are increased by the hypoxia-

inducible factor (HIF), a transcriptional enhancer activated by low oxygen, which raises the levels of "HIF-target" genes. "One of those genes is VEGF and this unfortunately has some negative consequences in the retina including the growth of leaky blood vessels that promotes both macular edema and also neovascularization," Dr. Sodhi explains.

Likewise, Dr. Sodhi's group has shown that increased expression of ANGPTL4 can have similar consequences. Dr. Sodhi theorizes that the reason that many diabetic patients don't respond adequately to anti-VEGF treatment alone may be because ANGPTL4 also plays an important role in diabetic eye disease.

Dr. Sodhi and fellow investigators are studying other factors as well, looking for potential new diagnostic and treatment approaches revolving around HIF, and considering potential therapies to block these new targets. "Our hope is that this will allow for more safe and effective treatment of patients with diabetic eye disease," Dr. Sodhi concludes. ■

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### Bright spot *continued from page 1*

currently is unknown how long the anti-complement factor needs to be given. So, to determine how often this agent might be needed, in the definitive trial, some patients will receive the drug every 4 weeks, while others will get this every six weeks instead, he explains. If both intervals are found to work, even longer periods between injections might be warranted in future studies.

Besides potentially confirming the preliminary results seen in the recently completed preliminary trial, investigators at Wilmer and elsewhere also will look at other parameters such as the impact of the treatment on reading, Dr. Bressler notes.

Dr. Campochiaro emphasizes that not all patients may get the

same effect from the drug. Some who have a variation in the gene for complement factor I may be predisposed to damage from geographic atrophy, he points out. "Such people may be more susceptible to complement-induced damage, including disease processes like AMD where complement may be involved in the death of RPE cells," he says. Such patients might be more likely to benefit from injections of Lampalizumab. To investigate this hypothesis, patients will be have testing to determine whether they have variations in the complement factor I gene.

While patients are just beginning to be recruited, Dr. Campochiaro is already optimistic. "For so long we haven't had any treatment and

now we have a hint that complement is involved. Then on top of that we have data from an early phase trial that has provided the first proof of concept in humans that suppressing the complement pathway with Lampalizumab may slow progression," Dr. Campochiaro says. "All of this makes us quite excited about this trial, which I think offers the first glimmer of hope for patients who have geographic atrophy."

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Those at Wilmer interested in participating in the geographic atrophy study can contact Dr. Campochiaro (pcampo@jhmi.edu) or Dr. Gulnar Hafiz (ghafiz@jhmi.edu), head coordinator of many retina clinical trials in the Retina Division. ■

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## Conquering Retinal Degeneration



Retinal degeneration from retinitis pigmentosa to Stargardt disease and more, threatens the sight of millions of

vulnerable patients around the world. The Wilmer Eye Institute is now welcoming back **Syed Mahmood Shah, MD**, who will be working together with Hendrik Scholl, MD, the Dr. Frieda Derdeyn Bambas Professor of Ophthalmology, to help tackle such conditions. Dr. Shah is not new to Wilmer and started his career here as part of pioneering research on developing anti-VEGF treatment for both age-related macular degeneration and diabetic macular edema.

He has now returned to help look for answers on the genetic aspects of retinal degeneration. “I believe the genes hold the key to not only the origins of the diseases but the treatments as well,” Dr. Shah says. During his fellowship, he had the opportunity to work with Dr. Scholl who he describes as a foremost expert on retinal degeneration, and now he

is excited to join forces of one of the largest groups in this field of clinical care and research.

Dr. Scholl is looking forward to this as well. He says the pair is slated to work on several groundbreaking trials. “One will be the first gene therapy at Wilmer for retinal degeneration called the StarGen project,” Dr. Scholl says. This will entail treatment for *Stargardt* disease while a second trial, UshStat, will focus on Usher syndrome. “So, we would establish gene therapy at Wilmer to treat those two conditions,” Dr. Scholl says. “Another program that we are working on together is the first pharmacotherapy for *Stargardt* disease.”

Meanwhile, Dr. Shah notes that the pair will also be focusing on developing outcome measures to detect the progression of diseases which will allow investigators to evaluate efficacy of new treatments in the shortest possible time. Ultimately, Dr. Shah is also excited about honing in on treatment here, which he is hopeful can one day be tailored to individual patients based on their genetic profile. ■

**Dry AMD** *continued from page 2*  
the strength of the immune response. However, Dr. Handa hypothesizes that impairment of 2 regulators, which control the activity of complement, may be needed before the system becomes overactive. Using mice with genetic mutations, he is testing whether impairing other complement regulators with cigarette smoke may cause something that looks like macular degeneration.

If his results substantiate this, prevention may come down to trying to reduce the oxidative-stress load. Also, if there are found to be multiple complement regulators impaired in AMD, this would give investigators a better idea what to target for treatment involving the complement system. ■

**New Crowd** *continued from page 3*  
being screened and more. “I’d like to figure out how I can teach the crowd new things and ask them new questions,” he says, adding that from there he hopes to find a way to garner FDA approval in this uncharted territory. ■