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. Bracken, 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 Boldi-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 1979, 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.

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.”

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 those 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. “At least the OCT can provide some feedback to patients about their vision.”

Using 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.
Williams J. Brunken, PhD, is keenly interested in the architecture of the eye’s light-sensitive outer layers that form 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 treatments that break through 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.

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 while they’re there,” he explains.

Without laminins and netrins, retinal development is disrupted and vision itself will 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 vasculature, much like one sees in children with retinopathy of prematurity, where inflammation and, eventually, the death of retinal tissue, disrupts the visual field.”

Other laminin mutations lead to rare but complex diseases that involve the eye along with other bodily systems. These diseases include Piven syndrome, Menkes-dependent muscular dystrophy, and Hurlzé (junctional epidermolysis bullosa). “Netrin-4 helps bundle axons in the retina together, enabling communication between the retina and the rest of the visual apparatus,” Dr. Brunken says. “It is not a synapse but a kind of synapse between the retina and the world.”

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 communica-

tion between the retina and the rest of the brain’s visual apparatus,” Dr. Brunken says. “Perhaps, most important, 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 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.”

The Exquisite Beauty of Ocular Architecture

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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 retina’s basement membrane (red line at bottom of the figure); the adhesion points are yellow. Some genetic deletions of laminin (B and D) but not C cause alterations in Müller cell and, secondarily, in retinal anatomy.

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 capillary 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.

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

Brahim Chaqour, PhD

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, weakened vessels invade the vitreous gel called proliferative retinopathy, these retinas send molecular signals that initiate the weakening of healthy retinal blood vessels and promote the formation of new, leaky ones.

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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-imparing 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.

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-term genes, Cyt61 and CTGF, from the family Dr. Chaqour has identified begin to express themselves in the retina. Their proteins accumulate in the space surrounding blood vessels, further exacerbating pericyte death.

That’s not the only role Cyt61 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. Chaqour’s lab discovered that vasculogenesis, the creation of entirely new blood vessels from stem cells, is promoted by the Cyt61 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 vasculogene sis took place only during embryonic development and then stopped altogether,” he says. By exposing stem cells to Cyt61 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, Cyt61 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 discover ies 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 miconcept peptides that will interrupt the growth of abnor mal 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.”

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 gateway to the brain, “the eyes are the window to the soul” never meant Daniel Rosenbaum, MD, however, whoever said the “eyes are the window to the soul” never met Daniel Rosenbaum, MD, chairman of neurology at SUNY Downstate.

“The distinction between apoptosis and necrosis is a vitally important one,” Dr. Rosenbaum explains. “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 (which 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.

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 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.
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, will eventually suffer from diabetic retinopathy, the leading cause of blindness among American adults.

Many important biological processes, 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, Braham Chaquor, “Decoding Diabetic Retinopathy,” p.30, for more information on CCN proteins).

“In their first experiment, the team used a bioengineered virus that reduced CTGF expression by 70 percent in cells in culture,” explains Dr. Teitelman. “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.

“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?” Dr. Teitelman and her team have developed recombinant molecules that bind to CTGF and prohibit its production. “It’s 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.”

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.

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, Braham Chaquor, “Decoding Diabetic Retinopathy,” p.30, for more information on CCN proteins).

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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.

“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.”