

Welcome to Neuro-Innovation



Welcome to the first edition of *Neuro-Innovation*, the Stanford Neuroscience Newsletter. We are excited to highlight several of our recent clinical and research developments designed to provide patients with the most advanced neurological consultation and care possible. The continued growth of patient populations served by Stanford and its affiliated hospitals throughout Northern California and beyond has driven the expansion and integration of Stanford's major clinical centers and its leading-edge academic programs. The results are unprecedented innovation and patient outcomes.

The fields of Neurology, Neurosurgery and Interventional Neuroradiology continue to evolve with the rapid development of new therapeutic approaches. At Stanford we build upon an already exceptional synergy between these specialties to apply innovative therapies and deliver outstanding care. Moreover, our dynamic collaborative relationships with Stanford colleagues in bioengineering, molecular biology, physics, computer science, genetics and stem cell research provide a rich and robust environment that places Stanford at the forefront of discovery and evaluation of diagnostic and therapeutic treatments.

Patients at Stanford spend less time in the hospital and experience greatly improved outcomes through the use of diagnostic tests and minimally invasive procedures that we pioneer. Diagnostic tests for stroke, multiple sclerosis, Alzheimer's disease, brain tumors, Parkinson's disease, pituitary disorders, moyamoya disease, chronic pain, intracranial aneurysms, and vascular malformations can now pinpoint pathology with remarkable accuracy. Minimally invasive microsurgical, endovascular, endoscopic and radiation treatments spare a patient from major surgery and significantly decrease risk.

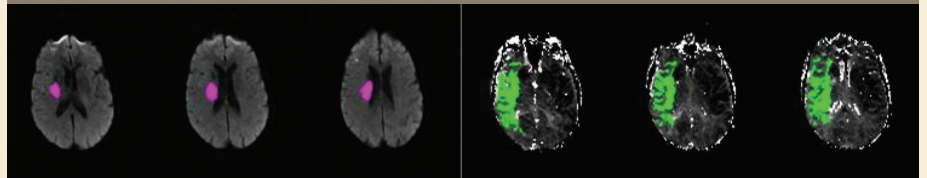
In partnership with the Stanford Institute of Neuro-Innovation and Translational Neurosciences (SINTN) we utilize stem cell transplantation and tissue

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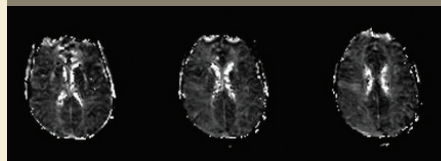
Providing State of the Art Care for Patients with Acute Stroke

FIGURE 1: 74 YEAR OLD FEMALE 9 HRS AFTER STROKE ONSET

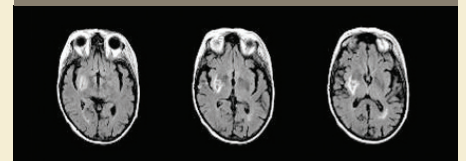
MRI scan upon arrival demonstrates a small area of irreversible injury (pink) but a large area of tissue that is likely to die if blood flow is not restored (green)



Blood flow was completely restored in the cath lab at 10 hrs with a mechanical thrombectomy device



Final stroke size (white) matches the volume of initial irreversible injury; the patient experienced a full recovery



MULTIMODALITY MR-IMAGING GUIDES INDIVIDUALIZED STROKE TREATMENT

Current treatment options for acute ischemic stroke rely heavily on the clock. Patients who arrive at the hospital within 3 hours of symptom onset are candidates for intravenous tPA. Patients who arrive at specialized centers between 3 and 8 hours are candidates for treatment in the cath lab.

Greg Albers, MD, Director of the Stanford Stroke Center and Professor of Neurology and Neurological Sciences at Stanford Medical School believes the time clock approach does not work well for the individual patient because everybody's brain responds differently to a stroke. Using novel MR imaging software developed at Stanford, Albers and his colleagues at the Stroke Center are trying to identify which patients are most likely to benefit from restoration of blood flow up to 12 hours after symptom onset.

Within minutes of the onset of stroke, specialized MRI sequences identify which areas of the brain are irreversibly injured and which areas are likely to die if blood flow is not restored soon. If the MRI reveals that the salvageable region is larger than the volume of already injured tissue, the Stanford group believes that restoring blood flow will improve the patient's outcome (see figure 1). This strategy is being assessed in Stanford's ongoing multicenter study called DEFUSE 2, which is funded by the National Institutes of Health. →

INSIDE THIS ISSUE

Providing State of the Art Care for Patients with Acute Stroke	1
Stanford TIA Program Champions Urgent Evaluation and Management	3
Surgical Management of Primary and Metastatic Spinal Tumors	4
Deep Brain Stimulation for Patients With Intractable Neurological Disorders	5
Stanford Begins Clinical Testing of SanBio's SB623 Stem Cell Therapy	6
Stanford Joins First Embryonic Stem Cell Therapy Clinical Trial	6
Neurosurgery Patients Benefit from the New Hybrid Room	7
Stanford Study Links Glioblastoma Pathogenesis to NFKBIA Gene Deletion	8
Resting-state fMRI for Alzheimer's Diagnostic Advancement	9
Using Resting-state fMRI to Identify Brain Circuitry Abnormalities in Parkinson's	10
Advances in 7-Tesla MRI Technology Lead to Insights About Alzheimer's	10

“For acute stroke treatment we focus on identification of salvageable brain tissue and determining the site of vascular obstruction, not on arbitrary time windows. Treatment strategies are individualized to maximize reperfusion of viable tissue.”

Greg Albers, MD



Intracerebral hemorrhage is a devastating stroke subtype associated with high morbidity and mortality. Although the most common cause of brain hemorrhage is chronic hypertension, there are many other potential causes such as coagulopathies, vascular malformations, sinus thrombosis, illicit drug use, tumors, and bleeding into an ischemic stroke. Patients with spontaneous intracerebral hemorrhage managed at Stanford routinely undergo multimodality MR imaging to detect a potential underlying structural lesion. According to the experience of the Stanford Stroke team, MR imaging yields important diagnostic information in one of four patients and affects treatment decisions in 15% of them.

To facilitate treatment of as many stroke patients as possible, Stanford Hospital & Clinics developed the Rapid Transfer System, an expedited referral and transfer system designed to get patients promptly transported to Stanford and immediately assessed on arrival. Stroke patients treated at Stanford also benefit from participation in clinical trials such as a new trial testing the efficacy of a device that may improve stroke outcome using near-infrared laser energy.

neurologists believe that effective and timely halting of bleeding will translate into better neurologic outcomes. Therefore, a multidisciplinary working group including hematology, pathology, neurosurgery, critical care nursing and pharmacy was formed under the direction of Chitra Venkatasubramanian, MD, Clinical Assistant Professor of Neurology and Neurological Sciences for “*Emergency Reversal of Anticoagulation in Life-Threatening Bleeding*.” The goal was to devise a safe, simple and standardized protocol that is automated, easy to use and can be started in the emergency room. The protocol uses a recombinant factor concentrate called ProfilnineSD, which replenishes the coagulation factors affected by warfarin almost instantaneously while using only 30 cc of fluid volume. Since its adoption, the Stanford team has seen several instances of success in arresting hemorrhage expansion using this protocol, as shown in figure 3.

NEUROCRITICAL CARE AS A ROUTINE PART OF COMPREHENSIVE STROKE CARE

Stanford’s stroke treatment team includes eight stroke neurologists with subspecialty training in vascular neurology, three interventional

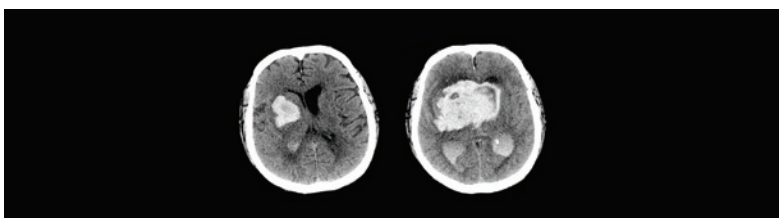


FIGURE 2

Initial CT scan of a 68 year old male on warfarin for atrial fibrillation who presented with left sided weakness, headache and an INR of 4. In the absence of complete normalization of blood clotting, the patient continued to bleed over the next 6 hours, the hemorrhage expanded 4-fold, and the patient died.

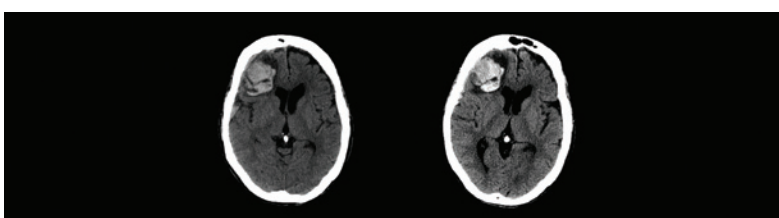
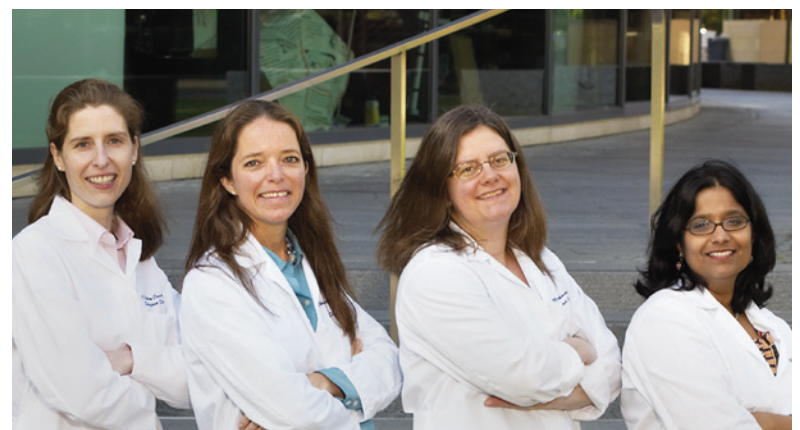


FIGURE 3

Brain CT scan of an 80 year old woman who presented with headache and confusion. She was taking warfarin for atrial fibrillation and her INR was 18.9 on admission. The warfarin reversal protocol was implemented and within a few hours her INR was brought down to 1.1. Her follow-up head CT showed stability of the hemorrhage. She has since returned home with minimal deficits.



STANFORD NEUROINTENSIVISTS PROVIDE EXPERT CARE FOR CRITICALLY ILL STROKE PATIENTS.

From left to right: Drs. Anna Finley Caulfield, Christine Wijman, Marion Buckwalter, and Chitra Venkatasubramanian

EMERGENCY WARFARIN REVERSAL IN ANTICOAGULATION INDUCED INTRACEREBRAL HEMORRHAGE

Anticoagulation induced brain hemorrhage is life threatening because the hemorrhage continues to expand in the absence of effective blood clotting. Conventional methods of restoring effective blood clotting by replenishing the clotting factors affected by warfarin include Vitamin K and fresh frozen plasma. However, frozen plasma requires up to a few hours for a large volume to be thawed and infused. The excess volume from plasma infusions may lead to pulmonary edema and transfusion-related allergic reactions. Stanford Stroke Center

neuroradiologists, three vascular neurosurgeons, and an outstanding nursing team. Four of the eight Stanford stroke physicians are also board certified in neurocritical care, providing expert care for the critically ill stroke patient requiring life support or intensive care monitoring. Stanford’s Neurocritical Care Program has been directed since its inception by Christine A.C. Wijman, MD, PhD, Associate Professor of Neurology and Neurological Sciences at Stanford Medical School. The Stanford Stroke team believes that neurocritical care is an important aspect of stroke management in comprehensive stroke centers, as studies have shown that neurointensivists and neurointensive care units improve the outcome of stroke patients, decrease mortality, and reduce costs.¹⁻⁴ ■

References are on page 11.

Stanford TIA Program Champions Urgent Evaluation and Management

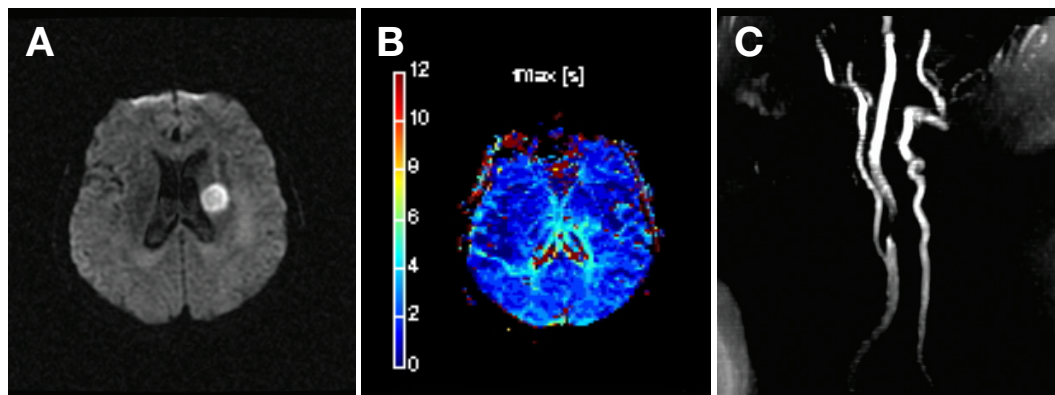


FIGURE 1: MULTIMODAL MRI PERFORMED WITHIN 12 HOURS AFTER SYMPTOM ONSET CAN REVEAL:

- A. Acute infarction on Diffusion Weighted Imaging sequence
- B. An isolated hypoperfusion on Perfusion Weighted Imaging
- C. A symptomatic internal carotid artery stenosis on the neck vessel MRA

The annual incidence of transient ischemic attack (TIA) in the United States is estimated to be 240,000 patients per year.¹ The risk of stroke following TIA is approximately 5% within the first 24-48 hours and up to 10% within the first few weeks.² The acute management of TIA can reduce the risk of stroke by 80%.³ Five years ago, the Stanford Stroke Center initiated one of the first TIA Programs in the United States with the goal of urgent evaluation and aggressive treatment to reduce the risk of stroke. In 2009, an expert committee from the American Heart Association emphasized the importance of an urgent specialized evaluation that includes brain MRI and vessel imaging for TIA patients.⁴

The Stanford TIA Program evaluates patients who are suspected of having an acute TIA (<48 hours) in a specialized hospital-like observation unit adjacent to the Emergency Department, which is available 24/7. Within 12 hours of arrival, TIA patients undergo multimodal brain MRI (see figure 1), as well as neck and brain MR angiography, a consult from a Stanford Stroke Neurologist, cardiac monitoring, and laboratory testing. Based on the results of this evaluation, the patient will either be discharged home with prescriptions for stroke prevention therapies and a plan for follow-up, or be admitted to the hospital. For patients experiencing a subacute TIA (>48 hours), the Stanford TIA Program will typically coordinate the necessary testing and complete a clinical evaluation within 3 business days. All patients receive phone follow-up at 1 week, 1 month, and 3 months for close monitoring and improved health outcomes.

The Stanford TIA Program's approach is to rapidly assess patients and incorporate the latest research findings to establish the etiology of the symptoms and optimize long-term prevention of stroke. Diffusion- and perfusion-weighted brain imaging as well as cervical and intracranial vessel imaging are the foundation of the diagnostic evaluation. The Stanford TIA Program has been conducting original research as well as partnering with other stroke centers on collaborative research projects.⁵⁻⁹ A recent study of 223 consecutive patients referred to the Stanford Emergency Department with a suspected TIA demonstrated the efficacy of the Stanford approach; 90 day stroke rates were <1%, which is considerably lower than expected.¹⁰ ■

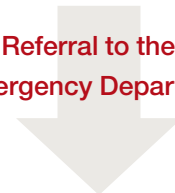
References are on page 11.

HOW TO REFER A PATIENT TO THE TIA PROGRAM

Immediate Care for Suspected Acute TIA

- Symptoms < 48 hours ago
- Recurrent TIAs
- Persistent Neurologic Deficit
- Known Internal Carotid Artery Stenosis

**Urgent Referral to the Stanford
Emergency Department**



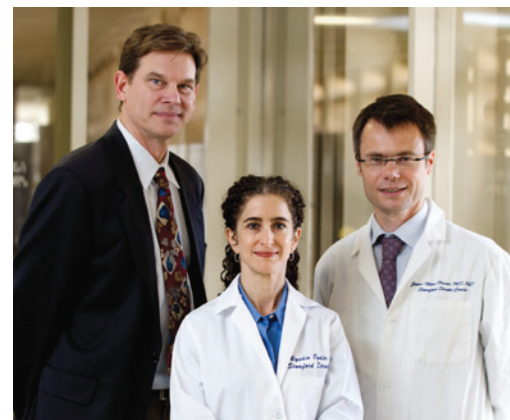
To advise the ED of urgent referral en route, you may call the Main ED line 24/7 at **650.723.7337**, or you may contact the call-back RN directly at **650.725.4492** (9:00am – 9:00pm).

Rapid Outpatient Referral

Please fax a referral to the Stanford Neurosciences Clinic at **650.724.6670** and include the following:

1. "Urgent Attention TIA Clinic" should be written at the top.
2. Referring provider's name and complete contact information.
3. Patient's complete contact and insurance information.
4. Pertinent records: history, notes, reports/location of previous imaging, lab work.

For non-urgent questions, please call the Stanford Stroke Center at **650.723.4448**.



STANFORD TIA PROGRAM

The Stanford TIA Program is directed by Drs. Greg Albers (left) and Jean-Marc Olivot (right) and coordinated by Nurse Practitioner Alyshia Ogdie (middle).

Surgical Management of Primary and Metastatic Spinal Tumors with Total En Bloc Spondylectomy

Spinal tumors are primary or metastatic lesions that can involve both the spinal cord and the vertebrae comprising the bony spinal column. Compression of the spinal cord or collapse of the spinal column may result in paralysis, loss of bowel and bladder function, pain, and loss of functional capacity. Stefan Mindea, MD, Director of Spinal Oncology at Stanford Medical Center is a fellowship-trained neurosurgeon specializing in the treatment of complex spinal tumors.

TREATMENT STRATEGIES

The cornerstone of treatment for metastatic spinal lesions has been palliation of pain and preservation of neurological function. Conversely, the central tenet of treating primary tumors of the spine, such as chondrosarcomas, sarcomas, and chordomas, along with select oligometastatic lesions, is complete margin-free en bloc resection.

TOTAL EN BLOC SPONDYLECTOMY

Total en bloc spondylectomy (TES) is a surgical technique aimed at achieving en bloc resection of these types of spinal tumors. The x-rays in figures 1 and 2 illustrate the results after surgery for a patient with the removal of two vertebral segments. The TES procedure has one primary goal: to completely and safely remove a spinal tumor such as the one shown in figure 3 and minimize the risk of recurrence. Dr. Mindea has successfully treated patients with very complex lesions using this advanced surgical technique. He explains, “With many of these types of tumors, you really have only one best chance at treating the tumor in a definitive manner.”

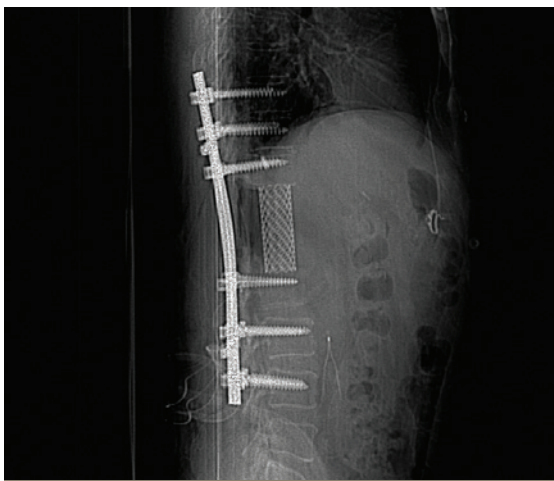


FIGURE 1
Lateral view demonstrating en bloc spondylectomy of T12 and L1 vertebral segments. A titanium cage is placed from T11 to L2 reconstructing the T12/L1 aspect of the spine.

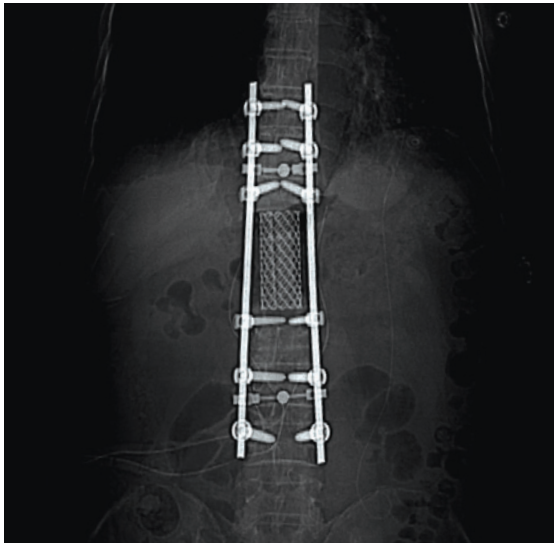


FIGURE 2
Anterior/Posterior view demonstrating instrumentation and stabilization through the surgically treated area.

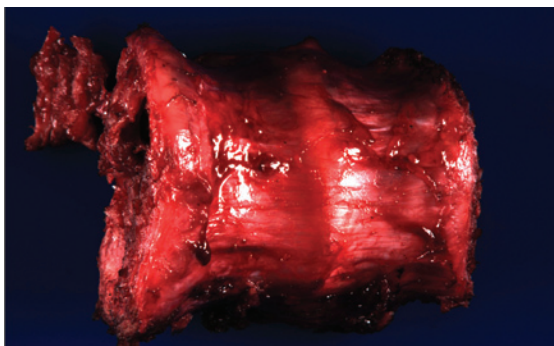


FIGURE 3
Growth Specimen: Anterior view of two-level vertebral body spondylectomy.

“With many of these types of tumors, you really have only one best chance at treating the tumor in a definitive manner.”

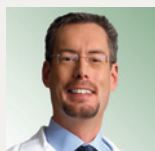
Stefan A. Mindea, MD



Most recently, TES continues to offer promise as a salvage strategy for patients failing treatment with radiation or radiosurgery. Ongoing research at Stanford Medicine seeks to study tumor specimens resected from surgery and analyze the specific mechanisms of radiation therapy and radiosurgery failure within the area of the vertebral body.

TES is recognized as a very technically challenging surgical procedure that is available at only a few medical centers in the world. “Stanford is a place that embraces innovation and seeks to provide world-class medical care. We’re very pleased that Dr. Mindea has added this novel procedure to the treatment armamentarium available for spine tumor patients at our hospital,” said Gary K. Steinberg, MD, PhD, Chairman of the Department of Neurosurgery. ■

NEW FACULTY ANNOUNCEMENTS



JOHN KEVIN RATLIFF, MD

Associate Professor of Neurosurgery (Acting)

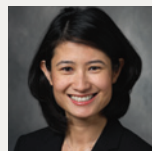
Specialty: Complex and reconstructive spine surgery, adult deformity and scoliosis surgery, minimally invasive spine surgery, peripheral nerve reconstruction, peripheral nerve tumors, and neurosurgical quality measures. *Start date: September 2011*



GORDON LI, MD

Assistant Professor of Neurosurgery (Acting)

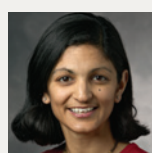
Specialty: Developing novel therapeutics for malignant gliomas in the laboratory, translating that research into clinical trials, and caring for patients with malignant brain tumors. *Start date: July 2011*



ROSALIND CHUANG, MD

Clinical Assistant Professor of Neurology and Neurological Sciences

Specialty: Genetics of movement disorders, such as dystonia, parkinsonian disorders, and ataxia. Identifying multiplex families to find novel genes. Characterizing clinical phenotypes of genetic diseases. *Start date: April 1, 2011*



SEEMA NAGPAL, MD

Clinical Assistant Professor of Neurology and Neurological Sciences and of Neurosurgery

Specialty: Caring for patients with adult brain tumors and neurologic complications of cancers. Research

Deep Brain Stimulation for Patients with Intractable Neurological Disorders

The Stanford Functional Neurosurgery Program combines advanced research with clinical expertise to provide our patients with the most effective diagnostic and treatment modalities. In particular, Stanford offers a number of pioneering techniques in deep brain stimulation (DBS) therapy for the treatment of Parkinson's disease, chronic pain and other disorders.

Our frameless technique provides patients with more freedom of movement and improved comfort during surgery. Quantitative movement measurements made during DBS surgery ensure that we place the electrodes into locations that allow each patient to achieve maximum improvement of symptoms. Postoperatively, we use a state-of-the-art image registration system to analyze a patient's lead location, which can then assist in programming adjustments or revisions.

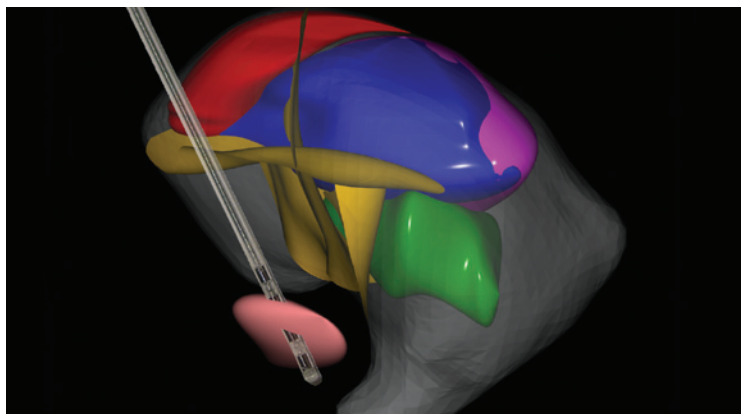


FIGURE 1
A patient-specific model of the thalamus and subthalamic nucleus showing a DBS electrode in position within the subthalamic nucleus.

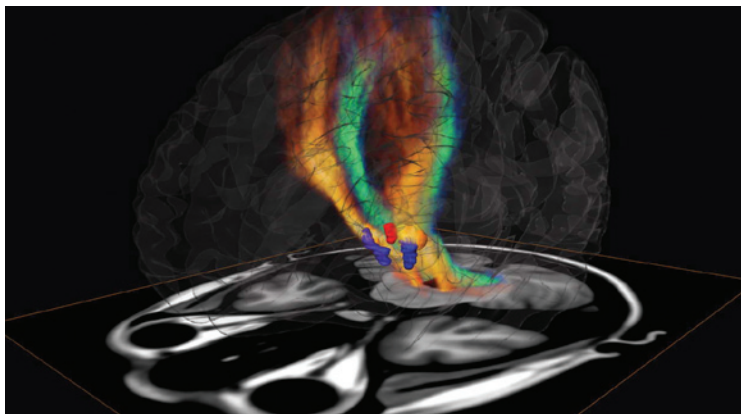


FIGURE 2
A probability map showing the connectivity between the cortex and the subthalamic nucleus (yellow) and between the cortex and red nucleus (blue-green). Mapping these tracts allows for precise targeting of DBS electrodes into the regions of highest connectivity, thus improving efficacy (*figure courtesy of Burkhard Mädler, PhD, University of Bonn*).

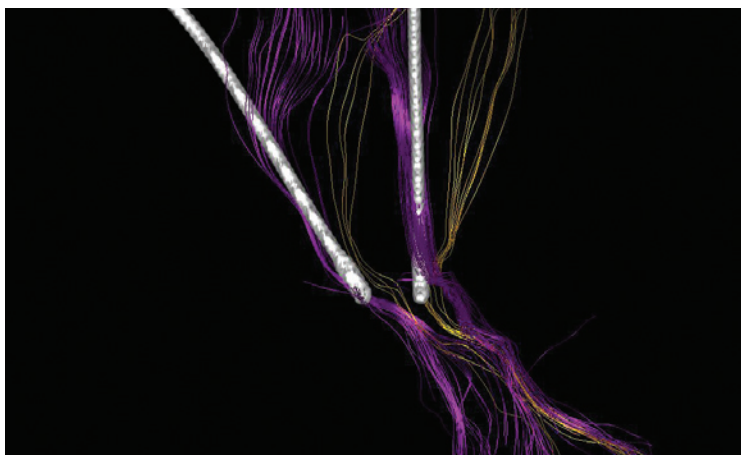
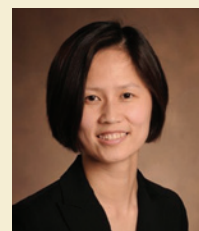


FIGURE 3
DBS electrodes (silver) placed at the site of maximal efficacy in the subthalamic region. The patient-specific connections between brain regions are shown in different colors.



Jaimie Henderson, MD (*left*)



Hong Yu, MD (*right*)

“Postoperatively, we use a state-of-the-art image registration system to analyze a patient's lead location, which can then assist in programming adjustments or revisions.”

Jaimie Henderson, MD, Director, Stereotactic and Functional Neurosurgery and Associate Professor of Neurosurgery, and Hong Yu, MD, Assistant Professor of Neurosurgery, have active research underway to investigate the mechanisms of DBS. The use of patient-specific 3D brain atlases (figure 1) coupled with diffusion tensor imaging tractography (figures 2 and 3) promises to revolutionize our understanding of DBS and expand the target sites and clinical indications.

Stanford Medicine is a participating center in several gene therapy trials for the treatment of Parkinson's disease. We are also actively investigating the application of DBS for diseases outside the realm of movement disorders. These include the use of DBS for the treatment of obsessive compulsive disorder, Tourette's syndrome, depression, epilepsy and pain. ■

includes the treatment of recurrent glioblastoma, quality of life for brain tumor patients, and early detection of central nervous system involvement in patients with metastatic breast cancer.

Start date: August 1, 2011

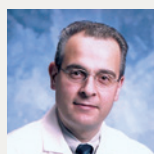


ROBERT COWAN, MD

Clinical Professor of Neurology and Neurological Sciences and, by courtesy, of Anesthesia Director, Stanford Headache Program

Specialty: Research and treatment for headache, complex migraine, facial pain and pain management. Headache disease advocacy.

Start date: July 16, 2011



SAFWAN JARADEH, MD

Professor of Neurology and Neurological Sciences Director, Stanford Autonomic Disorders Program (Acting)

Specialty: Treating patients with autonomic nerve disorders, peripheral nerve disorders, and disorders of the larynx and pharynx related to neurological and neuromuscular diseases. *Start date: October 1, 2011*

Stanford Begins Clinical Testing of SanBio's SB623 Stem Cell Therapy for Cerebral Stroke

Pioneers in stem cell therapy, Stanford University School of Medicine and SanBio, Inc. have joined forces to combat the disabling effects of cerebral stroke. On January 21st, 2011, Stanford University School of Medicine became the first institution to embark on the recently FDA-approved phase I-II study to test the safety and efficacy of SanBio's SB623 cells for patients with stable ischemic stroke. The SB623 human clinical trial is expected to enroll up to 18 patients and last up to two years.

This is the first clinical trial in the United States to test the therapeutic potential of stem cell therapy delivered directly to the brain of stroke patients. With very limited therapeutic options for stroke, huge societal costs of over \$65 billion in 2008, and staggering projected total costs from 2005 to 2050 of \$2.2 trillion, the implications of a successful clinical trial are enormous.

Gary K. Steinberg, MD., PhD, Bernard and Ronni Lacroute-William Randolph Hearst Professor in Neurosurgery and the Neurosciences and Chairman of the Department of Neurosurgery is principal investigator and team leader at the Stanford site. He has extensive experience studying models of brain injury in stroke and is currently also leading a team of Stanford researchers studying potential therapeutic treatments for stroke using neural stem cells to minimize, prevent, or repair brain injury caused by stroke. This work is supported by a recent 20 million dollar grant from the California Institute for Regenerative Medicine (CIRM).

Said Dr. Steinberg, "Stem cells as a therapeutic have the potential to modify or even reverse the damage caused by neurodegenerative disease or injury. Human clinical testing of SanBio's SB623 cells is truly a groundbreaking study with important implications for patients suffering from not only stroke injury, but also numerous other degenerative diseases of the central nervous system."

"Stem cells as a therapeutic have the potential to modify or even reverse the damage caused by neurodegenerative disease or injury."



Gary K. Steinberg, MD, PhD

SanBio Inc., a leader in the advancement of regenerative therapies for neurological disorders, developed the cells, which are based on research by Professor Mari Dezawa of Tohoku University in Japan. They are adult bone-marrow-derived stromal cells genetically engineered to transiently express the Notch gene, a known regulator of neuronal function and development. SB623 cells have been shown to protect neurons in models of ischemia and have caused improved neurological behavior in a rat model of stroke.

Because SB623 cells are allogeneic, a single donor can be used to treat thousands of patients. From 2.5 to 10 million SB623 cells will be stereotactically injected into the patient's brain directly adjacent to the area damaged by stroke. While primarily a safety study, efficacy parameters will also be evaluated, such as improvements in motor function and cognitive status. Study participants will be evaluated over a two year period following implantation with the cells.

For more information about the study, including the major eligibility criteria, please refer online at clinicaltrials.gov. ■



Stanford Joins First Embryonic Stem Cell Therapy Clinical Trial

The first clinical trial of cells derived from human embryonic stem cells began in October 2010 in a paralyzed patient at the Shepherd Center in Atlanta. On January 24, 2011 Stanford University School of Medicine and Santa Clara Valley Medical Center were jointly authorized to be the third site to participate in the trial, which will enroll up to 10 patients with spinal cord injuries at up to seven institutions nationwide.

The FDA-approved, phase 1 trial is testing the safety of the cells called GRNOPC1, which can develop into oligodendrocytes. Animal studies suggest these cells will migrate throughout the site of damage and mature into myelin-producing cells to re-insulate the affected neurons. If shown to be safe for use in humans, larger clinical trials will test whether the cells are better able than conventional treatments to improve a patient's condition.

Because the cells must be administered within two weeks of the initial spinal cord injury, the trial is open only to those with very recent trauma and only upon physician referral. To be eligible, patients must have non-penetrating damage to a specific region of their thoracic spine and the damage must have caused complete paraplegia.

Researchers at Menlo Park-based Geron Corp. collaborated with Hans Keirstead's laboratory at UC-Irvine to develop the cells. The trial is being run by Geron. Stanford Neurosurgeons Gary K. Steinberg, MD, PhD (principal investigator of the Stanford/SCVMC portion of the trial), and Marco Lee, MD, PhD will implant the cells at Valley Medical Center, one of the largest referral centers for acute spinal cord injury and rehabilitation on the West Coast.

"Until recently, we have not had any hope of restoring neurological function in people with spinal cord injury or stroke, or those with brain tumors or Alzheimer's disease," said Dr. Steinberg. "But now we're moving stem cell therapy into the clinic, which I feel is a tremendously important step. People are not mice or rats, and we can learn so much from clinical trials that we can never learn by studying animals." ■

NEUROSURGERY

CLINICALTRIALS.GOV IDENTIFIER	TITLE	PRINCIPAL INVESTIGATOR
NCT01217008	<p>A Phase 1 Safety Study of GRNOPC1 in Patients with Neurologically Complete, Subacute, Spinal Cord Injury</p> <p>The investigators hope to learn if GRNOPC1 will remyelinate spinal cord axons to facilitate a return of motor function in patients with complete thoracic level spinal cord injury. GRNOPC1 is derived from embryonic stem cells and will be implanted into the spinal cord within 14 days of injury.</p>	Gary K. Steinberg, MD, PhD
NCT01287936	<p>A Phase 1/2A Study of the Safety and Efficacy of Modified Stromal Cells (SB623) in Patients with Stable Ischemic Stroke</p> <p>A phase 1/2 safety and efficacy study of SB623 cells for patients with hemiparesis from stable ischemic stroke. SB623 are modified bone marrow-derived neuroprogenitor stromal cells that will be implanted into the peri-infarct region of the brain between 6-24 months after stroke.</p>	Gary K. Steinberg, MD, PhD
NCT00071565	<p>Familial Intracranial Aneurysm (FIA) Study</p> <p>This is an NIH-funded study to explore genetic and environmental factors associated with the incidence of familial intracranial aneurysms. The study has already enrolled a sufficient number of familial patients and continues to enroll non-familial affected patients.</p>	Gary K. Steinberg, MD, PhD
NCT01036529	<p>Evidence Study: Spinal Cord Stimulation with Precision SCS System Versus Reoperation for Failed Back Surgery Syndrome</p> <p>This is a post-market study to determine the effectiveness of spinal cord stimulation (SCS) on pain relief for patients who experience pain associated with failed back surgery syndrome (FBSS), compared to those who undergo repeat operations for pain relief. SCS is normally used on patients whose pain could not be relieved after multiple repeat operations.</p>	Jaimie Henderson, MD
NCT00958841	<p>An Open Label, Multicenter, Single Arm Study of Pasireotide LAR in Patients with Rare Tumors of Neuroendocrine Origin</p> <p>This study will evaluate the efficacy and safety of pasireotide LAR in patients with rare tumors of neuroendocrine origin who have disease progression despite standard therapy or for whom no standard therapy is available.</p>	Laurence Katznelson, MD
NCT00985517	<p>A Phase 1/2 Trial Assessing the Safety and Efficacy of Bilateral Intraputamin and Intranigral Administration of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin [NTN]) in Subjects with Idiopathic Parkinson's Disease</p> <p>Patients are randomized to a sham surgery control arm or treatment arm for implantation of the study drug into the substantia nigra and putamen. CERE-120 is an adenovirus genetically engineered to produce the neurotrophic growth factor neurturin (NTN).</p>	Jaimie Henderson, MD

NEUROSURGERY CONTINUED

CLINICALTRIALS.GOV IDENTIFIER	TITLE	PRINCIPAL INVESTIGATOR
NCT00946673	<p>A Phase 1 Trial of Vorinostat Concurrent with Stereotactic Radiotherapy in Treatment of Brain Metastases From Non-Small Cell Lung Cancer</p> <p>The purpose of this study is to determine the maximum tolerated dose (MTD) of vorinostat given concurrently with stereotactic radiosurgery (SRS) to treat non-small cell lung cancer (NSCLCA) brain metastases in patients with 1-4 lesions.</p>	Griff Harsh, MD
NCT01163539	<p>CyberKnife Radiosurgery and Quality of Life</p> <p>The purpose of this study is to look at pain control and quality of life improvement after treatment with CyberKnife radiosurgery for spinal metastases.</p>	Steven Chang, MD
NCT01007071	<p>Effects of Growth Hormone on Cognition and Cerebral Metabolism in Adults</p> <p>The aim of this study is to elucidate the effects of growth hormone replacement in patients with growth hormone deficiency on cognitive function using structural and functional neuroimaging and cognitive testing.</p>	Laurence Katznelson, MD

NEUROLOGY

NCT00445367	<p>Large-Scale, Multi-Disciplinary Sample and Data Repository for Multiple Sclerosis and Related Demyelinating Diseases</p> <p>This study will establish a large, longitudinal collection of high quality samples and data from subjects with MS and selected other demyelinating diseases for research into the causes of multiple sclerosis and selected demyelinating diseases. Samples and data will be available as a shared resource to scientists researching the causes, sub-types, and biomarkers of MS and related demyelinating diseases.</p>	Jeffrey Dunn, MD
NCT00643890	<p>Phase 2 Safety and Efficacy Study Evaluating Glutamic Acid Decarboxylase Gene Transfer to Subthalamic Nucleus in Subjects with Advanced Parkinson’s Disease</p> <p>The aim of this study is to determine the efficacy of gene transfer therapy with AAV-GAD patients who have medically refractory Parkinson’s disease.</p>	Kathleen Poston, MD, MS
NCT01301573	<p>Long Term Follow-Up Study for rAAV-GAD Treated Subjects</p> <p>The aim of this study is to evaluate the long term safety and efficacy of Parkinson’s disease patients treated with gene transfer therapy.</p>	Kathleen Poston, MD, MS
	<p>Brain Networks in Neurodegenerative Diseases</p> <p>The aim of this study is to prospectively evaluate the application of FDG PET to aid in the diagnosis of Parkinson’s disease and other atypical parkinsonian syndromes.</p>	Kathleen Poston, MD, MS
NCT01285414	<p>A Phase 2 Study of Verubulin with Radiation and Temozolomide for Adults with Newly Diagnosed Glioblastoma</p> <p>This study will be conducted in two parts. Part A determines the safety and tolerability of verubulin in combination with standard treatment. Part B investigates progression-free survival and overall survival of patients receiving verubulin at the dose determined in Part A, in combination with standard treatment vs. standard treatment alone.</p>	Lawrence Recht, MD

NEUROLOGY CONTINUED

CLINICALTRIALS.GOV IDENTIFIER	TITLE	PRINCIPAL INVESTIGATOR
NCT01268566	<p>A Phase 2 Study of MEDI-575 (Monoclonal Antibody) in Adult Subjects with Recurrent Glioblastoma Multiforme</p> <p>The primary objective of this Phase II study is to evaluate the progression-free survival at 6 months in adult subjects with a first recurrence of Glioblastoma Multiforme who are treated with MEDI-575.</p>	Lawrence Recht, MD
	<p>The Aging Brain: Risk for Dementia</p> <p>This study will enroll older individuals with or without cognitive problems at baseline. We will collect blood and spinal fluid samples, neuropsychological data, and clinical information, then observe the subjects over time with the goal of finding out what factors are most predictive of a risk of going on to develop dementia.</p>	Geoffrey Kerchner, MD, PhD
	<p>Resting-State Functional MRI for Diagnosing Alzheimer’s Disease</p> <p>Patients with mild cognitive impairment, Alzheimer’s disease, and other neurodegenerative conditions, as well as healthy controls, are being recruited to undergo resting-state fMRI, with a goal of developing a resting-state functional connectivity biomarker that is sensitive enough to detect signal in MCI and specific enough to distinguish AD from non-AD dementia at the single-patient level.</p>	Michael Greicius, MD, MPH
NCT00896441	<p>Functional MRI Before and After Treatment for Depression</p> <p>The purpose of this study is to help us understand how depression changes brain activity and how this relates to mood, anxiety, and cognitive functions like memory. We also hope to develop a brain imaging test that will predict either before or within 2 weeks of starting a medicine whether the treatment will work.</p>	Michael Greicius, MD, MPH
NCT01135810	<p>Resting State Functional MRI Investigation of Hypnotic Trance and Mindfulness Meditation</p> <p>This study seeks to determine if there are distinct patterns of brain activity that correlate with hypnotic trance, mindfulness meditation or both, and to relate these patterns to measurable markers of physical well-being. Precise neuroimaging of heightened attentional states will guide future researchers and practitioners toward more effective techniques of mind/body control.</p>	Michael Greicius, MD, MPH
	<p>Microstructural Brain Imaging Using Ultra-High Field 7-Tesla MRI</p> <p>Using a high-powered MRI to acquire very high resolution brain images, this study aims to find the earliest structural changes corresponding to Alzheimer’s disease and other neurodegenerative conditions, as well as how those changes correlate with memory and other behavioral measures.</p>	Geoffrey Kerchner, MD, PhD
	<p>A Phase II Trial of MABT5102A on Brain Amyloid and Related Biomarkers in Patients with Mild to Moderate Alzheimer’s Disease (ABBY)</p> <p>An 85-week treatment trial of an anti-beta-amyloid monoclonal antibody, to study its ability to reduce levels of beta-amyloid in patients with Alzheimer’s disease.</p>	Geoffrey Kerchner, MD, PhD
NCT01349946	<p>Diffusion Weighted Imaging Evaluation for Understanding Stroke Evolution Study-2: (DEFUSE-2)</p> <p>The aim of this study is to determine if MRI can help identify which patients ineligible for IV tPA therapy or who have failed IV tPA therapy should undergo an endovascular clot removal procedure.</p>	Gregory Albers, MD

NEUROLOGY CONTINUED

CLINICALTRIALS.GOV IDENTIFIER	TITLE	PRINCIPAL INVESTIGATOR
NCT00363662	<p>Diagnostic Utility of MRI in Intracerebral Hemorrhage</p> <p>The aim of this study is to measure the impact of new, state-of-the-art brain imaging technology on the diagnosis and treatment of patients with a spontaneous ICH with the goal of improving patient outcome.</p>	Christine Wijman, MD
	<p>Prognostic Value of MRI and Biomarkers in Comatose Post-cardiac Arrest Patients (COMA)</p> <p>This study is designed to assess the value of state-of-the art brain imaging techniques (MRI), and blood tests in predicting outcome in these patients.</p>	Christine Wijman, MD
NCT00991029	<p>Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trial</p> <p>The POINT phase 3 study seeks to determine whether the combination of aspirin and clopidogrel reduces the risk of stroke, heart attacks and other complications compared to aspirin alone.</p>	Gregory Albers, MD
NCT00224770	<p>Minimally Invasive Surgery Plus rt-PA for Intracerebral Hemorrhage Evacuation (MISTIE)</p> <p>This phase 2 study is designed to investigate the safety of minimally invasive surgery plus aspiration followed by the administration of a low dose of recombinant tissue plasminogen activator into intracerebral hemorrhage patients via a catheter inserted directly into the clot.</p>	Christine Wijman, MD
NCT00784134	<p>Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase 3 (CLEAR III)</p> <p>This study is designed to determine whether EVD placement with low-dose rt-PA improves modified Rankin Scale scores at 6 months (dichotomized Rankin 0-3 vs. 4-6) compared to subjects treated with EVD placement with placebo (normal saline).</p>	Christine Wijman, MD
NCT00091949	<p>Insulin Resistance Intervention After Stroke Trial (IRIS)</p> <p>This study is designed to determine whether pioglitazone, compared to placebo, will reduce the overall risk for fatal or nonfatal stroke or fatal or non-fatal MI among non-diabetic men and women over age 44 years with insulin resistance and a recent ischemic stroke or TIA.</p>	Maarten Lansberg, MD, PhD
NCT00856661	<p>Randomized, Double-Blind, Parallel-Group Placebo-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of Desmoteplase in Subjects with Acute Ischemic Stroke (DIAS-4)</p> <p>This study is designed to evaluate the effectiveness of desmoteplase 90 µg/kg versus placebo in terms of favorable outcome at Day 90 in subjects with acute ischemic stroke.</p>	Maarten Lansberg, MD, PhD
	<p>Prognosis of Critically Ill Neurological Patients</p> <p>The aim of this research is to determine 1) how accurate health care providers are in predicting future neurological outcomes, 2) if health care providers are similar or different in the prediction of outcome and 3) to assess the outcomes of this patient population.</p>	Anna Finley-Gaulfield, MD

NEUROLOGY CONTINUED

CLINICALTRIALS.GOV IDENTIFIER	TITLE	PRINCIPAL INVESTIGATOR
NCT01120301	<p>NeuroThera® Efficacy and Safety Trial - 3 (NEST-3)</p> <p>A double-blind, randomized, sham controlled, parallel group, multicenter, pivotal study to assess the safety and efficacy of transcranial laser therapy (TLT) with the NeuroThera® Laser System for the treatment of acute ischemic stroke within 24 hours of stroke onset.</p>	Gregory Albers, MD
	<p>Using Multiplex Families to Map Genes that Modify Susceptibility and Age of Onset in Parkinson's Disease (the PaGeR Study)</p> <p>The aim of this multi-center NIH-funded study is to evaluate families with two first degree relatives with Parkinson's disease and their unaffected relatives to determine genetic markers.</p>	Rosalind Chuang, MD
NCT01268280	<p>Protocol CY 4023: A Phase II, Double-Blind, Randomized, Three-Way Crossover, Placebo-Controlled, Pharmacodynamic Study of CK-2017357 in Patients with Generalized Myasthenia Gravis on Standard Therapy</p> <p>The primary objective of this early-stage clinical study is to demonstrate the effect of single doses of CK-2017357 on measures of skeletal muscle function and fatigability in patients with generalized myasthenia gravis (MG).</p>	Yuen So, MD, PhD
NCT01049217	<p>A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Trial of Pregabalin Versus Placebo in the Treatment of Neuropathic Pain Associated with HIV Neuropathy (Pregabalin A0081244)</p> <p>The purpose of this study is to evaluate the efficacy of pregabalin compared to placebo in reducing neuropathic pain associated with HIV neuropathy.</p>	Yuen So, MD, PhD
NCT01145417	<p>An Open-Label, Extension Safety Trial of Pregabalin in Subjects with Neuropathic Pain Associated with HIV Neuropathy (Pregabalin A0081251)</p> <p>This study is an open-label extension trial of study A0081244. It is designed to evaluate the safety and tolerability of pregabalin in patients with HIV associated neuropathy.</p>	Yuen So, MD, PhD
	<p>Population-based Studies of the Prevalence and Predisposing Factors of Peripheral Neuropathy</p> <p>Two studies are ongoing in collaboration with epidemiologists at the University of California at Berkeley to investigate the potential environmental or occupational risk factors that may lead to peripheral neuropathy.</p>	Yuen So, MD, PhD

RADIATION ONCOLOGY

NCT01120639	<p>A Phase 1/2 Trial of Temozolomide and Hypofractionated Radiotherapy in the Treatment of Supratentorial Glioblastoma Multiforme</p> <p>The safety and effectiveness of hypofractionated radiotherapy, performed in 1 week rather than the traditional 6 weeks, in combination with temozolomide for patients with GBM will be determined.</p>	Scott G. Soltys, MD Clara Y.H. Choi, MD, PhD
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RADIATION ONCOLOGY CONTINUED

CLINICALTRIALS.GOV IDENTIFIER	TITLE	PRINCIPAL INVESTIGATOR
NCT01120639	<p>A Phase 1/2 Trial of Temozolomide and Hypofractionated Radiotherapy in the Treatment of Supratentorial Glioblastoma Multiforme</p> <p>The safety and effectiveness of hypofractionated radiotherapy, performed in 1 week rather than the traditional 6 weeks, in combination with temozolomide for patients with GBM will be determined.</p>	Scott G. Soltys, MD Clara Y.H. Choi, MD, PhD
NCT00928226	<p>A Phase 1/2 Trial of Fractionated Stereotactic Radiosurgery to Treat Large Brain Metastases</p> <p>The optimal radiation dose for large brain metastases treated with hypofractionated stereotactic radiosurgery will be determined, with the potential of improving the control rate and decreasing side effects for patients.</p>	Scott G. Soltys, MD Clara Y.H. Choi, MD, PhD
NCT01364259	<p>A Study of Amifostine for Prevention of Facial Numbness in Patients Receiving Stereotactic Radiosurgery for Trigeminal Neuralgia</p> <p>This trial investigates whether the addition of Amifostine, a drug designed to prevent radiation side effects, can decrease the rate of facial numbness in patients with trigeminal neuralgia treated with stereotactic radiosurgery.</p>	Clara Y.H. Choi, MD, PhD Scott G. Soltys, MD
NCT01364272	<p>Investigation of Diffusion Tensor Imaging Magnetic Resonance Imaging (DTI MRI) as a Correlate to Pain Relief and Facial Numbness in Patients Following Stereotactic Radiosurgical Rhizotomy for Trigeminal Neuralgia</p> <p>This study investigates if MRI imaging reveals any anatomic correlate of pain relief or facial numbness for patients with trigeminal neuralgia treated with stereotactic radiosurgery.</p>	Clara Y.H. Choi, MD, PhD Scott G. Soltys, MD
NCT01364285	<p>A Study of Patient Reported Outcomes After Stereotactic Radiosurgery for Trigeminal Neuralgia</p> <p>The aim of this study is to learn patient experience (quality of life and treatment satisfaction) following radiosurgery treatment of facial pain from trigeminal neuralgia.</p>	Clara Y.H. Choi, MD, PhD Scott G. Soltys, MD

RADIOLOGY/ NEURORADIOLOGY

	<p>Quantifying Collateral Perfusion in Cerebrovascular Disease</p> <p>This study utilizes the new technology of magnetic resonance imaging (MRI) in improving the detection and assessment of collateral blood vessels in patients with diseases of the brain, such as Moyamoya disease and stroke.</p>	Greg Zaharchuk, MD, PhD
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INTERVENTIONAL NEURORADIOLOGY

	<p>Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT)</p> <p>This study is evaluating a new intracranial stent for intracranial stenosis.</p>	Michael P. Marks, MD
NCT01151748	<p>Intra-arterial Chemotherapy for Advanced Intraocular Retinoblastoma</p> <p>This study is recruiting patients with inoperable tumors of the eye, specifically retinoblastoma. We will treat these patients with selective intra-arterial infusion of chemotherapy for intraocular retinoblastoma.</p>	Jonathan W. Kim, MD Huy M. Do, MD

Neurosurgery Patients Benefit from the New Hybrid Room

A Fully Equipped Operating Room and Interventional Platform



The Hybrid Room at Stanford Hospital was designed specifically to allow on-scene collaboration between specialists in neurosurgery and neuroradiology. The room's centerpiece is a stereoscopic biplane digital subtraction angiography system, its curvilinear arms nearly reaching the ceiling, encircling a space as broad as a giant redwood trunk. It's a machine that captures 360 degree views of the brain while the patient lies still. Because fewer images are required to build 3D images with the necessary level of precision, the patient's exposure to radiation and contrast dye injection is greatly reduced.

In the old scenario, the brain remained exposed while the patient was wheeled back and forth between the OR and radiology to confirm the success of each step of the surgery. "It's a quantum leap up," said Robert Dodd, MD, PhD, who is both a Stanford neurosurgeon and interventional neuroradiologist. "We can have a full operating team in the room and we don't have to move the entire team and patient down the hall, up the elevator and back down again." That kind of back and forth, Dodd said, "can take all day, instead of four hours."

In addition, at 800 square feet, the hybrid room has the necessary space to accommodate additional team members should they be needed in an unanticipated turn of events, such as a catheterization that suddenly becomes a situation for surgery.

The improved imaging detail enhances patient safety as well as diagnosis and treatment. "The new angiographic hardware and software in the hybrid room gives us high resolution three dimensional image reconstructions of a patient's arterial system. We can understand anatomy better and more precisely navigate to areas we need to treat." said Michael Marks, MD, Chief, Interventional Neuroradiology.

The new Stanford Hospital will include one entire floor of this kind of multipurpose space, with several 1,000-square-foot units large enough to accommodate larger scale equipment and more people. ■

"The new angiographic hardware and software in the hybrid room gives us high resolution three dimensional image reconstructions of a patient's arterial system. We can understand anatomy better and more precisely navigate to areas we need to treat."



Michael Marks, MD



Stanford Study Links Glioblastoma Pathogenesis to NFKBIA Gene Deletion

A study fast-tracked for publication February 17, 2011, in the *New England Journal of Medicine* identified an important gene deletion in up to 25 percent of glioblastoma tumors. This deletion contributes to tumor development, promotes resistance to therapy and considerably worsens a patient's survival prospects. Griff Harsh, MD, Professor of Neurosurgery at the Stanford University School of Medicine is the collaborative study's senior author.

The deletion of the gene, known as NFKBIA, triggers biochemical processes similar to those resulting from the better-known aberration common in glioblastomas: alteration of the epidermal growth factor receptor, or EGFR. The fact that both defects produce the same outcome may help explain why efforts to treat the disease by targeting only one aberration have faltered.

Mutations in NFKBIA have been found in a wide range of cancers including Hodgkin's lymphoma, multiple myeloma, melanoma, and breast, lung and colon cancer. But the new study is the first to implicate the deletion of a copy of NFKBIA as a contributing cause of glioblastoma.

"It's been known for 25 years that EGFR plays a role in glioblastoma as well as many other cancers, and that this gene is aberrantly activated

and 2009 and found NFKBIA deletions in 25 percent of the samples. They also identified aberrations in EGFR in about 33 percent of these samples. Interestingly, only a handful of samples (about 5 percent) contained both gene aberrations. Thus, the two defects taken together accounted for a majority of glioblastomas examined. Moreover, the authors learned, patients with either the NFKBIA or EGFR abnormality had a significantly shorter survival, despite maximal therapy, than the remaining patients (roughly 40 percent) whose tumors bore neither genetic defect.

The defects of NFKBIA and EGFR similarly activate the transcription factor NF-kappa-B, but they do this by different mechanisms. The biochemical signal sent by overabundant or hyperactive EGFR activates NF-kappa-B, encouraging cancer-cell proliferation and resistance to chemotherapy. By contrast, NFKBIA codes for a protein called I-kappa-B, which inhibits NF-kappa-B. Under normal conditions, I-kappa-B binds to NF-kappa-B and prevents it from moving to the nucleus and altering gene expression. Thus, an NFKBIA deletion, which reduces levels of I-kappa-B in the cell, allows NF-kappa-B to go into overdrive, producing the same proliferative effect as EGFR hyperactivity.

In cancer cells, NF-kappa-B can induce not only proliferation but also refusal to die under conditions in which even cancer cells would otherwise opt to commit suicide — for example, when their DNA has been severely damaged by chemotherapeutic agents such as temozolomide.

The discovery of the role of The NFKBIA deletion in glioblastoma, and its dismal effect on survival, has near-term prognostic implications. "The way we identified this deletion for our study is not going to be efficient for general clinical-laboratory use," said Dr. Harsh. "Hannes

"The discovery of the role of the NFKBIA deletion in glioblastoma will provide clinicians with important prognostic insight and may lead to more effective treatments."

Griff Harsh, MD



in glioblastoma," said the study's principal investigator, Markus Bredel, MD, PhD, who is a visiting associate Professor of Neurosurgery at Stanford, associate professor at the University of Alabama-Birmingham and professor of neuro-oncology at the University of Freiburg in Germany. "We asked ourselves, what causes the majority of glioblastomas that don't have this defect?"

Drs. Bredel, Harsh and Branimir Sikic, MD, Professor of Oncology and clinical pharmacology at Stanford, had previously found that patients with low NFKBIA expression were resistant to temozolomide treatment. Based on that finding and on hints from other tumor types, Drs. Bredel, Harsh and their colleagues at Freiburg and Northwestern University focused on NFKBIA.

The investigators analyzed several hundred tumor samples collected from glioblastoma patients treated at several institutions between 1989

Vogel, MD, Professor of Pathology and Chief of Neuropathology at Stanford and a co-author of the study is developing an improved method— fast, cheap, reliable. That could happen within a year or so."

The new findings could also have implications for choice of treatment. The resulting categorization of a patient's glioblastoma according to its molecular defects should permit selection of a specific therapy more likely to be effective against that particular tumor. "If we can determine that a patient's glioblastoma has the NFKBIA deletion, we can target that tumor for treatment with drugs that stabilize I-kappa-B, NFKBIA's protein product," said Dr. Bredel. Drugs approved for treating other cancers (for example, bortezomib, for multiple myeloma) or currently under clinical investigation may have that capacity. An early-stage clinical trial of bortezomib for glioblastoma is now under way at Northwestern. ■



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Resting-state fMRI: Successfully Advancing Our Understanding of Brain Network Degeneration in Alzheimer's Disease

Dr. Michael Greicius, Assistant Professor of Neurology and Neurological Sciences and Assistant Professor of Psychiatry & Behavioral Sciences at Stanford University School of Medicine, has pioneered the use of a novel approach to the study of brain network degeneration in Alzheimer's disease (AD) and other dementias. This innovative approach, known as resting-state fMRI, measures temporal correlations in the spontaneous waves of brain activity across different regions. The spontaneous waves of activity are detected as a patient rests quietly in the scanner for eight minutes. If spontaneous waves in region X are strongly correlated with spontaneous fluctuations in region Y, these two regions are functionally connected. This technique can identify a host of distinct, large-scale brain networks that correspond to critical functions like vision, movement, language, emotional processing, and most importantly for AD research, memory (figure 1).¹

In a landmark 2003 study², Dr. Greicius' team was the first to identify this memory network using resting-state fMRI. In a follow-up 2004 study³, his group showed that the network was disrupted in AD. With an eye towards clinical applicability and development of an MRI biomarker of AD, the paper described a method for quantifying the strength of network connectivity at the single-patient level. Dr. Greicius now has a 5-year NIH grant to refine this approach with the goal of developing resting-state fMRI into a sensitive and specific test for Alzheimer's disease.

"Resting-state fMRI can identify large-scale brain networks that correspond to critical functions like vision, movement, language, emotional processing, and most importantly for AD research, memory."



Michael Greicius, MD

Unlike traditional task-activation fMRI, resting-state fMRI does not require MRI-compatible hardware for presenting stimuli or recording subject responses. It is also easier for patients with dementia to undergo because they are not required to perform a task in the scanner. As such, resting-state fMRI has the potential to be used in standard clinical imaging centers and across the entire spectrum of clinical severity. For these reasons, enthusiasm for the use of resting-state fMRI as a biomarker in AD has spread well beyond Stanford. The NIH has recently added resting-state fMRI to its multisite, \$60 million Alzheimer's Disease Neuroimaging Initiative (ADNI) study and appointed Dr. Greicius to its advisory panel.

Most recently, Dr. Greicius, working with colleagues at UCSF, has pushed the clinical relevance of resting-state fMRI into the realm of non-AD dementias (figure 2).⁴ Comparing patterns of brain atrophy with resting-state networks, this study demonstrates that 5 distinct neurodegenerative diseases progress along 5 distinct large-scale brain networks, opening the door for increasingly specific resting-state fMRI biomarkers of AD and non-AD dementias. ■

References are on page 11.

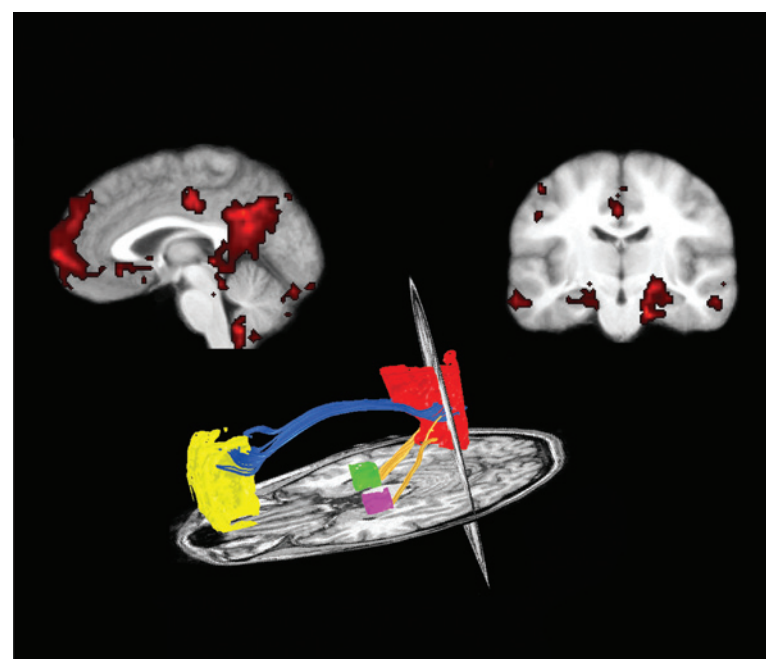


FIGURE 1: The resting-state memory network implicated in AD. Top: Resting-state functional connectivity in a group of 6 subjects. (L) Sagittal view of the PCC/RSC and MPFC clusters and (R) coronal view of the MTL clusters. Bottom: Structural connections (DTI fiber tractography). Yellow= medial frontal cortex (MPFC); Red= posterior cingulate cortex/retrosplenial cortex (PCC/RSC); Yellow tracts connect the bilateral medial temporal lobes (MTL) to the PCC/RSC; Blue tracts indicate the cingulum bundle connecting the MPFC to the PCC/RSC.

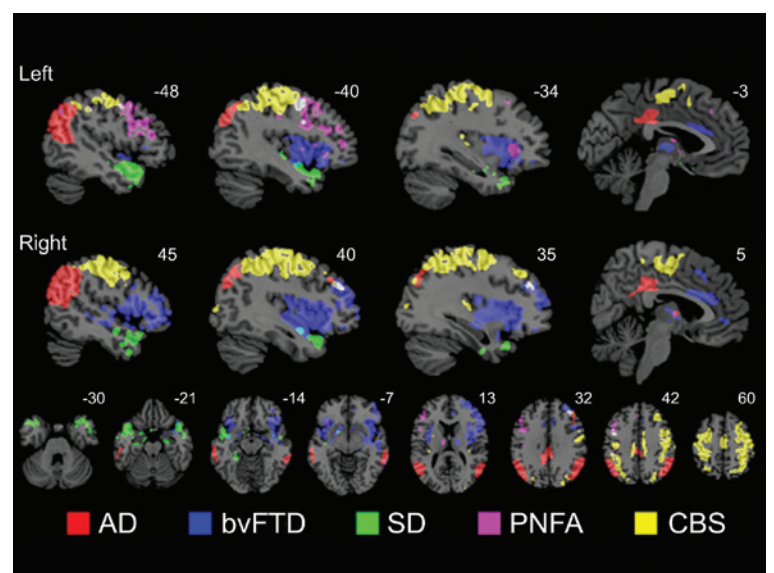


FIGURE 2: Colored regions highlight voxels found both in resting-state networks and maps of disorder-specific atrophy.

AD=Alzheimer's Disease; bvFTD= behavioral variant frontotemporal dementia; SD=semantic dementia; PNFA=progressive nonfluent aphasia; CBS=corticobasal syndrome.

Using Resting-state fMRI to Identify Brain Circuitry Abnormalities in Parkinson's Disease

Dr. Kathleen Poston, Assistant Professor of Neurology and Neurological Sciences and Neurosurgery at Stanford University School of Medicine, researches the application of both traditional event-related fMRI and resting-state fMRI to cognitive impairment in Parkinson's Disease (PD). The etiology of cognitive impairment in PD and the associated brain networks affected by the disease are still poorly understood. Once a lesser-recognized symptom than the motor disabilities that typically characterize PD, cognitive dysfunction and its early diagnosis increase in importance as patients survive longer and as treatments for motor symptoms continue to improve. More than 80% of patients 20 years into their PD diagnosis fit the criteria for dementia and up to a quarter have mild cognitive deficits at the time of diagnosis.

“Identifying connectivity abnormalities in PD will help us understand how and why cognitive impairment evolves.”



Kathleen Poston, MD, MS

Resting-state fMRI enables Dr. Poston to examine brain circuitry in PD patients with varied combinations of cognitive and motor impairment. Her multilateral approach also uses traditional event-related fMRI to clarify the cognitive roles of the basal ganglia and dopamine receptors in PD, testing with tasks that have fairly-well recognized effects and loci but little-understood mechanisms. Dr. Poston's goal is to identify connectivity abnormalities associated with PD and then to use these biomarkers to study how and why cognitive impairment evolves. ■

Advances in 7-Tesla MRI Technology Lead to Insights About Alzheimer's Disease

When it comes to understanding how Alzheimer's disease starts in the brain, one scientist at Stanford is going straight to the source: Geoffrey A. Kerchner, MD, PhD, Assistant Professor of Neurology and Neurological Sciences, studies the hippocampus in patients with Alzheimer's disease. Pathologists know from studying autopsy specimens that the hippocampus is one of the first brain areas to undergo neurodegenerative changes in Alzheimer's disease, starting even before the first symptoms emerge. Dr. Kerchner wants to be able to see these changes noninvasively in living humans, and with the help of a 7-Tesla MRI machine, he has gotten his first glimpse (figure 1). This ultra-strong magnet — about 140,000 times as strong as the Earth's magnetic field — yields spectacular images of the human brain at a resolution of about one fifth of a millimeter.

“The 7-Tesla's ultra-strong magnet— about 140,000 times as strong as the Earth's magnetic field— yields spectacular images of the human brain at a resolution of about 1/5 of a millimeter.”



Geoffrey A. Kerchner, MD, PhD

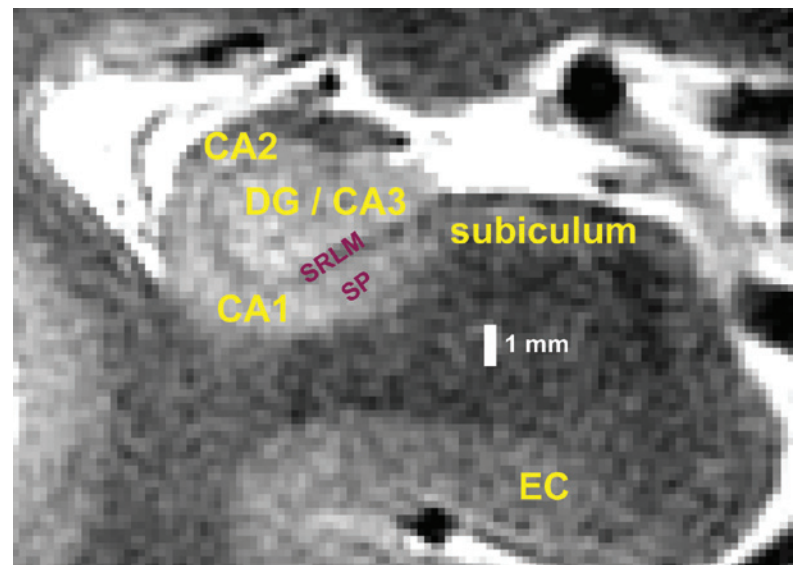
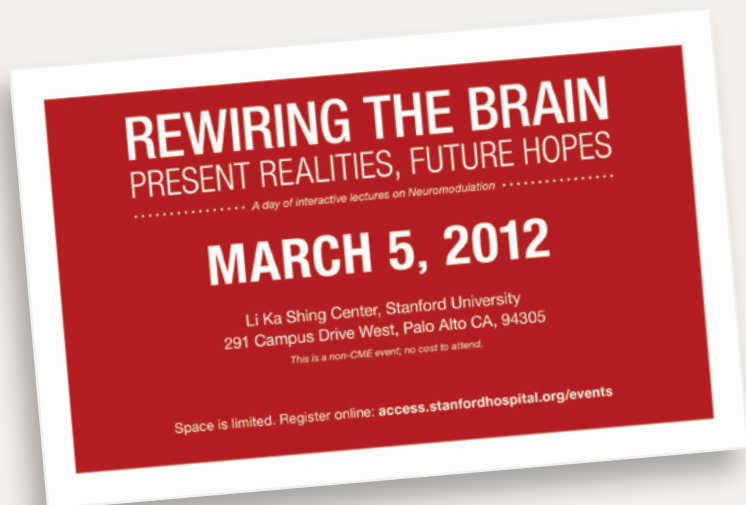


FIGURE 1: Illustrated here is a portion of a 7-Tesla MRI slice centered on the right hippocampus of a patient with Alzheimer's disease. The dentate gyrus (DG), cornus ammonis (CA) fields 1–3, the subiculum, and the entorhinal cortex (EC) are labeled, along with the stratum pyramidale (SP) and stratum radiatum / lacunosum-moleculare (SRLM) portions of CA1. It is in the SRLM that Kerchner has observed early atrophy in patients with mild Alzheimer's disease.

Dr. Kerchner has observed that among a group of patients with mild Alzheimer's disease, the only discernable imaging finding that differentiates them from age-matched normal controls is shrinkage of the CA1 apical neuropil — a tiny area of the hippocampus enriched in highly plastic synapses that are known to be important for learning and memory.¹ Using that finding as a starting point, Dr. Kerchner's research focuses on how microstructural features of the hippocampus correlate with neuropsychological measures of memory performance, and whether 7-Tesla MRI technology may be useful in the early diagnosis of Alzheimer's disease. ■

See the sidebar to the right for the cited reference.



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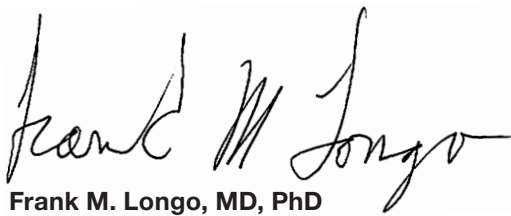
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Frank M. Longo, MD, PhD

George E. and Lucy Becker Professor

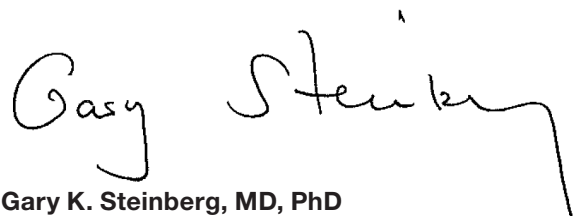
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As we continue to add faculty with diverse areas of expertise we look forward to the further expansion of our clinical programs in Neuromuscular Disease, Headaches, Neuro-Oncology/Brain Tumors and Spinal Disorders. Providing the very best care, service and groundbreaking therapies is our mission as clinicians, researchers and educators.

The Departments of Neurology and Neurosurgery and Stanford Hospital and Clinics are committed to meeting the needs of our referring physicians. Please contact our referral center at **1.800.800.1551**. As always our faculty will be receptive to your questions. To speak with us directly please call the numbers below. As we continue to share our Stanford updates through this newsletter we welcome the opportunity to collaborate with you on clinical trials, fundamental research and new therapeutic strategies.

Please join us at the 2011 Stanford Neuroscience CME course October 7th and 8th in the beautiful city of San Francisco where we will present additional clinical and research updates.



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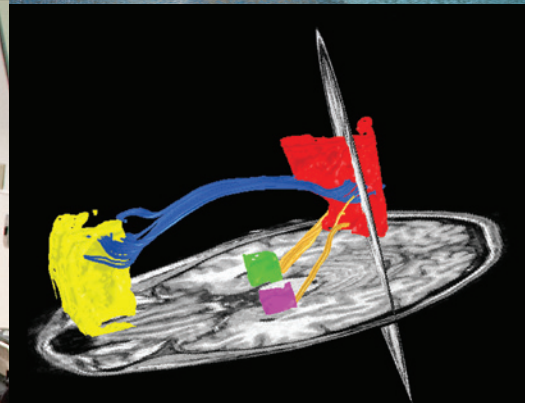
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