

The Department of Neurological Surgery at UCSF  
**2014 Year in Review**

**UCSF**

University of California  
San Francisco

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# Letter from the Chair

Dear Colleague:

I am thrilled to be sharing the Department of Neurological Surgery's annual review with you. In these pages you will find some of the major clinical and research achievements made by our faculty over the past year and have a look into new programs on the horizon.

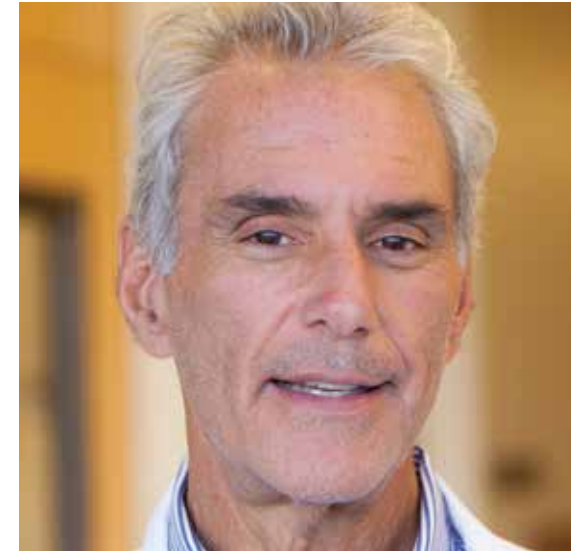
UCSF's neurosurgery and neurology programs have again been ranked among the top five in the nation – and best on the West Coast – by *U.S. News and World Report's* annual survey of Best Hospitals. In a new survey by Doximity and *U.S. News and World Report* that ranked residency training programs, the neurosurgical residency program at UCSF ranked first in the nation.

Our neurosurgery research programs were awarded the most NIH funding for the 13th consecutive year and our h-index, reflecting research publication productivity, was the highest of any academic neurosurgery program in the nation.

In 2014 our faculty received funding for several innovative programs that have the potential to greatly impact patient care. Neurosurgeons Edward Chang MD and Philip Starr MD, PhD will lead a project funded by the U.S. Defense Advanced Research Projects Agency to map the human brain circuits that go awry in neuropsychiatric disorders and employ advanced technology to correct these patterns (page 41).

At the Brain and Spinal Injury Center, Geoffrey Manley MD, PhD and his team are leading several national and international initiatives funded by the NIH to change research and clinical care for traumatic brain injury. This vastly undertreated condition has come under the spotlight in recent years, thanks in part to Dr. Manley's tireless efforts in this field (page 16).

As always, it is a great privilege to be a part of the team that serves your patients. We appreciate the continued support for UCSF Neurological Surgery and look forward to continuing to provide exceptional tertiary care for our community.



A handwritten signature in black ink, appearing to read 'Mitchel S. Berger'.

**Mitchel S. Berger MD**

Professor and Chairman, Department  
of Neurological Surgery

Berthold and Belle N. Guggenheim  
Endowed Chair

Director, Brain Tumor Research Center

# Brain Tumor Center

## New Clinical Trial of Nanoliposomal CPT-11 Epitomizes UCSF's Bench-to-Bedside Research for Brain Tumors

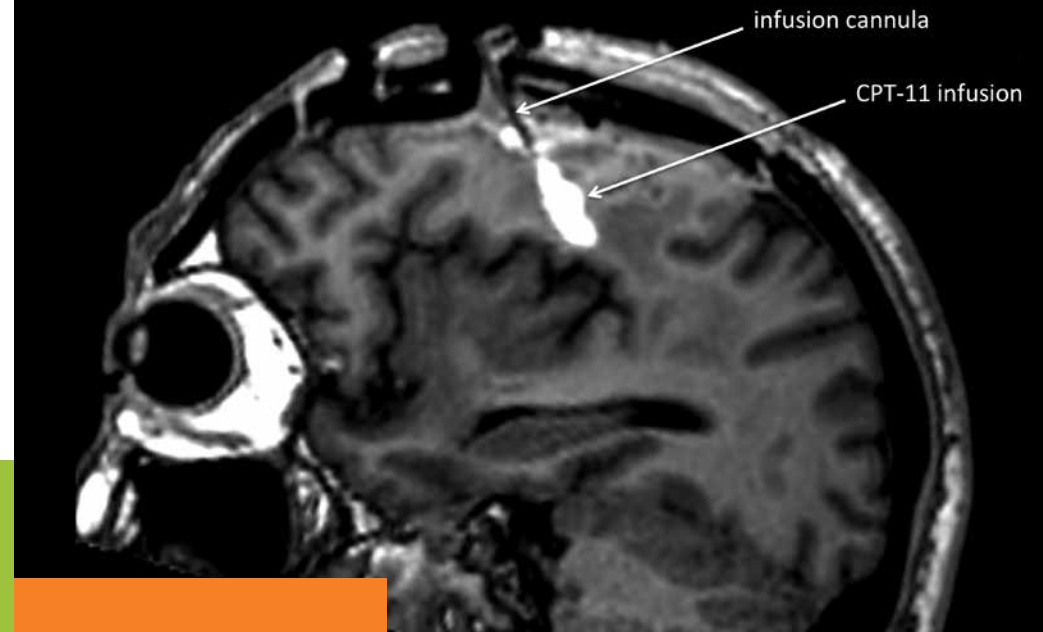
The Brain Tumor Research Center (BTRC) at UCSF was founded in 1972 on the principle of translational research. In an unusual model for the time, clinicians and basic scientists worked together, translating findings from biological laboratory studies into new therapies. Today, a new clinical trial combines several cutting-edge strategies for brain tumor treatment – many of which were developed at UCSF.

For several years, BTRC investigators have been studying ways to deliver therapeutic agents into the brain in sufficient concentrations to kill tumor cells, but minimize toxicity to normal tissues. With funding from a Specialized Program of Research Excellence (SPORE) award from the NCI in 2002, investigators John Park MD and Mitchel Berger MD began researching the use of liposomal nanoparticles to selectively target tumors.

Encapsulating a drug in a liposome alters the pharmacokinetic properties so that it is more stable and stays in tissue longer. After encapsulating several compounds and comparing their stability profiles in the lab, the investigators

chose the chemotherapeutic agent CPT-11 (also called irinotecan) for translational studies.

Through a collaboration with BTRC investigator Krystof Bankiewicz MD, PhD, liposomes were delivered to the brains of non-human primates using convection-enhanced delivery (CED). CED uses a pressure-driven, bulk-flow process to distribute an infusion over more area than a direct injection. This strategy showed superior localization and retention of the drug compared with systemic delivery, and the slow and sustained release of drug from the liposome provided an additional safety margin.



For a full list of clinical trials for adult and pediatric brain tumors, visit [neurosurgery.ucsf.edu](http://neurosurgery.ucsf.edu)

In a new clinical trial at the UCSF Brain Tumor Center, surgeons use ClearPoint to visualize the infusion of chemotherapeutic agent CPT-11 into the brain in real time. This technological advance allows them to ensure that enough of the infusion is reaching the tumor.

## Faculty

### Adult Neuro-Oncology

Susan Chang MD  
Nicholas Butowski MD  
Jennifer Clarke MD, MPH  
Jennie Taylor MD, MPH  
Michael Prados MD

### Adult Brain Tumor Surgery

Mitchel S. Berger MD  
Manish Aghi MD  
Sandeep Kunwar MD  
Michael McDermott MD  
Philip Theodosopoulos MD

### Neuropsychology

Caroline Belkoura PhD

(cont. on page 4)

## Faculty

(cont.)

### California Center for Pituitary Disorders

Manish Aghi MD, PhD  
Lewis Blevins, Jr. MD  
Sandeep Kunwar MD

### Brain Tumor Research Laboratories

Manish Aghi MD, PhD  
Arturo Alvarez-Buylla PhD  
Krystof Bankiewicz MD, PhD  
Arnau Benet MD  
Mitchel Berger MD  
Gabriele Bergers PhD  
Soonmee Cha MD  
Joseph Costello PhD

Aaron Diaz PhD  
Nalin Gupta MD, PhD  
Daphne Haas-Kogan MD  
Annette Molinaro MA, PhD  
Hideho Okada MD, PhD  
Claudia Petritsch PhD  
Arie Perry MD  
Joanna Phillips MD, PhD  
Russell Pieper PhD  
David Rowitch MD, PhD  
William Weiss MD, PhD  
Kyle Walsh PhD  
John Wiencke PhD  
Margaret Wrench MPH, PhD  
Shichun Zheng PhD

With funding from an NIH Program Project Grant in 2007, Dr. Bankiewicz and his colleagues incorporated advanced neuroimaging technologies to monitor CED of nanoliposomal CTP-11 labeled with gadolinium into the brains of dogs with spontaneous brain tumors. This project was done in partnership with UC Davis veterinarians and results were so successful that the investigators made plans to move the therapy into human trials.


Over the next several years, BTRC investigators worked with the NCI Drug Development Group and industry partners for GMP manufacturing, toxicology and clinical development of this new nanoparticle drug. It is now being used in a new trial, led by Nicholas Butowski MD and Manish Aghi MD, PhD, for patients with recurrent glioblastoma multiforme – a fatal form of brain cancer.

To ensure an even more efficient delivery of nanoliposomal CPT-11 to the tumor, the new trial will use the ClearPoint delivery platform to allow surgeons to visualize the CED infusion

in real-time using intraoperative MRI. Originally developed by Alastair Martin PhD, Philip Starr MD, PhD and Paul Larson MD to implant deep brain stimulation leads while patients are inside an MR scanner, the ClearPoint platform also uses advanced software to guide a cannula through a skull-mounted device and into the brain. The cannula is connected to an infusion line that allows delivery of the nanoliposomal vehicle and the infusion can be watched on MRI to ensure adequate delivery.

ClearPoint has also been used to administer Toca 511 – a therapy using a retrovirus carrying an enzyme that converts a nontoxic oral prodrug into a cytolytic agent in brain tumor cells. Using ClearPoint, the surgical team has been able to achieve a 10-fold higher viral infection rate than with CED alone.

For information about enrollment in clinical trials of nanoliposomal CPT-11 and Toca 511, contact the Neuro-Oncology nursing line at (415) 353-2652. Principal Investigator (PI): Nicholas Butowski MD; Surgical PI: Manish Aghi MD, PhD.



## New Precision Medicine Trial Gives Patients with Malignant Glioma Treatment Recommendations Based on Their Tumors' Molecular Profile

Supported by the Ben and Catherine Ivy Foundation, the UCSF Brain Tumor Center is initiating a feasibility study for a new personalized medicine strategy for patients with glioblastoma. Patients will undergo surgery, after which their tumor will be sequenced to reveal its gene expression profile.

A virtual tumor board made up of multidisciplinary experts from leading academic medical centers will then review current FDA-approved drugs to determine if any target the abnormalities found in the patient's tumors, such as overactive tyrosine kinases or growth factors.

Repositioning existing drugs is one way to more quickly offer alternative therapies to patients with life-limiting

illness who may not be eligible for other clinical trials. The goal is for patients to receive recommendations from the tumor board five weeks after undergoing surgery. The investigators hope that by harnessing genetic information, they can hone in on the compounds most likely benefit individual patients.

The tumor board is made up of brain tumor experts at UCSF, UCLA, Dana Farber Cancer Institute, Memorial Sloan Kettering, Massachusetts General Hospital, MD Anderson, and the University of Utah. The group discusses each patient together to arrive at a treatment recommendation.





Renowned scientist Hideho Okada MD, PhD is the new director of the UCSF Brain Tumor Immunotherapy Center.

## The Brain Tumor Immunotherapy Center at UCSF

The goal of immunotherapy is to make cancer cells recognizable and vulnerable to attack by the T-cells that are active in the central nervous system. There are now a variety of treatments that can elicit an immune response against tumor cells in the brain, and most produce mild toxicity and can often be combined with other treatment strategies.

This year, Hideho Okada MD, PhD joined UCSF to direct the Brain Tumor Immunotherapy Center. Dr. Okada has spent more than 20 years studying central nervous system immunology and immunotherapeutic strategies for brain tumors. His laboratory was the first to identify and fully characterize cytotoxic T-lymphocyte epitopes for gliomas and he has been a principal investigator for several clinical immunotherapy protocols, including those for brain tumor vaccines.

Working with UCSF's renowned neuro-oncology team, Dr. Okada is designing a new clinical trial of chimeric antigen

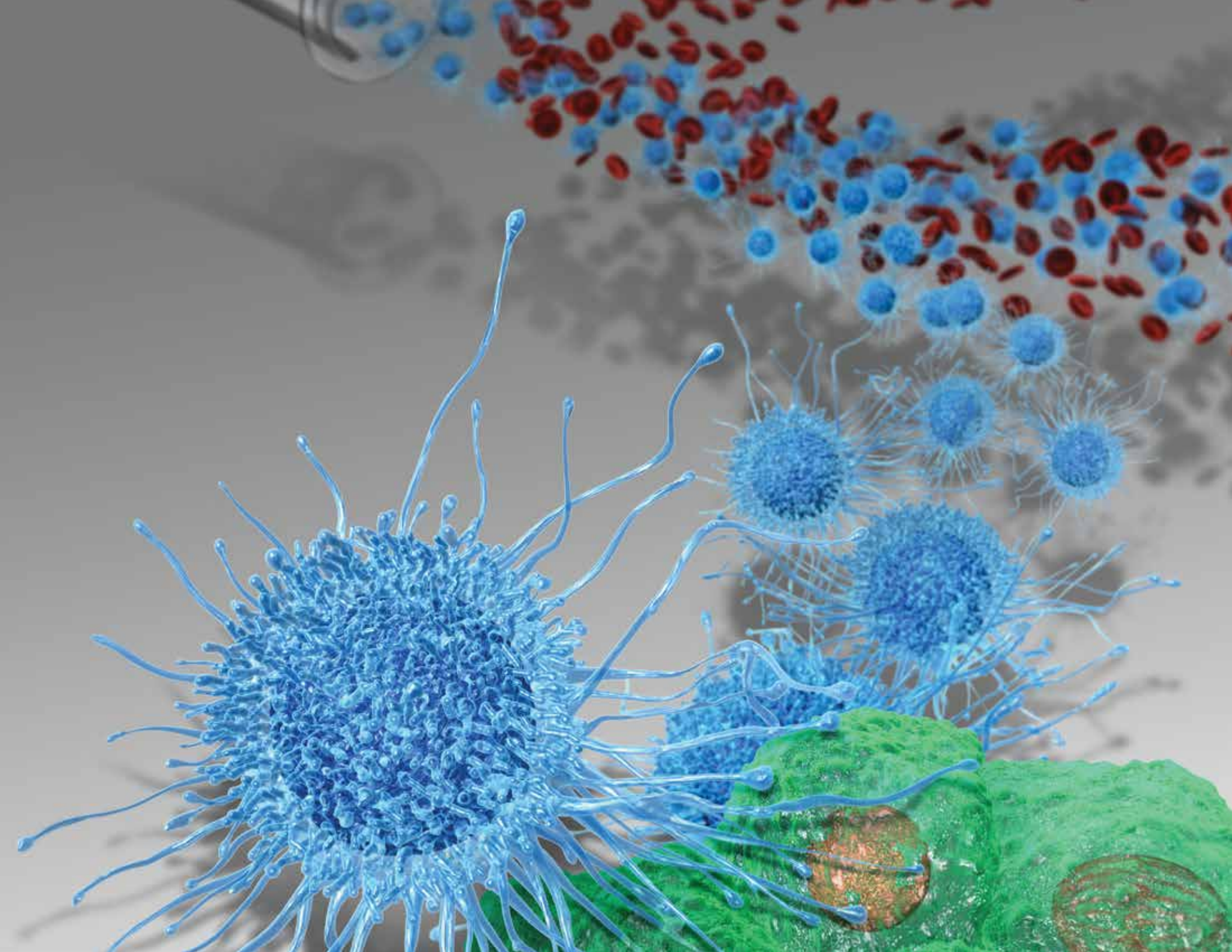
T-cell (CAR-T) therapy that will open for enrollment in 2015. With this treatment, patients' T-cells are extracted and transduced with an antigen receptor that recognizes antibodies for molecules commonly overexpressed in glioma, such as certain growth factors or tyrosine kinases. The newly armed T-cells are then injected back into patients with the ability to hone in on tumor cells with the target antibody.

CAR-T therapy may be an especially good strategy for patients with malignant gliomas whose immune systems have been compromised by the tumor or other therapies. Because the therapy uses the patient's own T-cells, it is less likely to be rejected by the body.

Dr. Okada is also the only North American principal investigator to participate in the Glioma Actively Personalized Vaccine Consortium – a network of institutions offering a clinical trial that uses high-throughput gene sequencing to design a vaccine that is specific for each patient's tumor.

Currently, UCSF is participating in a multi-institutional Phase II trial of a heat shock protein-peptide complex, which is also matched to a patient's tumor. Once the tumor is removed, the vaccine is created from proteins specific to that tumor and a heat-shock protein, and then injected back into the patient over time. This prepares the immune system to produce T-cells that find and kill new cancerous cells with proteins matching those extracted from the tumor.

New immunotherapy trials will be open for enrollment in 2015. For information, contact us at (415) 353-7500 or e-mail Dr. Okada at [Hideho.Okada@ucsf.edu](mailto:Hideho.Okada@ucsf.edu).





Margaretta Page MS, RN has been a member of the UCSF Neuro-Oncology team since 1985 and is nationally recognized for her expertise in caring for patients with brain tumors and in clinical trial protocols.

Over her 30-year career as a clinical nurse specialist, she has gained intimate knowledge of how the diagnosis of a brain tumor affects both patients and their families.

Recently, Page helped to design a program specifically to support caregivers of patients at UCSF. Here she talks about why it is important to recognize family members as partners in patient care and how UCSF is paving the way for maximizing quality of life for patients and their caregivers.

## Clinical Nurse Specialist Margaretta Page Talks About the Essential Role of Patient Caregivers and the Launch of the Gordon Murray Neuro-Oncology Caregiver Program at UCSF

### Why is supporting the caregivers of patients with brain tumors particularly important?

Recent changes in healthcare delivery, specifically that patients spend fewer days in the hospital and less time with health care providers in the outpatient setting, have increased the need for family members to take on diverse primary care roles.

Often with little or no training caregivers are asked to obtain and administer medications, manage symptoms, provide emotional support to the patient, handle medical insurance coverage, communicate with the health care team, and coordinate medical appointments. These tasks are often required in addition to their previous roles and responsibilities.

It is well documented that when patients have neurological impairments, cognitive changes, or neuropsychiatric symptoms, caregivers are at an even greater risk for stress and depression. This burden has the potential to affect the overall physical and mental health of the caregiver and, in turn, the quality of care that they are able to provide for the patient.

Supporting caregivers acknowledges that they are part of the health care team and the challenges they face

on a daily basis. More importantly, by offering support and connection to education and resources, we are able to enhance their ability to do “caregiver” work well, feel better about themselves, and improve their quality of life.

### What is the Gordon Murray Neuro-Oncology Caregiver Program at UCSF?

The Gordon Murray Neuro-Oncology Caregiver Program is a new program now offered to all patients being treated for primary brain tumors at UCSF. The goals of the program are to formally and routinely assess caregiver needs across the illness trajectory, from diagnosis until death. The program offers individualized care that may include providing information and education about the disease, symptoms and what to expect, offering direct emotional support, and facilitating connections to community caregiver resources.

The program team includes a physician, neuro-oncology nurse, social worker, and an administrator who have expertise in neuro-oncology caregiver issues. In addition to direct consultations, the team documents caregiver concerns and care in the electronic medical record. We also offer caregiver support groups, host



caregiver-specific workshops, and collaborate with other disciplines involved in neuro-oncology care, such as palliative medicine.

### What did it take to get the program off the ground?

First there was a call to action by two caregivers, Jack Glazer and Randi Murray. Both felt strongly that the care provided to their spouses was outstanding, but that we lacked a coordinated effort to make sure that their needs were met. Both felt strongly that this was an area where improvement was needed.

Dr. Susan Chang developed a proposal for the caregiver program and presented it to Randi Murray who spearheaded a fundraising initiative to get the program off the ground. Without philanthropic resources it would have been extremely difficult to get the dedicated time and staff, get the necessary approvals, evaluate the literature, educate the team, and begin to provide care and programming specific for caregivers.

### What do patients and their families gain from the program?

The patient remains the primary focus of the Neuro-Oncology team, but we have added individual support for the

caregiver with the understanding that the disease affects the whole family. Patients and caregivers are introduced to the program at their first visit to the clinic. Caregiver-specific support is offered at time points that have been documented to be times of high risk for caregivers.

Every family has different needs, some are struggling with insurance and work issues, some with parenting issues, others with neurological symptoms, and still others are coping with the diagnosis of a life-limiting illness. Families' needs are assessed and support is tailored for them. We hope that in providing this program, caregivers feel supported and are connected with resources that can help them to achieve mastery and a sense of self sufficiency in their role, as well as cope with the life-changing illness of their loved one. Our goal is to optimize their quality of life and in turn the quality of life of the neuro-oncology patient.

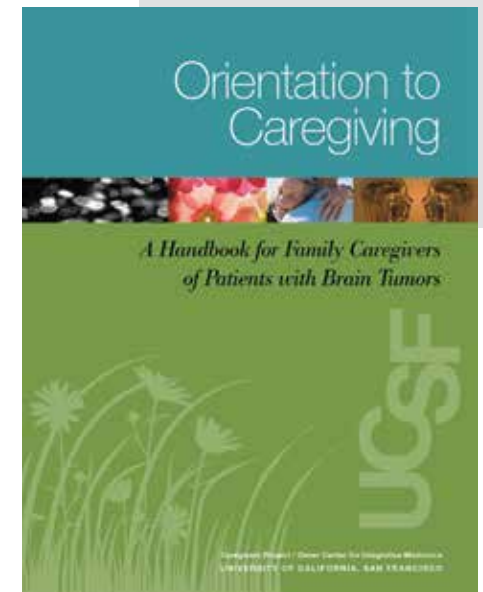
### What is peer-to-peer support and how does it work?

The Caregiver-to-Caregiver Peer Support Program offers new caregivers an opportunity to talk with experienced caregivers of brain tumor patients. Those seeking support are matched by tumor type, treatment, age, family

situation, or by personal preference to experienced caregivers who are trained volunteers. The volunteers are trained to provide confidential, emotional, practical, and informational support. This program allows caregivers the opportunity to speak with someone who has been in their situation. Data shows that this type of interaction has positive benefits for both those giving and receiving the support.

### You and your colleagues recently presented work at the American Society for Clinical Oncology that talked about the increase in caregiver stress during transitions in care, such as change in location, provider or goal of treatment. What does the caregiver team at UCSF do to make those transitions easier, especially during the transition to the hospice care setting?

We do several things. First, just acknowledging that transitions are a difficult time is incredibly important. The caregiver nurse coordinates contact with the facility, agency or doctor to whom care is being transferred. In the case of hospice, we reach out to the hospice agency that the patient is being referred to,



The 2<sup>nd</sup> edition of UCSF's Orientation to Caregiving handbook provides practical information specifically for caregivers of patients with brain tumors and is available online at [neurosurgery.ucsf.edu](http://neurosurgery.ucsf.edu).

introduce ourselves, and report on the patient and family now in their care. The goal is to make sure the agency is aware of any long-standing patient or family specifics, symptoms, or concerns that would be beneficial to know when caring for the patient.

We also offer to be a resource regarding any neurological or neuro-oncological issues or symptoms that the patient may encounter – seizures, weakness, speech or swallowing problems to name a few. After the transfer to hospice is made, we connect with the caregiver again so that he or she knows we have been in touch with the hospice to offer ongoing support and to make sure that they

feel that their needs are being met. The goal here is to prevent a sense of feeling abandoned. After a long-standing relationship in which UCSF was providing or coordinating care we want the caregiver to know that although not as hands on, we are still available to provide support and act as a resource.

### What are some things that physicians and other healthcare providers can do to support caregivers?

First and foremost, acknowledge that the disease affects the whole family. Be sure to make time in each visit to address both patient and caregiver concerns.

Know that there are times when burden or distress is particularly high, most notably at diagnosis, at progression, with an increase in symptoms, and during transitions in location and/or types of care delivered. Encourage or “prescribe” self-care to caregivers, including keeping up with their own medical care and seeking counseling if necessary.

Be aware of what resources are available for caregivers in your community and provide families with a resource sheet. There are existing materials that can be used as starting point to locate national and/or local resources.

### What career would you have if you were not a nurse?

I honestly think that nursing is my true calling and passion. But if I were not a nurse, maybe I would have liked to have been a back-country outdoor adventure trip planner and leader. I love exploring the outdoors!

The Gordon Murray Neuro-Oncology Caregiver Program officially launched with a ribbon-cutting ceremony on January 16, 2014. The Neuro-Oncology team celebrated with active supporters of the program, which provides additional support from a dedicated nurse and social worker to family members and caregivers of patients with brain tumors.



From left: Director of Neuro-Oncology Susan Chang MD, Randi Murray, Margaretta Page MS, RN, Program Coordinator Idonah Molina, and Neuro-Oncology Social Worker Judy Patt-Smoker in a new space dedicated for meeting with caregivers of patients with brain tumors.

The UCSF Neuro-Oncology team joined patients and their families and supporters in a 5K run/walk in Golden Gate Park to raise funds for Voices Against Brain Cancer.



## Neuro-Oncology Team Wins Patient Satisfaction Award

The Division of Neuro-Oncology received the 2014 Pinnacle Award for the highest ratings in patient satisfaction of any outpatient service at UCSF Medical Center. This is the seventh consecutive year that the Neuro-Oncology team has won the Pinnacle award.

This year, the team was joined by adult neuro-oncologist Jennie Taylor MD, MPH. Dr. Taylor is a graduate of the joint Massachusetts General Hospital, Brigham and Women's Hospital, Dana Farber Cancer Institute, and Harvard Medical School Neuro-Oncology Fellowship program.



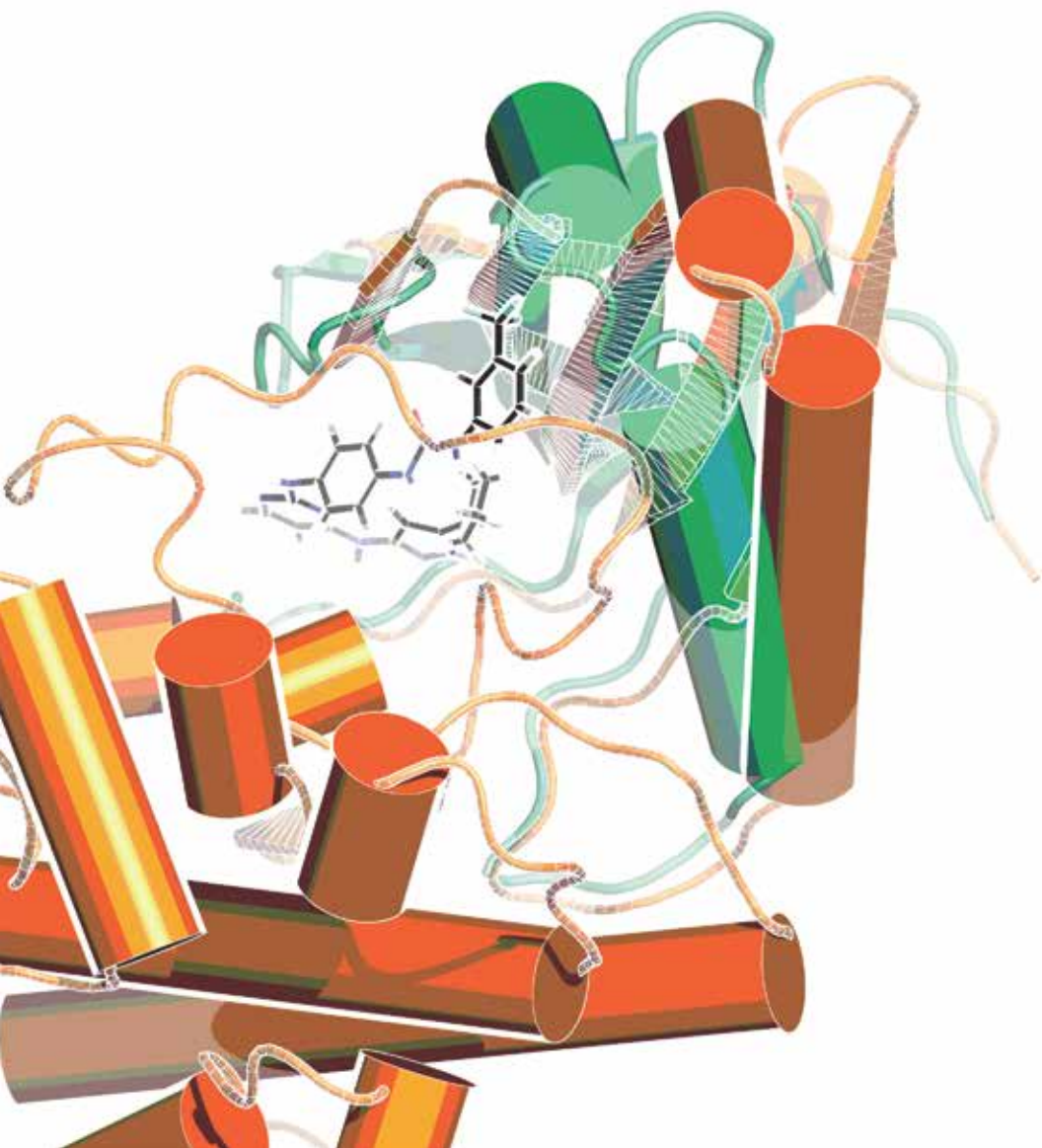
Patients with brain tumors and their families tackled a fun outdoor obstacle course at the Milton Marks Neuro-Oncology Family Camp.

## Milton Marks Neuro-Oncology Family Camp

The inaugural Milton Marks Neuro-Oncology Family Camp was held on October 17-19, 2014 at Camp Newman in Santa Rosa. The camp was conceived by Dr. Abby Marks, a former caregiver of the late Milton Marks, III, who had received care for a brain tumor at UCSF. Because the diagnosis of a brain tumor can impact everyone in the family, and can be associated with stress, as well as feelings of isolation and loss, Dr. Marks collaborated with the UCSF Neuro-Oncology team to offer a camp for 11 families.

Spanning three days, the camp provided much-needed respite from the daily burdens of illness, along with therapeutic workshops and activities. The camp included support groups and a special program for children, and staff members offered tools to improve communication, parenting, and coping skills. There was also time for relaxation with yoga, nature walks, and community-building with other families going through similar situations.

The Milton Marks Neuro-Oncology Family Camp is a project of the nonprofit Access Institute for Psychological Services. The camp consisted of a planning committee, which included multi-disciplinary staff members from UCSF Neuro-Oncology and Access Institute, alongside Dr. Marks, founder of the camp, and Susan Chang MD, Director of UCSF Neuro-Oncology.



## New Class of Protein-Conformation Inhibitors Could be Used Against Previously Undruggable Drivers of Brain Tumors

MYC proteins drive the formation of many types of cancers, including brain tumors. Overexpression of the MYC family member MYCN in particular is a common feature of the pediatric brain tumor medulloblastoma.

To date it has proved very difficult to develop drugs that can interfere with MYC protein function because it has no suitable binding site for small molecules, and targeting its transcription factors has been equally challenging. Instead, scientists have been trying to target kinases that interact with MYC in other ways.

Aurora A is one such kinase. It is needed to stabilize MYCN and has been an attractive target for cancer researchers because it is also involved in cellular mitosis and transformation. Drugs that target Aurora A kinase activity have had only modest effects on decreasing concentrations of MYCN in MYCN-driven tumors preclinically.

Aurora A stabilizes MYCN through a protein-protein interaction rather than through its kinase function. Now, a Brain Tumor Center research group lead by William Weiss MD, PhD has developed a compound that changes the conformation of Aurora A in a way that disrupts its interaction with MYC, leading to potent MYC degradation.

This new conformation-disrupting inhibitor, CD532, binds to Aurora A and changes its structure to disrupt both kinase activity and protein-protein interactions. Initial in vivo experiments show CD532 to be more efficacious against a medulloblastoma xenograft than the existing Aurora A inhibitor MLN8237. In the future, CD532 may also be combined with drugs that target other pathways that lead to MYC overexpression, such as the PI3K/mTOR pathway.

The laboratory of William Weiss MD, PhD introduced a new compound to target MYCN – a previously undruggable driver of medulloblastoma formation. The compound, called CD532, changes the conformation of the kinase Aurora A, which is needed to stabilize MYCN. Image by Zack and Justin Meyerowitz.

Gustafson WC, Meyerowitz JG, Nekritz EA, Chen J, Benes C, Charron E, Simonds EF, Seeger R, Matthey KK, Hertz NT, Eilers M, Shokat KM, Weiss WA. Drugging MYCN through an allosteric transition in Aurora kinase A. *Cancer Cell* 2014;26:414-27.

## Hyperpolarized $^{13}\text{C}$ Imaging: A Powerful New Tool for Evaluating Therapeutic Efficacy

The development of hyperpolarized  $^{13}\text{C}$  magnetic resonance spectroscopy (MRS) over the last decade gave a powerful new tool to oncologists. Using dynamic nuclear polarization, compounds labeled with  $^{13}\text{C}$  can be monitored as they move through metabolic pathways with a sensitivity 10,000 fold greater than thermally polarized compounds.

A tumor's metabolism can reveal important information about its biology and how it may be responding to therapy. Changes in metabolism can happen very fast, potentially allowing doctors to tell if a drug regimen is working days after it is administered. For patients with aggressive cancers, this could make a meaningful difference in choosing to abandon one regimen for another.

A UCSF team lead by Sarah Nelson PhD, Sabrina Ronen PhD and Russell Pieper PhD previously showed this to be the case in a rat model of glioblastoma treated with temozolomide. Tumor response to temozolomide occurs alongside a decrease in the conversion of pyruvate

into lactate, which the investigators were able to visualize with  $^{13}\text{C}$  MRS within 7 days of treatment. This methodology is being evaluated in patients with glioblastoma for the first time as part of the Brain Tumor Research Center's NIH Program Project Grant.

Now UCSF investigators have become the first group to apply  $^{13}\text{C}$  MRS to gliomas with a mutation in the gene coding for the isocitrate dehydrogenase 1 (IDH1) enzyme. IDH1 mutation is thought to be an early oncogenic event, confers a better prognosis than wild-type IDH status, and occurs almost exclusively in low-grade gliomas.

Because it has important implications for the course of the disease, IDH1 mutation status is being used for prognosis and to stratify patients in clinical trials. Inhibitors of mutant IDH1 are also being developed as new therapies.

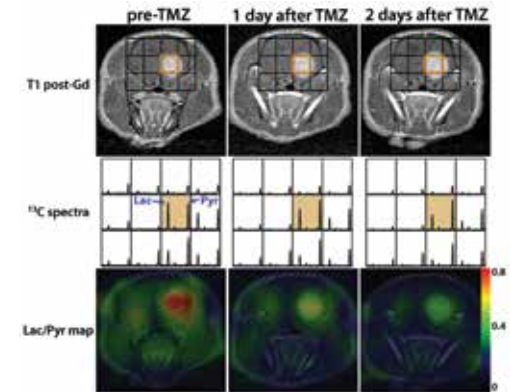
Among many other alterations in cellular metabolism, the mutant IDH1 enzyme causes  $\alpha$ -keto-glutarate ( $\alpha$ -KG) to convert to the metabolite 2-hydroxyglutarate (2-HG), leading to elevated levels of 2-HG in tumor tissues

but not normal tissues. In normal tissue  $\alpha$ -KG is converted into glutamate via an enzyme called BCAT1, and that activity is reduced in IDH-mutant gliomas.

To monitor these metabolic activities, the BTRC investigators developed [ $1\text{-}^{13}\text{C}$ ]  $\alpha$ -KG as a hyperpolarized probe and were able to detect the conversion of hyperpolarized [ $1\text{-}^{13}\text{C}$ ]  $\alpha$ -KG into hyperpolarized [ $1\text{-}^{13}\text{C}$ ] 2-HG and [ $1\text{-}^{13}\text{C}$ ] glutamate.

The success of this methodology in an in vivo orthotopic xenograft model indicates that it could be used to noninvasively monitor IDH1 status, and to help develop and monitor new targeted treatments.

Another interesting finding from Dr. Pieper's lab shows that although the IDH1 mutation generally confers a better prognosis overall, it also makes the tumors more resistant to treatment by enhancing their ability to repair DNA damage induced by chemotherapeutic drugs. Targeting this repair ability may extend survival for patients even further.



Chaumeil MM, Larson PE, Woods SM, Cai L, Eriksson P, Robinson AE, Lupo JM, Vigneron DB, Nelson SJ, Pieper RO, Phillips JJ, Ronen SM. Hyperpolarized [ $1\text{-}^{13}\text{C}$ ] glutamate: a metabolic imaging biomarker of IDH1 mutational status in glioma. *Cancer Res* 2014;74(16):4247-57.

Ohba S, Mukherjee J, See WL, Pieper RO. Mutant IDH1-driven cellular transformation increases RAD51-mediated homologous recombination and temozolomide resistance. *Cancer Res* 2014;74(17):4836-44.

Chaumeil MM, Larson PE, Yoshihara HA, Danforth OM, Vigneron DB, Nelson SJ, Pieper RO, Phillips JJ, Ronen SM. Non-invasive in vivo assessment of IDH1 mutational status in glioma. *Nat Commun* 2013;4:2429.

Park I, Mukherjee J, Ito M, Chaumeil MM, Jalbert LE, Gaensler K, Ronen SM, Nelson SJ, Pieper RO. Changes in pyruvate metabolism detected by magnetic resonance imaging are linked to DNA damage and serve as a sensor of temozolomide response in glioblastoma cells. *Cancer Res* 2014;74(23):7115-24.

## Longer Telomeres Linked to Risk of Brain Cancer

New genomic research from the BTRC reveals that two common gene variants that lead to longer telomeres – the caps on chromosome ends thought by many scientists to confer health by protecting cells from aging – also significantly increase the risk of developing gliomas.

The genetic variants, in two telomere-related genes known as *TERT* and *TERC*, are respectively carried by 51 percent and 72 percent of the general population.

Because it is somewhat unusual for such risk-conferring variants to be carried by a majority of people, the researchers propose that in these carriers the overall cellular robustness afforded by longer telomeres trumps the increased risk of high-grade gliomas, which are invariably fatal but relatively rare cancers. Senior author of the study, Margaret Wrensch, MPH, PhD, noted that the high barriers to developing gliomas likely exist because the brain has special protection.

In the first phase of the new study, researchers at UCSF and The Mayo Clinic College of Medicine analyzed genome-wide data from 1,644 glioma patients and 7,736 healthy control individuals, including some who took part in The Cancer Genome Atlas project sponsored by the National Cancer Institute and National Human Genome Research Institute. This work confirmed a link between *TERT* and gliomas that had been made in

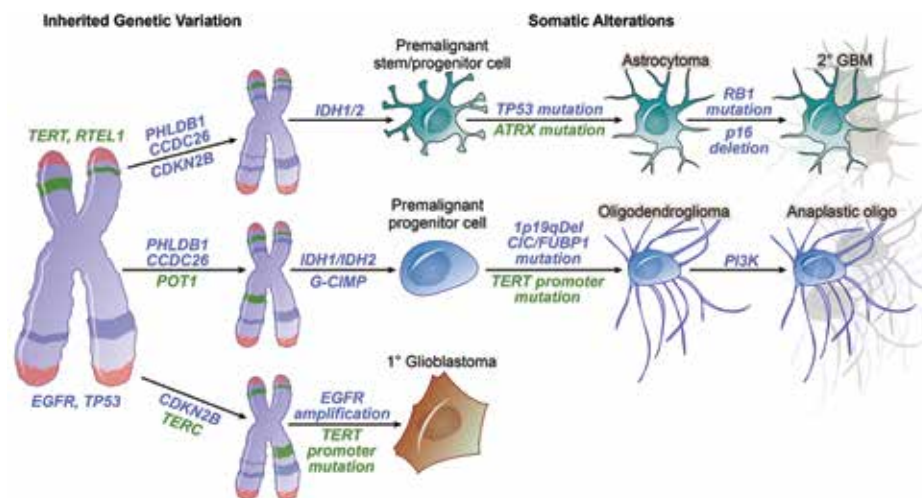
previous UCSF research, and also identified *TERC* as a glioma risk factor for the first time.

Since both genes have known roles in regulating the action of telomerase, the enzyme that maintains telomere length, the research team then analyzed a large dataset from the University of Leicester that cataloged telomere length in nearly 40,000 individuals. They found that the same *TERT* and *TERC* variants associated with glioma risk were also associated with greater telomere length.

### Telomere Length in Other Diseases

UCSF's Elizabeth Blackburn PhD, shared the 2009 Nobel Prize in Physiology or Medicine for her pioneering work on telomeres and telomerase, an area of research she began in the mid-1970s. In the ensuing decades, untangling the relationships between telomere length and disease has proved to be complex.

In much research, longer telomeres have been considered a sign of health – for example, Dr. Blackburn and others have shown that individuals exposed to chronic stressful experiences have shortened telomeres. But because cancer cells promote their own longevity by maintaining telomere length, drug companies have searched for drugs to specifically target and



Neuroepidemiologists at the Brain Tumor Research Center are uncovering how genetic alterations lead to specific tumor types.

block telomerase in tumors in the hopes that cancer cells will accumulate genetic damage and die.

Lead author Kyle Walsh PhD said the relevance of the new research should extend beyond gliomas, since *TERT* variants have also been implicated in lung, prostate, testicular and breast cancers, and *TERC* variants in leukemia, colon cancer and multiple myeloma. Variants in both *TERT* and *TERC* have been found to increase risk of idiopathic pulmonary fibrosis, a progressive disease of the lungs.

In some of these cases, the disease-associated variants promote longer telomeres, and in others shorter telomeres, suggesting that “both longer and shorter telomere length may be pathogenic, depending on the disease under consideration,” the authors write.

In addition to the Mayo Clinic and Leicester University teams, Drs. Wrensch and Walsh were joined by

colleagues from University Medical Center Groningen in the Netherlands. Other UCSF authors include Ivan V. Smirnov, PhD; Terri Rice, MPH; Helen M. Hansen; Annette M. Molinaro, PhD; Lucie S. McCoy, MPH; Paige M. Bracci, PhD, MPH; Belinda S. Cabriga; Melike Pekmezci, MD; Shichun Zheng, MD; Joseph L. Wiemels, PhD; Tarik Tihan, MD, PhD; Mitchel S. Berger, MD; Susan M. Chang, MD; Michael D. Prados, MD; and John K. Wiencke, PhD. Alexander R. Pico, PhD, of the Gladstone Institutes also took part in the research, as did members of the ENGAGE Consortium Telomere Group

*This story has been adapted from an article that first appeared in the UCSF News Center ([www.ucsf.edu/news](http://www.ucsf.edu/news)).*

Walsh KM, Codd V, Smirnov IV, et al. Variants near *TERT* and *TERC* influencing telomere length are associated with high-grade glioma risk. *Nat Genet* 2014; 46:731-35.



Minimally invasive endoscopic approaches can now be safely and effectively used to access tumors of the paranasal sinuses and skull base.

## UCSF Experience with Pituitary and Skull Base Tumors Shows the Benefit of Less Invasive Surgeries and Provides Guidelines for Counseling Patients

UCSF neurosurgeons have extensive experience with tumors of the pituitary gland and skull base, and several large case series on these pathologies were published in 2014. Transsphenoidal surgery – an operation that allows neurosurgeons to access tumors through the endonasal corridor without the need for a large craniotomy – has long been the standard of care for pituitary tumors. At specialized centers, transsphenoidal surgery is associated with low rates of morbidity, shorter recovery times and results in no facial scarring.

Analyzing over 1000 patients operated on in the last five years, the team at the California Center for Pituitary Disorders determined several factors leading to better preservation of endocrine function following endonasal pituitary surgery. The team also evaluated morbidity rates following repeat

transsphenoidal surgery, which had not previously been studied in a cohort of this size. The results of these studies can be used to better counsel patients undergoing pituitary surgery.

Over the last decade there has been a trend at academic centers to extend the favorable outcomes achieved with transsphenoidal pituitary surgery to neighboring pathologies of the skull base by using an endoscope to guide surgeons further through the endonasal corridor.

The Minimally Invasive Skull Base Surgery Center at UCSF offers endoscopic surgery to patients with tumors such as chordomas, craniopharyngiomas, chondrosarcomas, and meningiomas. Neurosurgeons partner with surgeons from the Department of Otolaryngology

– Head and Neck Surgery in a two-surgeon approach that results in faster and safer procedures.

In a recent UCSF study of 84 patients with newly diagnosed craniopharyngiomas, transsphenoidal surgery and gross total resection resulted in fewer complications and lower recurrence rates than transcranial operations and subtotal resections.

In a specialized surgical anatomy laboratory, physicians at UCSF are evaluating endoscopic routes to more complex skull base cases, such as chordomas that have extended laterally into the hypoglossal canal. By simulating surgeries in postmortem specimens, surgeons can develop more effective strategies and continue to better define the endonasal corridor.

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# Brain and Spinal Injury Center

## Clinical Trials for Traumatic Brain Injury Are the Focus of a New Collaboration Between Government and Industry

This year UCSF was one of the recipients of a \$17 million, five-year award from the U.S. Department of Defense to fund a public-private partnership specifically to improve clinical trials for traumatic brain injury.

Each year 1.7 million Americans seek care for TBI, but there are few effective treatment options. A lack of consensus over standard of care means that it can vary widely across hospitals and regions. Despite many clinical trials in the past 20 years, few therapies have emerged and none have been approved by the Food and Drug Administration (FDA).

Part of the problem is that the current classification scheme for TBI – mild, moderate, severe – does not take into account the underlying mechanisms of the injury. Two patients with “mild” TBI may have injuries with very different pathophysiology, and combing these patients into one treatment group in a clinical trial makes it difficult to adequately assess the therapy under study.

The new research initiative, called the TBI Endpoints Development (TED) Award, brings together leading academic clinician-scientists, the FDA, biotechnology and imaging technology leaders, patient advocacy organizations, and philanthropies.

The research collaborators will be collecting a broad range of long-term data from existing studies that have been performed in both the academic and private sector, and integrating these into a common database. With biomarkers from blood, new imaging equipment and software, and other tools that have not been previously available, the researchers hope to mine the existing data, representing clinical information from thousands of patients, and apply landscape analysis to identify effective measures of brain injury and recovery.

The information gained from TED will be combined with an existing multi-center study that is gathering data on newly diagnosed TBI patients (Transforming Research and Clinical Knowledge in TBI

### Faculty

#### Neurotrauma

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John Fike PhD  
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Linda Noble-Hacusslein PhD  
S. Scott Panter PhD  
Susanna Rosi PhD



[TRACK-TBI]). Identifying biomarkers for subclasses of TBI will be a major step towards improving the success rate of clinical trials.

TED is also specifically designed to overcome the difficulty in demonstrating the effectiveness of TBI drugs and medical devices by actively involving the FDA in clinical-trial design from the outset. The aim is for the FDA, through the agency's Critical Path Initiative, to approve new tools for drug and medical-device development for use in clinical trials.

Chief of Neurotrauma Geoffrey Manley MD, PhD is leading national efforts to improve clinical trials and therapies for traumatic brain injury.





## UCSF Leads New Spinal Cord Injury Research Network in California

UCSF's neurotrauma team, based at San Francisco General Hospital, is driving the establishment of a California-wide network of leading hospitals and trauma centers for clinical care and translational research related to spinal cord injuries (SCI).

Multidisciplinary teams of specialists from the fields of neurosurgery, emergency medicine, critical care, neurology, neuroradiology and anesthesia will collaborate to collect data; improve standards of care; and implement clinical trials. Data repositories for neuroimaging,

proteomic, and genetic biomarkers will facilitate the evolving use of these emerging technologies in SCI research.

Currently, clinical trials for SCI are made difficult because these types of injuries occur relatively infrequently. By developing a joint infrastructure, the new network can identify patients eligible for trial participation and route them to the appropriate treatment center.

Partnering with UCSF in this initiative are the Palo Alto Veterans Affairs Hospital, Santa Clara Valley Medical Center, and other UC Medical Centers.



Inoue T, Lin A, Ma X, McKenna SL, Creasey GH, Manley GT, Ferfuson AR, Bresnahan JC, Beattie MS. Combined SCI and TBI: Recovery of forelimb function after unilateral cervical spinal cord injury (SCI) is retarded by contralateral traumatic brain injury (TBI), and ipsilateral TBI balances the effects of SCI on paw placement. *Exp Neurol* 2013;248:136-47.

The UCSF Brain and Spinal Injury Center is based at San Francisco General Hospital – San Francisco's only Level 1 Trauma Center.

## Model of Simultaneous Brain and Spinal Cord Injury Shows Opportunity for Recovery Mediated by Contralateral Cortical Plasticity

A frequent complication in neurotrauma medicine is that traumatic brain and spinal cord injuries often occur together. Little is known about what direct effects treatment for one injury may have on the other. Likewise, there is no evidence guiding clinicians in the choice of which injury to treat first.

Researchers at the Brain and Spinal Injury Center have now created an animal model of this scenario that can be used to tease out these interactions and study the best rehabilitation strategies. Along the way, the investigators made an unexpected discovery.

To validate the model, rats were placed into one of four groups: unilateral cervical SCI + sham brain surgery; TBI + sham spine surgery; SCI + contralateral TBI; and SCI + ipsilateral TBI. Using validated measures of grooming and forelimb function, researchers gauged the extent of injury and recovery in each group. It was expected that rats experiencing contusions in both brain and spinal cord would do worse than those with an injury in only one area or the other.

The researchers found that when the injuries were contralateral, this held true and rats experienced severe and permanent neurological deficits. But

surprisingly, rodents with ipsilateral brain and spinal cord injuries had better forelimb function than rodents with spinal cord injuries and sham brain surgery.

This intriguing finding indicates that plasticity in the contralateral cortex is involved in functional recovery after an ipsilateral injury and that there may be more potential for recovery following these injuries in humans than previously recognized.

The results also show that there may be an opportunity to explore how neuromodulation of the brain could positively affect recovery following a spinal cord injury.

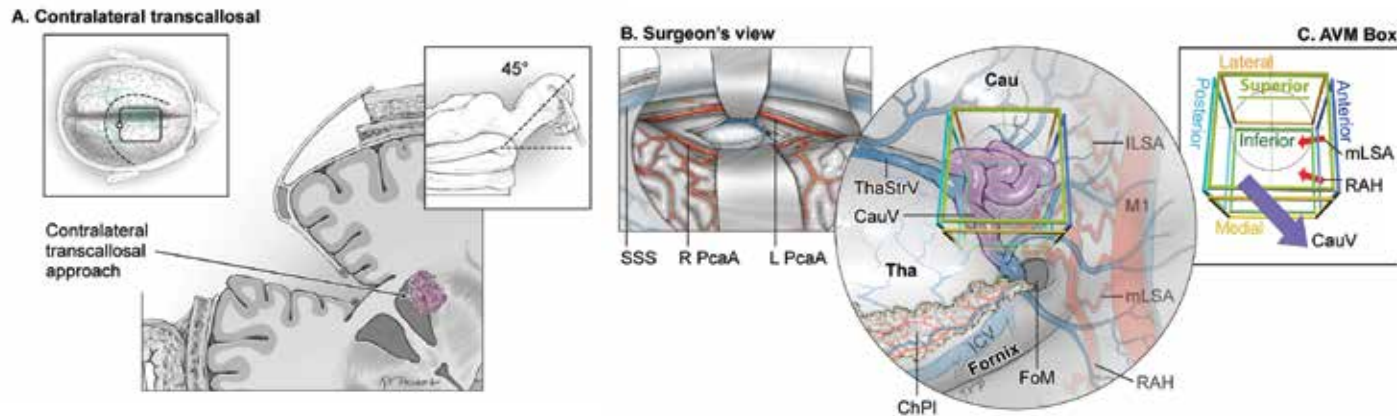
## Faculty

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Jialing Liu PhD  
S. Scott Panter PhD



## Selecting the Best Therapy for Arteriovenous Malformations

An arteriovenous malformation (AVM) is an abnormal tangle of arteries connected directly to veins, without intervening capillaries, resulting in a high-flow, low-resistance pathway for blood. This abnormal circulation makes AVMs susceptible to rupture, causing bleeding in the brain. AVM hemorrhage is fatal in 10% of patients and causes neurological deficits in 25%.

Although the disease is rare, over 650 patients have undergone surgery for AVMs at UCSF in the last 15 years. The optimal combination of treatment modalities and their sequence depends on the anatomy of the AVM and the patient's clinical presentation. Treatment options range from watchful

waiting to radiosurgery to microsurgical resection, and planning by an experienced team that can select the most appropriate therapy for each type of AVM is critical for providing patients with the best outcomes.

This year, several new articles from the UCSF neurovascular team offer insight into best practices for particular types of AVMs. From outlining how best to handle an intraoperative rupture to reporting the potential dangers of watchful waiting of posterior fossa AVMs, these studies continue to add to our collective understanding of how best to approach these complicated lesions.

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## Mission: BRAIN Expands to the Philippines

Since 2012, Chief of Vascular Neurosurgery Michael Lawton MD has been leading a group of volunteer neurosurgeons and other healthcare providers in an annual program called Mission: BRAIN (formerly Project Altruista) that provides pro bono surgeries and training for faculty at the University of Guadalajara in Mexico.

This year Mission: BRAIN expanded its work to the Philippines where Dr. Lawton performed pro bono surgeries for six patients with cerebrovascular disorders, including those with aneurysms, AVMs, and dural fistulas. Community neurosurgeons attended teaching courses and lectures, including a bypass course in a rodent model.



Using the Lawton-Young grading scale, this ruptured left frontal arteriovenous malformation was defined as supplemented Spetzler-Martin grade 4: S2V0E1/A1B0C0.

## New Study Validates Lawton-Young AVM Grading Scale

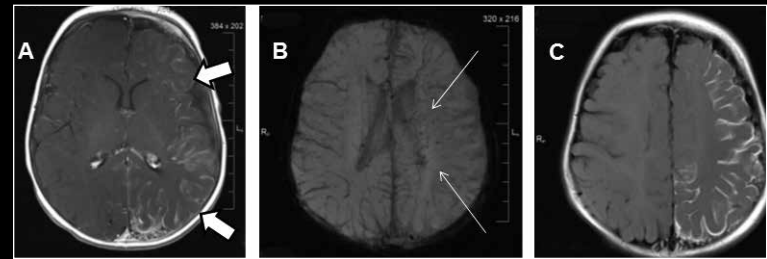
In 2010, Michael Lawton MD and William Young MD developed a grading scale for AVMs to supplement the traditional Spetzler-Martin scale and better predict which AVMs were amenable to surgery. The Lawton-Young scale added information on patient age, hemorrhagic presentation, and nidus diffuseness – all of which affect patient outcomes after surgery.

Now a multicenter study published in *Neurosurgery* has confirmed that combining Spetzler-Martin scores

with Lawton-Young scores gives the best preoperative risk assessment and should be used for patients considering surgery for AVM.

The new study examined over 1000 patients with AVMs and was conducted at UCSF, Barrow Neurological Institute, Massachusetts General Hospital, and Macquarie University in Sydney, Australia.

Kim H, Ablak AA, Nelson J, McCulloch CE, Bervini D, Morgan MK, Stapleton C, Walcott BP, Ogilvy CS, Spetzler RF, Lawton MT. Validation of the supplemented Spetzler-Martin grading system for brain arteriovenous malformations in a multicenter cohort of 1009 surgical patients. *Neurosurgery* 2015;76(1):25-33.



MR imaging findings of Sturge Weber Syndrome include prominent leptomeningeal enhancement in a gyriform pattern in affected areas due to a pial angiomatous malformation ipsilateral to the facial port wine stain. These findings are seen on T1-weighted sequences with gadolinium contrast (A and C), and signal drop out due to calcifications on susceptibility weighted imaging (B).

## NIH Renews Funding for the Brain Vascular Malformation Consortium

In 2014, the NIH provided five additional years of funding for the Brain Vascular Malformation Consortium (BVMC) with a \$6.5 million grant. Led by Michael Lawton MD at UCSF, the BVMC is a part of the NIH's Rare Diseases Network and focuses on collecting data on Sturge-Weber syndrome, cerebral cavernous malformations, and hereditary hemorrhagic telangiectasias (HHT).

Clinical and genetic information from patients at 10 primary study sites is entered into a database that can be studied by researchers across institutions. Because these diseases are so rare, there is little consensus on optimal management. By examining a

large longitudinal cohort of patients and biomarker specimens, there is greater potential to gather new information about brain vascular malformations and improve care for patients.

Previous information from the database allowed UCSF researchers to develop a mouse model of AVM based on HHT. They have since discovered that HHT leads to weakened and leaky pericytes, which are the support structure for blood vessels in the brain, and this is ultimately what causes AVMs associated with HHT to rupture. Researchers continue to study these models and use them to test new medical therapies that may stabilize an AVM that is not amenable to surgery.

## Faculty

### Epilepsy Surgery

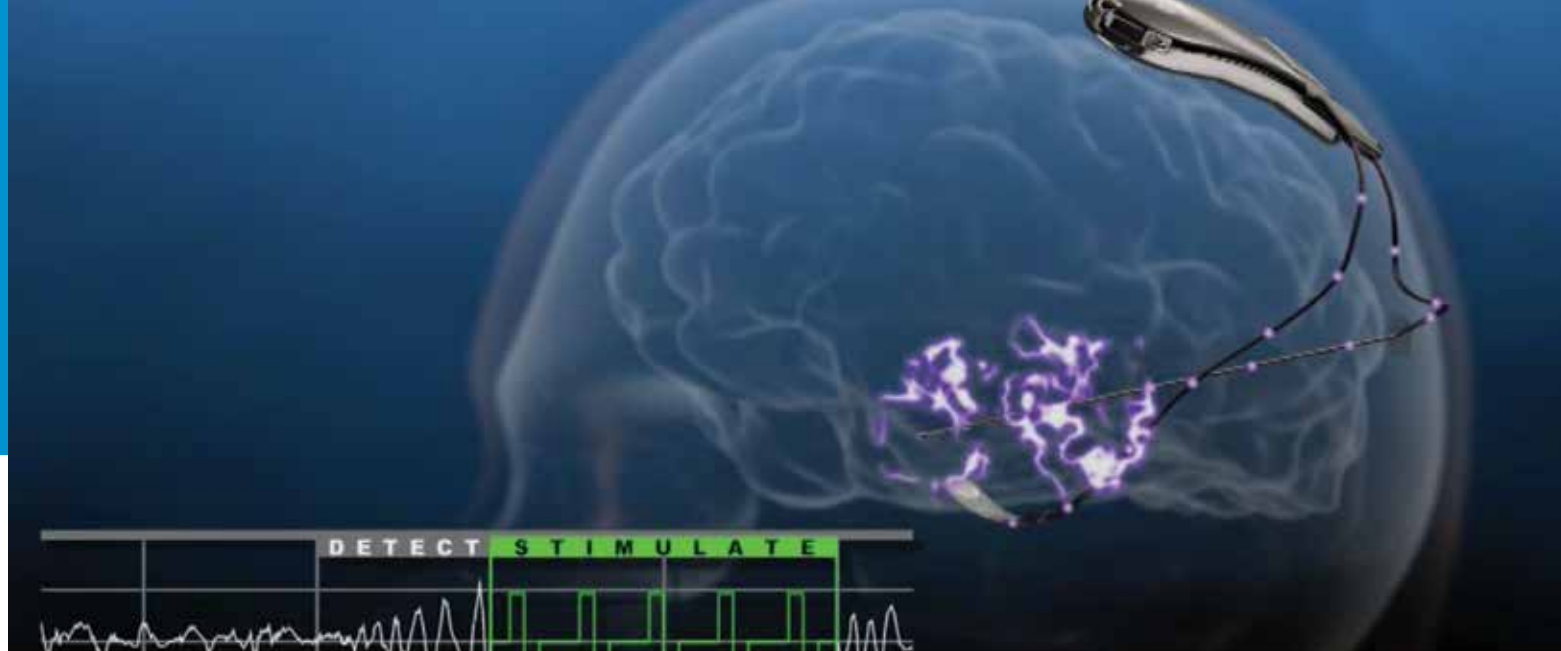
Edward Chang MD

Paul Larson MD

### Epilepsy Research Laboratories

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Edward Chang MD



# Epilepsy Surgery

## New Treatment for Epilepsy: Responsive Neurostimulation

About one-third of patients with epilepsy have seizures that are poorly controlled with medications alone. UCSF is one of the few centers in the nation offering responsive neurostimulation (RNS) for treating adults with medication-resistant epilepsy.

In this new approach, a small battery-powered device called a neurostimulator is surgically implanted in the skull. Leads that are connected to the neurostimulator are placed on the surface and/or inside of the brain. The neurostimulator monitors the electrical activity of the brain and detects abnormal activity that could lead to a seizure. When abnormal activity is detected, the neurostimulator delivers electrical stimulation to the brain through the leads to prevent seizures. The system is analogous

to cardiac pacemakers that detect abnormal heart rhythms and respond by delivering electrical stimulation.

For certain patients, using an implanted neurostimulator to treat seizures can be more effective than medications, and, because no brain tissue is removed, can involve less risk than other surgical options. RNS represents an exciting and much-needed therapeutic option for patients with seizures that arise from more than one brain region and/or from brain regions that cannot be removed surgically.

### Who is a candidate for responsive neurostimulation?

In general, adult patients with medication-resistant epilepsy who have frequent disabling seizures that arise from one or two brain

regions are candidates for responsive neurostimulation. A team of neurologists, neurosurgeons, and other providers with expertise in the diagnosis and management of epilepsy will determine an individual patient's suitability for this treatment.

### What are the advantages over other types of epilepsy surgery?

When seizures arise from more than one brain region, or from a single brain region that serves a critical function like speech or movement, surgical removal of the seizure-producing tissue may not be possible. RNS is advantageous in that leads can be placed in several different locations to detect and terminate seizures at multiple sites without removing any critical brain tissue. Unlike epilepsy

surgery, RNS is reversible, and the implanted device can be removed at any time. The RNS device continuously monitors brain activity, and the information it records can be used by providers to optimize treatment.

### What are the potential risks or side effects?

Although implantation of the neurostimulator and leads is less invasive than traditional epilepsy surgery, which requires larger surgical exposure, there are some risks. With any brain procedure, there is a chance of bleeding, infection, pain, and neurological impairment, though rates of these complications were

low in clinical trials of RNS. There is a chance that RNS will not improve seizure severity or frequency. There is also a very small chance that electrical brain stimulation will cause side effects, though the vast majority of patients do not notice the stimulation. Currently, patients who have the RNS device implanted cannot have MRI scans due to safety considerations in strong magnetic fields.

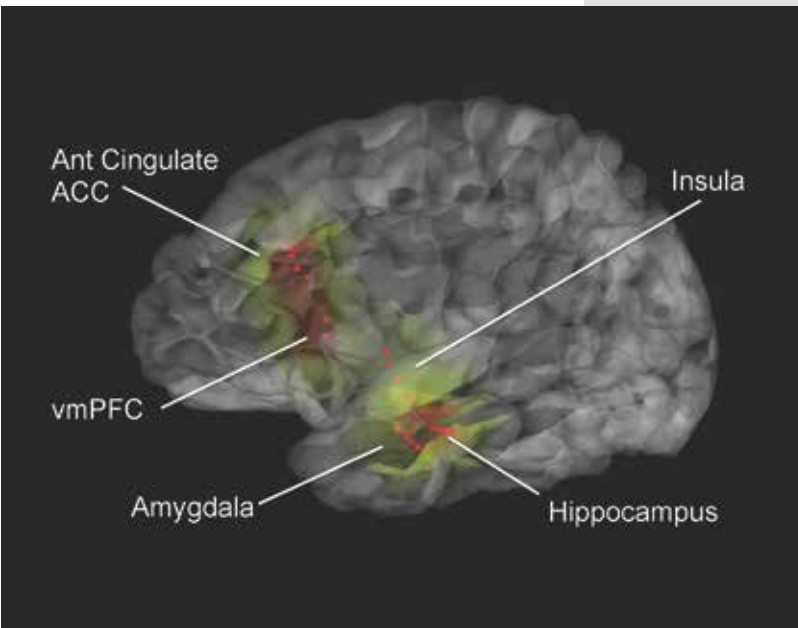
### Will the seizures be cured?

The NeuroPace RNS system was approved by the FDA in 2013. Given that this technology is relatively new, the long-term outcomes are not

completely known. In clinical trials, the efficacy of the device increased over time, and, after two years, more than half of patients had at least a 50% reduction in seizure frequency.

### How can a patient be evaluated for responsive neurostimulation?

For more information or to refer a patient for presurgical evaluation for RNS, contact Epilepsy Nurse Specialist Lucinda Rinaldo at (415) 514-5759 or by e-mail at: [Lucinda.Rinaldo@ucsf.edu](mailto:Lucinda.Rinaldo@ucsf.edu).



## Stereo-EEG Provides a Less Invasive Method to Pinpoint Source of Seizures

Adding to the cutting-edge diagnostic tools available at the UCSF Epilepsy Center, neurosurgeons have begun to use stereoelectroencephalography (SEEG) as part of the presurgical evaluation for select patients.

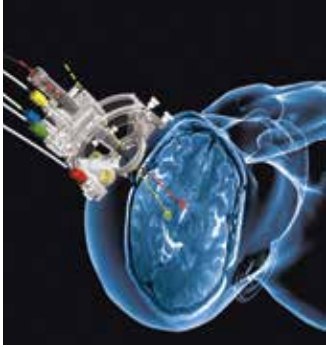
SEEG involves implanting depth electrodes – thin wires no wider than the tip of a pencil lead – through small openings in the skull. These electrodes can precisely characterize the electrical activity of deep structures in the brain, detecting patterns of electrical abnormality that can define the seizure foci, or the area of the brain where seizures are originating.

The standard procedure for localizing the seizure foci requires placing a large array of electrodes called a subdural grid on the surface of the brain. To expose the brain's surface, patients need to undergo a larger surgery called a craniotomy.

While subdural grids remain the gold standard for presurgical evaluation, SEEG may be used when suspected seizure foci is located in areas inaccessible to grids – like the singulate, insula, and orbitofrontal cortex – or for patients who are unable to tolerate a more invasive craniotomy.

The minimally invasive nature of SEEG makes it safer and patients are likely to have less pain and better wound healing. Candidates for this methodology are determined by MRI scans, type of seizures, and other patient-specific factors.

Sophisticated software and imaging technology is needed to monitor the placement of the depth electrodes, and only a handful of institutions in the United States have begun using this approach.



# Movement Disorders

## Implanted Device Records Brain's Electrical Activity to Reveal How Circuitry is Altered During Treatment for Movement Disorders

Analyzing electrocorticographic (ECoG) recordings of neuronal populations, neurosurgeon Philip Starr MD, PhD and his colleagues have detected a pattern of abnormal synchronization in the electrical spiking of neuronal populations in the motor cortex of patients with Parkinson's disease.

To treat Parkinson's disease, patients may be offered medications or deep brain stimulation (DBS), but the underlying mechanisms of these treatments are not clearly defined. Now the ECoG recordings have led to the hypothesis that these therapies control movement disorder symptoms by

reducing excessive synchronization across the cortex and returning neuronal firing to a more normal pattern. If this can be confirmed, new stimulation devices may be able to more precisely regulate electrical activity in the brain and cause fewer side effects for patients.

In a new pilot trial at UCSF, the investigational Activa® PC+S pulse generator, manufactured by Medtronic, is implanted into patients with Parkinson's disease and primary dystonia. It is able to record and store local field potentials from the basal ganglia and motor cortex through



Swann NC, de Hemptine C, Ostrem JL, San Luciano M, Starr PA. Chronic cortical and subcortical recordings in Parkinson's disease using a totally implanted bidirectional neural interface. Presented at: Movement Disorder Society Annual Congress, Stockholm, Sweden, June 8-12, 2014.

Postdoctoral scholar Coralie de Hemptinne PhD downloads data from a pulse generator implanted in a patient with Parkinson's disease. The data is being used in a project to design a new deep brain stimulation device that can detect abnormal rhythms in a patient's neural network and deliver stimulation on demand.



## Faculty

### Functional Neurosurgery

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 Phiroz E. Tarapore MD

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 John Forsayeth PhD  
 Paul Larson MD  
 Philip Starr MD, PhD

permanently implanted electrodes, and allow wireless, noninvasive downloading of that data. The device measures changes in the brain's electrical activity following drug administration or DBS to further define how these treatments affect brain circuitry.

Initial results from three patients were recently presented at the 2014 meetings of the Movement Disorders Society and the Society for Neuroscience showing that the data can be accessed and that there have been no surgical complications or

device malfunctions. The research team identified novel electrophysiological signatures related to a common side effects of medication and stimulation, the inadvertent production of dyskinesias (excessive involuntary movement). The UCSF team is the first to obtain chronic multisite recordings in humans with movement disorders.

Dr. Starr is currently the principal investigator of a Research Project Grant (R01) from the NIH to fund this work. Jill Ostrem MD, Coralie de Hemptinne PhD and Nicole Swann PhD are also investigators on this study.



## Using Deep Brain Stimulation to Treat Dystonia in Pediatric Patients

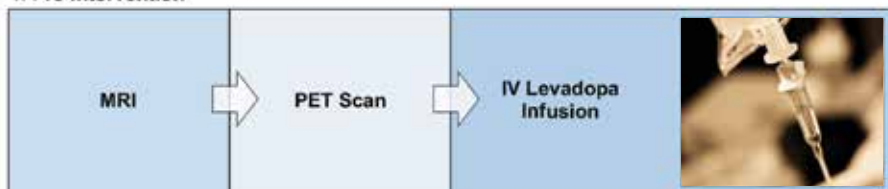
A new series published in *Journal of Neurosurgery: Pediatrics* reports outcomes following DBS with the ClearPoint system for pediatric patients with dystonia. Developed at UCSF, ClearPoint is an MR-compatible, skull-mounted aiming device that allows surgeons to implant deep brain stimulator leads into patients under direct MR visualization while the patients are under general anesthesia.

ClearPoint provides a significant advantage when treating pediatric patients who may not be able to tolerate an awake surgery, which is otherwise needed for DBS implantation. The technology also makes operations faster and more accurate. The results show that outcomes using ClearPoint are equal to the best reported results for DBS to treat pediatric dystonia using more traditional methods.

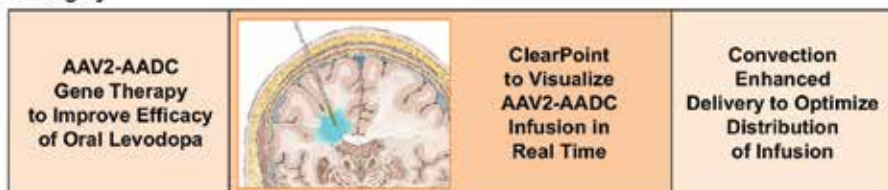
Starr PA, Markun LC, Larson PS, Volz MM, Martin AJ, Ostrem JL. Interventional MRI-guided deep brain stimulation in pediatric dystonia: first experience with the ClearPoint system. *J Neurosurg Pediatr* 2014;14(4):400-8.

## AADC Gene Therapy for Parkinson's Disease

### 1. Pre-Intervention



### 2. Surgery



### 3. Post-Intervention



## Visualizing Drug Infusions in Real Time Brings New Advantage to Gene Therapy Trial for Parkinson's Disease

Trials employing blind infusion of gene therapies into the brain have had some success, but have also left researchers with unanswered questions: What happened to the infusate after it was injected into the brain? Did it cover the targeted area? Did it stay in the brain tissue long enough to have an effect? Now, this therapy is being redesigned with a new arsenal of imaging technologies that may allow it to reach its full potential.

With Parkinson's disease, neurons that produce dopamine progressively die. The depletion of this critical neurotransmitter can cause tremors, slowing of movement, muscle rigidity and stiffness. Medication with oral levodopa can alleviate some of these symptoms but at the cost of inducing involuntary movement, or dyskinesia, that has become one of the hallmark signs associated with Parkinson's disease.

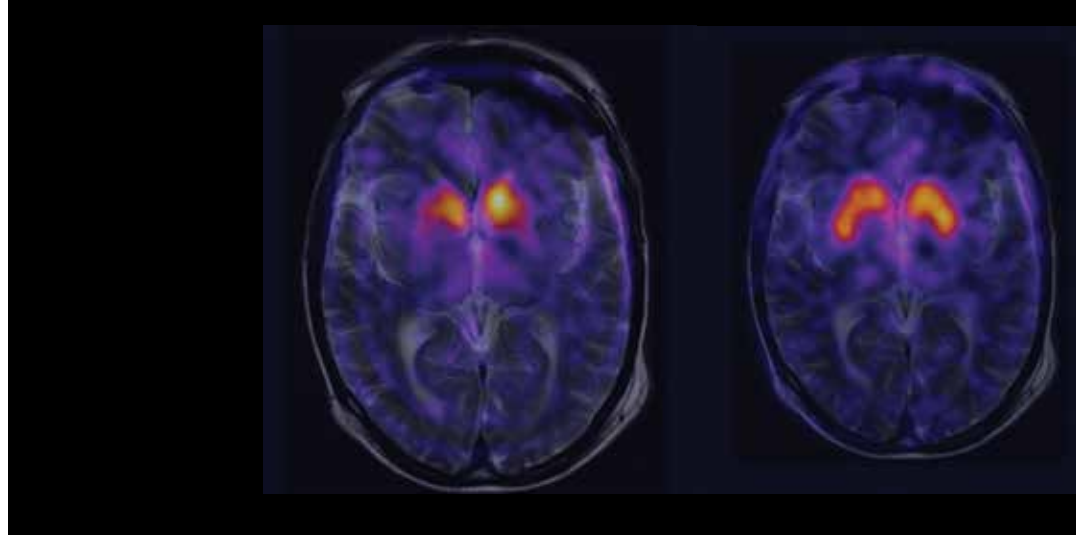
Oral levodopa also wears off quickly and unpredictably, causing severe fluctuations between rigidity and dyskinesia. Many patients with advanced Parkinson's disease are burdened with the task of adjusting their medications every 2-3 hours to manage the plateaus and crashes of dopamine levels in their brains.

UCSF is currently enrolling patients in an open label trial of adeno-associated virus encoding human amino acid

decarboxylase (AAV2-AADC). AADC converts oral levodopa to dopamine, and having a steady availability of AADC in the brain could allow patients to reduce dependence on medication and improve their symptoms and quality of life.

### The Advantage of Real-Time MR Imaging

To get the gene-carrying virus into the putamen – one area of the brain responsible for producing dopamine – previous trials have infused gene therapy vectors directly into the brain. Although some patients were able to reduce their medication doses (up to 35% of patients in one UCSF study), it was difficult to know how much of the putamen had actually been transduced with the viral vector. Investigators were left with unanswered questions. Was the drug getting where it needed to go?



PET scanning shows an increase in the conversion of oral levodopa into dopamine following gene therapy with AAV2-AADC.

These questions were partially answered in 2010 by autopsies from patients enrolled in a similar trial at another institution (the patients did not die of causes related to the study). The autopsies showed that the infusions were not covering as much area as was intended. Researchers realized that the available drug-delivery technology was limiting the potential of the therapy.

The same year, an MR-compatible, skull-mounted aiming device developed at UCSF was approved by the U.S. Food and Drug Administration. The device, called ClearPoint, allows neurosurgeons to visualize implantation of leads for deep brain stimulation or catheters for infusions while a patient is under anesthesia inside the MR scanner.

For the new AAV2-AADC gene therapy trial, the team can now see distribution of the infusate in real time and make adjustments if it isn't flowing between tissue or if there is backflow along the

catheter. The infusion can be stopped and the catheters repositioned to ensure delivery of an adequate dose.

The trial also employs convection-enhanced delivery – a method that takes advantage of pressure gradients to push more infusate between tissue and cover a wider area than a standard injection.

### Anatomy of a Trial

The effects of levodopa vary among individuals. To establish a baseline of “best” AADC conversion before intervention with the gene therapy, each patient enrolled in the new trial undergoes PET scanning immediately after taking oral levodopa. PET scanning is able to show the level of activity of AADC in the brain and investigators can quantify the amount of levodopa converted into dopamine. Patients also undergo an intravenous levodopa infusion test prior to surgery, which offers the most precise measure of time course and dose response. Currently,

Oregon Health + Science Center is one of the only institutions in the United States where this test is available and the UCSF team has collaborated with OHSU to incorporate it into a gene therapy trial for the first time.

Over two days, patients receive intravenous infusions of either saline or levodopa, while simultaneously having blood drawn. A neurologist blinded to the treatment evaluates changes in patients' symptoms to determine the optimal dose at which symptoms are managed. After establishing the dose of levodopa that best manages symptoms, patients undergo surgery to infuse AAV2-AADC into the putamen using ClearPoint to monitor its distribution.

Four to six months after surgery, a second PET scan is performed to monitor AADC activity and compare the level of conversion into dopamine with the patient's baseline scans. A second intravenous levodopa infusion test at

OHSU is also performed to validate whether the gene therapy has allowed a patient's symptoms to be managed at a lower dose.

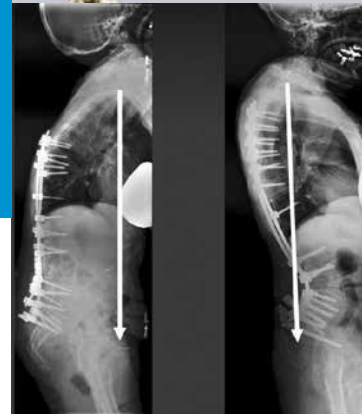
To date four patients have undergone surgery with no complications. The investigators obtained excellent visualization of infusate during surgery and were able to confirm that the full dosage was distributed to the intended zone.

This trial is currently open to enrollment. To request more information or inquire about enrolling a patient, contact Marin Thompson at (415) 353-9666 or e-mail [AADC@ucsf.edu](mailto:AADC@ucsf.edu). Find eligibility requirements on [clinicaltrials.gov](http://clinicaltrials.gov) with study identifier NCT01973543 (AADC Gene Therapy for Parkinson's Disease). PI: Paul Larson MD; Sponsor: Krystof Bankiewicz MD, PhD; Collaborator: Oregon Health + Science University



### Faculty

Christopher Ames MD  
 Dean Chou MD  
 Sanjay Dhall MD  
 Praveen Mummaneni MD  
 Rishi Wadhwa MD  
 Philip Weinstein MD



# Neurospinal Disorders

## UCSF to Launch California Institute for Spinal Deformities

Adult spinal deformity – caused by conditions such as disk degeneration, spinal arthritis and prior surgeries that fail to align the spine – is an increasing problem among aging Americans. Its effects on general health status and daily living are on the order of lower extremity amputation or cancer but are largely underestimated by many physicians. For a new generation of older Americans who expect to be more active in their later years, surgery is becoming a mainstay of treatment.

### A Regional Hub for Spinal Deformity

The California Institute for Spinal Deformities, co-directed by Christopher Ames MD from Neurological Surgery and Vedat Deviren MD from Orthopaedic Surgery, will provide multidisciplinary care in one space. From initial diagnosis through surgery and recovery, patients' treatment plans will be designed with input from specialists in spinal surgery, anesthesia, medicine, psychology, osteoporosis, rehabilitation, and pain management.

Treatment is individualized according to deformity type, age and other patient-specific factors and activity goals. Unlike adolescent idiopathic scoliosis, treatment of adult deformity is largely determined by the limitations placed on activities of daily living. Long-term rehabilitation plans for these patients are especially important to prevent complications and reoperation,

and the team approach helps manage co-morbidities such as osteoporosis and arthritis.

### The Value of Experience

The decision to establish an institute to specifically deal with the public health problem of spinal deformity was born out of the vast experience with the disease at UCSF. Over 150 operations are performed every year, making UCSF home to one of the largest spinal deformity practices in the United States. The most common types encountered include degenerative scoliosis, kyphosis, and global sagittal deformity related to prior surgery. UCSF neurosurgeons are at the forefront of pioneering better surgical techniques, collecting prospective outcomes data, and collaborating with organizations like the International Spine Study Group to raise the standards for spinal deformity treatment.

New practices developed at UCSF, such as the two-surgeon approach, have already improved care for patients with spinal deformity and are beginning to take hold at other institutions. During these surgeries an orthopaedic surgeon and a neurosurgeon operate simultaneously, cutting operating times in half and lowering complications and blood loss. These are critical factors for older patients who cannot tolerate surgeries that could take up to 12 hours when done by a single surgeon.

## UCSF Leads Hands-on Educational Programs for Community and Academic Neurosurgeons

A recent survey of the members of the American Association of Neurological Surgeons revealed a need for improved education on the topic of spinal deformity.

To address the need for postgraduate deformity surgery education, Medtronic has worked with UCSF neurosurgeon Christopher Ames to create the CATALYST™ ACCELERATE Deformity Program for academic neurosurgeons. Upon completion of the intense 4-6 month program, spine surgeon participants will be able to understand deformity principles, accurately assess

patients preoperatively using objective measurement tools and clinical guidelines, and perform correction techniques with increased confidence.

Visiting neurosurgeons will:

- receive a needs assessment upon arrival
- work with UCSF neurosurgeons in a cadaver lab using state-of-the-art simulation tools
- observe surgeries in the operating room

- observe methods for safely teaching advanced osteotomy techniques
- review cases with the UCSF team upon returning to their home institution in a first-of-its-kind remote mentorship program.

UCSF also provides a variety of visitation programs for community physicians designed around mentorship and based on individual needs and training level. For more information, contact the UCSF Office of Continuing Medical Education at: (415) 476-4251.

Clark AJ, Garcia RM, Keefe MK, Koski TR, Rosner MK, Smith JS, Cheng JS, Shaffrey CI, McCormick PC, Ames CP; and the International Spine Study Group. Results of the AANS membership survey of adult spinal deformity knowledge: impact of training, practice experience, and assessment of potential areas for improved education. *J Neurosurg Spine* 2014;21(4):640-7.

## Smaller Surgeries Improve Quality of Life for Patients with Spinal Tumors

When cancer metastasizes to the spine, it can compress the spinal cord and lead to paralysis. Most metastatic cancers involve the anterior portion of the spine and surgeons usually perform a corpectomy, which involves removing the entire vertebral body through a large opening and reconstructing the spine. Historically, this has required either a large opening through the chest—a thoracotomy—or a posterior incision that can be 12 inches or longer.

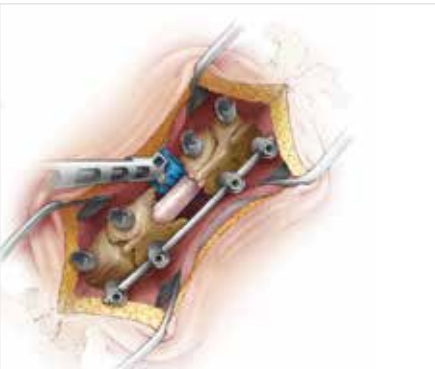
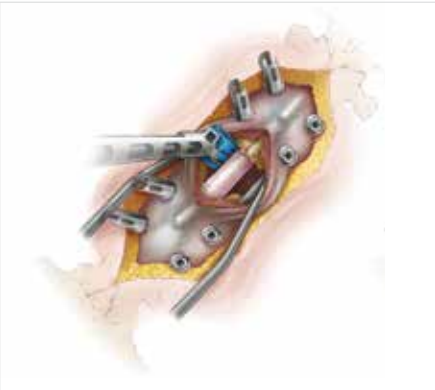
At UCSF, neurosurgeon Dean Chou has pioneered a technique called mini open transpedicular corpectomy for patients

with metastatic spinal tumors. The procedure takes advantage of minimally invasive percutaneous screws, which allows the fixation and reconstruction of the spine to be done through a 2-3 inch incision instead of the 12-inch incision required for a standard posterior transpedicular corpectomy.

After reviewing 49 patients, Dr. Chou and his team found that the less invasive surgery results in less blood loss, fewer complications, and shorter hospital stays. For patients with metastatic spinal tumors, less time

spent recuperating in the hospital has translated into a meaningful increase in quality of life.

The surgical series of mini open corpectomy done at UCSF will be published in a forthcoming issue of *Journal of Neurosurgery: Spine*.



Asher A, Watridge C, Mummaneni P, Knightly J, Oetting G, Theodore N, Gottfried O, Khairi S, Schmidt M, Boakye M, Kalkanis S, Rabin D, Ryken T, Balturshot G, Chadduck J, Fassett D, Reeder R, Miller C, Briggs T, Grahm T, Guthrie B, Harrington JF, Shaffrey C, Elowitz E, Foley K, Glassman S, McGirt M. The National Neurosurgery Quality and Outcomes Database (N<sup>2</sup>QOD) Pilot: Interim Analysis of Registry Feasibility, Data Integrity, and the Safety and Effectiveness of Surgical Spine Care. Presented at the 2014 Annual Meeting of the Congress of Neurological Surgeons, Boston, MA, October 18-22, 2014.

## Prospective Data Registry for Cervical and Lumbar Spine Surgery Will Provide Evidence-Based Data for Clinical Decision-Making

Three-month follow-up data from the National Neurosurgery Quality and Outcomes Database (N<sup>2</sup>QOD) was presented at the 2014 Annual Meeting of the Congress of Neurological Surgeons. N<sup>2</sup>QOD is a web-based, prospective, longitudinal outcomes registry gathering baseline, perioperative, 3-month and 12-month data on lumbar spine procedures from neurosurgical and orthopaedic practices at 47 hospitals in 24 states. UCSF became one of the first hospitals to report outcomes in the database in 2012.

The results demonstrated that there was significant improvement in pain, disability, and quality of life after surgery

and 75% of patients who planned to return to work after surgery were able to do so at 3 months.

On an individual patient level, results varied significantly according to patient-specific risk factors and clinical variables (eg, age, smoking history, BMI). Risk-adjustment for these variables is necessary for accurately measuring the safety and effectiveness of surgical spine care. According to neurosurgeon Praveen Mummaneni MD, who is leading the N<sup>2</sup>QOD effort at UCSF, using the registry data to identify characteristics shared by patients who do not benefit from surgery will help to improve patient selection and surgical care delivery on a national level.

## New Guidelines for Operating on Lumbar Degenerative Disease

In the July 2014 issue of *Journal of Neurosurgery: Spine*, the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Joint Section on Disorders of the Spine and Peripheral Nerves put forth a series of 17 articles updating guidelines on fusion procedures for lumbar degenerative disease. The original guidelines were published in 2005.

The issue, available on the journal's Web site, provides a comprehensive overview of outcomes for various techniques and is a valuable decision-making tool for physicians. UCSF neurosurgeons Praveen Mummaneni MD and Sanjay Dhall MD serve as members of the AANS/CNS Joint Section and co-authored the guidelines.

AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. *J Neurosurg Spine* 2014; 21(1):1-139.

## Seven-year Outcomes of Prestige Cervical Disc Replacement Show Improvement Over Fusion for Degenerative Disc Disease

Long-term outcomes for patients who participated in a prospective, randomized trial evaluating the Prestige Cervical Disc against anterior cervical discectomy and fusion were published in the October issue of *Journal of Neurosurgery: Spine*. The artificial disc replacement was designed to allow for movement of the spine that mimics its natural movement. Fusion surgery, the long-time gold standard for treating degenerative disc disease, can stabilize the spine and resolve pain, but creates rigidity in the spine that can severely restrict a patient's movement.

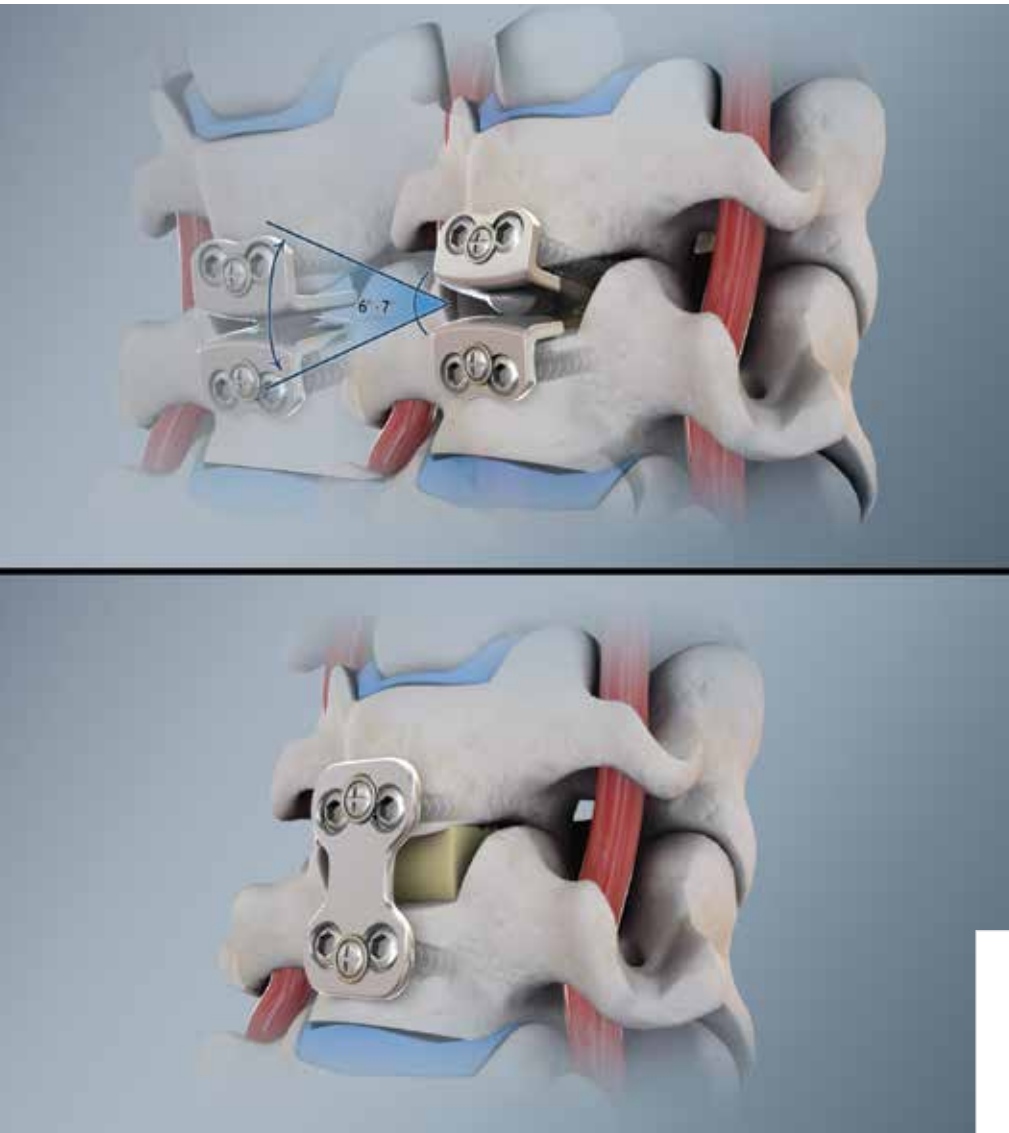
These are the fourth set of outcomes to be published from the multicenter study, and demonstrated that at seven years, the Prestige disc remains a

better solution for preserving motion at the operated level and offers increased biomechanical stability and global neck mobility over fusion.

The degeneration of spinal segments adjacent to the operated site is a frequent problem with fusion operations for degenerative disc disease. The study findings indicated that patients who received the Prestige disc also had lower rates of adjacent segment degeneration than those undergoing fusion.

The study evaluated patients with single-level cervical degenerative disc disease and radiculopathy – numbness, weakness and pain – that was not resolved with nonoperative therapies.

Burkus JK, Traynelis VC, Haid RW JR, Mummaneni PV. Clinical and radiographic analysis of an artificial cervical disc: 7-year follow-up from the Prestige prospective randomized controlled clinical trial. *J Neurosurg Spine* 2014;18:1-13.



Praveen Mummaneni MD and Christine Macasieb NP visit with Cecilia Foster after her posterior fusion surgery.

After a years of suffering from rheumatoid arthritis, Cecilia Foster is pain free. Here she shares how a posterior fusion performed by spinal neurosurgeon Praveen Mummaneni MD changed her life.

Cecilia Foster has lived much of her life with rheumatoid arthritis. A chronic autoimmune disease that affects over 1.5 million Americans, progressive rheumatoid arthritis can eventually deform joints and severely restrict mobility and function. In Foster's case, the arthritis began to destabilize her cervical vertebrae leading to debilitating neck pain. Once told that she would just need to live with the pain, today Foster is relatively pain free after cervical fusion surgery performed by UCSF neurosurgeon Praveen Mummaneni.

#### When were you first diagnosed with rheumatoid arthritis?

I was first diagnosed in 1969 and we had two small children. I didn't know how it was going to work out because

at that point I could barely turn over or get out of bed without my husband's help. He was the best caretaker.

My family doctor had said "You're just going to have to learn to live with it," and there was no offer of pain medication or information about an arthritis clinic. [My husband and I] had to find out about that ourselves.

#### How did you finally get relief from your symptoms?

I was given an injection of prednisone and I felt so much better. For about 10 years I hardly felt any pain and it seemed like it kind of went into remission. But then I started getting small ankle pains and pain in my finger joints. After getting X-rays, the doctors told me it was coming back. And then after a while I developed very bad knee and neck pain.



#### What led you to UCSF?

My doctors kept telling me that I needed to have surgery on my neck because the pain was so severe. They said I needed to go someplace with tertiary care so that they could take care of everything in one place.

#### How has your recovery been?

After the surgery I hardly had any pain in my neck. My experience at UCSF was wonderful. The care was really good and I liked my doctor, which always helps. I'm kind of in shock because everything has changed so much since I had surgery when I was younger. The pain is just gone and you're okay. It's a miracle.

I am still getting used to the limited motion in my neck though. Particularly when I go shopping or if I have to turn to look at something quickly.

#### What would you tell someone else who is suffering with pain from rheumatoid arthritis?

I would say that if you need to have the surgery, do it sooner rather than later. Because it just wastes so much time. I waited five years to do the surgery because I was afraid. I wish I hadn't.

**From Dr. Mummaneni:** Fear is a very big problem among this patient population. People suffer for a long time because they think nothing can be done to help them, especially because with rheumatoid arthritis the pain is everywhere and they learn to live with it. It can squeeze the spinal cord and they can lose hand and leg function. I think it's important for people to know that we can help a lot of these patients with surgery.





## Faculty

Line Jacques MD

# Peripheral Nerve Disorders & Chronic Neuropathic Pain

The Department of Neurological Surgery recently welcomed Line Jacques MD as its new chief of peripheral nerve and pain surgery. Dr. Jacques joins UCSF from McGill University – Montreal Neurological Hospital, where she led the pain and peripheral nerve services and the University's neurosurgical residency training program.

## What led you to specialize in pain and peripheral nerve surgery?

For me the nervous system has always been an interesting puzzle. Early in my career I pursued a master's degree in neurophysiology and found that I loved doing surgeries in the lab. I knew I always wanted to be a physician, so combining medicine with surgery and my fascination with the human nervous system made neurosurgery a perfect fit. When I pursued my neurosurgical

training, peripheral nerve surgery was perhaps the least developed area of neurosurgery leaving boundless opportunities. So after completing my neurosurgery training, I did a peripheral nerve surgery fellowship at Louisiana State University with the 'godfather' of peripheral nerve surgery, Dr. David Kline.

## What have the major advances been for peripheral nerve surgery in the last 10 years?

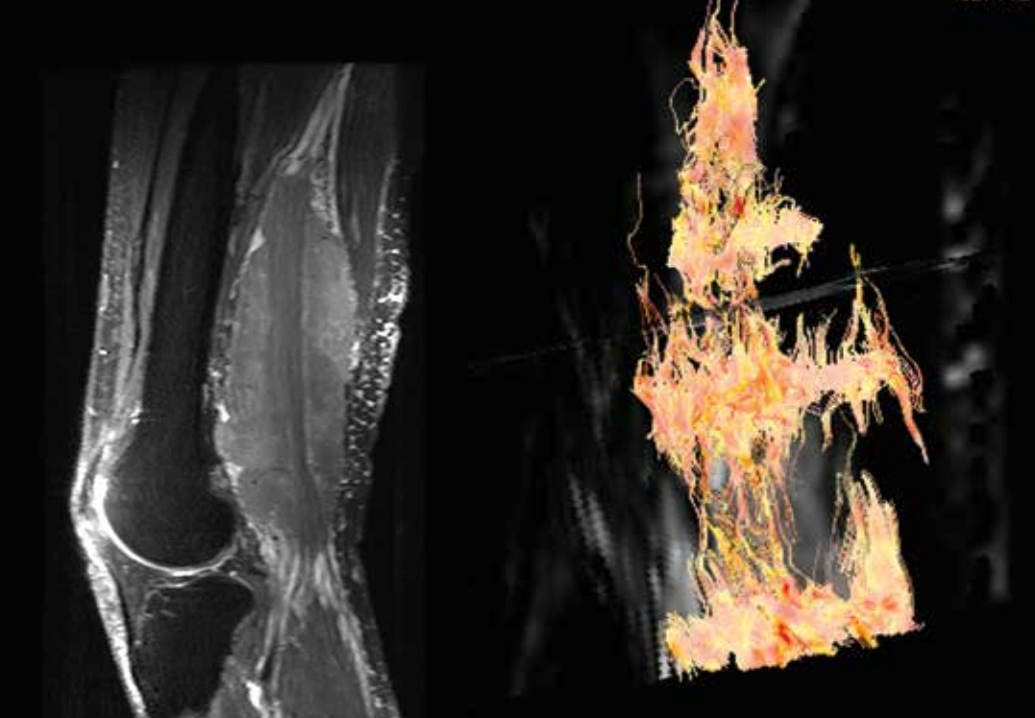
Neuroimaging and nerve conduit technology have been the biggest developments in treating nerve injuries. In the future, I think we will see a lot of improvements with nerve transfers and the enhancement of nerve regeneration, which will come with a better understanding of the electrophysiology and the molecular biology.

## What are the most common procedures you perform?

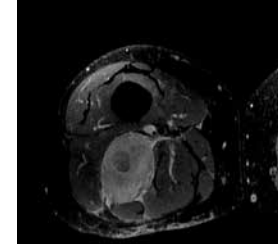
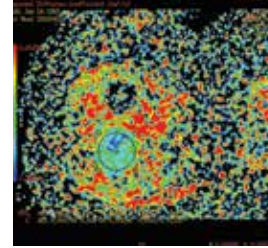
Carpal tunnel and ulnar nerve release surgery. Having come from and being part of an academic medical center, I also perform a significant number of complex brachial plexus reconstruction surgeries and nerve tumor removals.

## UCSF has a dedicated multidisciplinary clinic for neurofibromatosis patients. Why is there a need for a group of specialists to treat these patients?

That population is very unique, because neurofibromatosis (NF) is a complex genetic disorder. With NF1, patients may have cutaneous tumors, which are disfiguring and make it hard for them to live normal lives. With NF2, tumors are spread throughout the body in the brain, spinal cord, and nervous system.



UCSF neuroradiologists use diffusion tensor imaging to assess nerve damage caused by a peripheral nerve sheath tumor. By being able to visualize how the nerve fiber bundles have been moved by the tumor, neurosurgeon Line Jacques MD was able to plan a more precise surgery to remove the tumor and preserve nerve function. UCSF is one of few institutions to use this advanced imaging technology to improve patient outcomes.



Patients need to have imaging studies regularly to find their lesions so we may remove them before they cause significant neurological deficits. Unfortunately, 5-10% of neurofibromas can transform into malignant peripheral nerve sheath tumors, so it's very important to follow the patients closely. After transformation, the outcome is much worse, with 50-60% of patients dying within a year.

Our multidisciplinary NF clinic is staffed by specialists in neuro-oncology, neurosurgery, neuropathology and neurology to provide ongoing, comprehensive treatment plans. We also partner with medical geneticists at the NF/Ras Pathway Clinic who are well versed in providing care and counseling for patients with this rare condition.

Having access to all surgical specialties also means that we can quickly assemble a team for complex cases. We recently saw a patient with a schwannoma in the thoracic inlet that required a thoracic, ENT, and neurosurgeon in the operating room simultaneously removing the patient's tumor. At UCSF we work in a team environment with a common goal to provide the best patient care possible.

### How are peripheral nerve surgery and pain surgery linked?

It is called neuropathic pain because there is pain related to nerve damage. You have to consider how the patient's life will be changed by your surgery, and that means not just looking at motor recovery, but also considering the pain component. We could do a perfect nerve reconstruction, but if the patient can't return to work or does not have a reasonable quality of life because they are still in pain, the surgery cannot be considered a success. If you look at your patient's condition in its entirety, you will be able to provide a better outcome.

I am very interested in functional outcomes, and using validated tools like questionnaires, which can often help us determine whether the patient can be managed with nonsurgical therapies, or if neuromodulation fits into their treatment. Most of these patients have been in chronic pain for a significant length of time before they navigate their way to our clinical program, which has a significant impact on their quality of life. Being able to manage their pain and return their quality of life is very rewarding for our team.

### When should patients with chronic pain be seen for surgical evaluation?

After two years of chronic pain, it begins to have an impact on quality of life that is very difficult to treat and at ten years it is often irreversible. So the best time to be evaluated for surgery is six months to two years after the onset of chronic refractory pain.

### Is that because chronic pain rewires neurological pathways in the brain?

I think that could be true, but it is not very well understood and a lot more research needs to be done in this area. I have studied patients treated for failed back surgery syndrome, and despite an improvement in their functional outcome that enables them to participate more fully in life, they may still perceive themselves as handicapped. So their perception is modified by chronic pain and that's a big problem.

### If it gets more difficult to treat the pain over time, why do many patients not see pain specialists earlier?

Sometimes neuropathic pain can be very difficult to diagnose and sometimes it's a lack of knowledge

about the therapies that are currently available. In other cases, a patient may slowly get better with medication, but not enough, and then you get into a vicious cycle in which the patient keeps getting higher doses of narcotics over a period of years without frequent enough reassessments, preventing them from moving to the next therapeutic modality.

But there is more and more awareness about decreasing narcotics and using neuropathic drugs instead because narcotics are not useful for nerve pain. If patients don't respond to neuropathic drugs within six months to a year, they might be surgical candidates.

In particular, referrals for brachial plexus injury stretch avulsion can be much delayed, but surgery needs to be done quickly to provide better functional recovery. New studies also suggest that patients with complex regional pain syndrome need to be assessed and treated in the first 6 months of nerve injury if there is any hope of reversing or halting progression of their condition.

### Why did you choose to come to UCSF?

I was torn to leave behind a mature program that took me a long time to develop. After 17 years at McGill University-Montreal Neurological

Hospital, I had the largest nerve and neuromodulation practice in Canada. It took me many years and a significant amount of consultation with the government to develop a sustainable funding paradigm. The process, although daunting at times, provided me with a great deal of wisdom in program development.

When the UCSF position was presented to me, I realized what an incredible opportunity it would be to work with some of the most talented clinicians and researchers in the world. Developing a new peripheral nerve, pain, and research program at UCSF is very exciting. It is a chance to build on all of my previous experiences and take advantage of all the support teams' technologies that UCSF has to offer, such as advanced electrophysiology and radiology, which are not available in many centers. It is a treat to have access to these resources.

UCSF offers many types of treatment for complex pain syndromes, including:

- Spinal cord stimulation
- Peripheral nerve stimulation
- Peripheral nerve field steering
- Occipital nerve stimulation
- Intrathecal drug delivery
- Deep brain stimulation

# Pediatric Neurosurgery



## Faculty

### Pediatric Neurosurgery

Nalin Gupta MD, PhD  
 Kurtis Auguste MD  
 Mitchel S. Berger MD  
 Corey Raffel MD, PhD  
 Ronald Shallat MD  
 Peter P. Sun MD

### Pediatric Neuro-Oncology

Sabine Mueller MD, PhD  
 Anuradha Banerjee MD  
 Theodore Nicolaides MD  
 Michael Prados MD

### Pediatric Research Laboratories

Arturo Alvarez-Buylla PhD  
 Nalin Gupta MD, PhD  
 Theodore Nicolaides MD  
 Anders Persson PhD  
 Claudia Petritsch PhD  
 Joanna Phillips MD, PhD  
 David Rowitch MD, PhD  
 William Weiss MD, PhD

## Pediatric Brain Center at UCSF Benioff Children's Hospitals

### A Team Approach to Complex Disorders

Children who suffer from neurological disorders often need to see multiple specialists. The Pediatric Brain Center (PBC) at UCSF Benioff Children's Hospital was created so that families and referring physicians could have access to all the expertise they need in one place.

We provide a team-based approach to treatment that includes specialists from neurology, neurosurgery, neuro-oncology, neuroradiology, intensive care medicine, rehabilitation medicine, neuropsychology, and genetics.

Our team also includes a dedicated PBC nurse coordinator who is here to help families navigate the system and make the most out of their visit to the PBC, from identifying the team

of experts they need and coordinating multiple appointments, to helping with logistics like transportation. Whenever possible, patients are seen in multidisciplinary clinics so that they can meet with all the specialists they need during the same day.

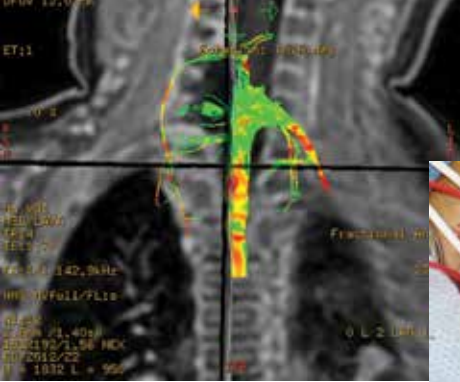
### UCSF Benioff Children's Hospitals in San Francisco and Oakland

In 2014, the UCSF Benioff Children's Hospital and Children's Hospital & Research Center Oakland became united following a \$100 million donation by philanthropists Marc and Lynne Benioff. Now called the UCSF Benioff Children's Hospitals, these two leading children's hospitals are providing more coordinated, comprehensive care to children across the Bay Area.

UCSF Benioff Children's Hospital San Francisco will open the doors to its

new home at the UCSF Mission Bay campus in February 2015. The state-of-the-art hospital features the most advanced treatment technologies, but was also designed with input from patients and families to fit their needs. The PBC will be centrally located here and includes over 20 subspecialty clinics and centers including:

- Brachial Plexus and Nerve Injury Clinic
- Brain Tumor Center (Neuro-Oncology)
- Concussion Clinic
- Epilepsy Center
- Fetal Treatment Center
- Movement Disorders Clinic
- Neurofibromatosis/Ras Pathway Clinic
- Spina Bifida Program
- Stroke and Cerebrovascular Disease Center



MR neurograms can reveal whether axonal regeneration is occurring following injury to the brachial plexus, assisting physicians in identifying the best window for surgical repair of the nerves.

## Inside the Brachial Plexus and Nerve Injury Clinic

Brachial plexus injuries in infants are common during difficult births. The incidence rate is 0.3 to 2 per 1,000 births, and the risk of injury is higher with larger babies; mothers with gestational or maternal diabetes; and mothers giving birth for the first time.

Most brachial plexus injuries are immediately recognized at birth. In the majority of cases, the nerve is stretched and recovery occurs over the first three to six months of life without any intervention. But approximately 5-10% of infants are left with permanent neurological deficit.

If the injury occurs in the upper trunk of the brachial plexus (usually at the C5 and C6 nerves), functional deficits are generally localized to the arm and shoulder, whereas lower trunk injuries (at C7 and C8 nerves) cause deficits in hand function.

Timely intervention can be critical for repairing damaged nerves, so it is important to monitor infants with injuries closely. At the Pediatric Brachial Plexus and Nerve Injury Clinic, physicians obtain MR neurograms two to three months after the injury to determine if there is imaging evidence of axonal regeneration, or if scar tissue is

preventing the nerve from regenerating axons. It may be especially useful for patients in whom electromyography and nerve conduction studies (EMG/NCS), and standard imaging studies are inconclusive.

If studies such as the MR neurogram or EMG/NCS clearly reveal that there will be no further improvement, then surgery can be performed earlier. If there is evidence of nerve function recovery, doctors can more confidently advise patients to wait a little longer. If at six months, there has still been no improvement, surgery is usually indicated.

Neurosurgery often involves removing scar tissue that has developed over the nerve and creating a nerve graft. As the child ages, he or she may benefit from a muscle transfer done by an orthopaedic surgeon. The goal is always to maximize function of the affected limb in each patient.

Importantly, an appointment at the Brachial Plexus and Nerve Injury Clinic gives patients access to a neurosurgeon, child neurologist, orthopaedic surgeon, and occupational therapist in the same place and same day depending on their needs.

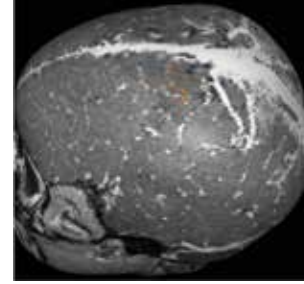
## Pacific Pediatric Neuro-Oncology Consortium Welcomes St. Jude's Children's Research Hospital and Launches New Protocol that Incorporates Molecular Profiling

In 2012, UCSF pediatric neuro-oncologists Michael Prados and Sabine Mueller lead the development of a clinical trials consortium that focuses on developing precision-medicine trials for children with brain tumors – the Pacific Pediatric Neuro-Oncology Consortium (PNOC).

This year St. Jude's Children's Research Hospital became the 11<sup>th</sup> institution to join PNOC, expanding the network of leading children's hospitals that can offer these innovative trials to their patients. As many of PNOC's clinical trials are surgically based, all hospitals in the consortium have well-established pediatric neurosurgical and neuro-oncology programs.

PNOC's newest trial is aimed at treating diffuse intrinsic pontine glioma, which typically carries a very poor prognosis. A patient first undergoes a biopsy, after which a specialized tumor board convenes to review the molecular profile of the tumor and make treatment recommendations based on its sequence. Patients may choose to undergo standard of care or follow recommendations for existing FDA-approved drugs that target the molecular aberrations found in their tumors.

For more information on trials offered through PNOC, visit [www.pnoc.us](http://www.pnoc.us).



## Transcranial Magnetic Stimulation Allows Surgeons to Non-invasively Map Motor Cortex in Pediatric Patients

In an ongoing effort to provide non-invasive alternatives to children undergoing brain surgery, the pediatric neurosurgery team has now added transcranial magnetic stimulation (TMS) to their list of procedures for mapping motor cortex in their patients. This technique is currently being used as a preoperative adjunct to other well-established mapping techniques, but has already made an impact for pediatric patients undergoing brain surgery near or in regions of the brain responsible for strength and movement.

Traditional methods of motor mapping in children often require exposure of the brain and direct stimulation of the cortex with electricity. Immature brains have less myelin, however, and intraoperative mapping can sometimes require extended surgery time or high levels of electric stimulation to illicit a response, both of which carry added risk. Additional surgery time increases risks of blood loss and infection. Delivering progressively higher electrical stimulation can provoke intraoperative seizures. Although other non-invasive imaging techniques are available for

motor mapping in children, they often require patient participation, which is often problematic for a very young child.

TMS uses small magnetic pulses through the skull to gently activate neuronal circuitry at the level of the cerebral cortex. The pulse is administered with a flat paddle and the resulting impulse travels down motor cortex and into motor pathways when properly placed over motor neurons. This impulse is not perceptible to the patient but can be detected with small electromyographic stickers on the arm, hand or face. Because the patients are unaware of the impulse, they are able to be awake, watching DVDs or playing with toys. They are often comfortably distracted in their parents' arms throughout testing.

As testing is carried out, the TMS paddle can be 'seen' by a navigation camera. Every point of stimulation is then co-registered to the patient's pre-operative MRI. The intensity of the EMG response for each point is then summated and scored automatically. This automatic process generates

color-coded points that are not only placed on their MRI but are also accessible during surgery where the pre-operative MRI is used to navigate along the brain surface. This new approach has now been directly compared to other well-established intraoperative techniques to map the motor cortex and TMS points have proven near 100% accurate. A full comparison study is underway, but the early results are very encouraging for this population of patients.

TMS has already proven to be safe and accurate in motor mapping children undergoing brain surgery. Preliminary findings with this technique also indicate that, at a minimum, intraoperative mapping time is reduced by >50%. In the not-too-distant future it may replace other mapping techniques for select patients without sacrificing precision. TMS has also been used successfully in assessing motor function in the rehabilitation setting, for treatment of certain forms of epilepsy, and for management of medically refractory depression.







# Center for Neural Engineering & Prosthesis at UC Berkeley & San Francisco

Since its inception in 2010, the Center for Neural Engineering and Prosthesis (CNEP) has been focused on understanding neural networks to develop brain-machine interfaces that can convert the thoughts of patients who are paralyzed into commands for a robotic limb or exoskeleton.

This year, the CNEP team was awarded a \$26 million grant to map the human brain circuits that go awry in neuropsychiatric disorders, such as depression, anxiety and posttraumatic stress disorder, and develop a new generation of biomedical devices for treatment.

The first step will be to use multisite electrode recordings to create a high-resolution map of the human mesolimbic circuitry in both normal patients and those affected by neuropsychiatric disorders. The recordings will be performed in patients with Parkinson's disease and medically intractable epilepsy who are already undergoing brain recordings as part of their clinical care. Neuropsychiatric symptoms commonly occur together with Parkinson's disease and epilepsy.

This project addresses neuropsychiatric disorders in a new way, taking a systems-level approach. Instead of focusing on specific neurotransmitters to target with drugs, the researchers will seek to understand these disorders as disruptions of a highly coordinated network.

As disrupted circuits specifically associated with neuropsychiatric disorders become defined, the research team will work to develop a precise stimulation therapy that guides the brain to strengthen alternative circuits. By leveraging the brain's natural capacity for neural remodeling and learning, this approach will potentially allow the newly strengthened circuits to bypass the disease-associated signals and thereby eliminate symptoms.

The new therapy would come in the form of an implanted device that can record spatiotemporal patterns of neural activity and modulate the brain when it detects a pattern of abnormality consistent with the patient's disorder. Patients would also participate in rehabilitation training during which they use the implanted device to interact with external stimuli for cognitive training.

The ambitious project is funded by the Defense Advanced Research Projects Agency, a major partner in support of President Obama's Brain Initiative, under the agency's recently launched SUBNETS (Systems-Based Neurotechnology for Emerging Therapies) program. SUBNETS seeks to bring together neuroscience, neurotechnology, and clinical therapy in innovative ways to address the burden of psychiatric disease among military personnel.

The project also involves more than a dozen scientists, engineers and physicians at the UC Berkeley-UCSF Center for Neural Engineering and Prosthesis, Lawrence Livermore National Laboratory, Cornell University and New York University, as well as industry partners Posit Science and Cortera Neurotechnologies.

For more information about CNEP and the team of investigators leading this project, visit [cnep-uc.org](http://cnep-uc.org)



## Postoperative Debriefings Amongst Multi-Disciplinary Operating Room Providers

Surgical teams have begun performing postoperative debriefings for the operating room (OR) team to recap the procedure done and ensure everyone is aware of the next steps to be taken. The team also reviews the acute postsurgical management plan, ensures any clinical specimens are sent to lab, and discusses any equipment or efficiency issues, which are then tracked by the Perioperative Quality Improvement (QI) team. Having equipment issues addressed before the next surgery takes place has the potential to increase OR efficiency and on-time starts for procedures.

The QI team is also using a validated tool – the Safety Attitudes Questionnaire for the Operating Room – to measure safety attitudes amongst OR providers and assess changes in safety culture scores as measures like the postoperative debriefings are implemented to increase multidisciplinary communication.



Hospitalist Catherine Lau MD leads Department programs to ensure the highest level of patient safety and quality care.

# Patient Safety & Quality Improvement Program

## Patient Safety Checklist Automates Safety Practices for Hospitalized Neurosurgical Patients

This year a new neurosurgery patient checklist has been introduced at all five UC Medical Centers to increase the quality and safety of care provided in the hospital. The aim of this checklist is to ensure that standardized safety practices are performed for every neurosurgical patient during their hospital stay. These safety practices were designated, reviewed and approved by neurosurgical providers and quality improvement champions.

While submitting their daily progress notes into an electronic system, neurosurgical providers are required to check off key tasks such as confirming the patient's neurologic status has

been assessed and that their surgical site has been inspected to spot any signs of wound infection early on.

This checklist also reminds providers to order physical therapy consults to encourage early mobilization, and serves to safeguard against urinary catheters and central lines being left in without a justified clinical reason.

By making the clinical checklist an automated part of the daily note, the neurosurgery services at all hospitals are working together to reduce the likelihood that a miscommunication or minor oversight results in a poor patient outcome.

In 2013, the UC Center for Health Quality and Innovation awarded a \$1.2 million grant to improve and standardize neurosurgery patient clinical outcomes and experiences at five UC Medical Center sites. UCSF is the primary site for the project.

In the first year of this grant several initiatives have launched in conjunction with the existing Neurological Surgery Patient Safety and Quality Program to engage both providers and patients in the mission to provide the safest and highest quality care.



## Designing More Relevant Patient Education Materials

Safe, high-quality care is not only about providing excellent surgical outcomes, but also making sure that patients and their families have the information necessary to reduce stress associated with hospital stays. Often, this begins before patients set foot in the hospital.

A newly designed educational initiative in the Department of Neurological Surgery aims to address the most common concerns, ranging from explanations of basic hospital procedures to providing better details on how to handle procedure-specific side effects.

- Preoperative Letter

As part of the Department of Neurological Surgery's service to our patients, each surgeon has begun to send a detailed preoperative letter on what to expect upon admission to UCSF. The letter identifies all members

of the care team, stages of procedures, timeline for recovery, and discharge expectations. By providing these details in advance, patients have been better informed and more comfortable during their hospital stay.

- Patient and Family Surveys

Another project to improve patient education materials was a collaboration with patients and their families. By surveying focus groups of participants on their care experiences in various settings – clinic, hospital and postoperative discharge – the QI team was able to identify areas of care procedures that needed more explanation.

New patient materials are now being generated to respond to those needs. For example, several families seemed unprepared for dealing with temporary aphasia as possible side effect of brain

tumor surgery. A new information sheet on what to prepare for at discharge addresses aphasia and other possible side effects of surgery.

- Online Patient Education Modules

Patients now have the option of using online educational modules to prepare them for what to expect in the hospital. These standardized modules, designed by the health education company Emmi, are meant to supplement information given during appointments and cover common questions, such as what to expect with anesthesia or the risks and benefits of a treatment. There are also some procedure-specific modules, such as for discectomy and aneurysm surgery, to cover specific issues relating to those surgeries.

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