RETINOPATHY RESEARCH TO SAVE SIGHT AND LIVES

The retina, the light-sensitive inner layer of the eye, is an area of great scientific significance. Not only does it enable vision, it is an extension of the brain. The retina is composed of neural tissue, much like that larger organ from which it emerges during fetal development. As a result, research into the workings of the retina has a great impact on medical science's understanding of and treatment of dysfunctions in the brain, as well as in the retina itself.

Douglas Lazzaro, MD, chairman of SUNY Downstate's Department of Ophthalmology, says "the retina is an area where there's tremendous new research activity going on," much of it featured here.

Downstate now has a director of ophthalmic research, William J. Brunken, PhD, whose investigations into retinal proteins called laminins and netrins may one day help restore sight to the visually impaired. Brahim Chaqour, PhD, investigates the molecular underpinnings of diabetic retinopathy, a microvascular disease that is one of the leading causes of blindness in the United States, all in an effort to develop treatments that may one day prevent the disease.

Gladys Teitelman, PhD, a diabetes researcher who has concentrated mostly on the regeneration of insulin-producing pancreatic beta cells, has widened her investigations to also include diabetic retinopathy. Daniel Rosenbaum, MD, chairman of Downstate's Department of Neurology, uses the retina as a model for understanding what happens to brain cells during strokes. And Ivan Bodis-Wollner, MD, DSc, director of the Parkinson's Disease and Related Disorders, Center of Excellence of the National Parkinson Foundation, explores how changes in the retina both signal and influence the development of Parkinson's disease.

"The research we're doing at Downstate is leading to new understandings of retinal diseases and the nervous system," Dr. Lazzaro says. "Most importantly, we're creating potential new avenues of treatment."

An Eye Into Parkinson's Disease

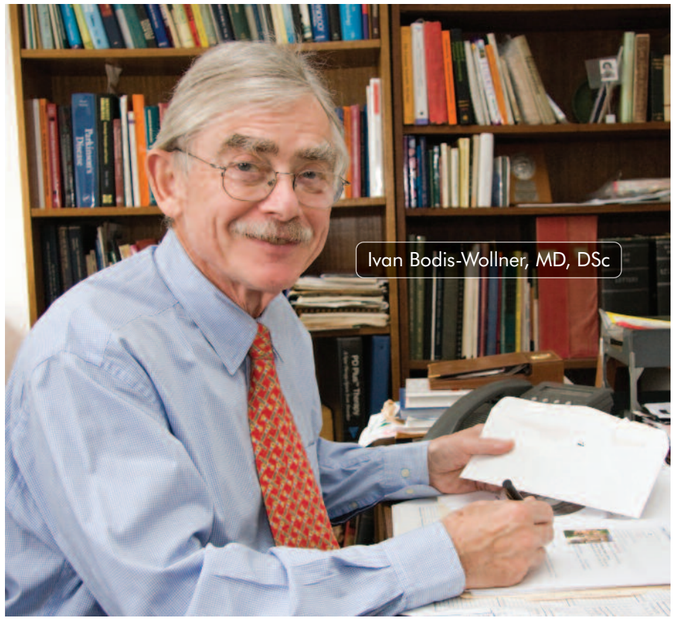
Like many illnesses affecting the nervous system, Parkinson's disease is difficult not only to treat but also to monitor.

New evidence suggests that the degenerative motor disorder begins in the peripheral nervous system and then works its way to the central nervous system — most importantly, to the brain. Once established there, this disease can cause a host of neurological problems: tremors, motor impairment, communications difficulties, and mental disturbances.

Visual problems were not thought to be part of Parkinson's disease, however. From the time the illness was first described in the early 1800s, until more than 150 years later, the loss of visual acuity and the difficulty in distinguishing contrast many Parkinson's patients experience were attributed to other causes, such as aging, cataracts, and glaucoma.

But in the late 1970s, Ivan Bodis-Wollner, MD, DSc, professor of neurology and ophthalmology and director of University Hospital's Parkinson's Disease and Related Disorders Center, one of the National Parkinson Foundation's Centers of Excellence, showed that Parkinson's disease itself can have a negative impact on vision.

In 1978, using electrophysiology — brain-wave monitoring through externally applied electrodes — he was the first to document delayed visual processing in the brains of individuals with Parkinson's disease. Following that, he used the method again, this time discovering among Parkinson's patients deficits in contrast-sensitivity — difficulty distinguishing an image from its background.


Ivan Bodis-Wollner, MD, DSc

Importantly, as part of that research, he showed that vision changes in tandem with neurological functioning. "When a patient doesn't move well," Dr. Bodis-Wollner explains, "he doesn't see well."

"The ability to image the retina may revolutionize the process of evaluating and monitoring the neuronal changes that occur in Parkinson's disease."

Motor problems in Parkinson's disease are caused by the death of neurons that secrete and process an important neurotransmitter called dopamine. Dr. Bodis-Wollner's research established that the death of these neurons, called "dopaminergic" cells, is also responsible for Parkinson's-related visual problems. "Without dopaminergic cells, dopamine-sensitive cells are deprived of dopamine" he notes, "and are no longer able to make very important decisions that relate to vision and to motor execution."

In the late 1990s, intrigued by the role dopaminergic cells play in the vision of Parkinson's patients, Dr. Bodis-Wollner developed a quantitative description of the relationship between the retina's dopaminergic and dopamine-sensitive cells. A major advance in the Parkinson's disease field, the model has been used to predict the retina's response to new and existing Parkinson's treatments.

In the last several years, Dr. Bodis-Wollner has employed a new imaging technology called Optical Coherence Tomography (OCT) to detect microscopic changes in the retina. Says Dr. Bodis-Wollner, "the ability to image the retina may revolutionize the process of evaluating and monitoring the neuronal changes that occur in Parkinson's disease."

Using OCT, he has been among the first to measure the retinas of individuals with Parkinson's disease. Often, they are 15 to 20 percent thinner than normal. "This loss may be a major reason why Parkinson's patients have trouble detecting contrast," Dr. Bodis-Wollner says. "And we've learned that the area of the retina affected in Parkinson's may impair visual cognition," the ability to respond to and categorize visual images.

Dr. Bodis-Wollner looks forward to furthering this research by acquiring the latest generation OCT equipment. "With these machines, we hope to be able to specify dopaminergic cells, in addition to measuring the retina's thickness," he notes. Giving researchers access to cell counts could dramatically alter the course of clinical trials for new Parkinson's treatments.

Until recently, "investigators have had to rely on clinical observations and wait a minimum of 18 months to discover the impacts of potential neuroprotective treatments on the brain's dopaminergic pathways and, thus, on disease progression," Dr. Bodis-Wollner explains. With the detailed counts of retinal dopaminergic cells and information on retinal thinning that advanced OCT equipment can provide, researchers may be able to assess much more quickly and accurately whether a new treatment has arrested neuronal degeneration.

Dr. Bodis-Wollner notes, "OCT should be able to help quite a lot in our quest for neuroprotective agents — agents that can stop the dying-off of dopaminergic cells." And with that, help stop the progression of Parkinson's disease itself.

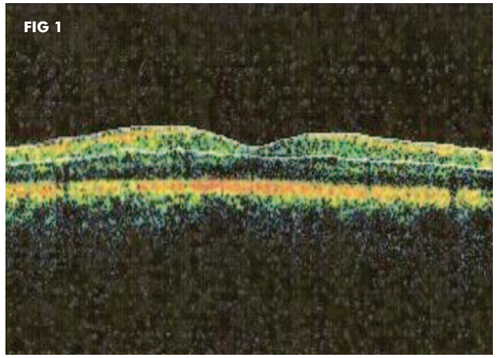


FIG 1

Fig 1 The OCT of the retina of a healthy subject (46 years of age). The bottom of the picture represents the outer layers of the eye; the top, the inner layers. The dip, or "valley", in the center is normal: retinal neurons are pushed to the side to allow light to penetrate to the outer layers, where photoreceptors are located.

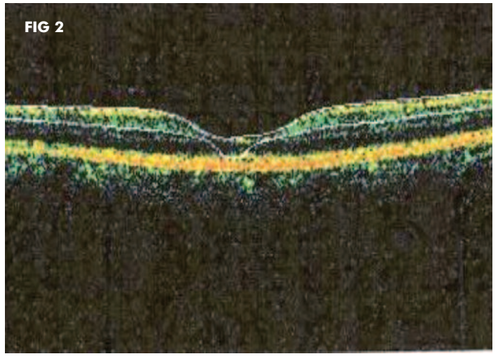


FIG 2

Fig 2 The OCT of the retina of a Parkinson's disease patient (50 years of age). The "valleys" - top and center - represent the loss of neurons in the inner retina, including the nerve cells which transmit visual information to the brain.


Dr. Bodis-Wollner with M. Asim Javaid, MD, postdoctoral research fellow, Sofya Glazman, MD, coordinator, Parkinson's Disease and Related Disorders Center of Excellence of the National Parkinson Foundation.

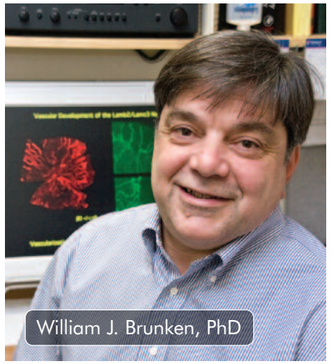
The Exquisite Beauty of Ocular Architecture

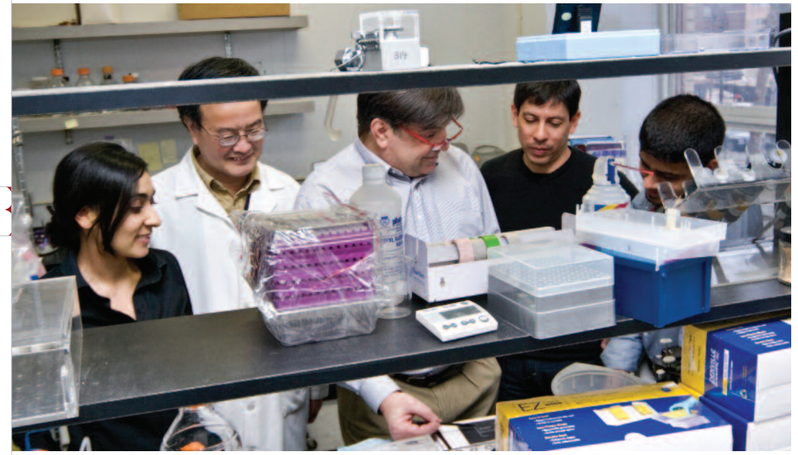
William J. Brunken, PhD, is keenly interested in the architecture of the eye's light-sensitive inner layer, the retina.

"As an undergraduate," says Dr. Brunken, an associate professor of anatomy and cell biology, ophthalmology, and neurology, "I got hooked on the retina's elegantly organized structure. Its columnar organization is very carefully constructed, with a gorgeous symmetry to it."

Dr. Brunken, director of SUNY Downstate's division of ophthalmic research, explores the molecular signals that create, maintain, and sometimes deform and destroy that structure.

His investigations into proteins found in the retina's extracellular matrix, the biological scaffolding that binds its cells together, may lead to treatment breakthroughs for a number of ocular diseases. These include diabetic retinopathy, age-related macular degeneration, and retinopathy of prematurity, a vision-loss problem associated with premature birth. His research may even help restore vision to those whose retinal problems have resulted in blindness.





Members of Dr. Brunken's lab: (left to right) Aarti Kuver, PhD student; Zeng-Xiu Liu, MSc, research associate; Dr. Brunken; Germán Pinzón-Duarte, MD, research associate; Gopalan Gnanaguru, PhD student.

Dr. Brunken has spent much of his recent career studying two specific retinal proteins, laminins and netrins, which he describes as guidance molecules. "They tell cells where to go and how to function when they get there," he explains.

Without laminins and netrins, retinal development is disrupted and vision itself may well be impossible. Moreover, laminins and netrins "stabilize synapses," the junctions between brain cells across which neural communication takes place, Dr. Brunken says.

The connections between the light-sensitive cells in the retina and the cells that convey visual signals to the brain are held together by laminins, "which are the chief organizers of one of the retina's and one of the body's, most important structures: the basement membrane."

In a series of papers published in *Neuron* and the *Journal of Neuroscience*, Dr. Brunken and his group were the first to demonstrate the presence of native laminins in the central nervous system.

Basement membranes in the retina, and elsewhere, serve as platforms onto which cells attach themselves. They also orient tissue development, "telling cells what is top and what is bottom, and therefore how cells should organize themselves," Dr. Brunken notes. "These properties make them critical for retinal development. If the basement membrane doesn't form properly, then the attachment of cells is irregular and the retina's columnar organization, and its ability to transmit visual signals, is lost."

Dr. Brunken's lab has identified four of the approximately forty laminin variants that are active in retinal tissue. Mutations in one of the genes that produces the laminin beta-2 protein, a gene called LAMB2, "completely disrupts vascularization of the retina during fetal development," Dr. Brunken notes. "What results is a very altered pattern of vascularization, much like one sees in children with retinopathy of prematurity, where inflammation and, eventually, the death of retinal tissue, disrupts the visual field."

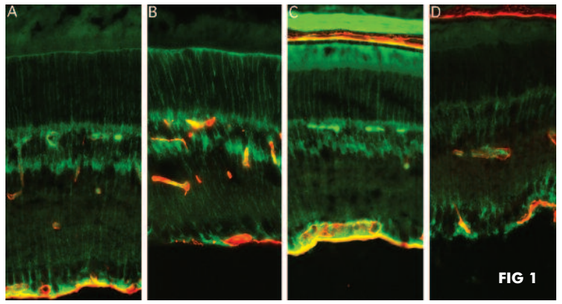


Fig 1. A section of the mouse retina stained with fluorescent protein markers. Support cells, Müller glia (green), span the whole retina and adhere to the retinal basement membrane (red line at bottom of the figures); the adhesion points are yellow. Some genetic deletions of laminins (B and D but not C) cause alterations in Müller cell and, secondarily, in retinal anatomy.

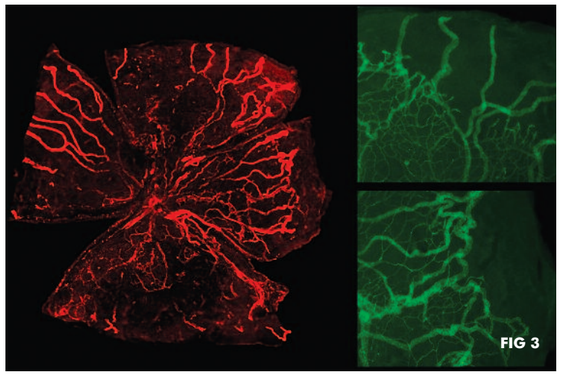


Fig 3. Blood vessels are under-developed in laminin mutants.

Other laminin mutations lead to rare but complex diseases that involve the eye along with other bodily systems. These diseases include Pierson syndrome, Merosin-dependent muscular dystrophy, and Herlitz junctional epidermolysis bullosa.

Dr. Brunken has created a mouse model in which two laminin genes have been removed. These mice have all the symptoms of eye-brain-muscle disease, a complex neurodevelopmental disorder.

Of particular interest to Dr. Brunken is the role netrins play in the retina's organizing structure. "A netrin is nothing more than a small piece of a laminin," he explains. "Laminins are cross-shaped molecules and netrins are the ends of the arms of the cross."

Working with Manuel Koch, PhD, of the University of Cologne, in Germany, Dr. Brunken's lab discovered that a novel type of netrin, called netrin-4, regulates axon guidance in the retina.

"Netrin-4 helps bundle axons in the retina together, enabling communication between the retina and the rest of the brain's visual apparatus," Dr. Brunken says. Perhaps, most importantly, netrin-4 regulates the branching of the retina's deepest capillaries.

Understanding the basic functions of these proteins may lead to new treatments for a number of eye diseases, Dr. Brunken says. "If we can separate out the cell-binding domains — the parts that interact with receptors on cell membranes of molecules — we can use those pieces for drug development."

Dr. Brunken's investigations may also lead to a new way of treating vision loss from retinal defects. "Given that laminins and netrins are guidance molecules and stabilize synapses," Dr. Brunken explains, "we hope we can incorporate them into a microchip-based neuroprosthesis that would promote a kind of synapse between the prosthesis and the retina. The hope would be to fool neurons into thinking a silicon chip is a photoreceptor."

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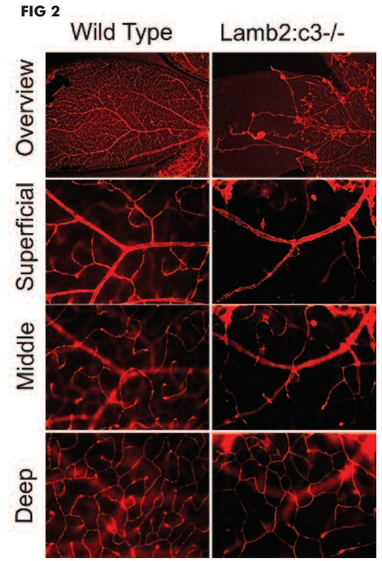


Fig 2. The development of retinal blood supply is dependent on laminin synthesis. Blood vessels spread over the normal retina (left side, overview) forming three different capillaries networks at the surface, in the middle, and deep within the retina. In animals with laminin gene deletions (right column) the development of blood vessels is altered dramatically. The entire surface of the retina is not covered with blood vessels (overview) and the branching of all three levels of the capillaries are disrupted. These effects mimic a human disease called retinopathy of prematurity, a blinding disorder found in some premature children.

Decoding Diabetic Retinopathy

Between 12,000 and 24,000 Americans go blind each year as a result of diabetic retinopathy.

Diabetic retinopathy usually develops over several years and has its origins in the body's poor control of blood sugar levels. At the onset, the tiny blood vessels in the retina begin to swell and leak. Next, some of these vessels close off. Then, as more of them are blocked, the retina sends molecular signals that initiate a frenzied formation of new and fragile blood vessels. In the advanced stages, called proliferative retinopathy, these weakened vessels invade the vitreous gel that fills the eye; when they leak, severe vision loss or blindness results.

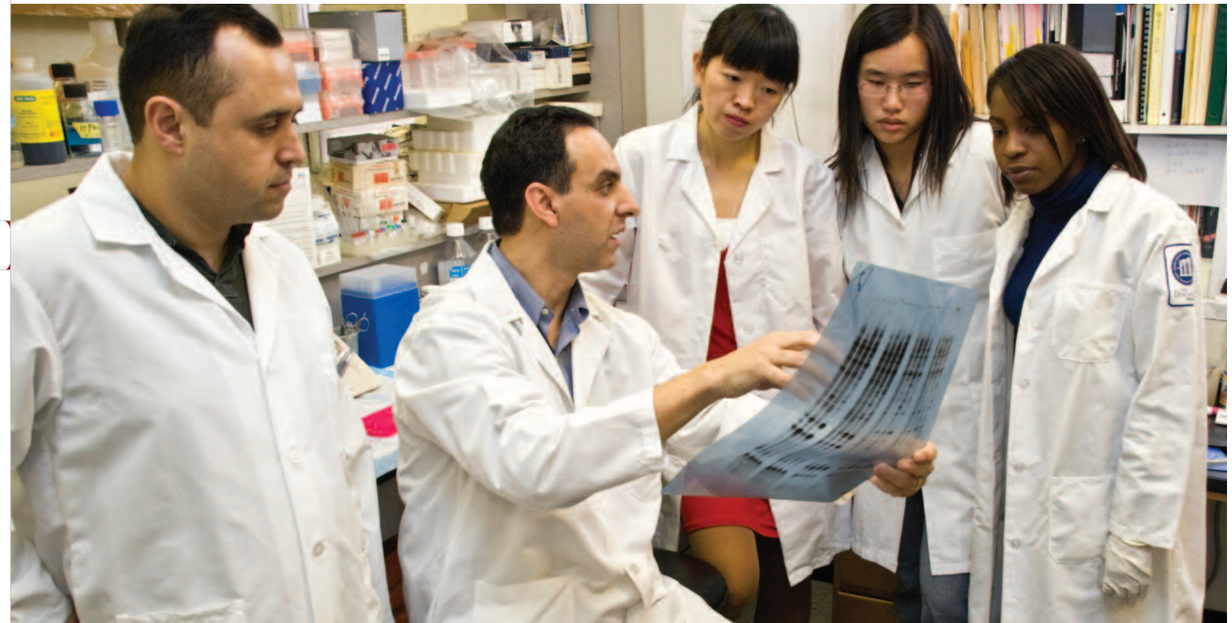
To date, a high-tech vision-saving technique called scatter laser surgery can, when administered early, improve the vision of people with diabetic retinopathy. But the procedure has limitations. Often, it can lead to the loss of peripheral vision, and, because new blood vessels continue to grow, the procedure must be repeated.

To develop better treatments for this vision-impairing disease, Brahim Chaqour, PhD, an assistant professor of anatomy and cell biology at SUNY Downstate, is decoding the molecular processes that underlie diabetic retinopathy. "My goal is to understand a number of mechanisms that affect blood vessel growth and degeneration," he says. These include the role of angiogenic factors, which lead to the proliferation of new blood vessel branches, and the role of anti-angiogenic factors, which lead to the destruction of pre-existing blood vessels and the formation of new blood vessel branches.

"A better understanding at the molecular level will help us learn how to control the process, both in the early and later stages of the disease," he says.

Dr. Chaqour has made great progress towards this goal. He has identified a "small family of genes," that, in the presence of hyperglycemia (high blood sugar levels), plays a crucial role in all phases of diabetic retinopathy. Working in tissue culture and with laboratory animals, he has documented how these genes, normally active only during embryonic and fetal development, initiate the weakening of healthy retinal blood vessels and promote the formation of new, leaky ones.

Members of Dr. Chaqour's lab: (from left to right) Jorge Espinoza, PhD student; Dr. Chaqour; Haibo Liu, PhD, postdoctoral fellow; and Hunter College interns Michelle Lee and Tyesha Williams.



On a fundamental level, Dr. Chaqour is interested in the ways that cellular environment affects cell behavior. In the hyperglycemic milieu of the diabetic retina, the pericytes, the smooth muscle cells forming the outer layer of capillaries, begin to die. That process further deprives the retinal tissues of oxygen. Dr. Chaqour and his colleagues discovered that when this oxygen deprivation occurs, two long-dormant genes, Cyr61 and CTGF, from the family Dr. Chaqour has identified begin to express themselves in the retina. Their proteins accumulate in the space surrounding blood vessel cells, further exacerbating pericyte death.

That's not the only role Cyr61 and CTGF play in diabetic retinopathy. During the most advanced stage of diabetic retinopathy, their over-expression contributes to the uncontrolled proliferation of new, leaky blood vessels, Dr. Chaqour has concluded. "The proteins these genes express even cause blood vessels to grow into the eye's vitreous gel, which, under normal conditions, is completely free of blood vessels. There's no control mechanism in these newly activated genes that allows them to stop."

Dr. Chaquour's lab discovered that vasculogenesis, the creation of entirely new blood vessels from stem cells, is promoted by the Cyr61 protein as well. Until recently, scientists believed that angiogenesis — the branching off of new blood vessels from existing ones — was the only blood vessel-formation mechanism involved in the disease. In fact, "scientists believed vasculogenesis took place only during embryonic development and then stopped altogether," he says. By exposing stem cells to Cyr61 in tissue culture, Dr. Chaqour and his colleagues demonstrated "this protein promotes the process of vasculogenesis involved in diabetic retinopathy."

Another of his important discoveries is a protein called MMP-2. "In the normal retina," Dr. Chaqour explains, "there's almost no MMP-2. But in diabetic animals, Cyr61 and CTGF induce expression of MMP-2." The protein destroys the extracellular matrix, the biological scaffolding that stabilizes and connects cells. "This further degrades the pericytes."

Dr. Chaqour is using these discoveries to develop pharmacological treatments that may derail diabetic retinopathy, even in the absence of tight blood sugar control. "We're trying," he says, "to put together recombinant peptides that will interrupt the growth of abnormal blood vessels and allow healthy retinal activity to occur."

Already, Dr. Chaqour and his colleagues developed several compounds, still unnamed, that block the destructive action of MMP-2. "That's not enough to stop diabetic retinopathy, yet," Dr. Chaqour says. "But it's a start. One day, we may discover a pharmacological treatment that enables patients to avoid the current surgical one."

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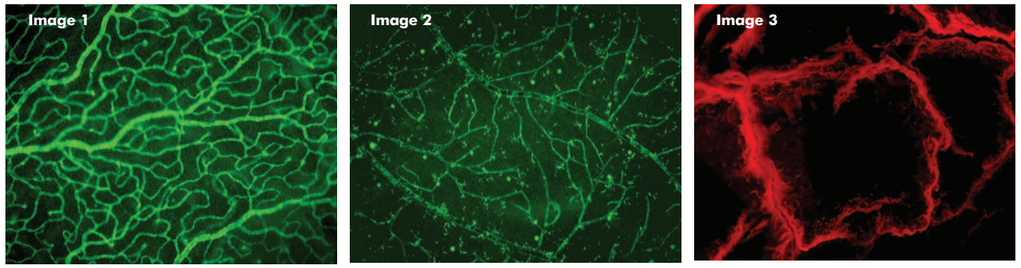


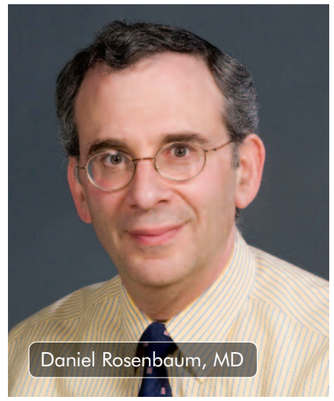
Image 1: A well-organized and functional network of blood vessels in the retina of an adult rat.
Image 2: A disorganized and dysfunctional network of blood vessels in the retina of an adult diabetic rat.
Image 3: An extensive degradation of blood vessels in the retina of a diabetic rat. Diabetes activates specific proteases responsible for the destruction of retinal vessels during diabetes.

The Eye: Gateway to the Brain

Whoever said the "eyes are the window to the soul" never met Daniel Rosenbaum, MD, chairman of neurology at SUNY Downstate.

Given the nature of Dr. Rosenbaum's research into the retina, the light-sensitive inner layer of the eye, the phrase might be slightly amended to: "the eyes are the window to the soul and the gateway to the brain."

The retinas are actually outcroppings of brain tissue. For Dr. Rosenbaum, intent on better understanding the causes of major strokes and developing treatments that may one day ameliorate or even prevent them, the eye has proven to be an ideal, if unanticipated, area of study. "Originally, I began my research in the brain itself," says Dr. Rosenbaum. "But, because of the eye's accessibility, there are certain topics that are much more readily researched there than in the brain itself."


Daniel Rosenbaum, MD

Among those topics are the types of damage that occur in neural tissue when it's deprived of oxygen and glucose, as happens during a stroke. Using rodent models, Dr. Rosenbaum is making important breakthroughs, discovering that some stroke-induced brain damage can be limited through the use of strategies that interrupt cell death. In addition, his research suggests the body's own protective mechanisms may be mobilized to protect those at highest risk for strokes.

What type of death do brain cells undergo during a stroke? Researchers assumed it was necrosis, a passive form of cell death "in which the cells simply explode," Dr. Rosenbaum explains.

In the early 1990s, however, Dr. Rosenbaum demonstrated that necrosis was far from the only type of cell death involved. "In cerebral ischemia," a consequence of a stroke or other condition causing inadequate blood supply, "the brain area that's most significantly ischemic, the core, will undergo necrotic cell death," Dr. Rosenbaum notes. "But there's a region surrounding the core, the penumbra, where the damage may not be severe enough to actually kill the cells immediately."

However, many of those cells eventually die off. Why? Because of apoptosis, or so-called programmed cell death.

Dr. Rosenbaum was among the first to demonstrate this phenomenon in neurons outside a stroke's core area of impact. Apoptosis is the body's "systematic and planned dismantling of cells," Dr. Rosenbaum explains. (In the study that led to this discovery, as in many others, Dr. Rosenbaum induced ischemia in his laboratory animals by restricting blood flow to the retina.)

"The distinction between apoptosis and necrosis is a vitally important one," Dr. Rosenbaum continues, "because if it's an active form of cell death, we can intervene and prevent cells from dying. With necrosis, we can't."

Indeed, in a study published in 1997 in the journal *Vision Research*, Dr. Rosenbaum was the first to demonstrate that during an ischemic event in the retina, the application of a compound called aurintricarboxylic acid halted apoptosis and thus preserved retinal function.

Ultimately and unfortunately, aurintricarboxylic acid proved to present serious life-risk when used systemically. But Dr. Rosenbaum's finding was important because it was proof of principle. "We now know for sure that if you find the right strategy, you can limit some of the apoptosis that occurs after stroke," he says.

Dr. Rosenbaum's research has led to a major discovery: Yet another type of cell death that occurs during stroke. Called necroptosis, this type of cell death shares characteristics with both apoptosis and necrosis. (The study of cell death involves the use of an inflammatory cytokine called TNF. In the presence of inhibitors of programmed cell death, or apoptosis, a TNF variant called TNF-alpha activates and exposes necroptosis for detailed analysis.) It is a finding that may increase the arsenal of stroke-fighting drugs because the agents that will one day block necroptosis "are going to be different than the agents that block apoptosis and necrosis."

In fact, future stroke-blocking agents may be based on molecules produced by the body itself, Dr. Rosenbaum has begun to learn. "One of the most exciting ways to limit apoptosis is with a compound called erythropoietin (EPO), which the retina begins to express when it becomes ischemic, as if to protect itself," he explains. Dr. Rosenbaum hopes EPO, or a modified version of it, will play a clinical role in limiting cell damage after stroke.

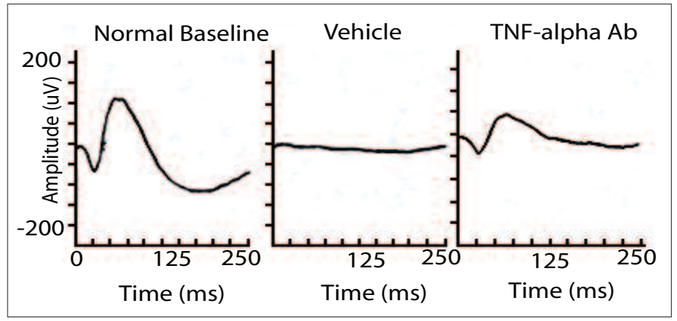
Using rodent models, Dr. Rosenbaum is making important breakthroughs, discovering that some stroke-induced brain damage can be limited through the use of strategies that interrupt cell death.

Similarly, his lab is exploring a phenomenon known as remote preconditioning, in which minor ischemic events protect brain cells from damage during later, more severe strokes. "In our animals, we found that if we make the hind legs ischemic for a short time and then come back 24 hours later with a severe insult, we see much less stroke injury."

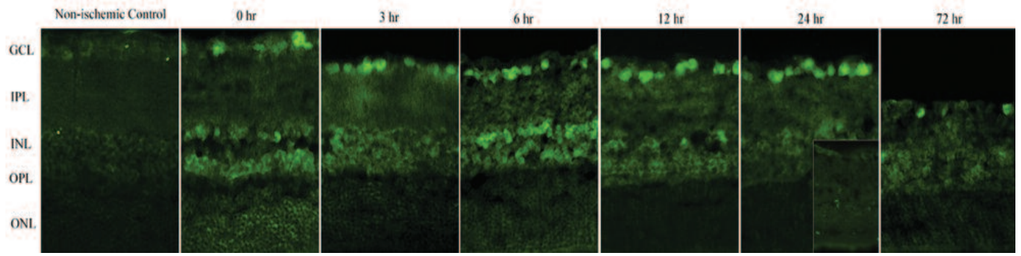
This finding may eventually help prevent strokes in cardiac bypass patients, who are at high risk for ischemic events. "Perhaps 24 hours before surgery, we could mimic preconditioning, and thereby increase protection against major strokes," Dr. Rosenbaum explains.

These discoveries could potentially change the course of stroke treatment and the lives of millions of stroke sufferers. They have been enabled as much by Dr. Rosenbaum's keen, observing eye as by the eye itself — window to the soul and gateway to the brain.


Frank Barone, PhD, director, basic research in cerebrovascular disease; Joel David, lab technician; and Dr. Rosenbaum.



Electroretinography (ERG) tests retinal function. By blocking TNF-alpha activity before and even after the ischemic insult, one can see protection of retinal function following the ischemic insult.



Cryosections of rat retina at different time points subsequent to 60 minutes of retinal ischemia. One can see that TNF-alpha is expressed following ischemic injury to the retina. By blocking TNF-alpha activity, one may be able to protect the retina against cell death.

Restraining Abnormal
Blood Vessel Growth in the Retina

In the United States, almost 21 million people — 7 percent of the population — are diabetic. Of these 21 million, an estimated 40 to 45 percent will eventually suffer from diabetic retinopathy, the leading cause of blindness among American adults.

Diabetic retinopathy has its origins in poor control of blood sugar levels. In the eye, high levels of circulating blood sugar, a condition called hyperglycemia, set off a years-long reaction that results in the formation of new, fragile blood vessels that grow along the retina and into the eye's clear vitreous gel. Ideally, people with diabetes can slow or even halt the advance of diabetic retinopathy by keeping their blood sugar levels under tight control. Such control, however, is difficult to achieve for the large majority of people with diabetes.

But what if unrestrained blood vessel growth, called proliferative retinopathy, could be kept in check with a recombinant molecule administered by injection or through eye drops?

That's the possibility being investigated by Gladys Teitelman, PhD, professor of anatomy and cell biology, and the two members of her lab, graduate student Jennifer Winkler and research scientist Mamdouh Kedees, PhD.

Dr. Teitelman is a diabetes researcher whose primary focus is the regeneration of insulin-producing B-cells in the pancreas (see *Profiles in Innovation*, 2007). Yet, she finds this new avenue of diabetes research and "the possibility that we might be able to intervene in diabetic retinopathy" compelling.

One promising focus involves proteins belonging to the CCN family, including connective tissue growth factor (CTGF), cystein-rich protein (Cyr61), and nephroblastoma overexpressed gene (NOV), which play a role in new blood vessel formulation and appear to be involved in the initiation of retinopathy's pathological changes (see, Brahim Chaquor, "Decoding Diabetic Retinopathy," p.20, for more information on CCN proteins).

Dr. Teitelman and Jennifer Winkler, PhD student.

Dr. Teitelman and her team are specifically focusing on the action of CTGF. "We're making progress in understanding how we might be able to interrupt its destructive action in the eye," she says.

Under normal conditions, CTGF is involved in a host of healthy biological processes that include wound healing, cell division, and nerve conduction. In the diabetic eye, however, its action can be life altering.

"Because CTGF is involved in so many important biological processes, it's not a good target for a systemic therapy," observes Ms. Winkler. "But the eye is encapsulated. Which means we can block the action of CTGF in the eye without concern for the treatment's impact on the rest of the body."


Mamdouh Kedees, PhD

Working first in tissue culture and then in diabetic laboratory rats, Dr. Teitelman and her team have developed recombinant molecules that bind to CTGF and prohibit its production. In their first experiment, the team used a bioengineered virus that reduced CTGF expression by 70 percent in cells in culture. Now, Dr. Teitelman's lab is using a small interfering RNA (sIRNA) to accomplish the same task in laboratory rats with induced diabetes.

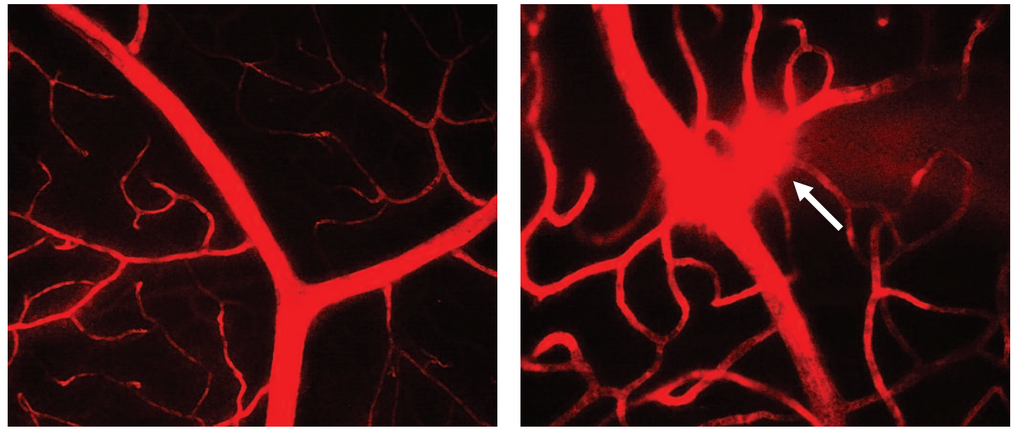
But what if unrestrained blood vessel growth, called proliferative retinopathy, could be kept in check with a recombinant molecule administered by injection or through eye drops?

"One of sIRNA's benefits is that it's very small — about a tenth of the size of the virus we engineered," says Dr. Kedees. The smaller size means any treatment that involves sIRNAs will be less likely to provoke immune or inflammatory responses.

Moreover, using sIRNAs rather than viruses will facilitate a treatment's entrance into involved cells, since viruses enter cells through receptors on the cells' surfaces. During this process, viruses' relatively large size can hinder their entrance. "sIRNA, on the other hand," Dr. Teitelman says, "is small enough to enter the cell simply through diffusion," by the natural movement of molecules in the body.

Dr. Teitelman is hopeful the team's research will result in an effective treatment for what is becoming, in the United States and around the world, an increasingly common illness. "With the first sign of diabetic retinopathy — the presence of leaky blood vessels, for instance — we may be able to intervene and prevent further complications of the disease," she explains.

Of course, Dr. Teitelman notes, "glycemic control is always important in preventing diabetic retinopathy. But given how hard that is to achieve, we must also pursue research that can lead to effective, minimally invasive treatments."


When blood vessels of the retina are infused with a red dye, leakage of the dye is found in retina of diabetic rats, but not in retina of rats with normal blood glucose levels. Arrow indicates area of leakage in the diabetic retina.