



Adrienne Scott, M.D.

Seeing Sickle Cell Retinopathy Anew

Adrienne Scott, M.D., chose to join the ranks of retina specialists because, she says, they are known as “the Marines of the eyes. We’re the people they call in when an urgent problem arises.” An assistant professor of ophthalmology in Wilmer’s Retina Division, Scott also serves as the chief of the Wilmer satellite office in Bel Air.

While she sees patients with all manner of retinal diseases, she has a specific interest in sickle cell retinopathy, a condition caused by sickle cell disease. Inspired by a patient who passed away a few

years ago from complications of sickle cell disease who told her “we need to cure this,” Scott decided to dedicate herself to studying sickle cell retinopathy.

The most commonly inherited

blood disorder, sickle cell disease occurs when the normally spherical-shaped red blood cells have a sickle shape, which deprives body parts of oxygen. “Sickle cell patients can have problems with every organ system in the body, but the eyes are particularly vulnerable given all the

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“I hear from people over and over, ‘You can take any sense of mine, but I cannot lose my eyesight.’”

Artificial Intelligence Achievements

From the Desk of Neil Bressler, M.D., Chief of the Retina Division:

ACCORDING TO A recently published article by Retina Division specialist **Adrienne Scott, M.D.**, Americans regard losing eyesight as having the greatest impact on their daily lives. The physicians of Wilmer's Retina Division, one of the largest university-based retina practices in the U.S., dedicate their time, energy and passion to combatting retinal diseases to preserve vision.

The research by the clinician-scientists of the Retina Division spans investigations from the laboratory to the clinic and frequently leads to publication in the nation's top medical journals. In addition, each year hundreds of patients seen by doctors in the Retina Division participate in clinical trials to help move the field forward.

Retina Division physicians disseminate the knowledge gleaned from their research through courses taught to thousands of other ophthalmologists, both in Baltimore and around the world each year. And while the Retina Division has been very successful at obtaining competitive research dollars from government and industry, these sources continue to be at risk of shrinking, making it even more important to continue to secure the very generous support provided by donors.

We share the successes and plans for that support in this *Retina Rounds* to keep you up-to-date on research and treatments that could have a substantial impact on your daily lives! ■



ARTIFICIAL INTELLIGENCE has become a new player in health care and one that **Neil Bressler, M.D.**, Wilmer's James P. Gills Professor of Ophthalmology and chief of the Retina Division, sees as an ally in the battle to save the vision of people with age-related macular degeneration (AMD) and other retinal diseases. How? By diagnosing the cases early enough that intervention can succeed.

"There are eight million people who have an earlier, often asymptomatic stage of AMD that need careful monitoring, but we estimate only about four million of them know they have it," says Bressler. He and his lab have teamed with the Johns Hopkins Applied Physics Lab to create Deep Convolutional Neural Networks (DCNNs), which are computer programs, to recognize the hallmark of AMD—drusen—on

fundus images of the retina. Drusen are debris accumulating behind the retina, the light-sensitive tissue that lines the inside back wall of the eye.

DCNNs fall under the umbrella of machine learning, a field that seeks to teach computers to teach themselves new information using generic algorithms that can be applied to a wide range of data sets. What Bressler's DCNN teaches itself is how to recognize drusen.

Accuracy in Diagnosing AMD

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According to Bressler, the DCNN is told what the “ground truth is” by viewing images fed to it of fundus photographs of the retina—these images are referred to as the

“training data set.” While viewing the training data set, the DCNN is told, ‘This fundus image has drusen, this one does not.’ After viewing thousands of sets of images, the program learns to sort the images into the two categories with increased accuracy.

Once the DCNN is trained, researchers feed it images without telling it, ‘This fundus image shows drusen, this one does not.’ Because the program has seen and sorted enough images in the training data set, it accurately recognizes images of drusen it has not seen before.

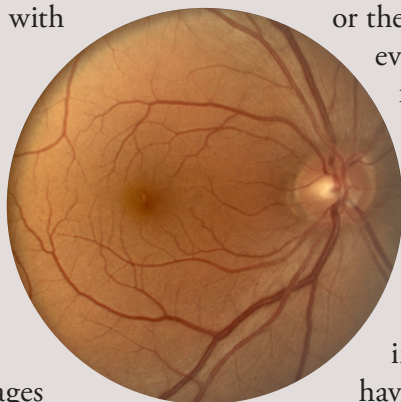
“What makes this artificial intelligence is that you’re not programming it and then it does its thing. You’re programming it to

program or teach itself,” says Bressler.

Bressler’s lab recently published the results of its efforts, which found that the DCNN accurately identified AMD between 88.4 percent and 91.6 percent of the time, in *JAMA (Journal of the American Medical Association) Ophthalmology*. Such accuracy is comparable with human expert performance levels.

Once the DCNNs become as accurate as possible, then Bressler sees an opportunity for pieces of optical equipment—perhaps attachments to smartphones or kiosks in drug stores—to be created that can capture the fundus images in a cost-effective way.

“We don’t have the resources or the personnel to get to everybody and screen for asymptomatic, common retinal diseases that need monitoring or treatment,” says Bressler. “But if we can find very inexpensive ways to have the images analyzed to indicate, ‘This person has a high likelihood to need monitoring for AMD, but that person doesn’t,’ that has the potential to help an enormous number of people around the world.” ■



A healthy retina

Sickle Cell continued from page 1
small vessels, especially within the retina,” says Scott.

With the arrival of new imaging techniques—such as optical coherence tomography (OCT) angiography—that can help visualize the retina in finer detail than ever before, Scott believes research into sickle cell retinopathy is poised for a breakthrough. “We’re using OCT angiography to visualize blood flow at a very detailed level. And we can not only visualize blood flow, but also in the case of sickle cell retinopathy, we can visualize lack of blood flow in the retinal circulation,” says Scott.

Traditionally, sickle cell retinopathy has been considered a disease of the periphery of the retina—and damage to this area causes the most severe vision loss. With OCT angiography, however, Scott has seen changes in the blood flow around the macula—the part of the retina responsible for central vision.

If Scott finds a correlation between lack of blood flow to the macula, which OCT angiography can visualize quite clearly, and lack of blood flow to the periphery of the retina, this could help doctors treat patients more effectively. OCT angiography could serve as a fast and noninvasive screening tool to predict which patients could be most at risk for future vision loss and thus require closer monitoring.

That would be a welcome development for this clinician-scientist whose focus on her patients propels her work. “I hear from people over and over, ‘You can take any sense of mine, but I cannot lose my eyesight,’” Scott says. “It’s a very critical sense and it’s an honor to be able to try to maintain that.” ■

Neil Bressler, M.D.

Looking for Common Ground

THE HUMAN BODY IS complex. The division of medical practice into subspecialties, focusing on the intricacies of a single organ or organ system, is one way health care has evolved to handle this fact. This solution, however, has its limits. And as medical research has progressed, the pendulum has begun to swing the other way—toward emphasizing the similarities between organ systems and the connections between specialties.

Such a shift makes sense to **Mira M. Sachdeva, M.D., Ph.D.**, who recently joined Wilmer’s Retina Division. As a retina specialist, Sachdeva sees these connections every day. “You’re literally looking at part of the brain by looking into the eye. The retina is an extension of the brain,” she explains. To that end, she recently began a research project under the mentorship of a neurologist at Johns Hopkins, Ted M. Dawson, M.D., Ph.D.—“a world expert in neurodegenerative diseases, specifically Parkinson’s,” says Sachdeva.

Why is a retina specialist interested in Parkinson’s disease? The mitochondria.

Frequently referred to as the “powerhouses” of the cell, mitochondria break down nutrients (fats, sugars, proteins) taken in by the cell and combine these with oxygen to create energy-rich molecules. “I’m interested in how mitochondrial metabolism in the retina affects cell survival and how abnormalities in this can lead to cell death and loss of retinal tissue,” says Sachdeva. “Even though the specific layer of the retina involved may differ, retinal neuronal death



Mira M. Sachdeva, M.D., Ph.D.

is essentially the endpoint of many retinal diseases, including macular degeneration and diabetic retinopathy. My goal is to identify new strategies to protect retinal neurons.”

Mitochondrial dysfunction plays a critical role in Parkinson’s disease as well, which is where Dawson’s research comes into play. “Dr. Dawson studies pathways of mitochondrial function in the dopamine-producing neurons in the brain that, when perturbed, contribute to neurodegeneration in Parkinson’s disease,” says Sachdeva. “I’m starting to look at whether there are parallel pathways in the retina that contribute to retinal neurodegeneration in diabetes.”

She thinks this line of inquiry could complement the existing focus of diabetic retinopathy research and treatment—which is on retinal blood vessels. Abnormalities in the retinal blood vessels are the diagnostic hallmark of the disease, Sachdeva says. And current treatments for diabetic retinopathy, such as anti-vascular endothelial growth factor (anti-VEGF), target those blood vessels.

“But there’s more and more evidence coming out that even before you see changes in blood vessels in patients with diabetes, you can see loss of retinal neurons. No one knows what causes this early retinal neurodegeneration in diabetes,” she says. “And if we could target another pathway and even another cell type, we might be able to prevent vision loss further. It’s exciting.” ■

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Harnessing the Super Power of Viruses

FOR THE CLINICIAN-SCIENTISTS at Wilmer, seeing patients has two benefits: making a difference in people's lives and creating a guide for lab research. "Because I treat patients in the clinic, I know the really pressing problems, the unmet needs that patients have," says **Peter Campochiaro, M.D.**, the George S. and Dolores Doré Eccles Professor of Ophthalmology and Neuroscience. "That has helped me to focus my laboratory work."

One of those needs is controlling a protein called vascular endothelial growth factor (VEGF), which plays a critical role in causing a number of retinal diseases, from neovascular age-related macular degeneration to diabetic macular edema. Since 2006, however, a doctor has been able to meet this need with anti-VEGF injections, which contain antibodies and proteins that bind to VEGF, in the vitreous of a patient's eye. "These proteins act like a sponge and soak up the VEGF," says Campochiaro.

While the anti-VEGF treatments are very effective compared with previous options, they are not without



Peter Campochiaro, M.D.

drawbacks. For many patients, especially those with macular degeneration, the therapy is usually effective for only four to six weeks at a time; thus, such patients must come in for shots frequently. Campochiaro is striving to eliminate this burden.

Rather than injecting the anti-VEGF directly into the eye, his strategy is to inject something that will produce the anti-VEGF within the cells of the eye—a virus.

"Viruses are very good at getting into cells," says Campochiaro. "We engineer the viruses so that we take out all of their inside machinery but we use the outside called the capsid, which is able to penetrate cells.

And we replace the bad viral genes with good genes that produce the therapeutic protein we now continually inject in the eye."

The therapy, which involves a 30-minute procedure, is now in a phase I/II clinical trial to test for both safety and efficacy. "We have a lot of indications that this treatment will produce the protein at a good level, for a very prolonged period of time," says Campochiaro—which could be life-changing for patients. "We could be able to reduce or eliminate injections in the majority of patients."

Campochiaro has worked on this solution as it has progressed from the lab to the clinical trial and has enjoyed the discoveries along the way. "When you find out something new that you can add to the body of scientific knowledge, it's really exciting," he says. "And then when you see how those new pieces of knowledge can add up to something that can help patients, then it really becomes rewarding." ■

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A New Frontier in Retinal Degeneration Research

ACTION. THAT IS THE NEW watchword for those who study, treat or suffer from retinal degenerative conditions, according to **Mandeep Singh, M.D., Ph.D., M.B.B.S.**, assistant professor of ophthalmology in Wilmer’s Retina Division. “In the past, with such chronic degenerative conditions, the main role of the physician was to support people through the process of visual change. But in recent years, it’s really become a field of positive action,” says Singh.

A giant hurdle was recently cleared with the launch of numerous clinical trials now available to patients. “For these conditions to be in good, well-run human clinical trials is a big threshold that we’ve crossed,” says Singh. “Finally, there’s a glimmer of hope that some of the ideas that have been incubating in labs for years are actually finding their way into trials.”

Singh sees Wilmer as a key player in this next phase of retinal

degeneration research because the institute is an academic medical center with “the right facilities, staff, expertise and number of patients” to qualify as a site to participate in these studies.

He also acknowledges the bravery of patients in this process. “For the patient to take the act of volunteering their body and their time and energy to be in a trial with so many unknowns is an act of tremendous courage and generosity,” says Singh.

Patients should be cautious when seeking clinical trial opportunities, however, Singh warns. He recommends consulting with a specialist to evaluate whether an experimental drug or procedure is “offered in the context of a well-run clinical trial, and has strong safety



Mandeep Singh, M.D., Ph.D., M.B.B.S

checks built in for the patients involved.”

Currently, clinical trials in stem cell therapy, gene therapy, electronic microchips and chemical compounds are in progress. “Name any other organ—from the liver to the spinal cord—where so many strategies are in clinical

trials,” says Singh. He implies that one cannot.

“Because of great partnerships between laboratories, industry and medical centers like ours, in the next decade we will hopefully see the approval of a range of new treatments for people with previously incurable conditions,” says Singh. “And we are honored, privileged and excited to be a site for clinical trial research in retinal degenerative diseases.” ■

To make a same-day appointment, call:
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