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State-of-the-art imaging studies using fMRI and PET are advancing findings in the development of Alzheimer’s disease and diagnostic risk assessments.
Neurology and Neurosurgery Highlights

Our experts in Neurology and Neurosurgery:

• Provide advanced care for more than 24,000 patients each year with combined outpatient visits of 31,900 and 13,300 inpatient visits;
• Deliver an array of medical therapies, minimally invasive neurosurgical treatments, and advanced diagnostic techniques. We perform more than 2,500 neurosurgical procedures each year;
• Lead an average of 25 clinical trials at a time, including trials that are rapidly expanding treatment options and changing the standard-of-care for many patients with neurological diseases;
• Pioneer basic science research, supported by $45.5 million in funds, that is advancing the understanding of the development and prognosis of neurological disorders.

This issue of Neurology and Neurosurgery Advances highlights a sampling of our latest neurology and neurosurgery activities including biomarker studies for multiple sclerosis, neuro-oncology research and surgery, biomarkers of vasospasm and subarachnoid hemorrhage, and diagnostic imaging for Alzheimer’s disease.

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Advanced Biomarker Studies for Multiple Sclerosis

The Brigham and Women’s Hospital Multiple Sclerosis Center is leading several advanced biomarker studies to find new ways to diagnose the disease and predict how patients will respond to treatment. “We are trying to understand the impact we have on the disease,” said Samia Khoury, MD, Co-director, Partners Multiple Sclerosis Center at Brigham and Women’s Hospital. “There are a lot of medications for MS, but we cannot predict how patients will respond to them in the long run. We are evaluating whether the biomarkers correlate with treatment response, and whether we can use them to predict outcomes.”

CLIMB: A Longitudinal Study of MS

As part of an effort to better understand how MS begins and progresses, the MS Center has launched a long-term study called CLIMB (the Comprehensive Longitudinal Investigation of MS @ Brigham) led by Howard Weiner, MD, Director, Partners Multiple Sclerosis Center at Brigham and Women’s Hospital, and Tajuna Chitnis, MD, Medical Director, CLIMB. The aim of the study is to follow enrolled MS patients and track the progression of their conditions over 20 years.

The researchers are collecting and storing blood samples to build a database of other clinical observations, including measures of walking ability and results of annual MRI screens. The CLIMB study plans to enroll 2,000 patients and has enrolled approximately 1,200 thus far.

CLIMB will allow researchers to expand the search for blood-based biomarkers to a larger population of patients and to correlate these biomarkers with the clinical data collected from patients enrolled in CLIMB.
For more information on CLIMB and enrollment, contact Principal Investigator Tajuna Chitnis, MD, at (617) 525-5374, tchitnis@partners.org.

Advanced Analytics for Blood-Based Biomarker Discovery

Immunological Profiles

Recent basic science work from Brigham and Women’s researchers, led by Dr. Khoury and Dr. Weiner, has begun to correlate clinical categories of MS with patterns of immune cell pathologies and demyelination, the nerve damage that causes the symptoms of MS.

Neurologist Phil De Jager, MD, and Drs. Khoury and Weiner led a study, published in *Brain* (Brain 2008 June 21;131:1701-1711), that found a potential immunological biomarker of MS. The researchers profiled blood from healthy subjects and patients with RRMS taken from both the MS Registry and from CLIMB.

The researchers used flow cytometry, which measures the frequencies of individual cell types in a given blood sample. The technique categorized cells based on 1,018 different features and found one particular type of CD8 T cells to be low in frequency in CIS and RRMS patients.

While the finding is an important step towards identifying biomarkers of MS in blood, these CD8 cells are not yet ready for application in clinical work. Rather, the finding suggests that immunological profiling should be studied in larger biomarker discovery studies. The team is now investigating these CD8 cells in diagnostic and prognostic algorithms, and they are working towards a more detailed phenotypic characterization of these cells.

Autoantibody Signatures

Similarly, in 2008, Francisco Quintana, PhD, working with Drs. Weiner and Khoury, employed innovative high-throughput techniques to examine how autoantibodies in blood samples react to arrays of antigens in an advanced biomarker study of MS. The investigators used these arrays of antigens rather than individual antigen reactivity tests to analyze serum samples and determine if patterns of reactivity might correlate to disease patterns.

The team found unique patterns linked to different stages of disease and different types of disease. They published their findings in the *Proceedings of the National Academies of Science* (PNAS 2008, Dec 2;105(48):18889-18894). “These new techniques allow us to tease out details that were not possible in the past,” said Dr. Khoury.

The team is now applying this new technique to samples collected through CLIMB to see if the antibody signatures correlate with treatment and response over time.

A Cooperative Clinical Study of Abatacept in Multiple Sclerosis (ACCLAIM)

Dr. Khoury has launched a Phase II, randomized, double-blind, placebo-controlled trial to test the safety and efficacy of abatacept in MS. The study is recruiting patients now and will run until December 2013. Dr. Khoury and colleagues reported promising results of their Phase I trial of Abatacept in *Neurology* (Neurology, 2008 Sep 16;71(12):917-24). The trial showed that the drug is well tolerated in MS patients and shows evidence of positive immunologic effects. Participants will receive eight intravenous treatments over a period of 24 weeks in the first phase of the study. During the second phase, eligible participants will receive another eight treatments over the following 24 weeks. Regular appointments will be used to monitor participants’ health and progress in the study. A total of 11 MRI procedures are scheduled during the study for each patient. The researchers will track MRI scans of enrolled patients to identify new inflammatory lesions and signs of atrophy as the primary means of evaluating outcomes. For more information, contact Principal Investigator Samia Khoury, MD, at (617) 525-5370, skhoury@partners.org
Research Targets Neurologic Complications of Cancer, Cancer Treatment

The Center for Neuro-Oncology at Dana-Farber/Brigham and Women’s Cancer Center and Division of Cancer Neurology, Brigham and Women’s Department of Neurology, cares for adult patients with primary and metastatic brain tumors, spinal cord tumors, and neurologic complications of cancer and its treatment. Specialists provide advanced treatment, including surgery, radiation therapy, and novel targeted drug treatment, as well as access to clinical trials of promising therapeutics. Surgical specialties include minimally invasive transnasal endoscopic surgery and expert skull-base surgical techniques for the most challenging intracranial tumor cases.

Novel Targeted Drugs for Glioblastoma
Cancer neurologists in the Center treat between 200 and 300 patients with glioblastomas each year. “Ten years ago we had little information on what was driving these tumors. Now, based on our research, we are beginning to develop drugs that block many of the major molecular changes that cause these tumors,” said Patrick Y. Wen, MD, Chief, Division of Cancer Neurology, Brigham and Women’s Hospital.

Trials of these novel drugs at the Center include:

Drugs Targeting the PI3K Pathway
Genetic mutations cause the PI3K signaling pathway to be overactive in almost all glioblastoma tumors. Four experimental new drugs block this pathway. The Center will be participating in Phase II multi-center trials to evaluate the safety and efficacy of all four drugs in 2011:

• A Phase I Dose-Escalation Study of XL765 in Combination With Temozolomide in Subjects With Malignant Gliomas. The goal of this study is to test the safety of XL765, a new drug that inhibits both PI3K and mTOR, another kinase involved in glioma growth and recurrence. This study is recruiting patients now.

• Exploratory Study of XL765 or XL147 in Subjects With Recurrent Glioblastoma Who Are Candidates for Surgical Resection. This study will examine the effect of the experimental drugs XL765 and XL147 on tumor tissue to inhibit re-growth of surgically removed recurrent tumors. This trial will open for recruitment in 2011.

• MK-2206 for Recurrent Malignant Glioma. MK-2206 inhibits AKT, a protein activated by PI3K activation. This trial will open for recruitment in 2011.

• BKM120 for Recurrent Glioblastoma. BKM120 is a potent inhibitor of all classes of PI3kinase. “The drug crosses the blood-brain barrier, which is an issue with many other drugs, so we’re excited about its promise,” said Dr. Wen. A Phase II trial of this agent in patients with recurrent glioblastoma will be open for recruitment in 2011.

For more information on these studies, please contact Principal Investigator Patrick Y. Wen, MD, at (617) 632-2166, pwen@partners.org.

Anti-Angiogenesis Drugs to Treat Drug-resistant Tumors
In 2009, the Center was part of a major, multi-center trial that led to FDA approval of the drug Avastin for glioblastoma. Although some patients see a reduction in tumor size with Avastin, tumors almost always come back. Researchers at the Center are exploring the use of new drugs that target other aspects of the angiogenesis pathway. Of several planned trials, one is in process:

• An Open-Label, Three-Cohort, Phase II Study of E7080 in Subjects With Recurrent Malignant Glioma. This multi-center trial will evaluate E7080, a potent inhibitor of multiple factors in angiogenesis, to determine if it stops disease progression and to evaluate toxicity. This study will open for recruitment in 2011.
For more information on this and other planned studies, please contact Principal Investigator Patrick Y. Wen, MD, at (617) 632-2166, pwen@partners.org.

**Novel Drugs Targeting Cancer Stem Cells**
Cancer stem cells may cause recurrence even after radiation and surgery have removed most of a tumor. Several molecular pathways contribute to the growth of tumor stem cells and allow them to evade treatments that kill other cancer cells, including the Notch and Sonic Hedgehog pathways. Dr. Wen and his colleagues are working on novel, experimental drugs that target glioma stem cells. The drugs, which Dr. Wen describes in *US Neurology* (US Neurology, 2010;6(1):55–63), include:

- Notch inhibiting agents MK-0752 and R4929097;
- Sonic hedgehog inhibitor GDC4409.

**Pituitary/Neuroendocrine Center**
The Brigham and Women’s Hospital Pituitary/Neuroendocrine Center treats patients with pituitary tumors, Cushing’s Disease, craniopharyngiomas, and other neuroendocrine disorders. The Center combines expertise in multiple disciplines with patient-focused care. Most patients receive appointments within a week of contact, especially if they are experiencing symptoms such as vision loss – an indicator of pituitary tumor growth.

“Our patients receive a complete, multi-specialist evaluation in a single visit,” said Edward R. Laws, MD, FACS, Director, Pituitary/Neuroendocrine Center. “It’s all in the organization. We assemble the whole team in advance. It’s rare that a patient needs to come back to see an additional specialist for evaluation.”

**Novel Applications of Minimally Invasive Surgery**
Dr. Laws has performed more than 5,300 transnasal microscopic and endoscopic operative procedures, which may be one of the largest practice-based programs in the world. The minimally invasive technique uses an endoscope to remove tumors through the nose rather than opening up the cranium for access.

Dr. Laws has investigated the novel application of this technique to treat pituitary tumors that cause acromegaly. According to a study by Dr. Laws in *Reviews in Endocrine & and Metabolic Disorders* (Rev Endocr Metab Disord. 2008 Mar;9(1):67-70), the technique produces little trauma and discomfort and, for patients with microadenomas, 70 percent have normal hormone levels after surgery.

Dr. Laws also has documented the success of this technique in the complete removal of craniopharyngioma with reliable improvement of vision. The procedure allows more thorough imaging to verify tumor removal, according to Dr. Laws’ report in *Neurosurgery Focus* (Neurosurg Focus. 2010 Apr;28(4):E9). He has also applied the technique to the removal of cystic pituitary growths and found that the minimally invasive approach for cystic lesions produces excellent results when coupled with proper surgical training and careful patient selection. These results appear in *Nature Clinical Practice*, (Nat Clin Pract Endocrinol Metab. 2008 Dec;4(12):662-3).

“We are expanding the range of conditions that are treatable through the nose to include those that traditionally have always required major, invasive skull-base approaches, thereby reducing both risk and trauma for patients,” said Dr. Laws.

**Skull-base Surgery**
For some brain tumors, including tumors that were formerly considered inoperable, surgery using a skull-base approach provides the hope for a cure. At the Center, Ossama Al-Mefty, MD, Director, Skull-Based Surgery, and neurosurgeon Ian Dunn, MD, perform these operative procedures on patients referred to them from around the world.

**Surgery and Treatment of Basal Meningioma and Chordoma Tumors**
The incidence rate of meningioma is increasing both because people are living longer and because people are receiving more frequent MRIs, which can identify menin-
Biomarkers of Vasospasm and Subarachnoid Hemorrhage

Sherry Chou, MD, CM, MMSc, a neurologist within the Department of Neurology’s Division of Stroke and Critical Care Neurology, is developing a novel infrastructure for translational research in patients with critical neurological injuries. Her research focuses on using advanced techniques to identify novel biomarkers that may explain the cause of vasospasm and poor clinical outcome in patients who suffer subarachnoid hemorrhage (SAH).

Brigham and Women’s Hospital provides specialized emergency and therapeutic care for ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage due to rupture of aneurysm and vascular malformations. Brigham and Women’s Neuroscience Intensive Care Unit is one of the largest in New England, with 20 dedicated beds, state-of-the-art imaging and intracranial monitoring equipment, and teams of specialists, including 100 neurocritical care nurses.

Brigham and Women’s Center for Cerebrovascular Disease has specialty-trained vascular neurologists, critical care neurologists, and vascular and endovascular neurosurgeons trained to take care of patients with critical vascular conditions such as cerebral aneurysm and SAH. There are approximately 30,000 cases of SAH reported each year in the United States. Despite many improvements in surgery and post-operative care, 30 to 70 percent of patients who survive aneurysm rupture experience vasospasm after the acute injury.

“The quest to save patients’ lives while preserving neurological function is at the leading edge of clinical translational neuroscience research. Just decades ago, SAH patients had worse outcome than what we see today,” said Dr. Chou. “With advances in neurological critical care, we can do a lot more for these patients today, but some of these options still come with significant risks.”

Biomarkers that predict complications and outcomes in acute brain injury may help doctors, patients and their families weigh the risks and benefits when determining treatment paths. Furthermore, discovery of new biomarkers may help further the understanding of the causes of complications and poor outcome, and provide potential new targets for new therapies.

Statins to Prevent Vasospasm
One possible class of drug that may benefit patients with SAH and vasospasm is statins, the drug more commonly known in the treatment of high cholesterol. In 2007, Dr. Chou led a randomized, double-blind, placebo-controlled pilot study of a statin, simvastatin, as potential treatment for patients with subarachnoid hemorrhage. This study, reported in *Stroke* (Stroke. 2008;39:2891-2893), confirmed that the drug is safe for use in patients recovering from SAH.

However, studies of the effectiveness of statins have shown mixed results. “These inconsistent results are partly due to the small number of patients included in each study, a wide variety of definitions of vasospasm and on differing measures of outcomes,” said Dr. Chou.

Biomarkers of delayed ischemic damage following subarachnoid hemorrhage
Dr. Chou leads an innovative translational research program to search for biomarkers in Neuroscience ICU patients

Call Our Physician Liaison
For direct assistance with patient referrals and consultations with our specialists, contact Physician Liaison Ellen Steward at (617) 732-9598 or esteward@partners.org.
The Brigham and Women’s Hospital Division of Cognitive and Behavioral Neurology treats patients with dementia and other forms of memory loss with a multidisciplinary approach that includes team-oriented care from neurologists, psychologists, social workers, and neuropsychologists. The Division also includes the Center for Alzheimer’s Research and Treatment, providing patients with opportunities to participate in advanced clinical research.

“Not only are we providing expert clinical care,” said neurologist Reisa Sperling, MD. “We are asking the questions that we hope will lead to the next generation of therapies.”

**Imaging to Understand the Cause of Alzheimer’s Disease**

Much has been learned recently about the biology of Alzheimer’s Disease. In 2008, Brigham and Women’s neurologist Dennis Selkoe, MD, discovered that an overabundance of a certain form of the protein amyloid-beta may mark the beginning of Alzheimer’s disease. The work was published in *Nature Medicine* (Nat Med. 2008 Aug;14(8):837-42). “Despite such advancements in the biological basis of AD, there’s a big black box between the molecular pathology and basic biology of AD and the clinical symptoms,” said Dr. Sperling.

To connect symptoms with biological changes, Dr. Sperling is integrating fMRI scans of brain activity with PET scans showing the presence of amyloid in the brain. In work published in *Neuron* (Neuron 2009 July 30;63, 178–188), PET imaging showed amyloid deposition in a set of regions in the brain called the default network. The amyloid deposits were associated with aberrant fMRI activity in the brains of older but non-cognitively impaired adults. These aberrant fMRI patterns resembled the patterns observed in AD patients in research by Dr. Sperling and others. “Our work with fMRI shows that areas of the brain important for memory formation overlap with amyloid deposit location,” said Dr. Sperling.

**Biomarkers of Early Alzheimer’s Disease**

Dr. Sperling believes that such diagnostic risk assessments will be possible for patients who already have mild cognitive impairment within the next year or two. Studies of promising diagnostic imaging approaches include:

- **Research Study for Identifying Early Biomarkers of Alzheimer’s Disease**
  This study is exploring the benefits of features of fMRI scans as biomarkers for use in clinical drug studies and studies of disease progression of patients with mild memory impairments, an early stage of memory loss and Alzheimer’s disease. This study will help determine if there are changes in the fMRI scan that occur over the course of mild cognitive impairment by examining the scans alongside clinical variables, memory task performance, gene type, and other imaging techniques. Research by Dr. Sperling published in *Neurology* (June 2010; 74: 1969-1975), shows that brain changes detectable via fMRI can predict cognitive decline over time. Comparisons will be made longitudinally, to track scan and symptom changes over time, as well as cross-sectionally to associate scan features with symptoms.

- **Implications of Amyloid Deposition in Clinically Normal Older Individuals**
  This study will investigate whether asymptomatic older individuals with increases of amyloid-beta in the brain are in the early stages of AD by testing to determine if these patients already show evidence of changes in the brain consistent with early AD. Tests will include PET and fMRI imaging, cerebrospinal fluid analyses, and memory and thinking exams. A validated method for identifying such at-risk individuals is needed to identify people for future studies of treatments to prevent or slow the development of the disease.

For more information on these studies, contact Principal Investigator Reisa Sperling, MD, at (617) 732-8085 or rasperling@partners.org.
giomas before patients experience major symptoms. Although 90 percent of meningioma tumors are benign, basal meningioma at the skull base represents a formidable challenge for safe curative removal.

“The development of approaches and techniques to treat meningiomas has improved their outcome remarkably,” said Dr. Al-Mefty. “Some benign meningiomas that are not totally eradicated might progress to more aggressive and malignant tumors as they recur.”

Dr. Al-Mefty has studied the transformation of meningiomas from benign to malignant. Research led by Dr. Al-Mefty into the cytogenetics and histology of these tumors, published in the Journal of Neurosurgery (J Neurosurg. 2004 Aug;101(2):210-8) and Neurosurgery (Neurosurgery. 2007 Sep; 61(3):495-503), helps neurosurgeons predict malignancy so they can better plan treatment and follow-up care.

Chordoma is a very rare tumor of the skull base and tends to behave aggressively. “Successful treatment requires major surgical resection using a variety of skull-based approaches that maximize the removal of tumor tissue,” said Dr. Al-Mefty. A study led by Dr. Al-Mefty and published in the Journal of Neurosurgery (J Neurosurg. 2009 Apr;110(4):715-24) suggests that the specific genetic abnormalities in chordoma tumor cells can predict recurrence and help in determining future outcomes.

Dr. Al-Mefty said, “We have been able to follow patients’ tumors from treatment and throughout the years, providing comprehensive care and clear understanding of the tumor’s nature and expertise needed in its management.”

Biomarkers of Vasospasm and Subarachnoid Hemorrhage ... continued from page 6

suffering from acute brain injuries such as SAH. Dr. Chou’s research team approaches all eligible patients and families for their permission to participate in this study. In patients who choose to participate, Dr. Chou’s team collects and stores biologic samples from them and follows them closely with regular assessments of their functional outcome.

Thus far, 213 patients have enrolled in this prospective biomarker study. Dr. Chou now has a tissue bank that contains more than 60,000 samples. Brigham and Women’s is one of few institutions in the nation developing such a comprehensive tissue bank for SAH and acute brain injury.

Dr. Chou is using advanced techniques to understand how molecules change, interact, ebb, and flow over time in a patient with SAH. Because proteins degrade rapidly in response to environmental changes, one of her many challenges has been developing an infrastructure for the proper handling and storage of samples once they have been collected from patients from the Neuroscience ICU. With the support of the Harvard Clinical Translational Science Center and the Center for Clinical Investigations at Brigham and Women’s Hospital, Dr. Chou has developed an infrastructure for patient recruitment and optimal handling of biologic samples at the Neuroscience ICU. This infrastructure can support and foster future translational studies in critically-ill BWH patients with brain injury.

The tools for studying molecular biomarkers are rapidly evolving. Dr. Chou has an extensive network of collaborators with multidisciplinary investigators from Brigham and Women’s Hospital, Harvard Medical School affiliated institutions, and worldwide.

Dr. Chou received specialized training in translational research through the Scholars in Clinical Science Program at Harvard Medical School funded by the National Institutes of Health. She is one of the first six scholars supported by the Harvard Clinical and Translational Research Center (Catalyst) KL2 Medical Research Investigator Training Program funded by the National Institute of Health. Her work is also funded by the American Heart Association.

Early Biomarker Discoveries

Early results from Dr. Chou’s work indicates that two biomarkers in the blood and cerebrospinal fluid, white blood cells and a protein called matrix-metalloproteinase-2 (MMP-2), may be associated with an increased risk for vasospasm after subarachnoid hemorrhage. Dr. Chou presented these findings at the 2010 Neurocritical Care Society meeting.

More recently, she has discovered inflammatory biomarkers that are associated with poor outcomes following SAH and will be presenting these new results in early 2011 at the International Stroke Conference.