

Vision *for the* Future

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University of Rochester
Eye Institute newsletter

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MESSAGE FROM THE DIRECTOR



Translational Research in Action

One of the cornerstones at the University of Rochester Eye Institute (UREI) is the idea of moving basic scientific discoveries into clinical applications beneficial to patients, commonly called translational research. As we've grown, we've paid close attention to creating the infrastructure and recruiting the faculty and staff necessary in support of this goal. Right now, we are completing one of the most important phases of construction at the Eye Institute, opening additional laboratory space dedicated to understanding and treating the mechanisms of eye disease. This new space now means that the majority of UREI's basic scientists, clinical researchers, clinicians and key collaborators share the same address, thereby accelerating the pace of innovation and moving bedside discoveries to the bedside at a pace more rapid than ever.

In this issue of *Vision for the Future* you'll see a prime example of translational research in action as we revisit **Krystel Huxlin, Ph.D.**'s visual retraining laboratory. In 2001, we reported about promising new experiments that could someday lead to visual recovery in stroke victims who had lost a portion of their sight. On page five, you'll meet a woman who was able to pass her driver's test because of technology developed at UREI. And, you'll see how this new technology may soon be commercialized, helping thousands more recover the vision needed do everyday things we sometimes take for granted.

This type of research — and the life-changing stories that result — couldn't be done without the ongoing support of the individuals and organizations who see the enormous potential in Rochester to do cutting-edge research in ophthalmology. In fact, some of Dr. Huxlin's work is made possible through the generosity of attendees to our first our annual Crystal Ball held two years ago. Their gifts helped fund the purchase of equipment necessary for her continuing work. I am grateful for this kind of support we receive from the community we serve, our research partners and from business luminaries such as **David Flaum**, who we celebrated at this year's Crystal Ball where he was honored as recipient of our Partner in Vision Award.

Sincerely,

Steven E. Feldon, M.D., M.B.A., Director of the Eye Institute

New Evidence in Transcription Factor Interaction Could Prove Useful in Glaucoma Research

In an ongoing effort to better understand how retinal cells develop during neurogenesis, UREI Associate Professor of Ophthalmology **Lin Gan, Ph.D.**, and his research group recently uncovered a novel regulatory mechanism in retinal ganglion cell differentiation. Their findings landed them on the cover of the June 2008 issue of *Development*. Their research suggests a synergetic effect between two transcription factors (ISL1) and (BRN3B) that regulate the development and survival of retinal ganglion cells (RCGs) — RCGs are the cells that die in glaucoma diseases. Dr. Gan's findings show that in the absence of ISL1 and BRN3B, nearly all RCGs die during neurogenesis through the programmed cell death pathway (apoptosis), a common mechanism for neuro-degenerative diseases like glaucoma. Understanding how these transcription factors regulate the development and ultimate survival of RCGs could help scientists create new agents that protect ganglion cells from dying and prevent the progress of neuro-degenerative diseases.



IMAGE COURTESY OF *Development*

Advancing the Vision

The University of Rochester Eye Institute is most grateful to its donors for their generous gifts and ongoing support. We are especially appreciative at this time to the friends, patients, alumni, and faculty who responded to our most successful Eye Institute Annual Fund appeal. The Annual Fund is an essential source of funding that will help continue our ground breaking work in vision care and research.

The following donors have contributed in various ways to UREI between May 1, 2008, and November 30, 2008. Gifts can be designated to the Annual Fund and mailed to: Assistant Director of Development, UREI, 210 Crittenden Boulevard, Box 659, Rochester, NY 14642. Or make a gift online by going to eyeinstitute.urmc.edu and clicking on "Support the Eye Institute."

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In July, Alumni Council Chairman **Karl Marchenese, M.D.**, presented our three new residents with *Basic and Clinical Science* course books. These volumes, vital to resident training, are now provided free of charge thanks to the generosity of alumni who support UREI through the resident education endowed fund.

At the Academy meeting in Atlanta, the Alumni Council welcomed **Cat Burkat, M.D. (M '99, R '03)**. Dr. Burkat is an oculoplastics specialist and assistant professor of ophthalmology at the University of Wisconsin. After welcoming her aboard, more than 50 alumni and friends of the program enjoyed themselves and caught up at the annual UREI reception.

The Eye Institute congratulates longtime supporter of the University of Rochester Department of Ophthalmology **Hobart Lerner, M.D. (R '49)**. Dr. Lerner received the 2008 Outstanding Advocate at this year's American Academy of Ophthalmology meeting in Atlanta. The award recognizes Academy members who participate in activities promoting ophthalmology at the state and (or) federal level. Dr. Lerner's tireless work lobbying on behalf of ophthalmology has resulted in better care for the patients we serve.

Fellowship Bound

Our third-year residents have big plans for the upcoming year as all of them were selected for medical fellowship programs.

Babak Jian Seyedahmadi, M.D., is off to Harvard and the Massachusetts Eye and Ear Infirmary where he will begin sub-specialty training as a vitreoretinal surgeon. **Michael Bradley, M.D.**, will begin his cornea fellowship at the University of California Irvine. **Salman Ali, M.D.**, accepted his fellowship appointment in glaucoma at Wayne State University's Kresage Eye Institute. Congratulations and good luck to them all.

Eye on the Community

Keeping area eyes healthy is a non-stop mission at UREI. And thanks to the generous support of our many donors, underwriters and community partners, physicians, residents and staff of the Eye Institute we are able to serve the community at large. This occurs through screenings of populations at risk for eye disease and by educating groups about better caring for their vision.

In September, the clinical trials team conducted screenings for dry eye and migraine headache at the Speaking of Women's Health event.

October was even busier as **Shakeel Shareef, M.D.**, helped a team of residents and members of the Friends of the Congressional Caucus Foundation conduct 117 glaucoma screenings at the annual Alesi Health Fair. Later in the month, **David Kleinman, M.D.**, educated more than 100 people about age-related macular degeneration and diabetic eye disease at the Highlands of Pittsford.

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We offer special thanks to Bausch & Lomb, Research to Prevent Blindness, and David & Eileen Flaum for their sustaining support.

CLINICAL TRIALS

- ⊙ Central Corneal Thickness Study in Normal Pediatric Population (*M. Gearinger, M.D.*)
- ⊙ MAP Migraine Treatment Trial (*D. Friedman, M.D.*)
- ⊙ A Multi-center Trial to Determine the Efficacy of Zylet for the Treatment of Pediatric Blepharoconjunctivitis (*M. Gearinger, M.D.*)
- ⊙ A Phase-3 Trial Comparing Antiangiogenic Agents VEGF Trap-Eye and Ranibizumab (Leucentis®), for Use in Wet AMD (*D. DiLoreto, M.D., Ph.D.*)
- ⊙ A Clinical Study to Assess Efficacy of Sub-Conjunctival Injections of Sirolimus in Patients with Diabetic Macular Edema Secondary to Diabetic Retinopathy (*D. Kleinman, M.D.*)
- ⊙ A Multi-center trial to determine whether patients who undergo closure of a Patent Foramen Ovale with an AMPLATZER® device have a reduction in both the frequency and severity of migraine headaches compared to medical management (*D. Friedman, M.D., and F. Ling, M.D.*)

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Please call for more information about these studies, as well as other ongoing studies.

Intra-tissue Refractive Index Shaping (IRIS) — the Future of Vision Correction?

Associate Professor of Ophthalmology **Krystel Huxlin, Ph.D.** and a team of researchers from the Eye Institute and the Institute of Optics reported an exciting discovery that could change the world of laser refractive surgery and vision correction in general. In December's issue of *Investigative Ophthalmology and Visual Science*, the group describes an application of low-pulse-energy, MHz femtosecond lasers for noninvasively modifying the refractive index of transparent ocular tissues without apparent tissue damage. This technology could someday supplant the creation of a flap with a laser or mechanical microkeratome in refractive surgery procedures like LASIK.

New RPE Gene Identified

Retinitis pigmentosa (RP) is a collection of inherited diseases affecting the photoreceptors and impacts the vision of more than 1 million people worldwide. **Mina Chung, M.D.**, along with collaborators at the University of Iowa and Associated Retinal Consultants (Traverse City, Michigan) recently uncovered a disease-causing gene previously not associated with RP. Their findings were reported in the September 2008 issue of *Archives of Ophthalmology*. Their studies centered on a six-generation family with members who were found to be clinically affected with autosomally dominant RP — autosomally dominant means that there is a higher probability for the RP mutation to be passed on to offspring. Genetic testing of family members identified the RDH12 gene as the site of autosomally dominant RP. Not only does this discovery demonstrate the wide variability of genes associated with retinal degenerative diseases, it could eventually provide for better screening for RP and provide further insight the workings of photoreceptors.

Scientists Receive Grants from Rochester Eye and Tissue Bank

The Rochester/Fingerlakes Eye and Tissue Bank has awarded more than \$30,000 to two UREI researchers to help fund various projects. **Richard Libby, Ph.D.**'s investigation, *Histological Analysis of Human Glaucoma*, will look to answer how and why retinal ganglion cells die in glaucoma and could play an important role in developing therapies for this disease. Fellow researcher **Geunyoung Yoon, Ph.D.**'s project, *Real-time Observation of in situ Tear Film Dynamics with Optical Coherence Tomography and Wavefront Sensor*, aims to better understand dry eye syndrome — a condition affecting more than 20 million Americans — and look at more effective treatments.

In 2001, Vision for the Future visited Dr. Krystel Huxlin's Visual Recovery Laboratory, where she was investigating the possibility of helping stroke victims recover their lost vision. We recently revisited Dr. Huxlin to see how the research is progressing.

How far has the concept of visual retraining come over the last seven years?

The advances have been phenomenal. The hotly debated premise that the adult visual system has plasticity — the idea that the brain can re-learn to process visual signals thought lost forever — is at the threshold of gaining scientific acceptance. To this point, we have just published our results in the highly respected *Journal of Neuroscience*. This is great news for people who have suffered blindness due to a stroke or other type of brain injury, because now there is hope that we can restore some of their vision.

How do strokes affect vision?

When someone suffers a stroke or traumatic brain injury, there is a reasonable likelihood that the primary visual or occipital cortex may be damaged. This is the area of the brain responsible for processing and making us aware of the visual signals collected by the eye. Damage to the primary visual cortex causes blindness over a large part, sometimes half, of a person's visual field. This type of blindness can be devastating because it severely impairs the ability to do routine things (like reading, driving a car or shopping in a crowded store). Scientific and medical opinion has traditionally said that the loss of vision is permanent because the neural tissue destroyed cannot regenerate.

How does visual retraining work?

At UREI, we believe we've found a way to get around the damaged caused to the V1 cortex. There is a region in the brain downstream of V1 called MT that usually remains intact after an occipital stroke. This area of the visual cortex specifically deals with how we process visual motion. Research has shown that visual signals related to motion don't necessarily have to go through the primary visual cortex to get to MT. By designing specific visual training tasks that use motion to stimulate MT, we can restore a significant amount of the vision that was lost.

Visual motion perception is a particularly important aspect of vision for us humans because we live in a world of continual motion. As a result, the vision that is recovered with our training paradigm works in many every day settings. To date, we have retrained 15 subjects with V1 damage. Everyone so far has regained some level of useful vision.

What's going on in the laboratory today?

We recently received a grant to use functional magnetic resonance imaging (fMRI) to study the effects of visual motion retraining. With fMRI, we are able to visualize how the brain recovers. This is essential if we are to design more effective, principled methods of retraining that recover more vision, more quickly for the patient.

Another set of studies we have begun uses a high-tech virtual world, in which we simulate a three-dimensional, realistic environment in motion. Here we challenge each patient to detect flying virtual basketballs that appear randomly from different directions, including some that encroach upon blind

Helping stroke victims recover their lost vision

portions of their visual field. Initially, patients are unable to detect any of the balls appearing in their blind field. After several months of motion training in their blind field, however, their brain begins to see the balls as the new pathways develop. Session by session, the balls are detected further and further into the damaged field of vision, giving us a good indication of how our visual training paradigm translates to a naturalistic, three-dimensional situation.

What are the clinical plans for this technology?

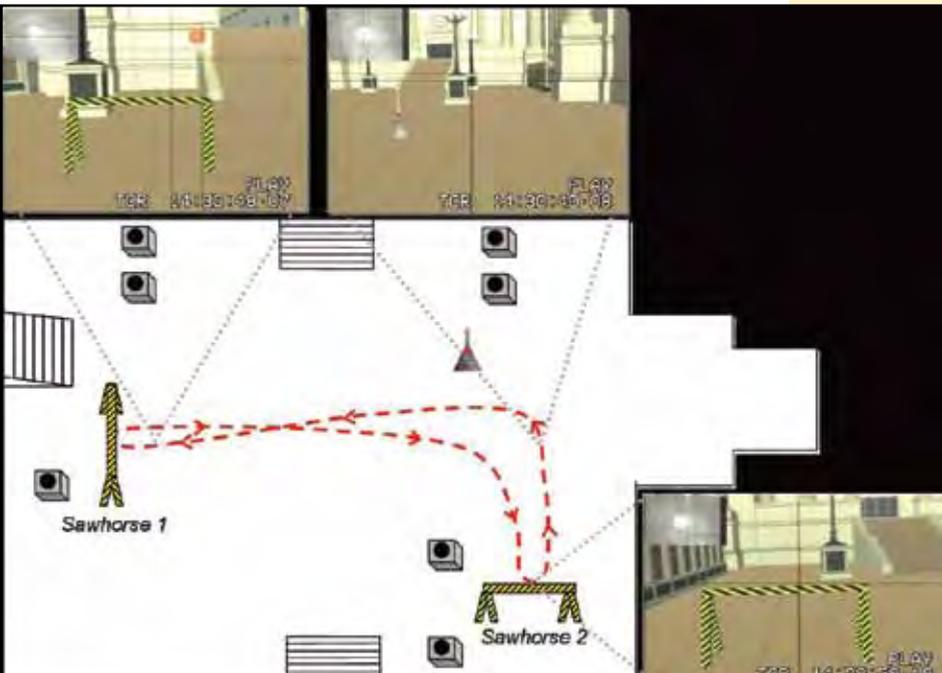
The obvious goal is to help retrain the vision of millions of patients who have suffered visual cortex damage. The good news is that we think the therapy will work for patients long after the damage occurred. As far as we know, ours is the only method that uses motion simulation to reroute visual pathways to MT. We soon hope to have approval on a patent that will facilitate licensing the technology for clinical uses.

Since we have found that visual training also works for people who do not have brain damage, we are also looking at other



Krystal Huxlin, Ph.D.

Krystal Huxlin, Ph.D., is an associate professor of Ophthalmology at the University of Rochester Eye Institute. Her research focuses on understanding the cellular basis and psychophysical characteristics of visual perceptual plasticity in adulthood. Dr. Huxlin has numerous publications and is the recipient of National Eye Institute, Research to Prevent Blindness and Gustavus and Louise Pfeiffer Research Foundation grants. She completed her B.S. and Ph.D. degrees at the University of Sydney in Australia.



Complex simulations allow patients to “walk” in a virtual world where their brains slowly learn to process complex visual signals again.

uses of this technology. For instance, there may be applications for helping low-vision patients (such as those with macular degeneration) by improving their ability to process the limited visual signals that they receive from a diseased eye. There may also be interest in sharpening the vision of people with healthy eyes, like pilots or athletes, who are engaged in occupations where keen eyesight and precise visual performance are critical.

Better Vision Through Motion

As visual motion training progresses, some of the lost vision in the blind field is gradually recovered. For one of the study subjects, the change was dramatic enough to restore her ability to drive.

In 2003, Millie Sauer suffered a stroke after having back surgery. Affecting her vision, she became unable to drive. “It was terrible,” she said. “I was just plain scared and depressed. My neurologist told me that the visual loss was permanent and to get used to living this way.”

Unwilling to accept her prognosis, Millie conducted an extensive Web search that led her to Dr. Huxlin. “I refused put up with things the way they were,” she said. “I felt I had nothing to lose, so I e-mailed Krystal and she admitted me to the study.

Since I started the training, enough vision has come back to help me cope with everyday life.” So much that when she recently went to renew her driver’s license, she surprised herself.

“I told them my problem and they gave me the forms for my doctor to fill out (requesting a restricted license). I asked if I could try their machine that tests peripheral vision to see how it would turn out. Of course my right side was normal, but when they did my left side, lo and behold I saw the dim flashes of light as they turned them on and off. I was in shock and couldn’t believe my good fortune. They said I passed the test and proceeded to renew my license for another four years. Unbelievable!”

“I don’t drive much now, and when I do it’s not on the expressways. But I am confident on the secondary roads and feel much more visually aware of myself in unfamiliar locations like grocery stores,” she said. “I know I’ll never be the same as I was (before the stroke) but Krystal has been a lifeline. She has my undying gratitude.”

Crystal Ball "THE SEQUEL"

Nearly 300 gathered in the Bausch & Lomb Wintergarden to celebrate vision and honor University of Rochester Eye Institute supporter and Advisory Board member **David M. Flaum**. The gala event, now in its second year, featured a boutique of glass art, photography and sunglasses and culminated in a spirited auction that included trips to Paris, Scotland and an appearance on USA Network's top-rated *Burn Notice* television show. Proceeds raised will help to fund the Eye Institute's mission of providing unparalleled eye care to people throughout the region and to develop new therapies and diagnostics vital to advancing the treatment and prevention of blindness. We especially recognize David Flaum's contributions to UREI and the generous support of all our sponsors, table captains and those who donated merchandise to the auction. We also gratefully acknowledge the support of the Crystal Ball planning committee led by **Rina Chessin** and **Diane Feldon** and thank all our volunteers from the Eye Institute and the University community at large.



A NIGHT WORTH SEEING...





CME Calendar

54th Rochester Ophthalmology Conference

On March 20–21, **Stanley Chang, M.D.**, and **Randall Olson, M.D.**, highlight an outstanding list of guest speakers as the annual Rochester Ophthalmology Conference enters its 54th year. In addition, the Bausch & Lomb Visiting Professor Lecture Series continues to draw some of the finest talent in ophthalmology to Rochester.

Bausch & Lomb Visiting Professor Lecture Series

February 21	Michael Kazim, M.D. (Columbia University) <i>Oculoplastics</i>
April 18	David Huang, M.D., Ph.D. (University of Southern California) <i>Cornea & Refractive Surgery</i>
May 16	Paul Sternberg, M.D. (Vanderbilt University) <i>Retina</i>
June 20	Emily Chew, M.D. (National Eye Institute) <i>Retina</i>

Translational Research Labs Completed: Moving in, Moving Forward.

There is noticeable excitement on the ground floor of the Eye Institute as researchers begin occupying 10,000 square feet of recently finished laboratory space. This brings to completion the \$5.5 million NIH-supported construction phase of UREI's research infrastructure development and further enhances the Eye Institute's mission to be a leader in eye-related translational research. The centerpiece of this construction are laboratories housing specialized programs and equipment that will help to further understand and treat eye diseases and visual disorders:

Fridenwald Award winner **David Williams, Ph.D.**, and collaborators (including UREI's **Mina Chung, M.D.**, **Alfredo Dubra, Ph.D.**, and **William Merigan, Ph.D.**) will study photoreceptors and the sub-cellular structures of the retinal pigment endothelium. They will do so using the world's only laser scanning ophthalmoscope equipped to do simultaneous two-photon fluorescence and adaptive optics imaging. The unprecedented detailed views of the back of the eye captured by this instrument could result in better treatment and diagnosis for diseases such as age-related macular degeneration (AMD) and spin-offs from this technology are already being commercialized for physician use.

James Aquavella, M.D., along with **Geunyoung Yoon, Ph.D.**, and **James Zavislan, Ph.D.**, will continue the search for better treatments for the 30 to 45 million Americans with dry eye. A unique new environmental chamber will allow the group to study the surface of the eye and tear film and establish the factors contributing to this condition that ranges in severity from a mild annoyance to severe discomfort and blindness in some. Their research could help pharmaceutical companies develop better therapies for dry eye patients.

Krystal Huxlin, Ph.D., will share time between two labs. The first involves her work with investigating perceptual plasticity of the damaged adult visual system. Here, patients' vision will be retrained using the world's only virtual reality system scientifically designed to restore visual motion sensitivity. In the other laboratory, Dr. Huxlin will continue her collaborations with **Wayne Knox, Ph.D.**, to further improve laser refractive surgical procedures and develop the next generation of refractive surgery technology.

In addition to his work in Dr. Aquavella's lab, **Geunyoung Yoon, Ph.D.**, will continue to pursue new ways to improve vision and vision testing through adaptive optics. His collaborations with **Scott MacRae, M.D.**, **Shobha Boghani, M.D.**, and Boston Foundation for Sight's **Perry Rosenthal, M.D.**, aim to improve sight for patients with keratoconus, dry eye and presbyopia.

Soon the Eye Institute will relocate the clinical trials group from the third floor to space adjacent to the new research laboratories. This will allow patients participating in clinical trials easy access to translational researchers and their unique equipment, further speeding the development and deployment of technologies that better diagnose and treat eye disease.

Dysgenesis Researcher Receives Career Development Award

Amy Kiernan, Ph.D., is the latest in a number of UREI researchers to receive a career development award from Research to Prevent Blindness (RPB). Dr. Kiernan will use the \$200,000 in funding to continue her investigation into better understanding of anterior segment dysgenesis. ASD occurs when a child's eye does not develop correctly and refers to a group of clinically-defined conditions (such as glaucoma) that may result in blindness and have severe cosmetic and associated psychological consequences for the child. The goal of her research is to decode the complex molecular interactions that take place during development of this part of the eye so that we can better diagnose, and eventually treat children suffering from ASD.

In related news, Dr. Kiernan also recently received notice of award of more than \$1.6 million from the National Institutes of Health to study notch signaling during sensory development and differentiation within the ear. Understanding these how these pathways work during the formation of sensory organs develop could provide key insights into devising strategies of how to regenerate cells and possibly provide therapeutic benefits in other sensory organs.



Alfredo Dubra, Ph.D.

New Faculty, Additions & Distinctions

The Eye Institute welcomes **Alfredo Dubra, Ph.D.**, to the research faculty. He joins UREI as assistant professor of ophthalmology after finishing his post-doctoral fellowship under the Center for Visual Science's **David Williams**. Dr. Dubra completed his doctorate in physics at the prestigious Blackett Laboratory of Imperial College, London, and is a 2007 winner of a Burroughs Wellcome Fund Career Award for his research proposal, "Understanding eye disease through structural and functional in vivo cellular imaging of the retina." Dr. Dubra's research will focus on applying advanced

microscopy techniques to visualize retinal structure and function in novel ways, with the aim of increasing the sensitivity and specificity of eye disease diagnosis. Emphasis will center on developing better screening methods for glaucoma by noninvasively imaging retinal ganglion cells (RCGs). Visualizing RCGs is important for early diagnosis of glaucoma, before it causes irreversible vision loss to the patient. The technology will also help drug companies evaluate the performance of new treatments for the disease.

- ▶ **Jill Schafer, O.D.**, has joined the clinical faculty full-time as assistant professor of ophthalmology. Dr. Schafer is a graduate of the Ohio State University College of Optometry and has been for the last six months seeing patients part-time as part of our comprehensive eye care group.
- ▶ We would also like to congratulate **Dorothea Castillo, C.O.A., C.R.A.**, on receiving honorable mention for her Fluorescein Angiogram at this year's Academy meeting. **Margaret Embrey, C.O.T.**, was also honored at the AAO meeting in where she won a Joint Commission of Ophthalmology scholarship for her submission to this year's essay competition "Ten Ways to Recruit Ophthalmic Medical Personnel into Certification Programs."

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OUR MISSION

*The mission of the
Eye Institute is to
develop and apply
advanced technologies
for the preservation,
enhancement, and
restoration of vision
through a partnership
of academic medicine,
private industry, and
the community
we serve.*