

University of California
San Francisco

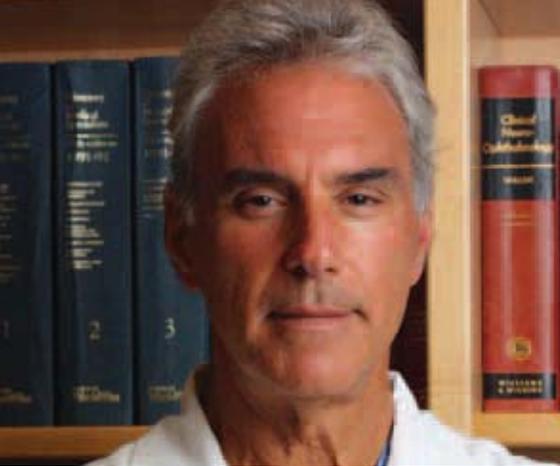
UCSF

Neurological Surgery

the department of neurological surgery at ucsf

A photograph of two surgeons in an operating room. They are wearing blue scrubs, blue surgical caps, and masks. They are focused on a patient lying on the table. The room is dimly lit, with two large overhead surgical lamps providing bright light. A monitor in the background displays the number 47. The overall atmosphere is professional and clinical.

2011 year in review



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Dear Colleague,

I am pleased to share with you some of the major achievements the Department of Neurological Surgery at UCSF has made over the past year. We were once again listed in the top five neurosurgery programs—and best on the West Coast—on *U.S. News & World Report's* annual list of Best Hospitals, and in January reporters from *U.S. News & World Report* spent two days at UCSF to watch our neurosurgical teams in the operating room (pages 18 and 20). The resulting 7-page news feature was published in the *U.S. News & World Report* special edition “Secrets of Your Brain,” and highlights new methods for surgically treating movement disorders, epilepsy, and brain tumors.

Among the many honors presented to our faculty in 2011, I would like to recognize the NIH Director's New Innovator Award given to Edward Chang MD for his work in brain mapping of speech function. Dr. Chang is the co-director of the year-old Center for Neural Engineering & Prosthesis at UC Berkeley/San Francisco (CNEP, page 33) and the ultimate goal of his New Innovator work is to develop a neuroprosthetic speech synthesizer for patients who cannot communicate due to severe paralysis. He joins UCSF neurosurgeon and scientist Daniel Lim MD, PhD as two of only 216 awardees since 2007. This year Dr. Lim was also selected to be a U.S. National Academy of Sciences Kavli Fellow and speaker at the 22nd annual Frontiers of Science symposium. This honor is given in recognition of scientific achievement for those under 45 years of age (or less than 15 years since completion of their PhD). These two faculty members exemplify the caliber of physician that distinguishes UCSF Neurosurgery worldwide.

letter from the chair

While our reputation for innovation continues to grow internationally, we are also expanding our services closer to home. The Department has established the new Center for the Management & Surgery of Peripheral Nerve Disorders, led by Michel Kliot MD, who brings a phenomenal expertise in this subspecialty to UCSF (page 23). This year we have also opened community extension clinics and began providing hospital services at Marin General Hospital in Marin, Queen of the Valley Hospital in Napa Valley, and Saint Francis Hospital and St. Mary's Medical Center in San Francisco. As our connections to the surrounding community grow stronger, we will continue to lead neurosurgery in patient care, research, and education in the years to come.

Mitchel S. Berger,
MD, FACS, FAANS

Kathleen M. Plant Distinguished Professor
and Chairman

Department of
Neurological Surgery

Director, UCSF
Brain Tumor Center



brain tumor center at ucsf

Faculty

Adult Neuro-Oncology

Nicholas Butowski MD

Susan Chang MD

Jennifer Clarke MD

Michael Prados MD

Adult Brain Tumor Surgery

Manish Aghi MD, PhD

Mitchel Berger MD

Edward Chang MD

Sandeep Kunwar MD

Michael McDermott MD

Andrew Parsa MD, PhD

Neuropsychology

Caroline Racine PhD

BTRC Laboratories

Manish Aghi MD, PhD
 oncolytic viral therapies,
 vascular biology of glioma

Arturo Alvarez-Buylla PhD
 developmental neuroscience;
 stem cell biology

Krystof Bankiewicz MD, PhD
 convection-enhanced drug delivery
 systems; gene therapy

Mitchel Berger MD
 brain mapping; molecular and
 genetic basis of brain tumors

Gabriele Bergers PhD
 angiogenesis; tumor invasion

Soonmee Cha MD
 perfusion magnetic resonance imaging

Joseph Costello PhD
 functional genomics

Nalin Gupta MD, PhD
 pediatric brain tumors;
 cell-cell interactions

Daphne Haas-Kogan MD
 apoptosis; genetic mutations;
 therapeutic irradiation enhancement

C. David James PhD
 molecular biology of CNS
 cancers; rodent model testing
 of experimental therapies

Andrew Parsa MD, PhD
 immunotherapy

Claudia Petritsch PhD
 brain cancer stem cells;
 asymmetric stem cell division;
 novel tumor suppressor genes

Joanna Phillips MD, PhD
 neuropathology; interaction between
 tumor cells and the microenvironment

Russell Pieper PhD
 signal transduction; models of human
 gliomagenesis and drug resistance

David Rowitch MD, PhD
 central nervous system
 development; tumorigenesis

William Weiss MD, PhD
 mouse models of human brain tumors

John Wiencke PhD
 biomarker development and application
 in brain tumor etiology

Margaret Wrensch MPH, PhD
 genetic and molecular epidemiology
 of adult glioma

Shichun Zheng PhD
 molecular neuroepidemiology



Otolaryngologist Ivan El-Sayed and neurosurgeon Manish Aghi use endoscope to access a chordoma of the skull base.



Minimally Invasive Skull Base Surgery Center

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

less morbidity and shorter recovery times for patients. This has made it an increasingly attractive option for removing skull base tumors, and the volume of MISB surgery cases at UCSF has increased by thirty percent in the last year. Center physicians are currently analyzing outcomes after long-term follow-up to compare them with outcomes of open procedures. They are also collecting tissue samples from patients to design animal models of skull base tumors, such as chordomas, for laboratory research.

In April 2012, the third annual Antero-Lateral Skull Base Approaches course will be available for 13 neurosurgical residents and 13 otolaryngology residents. Sponsored by the medical device company Stryker, residents will be given a comprehensive series of didactic lectures and case discussions on open and endoscopic approaches to the skull base, as well as an opportunity to examine these approaches in an anatomy lab. For information, visit <http://misb.ucsf.edu>.

The UCSF Center for Minimally Invasive Skull Base Surgery

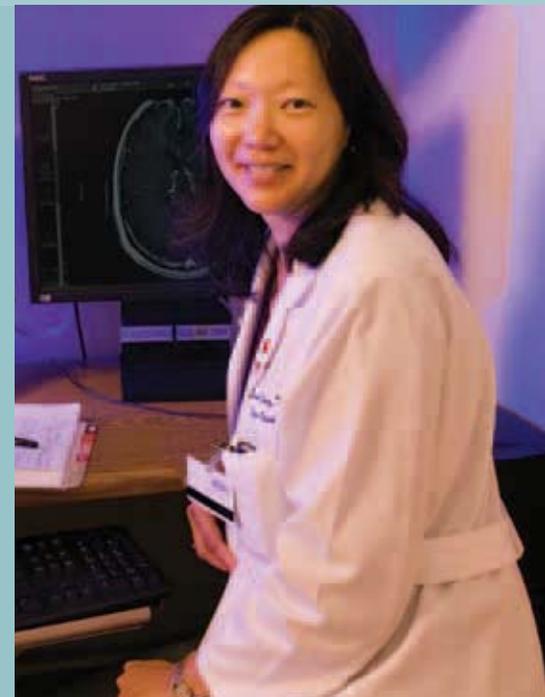
The UCSF Center for Minimally Invasive Skull Base (MISB) Surgery combines the expertise of neurosurgeons and otolaryngologists to apply endoscopic technology to the removal of tumors in the head and neck, skull base, and intracranial compartment. The technique provides extent of resection that is comparable to an open procedure, but with

UCSF Neuro-Oncologists Have Highest Patient Satisfaction Scores

The Neuro-Oncology Service was awarded the UCSF Medical Center Pinnacle Award for the fourth consecutive year. This award recognizes the UCSF medical service with the best patient satisfaction scores for outpatient care.



Neuro-oncologists Michael Prados, Jennifer Clarke, and Nicholas Butowski



Director of Neuro-Oncology, Susan Chang MD



Mitchel Berger, professor and chair of the Department of Neurological Surgery, left, talks about caring for patients with brain cancer and their caregivers during a panel discussion featuring Vicki Kennedy, right.



Vicki Kennedy discusses caring for her late husband, Senator Edward Kennedy, who died of brain cancer.

The UCSF Brain Tumor Center Kicks Off Initiative to Integrate Support for Caregivers into Treatment for Patients

Brain tumor specialists at UCSF are aiming to improve care for their patients by actively involving patients' families, friends and others who take a central role in helping their loved ones through brain cancer. There is evidence that engaging caregivers can improve outcomes for patients. But engaging caregivers means supporting them as well, since the emotional toll and burden of responsibility that falls onto a caregiver's shoulders can be overwhelming.

Earlier this year, Susan Chang MD, director of the UCSF Neuro-Oncology Program, and her colleagues published a report on a major clinical study outlining the needs caregivers experience as they help their loved ones through treatment for a brain tumor. One of the main issues caregivers identified was the need to have comprehensive but easily-digestible information available to help them understand the disease, its treatment and the ways in which they can help their loved ones. Many of the study participants reported feeling untrained and unprepared for their new roles.

Guided by the findings of the report, the Department of Neurological Surgery has been exploring ways to build better support for caregivers into the standard of care for brain tumor patients. They have been aided by three unique volunteers—Randi Murray, Marritje Greene, and Cathy Podell—who have begun a \$25 million fundraising campaign for brain tumor research and caregiver support. These three philanthropists

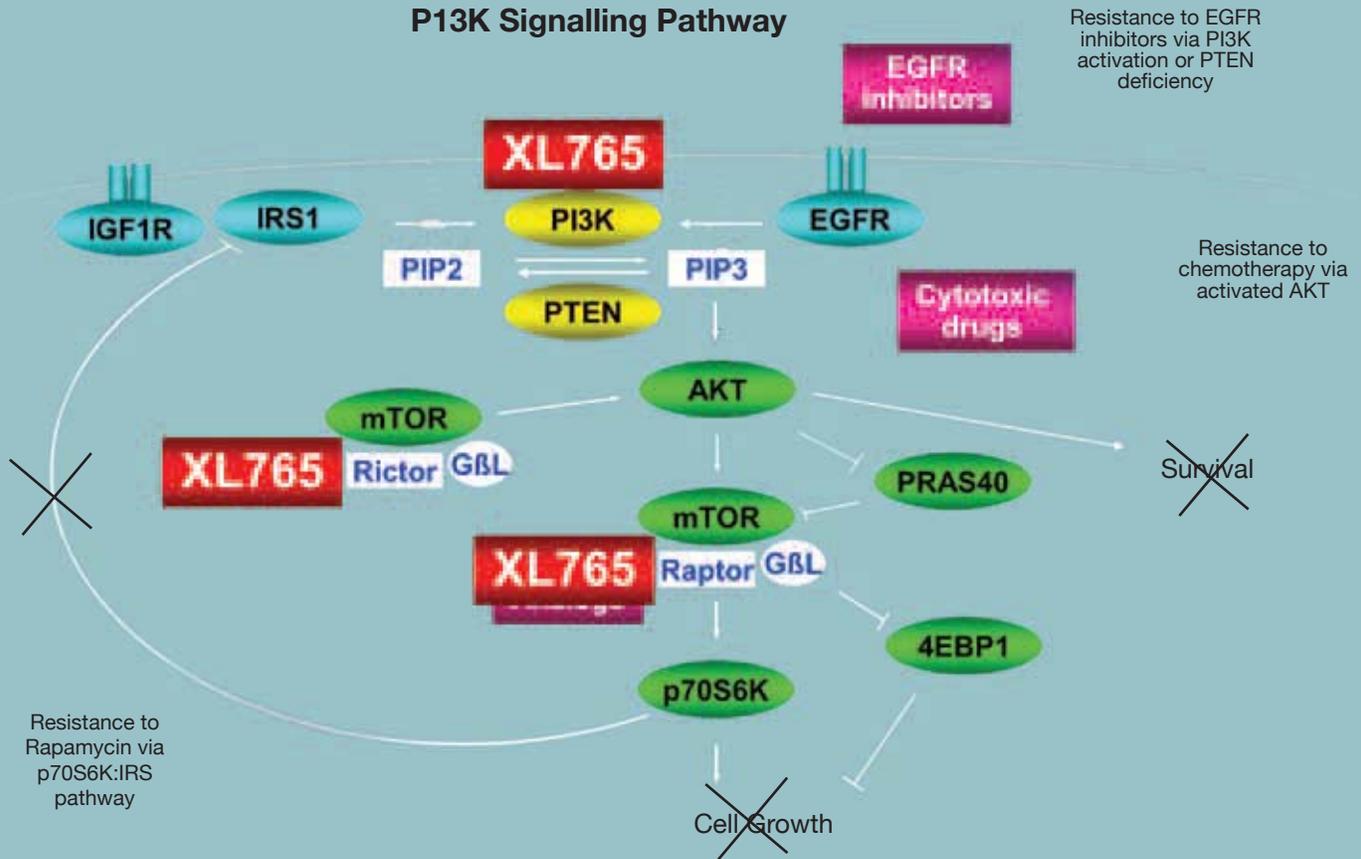
have all been deeply affected by cancer and recognized that the caregiver initiative would be one way to make an immediate and significant impact in the lives of patients and their families.

The new initiative will include:

- Additional nurses, social workers, and patient relations liaisons to assist both patients and caregivers with specific issues that arise
- Information resources for patients and caregivers to help them know what to expect and help them through the treatment process
- A new training program to help UCSF faculty and staff build stronger relationships with patients and their caregivers
- A Family Advisory Panel to identify the most helpful programs in the future.

The first Family Advisory Panel was held in October and headlined by Vicki Kennedy, an attorney, health care reform advocate, and caregiver. For 15 months Mrs. Kennedy was caregiver to her late husband, Senator Edward M. Kennedy, while he battled brain cancer. Other panelists who described the importance of addressing the needs of caregivers included neurosurgeon Mitchel Berger MD, professor and chair of neurological surgery; neuro-oncologist Jennifer Clarke MD; clinical nurse and brain tumor survivor Stayce Sullivan RN; and clinical nurse specialist Margaretta Page RN, MS.

P13K Signalling Pathway



The PI3K pathway plays important roles in tumor cell proliferation and survival, and is a promising therapeutic target for cancer.

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New in Clinical Trials for Brain Tumors

Ivy Foundation Trials Open in 2011

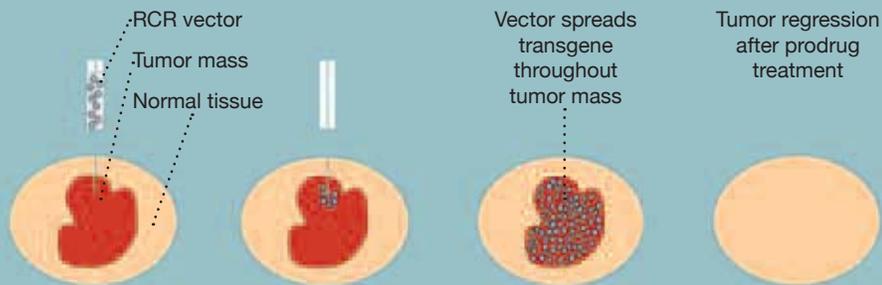
The Ben and Catherine Ivy Foundation has funded a consortium of six institutions, led by the Brain Tumor Center at UCSF, to perform small, enriched-patient clinical trials of molecularly targeted therapies for GBM. In addition to UCSF, the consortium includes MD Anderson, Dana Farber, UCLA, Memorial Sloan Kettering, and University of Utah. In its first year, the group has opened two clinical trials and a third is slated to open in 2012.

The first two trials tested agents that target the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) molecular cascade, which is frequently dysregulated in GBM. The dual mTOR/PI3K inhibitor XL765

was tested in patients with recurrent GBM and investigators compared its pharmacodynamic properties and distribution in tissue to that of the single PI3K inhibitor XL147. The trial is now completed and tissue analyses are currently underway to determine if a dual inhibitor targets the pathway more effectively than a single inhibitor. A second mTOR/PI3K inhibitor—BKM120—is currently being tested in patients with recurrent GBM.

The third Ivy Foundation trial at UCSF will open in 2012 to test the compound PLX3397, which inhibits Kit and Flt3. These targets are key components of the FMS pathway that is overexpressed in glioma and is involved in the processes of angiogenesis and invasion.

Prasad G, Sottero T, Yang X, Mueller S, James CD, Weiss WA, Polley M-Y, Ozawa T, Berger MS, Aftab DT, Prados MD, Haas-Kogan DA. Inhibition of PI3K/mTOR pathways in glioblastoma and implications for combination therapy with temozolomide. *Neuro-Oncol* 2011;13(4):384-92.



Phase I Trial of Toca 511 for Patients with Recurrent Glioblastoma Multiforme

The most serious drawbacks to chemotherapeutics for brain tumors are the levels of systemic toxicity and side effects that patients can experience as a result. In a new multi-center phase I trial for recurrent glioblastoma, a treatment regimen with strong anti-tumor activity is also giving patients fewer side effects.

Patients take the non-toxic oral drug 5-fluorocytosine (5-FC) and then a retrovirus carrying the enzyme cytosine deaminase (CD) is injected directly into the tumor. The virus spreads throughout the tumor by replicating itself in dividing tumor cells, while the CD it carries converts the 5-FC that has accumulated in the tumor cells into cytotoxic 5-fluorouracil (5-FU).

Manish Aghi MD, PhD, principal investigator, describes the regimen as combining the best of both chemotherapy and gene therapy. Toca 511 is selective for tumor cells and CD very efficiently converts oral 5-FC into 5-FU, but the retrovirus does not illicit an immune response, which has been a

problem for some gene therapies. The microenvironment created by the tumor to conceal itself from immune surveillance also appears to cloak the retrovirus, preventing elimination by the immune system.

The Toca 511 regimen might be especially beneficial for older patients or those with too many comorbidities to undergo an extensive craniotomy. These patients are generally excluded from clinical trials, but make up a substantial proportion of the population needing treatment.

The trial has been developed by Tocagen Inc. and study sites include UCSF, UCLA, UCSD, and Cleveland Clinic. The Brain Tumor Center at UCSF is currently halfway through the phase I component with encouraging initial results. A continuation protocol for patients enrolled in the phase I trial is in development. For more information or to enroll a patient, contact the Neuro-Oncology nursing line at 415.353.2652.

nonneoplastic/asymmetric



Asymmetrical cell division of oligodendrocyte progenitor cells is regulated by the segregation of the proteoglycan NG2 during cell division. Loss of the ability

tumor/symmetric



to divide asymmetrically is an early step in the neoplastic transformation of oligodendrocyte progenitor cells into oligodendroglioma.

Brain Tumor Research Center

New Insights into the Origin of Oligodendroglioma and how Oligodendrocyte Progenitor Cells Become Cancerous

New studies from the Brain Tumor Research Center (BTRC) laboratory of William A. Weiss MD, PhD have suggested the origin of oligodendroglioma is a progenitor cell, rather than a neural stem cell. Neural stem cells have been described as the cell of origin for other, more aggressive, types of glioma. This distinction explains why oligodendroglioma is more sensitive to treatment than other types of glioma and gives researchers new cellular pathways to target in developing therapies. While neural stem cells lie dormant and rarely divide, progenitor cells actively divide in the brain, making them susceptible to therapies that can target dividing cells.

Persson AI, Petritsch C, Swartling FJ, Itsara M, Sim FJ, Auvergne R, Goldenberg DD, Vandenberg SR, Nguyen KN, Yakovenko S, Ayers-Ringler J, Nishiyama A, Stallcup WB, Berger MS, Bergers G, McKnight TR, Goldman SA, Weiss WA. *Cancer Cell* 2010;18(6):669-82.

But how do oligodendrocyte progenitors stray from the path of becoming mature oligodendrocytes to become oligodendrogliomas? That question is being answered in the laboratory of Claudia Petritsch PhD, who has discovered that oligodendroglioma cells isolated from surgical tumor specimens lose their ability to divide asymmetrically and thus to produce differentiated daughter cells. Instead, they undergo aberrant symmetric divisions. The switch from asymmetric to symmetric divisions is associated with increased proliferation and a failure of cells to enter quiescence. It is emerging as a hallmark of tumorigenic precursors. Dr. Petritsch and her colleagues used genetically engineered mice to identify that epidermal growth factor receptor and a protein called NG2 control this switch, and they are working on ways to target genes that regulate the process as a way of treating oligodendroglioma and perhaps other brain tumors. Because the loss of asymmetric cell division occurs before the tumor forms, it may provide a point to intervene in the process of tumor initiation.

Sugiarto S, Persson AI, Munoz EG, Waldhuber M, Lamagna C, Andor N, Hanecker P, Ayers-Ringler J, Phillips J, Siu J, Lim DA, Vandenberg S, Stallcup W, Berger MS, Bergers G, Weiss WA, Petritsch C. Asymmetry-defective oligodendrocyte progenitors are glioma precursors. *Cancer Cell* 2011;20(3):328-40.



California Institute for Regenerative Medicine Funds Key Research for Brain Tumors at UCSF

In April of 2010, the UCSF Department of Neurological Surgery received an award from The California Institute for Regenerative Medicine (CIRM) for studying genetically modified stem cells for treating patients with recurrent glioblastoma. Working with collaborators at four other California institutions, UCSF Brain Tumor Research Center investigators have been analyzing stem cells that express cytosine deaminase (CD), which converts the nontoxic prodrug 5-fluorocytosine into the cytotoxic compound 5-fluorouracil. Early research for this project has shown comparable anti-tumor activity for CD-modified mesenchymal and neural stem cells, and continued effort is warranted for optimizing this exciting therapeutic approach.

This year, CIRM awarded \$1.8 million to the laboratory of BTRC investigator Daniel Lim MD, PhD, to improve cell transplantation therapies. Current technology to deliver stem cells to the brain consist of syringe and needle devices that require multiple brain penetrations and do not effectively distribute the cells. Dr. Lim and his colleagues are working to develop a device that can distribute cells to large brain areas through a single, initial brain penetration.

UCSF Establishes Tumor Microenvironment Network Center Focusing on Role of Vascular Niche and Force in GBM Aggression

This year, UCSF was one of only two institutions to receive an NIH Tumor Microenvironment Network grant (TMEN U54) for the study of brain tumors. The NIH awarded the grant to Gabriele Bergers PhD, professor of neurological surgery, and Valerie Weaver PhD, professor of surgery and anatomy, to establish the UCSF TMEN Brain Cancer Center (TMEN-BCC), a multidisciplinary, multi-institutional initiative directed toward improving understanding of the biophysical and molecular dialogue of glioma cells and the brain microenvironment.

The TMEN-BCC encompasses three projects. Project 1, led by Dr. Bergers, will investigate the regulation and function of the vascular niche in glioma, specifically the role of perivascular immune cells in regulating angiogenesis and tumor cell maintenance. Dr. Bergers' project also aims to identify vascular niche-produced factors that can promote an epithelial-to-mesenchymal-like acquisition and mesenchymal phenotype in glioblastoma (GBM) cells.

Project 2, overseen by William Weiss MD, PhD, professor of neurology, pediatrics, and neurological surgery, and Anders Persson PhD, assistant adjunct professor of neurology, will investigate the regulation and function of the vascular niche in glioma recurrence, especially following radiation therapy. Their project will focus on the potential contributions of infiltrating microglia, mechanical force, and b1-integrin signaling.

Dr. Weaver will direct Project 3, looking at the interplay between intrinsic and extrinsic force and glioma pathogenesis, particularly whether a mechanically challenged landscape and mechano-phenotype, as well as hyaluronan-induced changes, can drive GBM aggression. Project 3 will also determine whether tissue force and the GBM mechano-phenotype foster the vascular niche. TMEN-BCC projects will be supported by three cores with expertise in pathology, imaging, biochemistry, bioengineering, and project management.

Faculty

Sandeep Kunwar MD, Surgical Director

Lewis Blevins Jr. MD, Medical Director

Manish Aghi MD, PhD



california center
for pituitary disorders



Patient Suzanne Moreno with neurosurgeon Sandeep Kunwar.

“Being diagnosed with a pituitary brain tumor can be a very devastating experience for an individual and their family. However, there is expert help out there for you at the UCSF California Center for Pituitary Disorders. Having experienced surgery twice now at UCSF for this condition, I can say with all certainty that you will always be treated with the highest dignity, respect, and care.”

– Suzanne Moreno

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In 2011, the California Center for Pituitary Disorders (CCPD) celebrated four years of excellence as a multidisciplinary center dedicated to providing comprehensive care to patients with pituitary disorders. Bringing together a variety of specialists, the CCPD achieves high remission rates in patients with hormone-secreting neoplasms, complete surgical removal of a majority of pituitary tumors, and a low incidence of postoperative complications such as hypopituitarism and diabetes insipidus. The physicians at the CCPD include experts in neurosurgery, neuroendocrinology, radiation oncology, neuropathology, neurology, neuro-ophthalmology, and psychiatry. Many faculty members are involved in basic and clinical research for pituitary disorders, including outcomes research that has provided new guidelines for patient care.

News Highlights from 2011:

- CCPD co-directors Sandeep Kunwar MD and Lewis Blevins MD have been recognized on the Best Doctors in America 2011-2012 list. The CCPD was also included in Marin Magazine’s 2011 issue on Best Doctors.

- “Cushing’s Disease: Unraveling a Medical Mystery” – The PBS series Healthy Body Healthy Mind featured Dr. Blevins, who discussed common misdiagnoses and treatment for Cushing’s Disease. The episode can be accessed online at <http://bit.ly/qkLhIY>.

- Patient Tanya Argus had been battling gigantism resulting from acromegaly for 16 years when she came to the CCPD for help. After treatment with new medications and dosing, she is finally showing signs of improvement. abc 7 News (KGO-TV) chronicled her story and you can follow online at <http://bit.ly/aQQxcl> and <http://bit.ly/mXuimz>.

- “Treating Acromegaly” – KNTV Bay Area interviewed a patient with acromegaly who travels to the CCPD to receive ongoing therapy after surgery, which keeps any remaining hormonal dysfunction under control.

Pituitary Disorder Education

The physicians at the CCPD are committed to education and host the annual continuing medical education course “Pituitary Disorders: Diagnosis and Management” in San Francisco to provide the latest updates in the field (www.cme.ucsf.edu). CCPD faculty are also available to speak at conferences, seminars, and grand rounds.

Recent Publications from the CCPD

Jahangiri A, Lamborn KR, Blevins L, Kunwar S, Aghi MK. Factors associated with delay to pituitary adenoma diagnosis in patients with visual loss [published online ahead of print July 8, 2011]. *J Neurosurg*. DOI: 10.3171/2011.6.JNS101663.

Jahangiri A, Molinaro AM, Tarapore PE, Blevins L Jr, Auguste KI, Gupta N, Kunwar S, Aghi MK. Rathke cleft cysts in pediatric patients: presentation, surgical management, and postoperative outcomes. *Neurosurg Focus* 2011;31(1):E3.

Oh MC, Aghi MK. Dopamine agonist-resistant prolactinomas. *J Neurosurg* 2011;114(5):1369-79.

Potts MB, Jahangiri A, Lamborn KR, Blevins LS, Kunwar S, Aghi MK. Suprasellar Rathke’s Cleft Cysts: Clinical Presentation and Treatment Outcomes [published online ahead of print June 11, 2011]. *Neurosurgery*. DOI: 10.1227/NEU.0b013e318228bcea.

Sughrue ME, Chang EF, Gabriel RA, Aghi MK, Blevins LS. Excess mortality for patients with residual disease following resection of pituitary adenomas. *Pituitary* 2011;14(3):276-83.

Tarapore PE, Sughrue ME, Blevins L, Auguste KI, Gupta N, Kunwar S. Microscopic endonasal transsphenoidal pituitary adenectomy in the pediatric population. *J Neurosurg Pediatrics* 2011;7(5):501-9.

Faculty

Neurotrauma,
San Francisco General Hospital

Geoffrey Manley MD, PhD

Michael Huang MD

Shirley Stiver MD, PhD

Vincent Wang MD, PhD

BASIC Laboratories

Michael Beattie PhD
central nervous system repair

Jacqueline Bresnahan PhD
central nervous system repair

Adam Ferguson PhD
traumatic brain and spinal cord injury

John Fike PhD
neurogenesis and traumatic brain injury

Jialing Liu PhD
neurogenesis and functional recovery

Geoffrey Manley MD, PhD
basic, translational, and
clinical traumatic brain injury research

Linda Noble-Haesslein PhD
traumatic brain and spinal cord injury

S. Scott Panter PhD
cellular injury following stroke and
hemoglobin-based neurological injury

Susanna Rosi PhD
chronic neuroinflammation; learning and memory

San Francisco General Hospital Receives Nation's First Traumatic Brain Injury Certification

San Francisco General Hospital (SFGH) — a Level 1 Trauma Center — has become the first in the country to gain certification for traumatic brain injury. After a rigorous on-site survey in September 2011, the designation from the Joint

Commission recognizes the clinical excellence and research leadership at SFGH in the field of treatment for traumatic brain injury. The hospital will now serve as a model for other hospitals that seek the new Joint Commission certification.

brain & spinal injury center





Patient advocate Roman Reed tours the laboratories of the UCSF Brain and Spinal Injury Center.

Raising Awareness for Traumatic Brain Injury

Traumatic brain injury is becoming increasingly recognized as an undertreated condition and a major public health issue. In 2011, Geoffrey Manley MD, PhD, chief of neurosurgery at SFGH and co-director of the UCSF Brain and Spinal Injury Center (BASIC), was interviewed on over 30 national media programs, including the *Today Show*, *Good Morning America*, *Sports Illustrated*, *USA Today*, and the *San Francisco Chronicle*. Dr. Manley discussed topics ranging from the consequences of concussion sustained during sports to the aggressive treatment and rehabilitation process following serious traumatic brain injury.

For the PBS special “Sideline: Sports Concussions,” reporters came to UCSF to learn how researchers at BASIC are applying the latest in MRI and diffusion tensor imaging techniques to visualize how white matter connections break with specific types of brain injuries. The next step will be to correlate those breaks with symptoms such as memory loss, depression, and cognitive decline. To watch the episode, visit: <http://science.kqed.org/quest/video/sideline-sports-concussions>.

As one of the nation’s top programs for treatment of traumatic brain injury, the UCSF Brain and Spinal Injury Center is leading studies to better define traumatic brain injury and to standardize classification schemes and treatment regimens across the country.

Department Gains First Accredited Fellowship in Neurotrauma and Neurocritical Care

The Society of Neurological Surgeon’s Committee on Accreditation of Subspecialty Training has granted the Department of Neurological Surgery at UCSF the first accredited Neurotrauma and Neurocritical Care Fellowship in the nation. The fellowship is based at SFGH. Fred Stephens MD will be the first graduate of the newly accredited program.

New Clinically Relevant Models of Contusion and Spinal Cord Injury

The lack of new therapies emerging from studies of traumatic brain and spinal cord injury has been a point of frustration

for many scientists, patients, and advocates. In an effort to more effectively translate laboratory findings into therapies, new models of contusion and spinal cord injury in monkeys have been developed in the BASIC laboratory of Jacqueline Bresnahan PhD, and are supported by a recent award from the C.H. Neilsen Foundation and the Department of Veterans Affairs. These models will give researchers the opportunity to test new therapeutics in a setting that closely mimics the biology of humans with central nervous system injuries. This work is part of a multi-UC campus consortium of investigators from UC San Diego, Los Angeles, Irvine, Davis, and San Francisco. The group has recently been awarded a five-year continuation of a multi-PI R01 award from the NIH.

Rosenzweig ES, Courtine G, Jindrich DL, Brock JH, Ferguson AR, Strand SC, Nout YS, Roy RR, Miller DM, Beattie MS, Havton LA, Bresnahan JC, Edgerton VR, Tuszynski MH. Extensive spontaneous plasticity of corticospinal projections after primate spinal cord injury. *Nat Neurosci* 2010;13(12):1505-10.

Dr. Bresnahan and fellow BASIC investigator Michael Beattie PhD have also received a new five-year R01 award from the NIH to continue their work on the role of tumor necrosis factor in spinal cord injury and repair.

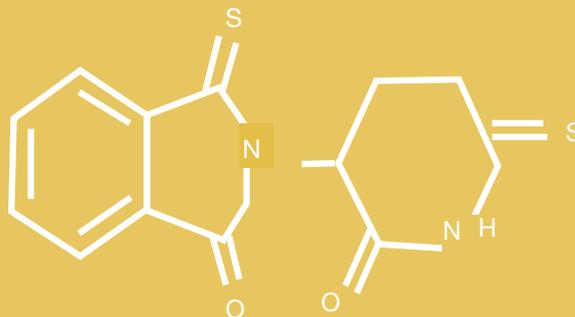
Roman Reed Visits BASIC

In September, BASIC was honored to host patient advocate Roman Reed, president of the Roman Reed Foundation, in a tour of UCSF focused on developing treatments for patients with spinal cord injury. As a result of Mr. Reed’s tireless efforts, the Roman Reed Spinal Cord Injury Research Act was passed in California, yielding \$12.5 million in state funds for scientists conducting research in spinal cord regeneration over the last 10 years.

Targeting Inflammation to Treat Alzheimer’s Disease

BASIC investigator Susanna Rosi PhD has been awarded a grant from the Alzheimer’s Association to study the role of tumor necrosis factor-alpha (TNFα) in brain inflammation that is associated with the onset of memory loss in patients with Alzheimer’s disease. She and her colleagues will test TNFα inhibitors in a rodent model of Alzheimer’s disease to determine if the treatment prevents the progression of Alzheimer’s-like pathology in the brain.

TNFα inhibitor 3,6'-dithiothalidomide

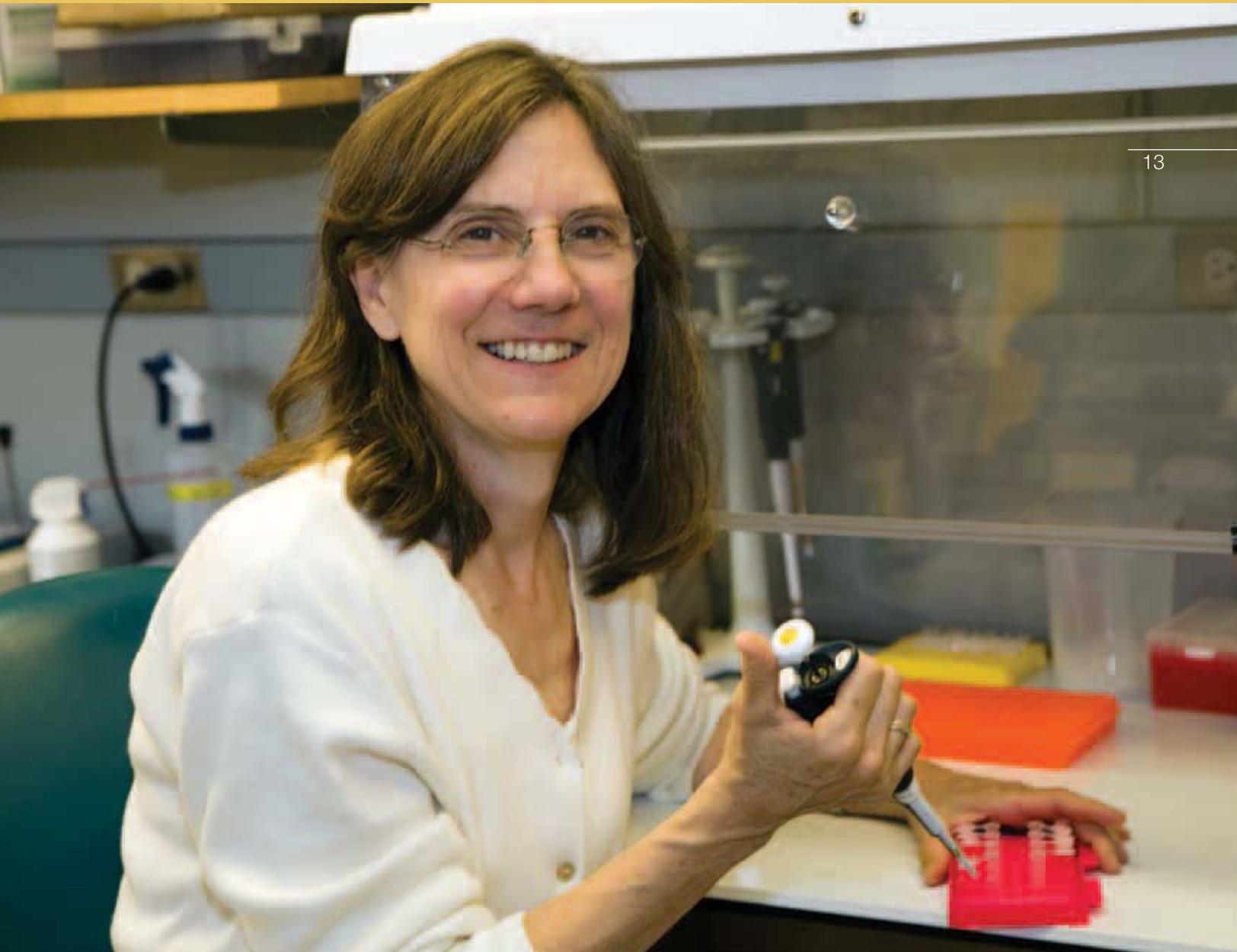


Preclinical Trial of MMP Inhibitor in a Naturally Occurring Canine Model of Spinal Cord Injury

Linda Noble-Haeusslein PhD, co-director of BASIC, is leading efforts to optimize delivery of a matrix metalloproteinase (MMP) inhibitor that could benefit both canine and human sufferers of traumatic spinal cord injuries (SCIs). Dr. Noble-Haeusslein has previously shown that an MMP inhibitor significantly improves neurologic recovery in a mouse model of SCI. Once Dr. Noble-Haeusslein's group has optimized drug delivery in this model, Jonathan Levine DVM, assistant professor at the College of Veterinary Medicine and Biomedical Sciences at Texas A&M University, will initiate a preclinical trial in dogs with naturally occurring thoracolumbar intervertebral disc herniation. Drs. Noble-Haeusslein and

Levine's nontraditional collaboration formed after Dr. Levine observed elevated levels of MMPs in the cerebrospinal fluid of dogs with naturally occurring SCIs, consistent with Dr. Noble-Haeusslein's observations in mice. Their work builds on Dr. Noble-Haeusslein's previous studies showing that a rise in MMPs early after spinal cord injury causes damage to the cord that was initially left intact after injury. It is this "secondary damage" that is likely blocked by the MMP inhibitor. If this collaboration proves successful, there will not only be a new therapy for SCI in dogs but translation of this drug to human clinical trials will be made possible. These studies, funded by a U.S. Department of Defense grant, will be completed over the next three years.

Linda Noble-Haeusslein PhD





vascular neurosurgery program

14

Faculty

Vascular Neurosurgery

Michael Lawton MD

Michael Huang MD

Michael McDermott MD (Gamma Knife Radiosurgery)

Cerebrovascular Research Laboratories

Michael Lawton MD

pathophysiology of arteriovenous malformation;
hemodynamics of aneurysms; radiation-induced arteriopathy

Jialing Liu PhD

neurogenesis and functional recovery after stroke

S. Scott Panter PhD

animal models of stroke and traumatic brain injury

William Young MD

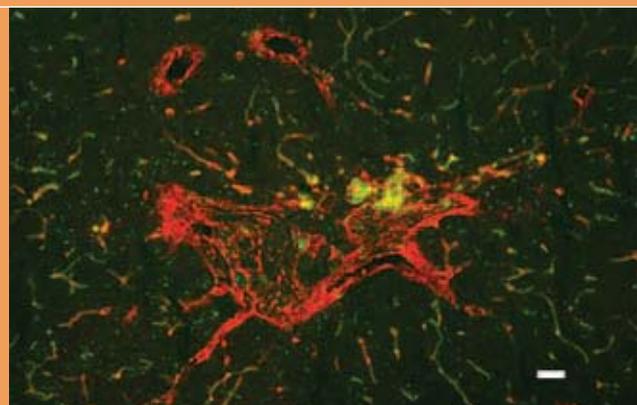
pathophysiology of arteriovenous malformation;
hemodynamics of aneurysms; predictors of brain
hemorrhage in patients with arteriovenous malformations

First Model of Arteriovenous Malformation

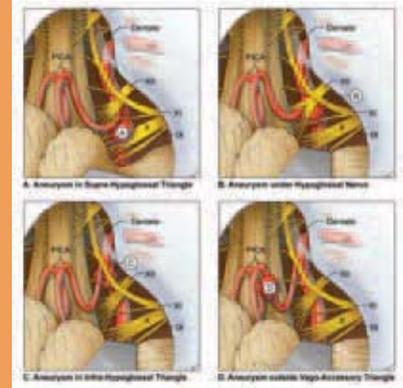
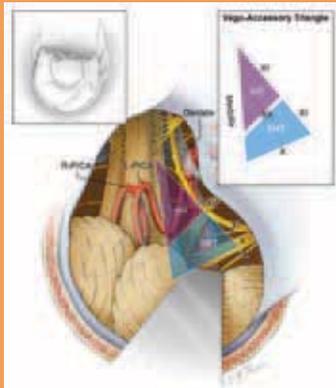
The first animal model of brain arteriovenous malformation (AVM) that recapitulates key features of the human disease was recently created at the UCSF Center for Cerebrovascular Research under the direction of William Young MD and Hua Su MD. The model manipulates the genotype known to cause the human disease hereditary hemorrhagic telangiectasia (HHT) type 2. Approximately 2% of AVMs are thought to be inherited and the vast majority of these are found with HHT.

Although AVM is widely thought to be a congenital disorder, in the new model AVMs form in adult mice, demonstrating that it may not be a developmental disease. This model will also be the first in which it will be possible to screen drugs for clinical trials.

Walker EJ, Su H, Shen F, Choi EJ, Oh SP, Chen G, Lawton MT, Kim H, Chen Y, Chen W, Young WL. Arteriovenous malformation in the adult mouse brain resembling the human disease. *Ann Neurol* 2011;69(6):954-62.



Abnormal connections between veins and arteries form in the brains of adult mice in a new experimental model of arteriovenous malformation. A large, dysplastic vascular structure is shown here; green lectin marks endothelial cells and red PDGFR β marks a profusion of pericytes covering the structure.



Anatomical triangles defining surgical routes to PICA aneurysms. Reprinted with permission from Journal of Neurosurgery, Copyright (2011).

Does Estrogen Protect Against Aneurysms?

In a new project funded by the NIH, UCSF Center for Cerebrovascular Research investigator Tomoki Hashimoto MD is studying why aneurysms occur more frequently in post-menopausal women than pre-menopausal women, and the potentially protective effect of estrogen. The results may allow us to understand more about how the body's biochemistry can influence the natural history of the disease.

Surgical Planning for Brain Arteriovenous Malformations

A recent article by the UCSF Brain Arteriovenous Malformation (BAVM) Study Project illustrated the different strategies for removing five types of AVMs defined by their location in the brain and whether or not they are superficial or deep. The authors reported surgical techniques and outcomes for 132 patients over 12 years.

Kim YB, Young WL, Lawton MT, for the UCSF BAVM Study Project. Parafalcine and midline arteriovenous malformations: Surgical strategy, techniques, and outcomes. *J Neurosurg* 2011;114(4):984-93.

Complex Bypasses for Aneurysms

Giant intracranial aneurysms of the anterior communicating artery have a number of characteristics that make them difficult to treat with standard clipping and coiling methods. A common option is to "trap" the aneurysm and occlude it, but recurrence rates tend to be high. In 2011, Chief of Vascular Neurosurgery Michael Lawton MD and his colleagues introduced the azygos anterior cerebral artery bypass, which offers a new option for occluding these aneurysms indirectly.

Mirzadeh Z, Sanai N, Lawton MT. The azygos anterior cerebral artery bypass: double reimplantation technique for giant anterior communicating artery aneurysms. *J Neurosurg* 2011;114(4):1154-8.

Dr. Lawton and his colleagues have also introduced the vertebral artery-posterior inferior cerebellar artery bypass for hemorrhagic dissecting aneurysms of the vertebral

artery. Although these aneurysms are usually treated with endovascular occlusion, the new bypass technique can be used for complicated cases, such as those in which the posterior inferior cerebellar artery originates from the aneurysm.

Czabanka M, Ali M, Schmiedek P, Vajkoczy P, Lawton MT. Vertebral artery-posterior inferior cerebellar artery bypass using a radial artery graft for hemorrhagic dissecting vertebral artery aneurysms: surgical technique and report of 2 cases. *J Neurosurg* 2011;114(4):1074-9.

Cerebellar Aneurysms – New Nomenclature and Surgical Routes

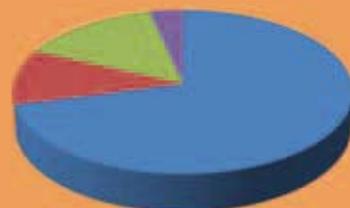
In a publication describing three anatomical triangles and their relationship to posterior inferior cerebellar artery aneurysms, Dr. Lawton and cerebrovascular fellow Ana Rodríguez-Hernández MD offer the first systematic definition of the surgical corridors that can be used to access these aneurysms. The three triangles – vagoaccessory triangle, suprahyoglossal triangle, and infrahyoglossal triangle – clarify the dissection routes by clearly defining their borders and the depth of dissection through the cranial nerves.

Rodríguez-Hernández A, Lawton MT. Anatomical triangles defining surgical routes to posterior inferior cerebellar artery aneurysms. *J Neurosurg* 2011;114(4):1088-94.

Drs. Lawton and Rodríguez-Hernández have also worked with Albert Rhoton MD to propose a new numbering system for cerebellar arteries that divides them into segments and is analogous to the established nomenclature used to describe cerebral arteries. This new nomenclature is simple and practical, and aims to help neurosurgeons understand each cerebellar artery's unique characteristics, branches, and relationships to adjacent neuroanatomy.

Rodríguez-Hernández A, Rhoton AL Jr, Lawton MT. Segmental anatomy of cerebellar arteries: a proposed nomenclature. Laboratory investigation. *J Neurosurg* 2011;115(2):387-97.

Vascular Neurosurgery Cases at UCSF in 2011



- Aneurysm (N=282)
- Ateriovenous malformation (N=43)
- Cavernous malformation (N=85)
- Carotid atherosclerotic disease (N=14)

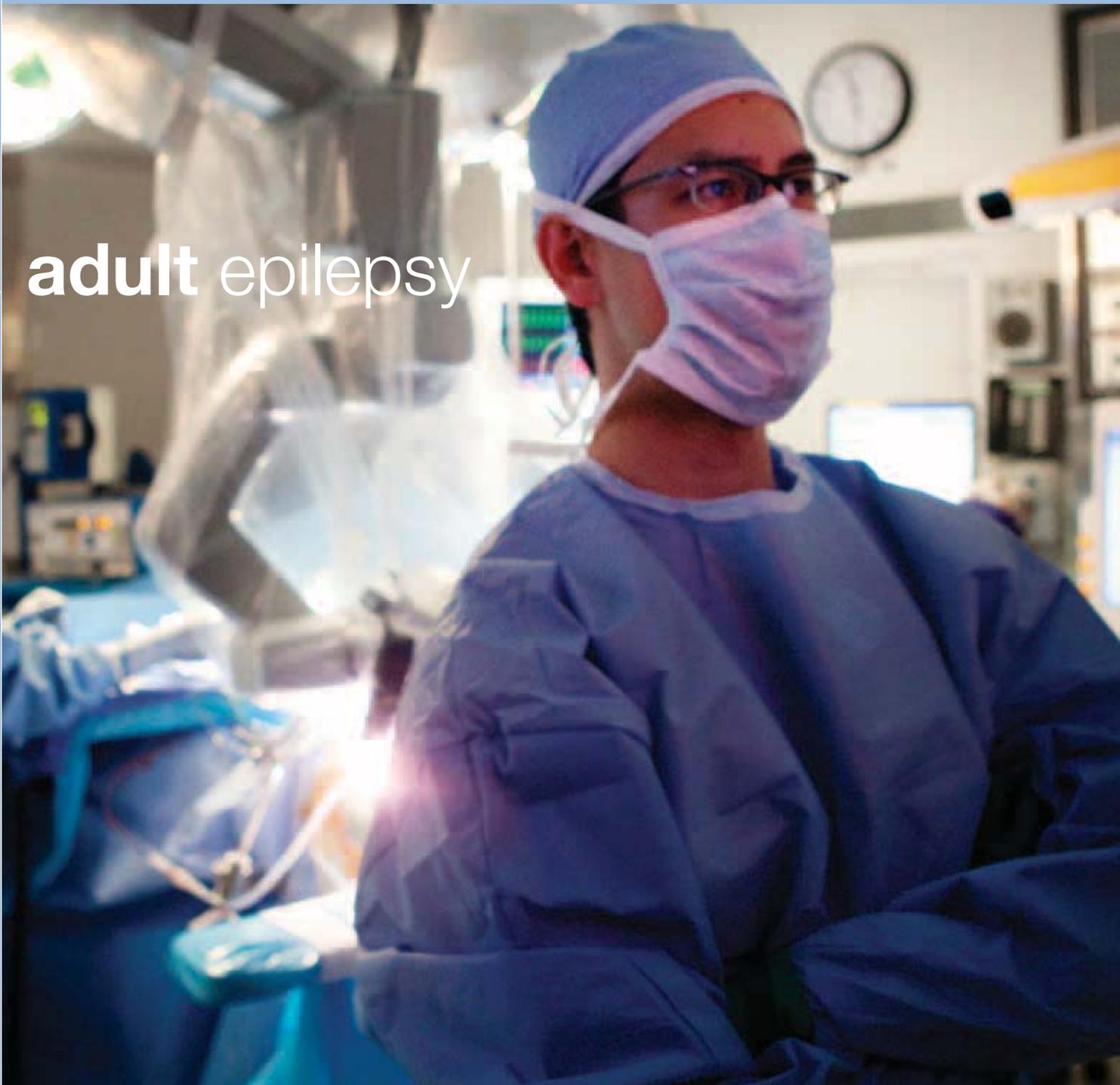
New Chief of Epilepsy Surgery

The Department of Neurological Surgery is pleased to announce that Edward Chang MD has become chief of adult epilepsy surgery. Dr. Chang is an expert in surgical therapies

for intractable epilepsy and conducted both his medical school and neurosurgical residency training at UCSF.

“UCSF is a pioneer in epilepsy treatments, and we continue to offer the most advanced care for the most difficult cases. Our highest priority is to improve our patients’ quality of life by delivering personalized care to achieve seizure freedom. Every patient is different and our treatment is tailored.” – Edward Chang MD

adult epilepsy



Faculty

Epilepsy Surgery

Edward Chang MD

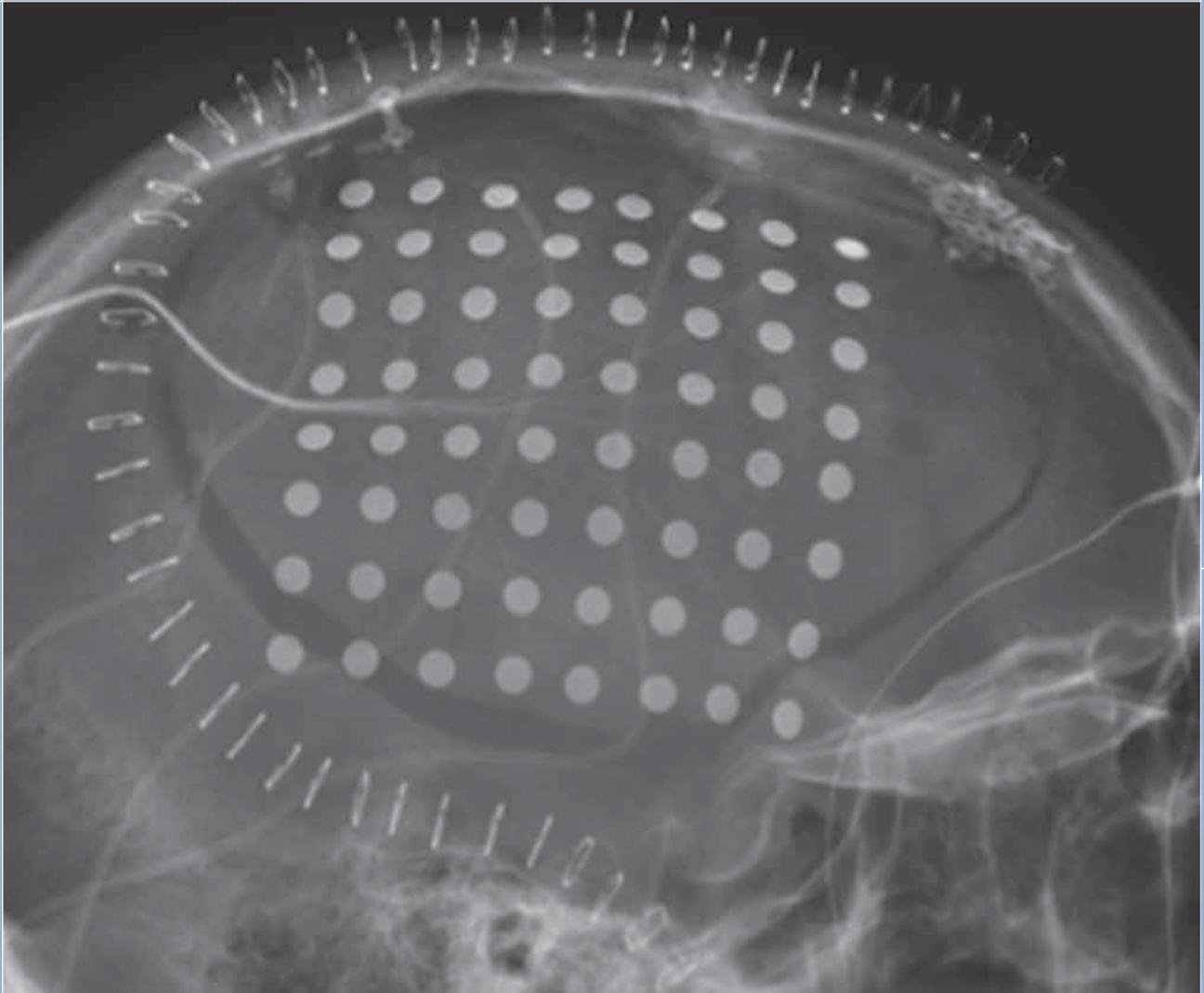
Paul Larson MD

Epilepsy Research Laboratories

Arturo-Alvarez Buyla PhD

Scott Baraban PhD

During surgery, subdural grids are used to precisely map the area of the brain that is the source of epileptic seizures.



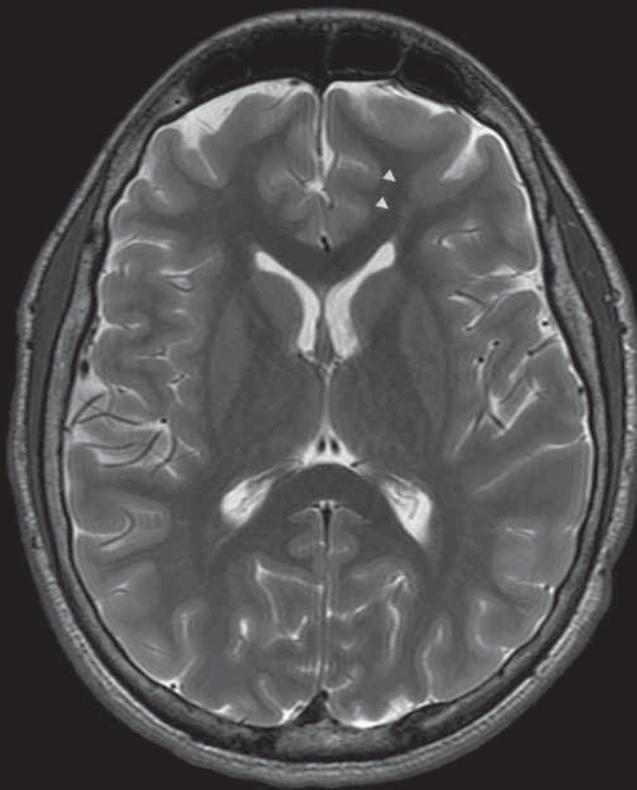
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Landmark Study Reveals that Epilepsy Surgery is Significantly Underutilized in the United States

A new report tracking trends in epilepsy treatment over the last 20 years in the United States shows that surgical cases have not increased despite clear evidence from randomized controlled trials demonstrating the effectiveness of surgery. By reviewing the National Inpatient Sample database, the UCSF Epilepsy Center team has shown that many patients who could benefit from surgery are not given the option.

While not all patients are surgical candidates, there is still a large under-served population that suffers unnecessarily from impairing seizures. These important findings won Dr. Chang the prestigious Young Investigator Award from the American Epilepsy Society.

Englot DJ, Ouyang D, Barbaro NM, Garcia PA, Chang EF. Epilepsy surgery trends in United States, 1990-2008. *Neurology, In Press.*



A transmantle dysplasia in the left orbitofrontal cortex (arrows) causing intractable epilepsy was surgically excised under guidance of intraoperative electrocorticography.

Long-term Seizure Freedom for Patients with Malformations of Cortical Development

Abnormalities during development of the cortex can lead to a wide range of structural malformations that may later cause epilepsy. This type of epilepsy is especially difficult to treat with medication, but a new study from UCSF shows that patients who are treated surgically can have long-term control of their seizures (67% of patients were completely seizure-free at 10 years). The most important predictor of good outcome is the successful localization of seizure focus, usually by invasive EEG recordings or high-resolution MRI.

Chang EF, Wang DD, Barkovich AJ, Tihan T, Auguste KI, Sullivan JE, Garcia PA, Barbaro NM. Predictors of seizure freedom after surgery for malformations of cortical development. *Ann Neurol* 2011;70(1):151-62.

Neuromodulation in Epilepsy

Dr. Chang co-edited the October 2011 issue of *Neurosurgery Clinics of North America*, which focused on the emerging role of neuromodulation in epilepsy. This up-to-date reference includes the basic science and clinical data behind current and next generation devices in epilepsy surgery. It also reviews vagal nerve stimulation, DBS, and responsive neurostimulation as non-resective alternatives to surgery.

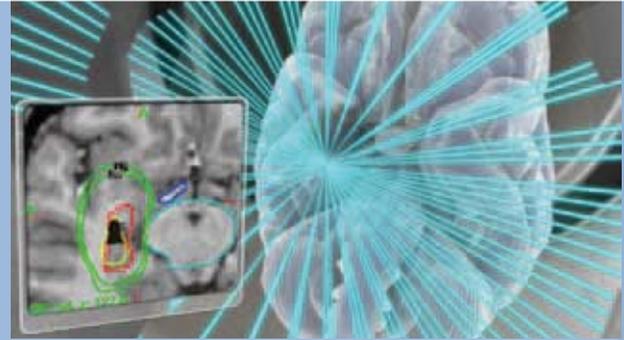
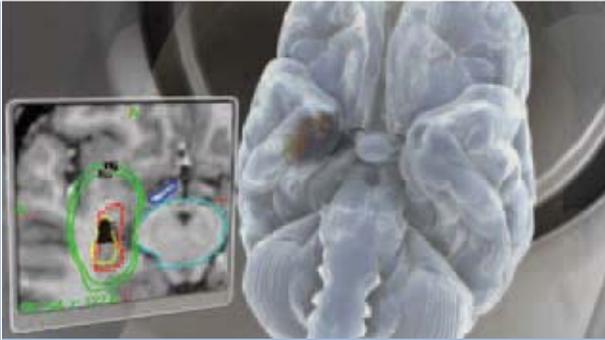
Chang EF, Barbaro NM (eds). Epilepsy Surgery: The Emerging Field of Neuromodulation. *Neurosurg Clin N Am* 2011;22(4):425-550.

A Major Discovery in Brain Mapping

Researchers in Dr. Chang's laboratory have developed a real-time brain-mapping algorithm for speech and motor function in neurosurgical patients. This novel methodology applies advanced signal processing and statistics on cortical signals passively recorded from the brain surface, thereby replacing electrical stimulation for pre-resection mapping. The current algorithm can process up to 256 electrodes simultaneously with mapping analysis completed within less than one second. Unlike cortical stimulation, there is no risk of induced seizures. These results were presented at the International Brain Mapping meeting in Milan, Italy. The work has been supported by NIH grants K99/R00, the NIH Director's New Innovator award, and the Klingenstein Foundation fellowship to Dr. Chang.

Secrets of Your Brain – Corpus Callosotomy for Severe Epilepsy

The 2011 special edition of *U.S. News & World Report*, "Secrets of Your Brain" issue features patient Savanna Kelley, who underwent a corpus callosotomy at UCSF for severe epilepsy that was causing her to experience unpredictable and dangerous drop attack seizures.



Gamma Knife radiosurgery precisely delivers a finely focused, high dose of radiation to well-defined, small targets in the brain, such as seizure foci in patients with epilepsy.

Radisurgery or Open Surgery for Epilepsy (ROSE) Trial

The Department of Neurological Surgery is leading a phase 3, multicenter, randomized trial of Gamma Knife radiosurgery for mesial temporal sclerosis. This NIH-funded study is currently enrolling patients and will determine if radiosurgery can provide a noninvasive, viable alternative to open surgery. The pilot study for the ROSE trial, published in 2009, showed that radiosurgery for unilateral temporal lobe epilepsy results in seizure remission rates comparable with those reported previously for open surgery. For information or enrollment, contact Erica Terry at (415) 476-2180.

A recent study by the Radiosurgery Epilepsy Study Group showed positive neuropsychological outcomes for patients after Gamma Knife treatment. Measures of neurocognition did not differ from baseline and quality of life improved significantly after seizures subsided.

Quigg M, Broshek DK, Barbaro NM, Ward MM, Laxer KD, Yan G, Lamborn K; Radiosurgery Epilepsy Study Group. Neuropsychological outcomes after Gamma Knife radiosurgery for mesial temporal lobe epilepsy: a prospective multicenter study. *Epilepsia* 2011;52(5):909-16.

“The majority of pediatric patients who undergo surgery for epilepsy at UCSF experience a dramatic reduction or complete resolution of their seizures without significant complications.”

– Kurtis Auguste MD, Director of Pediatric Epilepsy Surgery

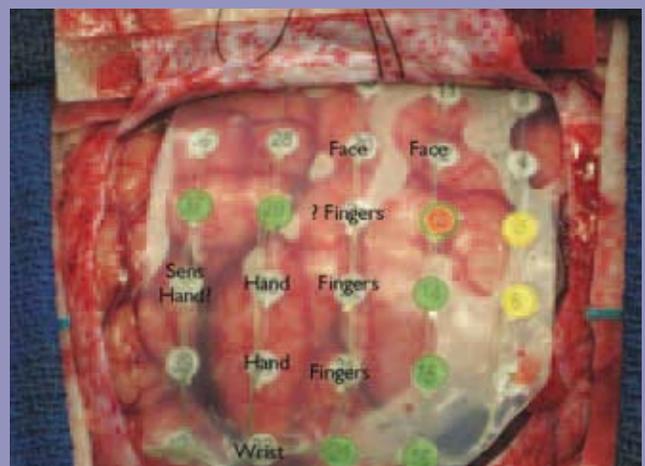
pediatric epilepsy center

Faculty

Kurtis Auguste MD

Nalin Gupta MD, PhD

At the UCSF Pediatric Epilepsy Center, pediatric epileptologists, neurosurgeons, and neuropsychologists provide specialized care for children with epilepsy. Children who do not respond to medication may be surgical candidates, and a variety of modalities are offered at UCSF, including focused resections, modified lobectomies, disconnection surgeries, vagal nerve stimulators, and Gamma Knife radiosurgery. During surgery, the surgical epilepsy team uses advanced neuronavigation systems that merge preoperative images from MRI, DTI, MEG, and PET onto a platform that optimizes seizure focus localization.



Subdural grids map seizure foci during surgery and identify areas of eloquent cortex.



Faculty

Movement Disorders Surgery

Philip A. Starr MD, PhD

Edward Chang MD

Paul Larson MD

Daniel Lim MD, PhD

Movement Disorders Research Laboratories

Krystof Bankiewicz MD, PhD
gene therapy and drug-delivery strategies
for Parkinson's disease

Paul Larson MD
neurotransplantation strategies for Parkinson's disease

Philip A. Starr MD, PhD
basal ganglia physiology in movement disorders

movement disorders program

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Not only are you completely [under anesthesia], but it is also more precise and faster. And that made it even more appealing." – Patient Linda Sharpe on the advantages of ClearPoint



Cutting-Edge Interventional MRI System Transforms Brain Surgery for Patients with Movement Disorders

The ClearPoint system is an integrated hardware and software platform for performing implantation of deep brain stimulator (DBS) electrodes or drug infusion cannulae using real-time MR imaging. This system, which can be used in any diagnostic MR scanner, has been used by the UCSF Surgical Movement Disorders team since it was approved by the FDA in June, 2010, with excellent results. The system allows patients to undergo implantation of DBS electrodes under general anesthesia instead of in the usual awake state. The alternative is especially appealing for treatment of pediatric patients with disorders like dystonia, who are often unable to tolerate an awake surgery.

ClearPoint was pioneered by UCSF neurosurgeons Paul Larson MD and Philip Starr MD, PhD together with MR physicist Alastair Martin PhD and the medical device company SurgiVision. The new technique has been so successful that many other neurosurgical centers have begun to adopt it in the care of their patients, including Cleveland Clinic, Emory University, and the University of Wisconsin. It was also highlighted in the special feature edition of *U.S. News & World Report* magazine, "Secrets of Your Brain," which documented the surgery for patient Linda Sharpe, 71, who was diagnosed with Parkinson's disease 10 years ago.



Neurosurgeon Philip Starr uses the ClearPoint system to perform deep brain stimulation surgery inside an MR scanner.

In 2011, the UCSF Surgical Movement Disorders group published their laboratory experiments demonstrating that the system is accurate to less than a millimeter for placing DBS electrodes, overcoming limitations of a previous iMRI system and resulting in less error and shorter procedure times.

Larson PS, Starr PA, Bates G, Tansey L, Richardson RM, Martin AJ. An Optimized System for Interventional MRI Guided Stereotactic Surgery: Preliminary Evaluation of Targeting Accuracy [published online ahead of print Jul 25, 2011]. *Neurosurgery*. DOI: 10.1227/NEU.0b013e31822f4a91

Deep Brain Stimulation for Pediatric Patients

The first large U.S. series of DBS for pediatric patients shows that results of the procedure in children are comparable to those in adults. Of the 31 patients documented, those with primary dystonia and no fixed orthopedic deformity experienced dramatic reduction of dystonic movements and dystonia-related disability following DBS (mean Burke Fahn Marsden Dystonia Rating Scale improvement was 78%). Patients with dystonia secondary to other conditions had

variable results, and many received minimal benefit from the procedure. Prior to this publication, there have only been a few case series worldwide to report the technical considerations and results of DBS in the pediatric population.

Air EL, Ostrem JL, Sanger TD, Starr PA. Deep brain stimulation in children: experience and technical pearls. *J Neurosurg Pediatr*, *In Press*.

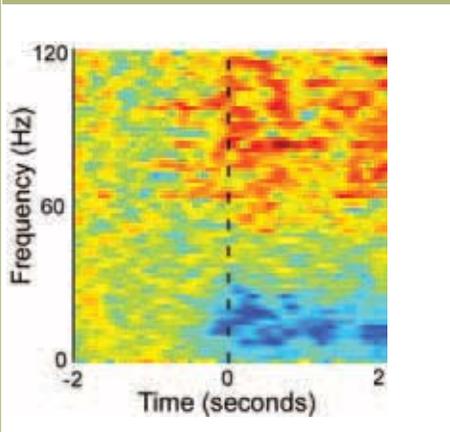
First Report on Electro-corticography in the Study of Movement Disorders Pathophysiology

A novel study shows that different movement disorders, like Parkinson's disease and dystonia, have characteristic physiologic signatures that are distinct from one another and can be decoded using electrocorticography (ECoG). The effect of basal ganglia disease on cortical function has previously been unknown, but by using ECoG, UCSF investigators are beginning to elucidate the mechanisms at the level of the primary motor cortex.

Crowell AL, Ryapolova-Webb ES, Ostrem JL, Galifianakis NB, Shimamoto S, Lim DA, Starr PA. Oscillations in sensorimotor cortex in movement disorders: an electrocorticography study. *Brain*, *In Press*.

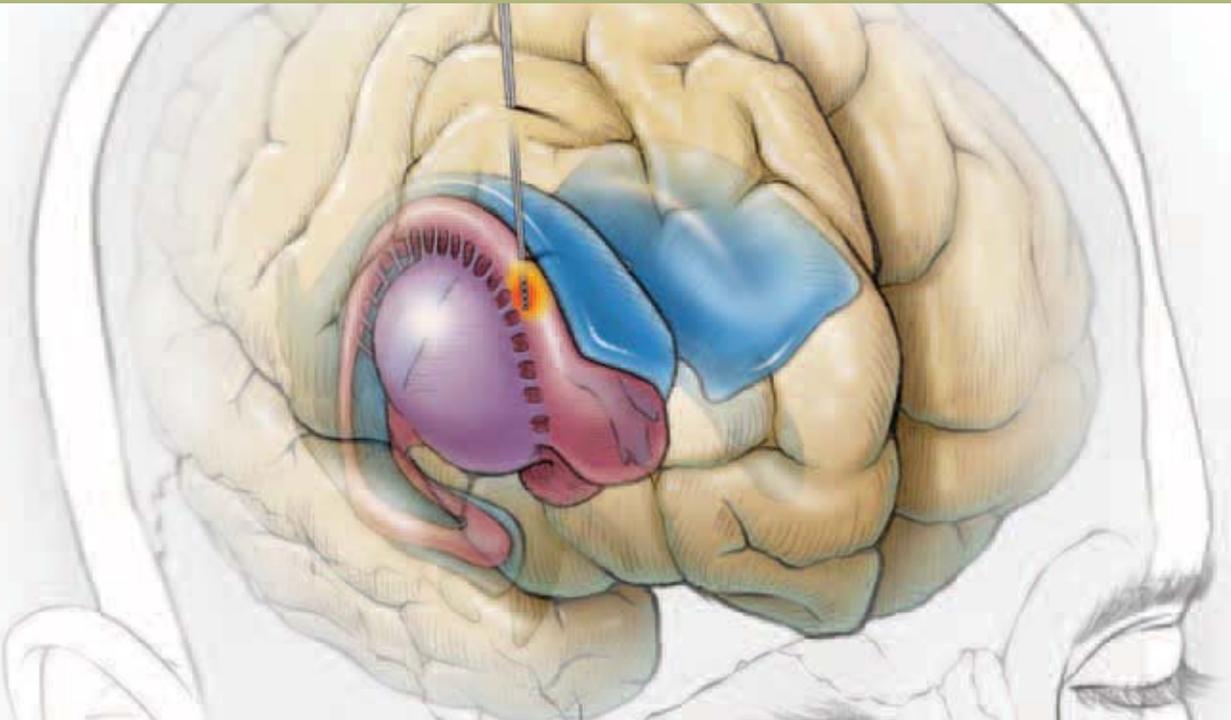
The SmartFrame® Device is an MRI-compatible frame for stereotactic neurosurgical procedures.





Michael J. Fox Foundation Funds Study of Cortical Physiology in Parkinson's Disease

The Michael J. Fox Foundation has granted Coralie de Hemptinne PhD and Dr. Starr a Rapid Response Innovation Award to study how DBS affects cortical function during movement planning in patients with Parkinson's disease. Little is known about the exact mechanism of action of DBS and there is very little information on how it affects the cortex. The investigators will use ECoG to record electrical signals from the cortex before and after DBS stimulation and while patients plan and execute computer-based tasks to fill this knowledge gap and explore the possibility of new cortically based therapies.



Deep brain stimulation to the caudate nucleus can modulate tinnitus. Reprinted from *Neuroscience*, vol. 169, issue 4, Cheung SW,

Larson PS, Tinnitus modulation by deep brain stimulation in locus of caudate neurons (area LC), pp. 1768-78, Copyright (2011), with permission from Elsevier

Deep Brain Stimulation in the Basal Ganglia Leads to a New Model of Auditory Perception

Dr. Larson and his colleague Steven Cheung MD in the Department of Otolaryngology at UCSF have previously shown that the loudness level of auditory phantoms in patients with tinnitus can be modulated using DBS in area LC of the caudate nucleus. The caudate nucleus is not a part of the known auditory pathway, and this was the first work to suggest that the caudate is involved in auditory perception.

In testing this new concept, Drs. Larson and Cheung have now shown that DBS in area LC can also trigger phantom sounds where there previously were none. In patients with tinnitus, who were undergoing DBS for Parkinson's disease, stimulation could trigger an additional sound and

either increase or decrease the familiar sound. In patients without tinnitus, electrical stimulation in area LC triggered a heterogeneous group of sounds with no external correlate. The caudate nucleus is located in the basal ganglia, which the investigators hypothesize are responsible for regulating reinforced behavioral responses to auditory phantoms and the gate to conscious awareness of sound. This study shows that neuromodulation with DBS could be a therapeutic solution for severe tinnitus and a pilot clinical trial would be needed to determine feasibility.

American Society for Stereotactic and Functional Neurosurgery (ASSFN) 2012 Meeting in San Francisco

As Past President of the ASSFN, Dr. Starr will host the society's biennial meeting in San Francisco, CA, June 3-6, 2012. For information, visit www.assfn.org

“Patients with peripheral nerve injuries and disorders need to be seen quickly by an attending physician. We are focused on providing rapid responses to point-of-first-contact physicians and quick and thorough evaluations for patients. By collecting as much information as possible before clinic visits, we can ensure that patients get the most out of their time with us.”

– Michel Kliot MD, Director, Peripheral Nerve Surgery



Faculty

Michel Kliot MD

center for the management & surgery of peripheral nerve disorders

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Removal of a schwannoma of the proximal median nerve in the upper arm.

The Department of Neurological Surgery has welcomed a new Director of Peripheral Nerve Surgery, Michel Kliot MD, who specializes in the evaluation and treatment of patients with all types of peripheral nerve injury and disease. Dr. Kliot is leading a highly accessible team that will respond to requests within 24 hours, ensure timely clinic appointments with short waits, and provide thorough follow-up care. State-of-the-art diagnostic techniques are used to quickly evaluate patients and develop comprehensive treatment and rehabilitation plans.

In addition to non-invasive treatment, the Center for the Management and Surgery of Peripheral Nerve Disorders offers inpatient and outpatient surgery for a wide variety of peripheral nerve problems, including:

- Common entrapment syndromes
 - Carpal tunnel syndrome
 - Ulnar nerve entrapment

- Unusual entrapment syndromes
 - Thoracic outlet syndrome
 - Meralgia paraesthetica
 - Piriformis syndrome
- Simple and complex traumatic nerve injuries, including brachial plexus injuries
- Peripheral nerve masses
 - Nerve sheath tumors (e.g., schwannomas and neurofibromas)
 - Malignant nerve sheath tumors (high-grade tumors with potential to metastasize).

The Center will also offer a specialized clinic for patients with neurofibromatosis.

Fetal Surgery for Spina Bifida More Effective than Operating After Birth

Recently published results from the Management of Myelomeningocele Study showed that prenatal surgery to repair a myelomeningocele reduced the need for shunting after birth, decreased the severity of the Chiari II malformation, and improved motor outcomes at 30 months. This NIH-funded, randomized study was conducted at UCSF, Children's Hospital of Philadelphia, and Vanderbilt University.

Adzick NS, Thom EA, Spong CY, Brock JW 3rd, Burrows PK, Johnson MP, Howell LJ, Farrell JA, Dabrowiak ME, Sutton LN, Gupta N, Tulipan NB, D'Alton ME, Farmer DL; MOMS Investigators. A randomized trial of prenatal versus postnatal repair of myelomeningocele. *N Engl J Med* 2011;364(11):993-1004.

Transsphenoidal Surgery for Pituitary Tumors in Children is Safe and Effective

This report describes the 10-year experience at UCSF using a microscopic endonasal transsphenoidal surgical approach to managing pediatric patients with pituitary adenomas.

Pituitary tumors in children are extremely rare and the majority are hormone-secreting prolactinomas. The data from this study show that despite the potential limitations of smaller anatomical features, this minimally invasive procedure is well tolerated in the pediatric population – there was little morbidity, few complications, and no mortality. Children and adults have similar rates of postoperative hormonal normalization and overall cure. In this series, 86% of pediatric patients had normal endocrine function after surgery and adjuvant therapy. Lifelong oral therapy can be a significant burden for young patients and it is reasonable to consider early surgical management as an alternative to lifelong medical therapy.

Tarapore PE, Sughrue ME, Blevins L, Auguste KI, Gupta N, Kunwar S. Microscopic endonasal transsphenoidal pituitary adenectomy in the pediatric population. *J Neurosurg Pediatrics* 2011;7(5):501-9.

pediatric neurological surgery

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Faculty

Pediatric Neurological Surgery

Nalin Gupta MD, PhD

Kurtis Auguste MD

Mitchel Berger MD

Ronald Shallat MD

Peter Sun MD

Pediatric Neuro-Oncology

Anuradha Banerjee MD, MPH

Sabine Mueller MD, PhD

Theodore Nicolaides MD

Michael Prados MD

Pediatric Research Laboratories

Arturo Alvarez-Buylla PhD
developmental neuroscience;
stem-cell neurobiology

John Fike PhD
neurogenesis and radiation injury

Nalin Gupta MD, PhD
pediatric brain tumors; cell-cell interactions;
drug-delivery strategies

C. David James PhD,
Director, Pediatric Brain Tumor Research Center
molecular biology of CNS cancer;
analysis of mutant epidermal growth factor
receptors in malignant gliomas; rodent model
testing of experimental therapies

Theodore Nicolaides MD
Braf oncogenesis in pediatric CNS tumors

David Rowitch MD, PhD
central nervous system development and tumorigenesis

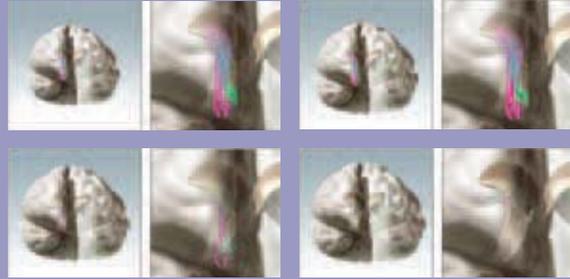
William Weiss MD, PhD
molecular basis of medulloblastoma



Pediatric neuro-oncologists Sabine Mueller, Anuradha Banerjee, Theodore Nicolaides, and Michael Prados

Postnatal Neurogenesis Most Active during Infancy – New Research from the Pediatric Brain Tumor Foundation Institute at UCSF

In a new report on neurogenesis in the postnatal human brain published in *Nature*, UCSF investigators demonstrate that the corridor of migrating immature neurons that begins in the subventricular zone (SVZ) changes from infancy to adulthood. Data from neurosurgical and autopsied specimens reveal that while neurogenesis is active during the first six months of life, this activity tapers off between six and 18 months of age and is nearly extinct by adulthood. The 18-month mark coincides with the development of the hypocellular gap – one of four layers in the human SVZ. The study is also the first to show that while the few remaining immature migratory neurons in adults travel from the SVZ to the olfactory bulb along what is known as the rostral migratory stream, the same neurons in infants also travel to the olfactory peduncle in the prefrontal cortex. The evidence that a robust period of neurogenesis and migration continue for a period after birth may have implications for our understanding of some neonatal neurological diseases.



Neurogenesis in the postnatal brain decreases significantly between infancy and adulthood

Sanai N, Nguyen T, Ihrie RA, Mirzadeh Z, Tsai HH, Wong M, Gupta N, Berger MS, Huang E, Garcia-Verdugo JM, Rowitch DH, Alvarez-Buylla A. Corridors of migrating neurons in the human brain and their decline during infancy. *Nature* 2011;478(7369):382-6.

pediatric brain tumor center

Pediatric Brain Tumor Clinical Trials

New Type of Phase 2 Clinical Trial for Brainstem Glioma – Moving towards Personalized Medicine in Practice

The Pediatric Brain Tumor Center at UCSF will partner with Dana Farber to lead the study “Phase II Trial of Molecularly Determined Treatment of Children and Young Adults with Newly Diagnosed Diffuse Intrinsic Pontine Gliomas.” Brainstem gliomas are usually inoperable and biopsies are rarely performed, which has led to a lack of information about the biology of these tumors.

The study will be the first to biopsy brainstem gliomas in children when they are first diagnosed, and to use this tumor tissue to specifically choose various chemotherapy treatments tailored to the biology of that child’s tumor. Taking tumor tissue through a small biopsy procedure has been shown to be safe in the majority of cases, and can yield enough tissue to inform clinical researchers about the specific metabolic pathways that are abnormal in the tumor.

Studying the Late Effects of Brain Tumor Therapy

The Pediatric Brain Tumor Center at UCSF has initiated two new clinical trials aimed at better understanding the long-term side effects of treatment:

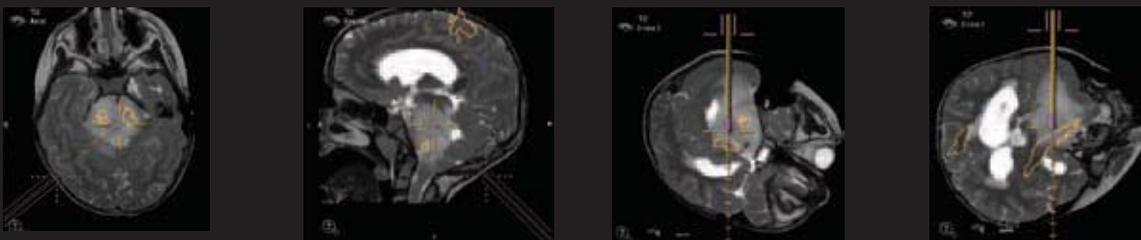
- **RadART-PRO:** This prospective trial will study how radiation therapy affects cerebrovascular structures in children. It will specifically study the rate of radiation-induced vasculopathy, as well as stroke and stroke recurrence, in children who received radiation to the brain or neck.

- **Neurocognitive Brain Tumor Study:** This prospective study will test the use of a computerized neurocognitive training program, developed at UCSF, in children with brain tumors. Pediatric brain tumor patients will participate in game-like exercises aimed at improving visual processing speed, auditory processing speed, and short-term memory.

Pediatric Brain Tumor Center at UCSF becomes a Phase 1 Trial Site for the Children’s Oncology Group

The Children’s Oncology Group (COG)—an NCI-supported clinical trials group devoted to childhood cancer research—has designated the Pediatric Brain Tumor Center at UCSF a phase 1 clinical trials site. Patients at UCSF will now be able to enroll in COG phase 1 trials (in addition to phase 2 trials) for pediatric brain tumors and have access to the newest potential treatments for their disease.

Intraoperative neuronavigation image demonstrating the biopsy procedure for a brainstem glioma. Preoperatively, diffusion tensor imaging allows identification of the corticospinal tracts (orange outlines), which can then be avoided to reduce the likelihood of a motor deficit.



UCSF is one of the largest and most comprehensive pain neurosurgery centers in the United States.



High-resolution FIESTA imaging of the cerebellopontine angle in evaluation of trigeminal neuralgia.

Facial Pain

Trigeminal neuralgia, or tic douloureux, is a neuropathic disorder characterized by episodes of intense pain in the face, originating from the trigeminal nerve. It is described as among the most painful conditions known.

UCSF provides the most advanced surgical treatment options for neuropathic trigeminal neuralgia, as well as glossopharyngeal neuralgia. All patients undergo detailed evaluation as well as advanced, high-resolution MRI and MR angiographic imaging. State-of-the-art intraoperative electrophysiology for cranial nerve monitoring is critical for safety. UCSF is a high-volume referral center, with a forty-year experience of treating over 1500 patients. Case volume has continued to increase and pain specialists currently treat three patients per week. Hospital volume is an important predictor of pain control success and low complication rates.

neurological surgery pain management program

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Intraoperative photograph of 'neurovascular conflict' prior to microvascular decompression for trigeminal neuralgia (left) and glossopharyngeal neuralgia (right).

Faculty

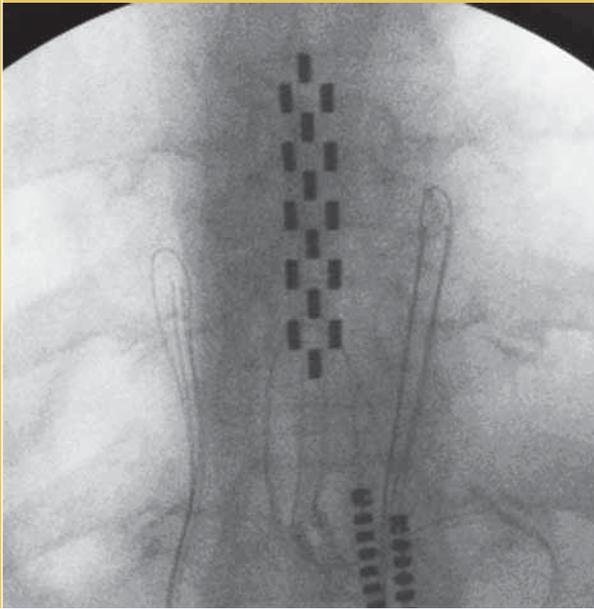
Edward Chang MD

Philip A. Starr MD, PhD

Neurosurgeons at UCSF also specialize in care for patients with non-neuropathic pain and atypical pain syndromes, and they collaborate closely with the UCSF Center for Orofacial Pain, directed Charles McNeill DDS (Department of Oral and Maxillofacial Surgery) and the UCSF Headache Center, directed by Peter Goadsby MD, PhD (Department of Neurology).

UCSF is one of few centers that can provide comprehensive surgical expertise across various treatment modalities, always tailored for patients:

- Microvascular decompression
- Gamma Knife radiosurgery
- CyberKnife radiosurgery
- Percutaneous radiofrequency lesioning
- Motor cortex stimulation



Chronic Pain

Spinal cord stimulation can relieve chronic pain in the back, arms, or legs. It works by electrically stimulating the spinal cord. Instead of pain, the patient feels a tingling or buzzing sensation.

The ideal patient for the spinal cord stimulator is one who has one of the following conditions who has not responded well to more conservative therapies:

- Radiculopathy secondary to FBS or herniated disk
- Postlaminectomy pain
- Epidural fibrosis
- Degenerative disc disease
- Causalgia
- Failed back surgery syndrome
- Complex regional pain syndrome
- Arachoiditis

Spinal cord stimulators can control chronic pain by sending electrical pulses to the spinal cord.

Headache

DBS for Cluster Headache

Neuroimaging studies over the past six years have supported the hypothesis that activation of posterior hypothalamic neurons have a pivotal role in pathophysiology of trigeminal autonomic cephalgias. Studies have prompted encouraging reports, including several from UCSF, that stimulation of this target can improve or eliminate pain caused by intractable chronic cluster headache.

Sani S, Shimamoto S, Turner RS, Levesque N, Starr PA. Microelectrode recording in the posterior hypothalamic region in humans. *Neurosurgery* 2009;64(3 Suppl):161-9.

Sillay KA, Sani S, Starr PA. Deep brain stimulation for medically intractable cluster headache. *Neurobiol Dis* 2010;38(3):361-8.

Occipital Nerve Stimulation for Migraine

UCSF has been selected as a study site for the Boston Scientific OPTIMISE trial evaluating occipital nerve stimulation for the indication of migraine. This randomized controlled trial will begin patient recruitment in early 2012 and be coordinated by the Division of Pain Neurosurgery and the UCSF Headache Center.

Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ; ONSTIM Investigators. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. *Cephalalgia* 2011;31(3):271-85.





UCSF Study Assesses Utility of MRI and Surgery for Chronic Low Back Pain

Back pain is one of the leading causes of loss of productivity in the United States, with costs of up to 100 billion dollars per year and 80 percent of Americans suffering from back pain at some point in their lives. Degenerative changes — such as annular tears and bulging discs — seen on MRIs of patients with chronic lower back pain (CLBP) sometimes result in a spinal surgeon referral, even if surgery may offer no benefit over nonsurgical treatment. A systematic literature review conducted by Dean Chou MD, associate professor of neurological surgery, and colleagues suggests that significant savings can be made in the time and resources currently invested in addressing degenerative MRI

changes and CLBP may exist but must be considered in the context of study quality and the lack of a direct link between degenerative MRI changes and CLBP. Furthermore, in the absence of deformity or symptomatic neural compression, there is no evidence to suggest that surgical treatment of degenerative MRI changes leads to improved outcomes over nonoperative care. Based on these findings, the authors strongly recommend against both the routine use of MRI in patients with CLBP and surgical treatment of CLBP based exclusively on MRI findings.

Chou D, Samartzis D, Bellabarba C, Patel A, Luk KD, Kisser JM, Skelly AC. Degenerative magnetic resonance imaging changes in patients with chronic low back pain: a systematic review. *Spine (Phila Pa 1976)* 2011;36(21 Suppl):S43-53.

neurospinal disorders

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New Minimally Invasive Technique for Spinal Tumor Resection Pioneered at UCSF

Standard open approaches to thoracic intradural tumors typically involve a large incision and are associated with significant tissue trauma, blood loss, and lengthy hospital stays. A recent retrospective study by UCSF neurosurgeons published in *Journal of Neurosurgery: Spine* compared the outcomes of a series of standard open intradural tumor resection cases to profile-matched cases of tumors resected using a novel, mini-open approach. Although both cohorts demonstrated comparable outcomes, the mini-open cohort experienced significantly lower blood loss and a shorter average hospital stay compared to the standard open cohort.

The authors predict that these results could be due a smaller incision length in the minimally invasive procedure, as well as the use of an expandable tubular retractor system, which allows more direct access to the entire dorsal aspect of the spinal cord with decreased disruption of surrounding tissues.

Lu D, Chou D, and Mummaneni P. A Comparison of Mini-Open and Open Approaches for Resection of Thoracolumbar Intradural Spinal Tumors [published online ahead of print March 11, 2011]. *J Neurosurg Spine*. doi: 10.3171/2011.1.SPINE09860.

Faculty

Christopher Ames MD

Praveen Mummaneni MD

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Philip Weinstein MD

Defining Risk of Surgery for Spinal Deformity

There have been few large series reporting the risk and outcomes for spinal deformity surgery at tertiary treatment centers. This year UCSF spine surgeons began leading new studies to determine the risk associated with complex spinal deformity procedures, allowing patients and physicians to make better decisions about treatment.

- The Department of Neurological Surgery is participating in the international trial SCOLI-RISK to study the risks associated with major deformity correction for scoliosis. Current biomedical literature indicates that the risk of serious complications and morbidity may be between 5-10%, but could be lower at centers of excellence for treatment of deformity. The UCSF site will be led by Christopher Ames MD, co-director of the UCSF Spine Center and director of spine tumor and deformity surgery. SCOLI-RISK will be the first multi-center, prospective trial to define risk of surgical intervention for these patients and will take place at 15 centers worldwide.

- At the 2011 Annual Meeting of the American Association of Neurological Surgeons, Praveen Mummaeni MD, co-director of the UCSF Spine Center and director of minimally invasive spine surgery, gave a plenary lecture on a study examining risk factors for major complications in spinal deformity surgery. The retrospective case-control study reviewed data for 953 patients at eight centers, 72 of whom experienced major complications. The authors determined that staged surgery and an anterior/posterior approach were the most significant variables leading to major complications and should be considered during surgical planning and discussed with patients pre-operatively.

Mummaneni PV, Smith JS, Shaffrey C, Schwab F, Hawkinson N, Lafage V, Hart R, Mundis G, Burton D, Line B, Akbarnia B, Boachie-Adjei O, Hostin R, Wood K, Bess S. Risk Factors for Major Perioperative Complications in Adult Spinal Deformity Surgery. Paper presented at: American Association of Neurological Surgeons 79th Annual Meeting; April 11, 2011; Denver, CO.



Orthopedic surgeon Vedat Deviren and neurosurgeon Christopher Ames collaborate during surgery for a high-risk patient, reducing operating time and blood loss.

Care for Elderly Spine Patients

Older patients, especially those with osteoporosis, have a high risk of spinal fractures and suffer from more complications during surgery. At the UCSF Spine Center, a team with wide-ranging expertise designs treatment plans specifically with the unique challenges of this patient population in mind.

High-Risk Spine Team

A high-risk spine team at UCSF identifies patients whose diets may need to be optimized by a nutritionist prior to surgery and operations are performed by a neurosurgeon and orthopedic surgeon who work together simultaneously. Recent data from UCSF show that blood loss for operations performed by two surgeons was less than half of the loss reported for operations by a single surgeon. Operating time for two surgeons was also 1.5 times shorter and the rate of major complications decreased by nearly twenty-five percent.

Ames C, Barry J, Berven S, Hu S, Weber M, Deviren V. Outcome of Pedicle Subtraction Osteotomy in 2 vs 1 attending surgeons. Presented at the Annual Meeting of the International Society for the Study of the Lumbar Spine, Gothenburg, Sweden, June 14-18, 2011.

Ames C, Keshavarzi S, Hu SS, Weber MH, Burch S, Deviren V. The UCSF Experience Evaluating the Effect of One vs. Two Attending Surgeons on Peri-Operative Morbidity for Pedicle Subtraction Osteotomy. Presented at the 18th International Meeting on Advanced Spine Techniques, Scoliosis Research Society, Copenhagen, Denmark, July 13-16, 2011.



Neurosurgeon Praveen Mummaneni performs minimally invasive spine surgery for degenerative scoliosis through a tube just 26 mm in diameter.

“Elderly patients are at an increased risk of complication during surgery for spinal disorders because they often have cardiac and pulmonary co-morbidities. This risk can be diminished with minimally invasive techniques.” – Praveen Mummaneni MD, Director of Minimally Invasive Spine Surgery

Overcoming Complications of Fusion for Scoliosis in Elderly Patients

Fusion for degenerative scoliosis in elderly patients can relieve pain and improve functional ability, but the biological approaches to spinal instrumentation can have a significant impact on outcome. In an analysis of bone substitutes for spine surgery, Dr. Mummaneni and his colleagues examined the costs and benefits of autografts, allografts, and synthetic bone material with a special emphasis on deformity surgery

in an aging population. While synthetic materials, primarily bone morphogenetic protein, are more costly than autografts or allografts, many patients over the age of 50 years have osteopenia or osteoporosis and harvesting autologous bone of poor quality is known to make the bone at the fusion site unable to heal.

Mummaneni PV, Meyer SA, Wu JC. Biological approaches to spinal instrumentation and fusion in spinal deformity surgery. *Clin Neurosurg* 2011;58:110-6.

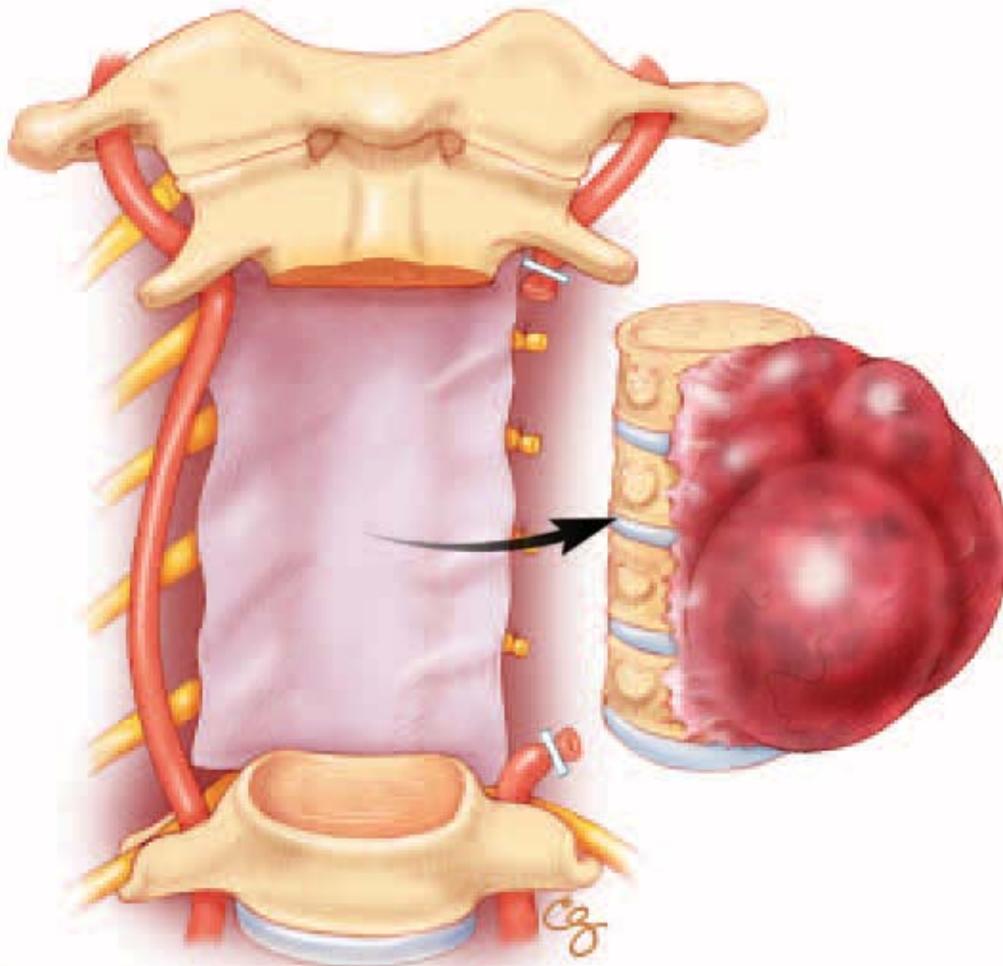
Largest Case Series for En Bloc Resection of Spinal Tumors Defines Recurrence Rates Following Surgery

En bloc resection is a technically demanding procedure that removes a spinal tumor in one piece using wide margins to avoid violating the tumor and reduce local spread of malignant cells. In the largest series reported to date on outcomes following en bloc resection, the average time to

recurrence was nearly 10 years for primary bone tumors, but just two years for metastatic tumors.

Cloyd JM, Acosta FL Jr, Polley MY, Ames CP. En bloc resection for primary and metastatic tumors of the spine: a systematic review of the literature. *Neurosurgery* 2010;67(2):435-44.

A large retrospective series shows that en bloc resection can provide better outcomes than piecemeal removal for primary bone tumors.



A. Pedicle subtraction osteotomy



Cobalt chrome rods provide more rigidity than titanium rods in a pedicle subtraction osteotomy for spinal deformity.

Advantages of a One-Stage Approach for Cervical Sagittal Imbalance

Dr. Ames and his colleagues have analyzed their experience using pedicle subtraction osteotomy (PSO) in the cervicothoracic region. Their PSO allows the operation to be performed in a single stage through an anterior approach instead of the two-stage Smith-Peterson osteotomy that is typically used in this region of the spine to restore sagittal balance. A single-stage operation can result in less morbidity, including less aspiration and trouble swallowing, which patients can experience following a posterior approach.

Deviren V, Scheer JK, Ames CP. Technique of cervicothoracic junction pedicle subtraction osteotomy for cervical sagittal imbalance: report of 11 cases. *J Neurosurg Spine* 2011;15(2):174-81.

Promising New Minimally Invasive Technique for Thoracolumbar Surgery

Dr. Chou has recently developed a new minimally invasive technique for transpedicular corpectomy with expandable cage reconstruction, which is used to perform anterior thoracolumbar surgery from a posterior approach. Earlier minimally invasive thoracolumbar corpectomy techniques typically required two incisions on either side to access the spine or an approach going through the chest cavity. In contrast, the new procedure, which is the only one of its kind currently in use in the United States, employs a bilateral approach and trap-door rib-head osteotomy, allowing for circumferential decompression and avoidance of entering the chest cavity all through a single incision. In a study published in the *Journal of Neurosurgery: Spine*, Dr. Chou described this novel technique for thoracolumbar pathology. While it may still be too early to conclude the superiority of the new technique, current data show that other minimally invasive techniques may have a lower infection rate and less blood loss compared to open procedures.

Chou D, Lu DC. Mini-open transpedicular corpectomies with expandable cage reconstruction. Technical note. *J Neurosurg Spine* 2011;14(1):71-7.

UCSF Spinal Biomechanics Laboratory Finds Cobalt Chrome to be a Superior Rod Material in Correction of Cervical Deformity

New research from the UCSF Spinal Biomechanics Laboratory shows that rod material and diameter has an impact on spinal stability after surgery. In a study published on the cover of *Journal of Neurosurgery: Spine*, investigators used the spines of cadavers to mimic ankylosing spondylitis and compared posterior rods made of cobalt chrome to the more widely used titanium. They found that a wider diameter for both materials provided more rigidity in flexion-extension and axial rotation, but cobalt chrome rods performed best overall.

Scheer JK, Tang JA, Deviren V, Acosta F, Buckley JM, Pekmezci M, McClellan RT, Ames CP. Biomechanical analysis of cervicothoracic junction osteotomy in cadaveric model of ankylosing spondylitis: effect of rod material and diameter. *J Neurosurg Spine* 2011;14(3):330-5.

Pain 101 Series Explores Broad Range of Pain Management Options

Pain is the most common reason for medical visits in the United States. "Pain 101: the Science, the Treatment, and the Impact," a six-part UCSF Osher Mini Medical School seminar series facilitated by Drs. Chou and Mummaneni, explores pain as it presents across multiple disciplines, as well as the array of pain management options available, both surgical and nonsurgical. Surgery does not always alleviate pain and may not be an option for some patients. Furthermore, treatments that work for one patient may not necessarily work for every patient. The seminar series, offered to the public from October to December, brings together experts from a broad range of specialties and informs attendees about cases in which surgery may prove beneficial and others in which alternative approaches, such as physical therapy and cognitive behavioral psychology, are better options.



Brain-Machine Interfaces and an Upcoming Trial of a New Neuroprosthetic for Human Patients: A Conversation with Dr. Karunesh Ganguly

Q. How and why did you become interested in neural engineering?

A. Along with my medical training, I completed a PhD in systems neuroscience, a field that tries to understand how areas of the brain interact with each other. A key aspect of

artificial electrical interface with the brain. In the normal body, bioelectrical signals flow from the brain to the muscles. In patients with a spinal cord injury or with severe muscle disease, this flow of information is interrupted. The brain itself, however, remains intact. The goal is to translate their intention to move through a direct interface with the brain.

center for neural engineering & prostheses at uc berkeley/ san francisco

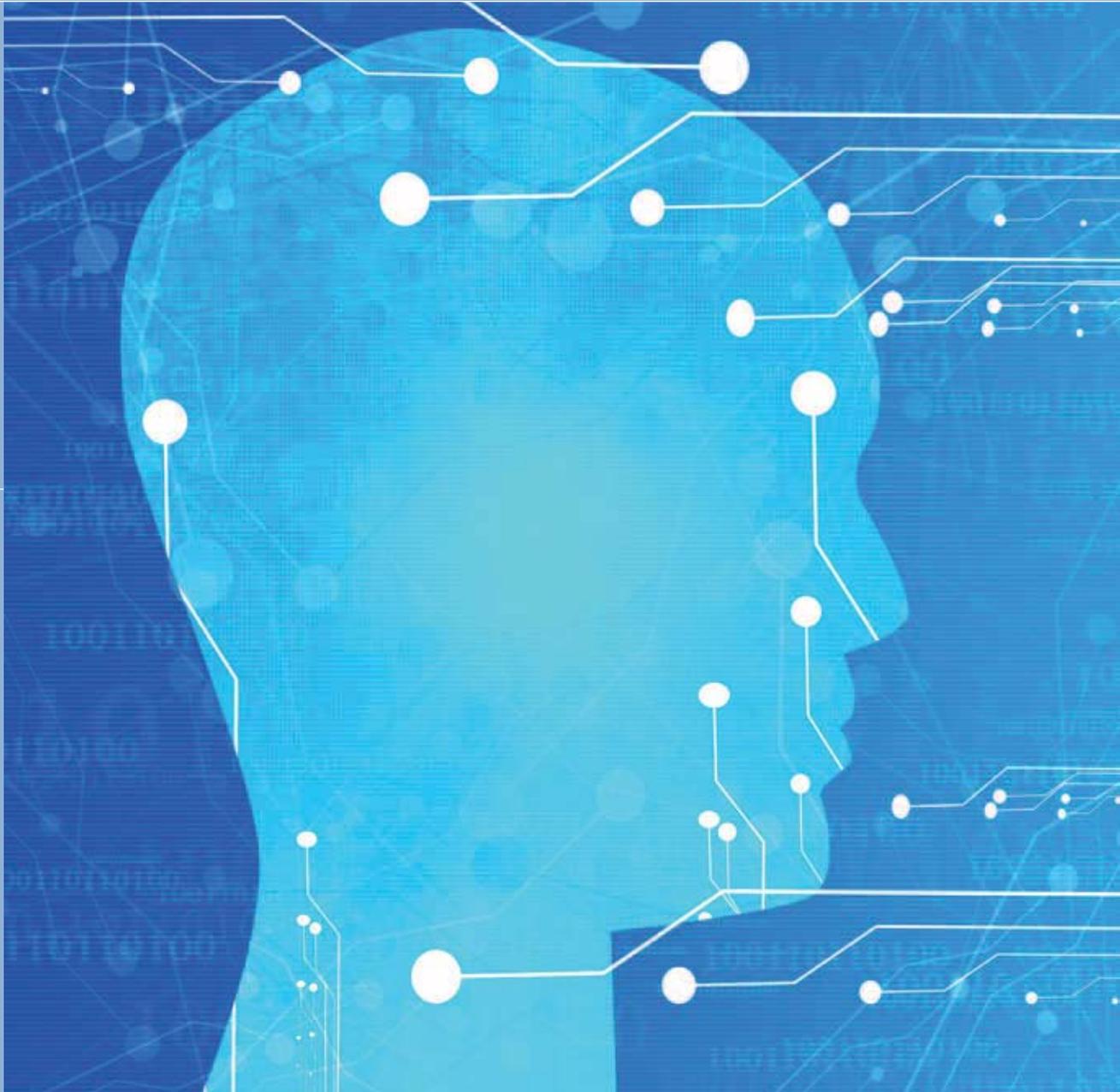
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systems neuroscience is to apply quantitative methods to form a detailed understanding of neural processing. Neural engineering focuses on using these same principles along with engineering methods to create new treatments for brain disorders. It provides a perfect pathway to combine my training in systems neuroscience and clinical neurology.

I recently completed a fellowship in neural engineering at UC Berkeley in the Electrical Engineering and Computer Sciences Department with Dr. José Carmena. I focused on the development of neuroprosthetics. Neuroprosthetics operate on the principle that the brain is a bioelectrical system. Thus we should in principle be able to create an

Q. You mentioned the idea of directly interfacing with the brain, or the brain-machine interface (BMI). Can you describe your preliminary research on BMIs as a postdoctoral fellow at UC Berkeley?

A. I applied my background in neuroscience to the development of BMIs. The primary goal was to use neuroscience principles to improve the reliability of BMIs. In one study (published in *Nature Neuroscience* in July), a grid of 100 electrodes was inserted into a monkey's motor cortex. These electrodes can simultaneously record large groups



of neurons. In the intact system, firing of these neurons is associated with movements. In the BMI setting, the subject learns to control external devices simply by thinking about movements. They do not actually physically move. In a BMI, neural signals are collected in real time and fed into an algorithm. This algorithm forms a mapping between the neural signals and the artificial limb.

At the time I started, I found that the current method did not always allow stable control across days and weeks. I found that taking into account how the brain learns control is fundamentally important for improving stability across time. Specifically, the previous algorithm design was not working in concert with long-term neural learning mechanisms. If you

think about it, the brain is the most sophisticated learning machine that we know of. Our research demonstrated that it is critical to take this into account when designing mathematical algorithms that allow neuroprosthetic control.

Q. How are you continuing this research at the UCSF Center for Neural Engineering and Prostheses (CNEP)?

A. One avenue of our research is to better understand the different resolutions of neural signals used in a BMI. Another important aspect is to understand how these different resolutions can best allow stable long-term performance of complex devices. In our clinical work, we are planning a

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feasibility trial of neuroprosthetics in human subjects using different technology than has been used before. Electrodes are placed on the brain surface to record signals. We know from the clinical setting that we can stably monitor these signals for years. What we don't know is whether we can use this in a paralyzed patient to control movement. [CNEP Co-Director] Dr. Edward Chang and I are closely collaborating on this project.

Q. When do you expect the clinical trial to begin?

A. We hope that the trial will start towards the end of 2012. We have partnered with an engineer who has developed a wearable exoskeleton. The idea is that paralyzed patients would place their arm and hand in the exoskeleton. The BMI would allow brain signals to control the exoskeleton. Essentially we hope to reanimate the limb. A key part of this translational research is to use components like this exoskeleton that we know can work well.

Q. You mentioned that the exoskeletal arm has been shown to work before. How will the proposed study improve upon the existing technology?

A. The exoskeleton was not originally designed for BMIs. It was designed at UC Santa Cruz for stroke patients who need physical therapy. Studies have suggested that some stroke patients improve after physical therapy, usually with a therapist providing a goal and a lot of repetitive training. This exoskeleton aims to automate the repetitive aspects of physical therapy. We hope to adapt it as a means to restore upper limb function.

Q. What patient groups does this new technology target?

A. The primary target is patients with severe bilateral upper extremity paralysis. Importantly, our target patients would

have to be cognitively intact. An example is someone with a high cervical spinal cord injury. Unfortunately, this is often a young person who is otherwise healthy. These patients are so disabled that restoration of rudimentary functions such as self-feeding, wheelchair control, etc., would be tremendous. There are also a whole host of others in the U.S. with muscular dystrophy and neuromuscular disease, which can total as high as 500,000 individuals.

Q. When do you envision the exoskeleton to be in common use among paralysis patients?

A. Demonstration of robust control in a clinically realistic scenario would be an important step. If our trial and others like it are successful, we anticipate moving to larger clinical trials. We will also work closely with patients to fully understand their needs and incorporate that into our design. Given the extent of disability in our target population, I would not be surprised if we have a device that can help restore function in a clinically meaningful way in about 10 years or so.

Q. What kind of a reaction do you get to your research from people outside the field?

A. Five years ago, a lot of people said, "This is just science fiction." Since then this line of research has been mentioned a lot in the media. At this point a more common reaction seems to be, "We know that these efforts are out there – when will [the technology] become available for clinical care?"

Q. What would you cite as the most rewarding aspect of your research?

A. To become a clinical scientist, you have to go through a lot of training. At a personal level, it has been gratifying to work in a field that perfectly combines my clinical and research interests. As a clinician, it is also really satisfying to move from the preclinical work in primates to a clinical trial for patients. I am really excited by the thought of ultimately applying this technology to disabled patients under my care.

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