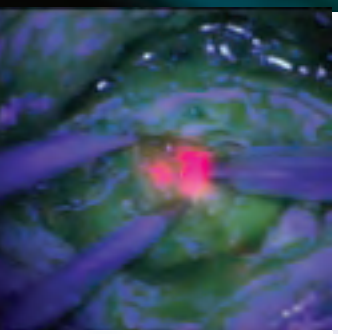
Year In Review 2010



The Department of Neurological Surgery at UCSF

University of California
San Francisco
UCSF
Neurological Surgery

Letter from the Chair

Since its inception in 1947, the Department of Neurological Surgery at UCSF has grown from a division of the Department of Surgery into one of the premier neurosurgical programs in the world. In 2010, we have neurosurgery services at all major hospitals in the Bay Area and we were again ranked in the top five neurosurgery programs on *US News & World Report's* annual list of Best Hospitals. We also ranked first in funding for neurosurgery from the National Institutes of Health for the fifth consecutive year. Our central mission is to give the best care possible to our patients; to improve therapies for neurosurgical disorders; and to train the future generation of academic neurosurgeons. In this review, we highlight some of the major accomplishments and findings from the Department in 2010.

In one of the more exciting developments, this month we launched the Center for Neural Engineering and Prostheses (CNEP, page 25) – a collaboration between UCSF and UC Berkeley. While bionics that meld mind and machine have long been the stuff of science fiction, this new program will build on current technologies that are already allowing patients to move artificial limbs with thought. By bridging the gap between neuroscience and cognitive science, CNEP is a true example of how technology will continue to improve our lives in the years to come.

Among the many honors given to our faculty in 2010, I would like to recognize Dr. Nicholas Barbaro's appointment as President of the Neurosurgical Society of America and Dr. Lawrence Pitts' appointment to Provost and Executive Vice President of Academic Affairs at the University of California, Office of the President.

I am exceedingly proud to have been chairman during a year marked by significant ingenuity and progress towards understanding and treating neurosurgical disorders, and to work with such a highly talented and dedicated group of faculty and staff.

Mitchel S. Berger,
MD, FACS, FAANS

Kathleen M. Plant
Distinguished Professor
and Chairman

Department of
Neurological Surgery

Director, UCSF
Brain Tumor Center

Contents

**Department of
Neurological Surgery**

University of California,
San Francisco

505 Parnassus Ave.,
Room 779 M

San Francisco, CA
94143-0112

Phone: (415) 353-7500

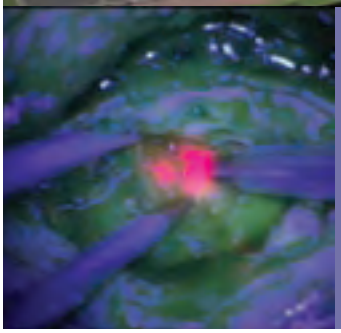
Fax: (415) 353-2889

neurosurgery.ucsf.edu

Design & layout:
Victoria Maier Magbilang

Illustration: Kenneth Xavier Probst

Photography: Noah Berger,
John Branscombe, Susan Merrell,
Kaz Tsuruta



The Brain Tumor Center at UCSF

The Brain Tumor Center at UCSF is one of the largest and most comprehensive programs for brain tumor treatment in the United States. It includes the Division of Neuro-oncology, the Brain Tumor Research Center, and the Division of Translational Research.

Top: Susan Chang MD, Jennifer Clarke MD, Nicholas Butowski MD

Bottom: 5-ALA causes tumor tissue to fluoresce during surgery

Clinical Trial Highlights

• The Department of Neurological Surgery is participating in a Phase II study of 5-aminolevulinic acid (5-ALA) to enhance visualization and resection of malignant brain tumors. The prodrug 5-ALA taken orally before surgery causes fluorescent porphyrins to accumulate in tumor tissue and can be visualized under fluorescent light during surgery to identify tumor cells and facilitate a more complete resection.

It has previously only been used outside the United States, and the European data show that it improves extent of resection and leads to longer progression-free survival for patients. 5-ALA is now being tested in the United States as an investigational new drug at a handful of select institutions, and UCSF is the only institution on the West Coast to offer this cutting-edge neurosurgical treatment.

• The Ben and Catherine Ivy Foundation has funded a new clinical trials consortium of five institutions across the United States, led by Michael Prados MD, director of the Division of Translational Research. The main objective of the consortium will be to perform small, enriched-patient clinical trials for recurrent glioblastoma. The goals will be to screen promising molecularly targeted agents and to validate drug distribution, pharmacokinetics, and pharmacodynamics in tumor tissue. Another objective will be to create a virtual tissue bank to prospectively identify patient subgroups who will be candidates for clinical trials done at time of tumor recurrence.

• The Department of Neurological Surgery is currently offering a Phase II clinical trial for a novel vaccine to treat glioblastoma, led by Andrew Parsa MD, PhD. Once a tumor is removed, a vaccine is created from proteins specific to that tumor and a heat-shock protein, and injected back into the patient over time. This prepares the immune system to produce T cells that find and kill new cancerous cells with proteins matching those extracted from the tumor.

• The UCSF Helen Diller Family Comprehensive Cancer Center has been chosen as one of five cancer centers in the United States to participate in the Merck Oncology Collaborative Trials Network (OncoNet), a global clinical trials network focusing on the development of Merck drug and vaccine candidates being investigated for the treatment and prevention of cancer, including brain tumors.

Collaboration provides funding for infrastructure, fast-track access to compounds and drugs for clinical trials, and a scientific educational exchange. Every year, the network will enroll approximately 1,200 patients in 30 to 40 investigator-initiated or company-sponsored trials.

Faculty

Adult Clinical Neuro-Oncology

Susan Chang MD

Nicholas Butowski MD

Jennifer Clarke MD

Michael Prados MD

Adult Brain Tumor Surgery

Mitchel S. Berger MD

Manish Aghi 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 neurobiology

Krys Bankiewicz MD, PhD

Convection drug-delivery systems; gene therapy

Mitchel S. Berger MD

Brain mapping; molecular genetic basis, biology, and therapy of brain tumors

Gabriele Bergers PhD

Angiogenesis; tumor invasion

Soonmee Cha MD

Perfusion magnetic resonance imaging

Joe Costello PhD

Functional genomics

Nalin Gupta MD, PhD

Pediatric brain tumors; cell-cell interactions

Daphne Haas-Kogan MD

Apoptosis and genetic mutations; therapeutic irradiation enhancement

C. David James PhD

Molecular biology of CNS cancer; analysis of mutant epidermal growth factor receptors in malignant gliomas; 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

Russ Pieper PhD

Signal transduction; models of human gliomagenesis and drug resistance

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

UCSF Neuro-Oncologists Have Highest Patient Satisfaction Scores

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

Brain Tumor Center Welcomes New Neuropathologists

Neuropathologists Joanna Phillips MD, PhD and Arie Perry MD have joined the Brain Tumor Center at UCSF, providing expertise in histopathological evaluation of CNS tumors. Their research interests lie in developing diagnostic and prognostic markers and improving classification and grading schemes for brain tumors. Dr. Phillips also directs the Molecular Morphology Laboratory, which is a core resource to assist investigators in optimizing techniques for immunohistochemistry, molecular in situ studies, and laser capture microdissection.

Brain Tumor Research Center

Continuously funded by grants from the National Institutes of Health (NIH) since 1972, the Brain Tumor Research Center (BTRC) at UCSF is internationally recognized as a major research and treatment center for adults and children with tumors of the brain and spinal cord.

Several new research projects were initiated in 2010, while many of our ongoing investigations yielded significant results.

• California Institute for Regenerative Medicine (CIRM) Disease Team Award: Funded by a $19 million grant from CIRM, the BTRC will lead studies with other California institutions to genetically engineer stem cells that deliver therapeutic agents to selectively kill glioblastoma cells. If approved by the FDA, it will be tested first in patients with recurrent glioblastoma.

• NIH Program Project Grant (P01): The BTRC has been funded by a program project grant for 35 years. In 2007, BTRC investigators took this program in a new direction by incorporating studies of convection enhanced delivery into the program's overall focus on neuroimaging.

Partnering with veterinarians at UC Davis, P01 investigator Krystof Bankiewicz MD, PhD used convection-enhanced delivery of nanoliposomal CPT-11 to treat dogs with spontaneous brain tumors, which are very similar to tumors that arise in humans. CPT-11 was infused directly into the brain tumors via convection-enhanced delivery, and its distribution was monitored in real time using intraoperative MRI. Three years later, many of the dogs' tumors have shrunk or stopped growing. There has been no evidence of toxicity to normal brain tissue – a serious drawback of many other brain tumor therapies.

Manish Aghi MD, PhD gives a neurological examination

The therapy has been so successful in canines that UCSF investigators are planning to initiate a Phase I trial for human patients with recurrent glioblastoma.

The exciting developments in this ongoing project were featured in the CBS5 HealthWatch story "Brain Cancer Treatment for Dogs Could Help Humans," which aired in May 2010.

Dickinson PJ, LeCouteur RA, Higgins RJ, Bringas JR, Larson RF, Yamashita Y, Krauze MT, Forsayeth J, Noble CO, Drummond DC, Kirpotin DB, Park JW, Berger MS, Bankiewicz KS. Canine spontaneous glioma: a translational model system for convection-enhanced delivery. Neuro Oncol 2010;12(9):928-40.

• The BTRC has received a T32 Training Grant in translational brain tumor research from the NIH. The goal of this grant is to provide high-quality training and development for future researchers, and it will support four postdoctoral fellows in BTRC laboratories.

• Specialized Program of Research Excellence (SPORE): UCSF is one of only four institutions in the United States to receive funding from the National Cancer Institute for a SPORE in brain tumor research. Funding five central projects, the SPORE program also funds several Developmental Research and Career Development Awards for junior investigators.

In 2010, a SPORE Developmental Research Award was granted to neuropsychologist Caroline Racine PhD and neuro-oncologist Nicholas Butowski MD to focus on cognitive and behavioral effects of tumor and treatments. The main goal of the project is to perform a more comprehensive battery of neuropsychological tests than has previously been accomplished with brain tumor patients. Studies to date have been confined to two or three tests, mostly focusing on left-hemisphere verbal tasks. Drs. Racine and Butowski will administer tests to analyze cognition and behavior for the whole brain, gaining insight into factors such depression, anxiety, and apathy, which are often overlooked. Questionnaires will also be given to care givers, who are sometimes better able to provide accurate information regarding changes in function.

Patients with newly diagnosed glioblastoma will be tested before surgery; after surgery but before radiation and chemotherapy; and four months after initiation of radiation and chemotherapy. A parallel Career Development Award was granted to Janine Lupo PhD in the Department of Radiology to develop imaging correlates related to cognitive function.

Caroline Racine PhD

Dr. Racine Talks about the Importance of Neuropsychology in Care for Brain Tumor Patients

Q: How will the neuro-psychological tests being given in your SPORE research translate to clinical care?

A: Thinking and behavior are often rated as the most important factors in a patient's quality of life. We want to know how the various treatments we give affect these symptoms, and ultimately quality of life.

Q: How does your experience as a postdoctoral fellow in the UCSF Center for Memory and Aging transfer to your work in the Brain Tumor Center?

A: There were a lot of lessons to be learned by watching how the brain changes with neurodegenerative diseases like dementia, specifically about focality. In brain tumor patients, there are often subtle changes in personality and behavior secondary to right hemisphere tumors that have been underappreciated in the literature.

Q: How do those changes effect patients?

A: Using the example of right hemisphere tumors, there are times when patients and their families have not been educated about what effects the tumor might have on their personality and thinking. By explaining that these changes are due to the tumor location and/or treatment, the "blame" is transferred to the disease, which can improve the relationship between the patient and their family. As well, this information can help their health care providers select appropriate interventions to improve the symptoms, which might otherwise go unrecognized.

Epigenomics

The BTRC laboratory of Joseph Costello PhD has recently discovered the methylation of a body of genes may influence expression as much as methylation of the promotor region of a gene. Their findings were published in the July 2010 issue of *Nature.*

Maunakea AK, Nagarajan RP, Bilenky M, Ballinger TJ, D'Souza C, Fouse SD, Johnson BE, Hong C, Nielsen C, Zhao Y, Turecki G, Delaney A, Varhol R, Thiessen N, Shchors K, Heine VM, Rowitch DH, Xing X, Fiore C, Schillebeeckx M, Jones SJ, Haussler D, Marra MA, Hirst M, Wang T, Costello JF. Conserved role of intragenic DNA methylation in regulating alternative promoters. **Nature** 2010;466(7303):253-7.

Dr. Costello and his colleagues are also working cooperatively with other Mapping Centers and the Data Coordination Center (EDACC) funded by an NIH Roadmap mechanism to comprehensively map epigenomes of select human cells with significant relevance to complex human disease.

Bernstein BE, Stamatoyannopoulos JA, Costello JF, Ren B, Milosavljevic A, Meissner A, Kellis M, Marra MA, Beaudet AL, Ecker JR, Farnham PJ, Hirst M, Lander ES, Mikkelsen TS, Thomson JA. The NIH Roadmap Epigenomics Mapping Consortium. **Nat Biotechnol** 2010;28(10):1045-8.

Brain Tumor Symposium Brings World-Renowned Experts to UCSF

On October 22, the UCSF Helen Diller Comprehensive Cancer Center sponsored a Brain Tumor Symposium at UCSF. The symposium brought international experts on brain tumor research, including Richard Gilbertson MD, PhD and Luis Parada PhD, to the campus for a day of lectures on brain tumor biology and therapeutics.

Neurosurgeon Manish Aghi MD, PhD and ENT surgeon Ivan El-Sayed MD perform minimally invasive skull base surgery to remove a brain tumor

University of California, San Francisco
SKULL BASE SURGERY PROGRAM

Skull Base Surgery Program

Minimally invasive skull base surgery has become an increasingly important aspect of skull base surgery at leading centers throughout the country, like UCSF. Minimally invasive skull base surgery is done through small corridors in which an endoscope is used to provide a wide view, rendering these corridors as effective as the large corridors through which skull base surgery has traditionally been done, without the morbidity associated with the larger exposures.

The most commonly used corridor for minimally invasive surgery is the endonasal corridor. Through the endonasal corridor, neurosurgeons working with ENT surgeons can access pathology of the anterior and central skull base, including some meningiomas, esthesioneuroblastomas, pituitary adenomas, and chordomas. For chordomas in particular, the change has been dramatic – whereas these tumors were typically resected through aggressive transcranial operations a decade ago, the endonasal approach has been used by the team of neurosurgeons at UCSF in 21 patients over the past 5 years with minimal morbidity and comparable extent of resection. Long-term follow up is underway to document the long-term recurrence rates of resections done through this approach, but results to date with minimally invasive skull base surgery are encouraging and this program has become an exciting development at UCSF.

The California Center for Pituitary Disorders at UCSF

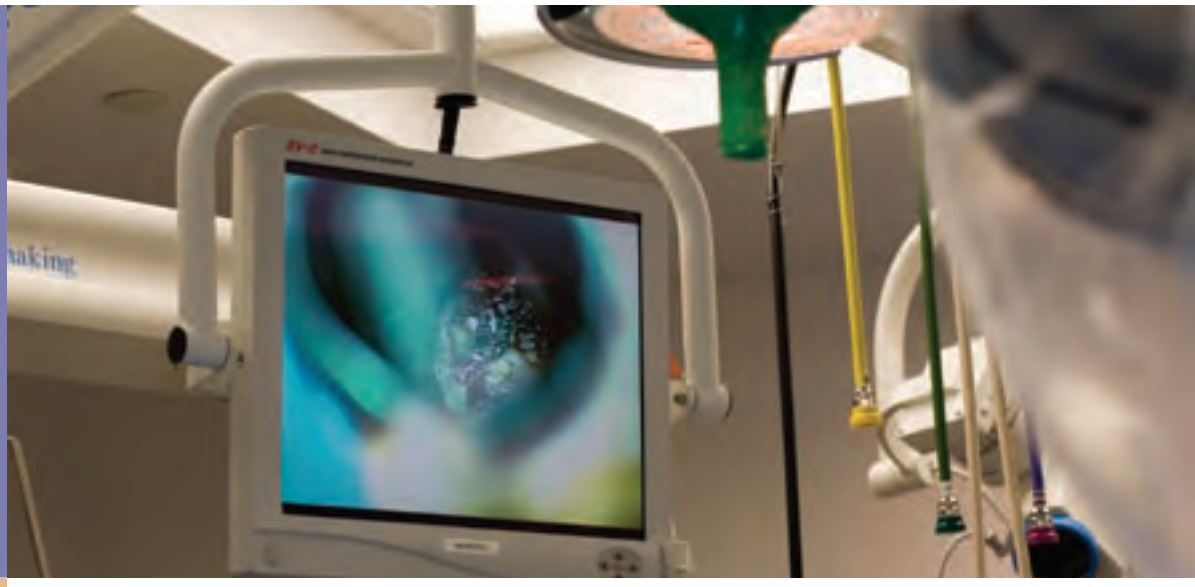
Since it was founded in 2005, the California Center for Pituitary Disorders at UCSF has become one of the largest practices for diseases of the pituitary gland and hypothalamus in the nation, treating over 500 patients in 2010.

Faculty

Lewis Blevins Jr. MD

Sandeep Kunwar MD

Manish Aghi MD, PhD



Sandeep Kunwar MD, Surgical Director and Lewis Blevins Jr. MD, Medical Director

• Investigators at the California Center for Pituitary Disorders have recently reported the largest series of patients with infected Rathke's cleft cysts (RCC), describing how to manage these patients. RCCs are benign sellar lesions that are generally asymptomatic but sometimes warrant transsphenoidal drainage. Their review found that suspected RCC infection, regardless of culture results, is a strong predictor of recurrence and may warrant antibiotic treatment. Among patients with suspected infections, but negative cultures, the recurrence rate was relatively high at 44%.

Tate MC, Jahangiri A, Blevins L, Kunwar S, Aghi MK. Infected Rathke cleft cysts: distinguishing factors and factors predicting recurrence. **Neurosurgery** 2010;67(3):762-9.

• Conivaptan is an arginine vasopression receptor antagonist administered to correct hyponatremia associated with SIADH. While overcorrection of hyponatremia is often a concern for physicians, the California Center for Pituitary Disorders has published the first report of its use in a neurosurgery unit, outside of an intensive care setting. The report concluded that the drug is safe and effective, but patients must be monitored closely.

Sughrue M, McDermott M, Blevins LS. Extreme correction of hyponatremia in a patient with intravenous conivaptan. **J Clin Neurosci** 2010;17(10):1331-4.

• Lewis Blevins Jr. MD, medical director of the California Center for Pituitary Disorders, was included in Marin Magazine's list of Best Doctors and was recently interviewed on the topic of acromegaly for the E! Entertainment TV show "Born Different: Unbelievable Medical Conditions."

Dr. Blevins was also interviewed by Patient Power on the topic of pituitary tumors. The show recording can be heard at: www.ucsfhealth.org/common/audio/blevins020910.mp3

Brain and Spinal Injury Center

Based at San Francisco General Hospital, the UCSF Brain and Spinal Injury Center (BASIC) is an internationally-recognized program for basic science research and clinical care for neurotrauma.

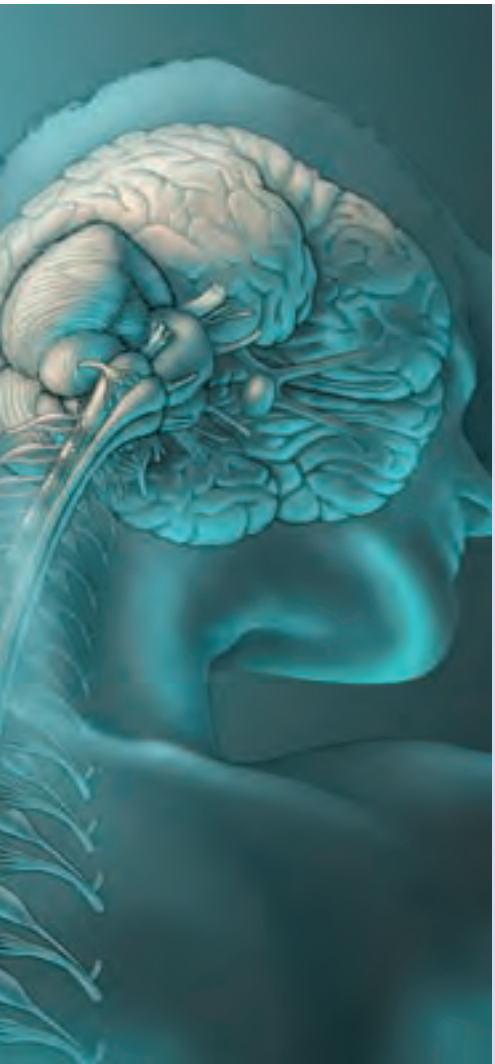
The goals of BASIC are to:

- Translate basic neuroscience into clinical practice
- Understand brain and spinal cord injury
- Train the next generation of neurotrauma clinicians and scientists
- Educate the public on neurotrauma research and clinical care

Grand Opportunity Grant – Transforming Care of Traumatic Brain Injury

Traumatic brain injury is one of the greatest unmet needs in public health – approximately 1.7 million Americans sustain a traumatic brain injury each year and 5.3 million have a chronic disability resulting from their injuries. Despite decades of research and over two dozen clinical trials, research into the mechanisms of traumatic brain injury has not translated into effective treatments. A substantial part of the problem is that the current classification system does not take into account the specific pathophysiology of each injury – it only divides them into the categories "mild, moderate, and severe."

Investigators at BASIC are leading a study funded by a $4.1 million Grand Opportunity Grant, a part of the American Recovery and Reinvestment Act, to overhaul and standardize classification for traumatic brain injury on a large scale. The multi-center study, led



Faculty

Neurotrauma, San Francisco General Hospital

Geoffrey Manley MD, PhD

Michael Huang MD

Nicholas Phan 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 after stroke

Geoffrey Manley MD, PhD

Basic, translational, and clinical traumatic brain injury research

Linda Noble-Haeusslein 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

Shirley Stiver MD, PhD

Cerebral angiogenesis in neurological injury and disease

by principal investigator and BASIC Co-Director Geoffrey Manley MD, PhD, will test and refine standards for data collection and use advanced neuroimaging methods to find better approaches for traumatic brain injury classification and outcomes. The study will follow 600 patients and 400 patients have already signed on in the first six months of enrollment.

Whyte J, Vasterling JJ, Manley GT. Common data elements for research on traumatic brain injury and psychological health: current status and future development. Arch Phys Med Rehabil, In Press.

Chun KA, Manley GA, Stiver SI, Aiken AH, Phan N, Wang V, Meeker M, Cheng SC, Gean AD, Wintermark M. Interobserver variability in the assessment of CT imaging features of traumatic brain injury. J Neurotrauma 2010;27(2):325-30.

Cohen MJ, Grossman AD, Morabito D, Knudson MM, Butte AJ, Manley GT. Identification of complex metabolic states in critically injured patients using bioinformatics cluster analysis. Crit Care 2010;14(1):R10.

San Francisco Neurological Emergencies Treatment Trials Network

The NIH-funded San Francisco Neurological Emergencies Treatment Trials (SF-NETT) network was created to provide infrastructure throughout San Francisco that allows BASIC investigators to conduct Phase III clinical trials in a wide range of neurological emergencies including status epilepticus, stroke, and neurotrauma. SF-NETT works with pre-hospital emergency medical services, the SF Department of Public Health, and all ambulance destination hospitals in San Francisco to coordinate these studies. Current trials include:

- RAMPART – a prehospital clinical trial of status epilepticus treatment
- ALIAS2 – a trial for acute ischemic stroke neuroprotection
- PROTECT III – a study to test progesterone as neuroprotection in traumatic brain injury
- POINT – a trial for acute intervention for transient ischemic attacks

BASIC Initiates Study of Combined Head and Spinal Cord Injury

Researchers at BASIC, led by Co-Director Michael Beattie PhD, have been awarded over $1.1 million by the Department of Defense Spinal Cord Injury Research Program to develop preclinical models of cases of combined head and spinal cord injury. The BASIC team is partnering with Graham Creasy at VA Health Service Palo Alto to examine the clinical condition of patients to design better animal models of combined head and spinal cord injury.

Geoffrey Manley MD, PhD and MythBusters host Grant Imahara

UCSF Neurosurgery Collaborates with the National Football League on New Head Injury Guidelines

In 2010, the Department of Neurological Surgery at UCSF has become actively involved at all levels of the concussion debate that is taking place within the National Football League (NFL). In 2010, Mitchel Berger MD, chair of Neurological Surgery at UCSF, was named to the NFL Head, Neck, and Spine Committee, focusing particularly on retired players' issues. The main goal of the committee is to draft new return-to-play guidelines and examine the consequences of repetitive head injury and concussion.

Dr. Manley also serves on the AAN Sports Concussion Guidelines Committee and was recently interviewed on ESPN's Outside the Lines, where he explained that more research, especially prospective, longitudinal studies that study players over time, is needed before we can understand the long-term effects of brain injury from concussions or high-impact collisions.

Bench Research for Spinal Cord Injury

Adam Ferguson PhD has been awarded a total of $1.8 million by the NIH in the form of two R01 research awards for the studies: "Metaplasticity and Recovery after Spinal Cord Injury: Cellular Mechanisms" and "Bioinformatics for Translational Spinal Cord Injury."

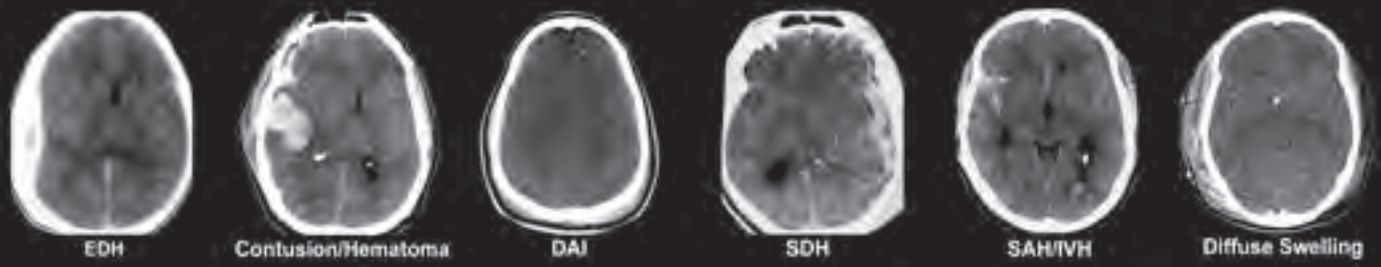
MythBusters Features BASIC Co-Director Geoffrey Manley MD, PhD

The Discovery Channel show MythBusters consulted Dr. Manley for an episode that tackled the question: "Do we really only use 10 percent of our brain?" Show host Grant Imahara met with Dr. Manley to discuss the battery of tests MythBusters would need to perform to debunk this myth. The episode aired on October 27, 2010.

NIAID Program in Radiation Combined Injury

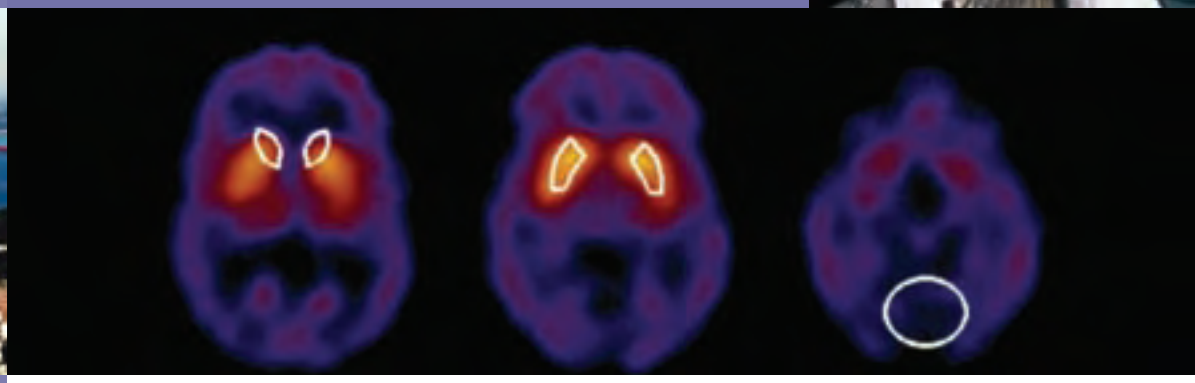
The National Institute of Allergy and Infectious Diseases (NIAID) of the NIH, initiated a program in 2008 focused on Medical Countermeasures Against Radiological and Nuclear Threats. Phased Innovation Awards (R21/R33) were first given in 2008 and the only grant focused on the central nervous system was awarded to BASIC researcher John R. Fike PhD, who is investigating the combined effects of ionizing irradiation and traumatic brain injury. After successfully completing the R21 element, Dr. Fike was awarded an R33 in 2010 for the project "Combined Radiation and Traumatic Injury Affects Hippocampal Structure and Function." The total award is for $1 million. Dr. Fike's combined injury studies are done in conjunction with BASIC investigator Susanna Rosi PhD, and they are complementary to his earlier NASA-funded studies on trauma and irradiation in the space environment.

Traumatic brain injury is primarily classified by severity and not by pathology, making standardization for clinical trials difficult. All of the injuries below are considered "severe," yet may require vastly different treatments. With funding from a federal Grand Opportunity grant, BASIC researchers are overhauling classification schemes for traumatic brain injury.




Nicholas Barbaro MD

Adult Epilepsy Surgery



Edward Chang MD Joins Epilepsy Team

In 2010, the surgical epilepsy team at UCSF was joined by neurosurgeon Edward Chang MD, who has clinical expertise in surgical therapies for intractable epilepsy. A former resident in the Department of Neurological Surgery, Dr. Chang specializes in advanced brain mapping methods and has research interests in the cortical mechanisms of language function. Together with Paul Larson MD, he is expanding UCSF's surgical epilepsy program at the San Francisco Veterans Affairs Medical Center (SFVAMC), which is a National Center of Excellence for Epilepsy. Neurological Surgery faculty at SFVAMC take a multidisciplinary approach to treating patients and work closely with neurologist Karen Parko MD and her team, who specialize in the diagnosis and treatment of epilepsy.

ROSE Trial

The Department of Neurological Surgery has begun enrolling patients in the Radiosurgery or Open Surgery for Epilepsy (ROSE) trial – a Phase III, multicenter, randomized trial of Gamma Knife radiosurgery for mesial temporal sclerosis. The NIH-funded study is led by Nicholas Barbaro MD, director of the surgical epilepsy program at UCSF, and will determine if Gamma Knife radiosurgery can provide a noninvasive, viable alternative to open surgery. There are currently 13 study sites in the United States, and three more will be opening in Canada and the U.K. in 2011.

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 more information or to enroll a patient, contact Erica Terry at (415) 476-2180.

Barbaro NM, Quigg M, Broshek DK, et al. A multicenter, prospective pilot study of Gamma Knife radiosurgery for mesial temporal lobe epilepsy: seizure response, adverse events, and verbal memory. **Ann Neurol** 2009; 65(2):167-75.

DBS for Epilepsy Not Approved

The U.S. FDA has yet to approve deep brain stimulation (DBS) as a treatment for epilepsy, despite the results of Medtronic Inc.'s SANTE (Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy) clinical trial, which demonstrated some benefit for patients. The European Medicines Agency approved DBS for intractable epilepsy in September 2010.

Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. **Epilepsia** 2010;51(5):899-908.

ROSE

Epilepsy Research

Progenitor Cell Transplantation for Epilepsy

Epileptic seizures result from uncontrolled electrical signaling in the brain, and failure of interneurons to inhibit excitatory circuits may play a role in the onset of seizures. In preclinical studies, the laboratories of Scott Baraban PhD, Arturo Alvarez-Buylla PhD, and John Rubenstein MD, PhD transplanted adult mouse progenitor cells into a mouse model of epilepsy, where they differentiated into interneurons. Transplanted interneurons were able to integrate into the neocortex and produce GABA – an inhibitory neurotransmitter – that blocked spontaneous seizures in the mice.

In 2010, several grants were awarded to Department of Neurological Surgery investigators to build on the breakthroughs of this work and examine the potential for developing a human progenitor cell therapy for epilepsy:

• California Institute of Regenerative Medicine Early Translational II Award "Inhibitory Nerve Cell Precursors: Dosing, Safety and Efficacy" (Principal Investigator: Arturo Alvarez-Buylla): This award will fund research to develop a human embryonic stem cell (hESC) line from progenitors in the medial ganglionic eminence (MGE) that can differentiate into interneurons. These neurons are expected to inhibit hyperactive neural circuits in a mouse model of epilepsy. UCSF investigators will implant the human-derived cells into mice to determine the dose needed to increase inhibition and to examine potential effects on the host neurons. This project will also involve developing assays to determine the stages of hESC differentiation into MGE cells prior to implantation.

• NIH R01 "An Interneuron-based Cell Therapy For Epilepsy" & NIH R21 "Interneurons and Epilepsy in Dlx1 Mutant Mice" (Principal Investigator: Scott Baraban): The grant proposals for these awards were scored in the top two percent by NIH reviewers. In these studies, mouse embryonic progenitor cells from the MGE, which can differentiate into interneurons, will be transplanted into the brains of adult mice with temporal lobe epilepsy and of adult mice with a genetic form of epilepsy (Dlx1 mutant mice). The goal will be to determine if interneurons arising from embryonic MGE progenitor cells can inhibit seizure activity caused by these distinct forms of epilepsy.

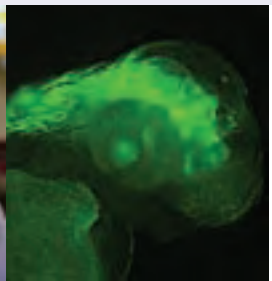
Baraban SC, Southwell DG, Estrada RC, Jones DL, Sebe JY, Alfaro-Cervello C, García-Verdugo JM, Rubenstein JL, Alvarez-Buylla A. Reduction of seizures by transplantation of cortical GABAergic interneuron precursors into Kv1.1 mutant mice. **Proc Natl Acad Sci USA** 2009;106(36):15472-7.

A New Model of Spontaneous Epilepsy in Zebrafish

The laboratory of Scott Baraban PhD has developed the first model of spontaneous epilepsy in a zebrafish. Dr. Baraban and his colleagues have shown that fish with a mutant form of the gene E3 ubiquitan ligase (mind bomb mutants) exhibit grossly abnormal brain structure during development and spontaneous epilepsy. Previously, epilepsy models in zebrafish were achieved by exposing the fish to convulsant drugs.

To date, microarray analyses of the mind bomb mutants have shown down regulation of several genes necessary for GABA-mediated signaling, which adds to a growing body of evidence indicating that a decrease in GABA plays a role in the onset of epileptic seizures. The new model will allow for high-throughput screening of potential targets involved in epilepsy, as well as new therapeutic agents.

Horotopan GA, Dinday MT, Baraban SC. Spontaneous seizures and altered gene expression in GABA signaling pathways in a mind bomb mutant zebrafish. **J Neurosci** 2010;30(41)13718-28.



Left: Zebrafish provide models of epilepsy for research.

Center: Scott Baraban PhD

Right: Mind bomb mutant zebrafish have abnormal brain development patterns and spontaneous epileptic seizures.

Movement Disorders Program

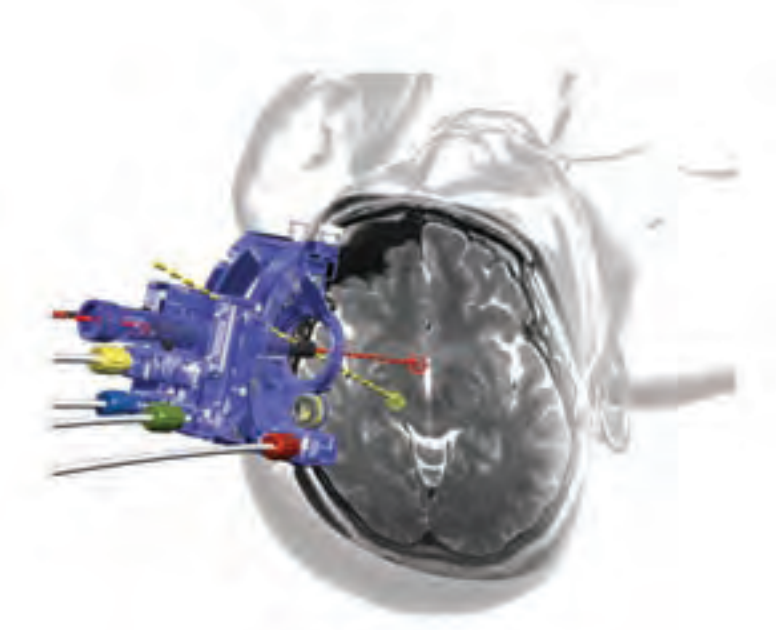
The Department of Neurological Surgery at UCSF is home to the largest movement disorders surgery practice in the Western United States – treating over 1000 patients since 1998 for debilitating disorders such as Parkinson's disease, essential tremor, spasticity, and dystonia. Our research is aimed at better understanding the fundamental mechanisms of these disorders and finding new therapies that can be moved to clinical trials. Our faculty are at the forefront of new techniques for surgical treatment, gene transfer, and drug-delivery methodologies that are changing the face of clinical care for movement disorders.

ClearPoint System for DBS Approved by the FDA

In June 2010, the FDA approved ClearPoint – a new system for performing deep brain stimulation (DBS) for movement disorders using interventional MRI. The system is used inside the scanner itself and has substantially shortened operating time for DBS cases. The technique is attractive to patients because they can have the surgery under general anesthesia, rather than in the awake state required for the standard surgical method for DBS implantation.

ClearPoint was developed by UCSF neurosurgeons Paul Larson MD and Philip Starr MD, PhD together with MR physicist Alastair Martin PhD and the medical device company SurgiVision. It includes an MRI-compatible skull-mounted aiming device and MR coils specifically designed to provide optimal imaging during surgery, eliminating the need for a stereotactic frame and physiological recording. The new software environment streams data from any manufacturer's 1.5T MRI scanner and guides the surgeon through the implantation procedure using a specially designed graphical interface. The scientific article describing the technique of DBS insertion using interventional MRI was featured on the cover of the March 2010 issue of *Journal of Neurosurgery.*

Starr PA, Martin AJ, Ostrem JL, Talke P, Levesque N, Larson PS. Subthalamic nucleus deep brain stimulator placement using high-field interventional magnetic resonance imaging and a skull-mounted aiming device: technique and application accuracy. J Neurosurg 2010;112(3):479-90.



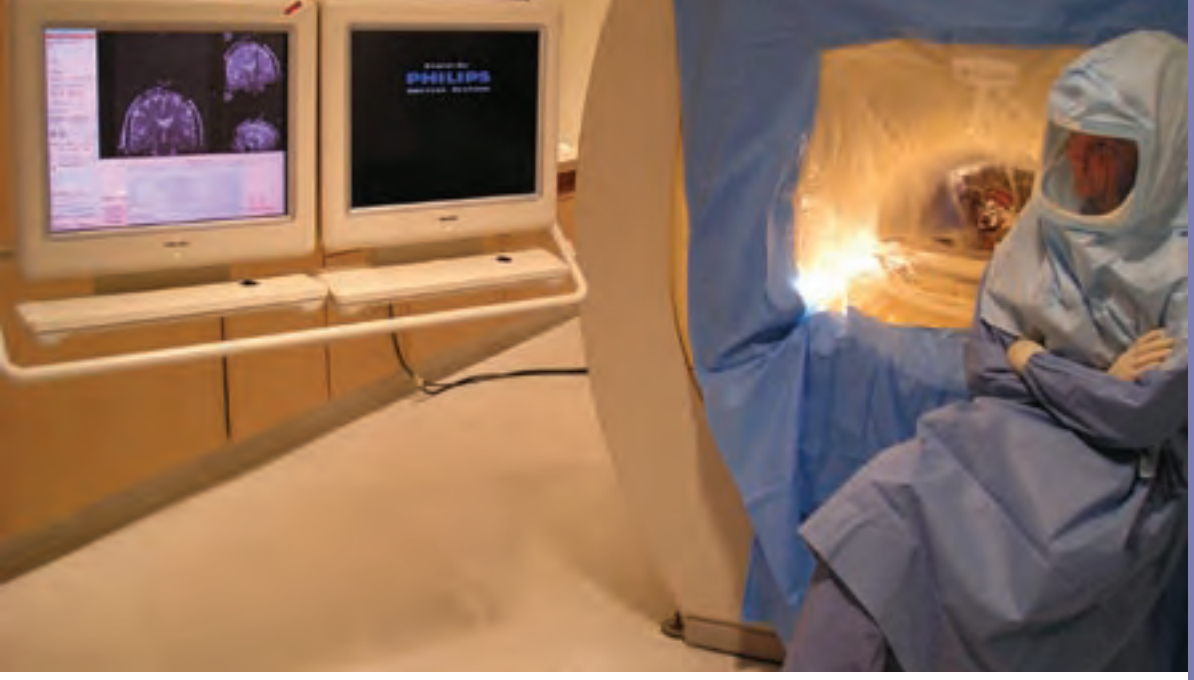
The ClearPoint system allows DBS for movement disorders to be performed using interventional MRI.

New Clinical Trial of AAV-Neuturin for Parkinson's Disease

UCSF is participating in an eight-center, Phase II trial of a gene encoding a dopaminergic growth factor (neurturin) for mid-stage Parkinson's disease. Unlike previous trials of this gene therapy that targeted the striatum, the current trial is injecting the gene into the nigra compacta. This is the area of the brain where cell bodies of degenerating dopamine cells exist, potentially making it a better delivery site for the therapy. The first patient in this new nation-wide study was operated on at UCSF in October 2010.

Verdict Reached on Region of Brain to Target with DBS for Parkinson's disease

In June 2010, the largest study of DBS for Parkinson's disease ever performed was published in the *New England Journal of Medicine.* Although DBS is the gold standard for the surgical care of movement disorders, there has been continued debate over which area of the brain is best to stimulate – the globus pallidis interna (GPi) or the subthalamic nucleus (STN). The trial was carried out at seven VA and



The interventional MRI suite at UCSF Medical Center

six university hospitals and randomized 300 patients (including 80 at UCSF) to receive DBS in either the GPi or STN.

The results showed that stimulation of GPi and STN were equal in motor benefit, but GPi was shown to be slightly safer for patients with impaired cognitive function or depression. These findings are now changing the way DBS surgery is performed for Parkinson's patients with those symptoms and leading doctors to consider factors other than motor function when deciding what area of the brain to target.

Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, Marks WJ Jr, Rothlind J, Sagher O, Moy C, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein JM, Stoner G, Starr PA, Simpson R, Baltuch G, De Salles A, Huang GD, Reda DJ; CSP 468 Study Group. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. **N Engl J Med** 2010;362(22):2077-91.

Novel Brain Target for the Treatment of Cervical Dystonia

Philip Starr MD, PhD, co-director of the Functional Neurosurgery Program, and UCSF neurologist Jill Ostrem MD have completed a prospective pilot trial of a novel approach to the treatment of cervical dystonia: DBS of the subthalamic nucleus. The technique is shown to reduce the incidence of debilitating adverse effects, in comparison with prior studies utilizing different brain targets.

DBS to Modulate Tinnitus

Recently featured on the September cover of *Neuroscience,* Paul Larson MD, Chief of Neurosurgery at San Francisco Veterans Affairs Medical Center, and colleague Steven Cheung MD in the UCSF Department of Otolaryngology have shown that using deep brain stimulation to acutely stimulate the caudate nucleus in patients with Parkinson's disease and tinnitus can result in a decrease in tinnitus loudness perception. The caudate nucleus is not considered to be part of the traditional auditory pathway, and this is the first work to suggest that the caudate is involved in auditory perception. The findings from this initial study will likely pave the way for new studies to investigate DBS as a future treatment for patients with severe tinnitus. The work was also featured in the October issue of Discover magazine.

Cheung SW, Larson PS. Tinnitus modulation by deep brain stimulation in locus of caudate neurons (area LC). **Neuroscience** 2010;169(4):1768-78.

Zimmer C. "Ringing in the ears" actually goes much deeper than that. **Discover.** October 27, 2010. http://discovermagazine.com/2010/oct/26-ringing-in-the-ears-goes-much-deeper.

Pathophysiology Studies of Movement Disorders

Dr. Starr has received an R01 award from the NIH to investigate cortical and basal ganglia local field potentials in movement disorders. By studying cortical physiology in patients with Parkinson's disease, primary dystonia, and essential tremor, as well subjects without movement disorders, Dr. Starr and postdoctoral fellow Coralie DeHemptinne, are testing the theory that the symptoms of movement disorders are produced by pathological oscillations in the circuit connecting the cortex and basal ganglia.

Faculty

Movement Disorders Surgery

Philip A. Starr MD, PhD

Nicholas Barbaro MD

Edward Chang MD

Paul S. Larson MD

Daniel A. Lim MD, PhD

Movement Disorders Research Laboratories

Krystof Bankiewicz MD, PhD

Gene therapy for Parkinson's disease

Paul S. Larson MD

Neurotransplantation strategies for Parkinson's disease; intraoperative neuroimaging

Philip A. Starr MD, PhD

Surgical treatment of movement disorders; basal ganglia physiology in movement disorders

Intaoperative Image-Guided Delivery

Direct, intraoperative delivery of genes or drugs into the brain has been a major area of interest for researchers of neurodegenerative disorders and brain cancers. However, until now, it was difficult to determine how much of the agent reached the target and how much of it may have leaked into the cerebrospinal fluid or gone to other sites in the brain.

Kyrstof Bankiewicz MD, PhD and members of his laboratory have designed a novel system to visualize delivery of agents into the brain in real time using MRI. Over 10 years in development, it is now being used in a variety of clinical applications, including the first clinical trials of image-guided intraoperative delivery of gene therapy, being performed at UCSF.

Funding to validate image-guided delivery as the method of choice for gene delivery was provided by the Michael J. Fox Foundation and the NIH.

Su X, Kells AP, Aguilar Salegio EA, Richardson RM, Hadaczek P, Beyer J, Bringas J, Pivirotto P, Forsayeth J, Bankiewicz KS. Real-time MR imaging with Gadoteridol predicts distribution of transgenes after convection-enhanced delivery of adeno-associated virus (AAV)2 vectors. **Mol Ther** 2010;18(8):1490-5.

Upcoming Clinical Trials with Intraoperative Image-Guided Delivery

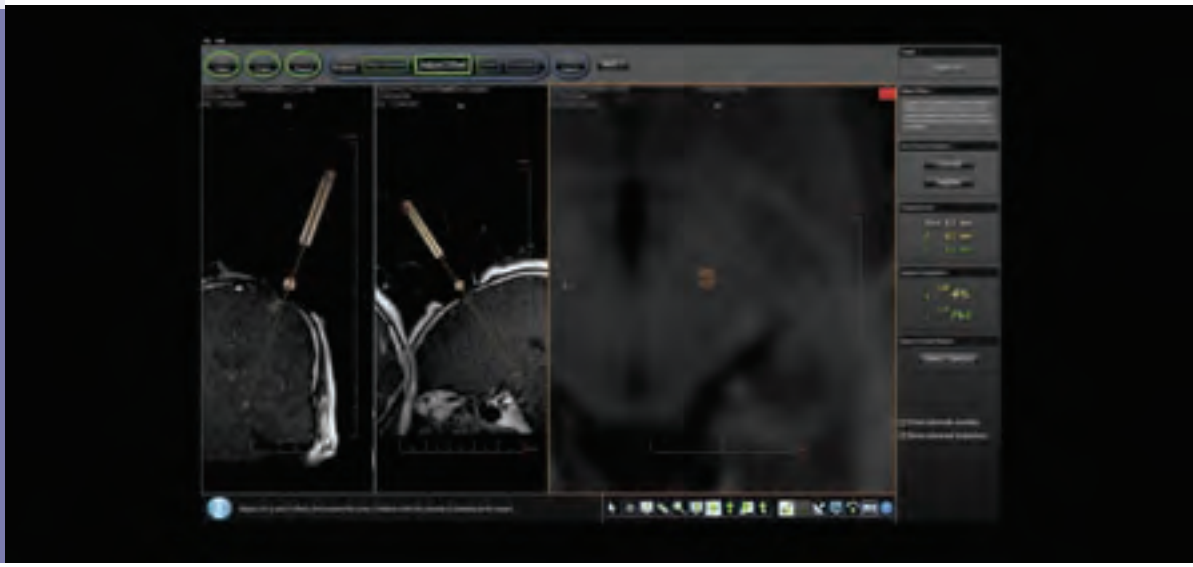
• With funding from the National Institute of Neurological Disorders (NINDS), a Phase I clinical trial of image-guided delivery of glial cell-derived neurotrophic factor (GDNF) for Parkinson's disease is in development. This will be the first trial for image-guided delivery of viral vectors in humans.

• In a Phase I clinical trial for Parkinson's disease performed at UCSF last year, the gene for the enzyme AADC, which converts L-dopa into dopamine, was delivered via convection enhanced delivery to 10 patients. All patients had improvement in off-label Unified Parkinson's Disease Rating Scale scores and persistent gene expression was demonstrated on neuroimaging. A Phase II trial using the new image-guided delivery system developed by the Bankiewicz laboratory will begin in 2011 at UCSF.

• UCSF will initiate a Phase I trial of AAV2-AADC using intraoperative infusion in children with AADC deficiency. AADC deficiency is an extremely rare pediatric disorder in which children are unable to form dopamine and serotonin, resulting in severe symptoms, similar to those seen in Parkinson's disease, or death. The study will be funded by the NIH Office of Rare Disease Research in their continued efforts to support research for orphan diseases.

Gene Transfer in Primate Models of Parkinson's Disease – Breakthroughs from the Bankiewicz Laboratory

• A study demonstrating that high GDNF expression promotes restoration of the



The ClearPoint software allows the surgeon to view the MR images in different orientations to guide DBS electrode implantation.

Neurological Surgery for Obsessive Compulsive Disorder

The first surgery to treat severe obsessive compulsive disorder with deep brain stimulation at UCSF was performed in October 2010. The treatment was FDA approved under a special humanitarian device exemption last year for patients with severe, medically refractory obsessive compulsive disorder. Neurosurgeon Paul Larson MD and psychiatrist Maria Pease MD performed the procedure on a woman from the Bay Area with both severe OCD and major depression. Potential patients for this cutting-edge therapy are being evaluated in the UCSF Department of Psychiatry under the direction of Dr. Pease and her colleague Dr. Carol Mathews, Director of UCSF's Obsessive Compulsive Disorders Clinic.

dopaminergic system in a primate model of advanced Parkinson's disease may provide impetus for clinical studies with new drug-delivery methodologies in patients with advanced stages of the disease. GDNF has previously only shown a neuroprotective effect in preclinical models because it was given prior to the appearance of extensive nigrostriatal degeneration, which is a hallmark of patients with Parkinson's disease. This study is important because it established the likely permanent nature of neurological gene therapy and its inherent safety.

Kells AP, Eberling J, Su X, Pivirotto P, Bringas J, Hadaczek P, Narrow WC, Bowers WJ, Federoff HJ, Forsayeth J, Bankiewicz KS. Regeneration of the MPTP-lesioned dopaminergic system after convection-enhanced delivery of AAV2-GDNF. **J Neurosci** 2010;30(28):9567-77.

• In the longest known study of AAV-mediated gene expression in nonhuman primate brain, primates infused with AAV2-human L-amino acid decarboxylase (hAADC) to treat Parkinson's disease exhibit strong expression of the gene and restoration of AADC activity (leading to restored normal response to levodopa) eight years after infusion.

Hadaczek P, Eberling JL, Pivirotto P, Bringas J, Forsayeth J, Bankiewicz KS. Eight years of clinical improvement in MPTP-lesioned primates after gene therapy with AAV2-hAADC. **Mol Ther** 2010;18(8):1458-61.

Axonal-Mediated Delivery of Genes to Cortex

A new method has been identified for axonal-mediated delivery of gene therapies to discrete regions of the cortex. Dr. Bankiewicz, together with John Forsayeth PhD and their colleagues, have shown that viral-vector delivery to specific regions of the cortex is possible by injecting the vector into the thalamus, where axonal projections transport the vector to the cortex via an anterograde transport mechanism. The laboratory is currently building on these novel findings by mapping the thalamus to predict the corresponding regions of the cortex. By understanding how to direct gene therapies to the appropriate part of the cortex, it might be possible to target diseases of the cortex much more precisely.

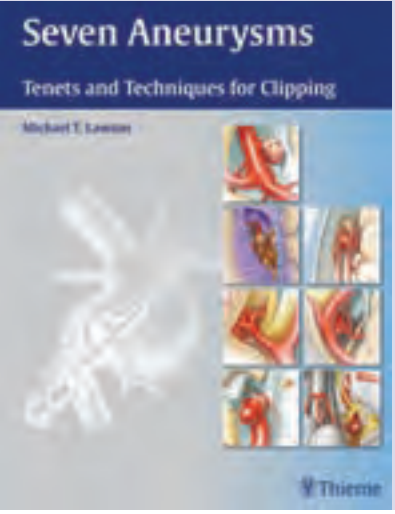
Salegio EA, Kells AP, Richardson RM, Hadaczek P, Forsayeth J, Bringas J, Sardi SP, Passini MA, Shihabuddin LS, Cheng SH, Fiandaca MS, Bankiewicz KS. Magnetic resonance imaging-guided delivery of adeno-associated virus type 2 to the primate brain for the treatment of lysosomal storage disorders. **Hum Gene Ther** 2010;21(9):1093-103.

Kells AP, Hadaczek P, Yin D, Bringas J, Varenika V, Forsayeth J, Bankiewicz KS. Efficient gene therapy-based method for the delivery of therapeutics to primate cortex. **Proc Natl Acad Sci USA** 2009;106(7):2407-11.

Varenika V, Kells AP, Valles F, Hadaczek P, Forsayeth J, Bankiewicz KS. Controlled dissemination of AAV vectors in the primate brain. **Prog Brain Res** 2009;175:163-72.

Designed Transcription Factors and Parkinson's Disease

The Bankiewicz group has been working with Sangamo BioSciences, Inc. to develop an artificial protein switch that can specifically turn on the gene for a growth factor, GDNF, which shows promise in restoring function in Parkinson's disease. They have shown that a viral vector containing the gene switch could turn on the endogenous GDNF gene when injected into rat striatum. More importantly, they showed that this approach could substantially retard the actions of a toxin that produces Parkinson's symptoms in rats. Recently, the Michael J. Fox Foundation awarded the team, lead by Steven Zhang PhD, a development grant to further improve the therapy before initiating clinical study in Parkinson's patients.



Vascular Neurosurgery Program

The Vascular Neurosurgery Program at UCSF specializes in treating brain aneurysms, subarachnoid hemorrhage, arteriovenous malformations, cavernous malformations, stroke, and intracranial hemorrhage.

Above: Seven Aneurysms: Tenets and Techniques for Clipping, by Michael Lawton MD, was published in 2010 and details common aneurysms treated by neurosurgeons.

Below: Michael Lawton MD uses advanced microsurgical techniques to perform a bypass for ischemia.

During the past year, members of the Vascular Neurosurgery Program have produced several notable publications aimed at advancing care and knowledge of cerebrovascular disorders:

• Seven Aneurysms: Tenets and Techniques for Clipping is a single-author text written by Chief of Vascular Neurosurgery, Michael Lawton MD. Summarizing Dr. Lawton's experience with 2500 aneurysms, this reference book contains 450 illustrations and covers techniques and strategies for common aneurysms that neurosurgeons will be treating in the future.

Lawton MT. Seven Aneurysms: Tenets and Techniques for Clipping. New York, NY: Thieme; 2010.

• The UCSF Cerebrovascular Research Center developed a new grading scale for arteriovenous malformations (AVMs), which supplements the Spetzler-Martin grading scale and is used to identify patients with AVMs who are good surgical candidates. While the Spetzler-Martin scale evaluates AVM site, venous drainage, and eloquence, the UCSF scale takes into account AVM bleeding, age of patient, and AVM diffuseness.

Lawton MT, Kim H, McCulloch CE, Mikhak B, Young WL. A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. Neurosurgery 2010;60(4):702-13.

• A large intracranial bypass series was published describing the advancement from extracranial-intracranial bypass to intracranial-intracranial bypass over a decade.

Sanai N, Zador Z, Lawton MT. Bypass surgery for complex brain aneurysms: An assessment of intracranial-intracranial bypass. Neurosurgery 2009;65(4):670-83.

• The UCSF experience with previously coiled aneurysms demonstrated that aneurysms that recur after coiling can be clipped and often bypassed.

Waldron JS, Halbach VV, Lawton MT. Microsurgical management of incompletely coiled and recurrent aneurysms: Trends, techniques, and observations on coil extrusion. Neurosurgery 2009;64 (ONS Suppl 2):301-17.

• UCSF neurosurgeons reported two variations of surgical approach that improve surgical access and exposure to cavernous

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

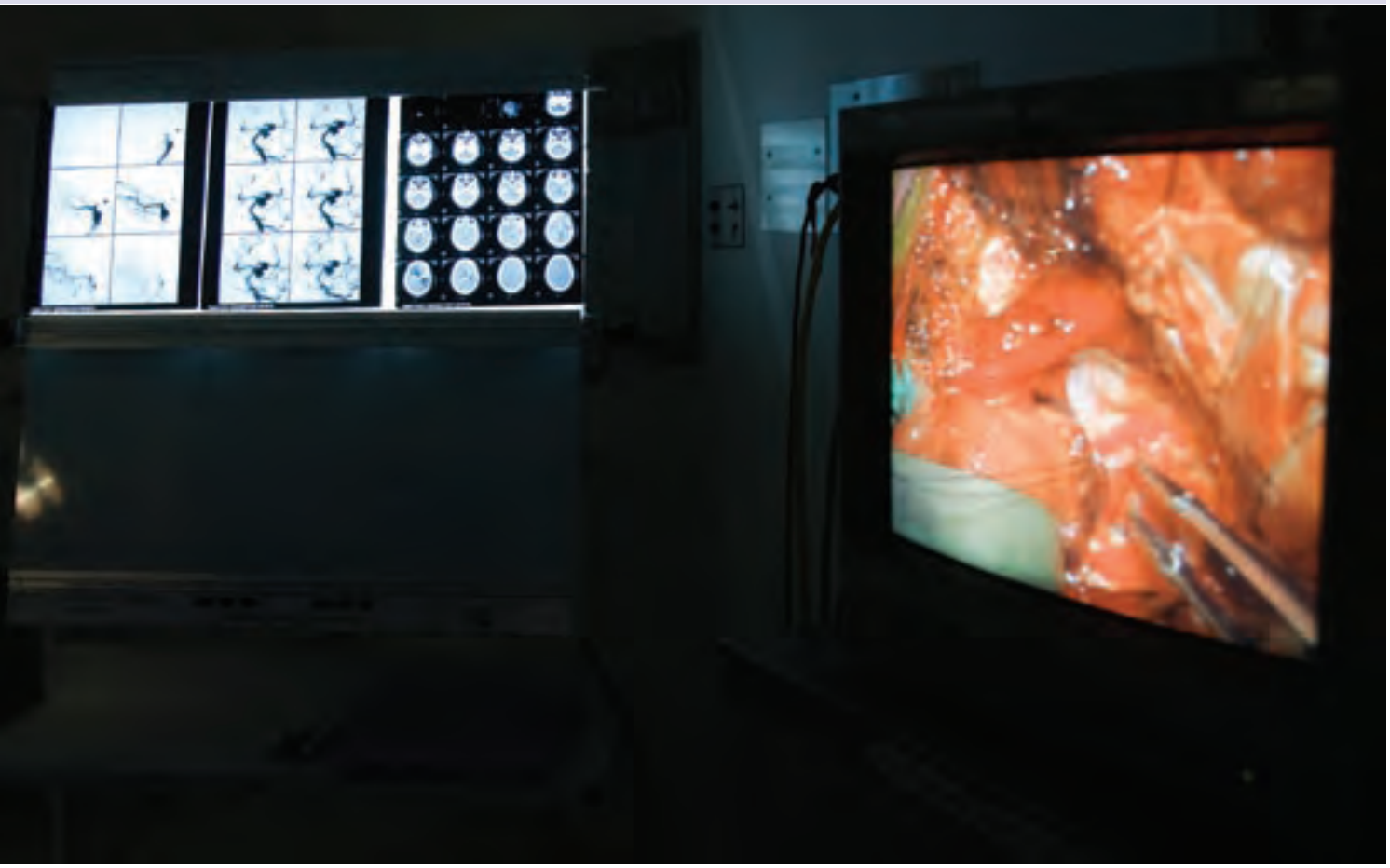
Neurogenesis and functional recovery after stroke

S. Scott Panter PhD

Animal models of stroke and traumatic brain injury

William Young MD

Pathophysiology of arteriovenous malformations; hemodynamics of aneurysms; predictors of brain hemorrhage in patients with AVMs



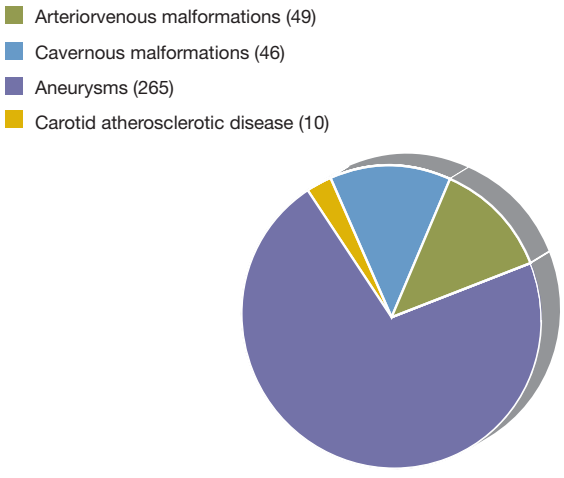
malformations and AVMs, making these procedures safer for patients.

Sanai N, Mirzadeh Z, Lawton MT. Supracerebellar-supratrochlear and infratentorial-infratrochlear approaches: Gravity-dependent variations of the lateral approach over the cerebellum. **Neurosurgery** 2010;66 (ONS 2): 264-74.

• A comparison of various surgical approaches to cavernous malformations with outcomes over a decade at UCSF was published to aid neurosurgeons in choosing the best approach for each case.

Chang EF, Gabriel RA, Potts MB, Berger MS, Lawton MT. Supratentorial cavernous malformations in eloquent and deep locations: Surgical approaches and outcomes [published online ahead of print July 2, 2010]. **Journal Neurosurg.** doi: 10.3171/2010.5.JNS091159

Vascular Neurosurgery Cases at UCSF in 2010



Neurospinal Disorders Program

The Neurospinal Disorders Program provides comprehensive treatment for all pathologies affecting the spine and peripheral nerves. The program is based in the Department of Neurological Surgery and is a component of the UCSF Spine Center.

Faculty

Christopher Ames MD

Praveen Mumaneni MD

Philip Weinstein MD

Dean Chou MD

Nicholas Barbaro MD

Multi-Center Collaborations

All members of the Neurospinal Disorders Program are also members of collaborative research teams that work to gather high-quality data and perform prospective, longitudinal studies on patients with spinal disorders.

• The International Spine Study Group (ISSG) — an international research group composed of leading physicians in spinal deformity surgery. Christopher Ames MD, co-director of the Neurospinal Disorders Program and director of spinal deformity, is currently involved in an ISSG study examining clinical outcomes for patients receiving lumbar osteotomy.

• NeuroPoint Alliance — a multi-center, prospective registry that collects data on patients who receive lumbar surgery for lumbar disc degeneration, herniated discs, or spondylolisthesis. By following these patients for a minimum of two years, the team will gather valuable data on outcomes following surgery for these disorders.

• The Scoliosis Research Society — a non-profit organization made up of physicians and health professionals dedicated to education, research, and treatment of spinal deformity. Dr. Ames was recently named to the Morbidity and Mortality Committee, which has examined complications associated with pediatric scoliosis surgery.

Reames DL, Smith JS, Fu KM, et al. Complications in the Surgical Treatment of 19,360 Cases of Pediatric Scoliosis: A Review of the Scoliosis Research Society Database [published online ahead of print Oct 28 2010]. Spine (Phila Pa 1976). doi: 10.1097/BRS.0b013e3181f3a326.

Improving Spinal Care for Elderly Patients: New High-Risk Spine Team and Research Models

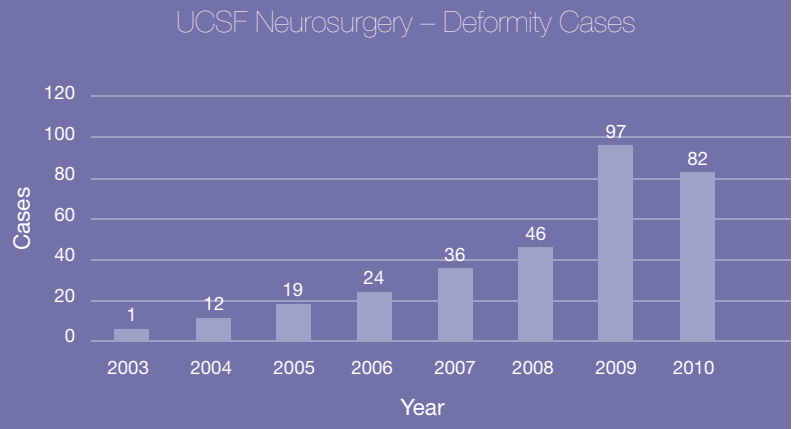
• A high-risk spine team has been formed at UCSF to improve surgical care for elderly patients (> 65 years) with spinal tumors or deformity, who are at increased risk for complication during surgery. Each patient is treated by a hospitalist and a nutritionist who optimizes the patient's diet prior to surgery. Surgery is performed by Dr. Ames and orthopaedic surgeon Vedat Deviren MD, who operate simultaneously on each case. Preliminary data has shown that blood loss during these surgeries is less than half of what is lost during a surgery performed by a single surgeon (at UCSF), and operating time is 2.5 hours shorter.

Cloyd JM, Acosta FL Jr, Cloyd C, Ames CP. Effects of age on perioperative complications of extensive multilevel thoracolumbar spinal fusion surgery. J Neurosurg Spine 2010;12(4):402-8.

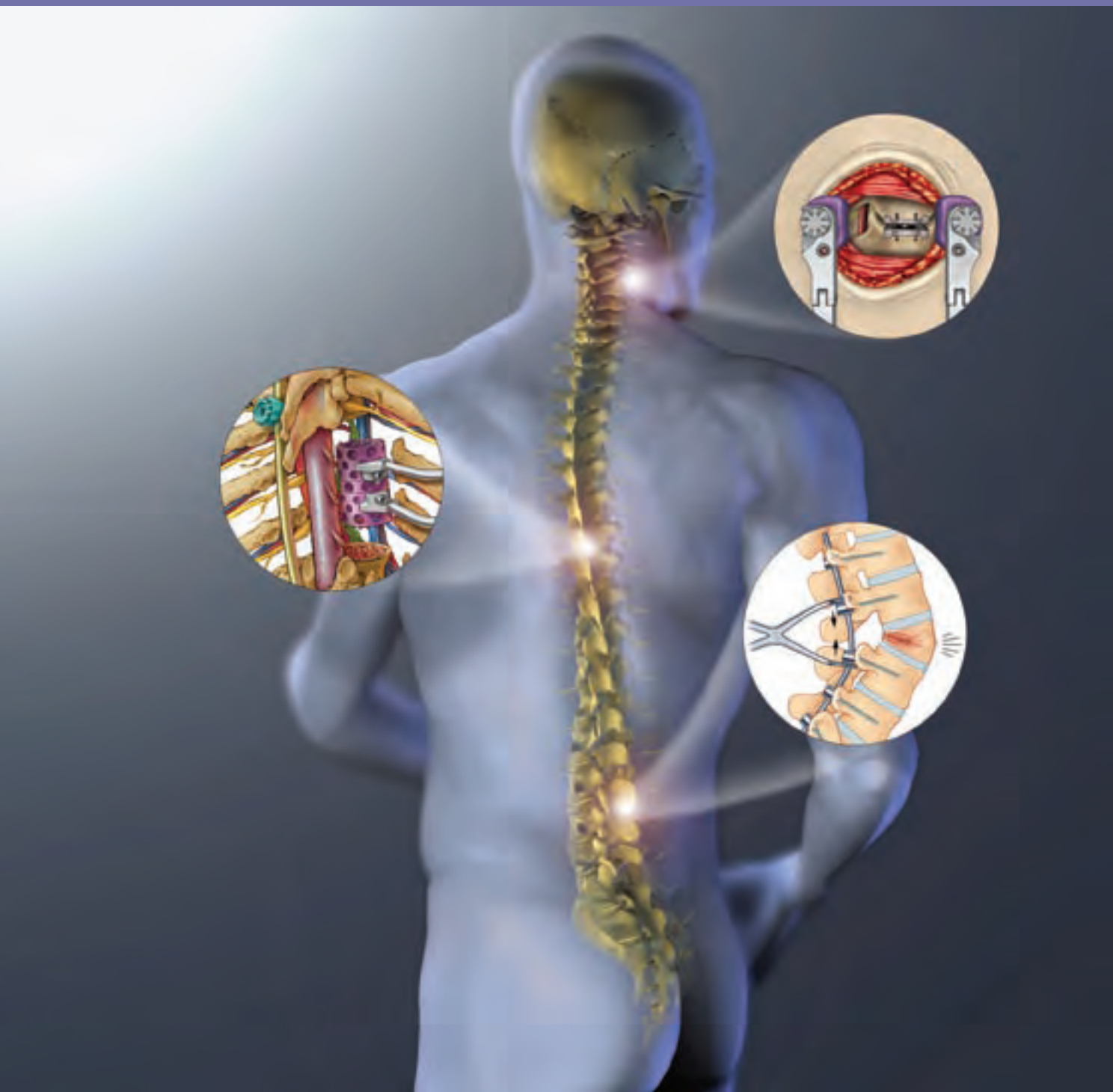
• Praveen Mummaneni MD, co-director of the Neurospinal Disorders Program, has recently begun a collaboration with scientists Jacqueline Bresnehan PhD and Michael Beattie PhD at the Brain and Spinal Injury Center to develop models of spinal cord injury in elderly patients. Very few animal models that accurately mimic an elderly spinal cord exist, even though this population is generally at greater risk for injury.

Spinal Deformity in Patients with Parkinson's Disease

Movement disorders and spine care specialists at UCSF work together closely to care for patients with both Parkinson's disease and spinal deformity. Although there is little guidance for management, this issue is becoming increasingly relevant with a growing elderly population of Parkinson's patients. Spinal deformity can be a consequence of Parkinson's disease, and a recent study at UCSF demonstrated a 50% complication rate for operations on these patients. Adjacent segment degeneration and junctional kyphosis are common in Parkinson's patients, and these patients often require multiple surgeries to treat spinal deformity.



Surgical case volumes for spinal deformity have been steadily increasing at the UCSF Spine Center



Upadhyaya CD, Starr PA, Mummaneni PV. Spinal deformity and Parkinson disease: a treatment algorithm (Review). Neurosurg Focus 2010;28(3):E5.

Prestige Cervical Artificial Disc – Five-Year Results

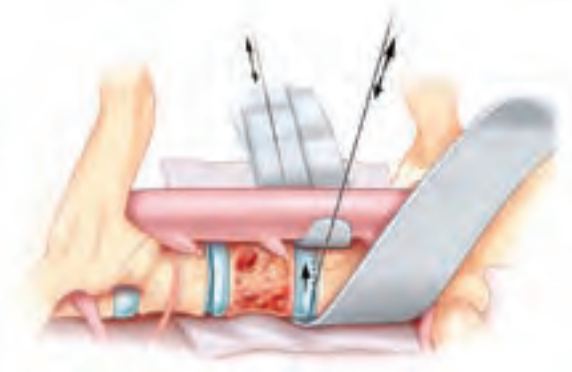
The five-year results of the Prestige® cervical artificial disc trial were published in September 2010 in *Journal of Neurosurgery Spine,* and showed that the replacement was effective at maintaining motion at five years. The study enrolled young patients needing one cervical disc decompression and reported the longest follow-up of any prospective, randomized cervical spine trial performed in the U.S.

Burkus JK, Haid RW, Traynelis VC, Mummaneni PV. Long-term clinical and radiographic outcomes of cervical disc replacement with the Prestige disc: results from a prospective randomized controlled clinical trial. J Neurosurg Spine 2010;13(3):308-18.

Minimally Invasive Spine Surgery for Scoliosis

The minimally invasive spine surgery program at UCSF, which focuses on outpatient and short-stay spinal surgery, continues to expand. Our team recently published one of few reports of outcomes for minimally invasive spine surgery for scoliosis, suggesting that it is a promising method for reducing surgical morbidity.

Wang MY, Mummaneni PV. Minimally invasive surgery for thoracolumbar spinal deformity: initial clinical experience with clinical and radiographic outcomes Neurosurg Focus 2010;28(3):E9.



They have also developed a new minimally invasive technique to remove spinal tumors that involves small openings, less blood loss, and less morbidity.

Chou D, Lu DC. Mini-open transpedicular corpectomies with expandable cage reconstruction. J Neurosurg Spine. In press.

Spinal Tumors

• Surgical Techniques

The members of the Neurospinal Disorders Program are experts in the treatment of primary and metastatic tumors occurring from the skull base to the sacrum. Over 150 spine tumor surgeries are performed at UCSF each year and our surgeons are continually at the forefront of developing new techniques for optimal resection.

Acosta FL Jr, Sanai N, Cloyd J, Deviren V, Chou D, Ames CP. Treatment of Enneking Stage 3 Aggressive Vertebral Hemangiomas With Intralesional Spondylectomy: Report of 10 Cases and Review of the Literature [published online ahead of print Sep 14 2010]. J Spinal Disord Tech.

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):435-45.

Scheer JK, Tang J, Eguizabal J, et al. Optimal reconstruction technique after C-2 corpectomy and spondylectomy: a biomechanical analysis. J Neurosurg Spine 2010;12(5):517-24.

• Neuropathology Review

In collaboration with UCSF neurospinal surgeons and neuroradiologists, the Division of Neuropathology has begun an intensive review of a database of 352 primary spinal cord and nerve root tumors treated since 1983. Pathological and anatomical characteristics of the tumors are being correlated with clinical outcome after surgery with respect to neurological deficit, tumor recurrence, response to radiation therapy, and need for repeat operations. Preliminary results in 134 ependymomas and 178 nerve sheath tumors have identified pathological characteristics that will more accurately define criteria for classification and prediction of results of surgery.

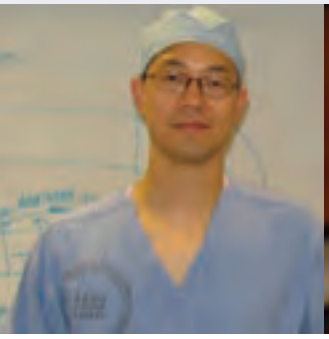
Naujokas A, Modera P, Weinstein P, Tihan T. Uncommon Patterns and Clinical Features of Peripheral Nerve Sheath Tumors of the Spinal Cord: UCSF Experience 1983-2010. To be presented February 26 – March 4, 2011 at the 100th Annual Meeting of the United States and Canadian Academy of Pathology, San Antonio, TX.

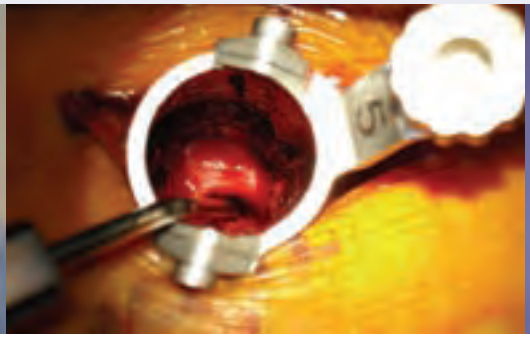
Naujokas A, Modera P, Weinstein P, Tihan T. Spinal Cord Ependymomas: UCSF Experience 1983-2010. To be presented February 26 – March 4, 2011 at the 100th Annual Meeting of the United States and Canadian Academy of Pathology, San Antonio, TX.

• Analysis of Surgical Technique Shows Improved Neurologic Recovery

For patients with spinal cord compression from tumors, infection, or trauma, Dean Chou MD and colleagues have shown that approaching these pathologies from the back instead of through the chest or abdomen leads to a better rate of neurological recovery. The team believes this may be because the decompression occurs in a circumferential manner, as opposed to just on one side. Although this represents preliminary data, it appears that this approach can improve neurologic recovery.

Lu DC, Lau D, Lee JG, Chou D. The transpedicular approach compared with the anterior approach: an analysis of 80 thoracolumbar corpectomies. J Neurosurg Spine 2010;12(5):583-91.





Opposite page, top:
Phillip Weinstein MD

Opposite page, bottom:
En bloc spondylectomy is the best treatment option for a variety of spinal tumors. This technique removes the tumor without violating its margins.

Far left: Dean Chou MD

Middle left: Minimally invasive transpedicular discectomy of the thoracic spine is performed through a tube just 26 mm in diameter.

Near left: Christopher Ames MD

Below:
Praveen Mummaneni MD

Pediatric Neurological Surgery

Nalin Gupta MD, PhD, Chief of Pediatric Neurological Surgery, performs the first surgery to implant human neural stem cells to treat Pelizaeus-Merzbacher disease.

Clinical Trials

The Pediatric Neurological Surgery program at UCSF is involved in a number of innovative clinical trials to evaluate promising therapies for pediatric neurosurgical disorders that are difficult to treat with standard regimens.

• PMD Clinical Trial: Chief of Pediatric Neurosurgery Nalin Gupta MD, PhD and Chief of Neonatology David Rowitch MD, PhD are principal investigators of a new Phase I clinical trial of neural stem cell transplantation for Pelizaeus-Merzbacher disease (PMD), a rare condition that prevents the formation of myelin in male children. The study is sponsored by StemCells, Inc. and is one of few human clinical trials testing the therapeutic potential of neural stem cells. As a Phase I study, the primary goal is to ensure the safety of the therapy, but investigators will also be using MRI scans to search for evidence of new myelin formation.

• Management of Myelomeningocele Study (MOMS): The Fetal Treatment Center at UCSF has nearly completed enrollment for the first clinical trial of fetal surgery for myelomeningocele – a condition that may cause paralysis, deformity, or hydrocephalus and is usually discovered during the second trimester. MOMS is a randomized surgical trial that is comparing the outcomes of infants treated in utero to those treated after birth.

Investigators for the trial, including Chief of Pediatric Neurosurgery Nalin Gupta MD, PhD, will be analyzing the results of this landmark study in the months to come.

• Pediatric Brain Tumor Clinical Trials: The Pediatric Brain Tumor Center at UCSF participates in Phase I and II trials of promising therapeutic drugs, new biological therapies, treatment delivery technologies, and radiation treatment strategies for all types of newly diagnosed and recurrent CNS tumors. Ongoing trials are performed through the Pediatric Brain Tumor Consortium and the Children's Oncology Group, as well as through several industry partnerships evaluating investigational agents sponsored by leading biotechnology companies.

Mishra KK, Squire S, Lamborn K, Banerjee A, Gupta N, Wara WM, Prados MD, Berger MS, Haas-Kogan DA. Phase II TPDCV protocol for pediatric low-grade hypothalamic/chiasmatic gliomas: 15-year update. J Neurooncol 2010;100(1):121-7.

Nicolaides T, Tihan T, Horn B, Biegel J, Prados M, Banerjee A. High-dose chemotherapy and autologous stem cell rescue for atypical teratoid/rhabdoid tumor of the central nervous system. J Neurooncol 2010;98(1):117-23.

New Pediatric Neuro-Oncology Faculty Join UCSF Benioff Children's Hospital

Theodore Nicolaides MD is a board-certified pediatric oncologist who treats children with brain tumors in the Cancer and Blood Disease Program at UCSF Benioff Children's Hospital. He is an active participant in clinical trials consortia for pediatric brain tumors and was recently awarded the Pediatric Cancer Career Development Award from the American Association of Cancer Research to study irreversible EGFR inhibitors in pediatric malignant glioma.

Sabine Mueller MD, PhD is a board-certified pediatric neurologist with special fellowship training in pediatric neuro-oncology in the Departments of Neurology and Pediatrics at UCSF. Dr. Mueller treats children with brain tumors and associated genetic syndromes, such as neurofibromatosis 1 and tuberous sclerosis. Her basic science research focus is to establish pediatric brain tumor models for in vivo drug testing, while her clinical research interests lie in studying the late effects of treatment on children with brain tumors.

Pediatric Brain Tumor Foundation Institute at UCSF

The research program of the PBTF Institute at UCSF focuses on medulloblastoma and brainstem glioma – alternately the most common and least treatable types of pediatric brain tumors. PBTF investigators are also involved in developing reliable animal models of various pediatric brain tumors to test new therapies prior to clinical trials.

William A. Weiss MD, PhD is the principal investigator of the PBTF Institute project studying the role of the oncogene MYCN in the formation of medulloblastoma. He and his collaborators have demonstrated that targeted expression of MYCN in a rodent model contributes to initiation, progression, and metastasis of medulloblastoma, further establishing it as a viable target for new pediatric brain tumor therapies.

Swartling FJ, Grimmer MR, Hackett CS, et al. Pleiotropic role for MYCN in medulloblastoma. Genes Dev 2010;24(10):1059-72.

Clinically relevant animal models of disease are critical for translating therapies from bench to bedside. The Department of Neurological Surgery's Animal Model Core, led by C. David James PhD, uses transplantable xenograft, allograft, and isograft tumor models in support of pediatric brain tumor translational research.

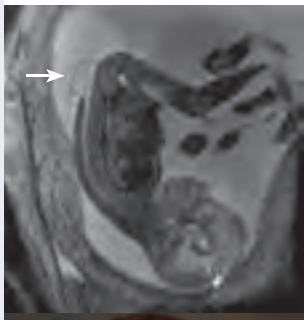
Hashizume R, Ozawa T, Dinca EB, Banerjee A, Prados MD, James CD, Gupta N. A human brainstem glioma xenograft model enabled for bioluminescence imaging. J Neurooncol 2010;96(2):151-9.

Hashizume R, Gupta N, Berger MS, Banerjee A, Prados MD, Ayers-Ringler J, James CD, VandenBerg SR. Morphologic and molecular characterization of ATRT xenografts adapted for orthotopic therapeutic testing. Neuro Oncol 2010;12(4):366-76.

Top: Fetal MR image showing a myelomeningocele sac (arrow) protruding from the posterior spine

Middle: Theodore Nicolaides MD

Bottom: Sabine Mueller MD, PhD



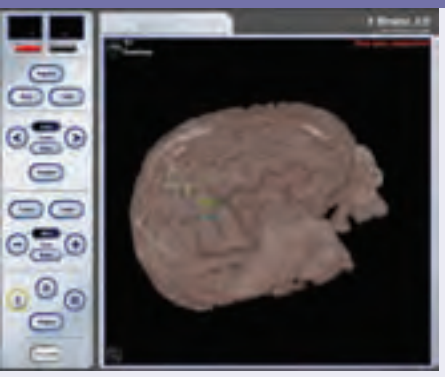
Pediatric Epilepsy Center

The pediatric epilepsy surgery program, directed by Kurtis Auguste MD, has continued its growth and expansion over the past year, and surgical case volumes have seen a 20% increase. The practice regularly cares for the most complex pediatric epilepsy patients. Treatment modalities range from Gamma Knife therapy and vagal nerve stimulators to implantation of indwelling subdural grids and hemispherectomies.

Pediatric cranial epilepsy surgery now routinely employs technology that merges the typical array of preoperative images (MRI, DTI, MEG, PET) onto intraoperative neuronavigation systems for optimal seizure focus localization. The vast majority of surgical patients have become free of seizures or have experienced a dramatic improvement in their seizure profiles without significant complications.

UCSF Nerve Injury Clinic

The UCSF Nerve Injury Clinic is one of the largest, multi-disciplinary practices for the diagnosis and treatment of complex injuries of the peripheral nervous system. The Clinic also cares for patients with nerve tumors and entrapment syndromes. Specialists in pediatric and adult neurological surgery, neurology, and orthopedic surgery collaborate to care for patients, and form diagnoses in conjunction with neuroradiologists using neurography and other investigations. Comprehensive treatment plans are provided, including non-invasive and surgical management. Surgery may include nerve exploration and repair using intraoperative nerve studies and nerve grafting.



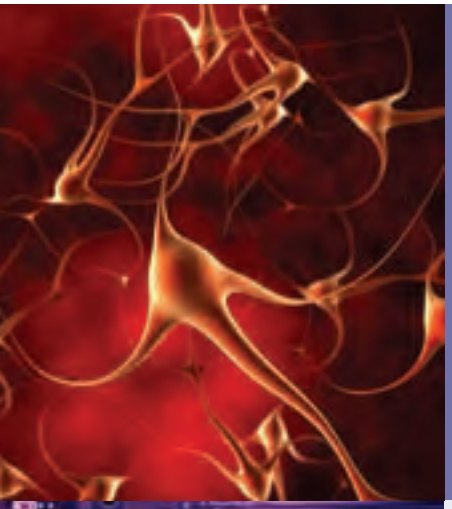
Framless stereotactic MR image with superimposed position of motor cortex stimulation electrodes. Motor cortex stimulation is the only surgical treatment option for patients with neuropathic facial pain that does not respond to medication.

UCSF Neurological Surgery Pain Management Program

The Department of Neurological Surgery at UCSF is home to top specialists in the treatment of severe facial pain syndromes, including trigeminal neuralgia.

We offer the most advanced surgical treatment options for neuropathic and non-neuropathic facial pain, including:

- Microvascular Decompression
- Gamma Knife Radiosurgery
- Radiofrequency Lesion
- Motor cortex Stimulation



Center for Neural Engineering and Prostheses

Launched in December 2010, the Center for Neural Engineering and Prostheses (CNEP) at UC Berkeley and San Francisco integrates cutting-edge engineering with world-class basic and clinical neurosciences to develop technology to restore sensory, motor, and cognitive function in patients suffering from disabling neurological conditions.

Faculty

Edward Chang MD,
co-director, UCSF

Jose Carmena PhD,
co-director, UC Berkeley

Our mission is to create a multi-disciplinary environment for 1) training future neural engineers and clinicians; 2) scientific research and neural prosthetic technology development; and 3) efficient translation of research into human clinical trials.

Research and Clinical Translation

The research goals of the CNEP are to combine expertise in engineering and neuroscience to develop novel technology and to further define basic principles of systems neuroscience.

In engineering, our goals are to apply expertise in material sciences, integrated circuits, machine learning, control theory, and robotics towards three core project areas: 1) bidirectional, wireless, fully implantable neural interface systems; 2) algorithms for estimation and control; 3) exoskeletons and prosthetic devices.

In neuroscience, our goals are to develop new animal models and computational methodologies to understand the basic neural signals underlying sensorimotor and cognitive function and learning. We will apply this new knowledge to develop biomimetic and intuitive technologies for preclinical models. We will use functional neuroimaging to discover new brain targets and circuits in humans for intervention and modulation.

The clinical goal of the CNEP is to implement a bench-to-bedside approach to efficiently translate basic research and technology into clinical practice. Our faculty have considerable experience with surgical implantation, ethics and regulation, and clinical trials to quickly move new discoveries to real-world clinical applications.

Education

At CNEP, we are training the next generation of technology innovators and care providers to develop devices that will interface with the central nervous system. A new track in the UCSF-UC Berkeley Joint Bioengineering Graduate Program will be developed, featuring integrated curriculum and coursework in:

- engineering (signal processing, neural interfaces, bioMEMS, integrated circuits, control systems)
- neurosciences (neurobiology, neural signal, computational neuroscience)
- clinical medicine (neurobiology of disease, hospital rotations in the clinic and operating room, bioethics)

UCSF Department of Neurological Surgery
505 Parnassus Avenue, 779 M
San Francisco, CA 94143-0112

UCSF
University of California
San Francisco
advancing health worldwide™

Department of Neurological Surgery

University of California, San Francisco

505 Parnassus Ave., Room 779 M

San Francisco, CA 94143-0112

Phone: (415) 353-7500

Fax: (415) 353-2889

neurosurgery.ucsf.edu