New transgenic mouse links structure, function deficits

**Schizophrenia re-modelled**

**By Lois Baker**

When two camps don’t talk to one another,” explains Michal Stachowiak, PhD, neuroscientist and senior researcher on a UB team that appears to have broken that stalemate. He and UB colleague Ewa K. Stachowiak created a transgenic mouse missing a critical brain component called the fibroblast growth factor receptor. The mouse displays the structural and neurochemical changes in dopamine neurons similar to those seen in PET scans of human patients with schizophrenia.

“Our new model has the potential to allow, for the first time, a way to search for new therapeutic treatments that target brain development or compensate for the abnormal structure of dopamine-producing neurons,” says Michal Stachowiak. “It provides a new unifying concept of schizophrenia as a neuroanatomical-biochemical disorder.”

“The mice display characteristic behavioral symptoms, such as an impaired processing of sensory information, which was reversed by a dopamine receptor antagonist used to treat schizophrenia. In other animal models, behavioral symptoms were induced by manipulating dopamine transmission only, without the underlying structural changes in the dopaminergic neurons. The two known conditions inherent in schizophrenic—underdeveloped dopamine-producing regions in their brains, but too much dopamine in their systems—seemed to contradict each other, says Stachowiak.

The crux of the research was proving that the two conditions were interconnected. In a paper published in the June 2006 issue of the *Journal of Neurochemistry*, the researchers describe how they found that both the dopamine-producing regions in the brain and the new cells within those regions were smaller than normal, prompting the neurons to overcompensate and overproduce dopamine.

Consequently, treating schizophrenics with drugs that block dopamine’s action only dampens this function, but doesn’t control it, Stachowiak notes.

Stachowiak is professor of pathological and anatomical sciences and chemistry, and director of the Molecular and Structural Neurobiology and Gene Therapy Program at UB. Ewa Stachowiak is research instructor in pathology and anatomical sciences and chemistry. Ilona Klejto, a postdoctoral researcher in Stachowiak’s laboratory, now at the Medical University of Gdansk, in Gdansk, Poland, is first author on the paper.

The neurobiology team, along with Robert Mardich, UB clinical associate professor of nuclear medicine, is currently searching for a “fingerprint” that identifies those at risk of developing the disease by looking for common brain symproms in schizophrenic patients and the animal model.

If such a risk factor could be found, says Stachowiak, children with behavioral problems or from families with a history of schizophrenia could be screened and treatment could be started before the disease becomes full-blown. Additional authors on the paper are Jason M. Meyers, graduate student; Thomas D. Corso, visiting professor, and Robert Hard, professor, all from the UB Department of Pathology and Anatomical Sciences; Jerry Richards and Kathy Hauknecht, student researchers, both from the UB Research Institute on Addictions; Angelo S. Gambino, a student researcher from Canisius College; Janusz Morys from the Medical University of Gdansk; and Pamela A. Maher from the Salk Institute in La Jolla, Calif.

“The research was funded by grants from the March of Dimes and Birth Defects, the John R. Oishei Foundation, the Medical University of Gdansk; and Pamela A. Maher from the Salk Institute in La Jolla, Calif.”

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—Michal Stachowiak, PhD

**Symptoms in Obese May Not Mean Asthma**

**By Lois Baker**

The study was conducted under four conditions: no intervention (normal), which serves as the control condition; chest loading to simulate a BMI of around 30, considered borderline obese; thigh and calf compression to create increased lung blood volume that might be experienced at a BMI of 30; and chest loading and leg compression together.

Volunteers also underwent chest compression equal to a BMI of 42, simulating gross obesity.

Cheating loaded involving wearing a vest with pockets filled with buckshot to mimic the weight distribution associated with these levels of obesity: Increased lung blood volume was simulated by using a modified antigravity suit similar to those worn by astronauts to prevent blood from pooling in the lower extremities during reentry to the earth’s atmosphere.

Under each study condition, volunteers received methacholine, a type of chemical in aerosol form used in airway challenge testing that produces airway constriction in persons with asthma.

Methacholine had no effect on the asthma-free participants during the control condition. However, when lung volume was reduced by chest loading, leg constriction and in combination, participants showed asthma-like symptoms. Those in the simulated BMI of 42 study had stronger reactivity.

“As the severity of simulated obesity increased, lung volume decreased and airways became hyperreactive,” reports Cerny. “Decreasing lung volume upsets the regulatory mechanisms that govern the smooth muscle lining the airways and the terethers that control airway responsiveness.”

“Both obesity and asthma are on the rise in developed nations and pose a major health challenge,” observes Cerny. “Our study implies that, at least in some persons, the changes in airway hyperresponsiveness associated with obesity may not be asthma, which is characterized by chronic airway inflammation, but may simply reflect structural changes in the lung.

“The message to physicians is ‘If you have obese patients who have asthma symptoms, it might be a good idea to get them to lose weight before putting them on medication,’” says Cerny.

Li-Ying Wang, a former UB doctoral student now at National Taiwan University, is first author on the study. Other authors, both from UB, are Thomas J. Kufel, MD, clinical associate professor of medicine, and Brydon J. B. Grant, MD, professor of medicine, and preventive medicine.

**The message to physicians is ‘If you have obese patients who have asthma symptoms, it might be a good idea to get them to lose weight before putting them on medication,’ says Cerny.**
Post-Concussion Syndrome

New treatment pioneered at UB

By Lois Baker

T HIS TRAGIC, BUT TRUE, vignette illustrates the problem of patients leaving emergency departments after suffering a concussion or mild traumatic brain injury without clear and thorough information about the signs of impending complications.

In a study published in the August 2006 issue of Brain Injury, researchers at the University at Buffalo found that discharging patients from 14 of 15 hospitals that were reviewed lacked at least one important sign of a possible hemorrhage. Ten of the hospitals were located in Western New York; five were located in southern Ontario, Canada.

In addition, most instruction sheets were written at too high a reading level. Furthermore, some suggestions for concussion management were simply wrong, says Willer.

There is no other known treatment specifically for PCS, which we define as persistent symptoms of concussion past the time they should have cleared, usually around three weeks,” adds Willer. “As far as we can determine, there is only one other group in North America that is using regulated exercise as part of the treatment for PCS.”

Willer and Leddy have used regulated exercise successfully with people who were as much as six months post-concussion. Their regimen is based on the hypothesis that the regulatory system responsible for maintaining cerebral blood flow, which may be dysfunctional in people with a concussion, can be restored to normal by controlled, graded symptom-free exercise.

“The treatment program is well tolerated by patients,” Willer explains. “Just being able to exercise often reduces the depressive symptoms. But it’s imperative that the patient not go beyond the exercise limits.”

“After the first three weeks of regulated exercise, we reassess the patient to see if there has been any change in physiology. The exercise program then is realigned successively to respond to the changes. In our experience thus far, symptoms disappear within several months for at least some of the patients,” he reports.

The researchers have worked with a small number of patients to date. They have included a UB soccer player who has returned to play and now is one of the team’s leading scorers. Another young athlete was able to return to cross-country running and attend school full-time.

A 40-year-old woman in good health falls and hits her head while visiting her roommate at her workplace.

After a trip to the emergency department, her roommate takes her home with limited instructions. Two days later she finds her dead in her bedroom from a brain hemorrhage.

The researchers described the treatment method in September about the results so far.

Professionals at the meeting were delighted that our approach to treatment of post-concussion syndrome doesn’t involve any medications and is very cost-efficient,” he says. “We were surprised to learn that we are among only a few investigators interested in people with symptoms that won’t go away.”

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**Mild Brain Injury**

Hospital discharge instructions faulty

Michael Fung, MD, a Canadian physician serving a fellowship in UB’s Sports Medicine Institute and the study’s lead author.

“We looked at information given to patients from hospitals on both sides of the U.S.-Canadian border in order to determine if the information provided was consistent with the research evidence on signs of hemorrhage,” explains Fung.

“We found no difference between the countries, but major differences between hospitals. In fact, not one hospital had all of the information needed in a simple, easy-to-understand format. We were especially surprised that the designated trauma hospitals in both countries had such inadequate discharge information sheets.”

The study authors include a proposed evidence-based emergency department discharge form they hope will result in universal discharge instructions for patients with mild traumatic brain injury.

The study notes that the signs accepted by brain specialists as associated most consistently with hemorrhage or equally dangerous swelling in the brain following a blow to the head are: vomiting, a worsening headache, amnesia or short-term memory loss, worsening mental status, loss of motor function or vision or speech and seizure. The idea for the study originated with a website managed by the Ontario Brain Injury Association that allows people to submit questions to concussion experts. Barry Willer, PhD, professor of psychiatry and rehabilitation sciences and lead author on a paper describing the new method, published in the September 2006 issue of Current Treatment Options in Neurology.

“Most people with PCS have symptoms of depression,” says Willer, “so antidepressant treatment makes sense. However, antidepressants do little more than relieve some of the depressive symptoms and in some cases make it more difficult for the patient to return to activity that places them at risk for a second concussion unless the brain is bleeding internally.”

One hospital suggested that patients could take aspirin. “Aspirin is a blood thinner that could increase the risk for hemorrhage,” says Willer. “We think doctors should be cautious about allowing patients to take any medications, at least for the first 24 hours, to avoid masking symptoms like worsening headache. A worsening headache may be a major indicator that the brain is bleeding internally.”

Douglas Mordard, MD, UB clinical associate professor of pathology and anatomical sciences, and John J. Leddy, MD ‘85, UB clinical associate professor of orthopedics, rehabilitation sciences and family medicine and associate director of the UB Sports Medicine Institute, also were study coauthors. 
**Medical Imaging, the Next Generation**

**Multiple-contrast systems to provide complementary information**

*By Ellen Goldbaum*

The fields of nanomedicine in which Dr. Prasad and his teams are working are developing extremely rapidly, and they are at the forefront," says Thomas E. Baker, president of the foundation. “The work of these grants has tremendous potential for significantly improving both the diagnostic capabilities of physicians and the clinical outcomes of patients.”

Once injected with these multimodal nanoparticles, the patient can undergo several imaging tests, the results of which will be combined to provide more comprehensive and complementary information, such as correlations between molecular and morphological changes at the cellular level. The result is a far more sensitive and comprehensive method of detecting the presence or progression of a disease. “At the same time, these imaging agents will provide pharmaceutical researchers and clinicians with powerful tools for more precise monitoring and tracking of drug action in real-time,” explains Prasad.

The multimodal platforms underway in Prasad’s group are based on versatile nanoparticles that the UB researchers have developed with previous Oishei Foundation funding that have been shown to be effective in a broad range of therapeutic applications. "The fields of nanomedicine in which Dr. Prasad and his teams are working are developing extremely rapidly, and they are at the forefront," says Thomas E. Baker, president of the foundation. “The work of these grants has tremendous potential for significantly improving both the diagnostic capabilities of physicians and the clinical outcomes of patients.”

The research also is being conducted with partial funding from UB’s New York State Center of Excellence in Bioinformatics and Life Sciences, a major supporter of the nanomedicine program at the Institute for Lasers, Photonics and Biophotonics. Prasad is affiliated with the Bioengineering/Tissue Engineering Team at the Center of Excellence.

“This new imaging work represents an exciting and timely extension of our existing nanomedicine portfolio that will be particularly important for the Center of Excellence initiatives in neurodegenerative disease and cancer,” says Bruce A. Holm, MD, PhD, UB senior vice provost and executive director of the Center of Excellence. “This research not only crosses a variety of UB 2020 Strategic Strength areas, but holds enormous promise for commercialization potential as well.”

The UB institute’s new emphasis on application of nanobiotechnology to medical imaging also distinguishes it from other nanotechnology research centers throughout the U.S., while enriching its current collaborations with The Johns Hopkins University, Roswell Park Cancer Institute and others. The nanoprobes are being developed for use with:

- Optical imaging techniques, especially those in which fluorescence and Raman scattering can probe the intracellular distribution of molecular events that are early signals of disease or responses to drugs.
- Magnetic resonance imaging (MRI), in which fluorine nuclear probes would be developed using the nanoparticles, providing more selective targeting of specific biological sites.
- Positron emission tomography (PET), in which radioisotopes are incorporated inside nanoparticles as contrast agents for more sensitive assessments of drug efficacy during therapy.
- Computed tomography (CT) and single photon emission computer tomography (SPECT), in which radio-opaque ions are incorporated inside nanoparticles as contrast agents for improved in vivo imaging.

In addition to Prasad, other key personnel involved in the research from the Institute for Lasers, Photonics and Biophotonics are E. J. Bergey, PhD, deputy director of biophotonics; Dushan Sukumaran, PhD, director of UB’s magnetic resonance center; Indrakoi Roy, PhD, postdoctoral associate; Tymish Y. Ohuchansky, PhD, postdoctoral associate; Haridas E. Pudivar, PhD, research assistant professor and Alik-sander Kachynski, PhD, research scholar, all in the Department of Chemistry. Also involved are Richard V. Mazur- chuk, PhD, director of the preclinical magnetic resonance imaging facility, and Ravindra K. Pandey, PhD, professor of biophysical sciences at Roswell Park Cancer Institute; Hani A. Nabi, MD, PhD, professor and chair of nuclear medicine at UB; and Benjamin Tsui, PhD, at Johns Hopkins.

The John R. Oishei Foundation is committed to enhancing the quality of life for Buffalo-area residents by supporting education, health care, scientific research and the cultural, social, civic and other charitable needs of the community. The foundation was established in 1940 by John R. Oishei, founder of Trico Products Corporation, one of the world’s leading manufacturers of windshield wiper systems.

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Since X-rays were discovered more than a century ago, triggering a revolution in medical imaging, clinicians have sought more powerful ways to “see” into the human body.

In keeping with this tradition, researchers in UB’s Institute for Lasers, Photonics and Biophotonics are applying their expertise in nanomedicine to the development of new, nanoparticle-based multi-probe systems, spurring development of a new generation of medical imaging technologies.

Their efforts were recently given a boost by a $1.1 million grant from the John R. Oishei Foundation, which will support research aimed at combining two or more medical imaging techniques to provide complementary information.

These nanoparticle systems—part of a new field called nanobiotechnology—are being designed by the UB scientists to contain multiple contrast agents for different imaging medical techniques.

The goal is to diagnose cancer and other diseases at their earliest stages by providing far more comprehensive data to clinicians. “Ultimately, clinicians want the most complete data possible that they can gather from medical images, ranging from tissue structure to metabolic processes to molecular markers,” says Paras Prasad, PhD, executive director of the Institute for Lasers, Photonics and Biophotonics and SUNY Distinguished Professor of Chemistry. “We are aiming to provide them with such data by developing nanoparticle platforms capable of carrying multiple contrast agents for complementary medical imaging techniques in the same nano-sized package,” he explains.

Once injected with these multimodal nanoparticles, the patient can undergo multiple imaging techniques to provide complementary information.

- Optical imaging techniques, especially those in which fluorescence and Raman scattering can probe the intracellular distribution of molecular events that are early signals of disease or responses to drugs.
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Online Resource Expands

Regional Knowledge Network adds health, human services

Which neighborhoods in the City of Buffalo have the highest percentage of disabled elderly? What is the distribution of lung cancer across Western New York? How does the rate of HIV mortality in Southern Ontario compare to that of Western New York?

Answers to these and other key questions on health in the binational Buffalo-Niagara region now can be found at the Regional Knowledge Network (RKN), an online information resource developed by UB's Institute for Local Governance and Regional Growth.

Launched in its first phase in March 2006, RKN (rkn.buffalo.edu) is designed to inform regional decision-making by providing access to data, maps, lists and resources on 10 topics for the region spanning Western New York and Southern Ontario. The latest enhancement to RKN is the addition of 79 data variables and dynamic mapping capacities for the Health and Human Services topic, a development supported by a major grant from the Oishei Foundation.

“RKN users may download data, produce customized maps or view reference maps, sort and download lists of other topical information and link to related resources. Lists and resources also are available for the other five topic areas, with data and maps in progress,” said Zhen Yan, PhD, a senior author on the study, along with Cain Feng, PhD.

Both researchers are associates professor of physiology and biophysics and members of the Neurodegenerative Disease Group in UB’s New York State Center of Excellence in Bioinformatics and Life Sciences.

“Many antidepressant, anti-anxiety and antipsychotic drugs target the norepinephrine system in the prefrontal cortex, is strongly linked to many neuropsychiatric disorders, including depression, anxiety, ADHD and schizophrenic,” says Zhen Yan, PhD, a senior author on the study, along with Cain Feng, PhD.

Answers to RKN include high rates of motor-vehicle injuries, a distribution of lung cancer across Western New York, answers to the number of years a foster child is in foster care in Western New York.

Viewer friendly Web interface also has been added to RKN as part of the latest round of developments. Funding from the Oishei Foundation will enable the institute to fully develop RKN by May 2008, with data and maps for all 10 topic areas and new information tools for pin-mapping, enhanced searches and advanced data charting and analysis. On tap for the addition of data and maps are the Regional Assets and Public Safety topic areas.

A major research and public service unit of UB, the Institute for Local Governance and Regional Growth plays a vital role in addressing key policy and governance issues for regions, with focused analysis of the Buffalo-Niagara region. An affiliate of the UB Law School, the institute leverages the resources of the university and binational community to pursue a wide range of scholarship, projects and initiatives that frame issues, inform decisions and guide change.

The 79 Health and Human Services data variables cut across the categories of disability, disease, mortality, health behaviors, mental health, child health and social needs.

The 79 Health and Human Services data variables cut across the categories of disability, disease, mortality, health behaviors, mental health, child health and social needs. Some patterns in regional health revealed by RKN include high rates of motor-vehicle fatalities in Western New York's rural counties, Chautauqua County as the top per-capita spender on Medicaid, and a mean of one to three years as the number of years a foster child is in foster care in Western New York.

For five of the 10 topic areas (Population and Demographics, Government, Economy, Education and Schools, and now Health and Human Services), RKN users may download data, produce customized maps or view reference maps, sort and download lists of other topical information and link to related resources. Lists and resources also are available for the other five topic areas, with data and maps in progress.

“RKN can tell provocative stories about regional issues,” Foster adds. “It is our hope that RKN becomes a go-to tool for research-ers, government officials, news media, and citizens in search of answers to these and other key questions on health in the binational Buffalo-Niagara region now can be found at the Regional Knowledge Network (RKN), an online information resource developed by UB’s Institute for Local Governance and Regional Growth.

For information about including UB in your plans, contact the Office of Planned Giving:

Wendy Irving, Esq., Senior Director of Planned Giving
(716) 645-2632 / (716) 645-2633
dev-pg@buffalo.edu

Pathway for Treating Mental Disorders

New critical drug target revealed

In their continuing search for promising targets for treating mental disorders, a group of neuroscientists in the School of Medicine and Biomedical Sciences has identified a pathway critical to the functioning of antidepressants, antipsychotic drugs and drugs for anxiety disorders.

In their research—the results of which were published in the November 13, 2006 issue of Proceedings of the National Academy of Sciences—the scientists focus on the norepinephrine system in the brain's prefrontal cortex. This is a region responsible for many high-level functions, such as cognitive processing, working memory and control of emotions.

“Normal operation of the norepinephrine system, one type of norepinephrine receptor in the prefrontal cortex, is strongly linked to many neuropsychiatric disorders, including depression, anxiety, ADHD and schizophrenia,” says Zhen Yan, PhD, a senior author on the study, along with Cain Feng, PhD.

Both researchers are associates professor of physiology and biophysics and members of the Neurodegenerative Disease Group in UB’s New York State Center of Excellence in Bioinformatics and Life Sciences.

“Many antidepressant, anti-anxiety and antipsychotic drugs target the norepinephrine system,” says Yan. “Until now it has been unclear how norepinephrine receptors perform the complicated functions carried out by the prefrontal cortex.”

The research team revealed that a critical target of norepinephrine receptors is the NMDA-type glutamate receptor channel, which also is a pivotal player in cognition and emotion. Glutamate is a neurotransmitter normally involved in learning and memory, but under certain circumstances it can be toxic and may cause nerve cell death in a variety of neuropsychi-degenerative disorders.

“We found that different norepinephrine receptors regulate the activities of NMDA receptor channels by activating specific intracellular signaling cascades,” says Yan.

Moreover, we have identified two important players that influence critically the regulatory effects of norepinephrine receptors, known as RGS4 and spinhin, which are involved in schizophrenia and depression, respectively.

“Modifying norepinephrine signaling has been considered one of the key therapeut-ical actions of many current drugs,” notes Yan. “To understand the functional roles of norepinephrine receptors, we needed to know their cellular targets. The NMDA receptor channel has been implicated in both normal cognitive processes and mental disorders, which makes it a potentially important target for drugs that may regulate prefrontal cortex functioning.”

Insights gained from this discovery eventually may provide new drug targets for various neuropsychiatric diseases, Yan says. Wenhuai Liu, PhD, and Evenue Y. Yuen, PhD, postdoctoral associates in Yan’s laboratory performed the experiments. Also contributing to the research were Patrick B. Allen from the Yale University School of Medicine, and Paul Greengard from Rockefeller University.

The work is supported by gifts awarded to Yan from the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute of Aging and the National Alliance for Research on Schizophrenia and Depression.