MAYO CLINIC

NeurosciencesUpdate

Neurologic Surgery and Clinical Neurology News

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INSIDE THIS ISSUE

Neural Regeneration at Mayo Clinic

At Mayo Clinic paradigms of neural regeneration take many forms — from fostering axonal projection in spinal cord and peripheral nerve injuries to promoting neurogenesis and neuronal regrowth in neurodegenerative disease. In a coordinated effort led by the chair of the Department of Neurologic Surgery, Fredric B. Meyer, M.D., neural regeneration strategies are one arm of Mayo's Center for Regenerative Medicine in Rochester, Minn. The goal of the center, directed by Andre Terzic, M.D., Ph.D., is to support research initiatives aimed at preventing cell destruction and promoting restoration and growth of function, as well as facilitating their translation to clinical application. Below are a few highlights of Mayo's work in neural regeneration.

Hippocampal Neurogenesis

In the nearly 50 years since adult neural stem cells were discovered in the mammalian brain, they have been found not only to differentiate into specific cell types but also to become functionally integrated into the circuit to contribute to specific cognitive functions. Mi Hyeon (Mi-Hyeon) Jang, Ph.D., a molecular biologist at Mayo Clinic, has made important gains in understanding the molecular mechanisms of "newborn" neuron development. With the goal of promoting neurogenesis, her work has implications for a wide variety of neuropathologic conditions.

Dr. Jang's work centers on the functional role of adult neurogenesis in the hippocampus, a structure that plays an important role in learning and memory and in the pathology of psychiatric disorders. Using a retroviral system and unique staining techniques to label neuronal progenitors, she and her colleagues were able to characterize the developmental stages of newborn neurons from a neural stem cell to a fully formed neuron with synapse formation (Figure 1), a process that takes two to four weeks. Using animal models, her lab

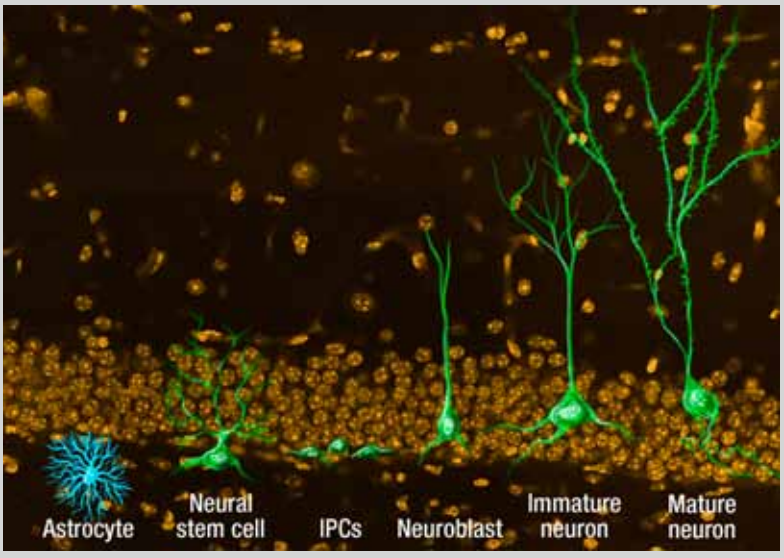

Figure 1. *Model of the sequential process of adult neurogenesis within the dentate gyrus of the hippocampus. The neural stem cell can remain quiescent, self-renew or proliferate to give rise to the astrocyte or intermediate progenitor cells (IPCs). The IPC differentiates into a neuroblast, which migrates and integrates itself into the inner granule layer as an immature neuron. It then differentiates into the mature granule cell, which extends its axon and dendrites — now comprising spines — to achieve functional integration.*

Fredric B. Meyer, M.D.

Mi Hyeon (Mi-Hyeon) Jang, Ph.D.

Richard Henley, Ph.D.

Robert J. Spinner, M.D.

is uncovering molecular and cellular mechanisms that regulate adult neurogenesis with the potential of conferring therapeutic benefits. For example, in research that will be published in 2013 in *Cell Stem Cell*, she and her team recently identified a protein that is involved in activity-dependent regulation of adult neurogenesis. The investigators have found that exercise and electroshock therapy appear to stimulate neurogenesis, while stress and aging may have an adverse effect on the process. Ongoing projects include evaluating the effects of deep brain stimulation and chemotherapeutic agents on adult neurogenesis.

Neuronal Regeneration in ALS: Clinical Safety Trial

Led by neurologist and molecular neuroscientist Anthony J. Windebank, M.D., Mayo Clinic researchers pioneered ways of re-engineering autologous mesenchymal stem cells to enhance their ability to produce trophic and growth factors. "What we're really developing is a transport mechanism for delivering growth factors to enhance neural growth in the brain," Dr. Windebank notes.

He and colleagues are currently conducting the first human safety trial for stem cell implantation in a series of 25 patients with amyotrophic lateral sclerosis (ALS). Stem cells from the patient's own adipose tissue are implanted via lumbar puncture to determine safety and optimal dosing. The next step will be a clinical trial to implant the re-engineered cells. If successful, the process could have implications for ALS and other neurodegenerative conditions.

Large-Gap Peripheral Nerve Injury: Clinical Safety Trial

The major obstacles in repairing large-gap peripheral nerve and spinal cord injuries are the array of intrinsic cellular and extrinsic molecular mechanisms that inhibit or misdirect axonal projection. Many of these external inhibitory signals come from the myelin itself, perhaps to prevent arbitrary or random neuronal projection. In the fully developed nervous system, nerve growth cones — the cone-like tips of axons and dendrites that extend and retract, "sniffing out" the molecules needed to help them connect with their targets — operate in effect without a compass. What has been needed is a permissive environment that could sustain growth and enable axons to connect with appropriate targets.

Michael J. Yaszemski, M.D., Ph.D., a Mayo Clinic orthopedic surgeon and biomedical engineer, developed a physical structure that could house such an environment. Made of a copolymer called polycaprolactone fumarate, it joins two compatible polymers never before brought together.

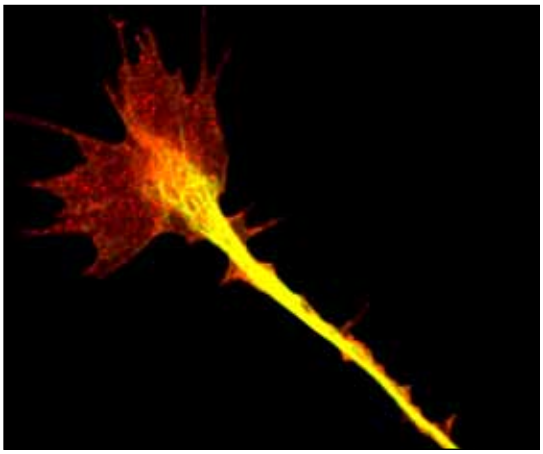

Figure 2. *Immunofluorescence image shows substrate adhesions in the nerve growth cone of a spinal neuron. Red indicates paxillin; green, microtubules.*

The resulting synthetic tubing provides a biodegradable scaffold between severed axons, within which neural growth factors, signaling molecules and guidance cues, can sustain new growth and axonal projection. It also provides physical channels through which axons can extend more readily, helping to prevent undirected peripheral nerves from forming neuromas. The scaffold degrades naturally when axons reconnect, a process that can take weeks to months.

The scaffold is now in a clinical trial at Mayo Clinic to determine its safety for human use. Robert J. Spinner, M.D., a neurosurgeon with peripheral nerve expertise, is implanting the scaffold in patients who require nerve biopsy. In partnership with the researchers at The Miami Project to Cure Paralysis, who have developed a means of manufacturing re-engineered Schwann cells, the Mayo researchers' next step will implant autologous Schwann cells in the scaffold with the needed growth factors to help axons reach across large-gap PNS injuries.

New Approaches to Spinal Cord Injury: Axonal Adhesion

John Richard Henley, Ph.D., a Mayo Clinic molecular neuroscientist and director of the Developmental and Regenerative Neurobiology Laboratory, has devoted his career to identifying and manipulating the cues that facilitate axonal attraction or repulsion and directional turning. In research published in the July 2010 issue of *Nature Neuroscience*, Dr. Henley and colleagues discovered that a major component of myelin prevents growing nerve tips from producing the adhesions needed to form anchoring sites with surrounding tissue and the traction to move forward.

Rather than targeting the negative, inhibitory factors in myelin with a neutralizing antibody, as has been tried in the past, Dr. Henley's team is

adding activators at a much earlier stage in the process to induce adhesion proteins. Using a treatment that can activate adhesion proteins in combination with a neurotrophin, the Mayo researchers are able to induce the formation of adhesions and a high rate of axonal outgrowth (Figure 2).

In 2011, Dr. Henley and his team moved from the petri dish to the zebrafish. Unlike mammals, zebrafish can regenerate their nervous systems. After injury, their spinal cords have the necessary permissive environment for neural regeneration. The team is testing the negative effects of the naturally occurring myelin inhibitor and the combinatorial neurotrophin treatment to reverse these effects after spinal cord injury (Figure 3). Robust behavioral testing is demonstrating dramatic functional recovery after the treatments, which holds significant promise for promoting neural regeneration in mammals.

Dr. Meyer, as both a neurosurgeon and head of neural regeneration, is guiding work to adapt the findings of Dr. Henley's team to the human setting. One arm of this ongoing work is testing therapeutic potential after delaying the treatment for up to six hours, mimicking the more likely interval between spinal injury and treatment in humans. Remarkably, the delayed treatment is proving to be successful — just one example of how Mayo's Center for Regenerative Medicine is facilitating a discovery-to-application model.

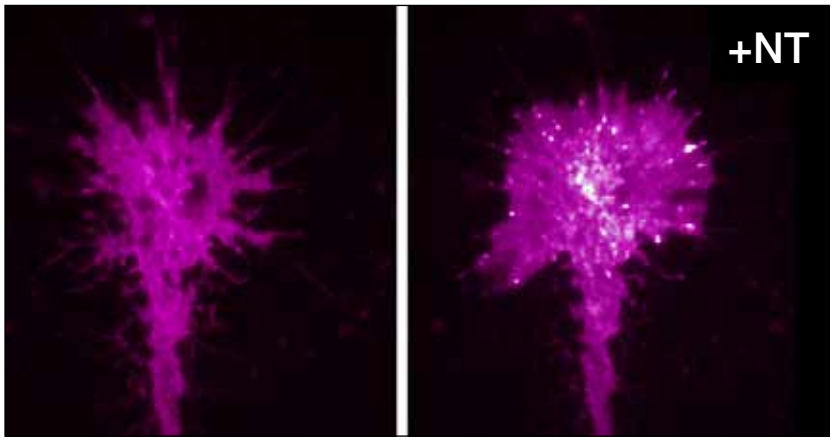

Figure 3. *Neurotrophin treatment (+NT) induces formation of nascent substrate adhesions (GFP-paxillin) revealed by total internal reflection fluorescence microscopy. Scale bar: 10 µm.*

For More Information

Hines JH, et al. Assymmetric endocytosis and remodeling of beta1-integrin adhesions during growth cone chemorepulsion by MAG. *Nature Neuroscience*. 2010;13:829.

Excellence and Innovation in the Neuro-ICU

A neurointensive care unit (neuro-ICU) doesn't only provide specialized therapeutic options for patients with serious neurologic illness. In addition, the vital issues arising from clinical practice in a neuro-ICU can stimulate research that ultimately benefits patients. All three Mayo Clinic sites have a neuro-ICU staffed by neurointensivists engaged in research that has wide implications for neurocritical care. "We have the neuroscience resources — the intensive care unit, the neurosurgeons and neurologists — that make it possible to align research and patient care," says William D. Freeman, M.D., a neurointensivist at Mayo Clinic in Jacksonville, Fla.

Florida: International Intraventricular Hemorrhage Trial

As a major neurocritical care center in the region, Mayo Clinic in Florida is participating in an international, randomized, phase III clinical trial assessing the benefit of clot removal for treating intraventricular hemorrhage (IVH). IVH is a neurologic emergency that often results in poor outcomes. "This type of stroke historically has a mortality rate of 80 to 100 percent," says Dr. Freeman, who is the international study's primary investigator at Mayo in Florida. Mayo Clinic in Arizona also is a participating center.

The current standard of care for IVH is placement of an external ventricular drain to remove blood from the ventricles and reduce intracranial pressure."But use of a drain alone to resolve IVH is probably inadequate, due to the presence of clotted blood within the ventricle that often blocks the drain catheter,"Dr. Freeman says.

The international clinical trial compares the use of clot-busting recombinant tissue plasminogen activator (r-TPA) injected inside the drain to a sterile saline injection (placebo) in the drain. Early results of the study are encouraging. The preliminary mortality data ranges from 20 to 30 percent in both treatment groups."It appears that patients are improving just by participating in the trial,"Dr. Freeman says."Both the placebo and the drug appear to have an effect on reducing the mortality of this disease. This is a vast improvement compared to not acting on this disease."

William D. Freeman, M.D.

Minnesota: A Treatment Model to Shorten Stays in the ICU

Delayed cerebral ischemia (DCI) is one of the major causes of poor outcome after aneurysmal

Alejandro A. Rabinstein, M.D.

Bart M. Demaerschalk, M.D.

subarachnoid hemorrhage. Because DCI can develop as many as 10 days after treatment of the ruptured aneurysm, patients often remain in the ICU for monitoring.

Researchers at Mayo Clinic in Rochester, Minn., have developed a simple model for identifying patients who are unlikely to develop DCI after aneurysmal subarachnoid hemorrhage, and who therefore can be moved to a general ward. Previous research determined that risk factors for DCI include younger age, smoking and poor clinical grade. But only a portion of patients with high risk factors will actually develop DCI. In a retrospective study — published in the March 2012 issue of *Stroke* — of patients with acute aneurysmal subarachnoid hemorrhage treated at Mayo's neuro-ICU from 2001 to 2011, the researchers identified three factors that were 100 percent predictive of the absence of DCI in the patients studied:

- Age 68 years or older
- World Federation of Neurological Surgeons score of I to III at presentation
- Modified Fischer grade 1 to 2

"Based on these results, older patients with good clinical and radiological grades can be safely discharged from the ICU soon after treatment of the ruptured aneurysm, in the absence of early complications or comorbidities," says Alejandro A. Rabinstein, M.D., a neurointensivist at Mayo in Minnesota and a study co-author. "Early recognition of which patients truly are at low risk of DCI can avoid invasive and unnecessary monitoring and testing in the ICU."

One of the major innovations from the neurocritical care unit is the FOUR Score scale for grading coma depth, developed in 2005 at Mayo Clinic in Minnesota and extensively validated since then. Other current areas of research include stroke resulting from internal carotid artery occlusion, status epilepticus and hypothermia after cardiac arrest. At Mayo, neurointensivists work closely with neurosurgeons, cardiologists and other critical care physicians.

"We have an academic-oriented, very patient-centered and multidisciplinary group," Dr. Rabinstein says. "What matters are good outcomes, in which patients not only survive the disease but regain function."

Arizona: Assessing Telemedicine for Coma

Mayo Clinic in Arizona is at the forefront of teleneurology: the use of audio-video telemedicine technology to provide clinical neurologic care at a distance. Having shown the clinical effectiveness of telemedicine in evaluating and treating stroke patients, Mayo researchers are embarking on a study of telepresence assessment of patients in coma.

"We wish to continue to push the frontiers of telemedicine. But we must ensure that we ultimately apply into clinical practice only telemedicine paradigms that have been studied for adequate reliability and validity," says Bart M. Demaerschalk, M.D., director of telestroke and teleneurology at Mayo Clinic in Arizona.

The study, already under way, will recruit 200 patients in any degree of coma, from mild to very deep, whose families give consent. Each patient will be assessed simultaneously by a neurologic intensive care specialist at the patient's bedside and by a neurologic intensive care specialist using the robotic platform from a distance. The physicians will conduct their assessments independently, using both the Glasgow Coma Scale and Mayo Clinic FOUR Score scale.

The coma study is the first in a series of planned studies of the effectiveness of telemedicine in diagnosing and managing neurocritical care syndromes. Other areas of interest include traumatic brain injury, both mild and severe; status epilepticus; central nervous system infection, such as meningitis and encephalitis; spinal cord compression; and acute neuromuscular paralysis, such as Guillain-Barré syndrome and myasthenia gravis.

"Mayo Clinic critical care units are fortunate to have a neurointensivist available around the clock," Dr. Demaerschalk says. "We're utilizing our neurocritical care environment to test a telemedicine model that can connect the expertise of a neurointensivist with a general intensive care doctor at a remote site, to improve patient outcomes."

For more information

Crobeddu E, et al. Predicting the lack of development of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *Stroke*. 2012:43:697.

New Option for Metastatic Brain Tumors

Metastatic brain tumors are much more common than primary brain tumors, occurring in 10 to 30 percent of all adult cancers. Left untreated, many patients die not from their primary cancer but from progression of the brain tumor. In the past, some stereotactic radiosurgery systems were limited in the number of metastases that could be treated and had significant difficulty in reaching widely spaced lesions in the brain.

Mayo Clinic's updated stereotactic radiosurgery system can treat many brain metastases, including widely situated tumors, often in a single 90-minute session. "With our old unit, we would rarely treat more than six metastases, and it was very complicated if a patient had lesions at opposite ends of the brain. The stereotactic head frame had to be removed and repositioned, and the patient rescanned, to reach those targets," says Michael J. Link, M.D., a neurosurgeon at Mayo Clinic in Rochester, Minn. "The new system has eliminated those problems. For cases that were considered somewhat hopeless, we have something new to offer."

Whole-brain radiation usually requires 10 to 15 treatments over a period of two to three weeks. Concern about long-term cognitive impairment may result in lower radiation doses, which can diminish tumor control. If new lesions develop, physicians may be reluctant to repeat whole-brain radiation. In addition to treating multiple lesions in a single session, stereotactic radiosurgery doesn't cause hair loss and can be used later to treat new lesions.

Among patients who can particularly benefit from stereotactic radiosurgery are young women with breast cancer that metastasizes to the brain. "These patients are going to be long-term breast cancer survivors, so we don't want to give them whole-brain radiation," Dr. Link says.

Michael J. Link, M.D.

Mayo is participating in an ongoing National Cancer Institute-Radiation Therapy Oncology Group study comparing treatment with stereotactic radiosurgery plus whole-brain radiotherapy to treatment with stereotactic radiosurgery alone, in patients with one to three brain metastases. "Our hope is that the results will show sufficient tumor control from stereotactic radiosurgery that whole-brain radiotherapy can be avoided," Dr. Link says.

Obstructive Sleep Apnea and Cardioembolic Stroke Risk

Moderate to severe obstructive sleep apnea (OSA) has been shown to increase the risk of ischemic stroke, by as much as three times in men. Although sleep apnea frequently goes undiagnosed, population-based studies indicate that as many as 1 in 15 adults has moderate to severe OSA. Researchers at Mayo Clinic in Rochester, Minn., are uncovering the mechanisms by which OSA increases ischemic stroke risk, as well as strategies for managing that risk in patients.

A recent Mayo study found that cardioembolic stroke is far more common in patients with OSA than in patients without OSA. The retrospective case-control study examined the records of 53 patients who had polysomnography at Mayo Clinic between 2000 and 2011, and who had an ischemic stroke within one year after the sleep study. Thirty-two of the patients met the criteria for OSA and were classified as cases; 21 did not meet criteria for OSA and were classified as controls.

Among the OSA cases, 71.9 percent had cardioembolic strokes, compared with 33.3 percent in the control group. Large artery atherosclerosis and small vessel occlusion were found to be more common in patients without OSA (Figure). In addition, the frequency of cardioembolic stroke rose with the severity of OSA. Among patients with OSA, 84 percent had at least one cardioembolic risk factor, such as dilated cardiomyopathy, compared with 52 percent of controls.

"It may be that OSA leads to structural and physiologic changes in the heart that can predispose patients to cardioembolic stroke

Melissa C. Lipford, M.D.

via mechanisms other than atrial fibrillation," says Melissa C. Lipford, M.D., a neurologist at the Center for Sleep Medicine at Mayo Clinic in Minnesota who led the study. "The higher rates of cardioembolic strokes in OSA patients may also be due to a greater proportion of undiagnosed paroxysmal atrial fibrillation in this group."

An important strength of the study is that patients were all diagnosed with OSA prior to the stroke. Had the study included patients diagnosed with OSA in the post-stroke period, it would be unclear whether OSA was a risk factor leading to the stroke or if the stroke itself caused the OSA, via oropharyngeal weakness or other mechanisms.

"These results suggest that a high level of suspicion for cardioembolism is warranted when a patient with OSA suffers a stroke," Dr. Lipford says. "When OSA patients present with a cryptogenic stroke, further cardiac work-up may be considered, such as transesophageal echocardiography to identify cardioembolic risk factors, Holter monitoring or even extended cardiac monitoring to identify paroxysmal atrial fibrillation. But we must still employ a multifaceted risk-reduction strategy because OSA also increases risk of large artery atherosclerotic and small vessel occlusion strokes."

Further research is needed to determine precisely how OSA increases stroke risk. But Dr. Lipford notes that OSA patients generally don't experience the 10 to 15 percent drop in systolic blood pressure that typically occurs during sleep. "During an apneic episode, the body asserts an amazing amount of effort to try to open the airway and get a breath in," she says. "Oxygen levels go down, and carbon dioxide levels go up." These repetitive apneic episodes are associated with sympathetic nervous system surges that increase blood pressure and cause heart rates to fluctuate, leading over time to hypertension and atrial fibrillation, which are prime risk factors for ischemic stroke.

Stroke Mechanisms

	All patients	OSA Group	Control Group
Cardioembolic	30 (56.6%)	23 (71.9%)	7 (33.3%)
Small Vessel Occlusion	14 (26.4%)	5 (15.6%)	9 (42.9%)
Large Artery Atherosclerosis	7 (13.2%)	3 (9.4%)	4 (19%)
Other (uncommon etiologies)	1 (1.9%)	1 (3.1%)	0 (0%)
Undetermined	1 (1.9%)	0 (0%)	1 (4.8%)

Figure. *In a Mayo Clinic study, cardioembolic was the stroke mechanism in 71.9 percent of patients diagnosed with obstructive sleep apnea (OSA) up to a year before having an ischemic stroke. For patients in the control group without OSA, small vessel occlusion was the stroke mechanism in 42.9 percent of cases compared to just 15.6 percent in the OSA group.*

Treating Sleep Apnea After Stroke

Whether or not sleep apnea was present before stroke, most patients experience OSA after stroke. OSA in stroke patients is associated with early neurologic worsening, decreased functional recovery and increased mortality.

Yet continuous positive airway pressure (CPAP), the typical therapy for sleep apnea, poses significant challenges for stroke patients. Aphasia may lead to challenges in communicating why CPAP is necessary. Facial weakness can make it difficult to achieve a seal with the CPAP mask, and limb weakness can hinder a patient's ability to put on and remove the mask."If somebody puts something over your face, you don't understand why, and if you don't have the dexterity to remove it, it can feel claustrophobic," Dr. Lipford says.

At Mayo, neurologists who are sleep specialists take additional steps to treat OSA in stroke patients. Time is spent determining the most appropriate mode of communication for explaining to the patient the rationale behind CPAP therapy. Nurses and respiratory technicians work with patients and their families to determine the most comfortable CPAP interface, including a nasal-only interface if possible. CPAP may be started gradually, such as during daytime naps, before use at night.

For patients who can't tolerate CPAP, Mayo sleep specialists suggest alternatives. "In some cases it may be as simple as sleeping on your side instead of your back, "Dr. Lipford says. "Even a reduction in OSA severity can be helpful." Other alternatives include weight loss, nasal expiratory positive pressure devices and mandibular repositioning appliances that shift the lower jaw forward to help keep soft tissues from blocking airways.

"At Mayo Clinic, we understand the challenges faced by stroke patients that make OSA treatment difficult,"Dr. Lipford says. "But OSA treatment is crucial. If sleep improves, patients are more alert during the day and more apt to participate in rehabilitation therapies. Treated patients have improved neurologic recovery and their ongoing risk of stroke is reduced."

Research Highlights in Neurology and Neurologic Surgery

Neurosciences Research

Toxic Interaction in Neurons That Can Lead to Dementia

The proteins TDP-43 and sortilin have been suspected of playing a part in the development of frontotemporal dementia. Researchers at Mayo Clinic in Jacksonville, Fla., have uncovered a toxic cellular process involving those proteins that can lead to neurodegenerative disease. Previous studies have focused on the role that TDP-43 and sortilin individually might play in neurodegenerative disease. But the Mayo team examined the interplay between TDP-43, which regulates the protein progranulin, and sortilin. Progranulin has protective effects on neurons, staving off cell death that leads to neurodegenerative disease. The Mayo researchers found that a lack of TDP-43 disrupts the messenger RNA splicing that precedes protein synthesis, resulting in the generation of a defective sortilin protein. The defective sortilin binds to progranulin, depriving neurons of progranulin's protective effects. In postmortem studies of brain tissue, the Mayo researchers identified significantly elevated levels of defective sortilin mRNA in cases of frontotemporal dementia. The Mayo research also has implications for amyotrophic lateral sclerosis which, with frontotemporal dementia, may represent a spectrum of disease. Understanding the biological processes leading to frontotemporal dementia may ultimately lead to the development of new therapies to prevent or combat the disease. (Prudencio M, et al. Misregulation of human sortilin splicing leads to the generation of a nonfunctional progranulin receptor. *Proceedings of the National Academy of Sciences*. 2012:109:215.)

Gene Variant Strongly Linked to Alzheimer's Disease

A gene that nearly triples the risk of developing Alzheimer's disease has been discovered by an international team including researchers from Mayo Clinic. Although rare, the R47H variant of the TREM2 gene is the most potent genetic risk factor for Alzheimer's identified in the past 20 years. The team comprised researchers from 44 institutions around the world, including Mayo Clinic in Jacksonville, Fla., and Rochester, Minn. TREM2 encodes a protein involved in triggering immune responses in macrophages and dendritic cells. Using new sequencing techniques, the researchers identified a set of rare variants in TREM2 that occurred more often in 1,092 Alzheimer's disease patients than in a control group of 1,107 healthy people. The most common variant, R47H, was then evaluated in follow-up studies of Alzheimer's disease patients and controls. Scientists at Mayo Clinic in Florida spearheaded the direct genotyping and analysis of R47H in DNA samples from 1,994 Alzheimer's disease patients and 4,062 control participants verified not to have Alzheimer's. These follow-up studies demonstrated substantial increased risk of Alzheimer's from R47H. "In our series, the TREM2 variant was present in 1.9 percent of the Alzheimer's patients and in only 0.37 percent of the controls. This strong effect rivals that of ApoE 4," says Minerva M. Carrasquillo, Ph.D., a Mayo neuroscientist who led the R47H lab work in Jacksonville. The Mayo researchers note that the study results fit well with other evidence linking the immune system to Alzheimer's disease, and variants like R47H could be used to identify healthy people at high risk of developing the condition. (Guerreiro R, et al. TREM2 variants in Alzheimer's disease. *New England Journal of Medicine.* 2013:368:117.)

ApoE4 and Quality of Life in Nonagenarians

The ApoE4 gene has been associated with neurodegenerative and cardiovascular conditions such as Alzheimer's disease, cognitive decline, stroke, coronary artery disease and vascular disease in diabetes. Previous studies exploring the relationship between ApoE4 and quality of life in the elderly have not focused on the oldest old. With the worldwide population of nonagenarians growing rapidly, researchers at Mayo Clinic in Rochester, Minn., examined ApoE4 and quality of life in that age group. The cross-sectional cohort study found similar quality of life between ApoE4 carriers and noncarriers. Physical, emotional and intellectual well-being, as well as social connectedness and coping ability, were found to be positively associated with quality of life. Male sex, dementia with stroke or parkinsonism or both, and pain frequency and severity were negatively associated with quality of life. Using a database of patient records in Olmsted County, Minn., the researchers found 121 participants ages 90 to 99 living on their own or in long-term care. The study participants completed an interview, a physical exam and a quality-of-life questionnaire. Participants were divided into groups based on their cognitive function, and blood samples were taken for genotyping. "The study shows that the ApoE4 genotype doesn't determine what your quality of life will be," says Maria I. Lapid, M.D., a Mayo Clinic psychiatrist and study co-author. "You can have good quality of life regardless of this gene." (Parsaik AK et al. ApoE and quality of life in nonagenarians. *Journal of the American Medical Directors Association.* 2012:13:704.)

To read more about Mayo Clinic neurosciences research and patient care, visit *www.mayoclinic.org/medicalprofs*.

Mayo Clinic
Neurosciences Update

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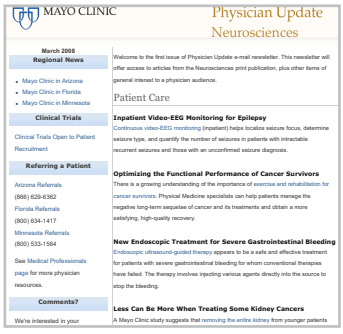
Education Opportunities

Mayo Clinic Headache Symposium
May 3-5, 2013, Hotel Nikko San Francisco, San Francisco, Calif.
This course provides attendees with an update in the diagnosis and management of both primary and secondary headache disorders. The format includes lectures, expert panel discussions, interactive question and answer sessions, and small-group discussions. For further information or to register, please contact 480-301-4580 or *mca.cme@mayo.edu*.

Clinical Autonomic Quantitation Workshop
May 17-19, 2013, Mayo Clinic, Rochester, Minn.
This course focuses primarily on the three autonomic function tests having CPT codes. The program integrates a series of lectures on the underlying physiology, patient preparation, indications for autonomic testing and factors affecting the results of these autonomic tests, and HCFA requirements. The heart of the workshop will be a demonstration of specific autonomic function tests. The tests demonstrated are the quantitative sudomotor axon reflect test (QSART); tests of cardiovagal function (heart rate response to deep breathing and to the Valsalva maneuver); and tests of the adrenergic function. Hands-on demonstrations are provided using commercially available equipment. A series of sessions on the interpretation of common and uncommon examples of tests is provided. Other lectures address a number of autonomic manifestations and disorders (such as POTS, syncope, autonomic neuropathies, multiple system atrophy, painful conditions associated with autonomic dysfunction). The remaining time is devoted to handling questions and demonstrating typical examples of abnormal findings seen in tests of autonomic function. For further information or to register, please contact 800-323-2688 (toll-free) or *cme@mayo.edu*.

New Frontiers in Endovascular Therapy
May 17-18, 2013, Simulation Center, Stabile North Building, Mayo Clinic, Jacksonville, Fla.
This program will emphasize the knowledge related to appropriate patient selection for carotid artery stenting and carotid endarterectomy. In addition, the selection of patients for fenestrated aortic aneurysm repair will be reviewed. Lastly, simulation-based learning of robot-based interventional procedure selection provided, as well as results of recent trials for stem cell application in chronic limb ischemia, and renal artery denervation for refractory hypertension. For further information or to register, please contact 800-462-9633 (toll-free) or cme-jax@mayo.edu.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Physician Update
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Regional News
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- Mayo Clinic in Florida
- Mayo Clinic in Minnesota

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We're interested in your

Welcome to the first issue of Physician Update e-mail newsletter. This newsletter will offer access to articles from the Neurosciences print publication, plus other items of general interest to a physician audience.

Patient Care

Inpatient Video-EEG Monitoring for Epilepsy
Continuous video-EEG monitoring (inpatient) helps localize seizure focus, determine seizure type, and quantify the number of seizures in patients with intractable recurrent seizures and those with an unconfirmed seizure diagnosis.

Optimizing the Functional Performance of Cancer Survivors
There is a growing understanding of the importance of exercise and rehabilitation for cancer survivors. Physical Medicine specialists can help patients manage the negative long-term sequelae of cancer and its treatments and obtain a more satisfying, high-quality recovery.

New Endoscopic Treatment for Severe Gastrointestinal Bleeding
Endoscopic ultrasound-guided therapy appears to be a safe and effective treatment for patients with severe gastrointestinal bleeding for whom conventional therapies have failed. The therapy involves injecting various agents directly into the source to stop the bleeding.

Less Can Be More When Treating Some Kidney Cancers
A Mayo Clinic study suggests that removing the entire kidney from younger patients

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Expedited Patient Referrals to Mayo Clinic Departments of Neurology and Neurologic Surgery

While Mayo Clinic welcomes appointment requests for all neurologic and neurosurgical conditions, patients with the following conditions are offered expedited appointments:

1. Cerebral aneurysms
2. Cerebral or spinal arteriovenous malformations
3. Brain, spinal cord, or peripheral nerve tumors
4. Epilepsy with indications for surgery
5. Carotid disease

MAYO CLINIC
mayoclinic.org
4500 San Pablo Road
Jacksonville, FL 32224
200 First Street SW
Rochester, MN 55905
13400 East Shea Boulevard
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