



**Irene Kuo, M.D., in the lobby of Wilmer, White Marsh, where she serves as chief**

## Keeping an Eye on Infection

**S**ay “adenovirus” and the heads of administrators of ophthalmology departments snap up. “They’re very hardy viruses,” says **Irene C. Kuo, M.D.**, chief of infection control and associate professor of ophthalmology at the Wilmer Eye Institute.

“They’re hard to eradicate from metal surfaces and plastics,” says Kuo. “And they can live up to 35 days on surfaces. I always tell patients be careful with the tongs at salad bars!” Other places of communal contact include elevator buttons, countertops and doorknobs, Kuo points out.

Although this family of viruses can attack multiple organs,

ophthalmologists are most concerned about adenovirus infections when seeing patients whom they suspect have viral conjunctivitis, often referred to as “pink eye” or “red eye.” Adenoviral conjunctivitis is a highly contagious eye infection. A particularly virulent category, epidemic keratoconjunctivitis, raises the most concern because it can cause permanent corneal scars and

chronic vision problems.

When Kuo became chief of infection control at Wilmer, she was tasked with developing an algorithm—or policy—for how to manage employees at the hospital who present with red eye. The policy prioritizes acting quickly when an employee has a red or pink eye. Of paramount importance is removing such employees from work and sending them to Johns Hopkins Occupational Health. If the nurse practitioners there believe the employee has adenoviral conjunctivitis based on signs and symptoms, they swab the employee’s

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# Providing Real Hope with Artificial Corneas



**Esen Akpek, M.D.**

**C**ORNEAL TRANSPLANTS ARE AMONG THE MOST successful organ transplantation procedures. This is wonderful news for people who live in places where donor corneas are plentiful and for patients who are good candidates for them. Unfortunately, many patients of **Esen Akpek, M.D.**, the Bendann Family Professor of Ophthalmology, do not fall into the latter category. Akpek sees patients at Wilmer's Ocular Surface Disease and Dry Eye Clinic, which she established in 2004.

For her patients, “the damage caused by their diseases means a transplant will likely end up failing,” says Akpek. In the U.S. alone, people in this situation—who need corneal transplants but are not good candidates—number 8,000 a year. Worldwide, that number reaches several million. In addition, donor corneal transplantation requires eye banking, which is expensive and not feasible in many developing countries.

Several years ago, W.L. Gore & Associates, a materials science company, approached Akpek to work on a solution for this unmet need. Akpek credits the reputation of the surgical team at Wilmer with attracting

the company's interest. “I was delighted. I thought—what a great idea because we have the clinical expertise and they have the material,” she says. The result is a new type of artificial cornea.

Currently, two products on the market referred to as ‘artificial corneas’ exist, but they each require a human donor cornea as a carrier material for a prosthesis. Without the human donor cornea attached to the prosthesis as a ‘carrier,’ the surgeon would not be able to suture the prosthesis into the eye because it is made of plastic. The partnership between Akpek and W.L. Gore, however, has yielded an entirely artificial device, with no donor cornea

**“I was delighted. I thought—what a great idea because we have the clinical expertise and they have the material.”**

needed. This means patients whose eye damage would likely lead to transplantation failure may soon have a different option.

The partnership joined each team's unique knowledge. “We modified their material based on our clinical and surgical expertise about what is

required for an ideal artificial cornea. We shaped it and jointly patented it,” says Akpek.

Though she cannot disclose the material, she can say that it is a derivative of Teflon. “It's inert material—like silicone—so the body won't reject it. And you don't have to immunosuppress the person,” says Akpek. “It's not going to become opaque, either. It will remain transparent.”

The “special cornea,” as Akpek calls it, behaves differently than the existing ‘artificial corneas.’ It bio-integrates into the recipient eye. “It's a combination of a porous skirt and a compact optical part. The skirt integrates into the surrounding recipient cornea. So, the special cornea forms a biological bond, which doesn't occur with any other devices,” says Akpek.

The team has been working on two prototypes for the past year and has just finished one set of preclinical experiments with “very good results,” according to Akpek. She estimates that her team could launch human clinical trials in about two years. “It might eventually replace all standard corneal transplants,” she says. “I don't see that happening next year, but I do see it happening in a few more years.” ■



# Teaming Up to Take on Battlefield Injuries



Samuel Yiu, M.D., Ph.D., and Kannan Rangaramanujam, Ph.D., in Wilmer's Smith Building

**W**HEN **Kannan Rangaramanujam, Ph.D.**, met **Samuel Yiu, M.D., Ph.D.**, they were about to become neighbors on the sixth floor of Wilmer's Robert H. and Clarice Smith Building—a research facility intentionally designed to bring about meetings of the minds.

“The moment we met and talked to each other, we realized how much we could do together,” says Kannan, Wilmer's Arnall Patz Distinguished Professor and co-director of the Center for Nanomedicine. “Samuel is a researcher, but he also does surgeries. He and I tried to figure out how we could bring the research that I was doing related to dendrimers to bat for surgical problems and dry eye disease.”

Dendrimers are molecules that

look “like a tree,” says Kannan. “My group, over the last 10 to 15 years, discovered that these dendrimers can target inflammatory cells. In the context of the eye, when you take the dendrimer and you apply it to the eye, the dendrimer specifically finds the injured cells in the cornea.”

Drug molecules can be attached to the dendrimers. An interesting characteristic of drug-loaded dendrimers is that they get picked up by only the injured cells. “Because the

drug is attached to the dendrimer, it doesn't get picked up by other cells. The goal is targeted, sustained drug delivery and reduced side effects,” says Kannan.

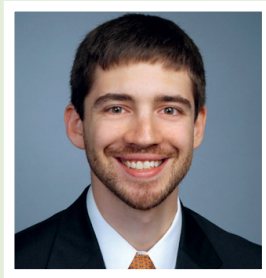
With that in mind, Yiu and Kannan brainstormed how best to use dendrimer-based therapeutic molecules. One project they came up with involves traumatic globe injuries in the context of battlefield injuries.

On the battlefield, life-threatening wounds are treated first. “When they come to the eye, if there's a hole there, traditionally there's nothing they can do. They put the gauze there and then transfer the soldier back to the hospital,” says Yiu. In addition, the first priority is to close the eye as quickly as possible. “If there is a

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## Meet Our Aliki Perroti Scholar... **Daniel Sarezky, M.D.**

**What is your focus?** There's so much to be learned in a cornea fellowship—whether it be different types of transplants, complex cataract and intraocular lens surgeries, or refractive procedures. In addition, I'm working on a project with Dr. Woreta focused on a



relatively new type of intraocular lens used in cataract surgery. This lens is supposed to have advantages over other types of secondary lenses—it

has four points of fixation as compared to the commonly used alternatives, which have just two points of fixation. We're doing a retrospective study to track the post-surgical outcomes of patients with this type of lens implanted.

**What are you excited about?** Ophthalmology has

had an unbelievable explosion of new technology in recent years, especially in the cornea subspecialty. I'm interested in looking at applications of this technology in an analytical way and figuring out how best to apply it to improve patient outcomes.

**Why the eye?** Vision is such an innate human quality. When

people lose their vision, it is absolutely devastating. If you're able to improve—or even just preserve—someone's vision, it is very gratifying.

**Interesting item:** I have been to all 50 states. The last state was Alaska, but the most difficult one to get to was North Dakota. ■

### **Teaming Up** *continued from previous page*

laceration of the cornea, then you will just put in sutures,” says Yiu. “But the problem with the sutures is you induce a lot of scarring. Even though we successfully can repair the eye, we have a big problem because the patient's eye is safe, but he can't see. We think we can do a lot more to preserve eyesight.”

The solution they created is a “nanoglue” that seals the wound, making sutures unnecessary. The nanoglue also contains dendrimer molecules loaded with drugs that help treat postsurgical inflammation and infection.

A unique aspect of the treatment is that someone on the battlefield can apply the glue directly to the eye and then seal it with a hand-held laser. The pressure on the nanoglue can be titrated, or adjusted, by how long the laser is held over the glue, which can help reshape the eye in the wake of an irregular wound.

“When they get back to a more stable environment where further interventions such as a transplant or retinal repair can be done, the seal can be peeled off easily without causing further damage—almost like a contact lens,” says Yiu.

To Kannan, their partnership is an example of the benefits of pairing basic science researchers with clinicians. “Because we have a good clinical perspective, we are not doing science for the sake of science or nanotechnology for the sake of nanotechnology. We are doing nanotechnology for the sake of precision medicine,” Kannan concludes. ■

### **Infection** *continued from page 1*

eye and send the swab to the Johns Hopkins pathology lab. The test to determine the presence of adenovirus, called polymerase chain reaction, is not commercially available and was developed at Johns Hopkins specifically for this type of eye infection because of Kuo's policy.

While waiting for the results, which usually come back the same day, the employee is told to go home, or “furloughed.” If the test is positive for adenovirus, the employee must stay home from work; depending on the type of virus, the furlough could last 14 days or longer. Before the employee returns to work, he or she must go to Occupational Health to get cleared.

The results of the policy have allowed for more accurate and cost-effective treatment of employees who pose an infection risk. Over a three-year period, 542 employees were suspected of having infectious conjunctivitis. “But when we did PCR, only 44 of them had adenoviral conjunctivitis. And only 14 of them had the really serious type—epidemic keratoconjunctivitis,” says Kuo.

“This algorithm controls spread of adenoviral conjunctivitis but also allows clinic and hospital operations to run smoothly so employees who are not infected can still work,” says Kuo. “The cost of this algorithm—PCR testing and employee furloughs based on accurate testing—was only 5 percent of the cost of what it would've been if we had actually just furloughed all 542 employees. And during this time, we had no outbreak of epidemic keratoconjunctivitis.” ■



# All the World's a Stage

**B**IOLOGICAL PROCESSES ARE OFTEN DYNAMIC—productions with players entering and exiting the stage at different times so that a picture at one point in time cannot create an accurate illustration of all the actors involved.

**Jeff Mumm, Ph.D.**, Wilmer's Helen Larson and Charles Glenn Grover Professor of Ophthalmology, knows this challenge well. Mumm focuses on one of these dynamic processes: regeneration in the eye. By learning who the key players are during regeneration, he explains, researchers can gain invaluable insight into how to promote healing in the eye.

Getting the full picture of regeneration over time, though, is difficult. Single time point analysis and standard histology are two classic strategies researchers have used, but such approaches share a significant drawback.

“Some of the players in dynamic processes, such as regeneration, are so fast that [using these strategies] was like having an antitheft system to catch bank robberies which had the unfortunate property of being able to take a picture only every 24 hours,” says Mumm. Researchers were likely missing a lot of information.

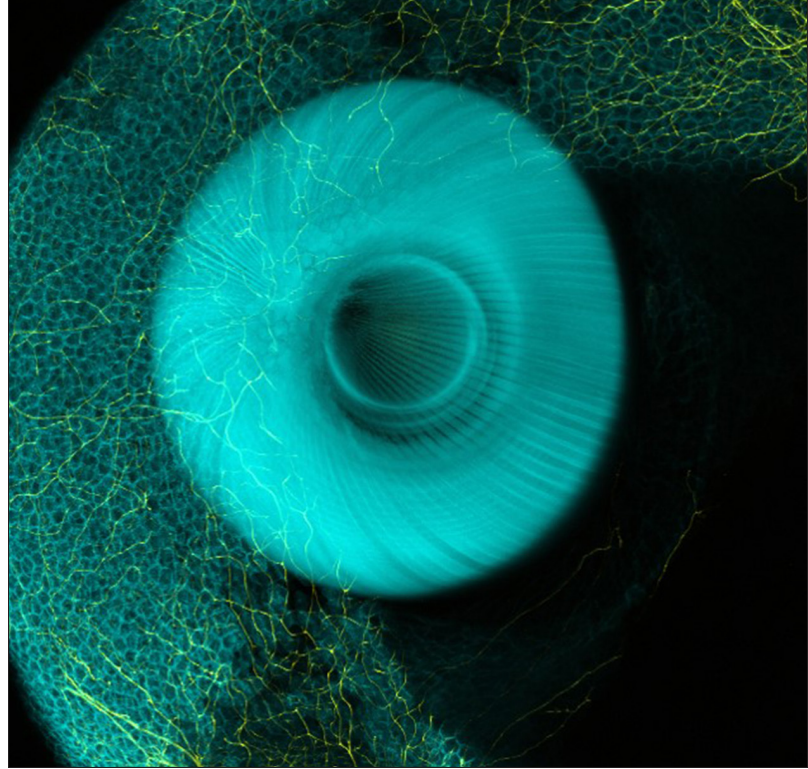
To address this problem, Mumm developed a way to directly watch living cells interact in the eyes of zebrafish. Mumm studies zebrafish because they have a remarkable capacity for regeneration and because their eyes share many characteristics with human eyes. His method to capture the full range of the regeneration process began by selectively eliminating disease-relevant cell types and then observing how other cells responded.

In order to track multiple cell types, Mumm and his team genetically modified the zebrafish so that when exposed to light, different cell types in the fish glowed distinct colors. He refers to this as “cell-type specific labeling.”

By combining these two approaches, Mumm and his lab could take time-lapse photos of the behavior



**Jeff Mumm, Ph.D.**



**Neurons (yellow) in the cornea (blue) of a living zebrafish**

of healthy ‘responder’ cells during the loss and replacement of cells linked to blinding diseases, such as retinal photoreceptors. These images were then strung together to make movies that could capture who the key players were during the regenerative process. These studies revealed that a specific type of immune cell, called microglia, played a pivotal role in controlling photoreceptor regeneration.

Now, his team has expanded its focus to include the front of the eye as well as the back. “We’re trying to map some of the things we’ve learned in looking at retinal regeneration to the cornea and take an in-depth look at the process of how the cornea repairs itself, and the role of the immune system in that process,” says Mumm.

“At the very outset of an injury there are many different kinds of immune cells. The first questions we ask are, of all the different kinds of immune cells that could respond to this injury, who are the first responders? Who are the second responders? Who stays around the longest? Who only respond transiently to the initial injury? And who are most likely to be crucial for fixing the problem?” says Mumm.

The answers will help researchers focus their efforts when developing ways to improve the healing process. “There are bit actors and then there are the main actors. By knowing who the main actors are we can try to develop a better script for them,” says Mumm. ■



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## Corneal Neurotization: Finding That Feeling Again

While the human cornea has no blood vessels, it is one of the most sensitive tissues in the body because of its density of nerve endings. If these nerve endings die—because of a disease such as a viral infection or as the side effect of brain surgery—dire consequences can follow.

When a patient presents with such a condition, called a neurotrophic cornea, Wilmer’s **Fasika Woreta, M.D., M.P.H.**, joins the team who performs the solution, a surgery known as corneal neurotization.

Woreta, assistant professor of ophthalmology, works in concert with **Richard Redett, M.D.**, an associate professor of plastic and reconstructive surgery and pediatrics at the Johns Hopkins University School of Medicine.

“Dr. Redett harvests a nerve from part of the leg. He connects it to

a nerve above the eye on the side of the patient’s face with normal sensation. He then tunnels the graft under the skin across the bridge of the nose to the abnormal side and makes an incision in the eyelid,” explains Woreta.

Here Woreta takes over. Underneath a microscope, she separates the nerve into five branches, called fascicles. She creates five pockets in the cornea. Next, she tunnels the fascicles through the conjunctiva and into the cornea, anchoring each fascicle into a pocket with a combination of glue and sutures.

The patient may not see the benefits of the surgery for about six months. “You have to be patient and still manage the neurotrophic cornea in the meantime,” says Woreta. This includes sewing the outside of the upper and lower eyelids together until



**Fasika Woreta, M.D., M.P.H.**

the cornea has regained sensation and having the patient aggressively moisturize the cornea.

Woreta is currently the only person at Wilmer who performs this operation. Of her desire to learn how, she says, “I was interested in doing it because there was no surgery that we could offer patients before for this procedure. We could only offer lubrication, closing the eyelids and other supportive measures. The fact that we can restore sensation and improve the health of their cornea is exciting.” ■

To make a same-day appointment, call:  
410-955-5080 or toll-free: 888-945-6374  
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