NEWYORK–PRESBYTERIAN
Neuroscience
Affiliated with **COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS and SURGEONS** *and* **WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY**

Fall 2006

Neuro-Oncologic Care Offers Full Support to Brain Tumor Patients

Over the past year, the management of brain malignancies at NewYork-Presbyterian Hospital/Columbia University Medical Center has been substantially reworked to make the medical care offered more comprehensive. While the therapeutic expertise remains unchanged, patients now enter a system designed to anticipate their needs throughout the diagnostic, treatment, and recovery process. This includes the psychosocial support often required to cope with the impact of the disease.

"The research activities we conduct are very important in defining the evolving standards of treatment, but we also see our function as providing a full-service clinic," reported Steven S.

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Upcoming CME Seminars

Brain Attack and Cerebrovascular Disease—Update 2006

November 17, 2006

This conference will review the latest approaches to the diagnosis, treatment and prevention of stroke and cerebrovascular disease focusing on controversial topics in the diagnosis and management of stroke.

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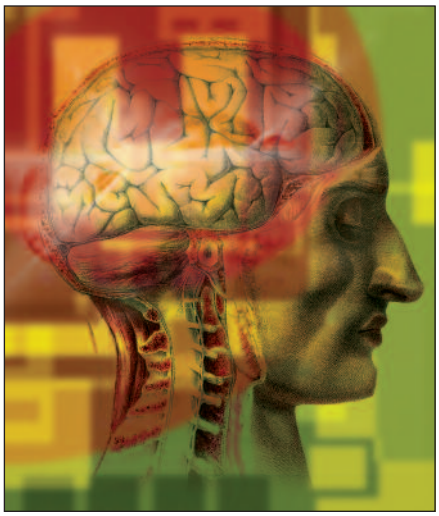
March 23 - 24, 2007.

NewYork-Presbyterian Hospital—Department of Rehabilitation Medicine

Uris Auditorium, Weill Medical College of Cornell University, New York, NY

Go to www.nyprehabmed.org for information and registration

Focus of Acute Stroke Research: Prevention and Rapid Intervention



The potential to circumvent the consequences of acute ischemic stroke by accelerating the time to reperfusion has investigators at both NewYork-Presbyterian Hospital medical centers involved in multiple projects that may increase survival or reduce disability. Some of the projects at NewYork-Presbyterian/Columbia and NewYork-Presbyterian/Weill Cornell are being performed independently, while some overlap, and others are part of a nationwide research collaborative effort called SPOTRIAS (Specialized Program On Translational Research In Acute Stroke) to which both campuses are contributing. The best approach to stroke is prevention, but the next-best approach is rapid intervention to preserve neurologic function.

"We are working on several initiatives simultaneously to identify patients at high risk, to educate those high-risk patients about the signs and symptoms of an ischemic event, and to speed therapies that will avoid or limit the consequences of stroke," reported Ralph Sacco, MD, of NewYork-Presbyterian/Columbia, who is

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NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Options To Combat Neuropathic Pain Expand With New Drugs, Nonpharmacologic Interventions

The investigators at NewYork-Presbyterian Hospital/Weill Cornell Medical Center are working to expand options for the control of neuropathic pain without overlooking the effective therapies already available. In some patients, the vicious cycle of self-sustaining neuropathic pain can be broken with simple anti-inflammatory drugs. Others may need more sophisticated interventions, such as an implantable device that delivers intrathecal drugs by catheter directly to pain receptors in the spinal canal. While clinical trials with a variety of new treatments are proceeding, the challenge today is getting the right therapy to the appropriate patient.

"We consider everything that we have available because each patient is unique, and a very effective therapy for one type of neuropathic pain may be a poor choice for another," reported Sudhir A. Diwan, MD. Some of the most-established therapies for neuropathic pain, such as anti-inflammatory drugs, antiepileptic drugs, and tricyclic antidepressants, remain highly effective when used selectively in the context of exercise and a comprehensive rehabilitation program. Conversely, oral opioid analgesics, although effective for pain relief, often compare unfavorably with better-tolerated therapies that do not impede patient function.

"At low doses, oral opioids are not very effective. At high doses, opioids relieve pain, but they are sedating and interfere with the ability of patients to return to normal activities, which is perhaps the most important goal of treatment," Dr. Diwan said.

The systemic effects of opioids were a major impetus to a consideration of the direct delivery of morphine to pain receptors in the subgroup of patients with intractable neuropathic pain. In one of the technologies now available for patients with persistent neuropathic spinal pain at Weill Cornell, an implantable intrathecal pump uses a small catheter to deliver analgesic medication (morphine) directly into the spinal canal.

A new analgesic called ziconatide, a synthetic chemical version of snail venom, is proving to be versatile in the control of neuropathic pain.

"The direct delivery of morphine to the receptors in the spinal canal means that treatment is targeted to specific receptors, bypassing all the other organs. The potency difference is approximately 300 to 1. This means that if adequate pain control requires 300 mg of oral morphine, only 1 mg will be sufficient if delivered by the implantable device to the spinal receptors. The patient is spared exposure to the other 299 mg, which was just contributing to adverse events," Dr. Diwan said. In the right individual, the results can be very impressive.

"We have patients who have returned to a completely normal lifestyle after prolonged periods of disabling neuropathic back pain. In one instance, the patient is back to scuba diving," Dr. Diwan reported.

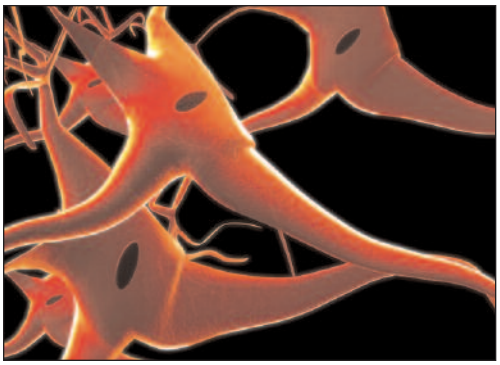
Several newer analgesic agents are being pursued, as are existing analgesics that have not been widely evaluated for the control of neuropathic pain. One drug in this latter group is methadone, a chemically synthetic morphine that has been shown to work on NMDA (*N*-methyl-D-aspartate) receptors, which are strongly implicated in mediating neuropathic pain. Again, the drug is useful only in selected patients, but the benefit-to-risk ratio in these patients relative to other options may be very favorable.

"There is substantial social stigma in the use of methadone, which most individuals associate with recovery from heroin addiction, but this is one of the drugs we have available that appears to act through the NMDA receptor, and it can be very effective," Dr. Diwan said.

A new analgesic called ziconatide, a synthetic chemical version of snail venom, is also proving to be versatile in the control of neuropathic pain. Investigators at NewYork-Presbyterian/Weill Cornell participated in the clinical trials for this agent and have been able to rapidly incorporate it into their options for neuropathic pain control.

"Along with my colleagues Drs. Shakil Ahmed and David A. Zylberger, we are now working on various strategies to further expand the utility of this agent, including combining this agent with other analgesics," Dr. Diwan said.

However, not all the approaches to controlling neuropathic pain involve drugs. Dr. Diwan reported that physicians at NewYork-Presbyterian/Weill Cornell have been active in using neurolysis to control chronic pain unresponsive to pharmacologic therapies. Neurolysis involves destroying peripheral sensory nerves that continue to fire impulses without stimulation. "With radiofrequency ablation, a probe is employed to locate the source of pain



and then deliver the energy that destroys the nerves. This can be very effective for reducing the requirement for pain medications and improving quality of life," Dr. Diwan observed, reiterating that, while it can be highly effective, it is appropriate only for selected candidates.

Another nonpharmacologic approach to chronic neuropathic spinal pain is to implant leads into the epidural space in the spinal canal to deliver low-frequency, high-amplitude stimulation to the spinal cord. According to Dr. Diwan, the patient experiences a buzzing sensation in the area of his or her pain—paresthesia—and the stimulation interrupts the pain signals going to the cerebral cortex, typically reducing pain by 70% to 80%. Again, one of the advantages of this device is to obtain pain control without benefit of pain medications, hence avoiding their associated side effects.

"Our goal is to provide pain control with minimal cost and minimum to no side effects and adverse events," said Dr. Diwan, who carefully selects therapies to maximize the benefit-to-risk ratio. Regardless of the type of neuropathic pain, patients managed at NewYork-Presbyterian/Weill Cornell have an excellent chance of achieving an acceptable degree of pain relief.

"We have an increasingly detailed understanding of the causes of neuropathic pain, and this is leading to more therapeutic options. Not everyone requires the newest tool to achieve pain control, but it is reassuring to have newer options to consider in the difficult cases," said Dr. Diwan, who noted that as the number of tools grows, so does the number of solutions.

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Study Aims To Prove Reliability Of Biomarker for Diagnosis of Amyotrophic Lateral Sclerosis

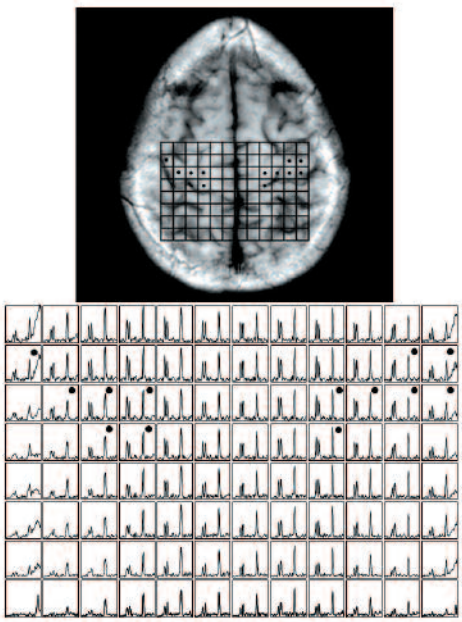
At a time when the search for quantitative objective markers for dysfunction in amyotrophic lateral sclerosis (ALS) is an area of intense scientific research, a study conducted by NewYork-Presbyterian Hospital researchers could provide novel insight into the pathobiology of this disorder.

In a comprehensive, 3-year, prospective, multidisciplinary study, Hiroshi Mitsumoto, MD, DSc, and colleagues investigated the diagnostic value at baseline and during disease progression of potential markers of upper motor neuron (UMN) and lower motor neuron (LMN) dysfunction, in relation to well-established clinical measures used in ALS.

"At present, no reliable biomarkers of the disease are available, so the diagnosis of ALS is made primarily on the basis of neurological evaluation and ancillary tests designed to exclude other causes or disorders," explained Dr. Mitsumoto.

In diagnosing the neuromuscular and neurodegenerative disorder ALS, which affects both the LMN and the UMN, clinicians and investigators use the widely accepted El Escorial diagnostic criteria based on clinical identification of LMN and UMN signs. A diagnostic electromyogram (EMG) is used to confirm clinically suspected LMN dysfunction as well as to detect clinically unrecognized LMN involvement. Muscle biopsy can also be used to identify LMN changes. In contrast, determination of UMN involvement depends solely on neurologic examination. According to Dr. Mitsumoto, objective confirmation of UMN signs is a continuing clinical challenge, since such signs can be masked when LMN involvement is severe.

Furthermore, identification of UMN signs often depends on subjective interpretation and the patient's physiologic status, as well as the inherent difficulty in detecting UMN signs in the torso and muscles innervated by cranial nerves. "Consequently, UMN involvement can easily be missed on clinical evaluation," Dr. Mitsumoto said. 'Therefore, having biomarkers that provide objective evidence of UMN involvement would be helpful, not only to improve diagnostic accuracy, but also for quantifying UMN and LMN impairment."



Partial proton MRSI grid from the brain of a typical ALS patient.

In the study, Dr. Mitsumoto and colleagues prospectively studied 64 patients with ALS and its subsets at baseline and every 3 months for 15 months using clinical measures, proton magnetic resonance spectroscopic imaging, diffusion tensor imaging, transcranial magnetic stimulation (TMS), and the motor unit number estimation (MUNE). These findings were compared to 29 control subjects. Patients with ALS were evaluated for eligibility and recruited at the Eleanor and Lou Gehrig MDA/ALS Research Center of Columbia University's Neurological Institute of New York.

The findings showed that proton magnetic resonance spectroscopic imaging measures of the concentration of the primary motor cortex N-acetyl-aspartate (NAA) were markedly reduced in ALS and in all UMN syndromes combined, when compared to controls. Central motor conduction time to the tibialis anterior was prolonged in ALS and in the combined UMN syndromes. MUNE was lower than it was in controls in ALS and in all LMN syndromes combined. All objective markers correlated well with the ALS Functional Rating Scale-Revised, finger and foot tapping, and strength testing, indicating that these markers reflected disease activity and clinically meaningful changes. "Additionally, MUNE changed rapidly over time, whereas neuroimaging markers changed more slowly and did not significantly differ from baseline," said Dr. Mitsumoto.

Dr. Mitsumoto commented that although MUNE was a highly sensitive technique that documented LMN loss long before clinical weakness or LMN signs appeared, it was unlikely to replace routine needle EMG as a diagnostic tool for the confirmation of LMN dysfunction. This is because MUNE values vary widely in the general population and because routine EMG, a widely available tool, has demonstrated clinical utility and validity in this area for many years. "However, this study has clearly confirmed that MUNE is a sensitive and reliable tool for quantitative detection of changes in the LMN over time in patients with ALS," said Dr. Mitsumoto.

The study findings showed correlations among a number of the objective UMN markers and clinical measures, not only at baseline but also during

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Neurological Intensive Care Units Manage the Crisis From Increased Intracranial Pressure

When the brain is subjected to any kind of damage—whether by traumatic injury, stroke, infection, or because of severe metabolic problems such as kidney or liver failure—the organ can swell rapidly within the confines of the skull and result in increased intracranial pressure (ICP). Specialists at NewYork-Presbyterian Hospital, long a leader in the emerging field of neurological intensive care, manage this dangerous condition with an array of newly developed devices and interventions.

In 1983, NewYork-Presbyterian Hospital/Columbia University Medical Center opened one of the nation's first neurological intensive care units (neuro-ICUs), combining neurology, critical care, neurosurgery, and anesthesiology to address the needs of these critically ill patients. Then, in late 2003, NewYork-Presbyterian Hospital/Weill Cornell Medical Center established a second neuro-ICU.

"Twenty years ago, there was a tendency to simply give up on these patients quickly, with a decision made early on that they were hopeless," said Matthew E. Fink, MD, of NewYork-Presbyterian/Weill Cornell, one of the founders of neurointensive care while at NewYork-Presbyterian/Columbia.

There has been a rapid expansion of diagnostic and treatment approaches, many of which are useful for ICP management. NewYork-Presbyterian Hospital's neuro-ICUs have, for example, optimized a number of monitoring modalities to measure pressure within the skull and brain, oxygen content within the brain, chemical metabolite levels, and blood flow.

One of the neuro-ICUs' most innovative devices is Licox (Integra LifeSciences), a cerebral oxygenation monitoring system. Increased ICP can quickly reduce cerebral perfusion and oxygen delivery in the brain, and thus a tool to assess the severity of this reduction is extremely useful when evaluating treatment options. "In patients with high ICP who would usually require aggressive management, sometimes the brain oxygen levels are normal, which demonstrates that the brain is just fine despite a stressful situation," noted Igor Ougorets, MD. In addition, the system can be used to judge whether hyperventilation, a common method to reduce ICP, may in fact lead to reduction of cerebral blood flow, consequently having the unwanted effect of reducing brain tissue oxygenation.

The neuro-ICUs are also employing another monitoring method, brain microdialysis, to measure minute levels of brain chemicals. The technique, which has been widely used in Europe, was originally developed to conduct laboratory research on animal models, but can now benefit humans.

"Both methods give us real-time physiological and biochemical measurements that reflect the functional activity of the brain," said Dr. Fink. "We can adjust our treatments literally from minute to minute to maximize the potential for recovery. That's really the essence of critical care."

Among the many specialized interventions, hypothermia stands out as particularly promising. The approach, which can be achieved through a variety of devices, lowers brain temperature by a few degrees for a period ranging from 24 to 72 hours. This cooling decreases the metabolic rate of the brain and reduces tissue damage. One device, called Arctic Sun (Medivance), employs external computerized cooling blankets in direct contact with the skin. A more invasive method is Celsius Control System (InnerCool), a central venous circulation heat exchange catheter.

Continuous EEG monitoring is another important new modality for detecting ongoing neurologic injury in the brains of coma victims. According to Stephan A. Mayer, MD, director of the NewYork-Presbyterian/Columbia neuro-ICU, "our extensive experience indicates that up to one third of critically injured neurologic patients experience nonconvulsive seizure activity, which is impossible to detect without digital continuous EEG monitoring. This technology has essentially made us aware of an entirely new mechanism of ongoing secondary neurologic injury. Although treatments for eliminating these seizures remain unknown, now that we see the enemy, at least we have a chance to stop this injurious process."

Another goal of NewYork-Presbyterian Hospital's program is to organize a network of neuro-ICUs in a cooperative group that will study the innovative techniques now being used, said Dr. Fink. "All of these monitoring devices and treatments have been used in a way we believe is beneficial but, in most cases, the benefit has not been proven through the gold standard of randomized, clinical trials. We hope to soon change that."

When managing patients with increased ICP, functional outcome improvement is the ultimate measure of success for neuro-ICUs. "After everything's said and done, it's not so much about dying or living," Dr. Ougorets said. "It's about whether the patient is going to a nursing home for the rest of his or her life, going to assisted living, or actually going home. That's where the real battleground is."

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Acute Stroke

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Principal Investigator for SPOTRIAS. These goals were echoed by Alan Z. Segal, MD, of NewYork-Presbyterian/Weill Cornell, who credited the strength of the stroke treatment program throughout NewYork-Presbyterian Hospital to collaboration that extends from basic researchers to critical care specialists and is present both at the main campuses and at the various satellite hospitals.

"Over the last year, we have substantially expanded our stroke team, bringing in several leaders in the study and treatment of stroke to expand our capacity," Dr. Segal reported. Like Dr. Sacco, he suggested that the greatest opportunity to prevent the consequences of stroke is to avoid the initial event, but there is increasing promise from new tools for treatment, particularly in patients who present at an emergency room soon after the appearance of symptoms.

Through participation in SPOTRIAS, a program funded by the National Institutes of Neurological Disorders and Stroke, one of the clinical trials under way at both NewYork-Presbyterian/Columbia and NewYork-Presbyterian/Weill Cornell is testing the effect of very high doses of statins for acute stroke. Experimental data suggest that statins may have a neuroprotective effect independent of their effect on blood cholesterol levels. In the multicenter Phase I clinical trial directed by Mitchell Elkind, MD, associate professor of neurology at Columbia University College of Physicians and Surgeons, acute stroke patients are being treated with statins in a dose-escalating study design with doses as high as 10 mg/kg.

"In the experimental animal models, high-dose statins have reduced the infarct size. In the planned clinical trials, the end point will be protection against disability," Dr. Sacco said.

Both centers are also participating in a clinical evaluation of the MERCI® (Mechanical Embolus Removal in Cerebral Ischemia) device that is an alternative to tissue plasminogen activator (t-PA) in destroying the clot to permit reperfusion. The device is already approved by the Food and Drug Administration, but protocols to maximize its utility and safety are in development. The MERCI device is inserted through the femoral artery in the groin and threaded up through the carotid artery to reach just beyond the clot. Once the clot is ensnared in the device, a balloon is inflated to halt blood flow while the clot is withdrawn. When the balloon is deflated, blood flow resumes.

"In the experimental animal models, high-dose statins have reduced the infarct size. In the planned clinical trials, the end point will be protection against disability."

Ralph L. Sacco, MD

"We have been enrolling patients in a study that is employing MRI [magnetic resonance imaging] to identify those acute stroke patients who are the best candidates for this device," said Dr. Segal, of NewYork-Presbyterian/Weill Medical. Simultaneously, NewYork-Presbyterian/Columbia is enrolling patients in the same study, which compares the device to the standard of care.

In a unique functional MRI study of acute stroke being conducted at the Columbia University College of Physicians and Surgeons by Randolph Marshall, MD, associate professor of clinical neurology, the goal is to evaluate changes in the opposite side of the injured brain at the time of stroke as predictors of outcome at three months. Patients are evaluated within 48 hours of the stroke; the study could provide insight about the progression of stroke and brain function over the acute period. According to Dr. Sacco, information generated by these studies could lead to new strategies to improve functional outcomes.

In another initiative at Columbia University College of Physicians and Surgeons, an interactive behavioral modification program called SWIFT (Stroke Warning Information and Faster Treatment), directed by Bernadette Boden-Albala, DrPH, assistant professor of sociomedical sciences in neurology, is being tested against standard methods of education in patients at high risk for stroke. The goal of the multimedia program is to equip patients with the information they need to recognize early signs of stroke and to seek rapid care. The patients are being followed by telephone after participating in the program to determine what information they have retained and whether this has led to behavioral change. More important, the study will evaluate whether those who do have stroke warning symptoms arrive sooner at the hospital than those who receive standard education.

"We could be placing more patients on highly effective therapies, such as t-PA, if we can get them to the hospital sooner," Dr. Sacco explained. "This is one of the strategies we are testing."

At NewYork-Presbyterian/Weill Cornell and NewYork-Presbyterian/Columbia, there have been multiple stroke outreach programs to increase awareness of the risk factors for stroke as well as early signs and symptoms of a cerebrovascular event. While modification of risk factors may avoid events altogether, the greatest opportunity for a favorable outcome in those who do have stroke is early treatment.

"We are very driven by the concept that prevention is the best option," Dr. Segal observed. However, he concurred

that in patients who do sustain a cerebrovascular event, progress in improving outcome depends on rapid diagnosis and therapy. Although both medical centers employ cutting-edge diagnostic strategies in the emergency room, such as high-speed computed tomography scanning, Dr. Segal emphasized that he has worked closely with critical care staff at area hospitals to accelerate their diagnostic and treatment processes. Drs. Sacco and Segal serve as co-directors of NewYork-Presbyterian Hospital's Network Stroke Directors Group, which has been instrumental in setting standard stroke protocols across the network for improving the quality of care.

"We need to create more stroke centers to handle acute events on an emergency basis. It is important that we have a state-of-the-art protocol at Weill Cornell, but we need to bring the care to the patients who present first to a regional hospital," Dr. Segal asserted. Similarly, at NewYork-Presbyterian/Columbia, Dr. Sacco emphasized getting optimal care to the patient.

"The question is whether we can get stroke patients to act more quickly," Dr. Sacco said. "If we can get patients to an emergency room equipped to deliver urgent therapies, we will see outcomes improve."

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Brain Tumor

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Rosenfeld, MD, PhD. "Patients with brain tumors have disrupted lives, and their needs extend beyond the goal of controlling the malignancy."

Dr. Rosenfeld noted that while research is critical, patient care is paramount. This philosophy is revisited on a weekly basis when the tumor board meets to discuss strategy for individual cases.

"Our tumor board brings together oncologists, neurologists, radiologists, social workers, and other staff who can make a contribution to the discussion of optimal care for an individual patient," Dr. Rosenfeld said. In cases of challenging tumors for which several therapeutic approaches are feasible, including experimental approaches proposed by different types of specialists, the tumor board reaches a consensus on which course to pursue.

"In the majority of cases, the course of action is self-evident, but when there is ambiguity, the relative risks and benefits are discussed by the board. The discussion continues until there is full agreement, including among those who have proposed alternative approaches," Dr. Rosenfeld reported.

Because of the large number of research initiatives being pursued at NewYork-Presbyterian/Columbia, patients who are not suitable for or not likely to benefit from conventional therapeutic regimens may qualify for one or more clinical trials. According to Dr. Rosenfeld, there is typically a range of basic and clinical research being conducted, including late-phase studies of new therapeutic agents sponsored by the pharmaceutical industry and new interventions generated from in-house clinical research. One Phase II trial that will begin shortly at NewYork-Presbyterian/Columbia involves the use of a component of scorpion venom—chlorotoxin—that has shown remarkable specificity for targeting malignant brain tumors.

"There have been a number of experimental studies suggesting that scorpion venom targets glioma cells. By attaching a radioactive agent or a toxin to the venom, there appears to be a high rate of tumor cell kill with relatively little damage to healthy tissue," Dr. Rosenfeld said.

Anti-angiogenesis drugs constitute another new area of investigation in the treatment of brain malignancies. These drugs are now being widely used in a variety of other solid tumors, such as those in the lung and colon, and the initial concern about manipulating vessel formation in the brain has not been supported so far by clinical studies. In the brain, as in other organs, drugs that inhibit molecular pathways to vessel formation, such as vascular endothelial growth factor, appear to arrest tumor growth and extend survival.

"This work is in relatively early stages, but it is a promising avenue of research. While drugs that block blood vessel formation typically prevent tumors from growing rather than lead them to regress, these therapies could be meaningful for extending survival or, when combined with cytotoxic treatments, be part of a combination treatment strategy," Dr. Rosenfeld explained.

When patients are referred from distant cities, the clinicians at NewYork-Presbyterian/Columbia work with their home physicians to manage those aspects of care that can be delivered elsewhere. Such patients are also closely followed by the Hospital's staff because neuro-oncology is a highly specialized field in which the complications of malignancy can be especially challenging.

"Ultimately, patients are best served by clinicians for whom this area of medicine is their whole focus. In providing a comprehensive care program, we want patients to feel comfortable in consulting with us on any issue related to their disease," Dr. Rosenfeld said. "Although we are a research institution, the research is conducted to provide better patient care. Our ability to provide comprehensive clinical care is fundamental to our mission, and we have reoriented ourselves with this outlook."

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ALS

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follow-up. "Significant correlation with clinical measures is essential if quantitative biomarkers are to be used as natural history markers and subsequently as surrogate markers to supplement clinical findings," said Dr. Mitsumoto.

Finger tapping and foot tapping, which were highly correlated with several of the objective markers, are simple and reliable clinical markers for quantitating UMN dysfunction. The NAA concentration also modestly correlated with the score of the ALS Functional Rating Scale-Revised. MUNE highly correlated with muscle strength, grip and pinch strength, and respiratory muscle strength, all of which are primarily influenced by LMN dysfunction.

TMS revealed significant differences between control data and patients with ALS or UMN syndromes. "At our clinical center," noted Dr. Mitsumoto, "we use TMS as an adjunct test to detect objective signs of UMN involvement." In this study, TMS was able to detect upper motor prolongation in at least 1 of 4 limbs in 77% of all cases, and 81% of UMN cases.

The researchers also found that the study had confirmed previously reported decreases in both the NAA concentration and the NAA/tCr (total creatine) ratio in the primary motor cortex of patients with ALS (and its UMN subsets) that might be due to neuronal loss, dysfunction, or both. "The central motor conduction time to the leg was also prolonged in ALS and UMN syndromes," said Dr. Mitsumoto, "indicating that the descending pyramidal fibers conducted at a slower rate." MUNE showed that patients with LMN dysfunction had a markedly diminished number of functioning lower motor units. Quantitative neuroimaging markers changed more slowly over time than clinical measures and other neurophysiologic markers.

"Many of the markers correlated well with clinical measures at baseline and during follow-up," said Dr. Mitsumoto, "suggesting that these novel biomarkers could detect clinically meaningful changes that may prove useful for diagnosis and tracking disease progression in ALS and its subsets."

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