The Exquisite Beauty of Ocular Architecture

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When the College of Medicine was founded nearly 150 years ago, it revolutionized medical education in the United States. It was the first medical school founded within a hospital, making bedside training an integral part of students’ education. This fact is part of our history, which has seen hundreds of our extended family impart their knowledge to many thousands of physicians, who have gone on to enlighten others.

Another part of our history involves the numerous scientific and treatment discoveries that have led to advances in scientific understanding and breakthroughs in a multitude of illnesses.

This vital component of who we are continues to weave its way through the fabric of our campus. It is underscored in this issue of Downstate Research: Profiles in Innovation, which looks at new questions being pursued by seasoned investigators and research at the intersection of ophthalmology and neurology that could lead to new treatments for diabetes- and Parkinson's-related vision loss.

This issue also showcases Downstate's young investigators, who are pursuing groundbreaking research in a host of biomedical disciplines from neuroscience to public health. For example, one of our young investigators is developing chairside mental health interventions for depressed and anxious patients with end-stage renal disease, while another is developing a brain-machine interface that could allow amputees to use their minds to control a robotic prosthesis.

As you read the articles in Downstate Research: Profiles in Innovation, please keep in mind that our successes belong to you — our faculty, staff, alumni, community leaders, legislators, and friends. We’re standing on your shoulders and those before who helped chart a course to better scientific and treatment discoveries — for today and tomorrow.

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Dean, College of Medicine
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Strategies that Work: Information and Access to Care Reduce HIV Transmission
The SUNY Downstate scientists profiled in this section are investigators whose work has been detailed in earlier editions of Profiles in Innovation. All continue to make major contributions to their fields of inquiry, sometimes garnering national and international attention for their discoveries.

Memory researchers Todd Sacktor, MD, and André Fenton, PhD, have delved deeper into research areas they have long pursued. In 2006, the pair proved that a neuro-enzyme called NR2Meta is the molecule that cements memory in the brain. That discovery was named one of the top 10 scientific breakthroughs of that year by the editors of Science. Sheryl Smith, PhD, whose past work focused on the effects hormones have on GABA receptors in the brain, has tackled new scientific questions related to her longstanding field of interest. Dr. Smith received international press coverage in 2007 for a finding that explains moodiness among teenagers.

Using complex imaging technology, neurologist Roger Traub, MD, and a group of colleagues proved the existence of cellular structures called gap junctions between certain types of brain cells. Ten years ago, Dr. Traub’s computer models of brain-cell networks in action predicted the existence of these gap junctions, despite the fact they had never been identified in the lab. These discoveries won Dr. Traub the German government’s prestigious Humboldt Research Award. Christopher Roman, PhD, continues to examine and identify genes and proteins responsible for lupus and other autoimmune diseases, as well as some cancers.
How the Hippocampus Multitasks to Avoid Confusion

André Fenton, PhD

In this case, the navigational task faced is a complex challenge in which the rats must find their way through stationary and rotating locations, while avoiding being shocked. The rats do this by being aware of two frames of reference simultaneously. The first is the rotating turntable on which they walk during the challenge, and where in one location a mild shock awaits them, the second is a stationary “arena,” as Dr. Fenton calls it, into which the turntable has been placed, and which, again, contains a zone rigged to provide a mild shock. Dr. Fenton’s research into the functional grouping of place cells offers new insight into how the brain organizes, activates, and suppresses information, memories, and feelings.

The challenge is based on Dr. Fenton’s discovery that cells in the hippocampus can organize themselves according to task — focusing on what they need to know and suppressing or ignoring extraneous details. First profiled in Profiles in Innovation in 2006, Dr. Fenton, a Downstate alum, has focused much of his research on understanding how “a single network of neurons may group perceptions into conceptual categories in order to avoid confusion of separate but simultaneously relevant information.”

His findings may have a practical and, indeed, viral application.

“There are several different diseases — mental dysfunctional states — that are characterized by an inability to filter out irrelevant thoughts and memories,” explains Dr. Fenton, an associate professor of physiology and pharmacology. Among those diseases are schizophrenia and psychosis. Both disorders are poorly understood, and current treatments, which have limited efficacy, address symptoms rather than underlying causes.

“With this new paradigm,” Dr. Fenton says, “we can ask new questions about how mental systems work and how to strengthen them when they’re broken.”

Dr. Fenton was the first to discover the so-called “functional grouping” of place cells. “Functional grouping is a mechanism to reduce, from a neural point of view, the mental conflict you might be confronted with when you need to pay attention to two things at once,” he explains. “It’s a mechanism for filtering out or dealing with things that interfere with the task at hand.”

Dr. Fenton and his colleagues observe this grouping through their recordings of rats’ neural activities. In the case of the rats working their way through the turntable challenge, among the phenomena documented is that while an experimental animal is at rest, about half of its place cells focus on the animal’s location on the turntable, the other half focus on the animal’s location in the arena. Once the lab rats begin their challenge, “you might expect half the place cells to continue to focus on the turntable and half to focus on the arena,” Dr. Fenton says. “But the vast majority of the place cells focus on only one of those frames of reference and only momentarily switch to the other to avoid being shocked.”

Dr. Fenton’s research into the functional grouping of place cells offers new insight into how the brain organizes, activates, and suppresses information, memories, and feelings. Dr. Fenton believes that, eventually, he and other scientists may discover what allows certain brain cells to work together in this process of focusing and ignoring what goes away when brain cells are unable to filter out irrelevant information and memories.

His lab has even developed a method for inducing temporary psychotic behavior in rats in an effort to explore how that behavior might be remedied. “Using these models,” he says, “we can ask, ‘What maintains functional grouping?’ What can regulate it?” This mechanism may help us better target our studies and our treatments of mental illness. “

Dr. Fenton and his PhD students: (from left) Hsin-Yi Kao, Eduard Kelemen, and Heekyung Lee
When the Immune System Confuses Self and Other

The way Christopher Roman describes it, a well-functioning immune system is a splendid thing. "There is a beauty to the natural world," says the associate professor of molecular biology and immunology. "But some of that beauty can only be witnessed indirectly or through a microscope."

When the immune system works properly, its efforts are amazing. "Imagine: You have this huge collection of T cells and B cells, which are major immune system components, and they can recognize threats they've never seen before — just about anything you can throw at them," says Dr. Roman. "It doesn't matter whether those threats are molecules from bacteria, viruses, or parasitic worms."

When the immune system malfunctions, however, the results can be devastating. Lupus is an example. In the United States, alone, this autoimmune disease affects as many as 1.5 million people, 90 percent of its sufferers are women. The illness, sometimes fatal, can cause kidney failure, heart disease, pulmonary problems, and disorders of the central nervous system. At present, lupus has no cure.

Much remains unknown about the disease. But, inspired by the promise that his work may contribute to an effective treatment for lupus and other autoimmune problems, Dr. Roman is teasing apart the complex regulatory pathways of the immune response on a molecular and genetic level. This, he believes, will lead to a greater understanding of what malfunctions in autoimmune disease.

Dr. Roman is teasing apart the complex regulatory pathways of the immune response on a molecular and genetic level. This, he believes, will lead to a greater understanding of what malfunctions in autoimmune disease. type that the immune system usually destroys. These antibodies attach themselves to free-floating DNA and other "self" molecules in the blood stream. "You then get these big, inflammatory complexes," Dr. Roman observes. Though these complexes find their ways into many types of tissue, one of the organs hardest hit is the kidneys. "The complexes get deposited there and cause a catastrophic inflammatory response that destroys them," he says.

In the last two years, Dr. Roman has focused his investigations on the process by which T cells manufacture CD40 ligand. With support from the Lupus Research Institute, the National Institutes of Health, and the dean of SUNY Downstate’s College of Medicine, Dr. Roman’s lab has discovered that two almost identical molecules, called TF3 and TFEB, are instrumental in CD40 ligand production. By designing an artificial protein that lacks the machinery to bind to the DNA responsible for producing these two molecules, Dr. Roman and his team were able to stop CD40 ligand production almost entirely. Dr. Roman believes this finding may one day be useful to developers of a CD40-ligand inhibitor for people with lupus.

All these investigations were accomplished by Dr. Roman’s research team, which includes senior molecular immunologist and research scientist Chongmin Huan, MD, PhD, and Susan R. S. Gottesman, PhD, MD, Downstate’s director of hematopathology and an expert in cellular immunity. Ellen Ginzler, MD, MPH, distinguished teaching professor and chief of rheuma-

Despite the progress made in Dr. Roman’s lab, much remains to be learned about the functioning and malfunctioning of the immune system in lupus. "We know relatively little about the checks and balances within the immune system and how that system functions at the molecular level," he explains. "And, of course, we want to know why lupus T cells produce so much CD40 ligand in the first place."
Dr. Todd Sacktor, MD

PKMzeta, Sentinel of Memory

Dr. Sacktor was the first to posit that a neuroenzyme called PKMzeta was the molecule that fixed memory in the brain. His and Dr. Fenton’s theory proved to be correct. PKMzeta is, in fact, the molecule that maintains memory in the hippocampus. Science published the results of their experiments in August 2006. Since then, in a similar experiment in 2007, Dr. Sacktor and colleagues from Israel’s Weizmann Institute of Science once again used this PKMzeta-blocking compound to erase unpleasant memories from the minds of experimental animals, this time in the neocortex, the outer layer of the brain. Drs. Sacktor’s and Fenton’s colleagues at the University of Wisconsin have documented PKMzeta’s role in maintaining memory in the amygdala as well, the part of the brain associated with fear and smell.

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Dr. Sacktor’s goal now is to understand fully PKMzeta’s role in memory formation and maintenance throughout the brain. “What is the physical substance of the memory trace?” he asks. While that answer is not yet completely clear, Dr. Sacktor, whose work on the molecular underpinnings of memory was first profiled in this publication in 2006, continues to make progress in understanding this compelling question. PKMzeta’s uniqueness initially drew Dr. Sacktor’s attention. “Unlike other enzymes in the brain, which turn on and off,” he says, “PKMzeta is different. Once created, it’s continually active, which makes sense for a memory molecule.” Yet, it was difficult to get many in the neuroscience community to embrace the idea that PKMzeta played a pivotal role in memory maintenance. The commonly accepted notion has been that what maintains memory is a change in brain anatomy. In fact, since the 1960s, neuroscientists have observed a physiological change in which the strength of the synaptic connections between brain cells increases after their stimulation. This phenomenon is called long-term potentiation (LTP) and for decades was thought of as a potential model for memory. The discovery that PKMzeta cemented both these strengthened synaptic connections and long-term memories provided the crucial link showing that LTP was indeed the underlying mechanism for memory storage.

The crucial experiment required several years of preparation. First, Dr. Sacktor developed a compound that would block the action of PKMzeta without destroying brain function. Then, though “most scientists believed that it was almost impossible to erase memories that were well established,” Dr. Sacktor set out to prove otherwise. Much as Dr. Sacktor predicted, the laboratory animals in his experiments with blocking PKMzeta have consistently forgotten learned behaviors, both in experiments at Downstate and at the Weizmann Institute. In his animals, the number of receptors on certain brain cells was reduced by half, to their pre-LTP count, after Dr. Sacktor administered the PKMzeta-blocking compound. Having made the major discovery of PKMzeta’s pivotal role in both the formation and the maintenance of memory in several key areas of the brain, Dr. Sacktor continues to explore the function of what some have called “the memory molecule.”

“There’s so much to learn about the molecular underpinnings of memory,” Dr. Sacktor says. “Right now, we can do that best by focusing on the workings of PKMzeta.”
Why formerly easygoing and agreeable children become moody and unpredictable teenagers

be surprised if, in response to an outburst, your teenager soon offers up the following apology: “It’s not me, Mom! It’s my GABA receptors.”

The impact of Dr. Smith’s discovery may be far-reaching. The finding illuminates the relatively underexplored subject of mood disorders in teens, and opens the door to new studies on learning and memory among adolescents. Says Dr. Smith, “It’s good to know there’s a physiological reason teenagers respond much more intensely to stress than adults do.”

Sheryl Smith hadn’t set out to study moodiness in teenagers — though, as a parent, she had the opportunity to watch that kind of volatility in action. Instead, her discovery got its start in what she considers “a happy accident.”

Here’s what happened: For many years, she has studied the calming hormone metabolite called allopregnanolone, which she has discovered is involved in quieting neural electrical activity. Often, Dr. Smith performed her experiments on pubescent mice. “Using young mice enabled us to manipulate the hormones,” she explains. “We didn’t want the mice’s own hormonal cycles to interfere with our research.”

During one set of experiments, the results were the opposite of what Dr. Smith anticipated. Mice that one would have expected to be calmed by allopregnanolone became much more agitated when faced with a complex challenge: “It turns out that one of our technicians used pubescent mice instead of the young ones,” Dr. Smith explains. “I thought, ‘This is a lucky break. Let’s follow it up.’”

So she and her colleagues “worked like crazy for the next two years,” documenting the existence of alpha4-beta2-delta GABA receptors in mice. “We didn’t want the mice’s own hormonal cycles to interfere with our research, but also more attentive to their environment and, thus, more apt to learn.”

Dr. Smith believes that even though her research subjects are rodents, what she has discovered is relevant to people. “All the changes we see accompanying this receptor are involved in human development. "Our study shows that adolescents are not just young adults. Their physiology and moods are different," she says.

Moreover, her findings may explain why some anti-depressant medications effectively treat anxious and depressed adults but may backfire in teenagers, at times with tragic results. "Drugs like Prozac and Zoloft increase the amount of allopregnanolone in the brain," Dr. Smith observes. "Since allopregnanolone increases anxiety in teens, these may not be the best drugs to give to teenagers who are having problems with instability." Dr. Smith thinks there’s an evolutionary reason why formerly placid children turn into moody fifteen-year-olds: “A heightened sense of anxiety may keep them focused and learning new skills” — the skills needed for independent living. Maybe this increased response to stress forces them to figure out their own solutions,” she speculates.

To test her theory that pubescent anxiety enhances learning and thus offers "an evolutionary advantage," Dr. Smith is now collaborating with Downstate researcher Armin Stelzer, MD, an expert in learning and memory. "Being at Downstate," where many researchers focus on learning and memory, "is great, because it facilitates collaboration," Dr. Smith says. "I can walk into a colleague’s lab and learn the techniques I need to perform these experiments."

These techniques and experiments may further elucidate the workings of the adolescent brain, and bring Sheryl Smith some well-deserved attention, yet again.  

A stress steroid reverses its effect at puberty in female mice. Before puberty (upper panel), the stress steroid THP enhances the function of target GABA receptors (upper right) on neurons in CA1 hippocampus (upper center) and decreases action potentials (upper right); thereby reducing anxiety as a compensatory for prolonged stress. However, at puberty (lower panel), novel forms of target GABA receptors (α4β5δ, lower left) ameliorate stress hormone effects, thereby increasing action potentials (lower right). This novel action of the steroid increases anxiety in response to prolonged stress in the adolescent brain.
Imagine the difficulties faced by neuroscientists hoping to record the electrical activity that occurs among brain cells. Implanting the necessary electrodes is notoriously difficult. And even when these hair-thin devices are used successfully, they are limited in what they can capture. The researcher is left with an incomplete picture of the neural networks that play a critical role in almost every aspect of human health.

“When you record from cells in vivo,” says Roger Traub, MD, professor of physiology and pharmacology “you don’t have access to all the physical processes in the system you’re studying.”

For years, these technological difficulties have hindered advances in understanding normal brain activity, and they have stymied research on epilepsy as well as other neurological disorders. But Dr. Traub, a prominent neurologist with a background in mathematics, is finding ways around this problem by creating startlingly accurate computer models of neural networks’ electrical activity. These models are so precise that it is difficult to distinguish the computer-generated images of the brain’s electrical activity from actual EEG recordings.

Dr. Traub has received international acclaim, including Germany’s prestigious 2007 Humboldt Prize, for this precision and for much more: His models can predict the existence of certain processes and structures within neural networks that researchers working directly with tissue have yet to discover.

In fact, last year, one of Dr. Traub’s predictions, which may have significant bearing on the future of epilepsy research, was finally validated in the PhD thesis of his graduate student, Farid Hamzei-Sichani. That finding, which was published in the Proceedings of the National Academy of Science (PNAS, 104:12548-12553, 2007), is further proof that Dr. Traub’s computer simulations can advance neuroscience in ways still unavailable to traditional bench scientists.

When Profiles in Innovation reported on Dr. Traub’s work in 2007, the University of Pennsylvania-trained neurologist was focusing his attention on seizure disorders. As a neuroscientist, Dr. Traub was well aware that most epileptic seizures originate in the cellular organization of the cerebellum, the part of the brain largely responsible for motor coordination. Problems within cerebellar networks can result in a number of disorders, including ataxia — the loss of motor control and severe lack of coordination — multiple sclerosis, Parkinson’s disease and, perhaps, even schizophrenia. Once again, Dr. Traub believes gap junctions may be implicated in the diseases “Some of the same principles apply, even though the cellular organization of the cerebellum is completely different than in the cerebral cortex.”

The task Dr. Traub faces in creating computer models of cerebellar networks is daunting. To date, scientists have had tremendous difficulty recording their electrical activity due to the cerebellum’s difficult-to-access location at the base of the brain. But recently, working in vitro, Dr. Traub’s long-time collaborator, Miles Whittington, PhD, a professor of neuroscience at England’s Newcastle University, discovered brain wave oscillations in the cerebellum that look like cortical oscillations. They depend on gap junctions,” Dr. Traub notes. With this data, Dr. Traub has modeled the action of a cluster of a thousand cerebellar Purkinje cells, the largest in that section of the brain. Still, research on the electrical activity of cerebellar cells produces in its infancy Dr. Traub hopes his Humboldt Research Award, the highest honor the German government bestows upon foreign scientists, will encourage other collaborations validating the importance of computer modeling. “I accept these models as real,” Dr. Traub says, “you can better understand why the electrical signals look the way they do. And more than that, you can make predictions about how and why things happen. That’s very helpful to the experimentalists.”
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. Brunklen, 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 Tietelman, 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.”

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.
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, M.D., D.Sc., 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. “And with that, help stop the progression of Parkinson’s disease.”

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William J. Brunken, PhD, is keenly interested in the architecture of the eye’s light-sensitive inner layers and 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 prematurity birth. His research may also 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 within those domains,” 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, says Dr. Brunken.

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, where the basement membrane doesn’t form properly, when 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.”

Other laminin mutations lead to rare but complex diseases that involve the eye, along with other bodily systems. These diseases include Peveren syndrome, Menkes-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. “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 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. “The hope would be to fool neurons into thinking a silicon chip is a photoreceptor.”

Dr. Brunken’s investigations may also lead to a new way of treating vision loss from retinal defects. “The hope would be to fool neurons into thinking a silicon chip is a photoreceptor.”

Support cells, Müller glial cells, span the whole retina and adhere to the retinal 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.
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.

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. This 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. Chaqour’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 scaffold that stabilizes and connects cells. “This further degrades the pericytes,” he says.

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.”

Dr. Chaqour has identified a “small family of genes,” that, in the presence of hyperglycemia, plays a crucial role in all phases of diabetic retinopathy.
The Eye: Gateway to the Brain

Whatever 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.”

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 systematically 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 it is 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.

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.


drdownstate.edu/vision/
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 cause 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).

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.”

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?

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.

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 formation and appear to be involved in the initiation of retinopathy’s pathological changes (see, Braham Chauqui, “Decoding Diabetic Retinopathy,” p. 35, for more information on CCN proteins).

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.

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

“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.”

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.

Dr. Teitelman and Jennifer Winkler, PhD student.

“One of sIRNAs 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 cell’s 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.”

“Restraining abnormal blood vessel growth, called proliferative retinopathy, could be kept in check with a recombinant molecule administered by injection or through eye drops.”
DOWNSTATE RESEARCH 2008

YOU NG I NVESTIGATORS, NOVEL I NSIGHTS

SUNY Downstate has much to offer young investigators: a prestigious faculty, a supportive and stimulating work environment, easy collaboration with mentors and peers.

They in turn are pursuing groundbreaking research in a host of biomedical disciplines, from neuroscience to public health.

Dr. Daniel Colon is developing chairside mental health interventions for patients with end-stage renal disease, who are depressed and anxious, that can be administered during dialysis sessions. Neuroscientist Joseph T. Francis, PhD, is working on a brain-machine interface — a computer-enabled connection between a brain and a mechanical device — that would allow individuals who are missing an arm to use their mind to control a robotic prosthesis.

Another neuroscientist, Downstate alumnus Sabina Hrabetova, PhD, is employing complex mathematical modeling and bench science to understand how molecules diffuse through the brain’s fluid-filled extracellular space. And, cognitive psychologist Tracey E. Wilson, PhD, develops HIV interventions that reduce the risk of transmission among those at highest risk.
Talk Therapy Eases Depression in Dialysis Patients

It’s not easy for patients with end-stage renal disease (ESRD). Because their kidneys function at less than one-tenth normal capacity, these individuals must undergo hemodialysis three times a week.

The procedure removes wastes, toxins, and excess fluids from their blood streams. But attending the four-to five-hour sessions makes it difficult for patients with ESRD to hold regular jobs or participate in social activities. The majority also suffer from other illnesses, such as diabetes and high blood pressure, which further curtail their daily activities. Often, ESRD patients are elderly, poor and have limited mobility.

“It can be a very difficult life, in addition to the time they spend on the machine,” says Daniel Cukor, PhD, assistant professor of psychiatry and behavioral sciences, who has a long-standing interest in the impact of physical illness on emotional well-being. Yet, there has been little research conducted on the mental health and mental health-treatment needs of people with ESRD.

Dr. Cukor, who has studied this issue, has found very high rates of untreated depression, anxiety, and other mental disorders among patients at University Hospital of Brooklyn’s Parkside Avenue outpatient dialysis center. “More than 70 percent had some form of psychiatric diagnosis,” Dr. Cukor relates. “But only 13 percent were in treatment with a mental health provider.”

These findings spurred Dr. Cukor to implement a pilot study of a drug-free treatment plan for depression that can be delivered chairside during dialysis sessions. Now funded by the National Institutes of Diabetes and Digestive and Kidney Diseases, he hopes to refine and test this treatment so it can be used in dialysis centers nationwide. Dr. Cukor’s goal is to offer the kind of help for depression that so many people undergoing dialysis need, without additional medications or doctors’ appointments.

Daniel Cukor didn’t start off as a researcher. In 2002, after receiving his doctorate in clinical health psychology from Yeshiva University, he came to SUNY Downstate as a postdoctoral fellow. Eventually, he hopes to conduct a multisite trial to compare chairside CBT to pharmaceutical interventions. This will allow him to test for a statistically significant difference between the two approaches and to determine whether CBT can improve physical outcomes as well.

“I want to make dialysis patients’ lives a little easier.”

Dr. Cukor’s goal is to offer the kind of help for depression that so many people undergoing dialysis need, without additional medications or doctors’ appointments.

Diabetes and Digestive and Kidney Diseases, he hopes to refine and test this treatment so it can be used in dialysis centers nationwide. Dr. Cukor’s goal is to offer the kind of help for depression that so many people undergoing dialysis need, without additional medications or doctors’ appointments.

Nevertheless, patients and doctors alike are reluctant to use antidepressant medications. “The last thing most of these patients want is another pill and another side effect,” Dr. Cukor explains. Hence the pilot study on CBT, which provided one-on-one therapy to 16 individuals during their dialysis sessions.

At first, people were a little uncomfortable. “But because at the initial meeting I was really offering education about depression, the participants became more relaxed,” Dr. Cukor says. As part of his introduction to cognitive therapy, Dr. Cukor explained that “the way you perceive life is often much more important than the way life actually is.”

Later sessions included behavioral therapy — teaching people to improve their mood by doing things they enjoy. “It could be a small thing, like going to the movies or playing music in the house when you’re alone,” Dr. Cukor says.

In fact, in his study the average depression scores dropped from 29 points on the Beck Depression Inventory to 15 points at the conclusion of the 15-week treatment. Three months later, the scores were only slightly higher — 18.8 points — indicating a sustained benefit from the CBT approach.

Among medically ill patients, 14 percent and above is considered severely depressed. Thus, many of the 16 patients in Dr. Cukor’s study remained depressed, they were far less depressed than before: “In trials for antidepressant drugs,” he notes, “five or six points of benefit is defined as remission.”

Now, Dr. Cukor hopes to refine the treatment and test it on a larger scale. Eventually, he hopes to conduct a multisite trial to compare chairside CBT to other medical schools.

Fig 1. Psychiatrist diagnostic categories. Percent of samples with SCID diagnoses (N=70).
Within His Grasp: Enabling the Brain to Run a Robotic Arm

The goal of Dr. Francis’s research is to create a brain-machine interface (BMI), a computer-enabled connection between a brain and a mechanical device that may allow individuals who are missing an arm to control a prosthesis simply by thinking.

Dr. Francis initially studied how to record neural activity from a brain implanted with electrodes, which are then used to control a robotic arm. He worked with Dr. Fred Chapin at the Downstate Medical Center to develop this technology.

The process by which Dr. Francis is bringing this closed-loop BMI into being is, like most scientific endeavors, a complex one. In 2002, he started implanting electrodes into the brains of rats and recording the signals they transmitted as they used their forelimb to operate levers. “With these data, we began to formulate how their brains must be representing the information and how their brains must be working when their forelimbs move,” Dr. Francis explains.

Dr. Francis and Dr. Chapin are using this information, and data collected from monkeys involved in similar but more complex tasks, to develop an algorithm that will convert brain-cell activity into robotic action. “Once we create models of how we think things are working, we can then translate the neural information so that it directs the motors in a robotic arm,” Dr. Francis explains. “We can give the animal control over the position of the limb, over the joint torques (the force used in moving the joints), or over a combination of those variables.”

Dr. Francis expects to begin work soon with the monkeys to explore how the nervous system relays information about touch to the brain and how such information might be used to operate a prosthetic arm. “Right now,” says Dr. Francis, “we’re attempting to use small electrical discharges in the thalamus to reproduce responses in the cortex like those that occur when an animal is touched on the hand.”

Both researchers have put their work cut to use for him. Still, he has no question about whether he and scientists like him can develop a BMI that operates a fully functional prosthetic arm. “Once we overcome the hurdle of the electrodes,” he says, “we’re probably a few years away. We’re much closer to developing this than one might think.”

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Between Cells: Diffusion in the Brain’s Extracellular Space

Sabina Hrabetova, PhD

What if the phenomenon you study is so minute and multidimensional that it defies observation through traditional scientific methods? And what if the techniques available for researching the subject are unable to separate the component parts into their individual domains? Those are some of the problems Sabina Hrabetova, MD, PhD, faces in trying to understand the dynamics of the diffusion of molecules through the brain’s little-understood extracellular space (ECS).

The brain ECS is the part of the brain between the cells. Filled with fluid and something called the extracellular matrix, a kind of scaffolding made of proteins and sugars that anchors cells and synapses and provides receptors onto which molecules can bind, “the brain ECS makes up about 20 percent of the brain by volume,” Dr. Hrabetova explains.

The dynamics of diffusion play a pivotal role in the ability of ions, neurotransmitters, and therapeutic agents to make their way through the ECS, “travels that enable and control many life processes.”

Nevertheless, through diffusion the brain ECS remains an enigma. To solve this puzzle, Dr. Hrabetova, assistant professor of anatomy and cell biology, employs a unique combination of computer modeling, theoretical biophysics, and good old-fashioned bench science. Dr. Hrabetova has been fascinated by the inner workings of the brain since her days as a medical student in Czechoslovakia. As a doctoral candidate in Dr. Todd Sudhof’s lab (see “PKMzeta, Czechoslovakia,” p. 8), she studied synaptic plasticity and the role in memory formation played by certain enzymes in the brain known as protein kinase C isoforms.

When she finished her doctoral degree in 1998, however, she “wanted to learn something new, something completely different.” Attracted to the work of Charles Nicholson, the world’s leader in brain ECS research, she joined his lab at New York University as a postdoctoral researcher. “There, I learned how important the brain ECS is for communication between brain cells and for drug delivery,” she says. “It was also an under-explored area, and nobody realized there was a lot I could discover.”

In 2007, she set up her own lab at Downstate. The research has not been easy. “It’s not yet possible to release a molecule in one part of the ECS and follow its movement to another,” she explains. Tools for measuring the brain ECS cannot easily separate the extracellular matrix from other components. And electron microscopy, often effective in imaging tiny objects such as cell components in fixed tissue, is not suited for documenting “molecules moving in three-dimensional spaces in living tissue.”

The difficulty in imaging diffusion is compounded by the question central to Dr. Hrabetova’s research: “What happens when the brain’s glial cell processes — the long, thin extensions of glial cells — wrap themselves around neuron bodies and around synapses?” Glial cells are the brain’s second major cell type and their processes often create barriers that complicate rapid or easy diffusion of neurotransmitters and therapeutic agents. “In the past 10 years, there’s been more and more evidence that glial processes can respond to neurotransmitters, release neurotransmitters themselves, and influence the signaling between neurons. It seems that glia are a more active cell type than we thought. And I want to find out whether these cells also regulate transport in the brain ECS,” she explains.

To address these questions, Dr. Hrabetova and her collaborators are using a series of mathematically based, computer-enabled simulations. “The experimental work is rigorously testing our hypothesis is still ahead of us,” Dr. Hrabetova says.

While still in Dr. Nicholson’s lab, Dr. Hrabetova discovered that molecules making up the extracellular matrix can have a significant impact on the diffusion of signaling molecules. “Some of the extracellular matrix molecules can slow down diffusion of calcium, a molecule that’s very important for axonal regeneration after injury,” she notes.

Likewise, she has learned that the structure, as well as the size, of molecules released into the brain ECS has a significant impact on diffusion. “If you make something bigger, it will move more slowly,” she says.

Using data from her computer simulations and lab experiments, Dr. Hrabetova and her colleagues are able to quantify the rate at which different substances diffuse through the brain ECS. “This is very useful as a way to test drugs in development, so that we can tell how far a drug is going to diffuse in an hour or a day,” she says. The technique should enable drug makers to better gauge and tailor the efficacy of their treatments, and is an important byproduct of the research questions that compel Dr. Hrabetova, despite many methodological difficulties: “What is the geometry of the extracellular space? What are the components? How does the brain ECS influence the normal signaling between brain cells?”

Yet even as the challenging questions Dr. Hrabetova says that she needs to answer if her research is to help patients.

Dr. Hrabetova with Fanrong Xiao, PhD, postdoctoral fellow (sitting), and Paula von der Heide, doctoral student.

A. Glia processes may form a major diffusion barrier in brain extracellular space (ECS).

B. Diffusion in ECS

5 min 7.5 10

50 µm

Glia processes may form a major diffusion barrier in brain extracellular space (ECS). A. Glia processes wrap themselves around neuronal bodies, processes, and synapses, and form pocket-like dead-space microdomains (DSMs) in the ECS. The DSMs can significantly influence the communication between brain cells and drug delivery by transiently trapping signaling molecules and therapeutic agents. B. Brainstem auditory nucleus (NTB) containing giant axosomatic synapses — the calyx of Held synapses — provides a model brain region to study the ECS. Fluorescent-labeled macromolecules show rhombohedral distribution in the rat NTB, possibly caused by the trapping of macromolecules in the DSMs (S. Hrabetova, unpublished).
Strategies that Work: Information and Access to Care Reduce HIV Transmission

In the absence of a cure for the human immunodeficiency virus (HIV), prevention is the most effective tool healthcare professionals have for reducing the infection.

According to Tracey E. Wilson, PhD, associate professor in the Graduate Program in Public Health at SUNY Downstate, multiple strategies are necessary to prevent transmission of the virus that causes AIDS. This is especially true among urban minority populations, who are at greater risk for infection, but often lack access to medical care and health education.

One of the most important ways to reduce HIV infection is to expand HIV testing. “After being diagnosed with HIV, people are more likely to reduce their level of sexual risk behavior,” explains Dr. Wilson.

It is estimated, however, that nearly half of new sexually transmitted HIV infections are transmitted by HIV-positive partners who know they are infected. Therefore, prevention must also focus on helping people with HIV reduce the risk of transmission. Dr. Wilson has worked closely with colleagues at University Hospital of Brooklyn’s STAR Health Center, which provides outpatient care to HIV patients, to develop, implement, and evaluate such programs.

One initiative, funded by the Centers for Disease Control and Prevention, evaluated risk reduction interventions delivered by medical providers to HIV patients during routine HIV primary care. The program successfully integrated risk reduction education with HIV care. Six months after the intervention, unprotected sex among patients was reduced from 42 to 26 percent.

Following this work, the CDC funded Dr. Wilson’s proposal to increase patient retention in HIV primary care. As part of this project, she is developing clinic-based approaches to increase the likelihood that patients with HIV access care regularly. Dr. Wilson notes that studies demonstrate that retention in care is associated with improved quality of life, as well as reduced HIV-transmission risk behaviors.

Another key approach to HIV prevention involves working with those who are at risk for HIV infection. This includes injection drug users and individuals who engage in high-risk sex behaviors. It also includes members of groups who have suffered from a disproportionate burden of HIV infection, such as African-Americans or men and women living in geographic areas with a high prevalence of HIV.

Dr. Wilson and her colleagues in Downstate’s Division of Infectious Diseases have developed and tested programs to reduce HIV risk in Brooklyn, including a partner notification program for men and women diagnosed with sexually transmitted infections (STIs). In this randomized controlled study, patients were encouraged to notify their sexual partners of their condition and support in their efforts to do so. Not only did the program increase the percentage of patients who informed their partners, it reduced subsequent STIs. Six months after initial diagnosis, the rate of new STIs was cut nearly in half, from 11 percent among the control group who received the standard level of care to 6 percent among those who received the intervention.

Dr. Wilson is now working with colleagues in her department and with longtime partners at the Arthur Ashe Institute of Urban Health (AAIUH) to develop approaches to risk reduction for African- and Caribbean-American men living in Brooklyn. The program, based on a model developed by the Ashe Institute for providing health education in nontraditional settings, will deliver HIV risk-reduction education through barbershops in Central Brooklyn and Flatbush.

According to Ruth C. Brown, ScD, co-principal investigator for the project and chief executive officer of AAIUH, “while most black men regularly go to the barbershop, many lack a regular source of health care. Community-based venues such as these can be supportive environments for promoting behavioral change.”

Dr. Brown and Wilson have collaborated on a similar program for a different target group and disease: women and breast cancer. Through beauty parlors, health educators taught women about the importance of mammography, demonstrated breast self-examination, and provided referrals for follow-up care.

“When people believe that we want to help their community, they are more willing to share information about behaviors that are often stigmatized,” says Dr. Wilson.

Equally important, adds Dr. Wilson, the programs must work for the needs of those at risk. The latter can only be achieved by working closely with the target population to identify prevention needs and appropriate strategies. “When people believe that we want to help their community, they are more willing to share information about behaviors that are often stigmatized,” says Dr. Wilson.

“Dr. Wilson believes the key to developing effective programs involves combining strong public health methods with knowledge of and sensitivity to the needs of those at risk. The latter can only be achieved by working closely with the target population to identify prevention needs and appropriate strategies.”

“When people believe that we want to help their community, they are more willing to share information about behaviors that are often stigmatized.”


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