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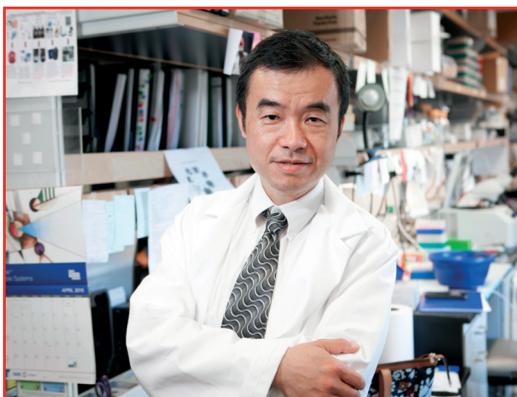
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Supporting Scientific Insight in Eye Disease

Research to Prevent Blindness (RPB), a leading health organization that supports eye research for the prevention, treatment, or eradication of all diseases that threaten vision, has awarded the Department of Ophthalmology at New York Presbyterian/Columbia University Medical Center two major grants that will contribute to the work



Dr. Xin Zhang

of distinguished research scientist **Xin Zhang, PhD**, and his Columbia ophthalmology colleagues. The first grant – which is unrestricted – positioned the Department to apply for and win RPB’s premier award, the Jules and Doris Stein Research to Prevent Blindness Professorship. The funding, which amounts to more than \$1 million, will support the Department’s ongoing research into the causes, treatment, and prevention of diseases that may cause blindness.

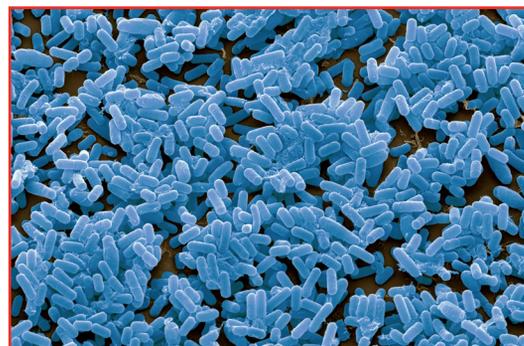
Both the unrestricted grant and the Stein Professorship are highly competitive and noteworthy honors, and New York Presbyterian/Columbia was the only institution in the country to receive the grant. “While the funding is reserved for basic scientists who conduct ophthalmological research, they are not necessarily or exclusively based in ophthalmology departments,” says **George A. (Jack) Cioffi, MD**, Chair of Ophthalmology and Ophthalmologist-in-Chief at New York Presbyterian/Columbia. “Columbia researchers

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Meeting the Complex Challenges of Uveitis

Uveitis, a term that can sour the mood of many ophthalmologists who desperately fight to restore light, encapsulates a group of potentially sight-threatening ocular inflammatory diseases primarily of the uveal tract, but typically includes extra-ocular inflammation as well. While uncommon, uveitis is not rare, with a worldwide prevalence as high as nearly one percent. Furthermore, it remains a common cause of blindness. Uveitis accounts for nearly 15 percent of all legal blindness in the United States and is the third leading cause of blindness in developed countries. As the disease targets primarily children and working-age adults, the socioeconomic impacts are significant.

Understanding this burden of disease, the Department of Ophthalmology at New York Presbyterian/Weill Cornell Medical Center recently established a Division of Uveitis and Ocular Inflammatory Disease to address this underserved niche of destructive eye diseases. “Recent studies



Scanning electron micrograph of Bacillus subtilis bacteria or bay bacillus, an aerobic, gram-positive bacillus that can be pathogenic in humans, causing severe eye infections such as anterior uveitis

have demonstrated that patients with uveitis who are followed in conjunction with specialists have improved outcomes,” says **Sarju S. Patel, MD, MPH, MSc**, the Division’s Director. “Recognizing this fact, Weill Cornell created a resource for local

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Supporting Scientific Insight in Eye Disease (continued from page 1)

will be able to expand existing studies into new vitreoretinal surgery procedures, the genetics of retinal diseases, stem cell therapy for retinitis pigmentosa, retinopathy of prematurity, and techniques for detecting glaucoma. More important, they can design and pilot new studies.”

The Stein Professorship will subsidize the research of Dr. Zhang, Associate Professor of Ophthalmic Sciences in Ophthalmology, Pathology and Cell Biology, for the next five to seven years.

The gift is particularly notable in its flexibility. Such support is unusual in the philanthropic world, according to **Brian F. Hofland, PhD**, President of RPB, who notes that their organization’s mission has been to expand research capacity in laboratories and allow researchers to develop new scientific inquiries. The Stein Professorship, he says, reflects one of RPB’s founding principles of bringing the bench to the bedside by combining basic science and clinical applications to advance ophthalmological research, and to use research findings to prevent and treat eye disease. “You need pairings, either physician-scientists or basic scientist-clinicians, to get firsthand observations from patients that lead to research hypotheses,” says Dr. Hofland.

“In a clinical setting, I am looking for inspiration. By interacting with clinicians, I hope to see problems as they exist. The most important information will come from the patients.”

— Dr. Xin Zhang

Dr. Zhang, who joined the Department of Ophthalmology in 2013 from Indiana University School of Medicine where he was Associate Professor in the Department of Medical and Molecular Genetics, conducts award-winning research on the genetics of eye disease. Dr. Zhang’s genetic research within the Department’s clinical program is intended to bridge the gap between laboratory science and clinical care. “I hope to use the clinical experience of my colleagues to stimulate research so it will have greater impact and elevate the level of our work,” he says.

After beginning his graduate studies in physics at The Johns Hopkins University, Dr. Zhang moved to the field of biology and received his doctorate in 1998. He focused his investigations on the regulation of genes, and during his postdoctoral fellowship in the Division of Genetics at Harvard Medical School, he became interested in the manipulation of genes from mouse eyes and, subsequently, in the genetic underpinnings of eye disease. This work was especially exciting, he says, because the changes that resulted from gene manipulation were easily visible. “Looking at the eye, you can really tell something is happening,” Dr. Zhang says. “When you manipulate genes within the eye’s lens, what frequently happens is the development of a cataract. So you can have a visual appreciation of what you’re doing.”

In humans, the same is true, he notes. Small genetic changes can lead to significant changes within the structures of the eye. “You have a single nucleotide change in the human genome that consists of three billion DNA base pairs and, as a consequence, patients may not have an iris.”

Dr. Zhang’s research has earned him wide recognition, as well as numerous grants from organizations that include the Ralph W. & Grace M. Showalter Research Trust Fund, March of Dimes, and American Diabetes Association. His investigations focus on the developmental aspects of eye disease, disorders of the lens, and congenital eye conditions, and involve manipulating and, in some cases, disabling genes to create disorders such as microphthalmia, coloboma, or aniridia.

One of Dr. Zhang’s primary goals is to understand the genetic mechanisms behind these conditions. By manipulating mouse eye genes he hopes to determine how these eye diseases develop in mice and whether similar genetic disruptions in humans would lead to the same diseases. “So far, we are just extrapolating,” he says. “Given the clinical opportunities at Columbia and the immense needs of patients with eye disease, these are possibilities we can explore.”

“The main focus of our research is the mechanism of cell signaling during eye development,” says Dr. Zhang. “The eye is a prominent system to study signal transduction, not only because of its biomedical significance, but also because of the rich resource of experimental tools available in eye research. Previous studies have also identified multiple signaling pathways including fibroblast growth factor signaling in mediating cellular interactions in the eye. However, the specific signaling components of these pathways and their precise *in vivo* functions in the eye remain poorly understood. With the advent of genome-wide analysis and the rapidly expanding collection of mouse models, it has now become increasingly important to determine the *in vivo* function of every mouse gene by genetic approaches. We therefore employ the formidable mouse genetic tools to definitively determine the signaling pathways governing eye development.”

Dr. Zhang also has two R01 research grants from the National Eye Institute to study signaling mechanisms of lens development and regulation of FGF signaling in lacrimal gland development, which will contribute to medical research in treating human congenital eye diseases and advance the understanding of the intercellular signaling paradigm. Collaborating with clinicians in the Department of Ophthalmology, Dr. Zhang is integrating his investigations into understanding how certain genetic mechanisms contribute to particular eye diseases. This includes comparing congenital symptoms in patients with those from his mouse model to predict the development of human eye disease, and sequencing patients’ genes to see if they reveal the characteristic changes that point to the cause of disease. Dr. Zhang’s goal is to connect genetic insight with therapeutic response.

“In a clinical setting, I am looking for inspiration,” he says. “By interacting with clinicians, I hope to see problems as they exist. The most important information will come from the patients.”

“The close collaboration between clinicians and scientists provides our best chance to prevent, treat, and cure complex diseases of the eye,” adds Dr. Cioffi. “The Harkness Eye Institute at Columbia University has a long history of innovative clinical research, and scientists like Dr. Zhang build upon this tradition.”

For More Information

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Meeting the Complex Challenges of Uveitis (continued from page 1)

physicians with challenging cases.” Since the creation of the Division, Dr. Patel and his colleagues have been inundated with an incredibly large volume of patients, further reinforcing the acute need for specialty care in this area.

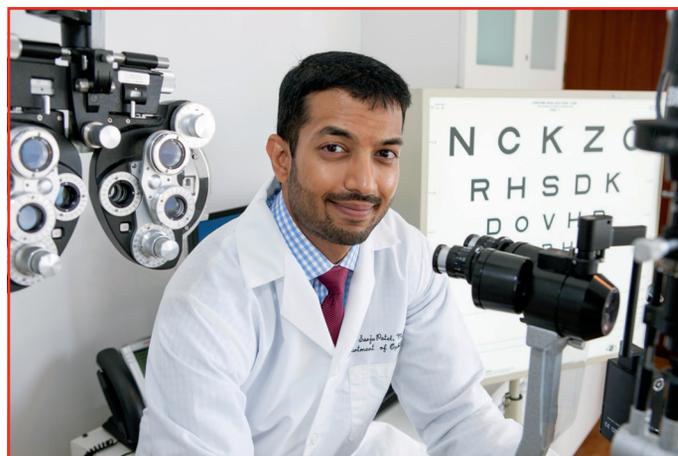
“One of the most important benefits the Division of Uveitis and Ocular Inflammatory Disease can provide patients is time,” says Dr. Patel. “All practicing physicians today are heavily constrained by time, and uveitic diseases require extensive appointments with full medical evaluations, patient education, and serious discussions as treatment often requires long-term immunosuppressive therapy. Furthermore, the care of these patients is centralized as the specialists can manage multiple aspects of the disease, resulting in the reduction of doctors visits, improving patient satisfaction, and conserving medical resources and costs.

“While patient care is at the heart of what we do, we do not forgo the mission to advance medicine,” adds Dr. Patel. “As these diseases are uncommon, having large numbers of cases under one service helps us to understand these diseases and learn better ways to evaluate and manage them. For example, we are currently seeking to characterize these diseases from a molecular and genetic standpoint, while exploring links to inflammatory bowel disease and other systemic entities, in an effort to help all physicians accurately diagnose and effectively treat these patients. In addition, we are also able to provide patients with access to ongoing clinical trials.”

Understanding Mycobacterial Ocular Inflammation

In one research endeavor, Dr. Patel, as lead investigator, explored mycobacterial ocular inflammation and factors impacting poor outcomes and increased morbidity. The reported outcomes of ocular mycobacterial infection are commonly unfavorable. This study, with results reported in *JAMA Ophthalmology*, was among the first to elucidate factors associated with poor outcomes, as well as highlight the continued controversies in therapy, particularly the role of oral corticosteroids.

According to estimates, one-third of the world’s population is currently infected with tuberculosis. Despite the high prevalence of systemic disease, ocular disease secondary to TB remains much less common. According to Dr. Patel, diagnosing ocular mycobacterial disease continues to be a challenge because of its relative rarity and myriad presentations without pathognomonic eye findings. While granulomatous inflammation is typical, it is not always present.



Dr. Sarju S. Patel

“Given the lack of uniform diagnostic criteria for ocular TB, the ophthalmologist must often rely on a combination of history, physical examination, and screening investigations,” says Dr. Patel. “Current recommended criteria for diagnosis of presumed ocular TB include positive tuberculin skin test, interferon gamma release assay, chest radiograph, or confirmed extraocular TB and supportive clinical ocular findings.”

More direct evidence, including acid-fast smear, tissue culture, and polymerase chain reaction [PCR] for bacterial DNA from ocular tissues, provides definitive support for the diagnosis. However, because of low bacterial load, the sensitivity of PCR in vitreous samples remains low, ranging from 33.3 percent to 46.9 percent. In addition, obtaining ocular fluids and tissue can be associated with ocular morbidity and may be of low yield.

“Ocular TB can be difficult to treat and is associated with significant morbidity,” adds Dr. Patel. “Therapy has been reported to be effective in only 40 to 70 percent of published cases, with an enucleation rate of up to 30 percent. Factors influencing treatment outcomes are yet to be clarified, which is why we performed this study.”

Dr. Patel and his colleagues conducted a retrospective review of 26 eyes of 17 patients diagnosed with mycobacterial ocular inflammatory disease from 1995 through 2010. Of the 17 patients, 13 had isolated ocular disease, one had miliary tuberculosis, two had TB lymphadenopathy, and one had active pulmonary TB. Fourteen had *Mycobacterium tuberculosis* and three had nontuberculous mycobacterial infection. Chest imaging was consistent with

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Ocular Mycobacterial Infection Outcome Measures and Risk Factors

Outcome Measure	Eyes No.	Risk Factor	P Value for Probability
Permanent loss of visual acuity (<20/200)	10 / 38.5%	Age >50 years	.04
		Delay in diagnosis (>500 days)	.03
Relapsing disease	10 / 38.5%	Posterior uveitis	.04
		Supplemental systemic steroids	.03
Uncontrolled disease	5 / 19.2%	Age >50 years	.03
Loss of eye	3 / 11.5%	Age >50 years	.05

(Source: JAMA Ophthalmology, June 2013)

Advances in Ophthalmology

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Meeting the Complex Challenges of Uveitis *(continued from page 3)*

granulomatous disease in 46.7 percent. The average delay from ocular disease onset to uveitis service referral was 755.3 days. Disease control was achieved in 81 percent, although 38.5 percent had profound visual loss associated with age older than 50 years and delay in diagnosis. Patients diagnosed after 500 days from initial ocular symptoms were more likely to lose their vision.

“Our findings concluded that ocular mycobacterial infection occurs in nonendemic areas and cannot be ruled out with negative chest imaging,” says Dr. Patel. “Tuberculosis and atypical mycobacterial infection should be in the differential diagnosis of ocular inflammation, regardless of patient ethnicity. As significant delays exist in instituting antimicrobial treatment and are associated with increased morbidity, we believe that early referral is necessary for patients who are not responding appropriately to anti-inflammatory therapy.”

About Dr. Sarju Patel

Dr. Patel graduated with honors from Brown University and then pursued graduate training in research sciences at the London School of Hygiene and Tropical Medicine. He earned his medical degree at Mount Sinai School of Medicine, graduating with a distinction in research. He then completed a Doris Duke Charitable Foundation Research Fellowship and received the Harold B. Lampport Biomedical Research Award.

Dr. Patel pursued residency training in ophthalmology at New York University, followed by fellowship training in ocular immunology and inflammatory diseases at the Illinois Eye and Ear Infirmary, where he received the Cless Family Foundation Award for outstanding fellow in clinical and academic ophthalmology.

A member of the American Uveitis Society, Dr. Patel is also listed as a uveitis specialist by the Ocular Immunology and Uveitis Foundation. In addition, he currently serves as a consultant for the Knowledge Base Panel for Uveitis of the American Academy of Ophthalmology.

“Uveitis provides unique challenges to clinicians and patients alike,” adds Dr. Patel. “The Division of Uveitis and Ocular Inflammatory Disease at Weill Cornell is a valuable resource to the community to help overcome these issues and provide patients the very best care.”

Reference Article

Patel SS, Saraiya NV, Tessler HH, Goldstein DA. Mycobacterial ocular inflammation: delay in diagnosis and other factors impacting morbidity. *JAMA Ophthalmology*. 2013 Jun;131(6):752-58.

For More Information

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