

# ADVANCES IN OPHTHALMOLOGY

 COLUMBIA UNIVERSITY  
College of Physicians  
and Surgeons

 Weill Cornell  
Medicine

**George A. Cioffi, MD**  
Ophthalmologist-in-Chief  
NewYork-Presbyterian/  
Columbia University Medical Center  
gac2126@cumc.columbia.edu

**Donald J. D'Amico, MD**  
Ophthalmologist-in-Chief  
NewYork-Presbyterian/  
Weill Cornell Medical Center  
djd2003@med.cornell.edu

## Dry Eye Disease: A New Look at a Common Condition

Dry eye disease, an immunoinflammatory disorder of the tear film and ocular surface, is one of the most common conditions seen by eye care practitioners, affecting some five million Americans. “And this figure is likely very underestimated,” says **Jessica B. Ciralsky, MD**, an ophthalmologist in the Department of Ophthalmology at NewYork-Presbyterian/Weill Cornell Medical Center, who specializes in treating severe forms of dry eye disease. “Many people don’t know they have dry eye; in fact, many of my patients have dry eye signs and symptoms that may not have classically been included in that estimate.”

Increased reliance on modern technology and display devices has contributed to dry eye, especially in the younger population, notes Dr. Ciralsky.

“Many people talk about computer vision syndrome, a condition resulting from focusing the eyes on a monitor for uninterrupted periods of time,” she says. “There are definitely risk factors pertaining to today’s technology. Staring at the screens without interruption and failing to blink

“Quantifying tear osmolarity and detecting MMP-9 have shown promise as diagnostic tools in dry eye disease.”

— Jessica B. Ciralsky, MD

regularly during intense periods of concentration contributed to drying out of the eyes.” Other causes of dry eye are wearing contact lenses for prolonged periods; medications, such as central-acting agents and diuretics to treat hypertension; certain antidepressants; and allergy medications, including antihistamines and decongestants. Individuals with rheumatoid arthritis, diabetes, thyroid problems, and Sjögren’s syndrome are more likely to have symptoms of dry eyes. Other eye problems can also contribute to dry eye such as blepharitis, entropion, and ectropion. Furthermore, eye surgeries can cause or exacerbate dry eye, including refractive eye surgeries such as LASIK.

*(continued on page 2)*

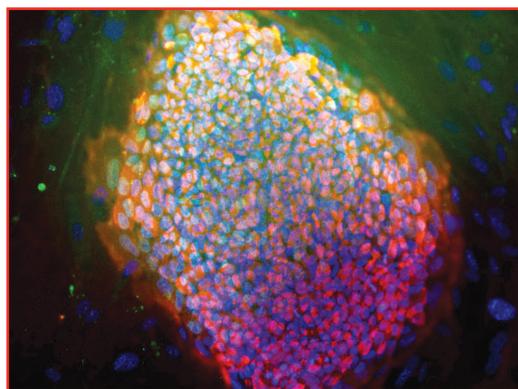
## Reprogramming Stem Cells and Genome Surgery to Treat Retinal Diseases

**Stephen H. Tsang, MD, PhD**, an alumnus of Columbia University Medical Center, is an internationally recognized clinician and geneticist specializing

in the treatment of retinal degenerative disorders at NewYork-Presbyterian/Columbia University Medical Center. Dr. Tsang is investigating the link between genome engineering and precision medicine within ophthalmology and, in particular, retinal diseases. He is one of a handful of NIH-supported clinicians directing the full spectrum of bench-to-bedside research.

Dr. Tsang explores cell-based treatments for retinal diseases, examines embryonic stem cells to model and replace diseased human retinal cells, and creates patient-specific disease models relevant to drug development. “The eye is an ideal testing ground for stem cell therapies because of its relative immune privilege and its ready accessibility for monitoring and imaging purposes,” explains Dr. Tsang.

*(continued on page 3)*



*Induced pluripotent stem cells*



New York’s #1 Hospital  
16 Years in a Row.

## Dry Eye Disease: A New Look at a Common Condition (continued from page 1)

Women are twice as likely to have dry eye than men. “We’ve classically categorized dry eye in an older population, particularly menopausal women, because of aging and changes in hormones,” says Dr. Ciralsky, “but we’ve come to realize that younger people and men can also suffer from dry eye.”

Symptoms include burning, dryness, itching, visual fluctuations, irritation, and even tearing, which seems counterintuitive, says Dr. Ciralsky. “Tearing is often a symptom of dry eye. Many patients complain about the impact of dry eye. It can interfere with their life, limiting how long they can sit at the computer or drive a car. This condition can be debilitating for some patients.”

Patients with mild dry eye may only need to be seen once or twice a year, says Dr. Ciralsky. However, a patient with moderate or severe dry eye may require multiple visits and treatments. “We are seeing a lot more people who have already sought their third, fourth, and fifth medical opinion for dry eye,” she says. “These patients are frustrated because they haven’t found relief with their prescribed regimen, and that is often where we come in.”

### Pinpointing the Cause

To date, the diagnosis and management of dry eye disease has been challenging, requiring analysis of clinical signs of disease and symptoms. Often, signs and symptoms don’t match which can make the diagnosis even more difficult. Over the last few years newer diagnostics have enabled physicians to look at different parameters of dry eye. “Some of the older tests examine tear production and staining patterns, and we still use them today,” says Dr. Ciralsky. “But currently we also look at inflammatory biomarkers. Research has shown that inflammation plays a large role in dry eye.”

Researchers and clinicians have long pursued a test that could objectively diagnose dry eye disease. “As our understanding of dry eye disease evolves, our knowledge of the underlying mechanisms of the disease has provided new strategies for diagnosis,” says Dr. Ciralsky. “The recognition of tear hyperosmolarity and ocular surface inflammation as key components of disease pathogenesis has led to the development of point-of-care tear film diagnostics. Some of our newer tests measure tear osmolarity and the amount of MMP-9 present in the tear film. MMP-9 is a cytokine produced by epithelial cells experiencing inflammation of the ocular surface, which is a key component of dry eye disease. If there is inflammation, we can follow that over time.”

### Providing a Range of Treatments

Historically, the most common treatment for dry eye has been over-the-counter lubrication drops. “While that approach is like putting on lotion for dry skin,” says Dr. Ciralsky, “the drops give the eye moisture and symptomatic relief and are certainly supplemental to treatment. However, this does not get to the pathophysiology.”

Anti-inflammatory medications include pulsed topical corticosteroids or topical cyclosporine, an immunomodulator that decreases swelling to allow for tear production. There is also a new topical anti-inflammatory medication approved for dry eye, which is topical lifitegrast. Oral medications, such as doxycycline and azithromycin, can also be prescribed for co-existing blepharitis.

Punctal plugs inserted into tear ducts decrease the outflow of tears. These tiny, biocompatible devices – no larger than a grain of rice – can



Dr. Jessica B. Ciralsky

be semi-permanent, typically made of long-lasting materials such as silicone, or dissolvable, made of materials such as collagen.

Autologous serum drops are also used to improve symptoms of ocular surface disease. The patient’s blood is drawn and placed into a centrifuge to separate blood components; the blood serum is diluted into a bottle of preserved artificial tears. “Serum drops very closely mirror the properties of a teardrop,” says Dr. Ciralsky.

When all else fails, Weill Cornell offers BostonSight™ PROSE (prosthetic replacement of the ocular surface ecosystem), an advanced therapy for patients with complex corneal disease. During PROSE treatment, physicians customize and fit a prosthetic device to replace or support damaged ocular functions. PROSE is a transparent dome filled with a sterile saline solution that serves as an artificial tear reservoir, providing constant lubrication to the eye and allowing oxygen to reach the cornea. About the size of a nickel and composed of gas permeable material, the device creates a smooth surface over the cornea.

“PROSE can be the ideal, and sometimes the only, treatment capable of restoring vision and dramatically reducing symptoms of eye pain and severe dry eye,” says Dr. Ciralsky. “It is similar to a contact lens in terms of vision correction, but it is unique in that it bathes the eye in fluid continuously. The patient wears it during waking hours and takes it out at night.”

Lastly Dr. Ciralsky recommends an ongoing regimen of eyelid hygiene if blepharitis co-exists. This may include warm compresses, over-the-counter lid scrubs or gentle, baby shampoo scrubs. “The key here is that dry eye disease is a treatable disorder. The earlier a patient is treated, the better the results are,” she says.

#### Reference Articles

Dohlman TH, Ciralsky JB, Lai EC. Tear film assessments for the diagnosis of dry eye. *Current Opinion in Allergy and Clinical Immunology*. 2016 Oct;16(5):487-91.

Dohlman TH, Lai EC, Ciralsky JB. Dry eye disease after refractive surgery. *International Ophthalmology Clinics*. 2016 Spring;56(2):101-10.

Kornberg DL, Dou E, Wang Y, St Clair R, Lee MN, Sood P, Fernandez AA, Ciralsky JB, Sippel KC, Rosenblatt MI. Clinical experience with PROSE fitting: significance of diagnosis and age. *Eye & Contact Lens*. 2016 Mar;42(2):124-28.

#### For More Information

Jessica B. Ciralsky, MD • jbc9004@med.cornell.edu

## Reprogramming Stem Cells and Genome Surgery to Treat Retinal Diseases (continued from page 1)

“The recent marriage of iPS cell technology with a technique called CRISPR genome surgery makes possible the correction and transplantation of stem cells derived from the patients themselves. Hence, we will soon be able to replace diseased cells with healthy ones by reengineering the patient’s own cells.”

— Stephen H. Tsang, MD, PhD

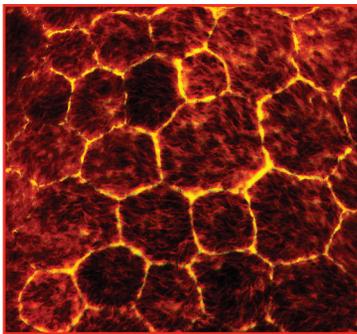
“Various assays can be used to non-invasively quantify transplanted tissue at multiple time points,” he adds.

Using induced pluripotent stem cells (iPS cells), Dr. Tsang is expanding ophthalmic research into inherited and degenerative retinal disorders. His laboratory was the first to restore visual function in a pre-clinical retinitis pigmentosa mouse model using patient iPS cells and to do so without inducing tumor formation. Preoperatively, these mutant mice exhibited an early onset of blindness characterized by profoundly reduced activity on the electroretinogram, proving to be an ideal recipient in which to study the efficacy of stem cell therapy for retinal pigment epithelial-related diseases.

To collect iPS cells from patients, Dr. Tsang obtains a 2mm skin biopsy from which he isolates fibroblasts to be reprogrammed into pluripotent cells, or cells that are not fixed in terms of their developmental possibilities. The process requires manipulating the cell’s specific properties to ensure their transplantation will help

regenerate cells anywhere they are used in the body. Reprogramming the iPS cells allows Dr. Tsang to minimize the chance of cell rejection after transplantation.

“This is not a transplant in the conventional sense, in which an organ comes from another donor,” says Dr. Tsang. “You are not in danger of rejecting the



Retinal cells derived from human iPS cells

donor cells; they are your own cells, taken from your body. All we have done is reprogram your cells in a way that provides the missing link that may cure whatever is ailing you.”

In one study, Dr. Tsang obtained iPS cells from two patients, each with retinitis pigmentosa. Retinitis pigmentosa has multiple genetic sources, but one of the gene mutations associated with the disease has an unknown function. Dr. Tsang studied this particular gene – known as membrane frizzled-related protein (MFRP). In addition to retinitis pigmentosa, its mutations have been associated with nanophthalmos, posterior microphthalmia, foveoschisis, and optic disc drusen in young children. Dr. Tsang’s research sought to investigate the defects this gene creates in cells.

With a goal to reverse these flaws, Dr. Tsang collected iPS cells and altered them using gene therapy. In doing so, he managed to interfere with the process of gene mutation and discovered that the specific defects that MFRP triggers can actually be reversed. This finding was a major step forward in the treatment of blinding diseases, including glaucoma and macular degeneration, although



Dr. Stephen H. Tsang

it also has significant implications for other degenerative disorders of the central nervous system, such as Alzheimer’s and Parkinson’s diseases. Patients suffering from these conditions could potentially benefit from the ability to regenerate cells and tissues from iPS cells. Now, a new technique called CRISPR genome surgery will make the gene editing process even more efficient, which will allow for greater application of iPS cell technology in the future.

“Using iPS cells is like having a patient in a dish,” says Dr. Tsang. The culture dish is a cost-effective and controlled space in which he can conduct experiments to test the success of gene therapy. The alternative, conducting these initial experiments *in vivo* or in live patients, is expensive and often unreliable. While the process of generating new cells from iPS cells has not yet been perfected, these discoveries are remarkable breakthroughs that represent precision medicine’s potential to eliminate human diseases.

### Reference Articles

Wu WH, Tsai YT, Justus S, Lee TT, Zhang L, Lin CS, Bassuk AG, Mahajan VB, Tsang SH. CRISPR repair reveals causative mutation in a preclinical model of retinitis pigmentosa. *Molecular Therapy*. 2016 Aug;24(8):1388-94.

Bassuk AG, Zheng A, Li Y, Tsang SH, Mahajan VB. Precision medicine: genetic repair of retinitis pigmentosa in patient-derived stem cells. *Scientific Reports*. 2016 Jan 27;6:19969.

Moshfegh Y, Velez G, Li Y, Bassuk AG, Mahajan VB, Tsang SH. BESTROPHIN1 mutations cause defective chloride conductance in patient stem cell-derived RPE. *Human Molecular Genetics*. 2016 May 18. [Epub ahead of print]

Li Y, Wu WH, Hsu CW, Nguyen HV, Tsai YT, Chan L, Nagasaki T, Maumenee IH, Yannuzzi LA, Hoang QV, Hua H, Egli D, Tsang SH. Gene therapy in patient-specific stem cell lines and a preclinical model of retinitis pigmentosa with membrane frizzled-related protein defects. *Molecular Therapy*. 2014 Sep;22(9):1688-97.

Yang J, Li Y, Chan L, Tsai YT, Wu WH, Nguyen HV, Hsu CW, Li X, Brown LM, Egli D, Sparrow JR, Tsang SH. Validation of genome-wide association study (GWAS)-identified disease risk alleles with patient-specific stem cell lines. *Human Molecular Genetics*. 2014 Jul 1;23(13):3445-55.

Li Y, Tsai YT, Hsu CW, Erol D, Yang J, Wu WH, Davis RJ, Egli D, Tsang SH. Long-term safety and efficacy of human-induced pluripotent stem cell (iPS) grafts in a preclinical model of retinitis pigmentosa. *Molecular Medicine*. 2012 Dec 6;18:1312-19.

### For More Information

Stephen H. Tsang, MD, PhD • sht2@cumc.columbia.edu



**New York's #1 Hospital  
16 Years in a Row**

## ADVANCES IN OPHTHALMOLOGY

New York-Presbyterian Hospital  
525 East 68th Street  
New York, NY 10065  
[www.nyp.org](http://www.nyp.org)

NON-PROFIT ORG.  
US POSTAGE  
PAID  
STATEN ISLAND, NY  
PERMIT NO. 169