

UCSF Neurological Surgery

2016-17 Annual Report



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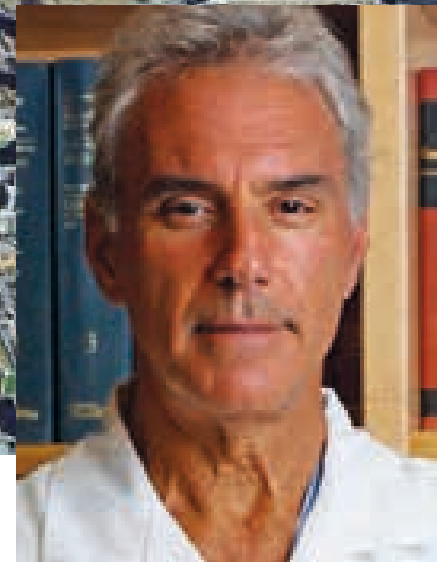
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Dear Colleague:

Last year UCSF received an extraordinary gift from Joan and Sanford I. "Sandy" Weill to establish the Weill Institute for Neurosciences at UCSF. Their gift, the largest single donation ever to UCSF, has unified the Departments of Neurological Surgery, Neurology, and Psychiatry under one umbrella to tackle the biggest problems in neuroscience today. The Institute has already begun supporting young faculty investigators and graduate students, and funding high-risk, high-reward research that will lead to the breakthroughs still needed for many neurological diseases.

In these pages you will find some of the ways that the Department of Neurological Surgery continues to strive for those breakthroughs on a daily basis. From stem cell implantations for spinal cord injury to a new generation of deep brain stimulators, our faculty continue to push the boundaries of technology for the benefit of our patients.

A handwritten signature in orange ink, which appears to read "Mitchel S. Berger".

Mitchel S. Berger, MD

Professor and Chair,
Department of Neurological Surgery

Berthold and Belle N. Guggenheimer Endowed Chair

Director, Brain Tumor Center

Brain Tumor Center

The Evolving Treatment Paradigm of Low-Grade Glioma

Incorporating Molecular Profiles

Low-grade glioma is a still a disease for which there is little consensus on standard treatment. While a greater extent of surgical resection can prolong survival for patients, the majority of these tumors eventually recur and often transform into malignant, high-grade gliomas. But the behavior of an individual tumor is difficult to predict. Following extensive resection, some oncologists advocate a watch-and-wait strategy, only prescribing chemotherapy or radiation when disease recurrence appears on MRI. Others recommend adjuvant therapy immediately after surgery.

Molecular profiles are now giving physicians a more detailed picture of each patient's tumor and the likelihood that it may transform into an aggressive variant. The 2016 World Health Organization classification of brain tumors, co-authored by UCSF neuropathologist Arie Perry, MD, incorporated the molecular characteristics of a tumor in addition to its histological features for the first time. For low-grade gliomas, this includes noting known prognosticators like IDH mutation and co-deletion of the chromosomes 1p and 19q. Capturing this information is helping UCSF physicians better counsel patients and families about the best course of treatment for an individual tumor.

Mutations in the gene encoding IDH1 occur in over 80% of lower grade glioma, and are considered to be a driving force in the disease. Recent work from the laboratory of Russell Pieper, PhD, published in *Cancer Research* showed that IDH1 mutations not only alter the metabolism of tumor cells, but also contribute to the ability of cells to reactivate the TERT gene. This gene is normally inactive during adulthood, and reactivating it can extend the tumor cells' telomeres, stabilizing their chromosomes and allowing them to replicate and survive longer than normal cells.

UCSF500 Cancer Gene Panel

The Brain Tumor Center's Clinical Neuropathology Service developed the UCSF500 Cancer Gene Panel, which uses targeted capture and next-generation sequencing to analyze the coding regions of over 500 cancer-associated genes, select introns, and the TERT promoter.

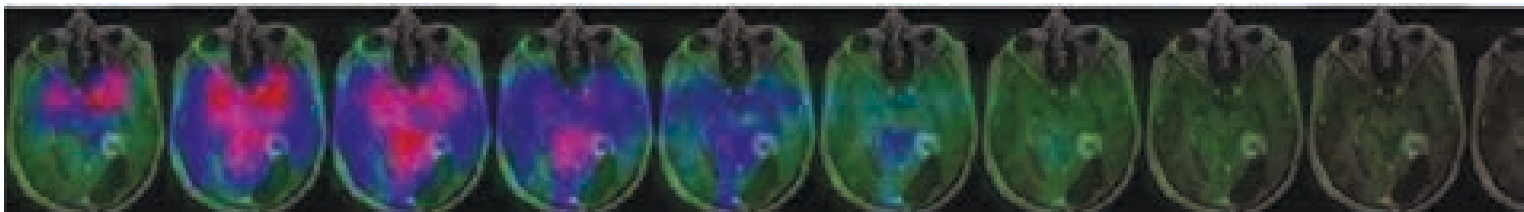
Noninvasive Characterization of Oligodendroglioma (NICO) Project

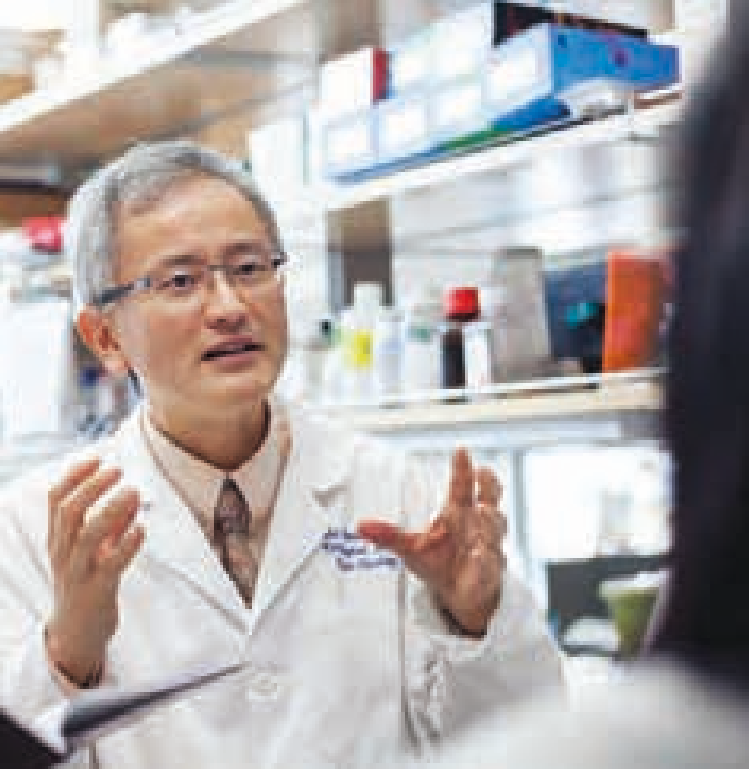
While the ability to delay radiation and chemotherapy is important for reducing side effects and optimizing quality of life, the relatively slow rate of change in low-grade lesion volume seen on standard MR imaging can make it difficult to determine the optimal time for initiating treatment.

In the NICO Project, ^{13}C MRI is being used to monitor tumor metabolism that correlates with the presence of an IDH mutation, indicating tumor recurrence. If metabolic changes that signify transformation can be detected early on, treatment can start much earlier, giving oncologists a better chance to prevent tumor growth. The investigators working on this project are also looking for imaging biomarkers of TERT promoter mutation, which may be used as indicators of tumor recurrence.

The funding for the NICO Project was generously provided by philanthropists to the UCSF Brain Tumor Center.

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Vaccine Trials for Low-Grade Glioma

Two new clinical trials at UCSF are testing vaccines for low-grade glioma – a treatment that works by priming the immune system to recognize and kill tumor cells.

The first vaccine is in the form of a lysate derived from an allogenic tumor cell line with glioblastoma stem cell characteristics. The second contains 10 specific peptide antigens known to be overexpressed in glioblastoma, as well as an antibody against CD27, which activates T-cell activity.

Patients in both trials will also receive injections of poly-ICLC, a compound that has been shown to improve the anti-tumor effect of cancer vaccines in preclinical studies and phase I clinical trials.

“Low-grade gliomas frequently recur as high-grade tumors after initial treatment, so by training the immune system to recognize the antigens found in high-grade glioma we hope to prevent malignant transformation,” says Hideho Okada, MD, PhD, who is leading the trials. “However, many of these antigens are also found in low-grade glioma, and our intent is that the treatment will be both therapeutic [against the initial tumor] and prophylactic [against high-grade recurrence].”

Patients with low-grade tumors may also be better candidates for these types of vaccines because their immune responses are generally less compromised than those of patients with high-grade glioma.

All patients eligible for the study are scheduled to undergo resection as part of standard treatment for their tumor and will receive vaccine for several weeks leading up to surgery.

“This will be one of the first trials that will be prospectively evaluating the activity of a brain tumor vaccine in immunocompetent patients,” says Okada. “By analyzing the tumor tissue after surgery we will be able to determine the vaccine’s effect on the tumor microenvironment.”



Scientific PI: Joseph Costello, PhD
Administrative PI: Russell Pieper, PhD
Co-PI: Mitchel Berger, MD

The loglio Consortium

The loglio consortium is a new collective of 32 investigators across eight institutions, including UCSF, collaborating to accelerate research on low-grade glioma. Working in six teams, the investigators are tackling projects related to epidemiology, cell biology, immunotherapy, targeted drug therapy, and neuroimaging.

Team 1: Discovery and Refinement of Risk and Prognostic Factors for Grade II/III Gliomas

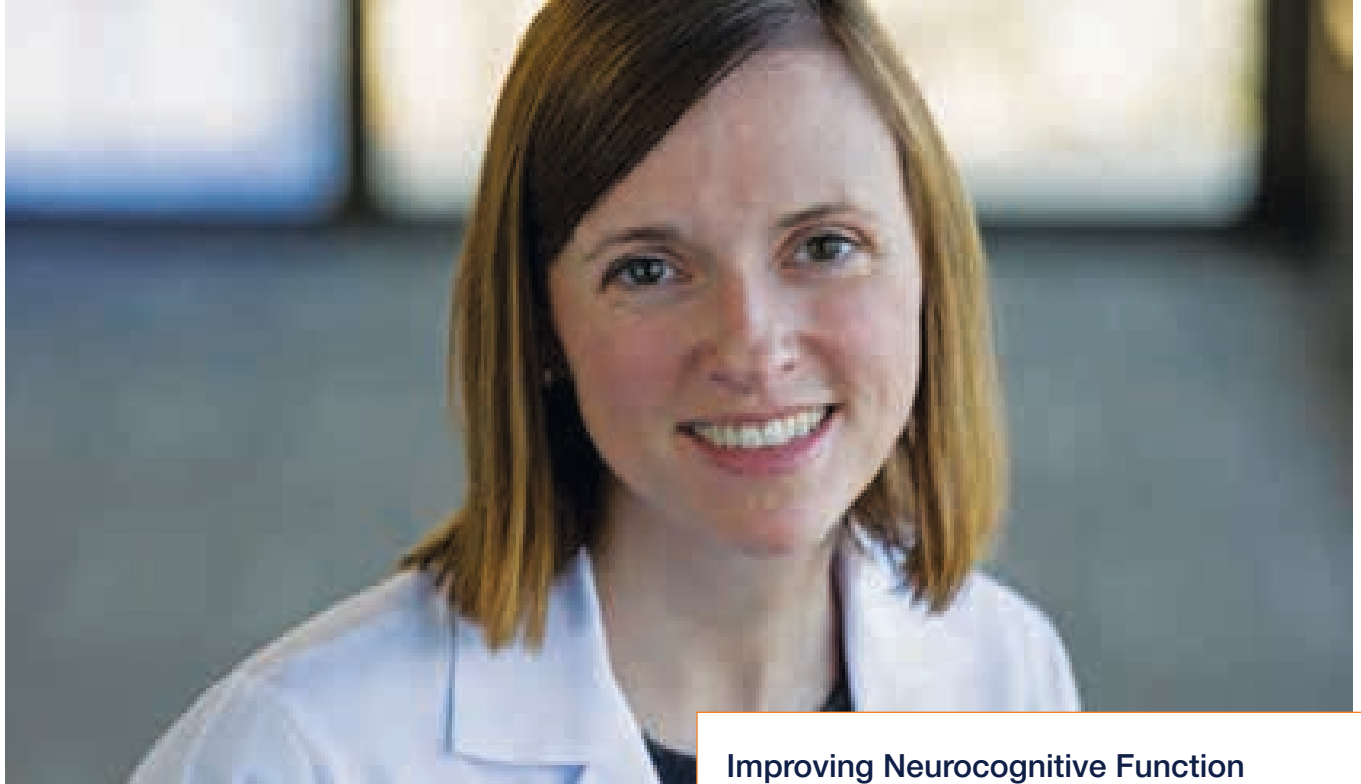
Team 2: Imaging-inspired Genomics: Life History of Low-grade Glioma from the First Cells

Team 3: Development of Therapeutic Approaches Based on the Unique Properties of Low-grade Glioma

Team 3B: Development of Low-grade Glioma Therapeutic Approaches Based on IDH1 Mutation

Team 3C: Inhibitor of GABP to Block Telomerase Activity

Team 4: Improving the Immunoreactivity of Low-grade Glioma



New Division of Biostatistics

A new Division of Biostatistics within the Department of Neurological Surgery has been formed to centralize biostatistical consulting and analysis services to the neurological surgery research and clinical community. Faculty and staff within this division will include experts in biostatistics, bioinformatics, clinical trial design, and image processing. Their work includes supporting computational genomic analyses, medical informatics, outcomes research, and clinical studies.

The Division is directed by Annette Molinaro, PhD, who cites the continued growth of the Department's clinical and basic science research programs as the impetus for creating a centralized service for biostatistics. "In addition to the needs of individual investigators, the Department has large research programs with external partners that also require dedicated biostatistical support," she says.

Among these programs are studies funded by the loglio Consortium and the Ivy Foundation Early Phase Clinical Trials Consortium, which are focused on low-grade and high-grade gliomas, respectively. One of the first major tasks of the new division will be to create a glioma database containing clinical, genomics, imaging, pathology, and outcomes information from all UCSF and Ivy Foundation studies. "It is not uncommon for research to be slowed or hampered by data accessibility problems," says Molinaro. "Putting all of this information in a modern, easily searchable database will greatly facilitate research at UCSF and those institutions we partner with."

The Division will also continue to support the seven research projects that are ongoing as part of the Department's NCI-funded Specialized Program of Research Excellence (SPORE) in Brain Tumors and its Program Project Grant (P01).

Improving Neurocognitive Function with iPads

In 2016 the Neuro-Oncology Service at UCSF launched a pilot study to evaluate a computerized neurocognitive training tool for patients with glioma. Currently there is no standard of care to treat the neurocognitive deficits that commonly arise from treatment.

Patients with grade II or III glioma can often return to normal activity, such as work and driving, following initial treatment. However, many have persistent side effects from therapy and the tumor. These include problems with neurocognitive domains such as memory and multi-tasking, as well as symptoms like fatigue and headache.

Jennie Taylor, MD, MPH, is leading the study at UCSF to determine whether an iPad-based program can improve any of these domains in patients who are off active treatment and are only being monitored with MRI.

"Options for treatment with occupational rehabilitation and psychological therapy are scarce, costly, and time-consuming," she says. "We were looking for something accessible and affordable. With the iPad training program, patients can complete the intervention independently and at home, but still maintain regular communication with their health care team."

The iPad app was developed by researchers in the Netherlands, funded by the Health Insurers Innovation Foundation. It was specifically aimed at improving deficits in attention and information processing, which are among the most common problems experienced by patients with glioma. Their preliminary data suggest that improvements in neurocognitive deficits, while not seen right away, can be observed after several months.

"This is a feasibility study to determine whether the app can be effectively used by patients and physicians," says Taylor. "If we can show that it is feasible, our next goal will be to implement a larger trial in a broader patient population and earlier in the course of treatment."

New Study Aims to Understand Factors for Long-term Survival in Malignant Glioma

UCSF is participating in an international trial taking place at 26 centers to analyze the characteristics of long-term survivors of malignant glioma. Patients with this type of tumor survive, on average, 12 to 14 months after diagnosis. But a small minority can go on to survive five years or more, and these patients are considered long-term survivors.

“Currently there are no valid predictors for whether a patient with malignant glioma could be a long-term survivor,” says UCSF Principal Investigator Jennifer Clarke, MD, MPH.

Examining tissue and neuroimaging from both living and deceased long-term survivors, the researchers will be looking for shared characteristics in the tumors’ molecular profiles and

patients’ MRI scans. They will also examine immune markers found in peripheral blood and tissue. In patients who are still alive, quality-of-life and neurocognitive assessments will be performed to see what impact those factors may have on survival.

“The goals are for us to be better able to predict survival and to identify any factors we can affect to increase the percentage of patients who are long-term survivors,” says Clarke.

Neuro-Oncology Team Honored for Best in Patient Care

For the ninth consecutive year, the Division of Neuro-Oncology has received the highest patient satisfaction ratings of any outpatient care team at the UCSF Medical Center, earning them the 2016 Hall of Fame Award. Questionnaires administered by the independent company Press Ganey consistently score patients’ satisfaction with brain tumor care and treatment at UCSF above 97%. The dedicated group of physicians, nurses, and staff that make up the neuro-oncology team have won the award every year since it was established in 2008.





Han SJ, Reis G, Kohanbash G, Shrivastav S, Magill ST, Molinaro AM, McDermott MW, Theodosopoulos PV, Aghi MK, Berger MS, Butowski NA, Barani I, Phillips JJ, Perry A, Okada H. Expression and prognostic impact of immune modulatory molecule PD-L1 in meningioma. *J Neurooncol* 2016;130(3):543-552.

Magill ST, Lau D, Raleigh DR, Sneed PK, Fogh SE, McDermott MW. Surgical resection and interstitial iodine-125 brachytherapy for high-grade meningiomas: a 25-year series. *Neurosurgery*. 2016 Jun 1. [Epub ahead of print].

Meningioma Care and Research at UCSF

Meningiomas are the most common primary brain tumor and occur over the cranial vault and along the skull base. The five-year survival rate for benign meningiomas is approximately 70 percent, but side effects of treatment and quality-of-life issues, such as seizure control, are understudied. For malignant meningiomas, the five-year survival rate drops to 55 percent, and neurosurgeons and scientists at UCSF continue to search for better treatment options for these patients.

The surgical team at UCSF has operated on more than 2,000 meningiomas since 1992, many of which have been stored in the Brain Tumor Center Tissue Bank and used for research. Investigators are currently aiming to improve the clinical stratification of meningioma based on molecular profiling, including RNA sequencing and DNA methylation analysis. The Brain Tumor Center's Preclinical Core has also generated several cell lines and xenografts from recurrent or anaplastic meningiomas resected at UCSF, and researchers are currently testing a novel FAK inhibitor against these tumors.

Immunotherapy Targets for High-grade Meningioma

In a recent study published in *Journal of Neuro-Oncology*, Brain Tumor Center investigators led by Hideho Okada, MD, PhD, showed that there were high levels of programmed death ligand (PDL-1) expression in high-grade meningiomas, especially those that had been previously irradiated, and higher PDL-1 expression was predictive of shorter overall survival. Aberrant expression of PDL-1 is found in a number of cancers and is thought to suppress the immune system's ability to fight cancer. Immune checkpoint inhibitors have been successfully used to target PDL-1 in cancers like melanoma and non-small cell lung cancer, and this study suggests that they may also be useful for certain types of high-grade meningioma.

New Quality-of-Life Tool

While quality-of-life studies for aggressive brain tumors like glioblastoma have been increasing over the last decade, there have been few for other tumor types. A new tool developed at UCSF is designed to gather data on quality of life for meningioma patients. Led by Michael McDermott, MD, this initiative will be one of the first to look at quality-of-life measures specific to intracranial meningioma sites. The new tool, called MENG-QOL, is a modified version of the Functional Assessment of Cancer Therapy-Brain and the SF-36 outcome instruments. Following surgery or radiosurgery, patients fill out a web-based questionnaire to rate quality-of-life metrics such as pain, coordination, and ability to perform activities of daily living.

Brachytherapy Outcomes

UCSF has one of the largest institutional experiences with brachytherapy for meningioma, and a 2016 report of adjuvant interstitial iodine-125 brachytherapy for recurrent atypical and malignant meningioma described outcomes for patients treated at UCSF over a 25-year period. The study found that while there can be significant complications with brachytherapy, there are limited treatment options for recurrent meningiomas and survival rates were higher for patients treated with brachytherapy than for historical controls. The UCSF report lends support to the position that brachytherapy can be a useful part of a treatment regimen for recurrent meningioma, and sources of radiation other than I-125 may produce fewer side effects and should be explored in prospective studies.



National Cancer Moonshot Initiative, Blue Ribbon Panel Report

In 2016, Mitchel S. Berger, MD, Chair of the Department of Neurological Surgery, and Jeff Bluestone, PhD, a UCSF immunology expert, served on the Blue Ribbon Panel of scientific experts, cancer leaders, and patient advocates to guide the National Cancer Moonshot Initiative. The initiative was launched by former Vice President Joe Biden, who embarked on a national “listening tour” with his wife Jill Biden, PhD, to better understand the state of cancer research and care, which included a visit to UCSF.

The 28-member panel issued 10 recommendations in the Blue Ribbon Panel Report, aimed at achieving the ambitious goal of making a decade’s worth of progress in cancer prevention, diagnosis, and treatment in just 5 years:

- Network for direct patient engagement
- Cancer immunotherapy clinical trials network
- Therapeutic target identification to overcome drug resistance
- A national cancer data ecosystem for sharing and analysis

- Fusion oncoproteins in pediatric cancer
- Symptom management research
- Prevention and early detection: implementation of evidence-based approaches
- Retrospective analysis of biospecimens from patients treated with standard of care
- Generation of human tumor atlases
- Development of new enabling cancer technologies

“It was an honor to represent my specialty of neuro-oncology and neurosurgery and it was an honor to represent UCSF as one of the 28 panelists,” said Berger, who also was one of three panelists selected to address the vice president about the group’s work.

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Neuro-Oncology Caregiver Retreat

UCSF’s annual retreat for caregivers of patients with brain tumors was held in November 2016 with support from the Gordon Murray Neuro-Oncology Caregiver Program. The all-day retreat is centered on the informational and emotional support needs of caregivers, and included self-care activities like chair massage and guided meditation. In addition to listening to talks on common issues that arise while caring for a loved one, caregivers also learned from one another’s experiences during discussion groups. One



participant shared, “It made me feel less alone. And has reiterated to me how important it is to take care of myself. [I am] so grateful to UCSF for the experience we had there for a short time.”

CRISPR-based Study Identifies a Role for lncRNAs in Glioma Development and Growth

Drug development for brain tumors has primarily been focused on damaging cell DNA or targeting proteins whose expression or function is altered in the disease. Despite the abundance of potential targets, many proteins that are expressed by brain tumor cells remain important for the function of normal cells and targeting them can produce severe, unintended toxicity. Now, scientists at UCSF have identified hundreds of long non-coding RNAs (lncRNA) that are critical for cell growth and survival, and many have function highly specific to cancer cells.

The genes encoding lncRNAs produce RNA transcripts but do not appear to make proteins. While a small number of lncRNAs are known to play a role in some diseases, the function of the vast majority of these molecules remains largely unknown. Researchers from the laboratories of Daniel Lim, MD, PhD, and Jonathan Weissman, PhD, set out to look for lncRNAs required for the growth of many different types of cancer cells. They found that each cancer cell line they tested relied upon a different set of lncRNAs for growth and survival.

MD-PhD students John Liu of the Lim lab and Max Horlbeck of the Weissman lab jointly led the experiments and were co-first authors of the report, published in the journal *Science*. The two labs teamed up to develop a genome-scale platform to study lncRNA biology using CRISPR-interference (CRISPRi), a technique established in the Weissman lab with Stanley Qi, PhD, now of Stanford University, that enables researchers to precisely shut off the activity of specific genes.

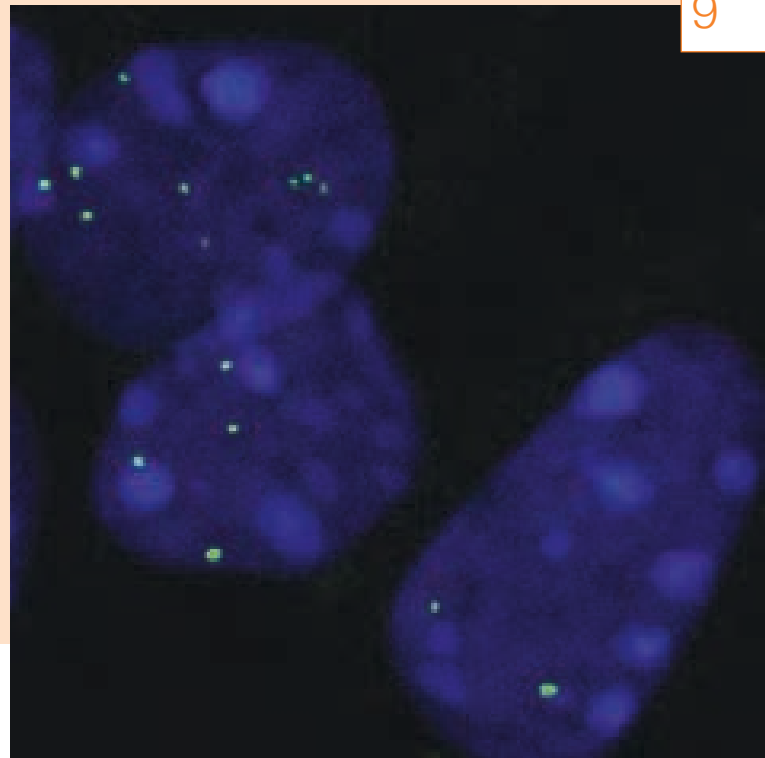
The UCSF team assembled a large library of CRISPR guide RNAs to systematically screen 16,401 different lncRNA genes — a substantial portion of all known lncRNAs — then used CRISPRi to selectively inactivate each gene in a panel of seven human cell lines, including glioma cells, and a line of induced pluripotent stem cells (iPSCs).

The team found that although about 5,000 different lncRNA genes were actively expressed in each cell line, across all cell types studied only 499 lncRNAs significantly impacted cellular growth when they were inactivated. Of these, 65 were necessary for the growth of glioma cells. Moreover, although the researchers had initially thought that there would be a

set of lncRNAs that were essential to the survival of all cells, no such core set of essential lncRNAs were found. In fact, they found that the opposite was true: 89 percent of the “essential” lncRNAs were crucial for only one cell type, and had no effect on the other cell types studied.

This surprising specificity suggests that lncRNAs might be promising targets for precision cancer therapies or combination therapies with cytotoxic drugs. With 20,000 to 50,000 lncRNAs known to exist, the number of potential brain tumor therapy targets for researchers to explore has greatly increased with these findings.

Other authors on the paper include, Harjus S Birk, Martina Malatesta, PhD, Daniel He, Frank J Attenello, MD, Jacqueline E Villalta, Min Y Cho, Yuwen Chen, Mohammad A Mandegar, DPhil, Michael P Olvera, and Luke A Gilbert, PhD, of UCSF and Howard Chang, MD, PhD, and Seung Woo Cho, PhD, of Stanford University. Cancer cell lines used in these experiments included a chronic myeloid leukemia cell line, the HeLa cervical cancer line, a line of transformed HEK cells, a glioblastoma line, as well as two mammary adenocarcinoma lines, the latter supplied by co-author Howard Chang, MD, PhD, of Stanford University.





Zuckerberg San Francisco General Hospital has been recertified by the Joint Commission for traumatic brain injury. The newly redesigned trauma center features an expanded neuro ICU, including state-of-the-art monitoring equipment and 3T MRI scanners.

Brain and Spinal Injury Center

Translating Research and Clinical Knowledge in Traumatic Brain Injury

TRACK-TBI is a 5-year, 12-site, longitudinal study of traumatic brain injury that enrolls participants through Level 1 Trauma Centers across the U.S. It is funded by the National Institute of Neurological Disorders and Stroke through a 5-year U grant for \$18.5 million. Participants represent the entire spectrum of age, demographics, and injury severity. The overall goal of TRACK-TBI is to improve TBI classification/taxonomy for targeted clinical treatment trials, in order to:

- Improve TBI outcome assessments, such that the size and costs of clinical trials can be reduced
- Identify the health and economic impact of mild TBI patient disposition
- Create a legacy database with analytic tools and resources to support TBI research

The expected outcome for this international resource is to identify new diagnostic and prognostic markers and refine outcome assessments, which will lead to successful clinical treatment trials. The study collects and analyzes CT/MRI imaging, blood biospecimen, and detailed clinical outcome assessments of the enrolled TBI participants, following them for an entire year following their injury. To date, the TRACK-TBI Biospecimen Core contains the largest collection of biospecimens from TBI patients ever collected, holding more than 42,000 samples.

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TRACK-TBI by the Numbers

Over **70,000** records for
nearly **1,700** subjects.

Over **4,000** follow-up visits
completed, including **2-week** and
6-month MRIs in **600** subjects.

Over **14,000** fields in study database.

Collection of over **42,000**
biospecimen samples in biorepository.

TBI Endpoints Development

Under the direction of Chief of Neurotrauma, Geoffrey Manley, MD, PhD, and an Executive Committee, the TBI Endpoints Development (TED) team of internationally prominent academic clinician-scientists from 35 academic institutions, along with innovative industry partners in biotechnology and imaging technology, patient advocacy organizations, and philanthropies (collectively, 55 entities), works directly and collaboratively with the U.S. Food and Drug Administration (FDA) to identify and validate effective measures or “endpoints” of brain injury and recovery. Core teams in the domains of biofluid biomarkers, neuroimaging biomarkers, and clinical outcome assessments (COAs) have begun to examine biospecimens and clinical data from thousands of athletes, soldiers, and the general population, including those enrolled in the TRACK-TBI study. This enormous and well-characterized dataset will be powered to achieve TED’s ultimate goal to validate and qualify a group of such biomarkers and COA measures, which the FDA can accept as endpoints with prognostic and diagnostic value for future clinical trials of TBI therapeutics.

Translating Research and Clinical Knowledge in Spinal Cord Injury

BASIC investigators have been granted \$2.3 million from the U.S. Department of Defense and \$1 million from the Craig H. Neilsen Foundation to fund a project called Translating Research and Clinical Knowledge in Spinal Cord Injury (TRACK-SCI). Following the success of a parallel project for traumatic brain injury (TRACK-TBI), the primary goal will be to perform standardized high-resolution imaging, gene sequencing, and blood work and correlate findings with critical care outcomes of patients with spinal cord injury.

Principal investigators hypothesize that particular gene expression patterns may be linked to better or worse recovery, guiding individualized treatment decisions for patients. There has also been preliminary evidence that infection and functional outcome can be traced back to early immune response following injury. For example, cytokines that suppress immune function increase in expression after injury, possibly hindering short-term or long-term recovery.

The goal of TRACK-SCI will be to form a coalition of centers that will collaborate to continually improve and implement best practices to optimize care and outcomes for patients with SCI,

and to dramatically increase access to spinal cord injury clinical trials. This will include tracking patients through discharge, rehabilitation, and community placement to provide consistent care and monitor long-term outcomes.

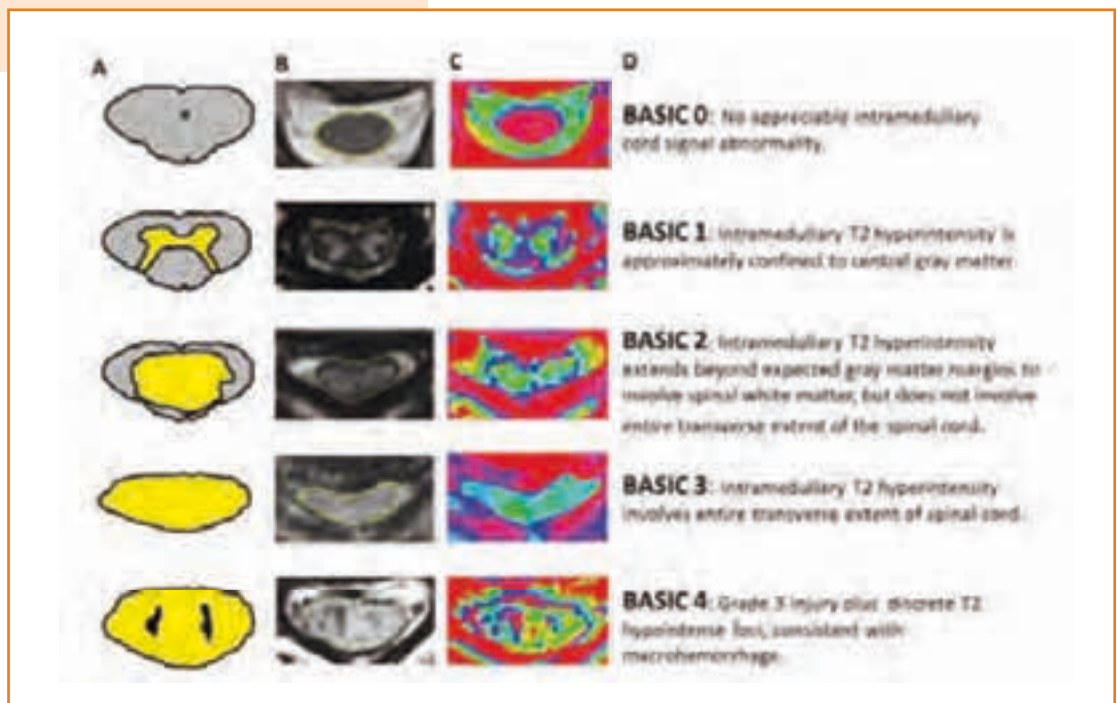
Improving Imaging Biomarkers

TRACK-SCI will also look to validate early biomarkers of outcome with cross-sectional MRI and diffusion tensor imaging. The BASIC score for acute cervical spinal cord injury, published in 2015 in *Journal of Neurosurgery: Spine*, uses T2-weighted axial MR images to grade acute cervical spinal cord injury based on five imaging patterns that correlate with outcome. Prior to this publication, this type of injury was typically graded according to the length of a T2-signalling abnormality on sagittal imaging, and very little neuroimaging work in humans had been done in examining the intrinsic structure of the spinal cord through slices of the axial plane.

In a 2016 study led by UCSF neuroradiologist Jason Talbott, MD, PhD, nonlinear principal component analysis was used to determine how the BASIC score correlates with other conventional measures of acute spinal cord injury and how accurate each was at predicting short-term outcomes in a retrospective review of 95 patients. The BASIC score had a strong correlation with lesion length and sagittal grade, and was also the most accurate scoring scheme for predicting American Spinal Injury Association Impairment Scale score at discharge. By prospectively obtaining multidimensional imaging metrics, including BASIC scores, from patients enrolled in TRACK-SCI, clinicians at BASIC hope to provide better prognostic information to patients and families and improve classification schemes for stratifying patients into clinical trials.

Talbott JF, Whetstone WD, Readdy WJ, Ferguson AR, Bresnahan JC, Saigal R, Hawryluk GW, Beattie MS, Mabray MC, Pan JZ, Manley GT, Dhall SS. The Brain and Spinal Injury Center score: a novel, simple, and reproducible method for assessing the severity of acute cervical spinal cord injury with axial T2-weighted MRI findings. *J Neurosurg Spine* 2015;23(4):495-504.

Haefeli J, Mabray MC, Whetstone WD, Dhall SS, Pan JZ, Upadhyayula P, Manley GT, Bresnahan JC, Beattie MS, Ferguson AR, Talbott JF. Multivariate analysis of MRI biomarkers for predicting neurologic impairment in cervical spinal cord injury. *AJNR Am J Neuroradiol* 2016 Dec 22. [Epub ahead of print].



Human Neuron Transplants Treat Spinal Cord Injury in Mice

Chronic pain and loss of bladder control are among the most devastating consequences of spinal cord injury, rated by many patients as a higher priority for treatment than paralysis or numbness. Now a UCSF study led by the labs of Linda Noble-Haeusslein, PhD, and Arnold Kriegstein, PhD, has transplanted immature human neurons into mice with spinal cord injuries, and shown that the cells successfully wire up with the damaged spinal cord to improve bladder control and reduce pain. This is a key step towards developing cell therapies for spinal cord injury in humans, and the UCSF researchers are currently working to develop the technique for future clinical trials.

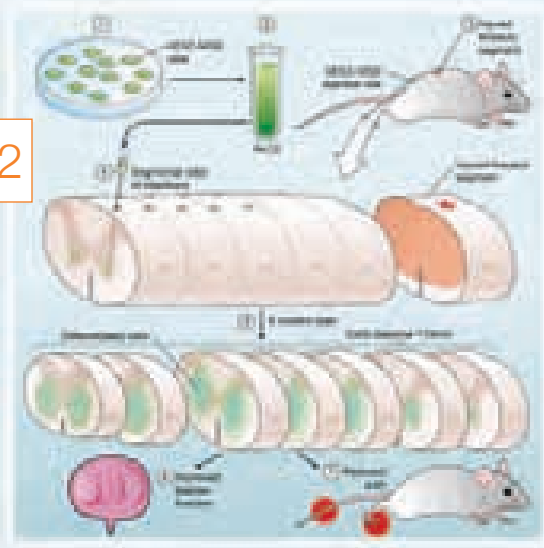
Chronic pain and loss of bladder control are caused by widespread inflammation immediately following acute spinal injuries, which can lead to more wide-spread damage further from the site of injury. In particular, inflammation damages inhibitory neural circuitry that uses the neurotransmitter GABA to keep spinal circuits' activity under control. When GABA-producing cells are weakened, the spinal cord loses control over circuits controlling pain sensation as well as those responsible for emptying the bladder.

The UCSF investigators incited lab-grown human embryonic stem cells to differentiate into MGE-like inhibitory neuron precursors, then transplanted the immature human cells into mice two weeks following injury of the thoracic spinal cord (about half-way up the back). Six months later, the cells, which had been introduced just below the inflamed lumbar region of the spine where bladder function is controlled, had successfully migrated toward the site of injury, developed into mature inhibitory neurons and made synaptic connections with the local spinal cord circuitry.

While untreated mice with spinal cord injuries developed hypersensitivity to touch and painful stimuli as well as abnormal scratching and grooming, mice with new human inhibitory neurons showed significantly fewer of all these signs of neuropathic pain by three to six months after transplantation. Treated mice also exhibited significantly improved bladder function – measured by decreased bladder pressure, lower amounts of urine in the bladder, and improved function of bladder muscles. As a result, the researchers observed, the mice were able to produce more normal, voluntary patterns of urination in their cages.

The researchers hope the new findings will lead to the use of neural progenitors to improve the quality of life of patients with spinal cord injury, but the findings will first need to be replicated and studies of the optimal timing of intervention will need to be performed. There are also safety concerns regarding transplanting neurons into the spinal cord: although the researchers saw no evidence of negative impacts on movement control or other spinal functions in experiments in uninjured control mice, more detailed safety studies still need to be done.

Adapted from original article by Nicholas Weiler in UCSF News on September 22, 2016.



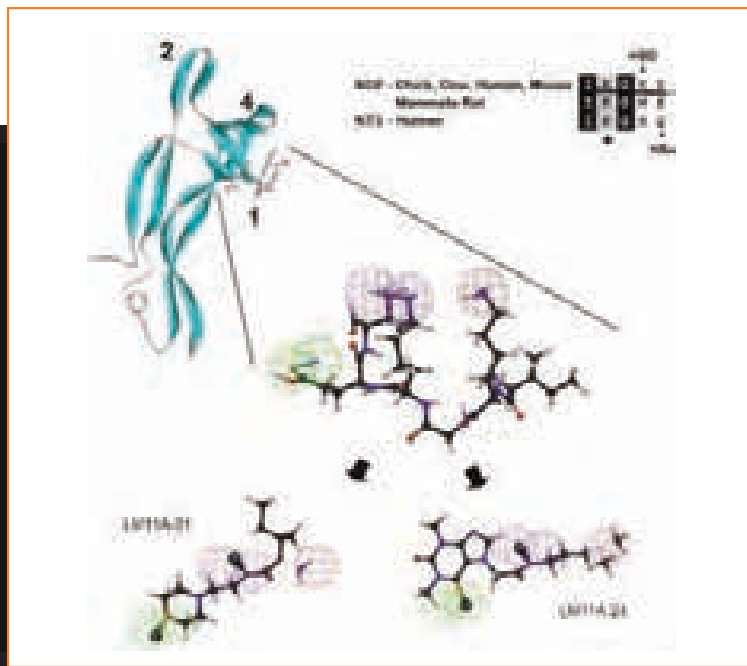
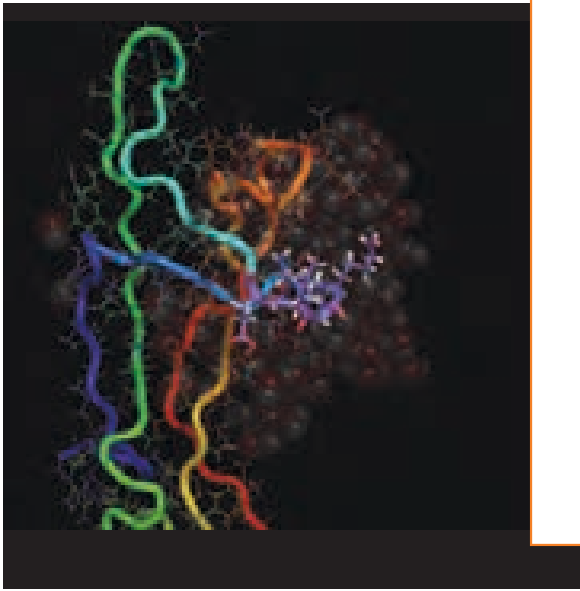
Fandel TM, Trivedi A, Nicholas CR, Zhang H, Chen J, Martinez AF, Noble-Haeusslein LJ, Kriegstein AR. Transplanted human stem cell-derived interneuron precursors mitigate mouse bladder dysfunction and central neuropathic pain after spinal cord injury. *Cell Stem Cell* 2016;19(4):544-557.

UCSF Neurosurgeons Receive Weill Innovation and Scholar Awards

Geoffrey Manley, MD, PhD, and Daniel Lim, MD, PhD, have been named among the first recipients of the UCSF Weill Innovation and Scholar Awards as part of the institute's goal to support high-risk, high-reward research. The highly competitive selection process concluded with nine Innovation Awards and six Scholar Awards being granted by the new UCSF institute, made possible by a \$185 million gift from Joan and Sanford I. "Sandy" Weill.

Manley and Lim will be studying long noncoding RNAs (lncRNAs) as highly specific biomarkers of brain injury. The goal of this project is to develop a highly specific and sensitive diagnostic blood test for mild traumatic brain injury (mTBI) via the detection of lncRNAs. Since many lncRNAs are expressed specifically and abundantly in the brain, they have great potential to serve as a biomarker of brain injury. If successful, the proposed diagnostic technology could directly improve the care of millions of patients with mTBI by providing a more accurate, less subjective test for the management of those with brain injury.





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p75NTR as a Therapeutic Target Following Brain and Spinal Cord Injury

Neurotrophins and their receptors are the focus of many central nervous system (CNS) injury studies owing to their role in the growth and survival of neurons. Scientists at BASIC have become especially interested in the neurotrophin receptor p75NTR, which is highly expressed during early human development but declines in adulthood. After CNS injury, its expression increases again.

p75NTR can initiate a myriad of cell-signaling pathways, and it can facilitate either life or death of neurons depending on its interactions with other receptors. For example, when it interacts with the neurotrophin receptor *trkA*, it is protective, but when it forms oligomers with some other receptors, like sortilin, it induces apoptosis. In the setting of acute injury, p75NTR is more likely to bind to molecules that will induce apoptotic pathways than survival pathways.

Investigators in the laboratory of Michael Beattie, PhD, and Jacqueline Bresnahan, PhD, have recently shown that p75NTR may also play a role in the peripheral inflammatory response – a well-established cause of secondary injury following a primary CNS insult. In a mouse model of CNS injury, inhibiting p75NTR four hours after injury blocked the inflammatory response *in vivo*, and circulation of peripheral, pro-inflammatory monocytes was greatly reduced, leading to better functional outcomes.

In light of this research, the Beattie–Bresnahan laboratory received a Congressionally Directed Medical Research

Programs (CDMRP) grant to study an inhibitor of p75NTR to further define its role in the inflammatory response, amassing preclinical data for eventual testing in humans.

The drug they will be testing—called LMA11-31—was discovered at UCSF by Steven Massa, MD, professor of neurology at UCSF, and Frank Longo, MD, PhD, former chief of neurology at San Francisco Veterans Affairs Medical Center and now Professor and Chair of Neurology at Stanford University and head of the biotechnology company Pharmatropix, which will manufacture the drug. Massa and Longo began studying p75NTR in the 1990s, and used molecular dynamics modeling to study p75NTR's binding sites and test potential inhibitors, including LMA11-31. The drug's ability to block neuronal cell death has also been tested in a phase 1 study of Alzheimer's disease, and is now entering a phase 2a study.

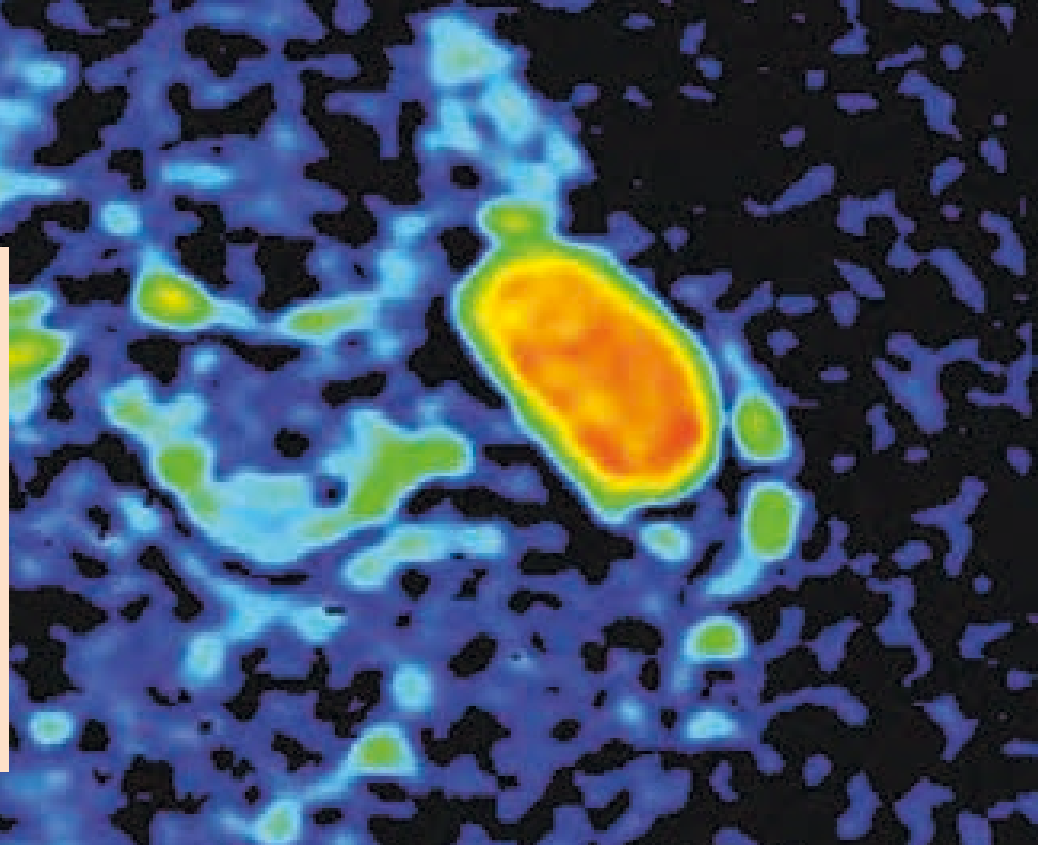
While the role of p75NTR in cell death has been studied for some time, the new findings by Beattie and Bresnahan regarding its role in early inflammation come at a time when the status of the immune system is becoming increasingly recognized as important to functional outcome following traumatic brain and spinal cord injuries. If LMA11-31 can also modulate the inflammatory response, it may be able to affect multiple mechanisms related to poor outcome following CNS injury.

Lee S, Mattingly A, Lin A, Sacramento J, Mannent L, Castel MN, Canolle B, Delbary-Gossart S, Ferzaz B, Morganti JM, Rosi S, Ferguson AR, Manley GT, Bresnahan JC, Beattie MS. A novel antagonist of p75NTR reduces peripheral expansion and CNS trafficking of pro-inflammatory monocytes and spares function after traumatic brain injury. *J Neuroinflammation* 2016;13(1):88.

Delbary-Gossart S, Lee S, Baroni M, Lamarche I, Arnone M, Canolle B, Lin A, Sacramento J, Salegio EA, Castel MN, Delesque-Touchard N, Alam A, Laboudie P, Ferzaz B, Savi P, Herbert JM, Manley GT, Ferguson AR, Bresnahan JC, Bono F, Beattie MS. A novel inhibitor of p75-neurotrophin receptor improves functional outcomes in two models of traumatic brain injury. *Brain* 2016;139(Pt 6):1762-82.



An annual two-day cadaver workshop provides UCSF neurosurgery residents with a comprehensive training session on anterior and posterior approaches to peripheral nerve disorders.



The Department of Neurological Surgery leads a multi-disciplinary peripheral nerve clinic that includes neurosurgeons, neurologists, neuroradiologists, neuropathologists, orthopedic surgeons, and rehabilitation specialists. Comprehensive evaluation and treatment are provided, including non-invasive and surgical management. The surgical team includes experienced electrophysiologists who monitor nerve function during surgery to prevent damage to functional nerve fibers.

Peripheral Nerve Disorders

Vagal Nerve Neurofibromas

Patients with neurocutaneous disorders such as NF1 are at high risk of developing the benign peripheral nerve sheath tumors known as neurofibromas. Vagal nerve neurofibromas, however, are rare, even in this patient population.

Although neurofibromas are generally benign, approximately 10 to 15 percent of patients with NF1 have neurofibromas that undergo malignant transformation. Survival rates following transformation are approximately 40 to 50 percent at one year.

While complete removal of vagal nerve tumors can be difficult to achieve without damaging this critical nerve, an attempt at gross total resection by a multidisciplinary surgical team that includes neurosurgeons and otolaryngologists is the best chance for preventing malignancy.

In a recent report in the *Journal of Brachial Plexus and Peripheral Nerve Injury*, a UCSF team led by Chief of Peripheral Nerve Surgery, Line Jacques, MD, describes a procedure that resulted in total removal of a vagal nerve neurofibroma and preservation of the vagal nerve. They note that vocal cord damage is a frequent postoperative complication with surgery for these tumors.

Their report also demonstrated the utility of diffusion-weighted imaging in addition to MRI, which allows for direct visualization of specific nerve tracts entering and leaving the tumor. Diffusivity measurements, such as apparent diffusion coefficient, from this type of imaging can also help differentiate between benign and malignant tumors.

Chan AK, Bray DP, Chin CT, Jacques L. Large vagus nerve tumor in a patient with neurofibromatosis type 1 treated with gross total resection: a case report. *J. Brachial Plex Peripher Nerve Inj* 2016;11(1):e48-e54.

Pain Disorders

Long-term Pain Relief for Trigeminal Neuralgia

Trigeminal neuralgia is a rare neuropathic condition characterized by episodes of intense, stabbing facial pain originating from the trigeminal nerve. If medication is ineffective, a variety of surgical procedures are available to treat the disorder.

With ablative procedures, such as radiofrequency rhizotomy and stereotactic radiosurgery, the trigeminal nerve is damaged to reduce the transmission of pain signals. With microvascular decompression (MVD), a blood vessel that may be compressing the nerve is moved away so that it is no longer in contact with the nerve, which treats the underlying cause of the disorder in many cases.

Each of these procedures has published rates of efficacy, but there have been few direct comparisons of ablative and nonablative modalities in a homogenous patient population that includes long-term follow-up. In a recent study led by UCSF neurosurgeon Edward Chang, MD, prospective data were collected from 340 patients undergoing surgery for the first time for trigeminal neuralgia between 1997 and 2014.

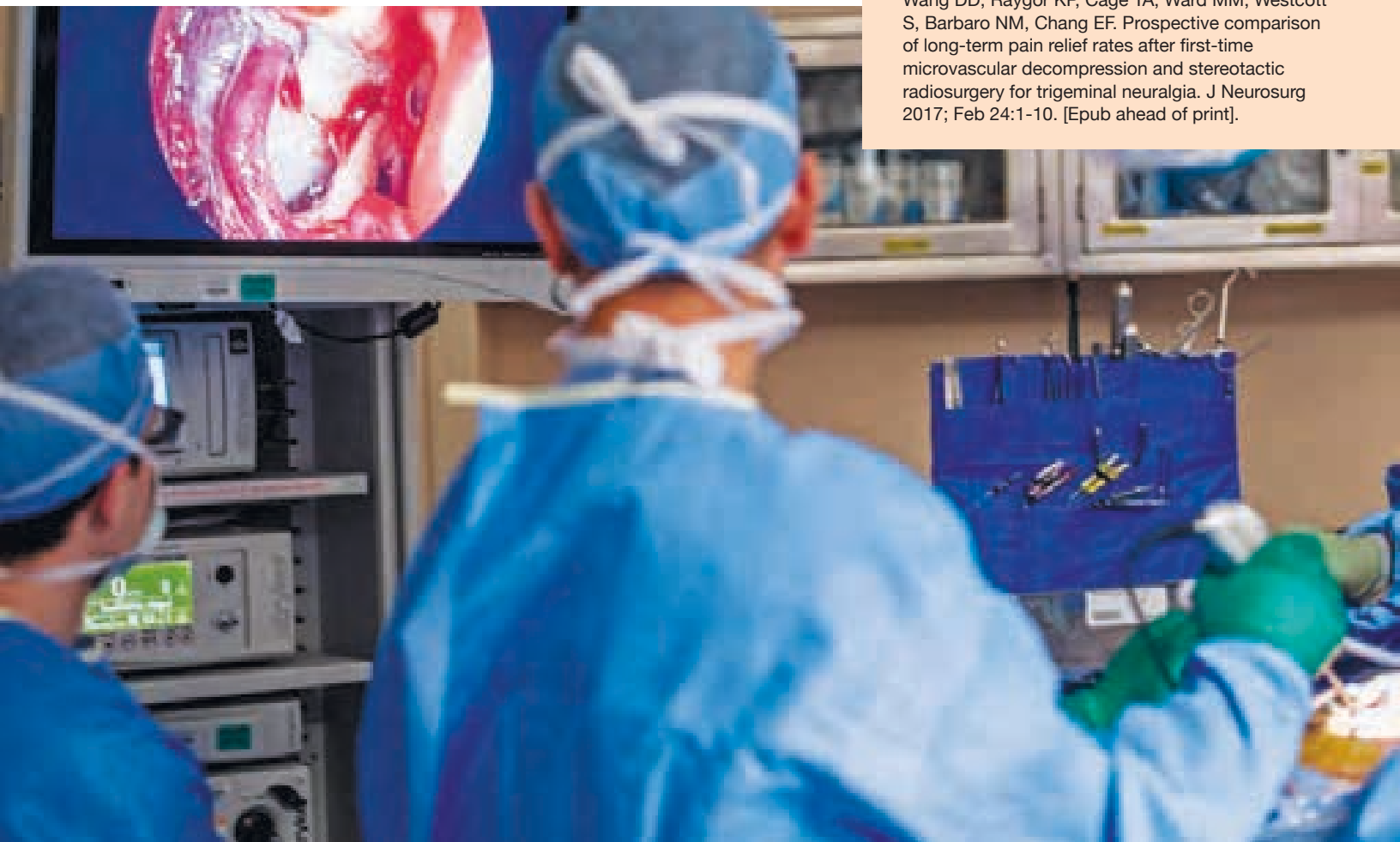
Chang and his colleagues found that MVD resulted in a higher rate of pain control than radiosurgery immediately following treatment (96 percent vs. 75 percent) and also resulted in a more durable response. While the rate of pain control decreased over time for both procedures, the rate at five years was 61 percent for MVD and 47 percent for radiosurgery.

At 10 years, it was 44 percent for MVD and 27 percent for radiosurgery. In the MVD group, median time to pain recurrence was almost eight years, while in the radiosurgery group it was approximately four and a half years. This represents one of the only studies to follow patients for longer than five years.

For patients undergoing MVD, a shorter duration of symptoms prior to treatment was predictive of better outcome. Perhaps surprisingly, vascular compression of the trigeminal nerve that could be seen on MR imaging and vascular compression confirmed intraoperatively were not associated with better outcomes following MVD, and patients receiving MVD and partial sensory rhizotomy had shorter pain-free intervals than those receiving MVD alone.

While these results confirm other reports in the literature citing MVD as a superior procedure for pain control, the study's authors note that no single procedure works for every patient and it remains critical to provide a full range of treatment options. Trigeminal neuralgia is a complicated disorder, not only with regard to the complicated nature of pain transmission, but also in that it may arise not only from nerve compression but also inflammation, demyelination, or another unknown source. If pain recurs following initial surgery, performing a different procedure can result in long-term pain control.

Wang DD, Raygor KP, Cage TA, Ward MM, Westcott S, Barbaro NM, Chang EF. Prospective comparison of long-term pain relief rates after first-time microvascular decompression and stereotactic radiosurgery for trigeminal neuralgia. *J Neurosurg* 2017; Feb 24:1-10. [Epub ahead of print].





UCSF is a participating site in a multicenter, prospective, randomized trial to gather class I evidence regarding outcomes following anterior vs. posterior approaches to treating cervical stenosis with myelopathy. The study is an initiative of the Patient-Centered Outcomes Research Institute.

16 Neurospinal Disorders

Total Care for the Cervical Spine

Our specialists in spinal neurosurgery lead the field in providing a full range of treatment options for the pathologies that can affect the cervical spine. With minimally invasive endoscopic surgeries and a variety of approaches to relieve compression throughout the entire cervical spine, there are more options than ever before to tailor procedures to each patient's needs.

Endoscopic Transoral Approach to the Craniovertebral Junction

UCSF has been among a handful of leading centers to adopt the endoscopic transoral approach to the craniovertebral junction (C1-C2). The technique was first developed in 2014, and can be used to access tumors, infections, arthritic pannus, osteophytes, or fracture fragments that are causing spinal cord compression. Surgery in this area of the spine previously required considerable soft tissue dissection, resulting in significant scarring and long recovery times. A 2016 study by UCSF neurosurgeons and otolaryngologists demonstrated that the endoscopic transoral approach avoids manipulation of the nasal cavity, palatal splitting, and mandibulotomy. Because of the low rates of morbidity and excellent access to the craniovertebral junction afforded by this technique, patients are offered endoscopic transoral surgery when feasible.

Cord Compression in the Mid-Cervical Spine

Cervical cord compression and myelopathy in the mid-cervical spine is often caused by arthritic changes, but can also be due to ossification of the posterior longitudinal ligament. Ossification

of the posterior longitudinal ligament disproportionately affects Asian and Caucasian populations, and although it is rare, UCSF neurosurgeons have treated hundreds of cases. Procedures used to treat patients with cervical spinal cord compression include anterior decompression and fusion, posterior decompression (with or without fusion), and laminoplasty.

Techniques for Prioritizing Vocal Function

Anterior cervical spine approaches are associated with mild postoperative pain and low blood loss. However, dysphagia or a vocal hoarseness can be drawbacks to the anterior approach for those patients who rely on their voice in daily life, such as radio hosts or professional singers. Being able to provide patients with multiple anterior and posterior surgical options, using the latest techniques in neuromonitoring, helps in tailoring surgery for the specific needs of every patient.

Chan AK, Benet A, Ohya J, Zhang X, Vogel TD, Flis DW, El-Sayed IH, Mummaneni PV. The endoscopic transoral approach to the craniovertebral junction: an anatomical study with a clinical example. *Neurosurg Focus* 2016 Feb;40(2):E11.

Costs Related to Minimally Invasive Surgery for Spinal Deformity

Patients undergoing surgery for adult spinal deformity often have lengthy stays in the hospital following their operations, increasing costs associated with treatment. However, over the past two decades, an increasing number of minimally invasive procedures have been pioneered for many types of spinal deformity, usually resulting in shorter recovery times and less blood loss.

As minimally invasive surgery becomes more common, members of the International Spine Study Group (ISSG), including UCSF neurosurgeons Dean Chou, MD, and Praveen Mummaneni, MD, have been studying how these procedures affect length of hospital stay and Medicare reimbursement rates.

Reviewing a multicenter database of 426 patients who underwent adult deformity correction between 2009 and 2012, they found that for patients undergoing surgical correction of mild to moderate spinal deformity, circumferential minimally invasive surgery resulted in significantly less time spent in the ICU, in addition to less blood loss. Time spent in the hospital overall was also lower, though not statistically significant (7.9 days for minimally invasive surgery and 9.6 days for open surgery).

When Medicare reimbursement data were obtained from 12 institutions participating in the ISSG, it was found that reimbursements based on diagnosis-related group (DRG) were affected by type of case and patients' comorbidities. For instance, use of minimally invasive posterior percutaneous fixation without dorsal fusion resulted in a 13 to 16 percent lower cost for patients who already had anterior fusion for spinal deformity.

The ISSG authors concluded that for hospitals to be able to offer cost-effective complex spinal surgeries in the future, they will need to be aware of the procedure and coding issues that affect reimbursement rates.

Chou D, Wang MY, Blaskiewicz DJ, Nguyen S, Shaffrey CI, Okonkwo DO, Kanter AS, Deviren V, Uribe JS, Eastlack RK, Nunley PD, Anand N, Park P, Mundis GM. The impact of minimally invasive spinal deformity surgery on ICU and hospital stay [abstract 90]. *Spine J* 2015;15:127S.

Nunley PD, Fessler RG, Park P, Zavatsky JM, Mundis GM, Uribe JS, Eastlack R, Nguyen S, Chou D, Wang My, Anand N, Kanter AS, Shaffrey CI, Mummaneni PV. How do case type, length of stay, and comorbidities affect medicare diagnosis-related group reimbursement for minimally invasive surgery for deformity? [abstract 371] *Neurosurgery* 2016;63(CN_suppl_1):210.





Tiffany Pong, PA-C

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Tiffany Pong is a physician assistant at the UCSF Spine Center and focuses on the area of minimally invasive spine procedures with neurosurgeon Aaron Clark, MD, PhD. She joined the UCSF team in 2013, after graduating from the PA program at Shenandoah University. She is an avid field hockey player and a former youth Hong Kong national team player. She loves to eat her way around the world with her husband Drew.

When did you know you wanted to go into the medical field?

I cannot remember a time before wanting to work in medicine. My parents prioritized travel to allow my brother and I to see the world at a young age. Visiting developing countries like Cambodia and India made a lasting impact on me. Seeing first-hand the universal aims of happiness and health cemented in me a desire to give back through medicine.

At the University of Michigan, I studied in the Health Sciences Scholars Program, a learning community oriented around health care. I was introduced to professions beyond the medical doctor. I realized that health care is afforded by a multidisciplinary team, each member playing an important role. The role of physician assistant best suited me.

Why did you choose spinal disorders as your specialty?

I majored in brain, behavior, and cognitive science and researched gait patterns in children with Down's syndrome and spina bifida. I really enjoyed working with that patient population. When I matriculated to PA school, the surgical specialty was attractive because I could provide patients with immediate improvement in their quality of life. I could see my patients through their entire path to recovery.

What's the most interesting thing about the human spine?

There is so much we do not know about the human spine yet. A spinal cord or nerve injury can be so devastating, yet neuroregenerative research continues to progress. For all the talk of its fragility, the human spine is resilient. We frequently see patients who defy our expectations.

As an essential member of a patient's health care team, what kind of support do you provide?

The most crucial role I play is patient education. The thought of spine surgery is often overwhelming to patients. They frequently return home after visiting with the surgeon, failing to recall the conversation. That is where I step in. I take time to explain the procedure, the recovery process, and to align expectations. By patiently answering their questions, I aim to make the thought of surgery less daunting.

What's the best part of working at UCSF?

At UCSF you're working among the elite providers and seeing the most difficult cases. As a research hospital, we have early access to the newest research and techniques. The environment elevates us all to be our best selves.

What's the most common question you get from your patients?

What can I do if I do not want surgery? When surgery is not urgent, we encourage our patients to pursue conservative management before considering surgery. Optimizing physical therapy, steroid injections, and managing pain are the mainstays of our specialty and should be maximized before attempting surgery, with rare exception.

New Adult Spinal Deformity Frailty Index for Surgical Risk Stratification

Frailty indices are increasingly being used as part of risk stratification for patients undergoing surgery, and have been shown to be better predictors of major complications than age alone in general surgery cohorts. An adult spinal deformity frailty index (ASD-FI) has now been developed by members of the International Spine Study Group (ISSG), including UCSF neurosurgeon Christopher Ames, MD, and validated in two independent datasets.

The first study population consisted of adult deformity patients registered in a prospective, multicenter database of the European Spine Study Group. The ISSG authors were able to show that frailty, as measured by the ASD-FI, was associated

with increased length of hospital stay and major complications, such as wound infection and proximal junctional kyphosis.

The ASD-FI was then used to analyze the multicenter Scolio-Risk 1 database, which only includes patients with severe deformity undergoing complex procedures. Degree of frailty again correlated with length of hospital stay and risk of major complication.

These studies indicate that the ASD-FI may be a valuable new tool for helping physicians with surgical planning, preoperative risk stratification, and preoperative patient counseling.

Miller E, Sciubba DM, Neuman BJ, Smith JS, Kebaish KM, Kleinstuck F, Obeid I, Perez-Gruesso FJ, Pellise F, Ames CP, EESG European Spine Study Group. Development and external validation of the adult spine deformity (ASD) frailty index (ASD-FI) [abstract 208]. *Spine J* 2016;16:S213.

Miller E, Jain A, Daniels AH, Neuman BJ, Soroceanu A, Ailon T, Sciubba DM, Bess S, Line B, Lafage V, Scheer JK, Kebaish KM, Smith JS, Ames CP, International Spine Study Group. Assessment

of a novel adult spinal deformity (ASD) frailty index (ASD-FI) to assist with risk stratification for ASD surgery [abstract P165]. *Spine J* 2016;16:S323.

Miller E, Lenke LG, Espinoza-Rebmann K, Neuman BJ, Sciubba DM, Smith JS, Qiu Y, Dahl B, Matsuyama Y, Fehlings MG, Cheung KM, Carreon LY, Ames CP, International Spine Study Group. Use of adult spinal deformity (ASD) frailty index (ASD-FI) in the Scolio-Risk 1 multicenter, international patient database [abstract 22]. *Spine J* 2016;16:S123.



Epilepsy

EEG of an electrographic seizure recorded at the scalp in a standard bipolar montage. This seizure is very difficult to localize other than to roughly interpret as most likely arising from the left hemisphere, more posterior than anterior.

EEG Source Localization: A New Tool for Surgical Evaluation of Epilepsy

About 2.3 million people in the United States have epilepsy. Epilepsy surgery offers the best option for halting disabling seizures when medications alone are not sufficient. It is estimated that nearly 200,000 medically intractable epilepsy patients are candidates for surgery, but it remains a dramatically underutilized treatment. In the United States, only 300 to 450 patients per year receive surgery that allows them the chance of lifelong freedom from seizures.

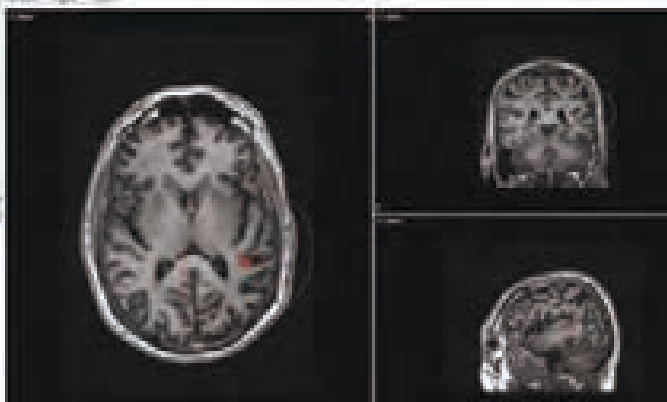
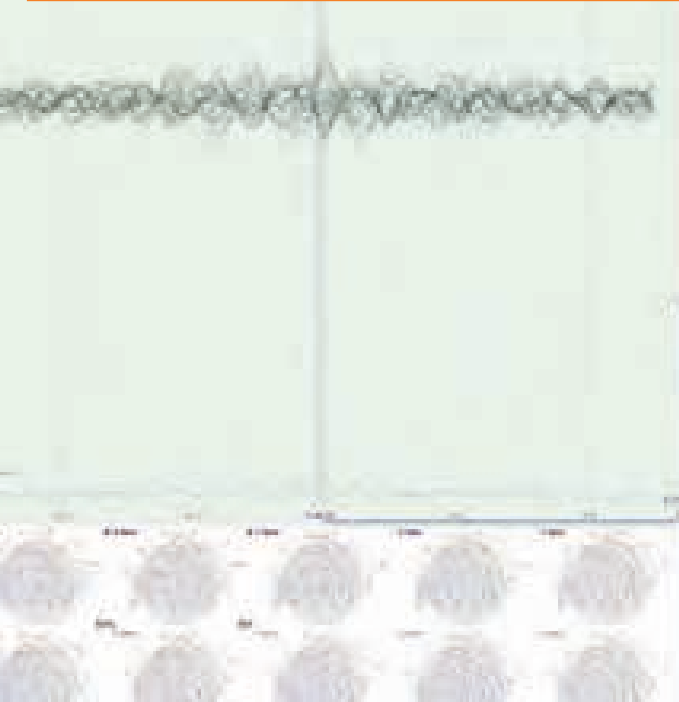
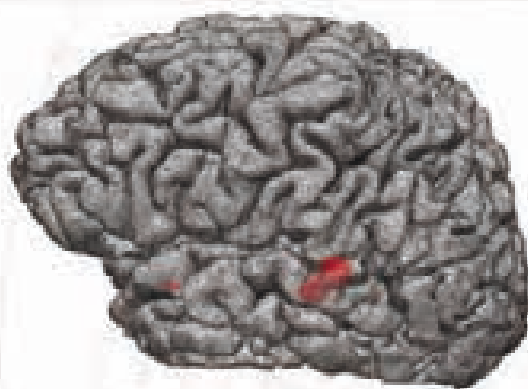
The most important and challenging aspect of presurgical evaluation is locating the area of the brain where seizures arise. And epilepsy localization is unique for every patient.

The only test that can directly identify this region is electroencephalography (EEG), which remains largely unchanged since its invention over 80 years ago. Localization is inferred based on two-dimensional montage arrangements of the recording electrodes, estimates that at best indicate which side and quadrant of the brain the seizures may arise from.

With the advent of magnetoencephalography (MEG) much more recently, clinicians had a method to create three-dimensional images that could pinpoint the area where seizure-related brain activity arose from more accurately. MEG took advantage of source localization methods – advanced

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EEG source localization using a complex forward model to account for conductivity differences in the skull, scalp, and CSF that are specific to this patient. The large red sphere represents the best fitting dipole for an average of the initial ictal waves.



neuroimaging and computational tools to translate abnormal activity recorded outside of the skull, as seen on magnetic field recordings, into maps of the most likely origin of that activity. MEG was also considered superior to EEG due to the inherent differences in the recording of magnetic fields versus electrical potentials at the scalp. However, MEG remains expensive, is difficult to perform, and is only available at a handful of specialized medical centers.

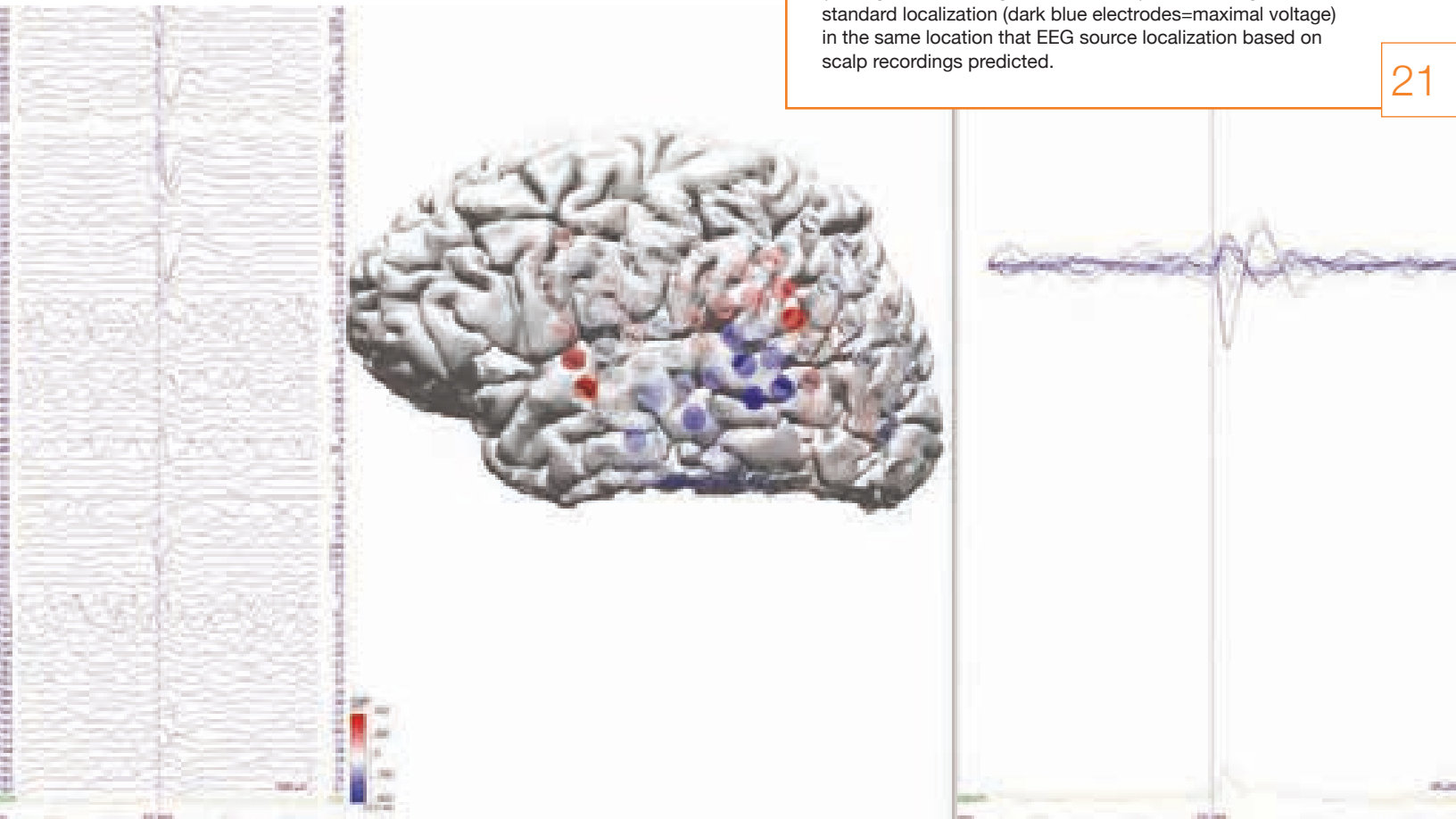
Today EEG source localization (ESL) is an exciting new advance in epilepsy localization, and many of the technological challenges of attempting source localization with EEG can be overcome with modern computing power and advanced image processing.

Like MEG, ESL models abnormal spikes seen on EEG into a dipole that can be superimposed onto MRI to create a source image. There are also an increasing number of systems by which to practically record electrical activity with higher EEG electrode density than was previously possible.

Clinical researchers at UCSF have embarked on studies to determine the most valuable and clinically useful protocols for implementation of ESL. The central aim of their work is

to determine if widely available EEG recording systems (32 channels) can be exploited for accurate ESL. This includes taking advantage of long-term recordings necessary to capture seizures, which is rarely possible with the newer high-density EEG systems. Capturing seizures provides highly valuable data points to increase source localization accuracy.

Preliminary findings presented at the Annual American Epilepsy Society Meeting in 2016 show that ESL was able to accurately localize seizures in over 90 percent of patients and produced results similar to other advanced methods such as MEG, ICEEG, and ictal SPeCT. While these results are from a small group of patients, if confirmed, they could change the practice of epilepsy. ESL using advanced computational models with standard EEG systems would provide demonstrably more accurate noninvasive epilepsy localization, and would be widely available to clinicians in all types of medical practices.





Aliesha Griffin, postdoctoral researcher in the laboratory of Scott Baraban, PhD, has been involved in developing a high-throughput screening technique to identify existing drugs that may work against epilepsy.

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Pediatric Neurosurgery

Zebrafish-to-Patient Approach Speeds Search for Childhood Epilepsy Treatments

UCSF-Led Research Drives Unique Clinical Trial of New Drug Candidate

In an unprecedented leap from lab to patients, a potential treatment for childhood epilepsy identified in experiments with zebrafish by UCSF scientists was administered in a clinical trial to children with Dravet syndrome, a rare and devastating genetic form of epilepsy that can cause hundreds of seizures per day. The therapy tested in the small, compassionate-use trial, a drug known as lorcaserin (Belviq), significantly reduced the frequency of seizures in all five patients enrolled in the trial, and two of those children continue to take the drug with no increase in seizure activity.

The decision to evaluate lorcaserin as a Dravet therapy grew out of research in the UCSF laboratory of Scott C. Baraban, PhD, professor of neurological surgery, who has developed platforms with which hundreds of drug compounds can be rapidly assessed for effectiveness in zebrafish larvae that carry gene mutations paralleling those known to cause childhood epilepsy.

“This is the first time that scientists have taken a potential therapy discovered in a fish model directly into people in a clinical trial,” said Vicky Whittemore, PhD, program director at the National Institute of Neurological Disorders and Stroke (NINDS), a division of the National Institutes of Health that provided funding for the new study. “These findings suggest that it may be possible to treat neurological disorders caused by genetic mutations through an efficient and precision medicine-style approach.”

The clinical trial results, as well as the basic research leading up to the trial, were reported in the March, 2017 issue of *Brain*.

In children, Dravet syndrome is caused by mutations in a gene known as SCN1A, and the Baraban lab has previously shown that mutations in a corresponding zebrafish gene have similar effects: the fish larvae, which are no bigger than a human eyelash, have frequent spontaneous seizures and their brain waves during these events resemble those seen in human Dravet patients.

In a 2013 study that tested more than 300 compounds already approved for other uses by the Food and Drug Administration (FDA), Baraban's research group found that clemizole, an antihistamine developed in the 1950s that has since fallen out of use, significantly reduced seizure activity and normalized brain waves in zebrafish carrying Dravet-like mutations.

But despite clemizole's apparent effectiveness in the fish, the finding was puzzling, said Baraban, the William K. Bowes, Jr., Endowed Chair in Neuroscience Research and a member of the UCSF Weill Institute for Neurosciences. "There was no reason to believe that antihistamines could suppress seizures, and when we looked at all the other antihistamines in our library—about 40 or 50 drugs—none of them had antiepileptic activity."

These negative results led Baraban and colleagues to suspect that clemizole must be acting on a target other than histamine, which in addition to its well-known role in mucus production also acts as a neurotransmitter in the brain.

Led by postdoctoral scholar Aliesha Griffin, PhD, the team used funds from UCSF's Catalyst program to commission a binding study, a research technique that shows how drug molecules interact with a wide range of targets. This work revealed that clemizole also acts on certain receptors for the neurotransmitter serotonin, which made more sense, Baraban said, because these serotonin receptors are known to be involved in regulating the brain's overall excitability and had previously been reported to exhibit antiepileptic actions.

Clemizole is currently unavailable in a clinical-grade formulation, so the team next began a search for other FDA-approved compounds that might act like clemizole on the serotonin receptors in question, and they identified both trazodone, often used as a sleep aid, and lorcaserin, which is prescribed as a weight-loss drug.

In experiments with zebrafish carrying the Dravet-like mutation, neither trazodone nor lorcaserin was as effective as clemizole in suppressing seizures, but the safety, commercial availability and side-effect profile of lorcaserin suggested it could be useful for children with Dravet who do not respond to therapies already in use, or who have developed resistance to antiepileptic drugs.

Kelly Knupp, MD, associate professor of pediatrics-neurology at the University of Colorado School of Medicine, agreed to lead a small compassionate-use, off-label trial of lorcaserin in five Dravet patients from 7 to 18 years old, all of whom experienced frequent seizures and were resistant to several existing drugs.

As reported in *Brain*, one patient was initially seizure-free for three weeks, one was seizure-free for two weeks, and a third had one to two seizure-free days per week. All five patients exhibited a reduction in the total number of seizures. Generalized tonic-clonic seizures, which involve the whole body and can induce loss of consciousness, were significantly reduced in three patients, one of whom experienced a 90 percent reduction in these seizures with no need for additional medications. Lorcaserin was well-tolerated, with the most frequent side-effect being, as expected, a loss of appetite.

Given clemizole's superior efficacy in zebrafish, however, Baraban has joined forces with Adam Renslo, PhD, associate professor of pharmaceutical chemistry in the UCSF School of Pharmacy and with postdoctoral funding from the Dravet Syndrome Foundation, to begin to develop what he calls "clemologs," newly designed compounds that will reduce clemizole's affinity for histamine while preserving, or enhancing, its targeting of serotonin receptors.

Baraban is also making good progress on a project to create zebrafish models of all 70 gene mutations known to be involved in childhood epilepsy, and is continuing to screen new drugs.

"Thanks to the flexibility offered by zebrafish, we can do these things extremely rapidly. The NIH's Epilepsy Therapy Screening Program, which was established 40 years ago, screens approximately 200 drugs per year. We've screened more than 2,700 in the last three years alone, and are working at a pace of 100 drugs per month," Baraban said. "Just because these are the few effective drugs we found doesn't mean they're the best possible drugs, so we'll keep searching."

Baraban, Griffin, and Knupp were joined in the research by UC Berkeley's SoonGweong Hong, PhD, a postdoctoral fellow, and Luke P. Lee, PhD, the Arnold and Barbara Silverman Distinguished Professor of Bioengineering, Biophysics, Electrical Engineering, and Computer Science. In addition to funding from the NINDS and a UCSF Catalyst Award, Baraban's work was supported by the Raymond and Beverly Sackler Center at UC Berkeley.

This article was written by Peter Farley and first appeared on UCSF News March 3, 2017.

Scott Baraban Honored for Excellence in Epilepsy Research

Scott C. Baraban, PhD, received the prestigious Research Recognition Award, Basic Science, from the American Epilepsy Society for his promising translational and basic science research.

Baraban's research has focused on translational questions in epilepsy, and currently includes work on models of pediatric epilepsy in zebrafish, drug discovery, and interneuron-based cell therapies.



New In Clinical Trials at the Pacific Pediatric Neuro-Oncology Consortium

The Pacific Pediatric Neuro-Oncology Consortium (PNOC), led by UCSF, is adding cutting-edge imaging and immunotherapy studies to the list of clinical trials available for pediatric patients with brain tumors. The focus of PNOC is to advance personalized medicine for children—it was the first consortium to launch a trial that used molecular profiling of a patient's tumor to guide a treatment plan—and these new trials continue to pursue the individualized therapies that guide PNOC's mission.

Immunotherapy Clinical Trial for Pediatric Brainstem Gliomas

Recent studies have revealed that malignant gliomas in children often show recurrent missense mutations in H3F3A, which encodes the replication-independent histone variant H3.3. This trial is evaluating the safety and immunological activity of a vaccine using a specific synthetic peptide for the H3.3K27M epitope in HLA-A2+ children with newly diagnosed diffuse intrinsic pontine glioma or other gliomas that are positive for the H3.3K27M mutation.

Pilot Study of ^{13}C MRI for Children with Brain Tumors

This study is evaluating a new imaging method that can assess the metabolic state of brain tumors. Typically, treatment response is assessed by anatomical changes seen on MR images that would show whether a tumor is shrinking or growing back. Predicting the efficacy of therapy and developing reliable response criteria is challenging using this conventional technique. ^{13}C MRI can detect changes in pyruvate metabolism within a tumor, indicating whether or not the tumor has responded to therapy and allowing physicians to guide treatment plans more effectively.

Oncolytic Virus Clinical Trial for Recurrent Medulloblastoma or Atypical Teratoid/Rhabdoid Tumors

PNOC is currently enrolling patients in the first trial of an oncolytic virus treatment against medulloblastoma and atypical teratoid/rhabdoid tumors. Medulloblastoma is the most common type of brain tumor that affects children, and approximately 30% of cases are refractory to treatment. The virus being tested in this clinical trial is a modified measles virus that binds to the protein CD46, which is highly expressed in these tumors. While CD46 expression is found in normal cells, it is not expressed at high enough levels that would initiate infection with the virus. After binding to the protein on a tumor cell, the virus lyses the cell. If successful, this therapy could provide patients with refractory forms of these tumors a much-needed alternative to standard therapies.



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For a full list of trials, visit pnoc.us.



Specialized Program for Cerebral Palsy and Spasticity

Cerebral palsy and spasticity can result in a wide spectrum of symptoms that should be managed by a multidisciplinary team. The spasticity clinic at UCSF Benioff Children's Hospital Oakland, led by Peter Sun, MD, is one of the few places in Northern California where children can receive this type of specialty care.

Depending on the severity of their symptoms, many children can be helped with physical therapy, while others may benefit from botox injections or medications. Patients with the most severe forms of the disease may be candidates for selective dorsal rhizotomy—a neurosurgical procedure that sections some of the sensory nerve fibers that enter the spinal cord and reduces leg muscle stiffness and spasticity.

This procedure can dramatically and permanently improve patients' ability to walk and be independent.

Patients undergoing rhizotomy are admitted to an intense inpatient rehabilitation program for 4 to 6 weeks to assist with recovery and learning to walk again. Orthopedic deformities are also common in these children and approximately one year after rhizotomy, patients are evaluated by pediatric orthopedic surgeons to consider treatments for these deformities, which is generally the final phase of treatment to ensure the most mobility for the patient's lifetime.



Swann NC, de Hemptinne C, Miocinovic S, Qasim S, Wang SS, Ziman N, Ostrem JL, San Luciano M, Galifianakis NB, Starr PA. Gamma oscillations in the hyperkinetic state detected with chronic human brain recordings in Parkinson's disease. *J Neurosci* 2016;36(24):6445-6458.

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Movement Disorders

Hyperkinetic dyskinesia has become a hallmark of Parkinson's disease and can be a serious side effect of both dopaminergic medication and deep brain stimulation (DBS). However little is known about how disruptions in neural networks correlate with these abnormal movements.

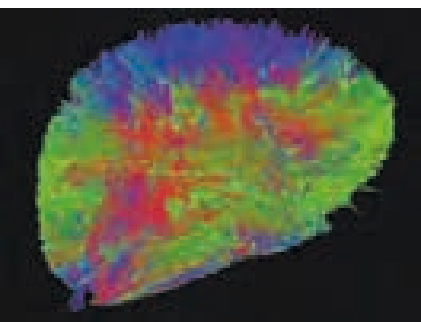
The laboratory of neurosurgeon Philip Starr, MD, PhD, studies brain circuitry to understand the underlying neural basis of movement disorders. Recently they used a totally implanted, investigational device to obtain multisite, long-term recordings from five patients while they were at rest and engaged in voluntary movement.

The device, called Activa PC + S, can store electrocorticography and local field potentials, and is also able to provide the same type of stimulation as a standard DBS device.

Starr and his colleagues found that dyskinesia is associated with a narrowband gamma oscillation in the motor cortex. They had previously shown that the rigidity and akinesia seen in patients with Parkinson's disease are associated with excessive synchronized activity in the beta band. Deep brain stimulation is able to disrupt this synchronization, thereby alleviating symptoms. The Starr lab is now developing a system that can adjust DBS settings automatically when excessive cortical synchronization is detected.

Currently, deep brain stimulators deliver constant stimulation to the brain, which can cause side effects. In 2016, a U.S. patent – for “Methods and Systems for Treating Neurological Movement Disorders” – was issued for the system to Starr, Jill Ostrem, MD, Coralie de Hemptinne, PhD, and Nicole Swann, PhD.

The narrowband gamma oscillation in the motor cortex may now be another marker that an implanted brain device could use to adjust stimulation settings, thereby reducing side effects of medications or DBS.



Vascular Neurosurgery

Michael Lawton, MD, performed his first surgery at UCSF, for a giant paraclinoidal carotid artery aneurysm, on July 31, 1997. He had recently been recruited from the Barrow Neurological Institute in Phoenix, AZ to the UCSF Department of Neurological Surgery to build a new program in cerebrovascular surgery. At that time, the Department was just beginning to evolve into the highly subspecialized program it is today. Approximately 30 aneurysms were treated with open microsurgery per year, the remaining cases being treated with the relatively new technique of endovascular coiling.

As Lawton expanded the microsurgical program, he raised bypass surgery to an art, inventing novel bypasses that were more efficient than previous techniques. These included

bypasses that used intracranial connections between adjacent vessels instead of extracranial-intracranial connections that were more invasive and required additional effort or incisions to harvest donor arteries or grafts. Today, approximately 280 aneurysms per year are referred to the Department's vascular neurosurgery program and over 4,000 have been treated microsurgically by Dr. Lawton since 1997.

Publishing hundreds of peer-reviewed manuscripts on vascular neurosurgery techniques and outcomes, Lawton demonstrated the critical role for open surgical techniques in modern neurosurgery, while emphasizing the importance of subspecialty training to achieve optimal outcomes. While many other institutions had been abandoning open surgery

Milestones in Vascular Neurosurgery at UCSF



1964

At a meeting of the Neurosurgical Society of America, Joseph DeWitt, MD, and John Adams, MD, describe the first use of the microscope in operations for intracranial aneurysms

1981

Interventional neuroradiologist Grant Hieshima, MD, introduces silicon balloon embolization for aneurysms

Yoshio Hosobuchi, MD, joins UCSF faculty and introduces electrothrombosis for carotid-cavernous fistula



1991

Guglielmi Detachable Coil introduced

Michael T. Lawton, MD, becomes Chief of Vascular Neurosurgery at UCSF

1997



Lawton performs 1000th aneurysm surgery

2005

2008

Lawton performs 2000th aneurysm surgery

2009

2004

The Aneurysm and AVM Foundation is established, with Lawton as a founding member

Cerebrovascular surgery observership program established

2008

U54 Grant Awarded from the NIH to establish the Brain Arteriovenous Malformation Consortium



in favor of endovascular techniques, UCSF became a hub for other surgeons to visit and learn microsurgical techniques. The vascular neurosurgery fellowship was established in 2013 and has graduated five fellows. The cerebrovascular observership program began in 2008, and to date has hosted over 100 visiting surgeons from around the world. It allows less-experienced surgeons to observe advanced procedures in the operating room and participate in a surgical skills laboratory and didactic lectures.

Seven Aneurysms and Seven AVMs

Lawton's extensive experience with aneurysms and AVMs was eventually consolidated into two exhaustive, award-winning textbooks. *Seven Aneurysms: Tenets and Techniques for Clipping* and *Seven AVMs: Tenets and Techniques for Resection* have quickly become definitive guides to surgical techniques for these diseases, systematically breaking down steps for treatment and serving as invaluable resources for neurosurgeons looking to gain a higher level of expertise. Lawton is nearing completion of the third book in the trilogy, *Seven Bypasses: Tenets and Techniques for Revascularization*.

Active in resident teaching, Lawton has directed the CNS Anatomy Course for Senior Residents and industry-sponsored anatomy courses, and has co-directed the AANS Vascular Skills Course. He has received both the Harold Rosegay Teaching Award and the Diane Ralston Clinical and Basic Science Teaching Award.

Center for Cerebrovascular Research

In 2000, William Young, MD, joined the Department of Anesthesia and Perioperative Care, studying arteriovenous malformations (AVMs) and other vascular disorders of the brain. His mentorship enabled Lawton to receive his first NIH grant, a K08 award to study radiation arteriopathy in an experimental model of AVMs in transgenic mice. He and Lawton established the Center for Cerebrovascular Research (CCR) to study the genetics, epidemiology, and clinical course of these diseases, as well as develop computational models of cerebral circulation. The CCR was continuously funded by an NIH Program Project Grant from 2003 to 2013 for a study of brain vascular malformations that integrated basic and clinical research projects to better understand the underlying biology of these disorders.



2010

2010

2011

Mission: BRAIN
launches in
Guadalajara, Mexico

2012

Lawton-Young
AVM grading scale
published in Journal
of Neurosurgery

*Seven Aneurysms:
Tenets and
Techniques for
Clipping* published
by Thieme Medical
Publishers

Lawton completes
UCSF fellowship in
endovascular surgery

2011

Surgical anatomist
Arnau Benet, MD,
joins UCSF faculty to
establish the Skull Base
and Cerebrovascular
Laboratory



In 2009, the CCR was awarded a five-year U54 grant to establish the Brain Vascular Malformation Consortium (BVMC), an integrated group of academic medical centers, patient support groups, and clinical research resources dedicated to conducting clinical research in different forms of brain vascular malformations and improving the care of patients with cerebral cavernous malformations, AVMs in hereditary hemorrhagic telangiectasia (HHT), and Sturge-Weber syndrome. A parallel project at UCSF — the UCSF Brain AVM Study Project — built a prospective registry of AVMs and other vascular malformations of the brain to track treatment results and patient outcomes.

Studies funded through these two initiatives have produced information about specific genetic mutations that occur in patients with cavernous malformations and HHT, providing new potential targets for therapy. The insights gained from studying AVMs in HHT patients led to the creation of the first animal model of brain AVM in transgenic mice with regional, conditional gene deletions. In 2014, the NIH provided five

additional years of funding for the BVMC with a \$6.5 million grant. The BVMC is part of the Rare Diseases Clinical Research Network and operations are directed from UCSF, with Lawton serving as principal investigator.

Mission: BRAIN

In 2011, together with former UCSF Neurological Surgery resident Alfredo Quinones-Hinojosa (currently the chairman of neurosurgery at the Mayo Clinic in Jacksonville, FL), Lawton began annual trips to Guadalajara, Mexico to provide pro bono surgeries and free training to Mexican neurosurgeons. In 2014, that mission was expanded to Manila, Philippines, where Lawton performed six surgeries for cerebrovascular disorders. In 2016, that mission was expanded again to Mexico City, Mexico. Lawton also participates in live surgery courses internationally as part of the mission to teach advanced neurosurgical techniques to neurosurgeons worldwide, with appearances at courses in Helsinki, Finland and Sapporo, Japan.

Adib Ablá to Join UCSF as New Chief of Vascular Neurosurgery

June 2017 marks the retirement of one of UCSF's most recognized graduates, Robert Spetzler, MD. A graduate of the program in 1977, Spetzler has chaired the Barrow Neurological Institute for 34 years and directed its rise to international prominence. Lawton was selected to succeed Spetzler as chairman of neurosurgery and President/CEO of the Barrow Neurological Institute, and will begin this new role on July 1, 2017.

Adib Ablá, MD, will take over as UCSF's Chief of Vascular Neurosurgery, bringing a wide range of microsurgical and endovascular experience to the role. Ablá specializes in the treatment of brain aneurysms, arteriovenous malformations and fistulae, intracranial surgical bypass, and carotid stenosis. He

performs both surgical and endovascular treatment of aneurysms, arteriovenous malformations, and carotid disease, allowing for an unbiased approach to complex cerebrovascular disease entities.

Ablá has undergone extensive specialized training for vascular neurosurgery, including an open vascular neurosurgery fellowship under Lawton at UCSF and a second fellowship under Spetzler at Barrow Neurological Institute, where he also completed his neurosurgical residency. He obtained experience in endovascular neurosurgery during residency at Barrow and at University at Buffalo, State University of New York.





Benet A, Griswold D, Tabani H, Lawton MT. Intracranial-intracranial A1-M2-M2 double reimplantation bypass for a giant middle cerebral artery aneurysm. 3D operative video. Operative Neurosurgery, In Press.

The Brain in 3D

The Skull Base and Cerebrovascular Laboratory at UCSF, led by Arnau Benet, MD, is a cutting-edge program for surgical anatomy research. Through surgical simulations, Benet, Chief of Vascular Neurosurgery Michael Lawton, MD, and their team have developed safer routes as alternatives to traditional surgeries, as well as new approaches to areas previously considered inoperable.

Master technicians, Lawton and Benet are frequent contributors to the libraries of 3D videos published by leading neurosurgery journals. These peer-reviewed interactive articles have seen a surge of interest in last five years as viewing technology has improved.

3D video is especially suited to cerebrovascular surgery, which often takes place in deep locations within the brain. "With 2D images, there is an objective loss of information regarding the relationships of key structures in the depth of field," says Benet. "3D video gives you a real sense of the actual distance between these structures, which is very important to understanding the risk of any surgical maneuver."

During surgery, a 3D camera is mounted onto the operating microscope, recording everything the surgeon sees and generating, on average, five hours of raw footage. Benet's team then imports the raw data into video processing software and edits it into a compelling story that is told in five to ten minutes.

Following an introduction to the case, each video shows the approach to the lesion, its treatment, and intraoperative angiography demonstrating that the treatment was successful and that adequate blood flow has been restored. The narration also includes rationale behind surgical maneuvers and discusses outcomes.

While the video file is shot with a high-definition 3D camera and is best viewed on a 3D monitor, the files can also be viewed on YouTube with simple, widely available 3D glasses or in 2D.

This video shows a bypass for a giant aneurysm of the middle cerebral artery (MCA) bifurcation. With a radial artery graph, Chief of Vascular Neurosurgery, Michael Lawton, MD, uses the anterior cerebral artery to supply the entire MCA territory, allowing him to preserve flow to the distal MCA branches that are vital to eloquent cortex. After confirming patency of the bypass using intraoperative angiography, Lawton deflects and traps the giant aneurysm. Although technically difficult, this approach provided a definitive and permanent treatment for the aneurysm while also treating the mass effect it had caused.

"In my lab we use 3D projection and 3D monitors for teaching residents and fellows, which provides them with an excellent experience of the anatomy," says Benet. "But it is important to note that when we publish these cases, the same files can be viewed with simple 3D glasses or just by looking at either the left or right panel in two dimensions."

While not intended to be a substitute for microsurgical training, video publications are making it easier for trainees to understand the intricate anatomy of the brain's vascular systems and the rationale behind surgical decision-making. "We want residents and fellows who are not exposed to complex cases to be able to have the same view as an assistant surgeon in that case," says Benet.

The Skull Base and Cerebrovascular laboratory has developed over 20 operative videos in an effort to build a virtual library of novel or complex neurosurgical cases. While they have published a variety of cutting-edge techniques, they are also interested in presenting classic techniques that will benefit from the additional depth provided by the 3D viewing experience.



Center for Neural Engineering and Prostheses at UC Berkeley and San Francisco

Fourteen University of California researchers were awarded \$9.5 million from the federal government's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative in 2016. Four of these researchers are members of the Center for Neural Engineering and Prostheses at UCSF and UC Berkeley. This is the third round of grants to support the goals of the BRAIN Initiative announced by the federal government in 2013, funding 170 investigators across 60 institutions.

The initiative aims to help scientists develop new tools and technologies to map the circuits of the brain and understand how they give rise to humanity's unique cognitive and behavioral abilities. This deeper understanding of neural circuit function will be used to fill in the gaps in our current knowledge and to accelerate the creation of new treatments for neurological disorders.

CNEP Brain Initiative Projects

Closed loop deep brain stimulation for Parkinson's disease

Principal Investigator: Philip Starr, MD, PhD (UCSF)

Deep brain stimulation (DBS) has an important clinical role in the management of movement disorders, including Parkinson's disease. However, current DBS therapy for movement disorders relies on continuous stimulation, regardless of changes in brain circuit function related to changes in disease expression (i.e., oscillation between too little and too much movement). In this project, Starr and his team will use next-generation DBS devices to develop and test a method of automatically adjusting stimulation parameters based on brain signals that reflect the patient's clinical state, to optimize DBS for Parkinson's disease. In a small number of patients, they will measure local brain activity in each patient and use that information to develop individualized stimulation paradigms; these algorithms will then be programmed into the DBS devices to demonstrate proof of principle for this novel, closed-loop DBS system.

Optimizing peripheral stimulation parameters to modulate the sensorimotor cortex for post-stroke motor recovery

Principal Investigator: Karunesh Ganguly, PhD (UCSF)

Somatosensory peripheral nerve stimulation (PNS) has had some success in improving recovery of hand motor function for stroke patients, but benefits are not consistent for all patients. PNS tailored to maximize recovery requires greater understanding of how stimulation interacts with cortical neurophysiological dynamics in the region impacted by the stroke. Ganguly and colleagues will employ a translational approach using animal model systems and human patients to study the link between PNS and changes in cortical activity in a dose-dependent manner. This work

will elucidate how PNS modulates cortical activity and subsequent motor behavior, leading to the development of highly individualized PNS treatments for maximal restoration of function.

Functional architecture of speech motor cortex

Principal Investigator: Edward Chang, MD (UCSF)

Speaking is one example of a complex behavior that most humans can perform effortlessly, but scientists do not fully understand how the brain is able to drive speech production. Building on their prior work on the neural representation of articulatory and acoustic feature representations of speech, Chang and his team will conduct ultra high-density electrocorticography in epilepsy patients to study how the ventral sensorimotor cortex encodes the movements that produce speech, and how the prefrontal cortex is able to exert inhibitory control over speech. This work will advance our understanding of communication disorders, and refine the ability of clinicians to map speech areas of the brain in their patients.

Wireless recording in the central nervous system with ultrasonic neural dust

Principal Investigator: Jose Carmena, PhD (UC Berkeley)

This research team aims to develop implantable sensors for neural recording, called neural dust, that are based on miniature, wireless ultrasound technology. The technology will have three components: implanted neural dust particles for detecting and reporting extracellular electrical signals from neurons, an ultrasound power source placed under the skull, and an external wireless receiver. Compared to standard microelectrode arrays, this technology promises to be less damaging to tissue, and has the potential for broader coverage of brain areas.



Cutting Through the Clamor: How the Brain Helps Us Understand Spoken Words in Noisy Setting

Humans are exquisitely skilled at perceiving spoken words, even when speakers' voices are intermittently overwhelmed by noise, as happens in the din of construction sites or on busy urban streets. Now, in a study conducted in a group of patients preparing for brain surgery, UC San Francisco scientists have discovered an unexpected mechanism the brain uses to seamlessly compensate when speech sounds are obscured by noise.

The research team monitored neural activity during listening tasks in a group of epilepsy patients awaiting surgery, using recording devices placed directly on the surface of the brain. As reported in the Dec. 20, 2016, issue of *Nature Communications*, the resulting neural recordings captured the real-time dynamics of this perceptual "filling in," which takes just tenths of a second, and also showed that a region outside the brain's canonical speech areas plays a critical role in this process.

The group found that the part of the brain most deeply involved in speech perception responded to missing speech sounds as if those sounds were actually present.

But most intriguingly, the researchers discovered that a brain region separate from main speech-processing areas somehow "predicts" which word a listener will hear when that word is partially masked by noise, well before that noise has even begun to be processed by auditory areas.

In the new research, Matthew Leonard, PhD, assistant professor of neurological surgery and a member of the UCSF Weill Institute for Neurosciences, and colleagues worked with five patients about to undergo surgery to treat epilepsy that was not manageable with medications.

Devices Placed Directly On the Brain

To locate the anatomical origins of these patients' seizures for surgery, and to create surgical plans that would protect crucial brain areas, flexible panels containing 256 recording electrodes had been placed on the surface of either the right or left side of the brain. These electrode arrays provided dense coverage of a region known as the superior temporal gyrus (STG), which is crucial to speech processing, a recording arrangement that has proven valuable in previous research on speech in the UCSF laboratory of neurosurgeon-scientist and senior author Edward Chang, MD, professor of neurological surgery.

It has been known since the 1970s that when critical speech sounds that distinguish one word from another – the “s” and “k” sounds that distinguish faster from factor, for example – are excised and replaced by noise (such a stimulus can be represented as “fa#tor”), listeners will nonetheless report hearing a complete word, a phenomenon called “phoneme restoration.”

According to Leonard, for stimuli like fa#tor, where only two actual English words related to the stimulus exist, phoneme restoration is a “bistable” auditory illusion, somewhat analogous to well-known visual illusions like the “duck/rabbit” drawings that shift between two perceptual interpretations. When listeners hear fa#tor, they report hearing either faster or factor, even though neither word is truly present in the stimulus.

When the patients listened to various bistable stimuli, recordings from the STG were consistent with whichever word they reported hearing: if they perceived factor, for example, the part of the STG normally activated by “k” sounds emitted a signal, even though no “k” sound was actually present; likewise, when they perceived faster, the STG region corresponding to “s” sounds was activated.

A Perennial Question in Speech Perception

These responses occurred less than two tenths of a second after the noise-obscured gaps in the stimuli began to be processed – the same time frame as when the difference between the actual words faster or factor was processed – which provides the beginnings of an answer to a perennial question in speech perception, Leonard said.

“One of the oldest debates in the field is whether there’s a ‘top-down’ signal that actually changes the listener’s perception ‘online,’ in real time, or whether this is achieved by some sort of decision-making process that rapidly

arrives at an interpretation after the missing sound segment has been processed,” Leonard said. “Our data seem to support the former idea.”

Surprisingly, the patients’ word choices were unaffected when noise-masked words were embedded in sentences that would seem to strongly favor one choice over another, a technique called “semantic priming.” For example, hearing “On the highway, he drove the car much fa#ter” would seem to bias a listener toward hearing “faster,” but the researchers found that the patients were just as likely to say they heard “factor.”

Since phoneme restoration was essentially instantaneous, and because semantic priming had so little effect, the research team wondered whether brain areas other than the STG might somehow be contributing to the listeners’ perception.


The group was surprised to find that an area toward the front of the brain was selectively active about half a second before the STG signals associated with phoneme restoration were seen. This activity actually predicted which word patients would report hearing, suggesting that this region somehow helped to drive that perception.

“Whether you hear a bistable stimulus as factor or faster on a given trial seems to depend on random fluctuations in the brain’s state at that moment, something you really don’t have any control over,” Leonard said. “We don’t have a definitive idea of what this frontal signal is yet, but we’ll be exploring that question in future research.”

Taken together, said Leonard, the new results show that “there are brain mechanisms that are constantly working behind the scenes to make sure we don’t get tripped up every time there’s a sound that could prevent us from understanding speech.”

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The UCSF logo is displayed in white text on a dark blue rectangular background. The letters 'UCSF' are in a bold, sans-serif font, with the 'U' and 'C' connected, and the 'S' and 'F' connected.A close-up photograph of a surgical procedure. Two surgeons wearing blue scrubs and white gloves are performing a delicate operation. They are using various surgical instruments, including forceps and a scalpel, to work on a patient's head. The patient's head is covered with a white surgical cap and is positioned on a blue operating table. The background is a sterile, brightly lit operating room.

For consultations or referrals, contact us at (415) 353-7500. Visit us online at neurosurgery.ucsf.edu.