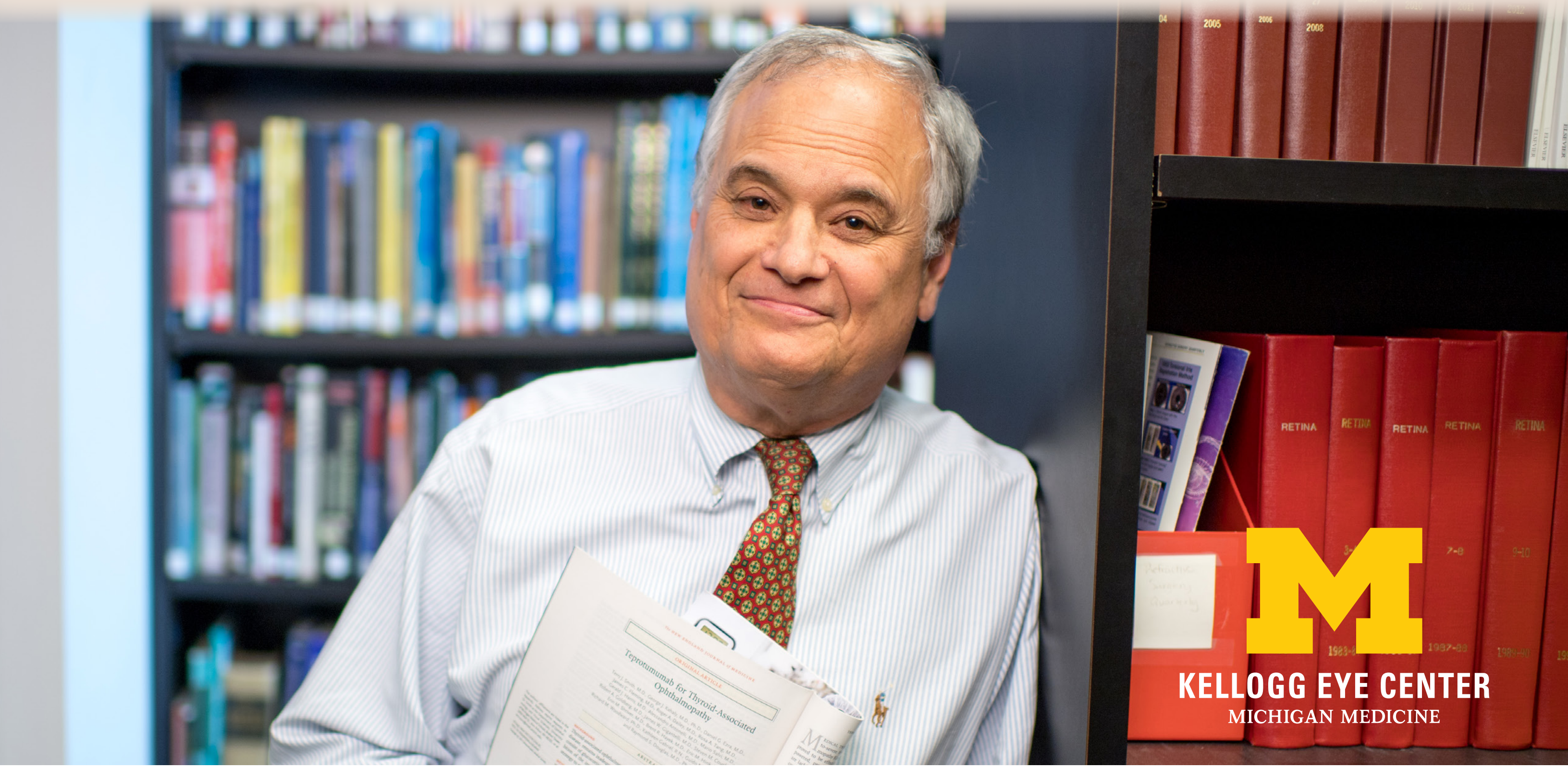
THE UNIVERSITY OF MICHIGAN KELLOGG EYE CENTER

ADVANCES IN OPHTHALMOLOGY



New Drug Shows Promise for Ophthalmic Damage in Graves Disease

Kellogg's professor Terry J. Smith, MD, was the lead investigator of a multicenter trial published in the New England Journal of Medicine

Physicians have long been searching for a more effective remedy for the vision-threatening and other effects of Graves disease, called "thyroid-associated ophthalmopathy." The basic science research of Terry J. Smith, MD, the Frederick G.L. Huetwell Professor of Ophthalmology and Visual Sciences at Kellogg, moves us closer to that goal.

On the basis of his research into the immunology of Graves disease, Dr. Smith, an endocrinologist, was named the lead investigator in a multicenter trial of teprotumumab, a new monoclonal antibody, as a treatment for thyroid-associated ophthalmopathy. He recruited his long-term colleague Raymond S. Douglas, MD, PhD, former Kellogg professor, to help design the trial. Its results were reported in the New England Journal of Medicine in May 2017. They look very promising.

Graves disease is an autoimmune disorder that leads to overactivity of the thyroid gland, often resulting in enlarged eye muscles that cause protruding eyes, called proptosis, double vision, and damage to the optic nerves leading to blindness. Traditional treatment is with corticosteroids, but they have limited efficacy and many side effects. Removal of orbital bones to allow more room for the enlarged muscles is an alternative, but it demands surgical skill and can cause complications even under the best of circumstances. Barbara and George H.W. Bush both famously suffered from Graves disease.

Dr. Smith has been interested in the causes and treatment of Graves disease since his days in medical school at the University of Missouri. His research at Kellogg disclosed that a protein called insulin-like growth factor (IGF-IR) is intimately involved in ophthalmopathy. Teprotumumab binds to IGF-IR and inhibits its activity.

In the just-reported placebo-controlled trial of teprotumumab (Kellogg was one of 15 participating international sites), 69% of the patients treated with teprotumumab improved and many showed therapeutic effects after only 6 weeks. "This drug appears to be resetting the immune system," Dr. Smith says. He thinks there may ultimately be similar results in other autoimmune diseases such as rheumatoid arthritis and Crohn disease.

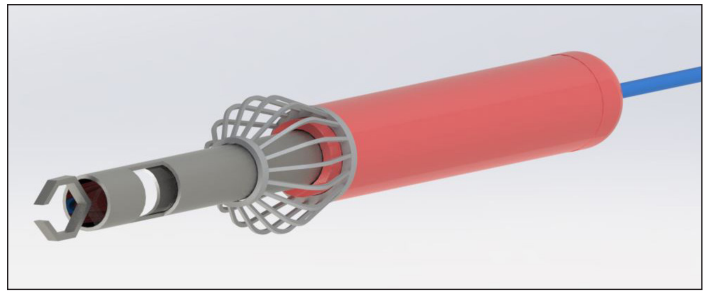
Kellogg Teams With U-M Biomedical Engineering to Develop Light-Bearing Vitreous Forceps

Retinal surgeons are always looking for ways to bring more light into the inside of the eye when they are operating.

Kellogg Assistant Professor of Ophthalmology and Biomedical Engineering Yannis Paulus, MD posed that challenge to the students in U-M Biomedical Engineering Professor Jan Stegemann's Graduate Innovative Design class. A team of creative engineers came forward. Current solutions were not ideal, explained participant Richard Nakkula, because they caused shadows and glare, and some require an assistant to hold the light for the surgeon. "We understood that the surgeon wants to control all instruments inserted into the eye," Nakkula said.

From having worked on product development at 3M, Nakkula knew that if he and his team were to make a better product, they would have to learn how retinal surgeons operate because "you don't want to make them change their habits."

His iSurgery team—Andrew Hartman, Jordan Sykes, Thai-Son Nguyen, and Brian Downey—created a giant prototype of an illuminated forceps for bimanual vitrectomy surgery from cardboard, tin foil, and string as an early concept. After a number of design changes, working through Spring Break, they manufactured some parts in house and others in a machine shop using 3D printing to make a device only 6 times larger than their final goal.



Illuminated vitreous forceps designed by U-M biomedical engineering graduate student team

"When we showed Dr. Paulus what we had developed, he shared it with others at Kellogg and they gave us great feedback," Nakkula says. Their efforts won the iSurgery team a U-M competition that enabled them to represent the school in a nationwide contest called BMEidea, where they were awarded an honorable mention.

Our U-M innovators have all graduated. They are spread around the nation, but Nakkula, who is now an engineer with Boeing in St. Louis, is committed to seeing the project through by working with a company that makes vitreous cutters to create a smaller scale model. Their challenge is to make sure that it brings in enough light. Dr. Paulus remains in the loop. "We're all passionate about getting this to work perfectly," Nakkula stated.

Crystallin Proteins May Provide Answers in Diabetic Retinopathy

Visiting ophthalmologist Anne Ruebsam, MD won the 2017 Kellogg Award for Excellence in Basic Research

Laboratory research at Kellogg shows that a retinal protein may preserve vision in diabetes. It comes from the work of Kellogg research faculty member Patrice Fort, PhD, and Anne Ruebsam, MD, a visiting research scholar from Germany. Dr. Ruebsam's contribution won her the 2017 award for Excellence in Basic Research at Kellogg.

It was during her ophthalmology residency at Berlin's Charité Hospital, one of the largest in Europe, that Dr. Ruebsam was propelled into research in diabetic retinopathy, having examined many patients who had gone blind from that condition.

She realized that effective treatment would have to focus on early molecular changes in the retina. "With our current treatments," she explained, "we target advanced stages of the disease when vision is already irreversibly lost."

As she reported at Kellogg's Research Day in June 2017, her research targets the retinal protective effects of stress-induced proteins called alpha A crystallins. These proteins lose their protective effects in diabetes. The goal of her project is to discover the metabolic pathways by which alpha A crystallins normally exert their protective effects and how these effects are lost in diabetes.

Anne Ruebsam, MD investigates retinal alpha crystallins with Kellogg assistant professor Patrice Fort, PhD

She and Dr. Fort found that these crystallins promote survival through different pathways in retinal neurons and Müller glial cells. Diabetic mice that lacked alpha A crystallins suffered an exaggerated degree of retinal cell death.

The hope is that their work will lead to new treatments for diabetic retinopathy and other diseases.

Dr. Ruebsam returns to Charité Hospital in October 2017, where she will once again examine patients with diabetic retinopathy and continue her research efforts. Based on her research at Kellogg, she has received grant support and a promise that 50% of her time will be devoted to further work on diabetic retinopathy. Of her experience here, she says that "it has been a huge honor to work at Kellogg. My research will allow me to continue looking at this fascinating problem for many years."

Kellogg Researchers Find That Doctors Over-Prescribe Antibiotics for Conjunctivitis

First large-scale study shows that 58% of patients with acute red eye receive prescriptions for topical antibiotics

Kellogg 3rd year ophthalmology resident Nakul Shekhawat, MD, MPH joins Kellogg Professor Joshua Stein, MD, MS in study of nationwide treatment of acute red eye.

The American Academy of Ophthalmology recommends avoiding antibiotic treatment for viral conjunctivitis and deferring antibiotics when the cause is unknown. Even so, Kellogg professor Joshua D. Stein, MD, MS suspected that doctors were over-prescribing antibiotics for conjunctivitis, a condition often caused by viruses or allergies, which do not benefit from antibiotic treatment.

Along with Kellogg ophthalmology resident Nakul S. Shekhawat, MD, MPH, and Kellogg Center for Eye Policy and Innovation researchers Roni M. Shtein, MD and Taylor S. Blachley, MS, Dr. Stein analyzed de-identified billing records from more than 340,000 enrollees in a large nationwide managed care network from 2001 through 2014 who were diagnosed with acute conjunctivitis. His goal was to identify the proportion of patients filling prescriptions for topical antibiotics within two weeks of initial diagnosis. The study was published in the April 2017 issue of Ophthalmology.

"You can learn a lot about healthcare from studying billing records," Dr. Stein says. Indeed, the team found that 58% of people with newly diagnosed acute conjunctivitis had filled prescriptions for topical antibiotics. Most of the patients (83%) were under the care of non-eye care providers, such as pediatricians, family practice physicians, internists, and urgent care providers. Patients of ophthalmologists had the lowest percentage of filled antibiotic prescriptions (36%); urgent care patients had the highest (68%). The most popular antibiotic class was fluoroquinolones, some of which can cost up to $200 for one bottle. Individuals in the higher income brackets were more likely to have filled prescriptions.

Another important finding was that nearly 1/5 of antibiotic prescriptions contained corticosteroids, a combination that can actually worsen a viral infection. Ophthalmologists and optometrists prescribed antibiotic-corticosteroid combinations more often than did non-eye care providers.

The authors reminded readers that overuse of antibiotics is not only costly but may contribute to the proliferation of drug-resistant strains of bacteria. "Clearly, we need to do a better job educating non-eye care providers," Dr. Stein says. But the frequent prescribing of antibiotic-corticosteroid combination medications for acute conjunctivitis by eye care providers is also a troubling finding.

A key factor contributing to the overuse of antibiotics for conjunctivitis is current healthcare policy in most states. According to Dr. Stein, 20 out of 43 state health departments require proof of an antibiotic prescription before students can return to school. "It's a knee-jerk reaction," remarks Dr. Stein. "Since conjunctivitis often resolves anyway, people assume the antibiotic must have helped." Adding to the problem is that antibiotic treatment of viral conjunctivitis, which may be very contagious, does not prevent its rapid spread. In fact, antibiotic prescription may deflect from the correct approach, which is to obey proper hygiene rules. "The people making the policy may not be talking to ophthalmologists," he says.

A former fellow with U-M's Center for Healthcare Research and Transformation, Dr. Stein says finding the right policymakers, mainly the staff of governmental officials, will be crucial if healthcare policy is to improve. He plans a before-and-after study of antibiotic use in a few years, with help from Kellogg ophthalmology residents, who are becoming more engaged in ophthalmic public health and health services research as the result of his mentorship.

Upcoming CME Programs

Friday, September 15, 2017
23rd Annual Fall Reunion Day
Register online for Fall Reunion Events

www.kellogg.umich.edu/education

KELLOGG EYE CENTER
Department of Ophthalmology and Visual Sciences
1000 Wall Street, Ann Arbor, MI 48105

www.umkelloggeye.org

NON-PROFIT ORG.
U.S. POSTAGE
PAID
ANN ARBOR, MI
PERMIT NO. 144

U-M Engineering Student Provides 3D Printing Know-How to Aravind's Instrument Production Laboratory

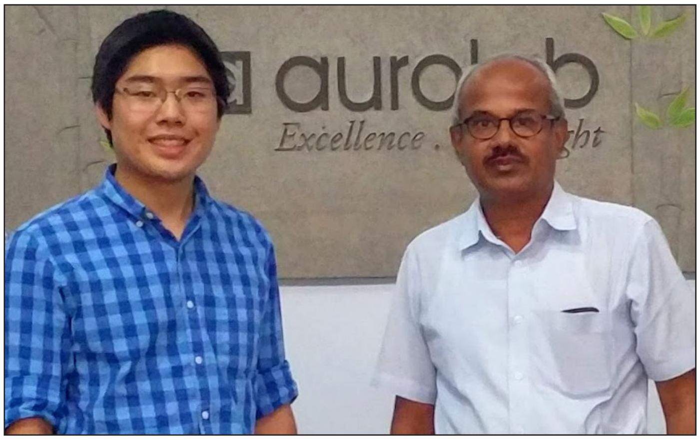
In conversation with R. D. Thulasiraj, MBA, executive director of the Aravind Eye System in Madurai, India, Kellogg chair Paul Lee, MD, JD, learned that Aravind's 3D printing in its instrument production laboratory needed an upgrade.

So Dr. Lee contacted Lauro Ojeda, MS, assistant research scientist at U-M's College of Engineering, who had been assisting Kellogg in instrument innovation. Ojeda put out the challenge to U-M engineering students. Aaron Chow, a 19-year old sophomore student, jumped at the chance.

Chow is already an old hand at 3D printing, having worked during high school at GE Aviation in his native Cincinnati. There he watched GE "print" metal turbine blades, but his studies at U-M have mostly involved plastics and polymers.

He and his friends in the Michigan Neuroprosthetics Club have made full-built prosthetic limbs. He has been building 3D printers since 2015. "If you have one task, you can design a printer parameter," Chow says. "The eye is fascinating. When I spoke with Dr. Lee, I figured out that there are some really cool 3D printing applications for ophthalmology."

Aurolab had begun manufacturing intraocular lenses and other medical instruments years ago with injection molding.



Aaron Chow, U-M sophomore engineering student, with R. D. Sriram, BE, director of Aravind's Aurolab.

Chow was able to introduce them to the capabilities of a high end 3D printer. Before making the trip to Madurai, Chow conferred with Mr. Thulasiraj, MBA, and R.D Sriram, BE, director of Aravind's Aurolab, giving them a list of his needs.

"It was a little tense at the beginning since Aravind's engineers are in their 30's and 40's and their boss brought in this 19-year old kid," Chow says. But the group quickly warmed up to Chow, who helped upgrade their 3D production. Chow's expertise led to a needle injector for IOLs that might have taken weeks to produce with injection molding but was 3D-printed in only 2 days!