

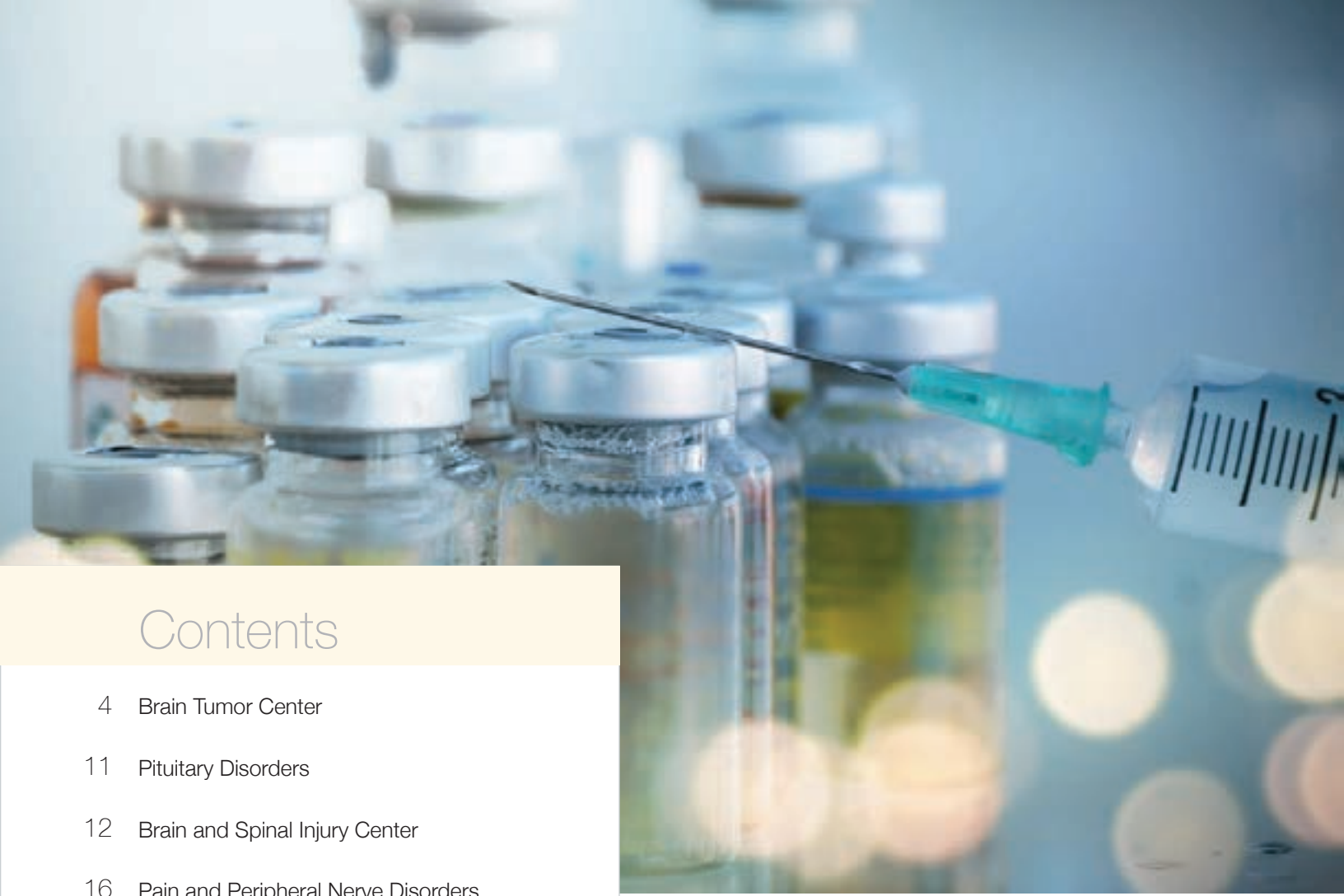


# UCSF Neurological Surgery

2017 Annual Report



University of California  
San Francisco



## Contents

- 4 Brain Tumor Center
- 11 Pituitary Disorders
- 12 Brain and Spinal Injury Center
- 16 Pain and Peripheral Nerve Disorders
- 18 Neurospinal Disorders
- 21 Epilepsy
- 24 Center for Neural Engineering and Prostheses
- 26 Pediatric Neurosurgery
- 30 Movement Disorders
- 33 Vascular Neurosurgery
- 34 Community Outreach

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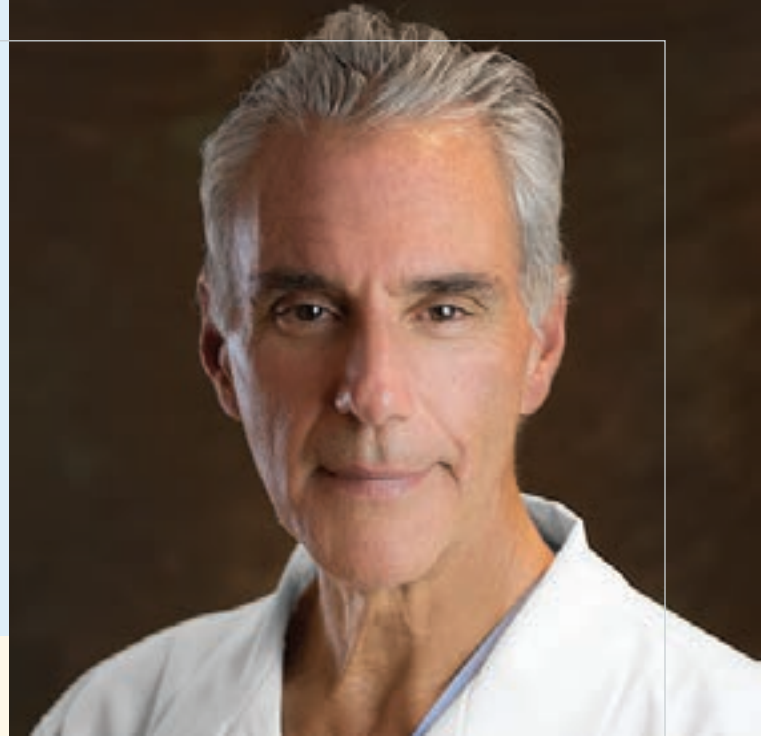
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## Dear Colleague:



In our annual report, you'll find clinical and research highlights from all of the subspecialty programs within the Department of Neurological Surgery at UCSF. We have again been ranked in the top five of U.S. News and World Report's list of top neurology and neurosurgery programs in the country – and the best on the West Coast. I am honored to work alongside the faculty and staff members whose passion, dedication and professionalism allow us to be designated a top program year after year.

We continue to recruit incredible physicians to join that group, and this year we have added five new faculty members. Adib Abl, MD, is leading our vascular neurosurgery program and brings rare expertise in both open and endovascular surgery for cerebrovascular disorders. Brain tumor surgeon Shawn Hervey-Jumper, MD, continues our department's long tradition in leading the field of brain mapping, and has a particular interest in cognitive rehabilitation and neural plasticity. Lee Tan, MD, joins the talented group at the UCSF Spine Center, where he adds perspective from an orthopaedic spine surgery fellowship to his training as a neurosurgeon.

Adding to our highly successful Community Extension Program, Margaret Riordan, MD, and Sun Ik Lee, MD, are providing full-time services at Highland Hospital in Oakland. With clinics in Marin, Napa Valley, San Jose, and now Oakland, we have been able to integrate specialized neurosurgical care with our patients' local health care teams and build successful partnerships.

Fueling the advanced clinical care we strive to provide for our patients is an incredibly diverse research program. We have again been ranked first in NIH funding among academic neurosurgery programs in the United States, which is a

reflection of the visionary paths our principal investigators are pursuing in all areas of neuroscience. Among our many scientific achievements in 2017 are a new experimental drug to reverse impairments caused by traumatic brain injury, new gene therapy trials for Parkinson's disease and AADC deficiency, and a promising new area of study (called immunomethylomics) to noninvasively assess prognosis and response to therapy for patients with brain tumors.

While neurosurgical disorders are by their nature serious conditions, the stories in our annual report are a source of inspiration and optimism for a future in which many of the diseases we treat will be more easily managed.

A handwritten signature in blue ink, appearing to read "Mitchel S. Berger".

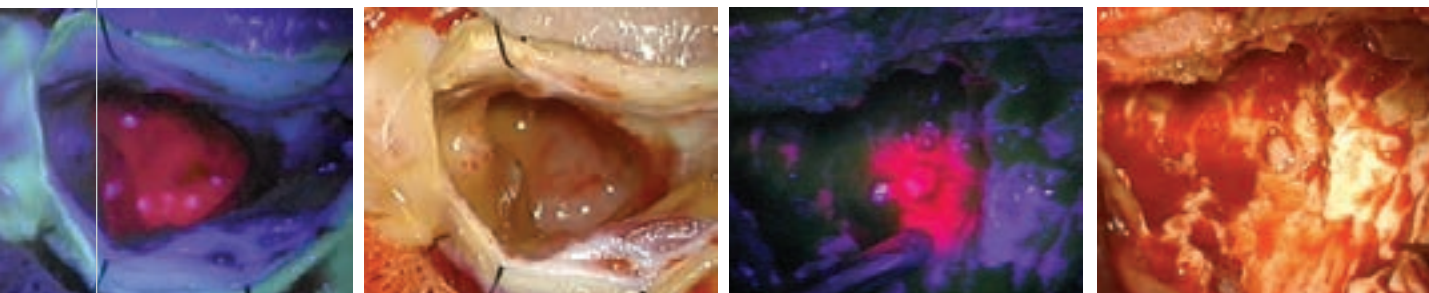
**Mitchel S. Berger, MD**

Professor and Chair

Department of Neurological Surgery

Berthold and Belle N. Guggenheimer Endowed Chair

Director, Brain Tumor Center



5-Aminolevulinic acid causes fluorescent porphyrins to accumulate in brain tumors, helping UCSF neurosurgeons achieve a maximum extent of resection by revealing areas of infiltration beyond a tumor's defined margins. Images courtesy of Georg Widhalm, MD.

# Brain Tumor Center

## Advanced Techniques, Technologies Improve Extent of Tumor Resection

Evolving surgical treatments are making tumor removal safer and more efficient, even as a growing body of research supports the idea that removal of as much tumor as possible prolongs survival in brain tumor patients, says Mitchel Berger, MD, director of the UCSF Brain Tumor Center.

A pioneer in the use of brain mapping, Berger says that the technique is one important piece of the surgeon's armamentarium – essential for helping surgeons more clearly view the extent of the tumor, while also identifying and avoiding injury to sites of language, motor and sensory function.

"Newer surgical navigation systems enable confirmation of tumor location under the scalp and bone during incision planning and under the brain surface during the operation," says Berger.

In addition, the department is deeply involved with multisite research on the use of 5-aminolevulinic acid (5-ALA) to enhance tumor visualization. Patients take the drug orally before surgery, causing fluorescent porphyrins to accumulate in malignant gliomas. The fluorescent light reveals both the tumor and areas of infiltration outside its defined margins.

UCSF was the first institution on the West Coast to offer 5-ALA-enhanced procedures, and this year, Berger co-authored a paper in the *Journal of Neurosurgery* that describes a new advance in this arena: a wavelength-specific lighted suction instrument for 5-ALA fluorescence-guided resection of deep-seated malignant glioma.

"We have to continue pursuing these types of advances if we are to continue to prolong the lives of brain tumor patients," says Berger.

"Newer surgical navigation systems enable confirmation of tumor location under the scalp and bone during incision planning and under the brain surface during the operation."



## Clinical Trials Next Step for Convection-Enhanced Delivery

Imaging advances and improvements in catheter technology – many of which emerged from UCSF – are enabling clinicians to test new convection-enhanced delivery (CED) techniques with promising drugs for the treatment of glioblastoma.

CED enables direct, targeted delivery of drugs to brain tumors through a pressure-driven, bulk-flow process that distributes an infusion over more area than a direct injection, thus optimizing tumor death while minimizing damage to surrounding tissue.

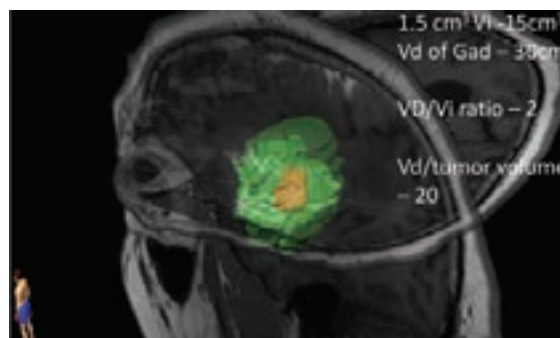
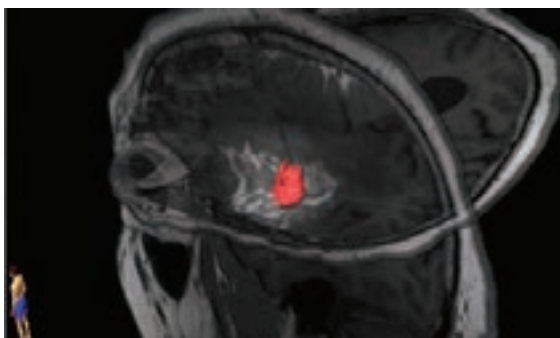
UCSF remains a lead institution for one ongoing study that uses CED to deliver nanoliposomal CPT-11 labeled with gadolinium. Led by UCSF neuro-oncologist Nicholas Butowski, MD, and neurosurgeon Manish Aghi, MD, PhD, this trial is for patients with recurrent glioblastoma multiforme – a fatal form of brain cancer. Encapsulating the drug in a liposome achieves a slow, sustained release, which is safer and allows for greater uptake. Watching the infusion in real time, via MRI, helps ensure precision in terms of both location and volume.

In 2017, a second multisite trial opened with Butowski as co-principal investigator of the nationwide team. This single-arm, open-label study is testing CED delivery of MDNA55

in adults with glioblastoma that has recurred or progressed after failure of first-line therapy. MDNA55 is a novel targeted immunotherapeutic agent consisting of a circularly permuted interleukin-4 (cpIL-4) fused to a truncated version of *Pseudomonas* exotoxin A. The researchers believe MDNA55 could be effective, in part because its cell-killing ability is not growth rate-dependent and because it appears to be effective against hypoxic cells in the tumor inner core, which often become resistant to radiation and chemotherapeutic drugs.

In both studies, imaging advances ensure clinicians can target as much tumor as possible – and only the tumor – while more flexible catheters allow patients to absorb greater volumes and concentrations of the drugs over a longer time period.

“The increased flexibility of the catheters increases the comfort and safety and makes it easier to make adjustments, so we can infuse for 24 hours, instead of just two to three,” says Aghi. “We hope ultimately to be able to leave the catheters in for more extended periods.”



Gadolinium mixed with an infusate of CPT-11 (green) allows investigators to monitor coverage of the tumor (red) on an MRI taken after a 24- to 48-hour infusion.

## Scientific Collaborations Improve and Accelerate Studies

In 2017, the Ivy Foundation Early Phase Clinical Trials Consortium will have reached its goal of creating a virtual tissue bank of nearly 1,500 patients, imaging to go along with the samples, and molecular characterization for about 500 patients, according to UCSF neuro-oncologist Nicholas Butowski, MD, the consortium's principal investigator.

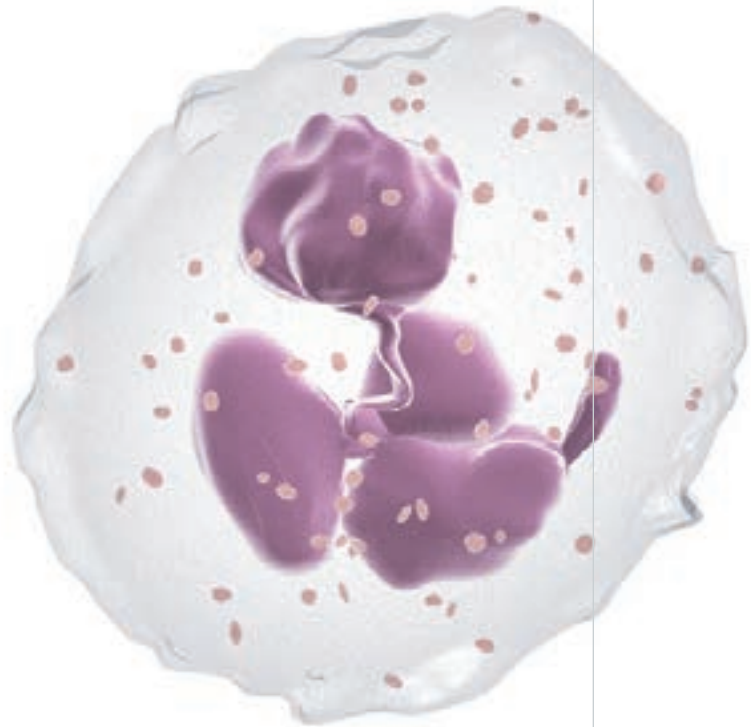
“We believe ours will be the largest bank of its kind, and our plan is to make it available to other researchers for any interrogation they want to perform,” says Butowski.

The Ben and Catherine Ivy Foundation funds the consortium's varied clinical trials and preclinical molecular sequencing and imaging projects.

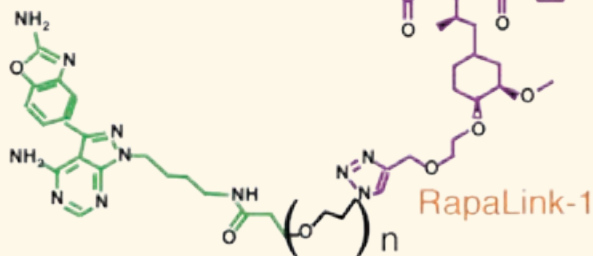
## Basic Scientists Offer Important New Insights into How Cancer Works

In 2017, important scientific discoveries and publications continued to emerge from the UCSF Brain Tumor Center's basic science laboratories.

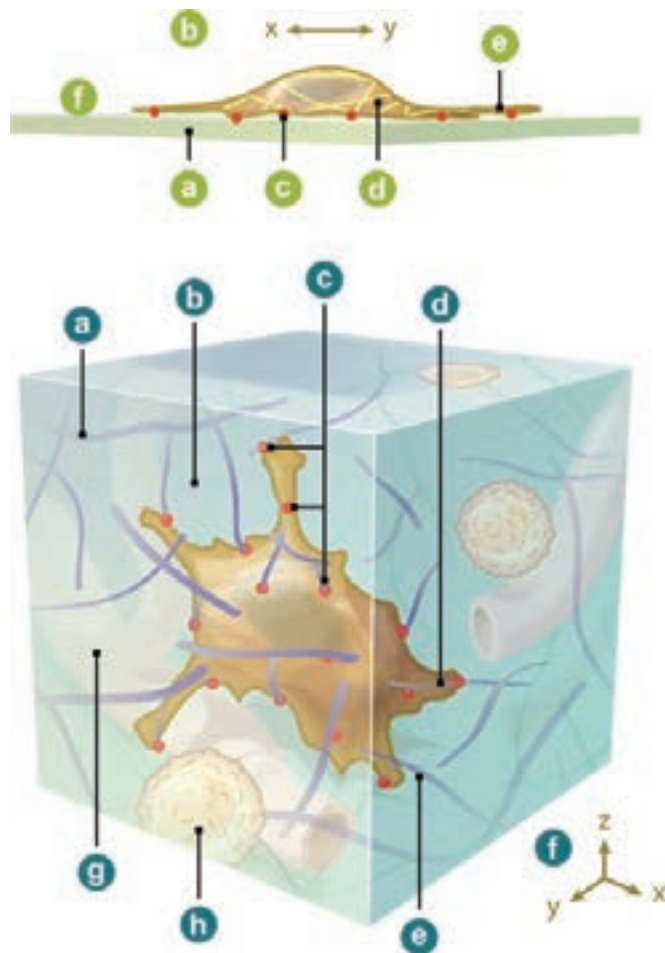
- Researcher John Wiencke, PhD, and his team published a study in *Clinical Epigenetics* that introduced a new approach – they dubbed it immunomethylomics – for assessing glioma survival using the blood neutrophil-to-lymphocyte ratio. This ratio is an indication of immunosuppressive cells in cancer patients, and the researchers believe monitoring the methylation process they discovered could offer a more unbiased way to assess tumor burden, therapeutic response and prognosis. Specifically, the research team concluded that the methylation-derived cell composition estimates (based on DNA methylation) could serve as a novel biomarker that represents immunosuppressive myeloid cells within the blood of glioma patients.



MLN0128



- A paper in *Cancer Cell* – for which William Weiss, MD, PhD, was senior author – re-established mTOR as a central target in glioma treatment and traced the failure of existing drugs to incomplete and/or nondurable inhibition of mTORC1. In their study, the researchers found that Rapalink-1 – an agent linking an mTOR kinase inhibitor (TORKi) to rapamycin – showed better efficacy in tumor-bearing mice than rapamycin or TORKi alone (two earlier-generation mTOR inhibitors).

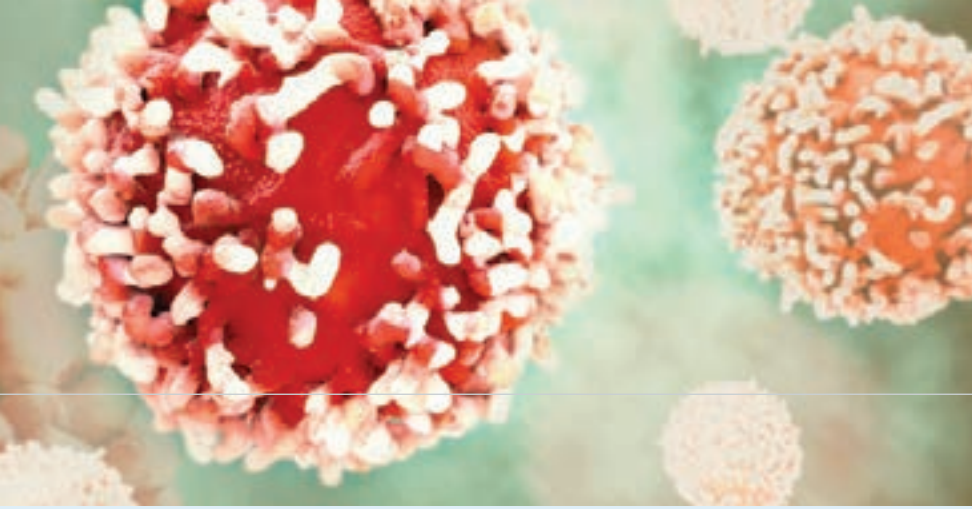


2D	3D
Thin continuous matrix layer	<b>a</b> Discrete matrix fibrils dispersed randomly
Absence of cytokine & growth factor gradients	<b>b</b> Presence of cytokine & growth factor gradients
Focal adhesions limited to one plane	<b>c</b> Focal adhesions distributed in all 3 dimensions
Stiffness elevated (GPa range)	<b>d</b> Stiffness lower (kPa range)
No steric barriers to migration in one plane	<b>e</b> Cell migration sterically hindered in all planes
Cells restricted to apical-basal polarity	<b>f</b> No restriction in polarity
	<b>g</b> Ability to contrast mechanisms of perivascular vs. parenchymal invasion
	<b>h</b> Ability to incorporate immune cells

• Manish Aghi, MD, PhD, has begun collaborative work with UC Berkeley bioengineers and industry partners to explore the relationship between the tumor microenvironment and the lethality of glioblastoma. “If we can understand the genetic programming that’s driving the migratory capacity of these tumor cells – how signaling alters certain macrophages and neutrophils in cancer patients – we could begin to make some progress on new potential targets,”

he says. To that end, Aghi’s team is investigating novel mediators of invasion in a high-throughput manner using three-dimensional platforms developed in collaboration with bioengineers at UC Berkeley. They are sequencing single cells and confirming the corresponding protein changes at the single-cell level to screen for those signaling processes that make the tumors so difficult to cure.

“If we can understand the genetic programming that’s driving the migratory capacity of these tumor cells – how signaling alters certain macrophages and neutrophils in cancer patients – we could begin to make some progress on new potential targets.”



“We hope at the end of one year to have preliminary outcomes for tumor-specific sites that can help us better prepare patients and families, lead to more informed choices about the surgeries and help patients think about what type of support they will need postoperatively, including psychological care.”

## A New Instrument to Measure Quality of Life for Patients with Meningiomas

While quality-of-life studies for aggressive brain tumors have proliferated over the last decade, there have been few for other tumor types. With that in mind, UCSF neurosurgeon Michael McDermott, MD, has led the development of a new tool aimed at gathering data on quality of life for meningioma patients. This initiative will be one of the first to look at quality-of-life measures specific to intracranial meningioma sites.

“There can be a significant difference between what surgeons and patients think is a good surgical outcome,” says McDermott. “We know our patients can experience things such as numbness, double vision and reduced hearing. But we need data to help us understand how the treatments we choose affect our patients’ daily lives and where we may need to improve.”

The new tool, called MENG-QOL, is a modified version of the Functional Assessment of Cancer Therapy-Brain and the 36-Item Short Form Health Survey (SF-36) outcome

instruments. Following surgery or radiosurgery, patients fill out a web-based questionnaire to rate quality-of-life metrics such as pain, coordination and ability to perform activities of daily living.

The tool is currently being used at the UCSF Brain Tumor Center, but with philanthropic support, McDermott and his colleagues are expanding the data collection to a total of 11 other sites. That work began with an underwritten webinar, in which eight academic medical centers in the United States joined institutions from Ireland and England.

“We hope at the end of one year to have preliminary outcomes for tumor-specific sites that can help us better prepare patients and families, lead to more informed choices about the surgeries and help patients think about what type of support they will need postoperatively, including psychological care,” says McDermott.



## Meningioma Trial Aims to Offer Treatment Options

Meningiomas are the most common type of primary brain tumor, with surgery and radiation currently the only known effective treatment options. Yet not all meningiomas are operable, and even those that are can recur, malignantly transform and cause significant symptoms. Decades of clinical trials have failed to find effective systemic agents, but according to neuro-oncologist Jennie Taylor, MD, MPH, “Our rapidly increasing understanding of the genetic mutations that drive tumor development opens the door for precision medicine approaches for meningiomas.” Taylor is the site principal investigator for a multisite phase II clinical trial now open at UCSF.

The trial has two arms. One uses vismodegib – a Food and Drug Administration (FDA)-approved medication for other cancers, including basal cell carcinoma – to target *SMO* and *PTCH1* mutations in the hedgehog pathway; this arm is still enrolling. A second arm targets the *NF2* mutation with an experimental medication. Eventually, the researchers will use the same protocol to open a third arm, targeting *Akt* mutations.

“Our hope is that by increasing use of available tools – like the UCSF500 Cancer Gene Panel – we can identify other possible targets to attack meningiomas in novel ways,” says Taylor.

Jennie Taylor, MD, MPH, is leading a phase II clinical trial at UCSF for patients with meningioma.



“Our hope is that by increasing use of available tools – like the UCSF500 Cancer Gene Panel – we can identify other possible targets to attack meningiomas in novel ways.”



Nurse practitioner Margaretta Page, philanthropist Marritje Greene, UCSF Medical Center CEO Mark Laret, Director of Neuro-Oncology Susan Chang, and philanthropists Randi Murray and Cathy Podell attend a performance of *Hamilton* to benefit the UCSF Neuro-Oncology Gordon Murray Caregiver Program.

## Philanthropy Expands What a Brain Tumor Center Can Accomplish

### *Hamilton* Sings in Support of UCSF Brain Tumor Center

On March 16, 2017, a special performance of the critically acclaimed musical *Hamilton* benefited the UCSF Neuro-Oncology Gordon Murray Caregiver Program. Organized by longtime supporters Randi Murray, Cathy Podell and Marritje Greene, the event raised funds for a unique program that has become a model for other health care organizations around the country.

The Neuro-Oncology Gordon Murray Caregiver Program, named for Randi Murray's late husband, provides resources and an extra layer of support for the caregivers of patients at the UCSF Brain Tumor Center. Family members are often overwhelmed by the emotional toll and responsibility that come with caring for a loved one with a brain tumor. By providing family members with the tools they need to succeed in that role and care for themselves, the program can often help patients achieve better outcomes and quality of life.

"The funds raised through this event have a direct impact on improving the lives of the patients and families we serve," says Susan Chang, MD, director of the Division of

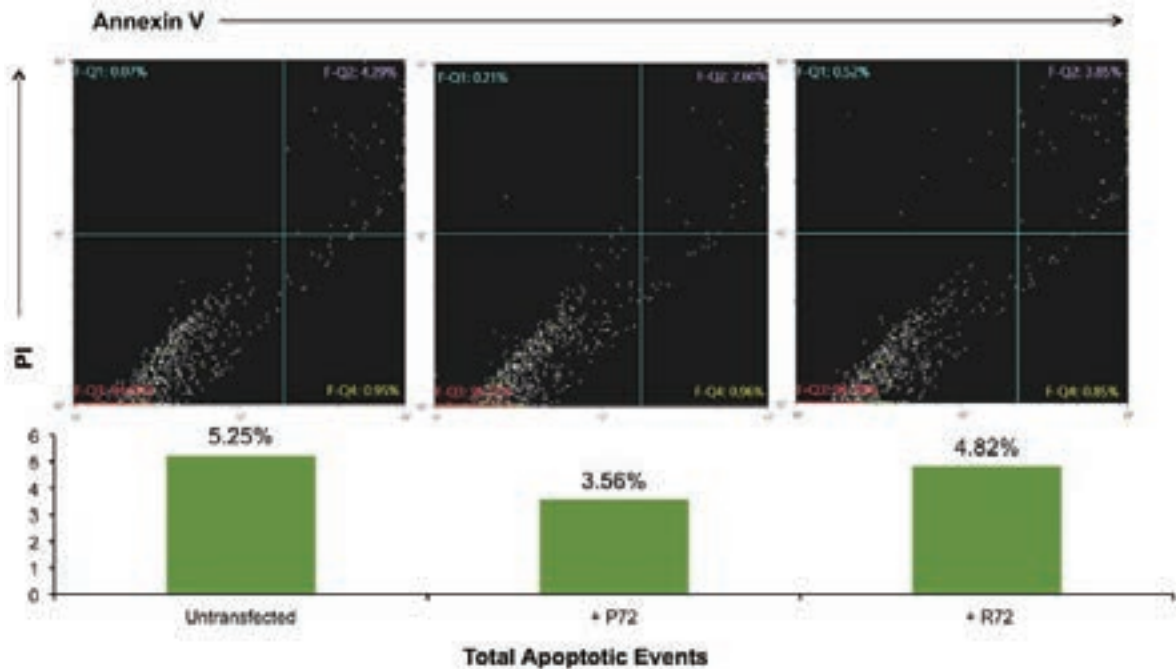
Neuro-Oncology. "We are immensely grateful to everyone who came to support our work and especially to Randi, Cathy and Marritje, whose tireless efforts have made this program a success."

### Anonymous Gift Supports Students and Research

A grateful patient's anonymous \$250,000 donation to Michael McDermott, MD, and the UCSF Department of Neurological Surgery will support two important new initiatives:

- Beginning in 2018, approximately 10 percent of the gift will fund what will be known as the LVM Neurosurgical Summer Research Stipend (for the anonymous donor). The stipend will support a medical student or resident for six to eight weeks on a clinical research project.
- The remaining funds will support the LVM Brain Tumor Research Grants. Proposed pilot studies will be peer reviewed by McDermott and department colleagues Susan Chang, MD, Mitchel Berger, MD, and Russell Pieper, PhD. The application process has already commenced.

# Pituitary Disorders



## Study Characterizes Gene Instrumental in NFPAs

UCSF neurosurgeon Manish Aghi, MD, PhD, led a study addressing the fact that past studies of the molecular etiology of nonfunctioning pituitary adenomas (NFPAs) failed to identify prevalent genetic changes that could enhance treatment options. Working from prior work that suggests p53 has a role in NFPA development, Aghi's research team sought to describe *TP53* gene alterations in NFPAs.

In a paper published in 2017 in *Molecular and Cellular Endocrinology*, the team found that the polymorphism rs1042522:C>G in codon 72 of exon 4 of the *TP53* gene,

whose C variant produces a proline and is more common in most ethnicities, has a G variant producing an arginine that is fairly ubiquitous in nonfunctional adenomas and prolactinomas. This, in turn, causes patients to present a decade earlier with symptomatic adenomas, reduces expression of cell cycle arrest protein p21 and increases adenoma cell proliferation. These findings suggest that the *TP53* gene influences adenoma development in the pituitary gland.

## California Center for Pituitary Disorders Celebrates 10 Years

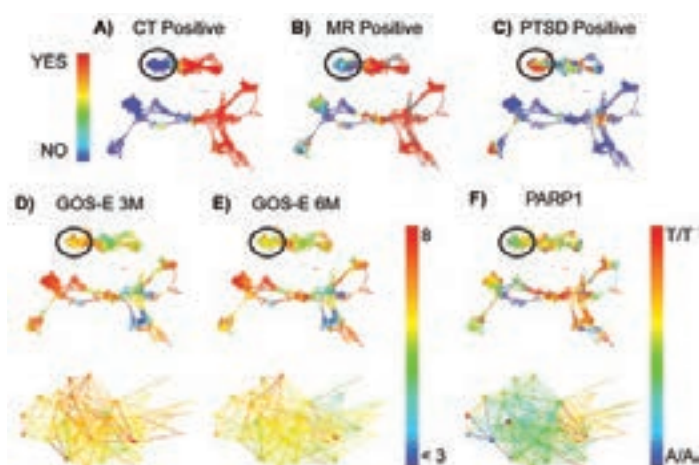
On May 1, 2017, the California Center for Pituitary Disorders (CCPD) at UCSF celebrated its 10-year anniversary. In that time neurosurgeons at UCSF have performed 2,110 microscopic and endoscopic transsphenoidal surgical procedures to remove pituitary tumors. The CCPD now averages 240 operations and over 2,000 outpatient visits annually, making it one of the most active and specialized pituitary treatment centers in the nation. Over the last decade, faculty members at the CCPD have published over 70 journal articles and two books, including the most recent evidence-based guidelines on management for nonfunctioning pituitary adenomas.

Sandeep Kunwar, MD, Lewis Blevins Jr., MD, and Manish Aghi, MD, PhD, combine their expertise in neurosurgery and neuroendocrinology at the California Center for Pituitary Disorders at UCSF.





# Brain and Spinal Injury Center



Using topological data analysis (TDA), UCSF BASIC researchers uncovered a novel subtype of mild (CT-negative) traumatic brain injury that was associated with high rates of post-traumatic stress disorder and degeneration of TBI clinical outcomes from three to six months after injury. By screening blood samples for biomarker discovery, the team identified several genetic predictors of this novel poor-recovery phenotype, including a *PARP1* single-nucleotide polymorphism (shown), among others.

## Artificial Intelligence Could Aid Diagnosis and Lead to Precision Traumatic Brain Injury Treatment

Traumatic brain injury (TBI) results in approximately 52,000 deaths, 257,000 hospitalizations and 2.2 million emergency department visits in the U.S. annually, according to the Centers for Disease Control and Prevention's Injury Center. UCSF is leading a National Institute of Neurological Disorders and Stroke-sponsored, multisite study called TRACK-TBI (Transforming Research and Clinical Knowledge in TBI) that aims to identify new diagnostic and prognostic markers, and to refine outcome assessments.

TRACK-TBI investigators – led by the UCSF Brain and Spinal Injury Center (BASIC) at Priscilla Chan and Mark Zuckerberg San Francisco General Hospital and Trauma Center – have used a unique computational technique to sift through big data and identify a subset of concussion patients with normal brain scans who may deteriorate months after diagnosis and develop confusion, personality changes and differences in vision and hearing, as well as post-traumatic stress disorder. This finding, which is corroborated by the identification of molecular biomarkers, is paving the way for a precision medicine approach to the diagnosis and treatment of patients with TBI.

### Expanding a Proven Technique to Biomedicine

In the study, which appeared in *PLoS One* on March 3, 2017, the researchers analyzed an unprecedented array of data, using a machine learning technology called topological data analysis (TDA), which provides a way to easily visualize patient differences across the full spectrum of traumatic brain injury, from concussion to coma.

Mapping of outcomes using TDA revealed that concussion, or mild traumatic brain injury, could be stratified into multiple subgroups with diverse prognoses. Among them was a large group of patients who, despite normal brain scans, demonstrated poor recovery and a tendency to get worse three to six months after the injury.

“These are patients with clear scans that would have been discharged from the hospital with nothing more than a recommendation to take over-the-counter medications,” says senior co-author Adam Ferguson, PhD, associate professor in the Department of Neurological Surgery. “By recognizing these patients as a distinct subgroup, clinicians may be able to anticipate future symptoms and treat them proactively.”

According to first author Jessica Nielson, PhD, also of the UCSF Department of Neurological Surgery, the most challenging symptoms to treat are those that are not apparent immediately after an injury. “Eventually we hope to identify treatment targets early after injury to prevent this gradual decline and boost our ability to intervene and improve outcomes for patients,” she says.

In addition to variants in *PARP1*, researchers found other biomarkers in patients' blood samples that were predictive of poor recovery, including *ANKK1* and *COMT*. These genes are associated with signaling by the neurotransmitter dopamine and may provide critical clues to recovery and drugs' responsiveness. A future goal of TRACK-TBI is to contribute to the design of clinical trials to develop therapeutic drugs for traumatic brain injury – perhaps even tailored to a patient's blood-based biomarkers.



## Drug Reverses Memory Failure Caused by Traumatic Brain Injury

In an unprecedented finding, UCSF scientists – including researchers from the Brain and Spinal Injury Center – used an experimental drug to completely reverse severe learning and memory impairments caused by traumatic brain injury (TBI) in mice. Surprisingly, the drug fully restored the ability to learn and remember in the brain-injured mice even when the animals were first treated as much as a month after injury.

The latter results are particularly striking, as most research on brain injury and stroke has suggested that treatments must be initiated as quickly as possible to preserve normal function.

The researchers say the new study offers a promising new avenue for the treatment of TBI in humans, which affects over 2 million individuals annually in the U.S. In addition to causing serious cognitive deficits, which can be short-lived or permanent, TBI is also a leading risk factor for the development of Alzheimer's disease and other forms of dementia. Yet dozens of seemingly promising treatments have failed in clinical trials, and no approved therapies are currently available.

### Two Types of Brain Injuries

The drug used in the new research, known as ISRIB, was discovered in 2013 in the laboratory of Peter Walter, PhD, professor of Biochemistry and Biophysics at UCSF and co-

senior author of the new study, which was published online in *Proceedings of the National Academy of Sciences*, on July 10, 2017.

"This is extraordinarily exciting," says Walter. "We think that ISRIB may uncover an untapped reservoir in the brain that allows damaged memory circuits to be repaired."

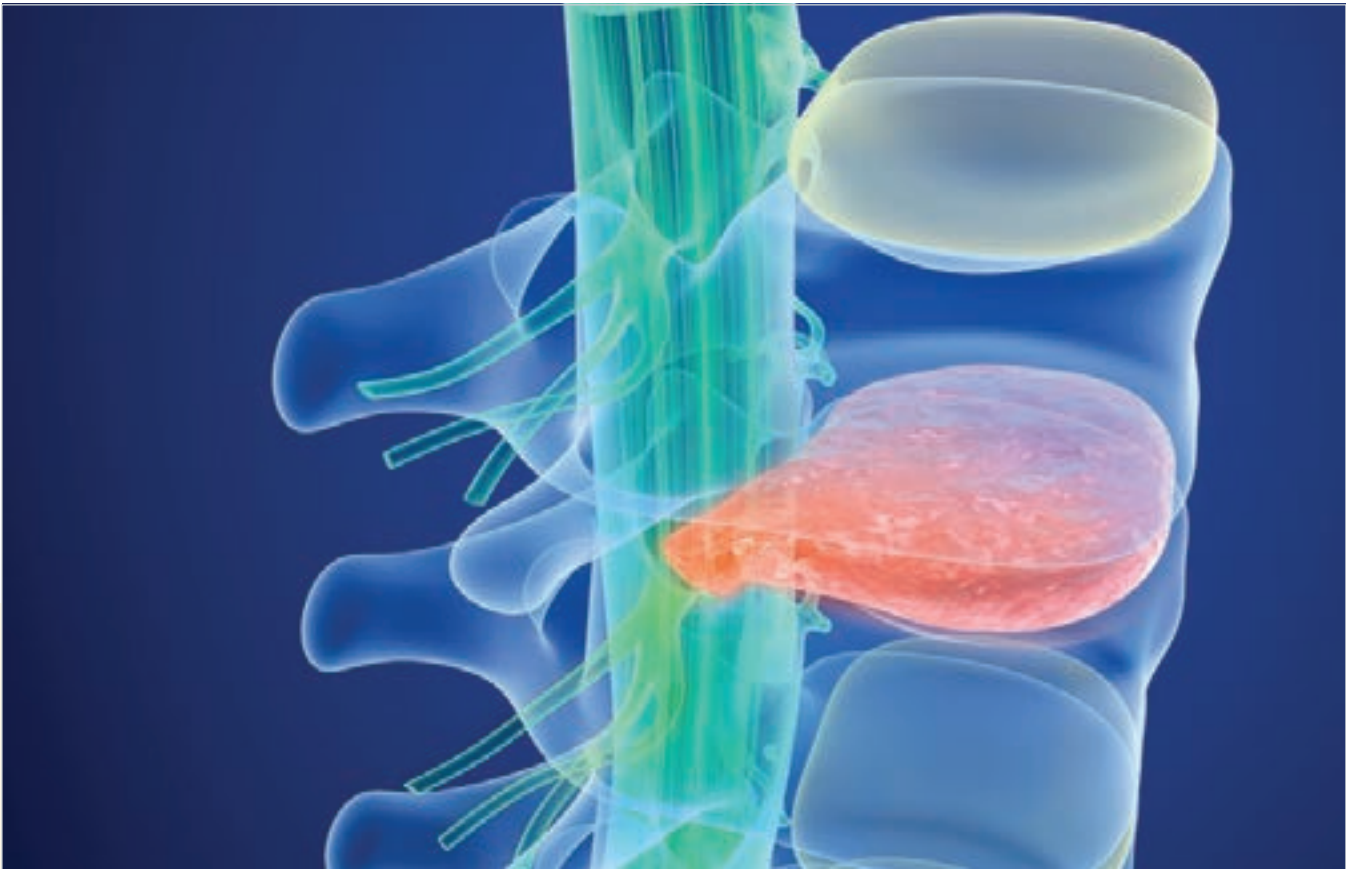
In the new research, scientists in the laboratory of co-senior author Susanna Rosi, PhD, professor of Physical Therapy and Rehabilitation Science and of Neurological Surgery at UCSF, tested whether ISRIB – which had previously been shown by Walter and his colleagues to enhance memory in normal mice – could improve the ability to learn and form memories in mice with two different types of brain injury, each of which is known to degrade learning and memory in humans.

"In general, animals with these injuries never learn well again," says Rosi, director of neurocognitive research at UCSF's Brain and Spinal Injury Center. "So it's remarkable that ISRIB could restore the ability to form new memories even when we delayed giving the drug for four weeks after the injury. This has not been considered possible. We need to do much more research, but I have high hopes that this drug can bring back lost memory capacity to our patients who have suffered brain injuries."

Susanna Rosi, PhD, studies the pathogenesis of cognitive deficits following central nervous system injury.



"I have high hopes that this drug can bring back lost memory capacity to our patients who have suffered brain injuries."



## TRACK-SCI Team Expands Its Network

Transforming Research and Clinical Knowledge in Spinal Cord Injury (TRACK-SCI) is a prospective study that enrolls all patients with acute traumatic spinal cord injury at Priscilla Chan and Mark Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG), with the aim of detailing acute care variables, intraoperative and intensive care unit monitoring, immune status and long-term outcomes. It

builds on the TRACK-TBI effort. This year UCSF Fresno became the first site in TRACK-SCI's planned expansion to sites beyond ZSFG as UCSF Fresno began enrolling patients in an observational spinal cord injury trial. The TRACK-SCI team will use a \$1 million special projects award from the Craig H. Neilsen Foundation to continue to expand to other sites.

## FAIR Data Sharing to Accelerate Discovery in Spinal Cord Injury Research

A paper published in *Experimental Neurology*, co-authored by UCSF Brain and Spinal Injury Center (BASIC) scientists leading the TRACK-SCI effort, described how rapid growth in data sharing should use "FAIR data principles." Such principles assert that if data is to have broad scientific value, then digital representations should be findable, accessible, interoperable and reusable (FAIR).

The paper described a 2016 workshop that the National Institute of Neurological Disorders and Stroke at the National Institutes of Health hosted in collaboration with the Open Data Commons for Spinal Cord Injury, aimed at creating a "FAIR share community." The workshop brought together junior-

and senior-level experts, including preclinical and basic SCI researchers, to examine the current landscape for data sharing in SCI research and sought to provide a path to its future.

In 2018, the Open Data Commons for Spinal Cord Injury will launch a multicenter, multispecies database of SCI research data spanning a wide spectrum of SCI severities, treatments and outcomes. To fully harness the potential of SCI big data, BASIC investigators – along with a variety of academic, government, philanthropic and industry sponsors – are building a digital infrastructure to democratize SCI data science, allowing outside researchers to access existing SCI big data, contribute their own data and access user-friendly tools for big-data analytics to facilitate knowledge discovery within SCI research.

## 2017 BASIC Publications

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Chief of Peripheral Nerve and Pain Surgery Line Jacques, MD (center), trains residents Caleb Rutledge, MD (left), and Darryl Lau, MD (right), during a peripheral nerve anatomy workshop.

## Kline Lectureship Highlights Cadaver Workshop on Peripheral Nerve Procedures

In October 2017, the Department of Neurological Surgery hosted its second annual cadaver workshop aimed at teaching residents and other UCSF physicians the posterior and anterior surgical approaches for peripheral nerve surgery. Renowned neurological surgeon David Kline, MD, of the Louisiana State University School of Medicine, attended this year's workshop, and the department is initiating an annual Kline Lecture on peripheral nerve topics.

# Pain and Peripheral Nerve Disorders

## Study to Test Dorsal Root Ganglion Stimulation for Complex Regional Pain Syndrome

UCSF neurosurgeon Line Jacques, MD, is co-leading a study to test whether dorsal root ganglion (DRG) stimulation can effectively manage intractable focal pain in the lower limbs due to complex regional pain syndrome (CRPS) types I and II.

"Our phase I study showed this procedure is safe, and I'm confident that the efficacy will bear out in our phase II study," says Jacques of the multisite study, which will take place at UCSF and St. Jude Medical Center and enroll approximately 100 patients. The researchers will compare an implantable DRG stimulation device with traditional neurostimulation.

CRPS affects the arms, legs, hands or feet and is usually the result of trauma or injury to the affected limb. The researchers are testing an FDA-approved system that

includes an implantable neurostimulator, its leads and an external device that monitors the stimulator and leads and adjusts the stimulation settings. Patients will undergo one three- to seven-day trial implant and, if there are no complications, will be able to undergo surgery for a permanent implant. They will then have follow-up visits at one, three, six and 12 months to monitor the efficacy of the device.

"Chronic, focal pain associated with peripheral nerve injuries is an enormous burden for patients," says Jacques. "Earlier studies have been very encouraging, and we believe that DRG stimulation is a better way to address these neuropathies because it's more site-specific – traditionally, we stimulate the spinal cord – and, so, gets directly at the area of nerve distribution."

"Our phase I study showed this procedure is safe, and I'm confident that the efficacy will bear out in our phase II study."



## Case Study

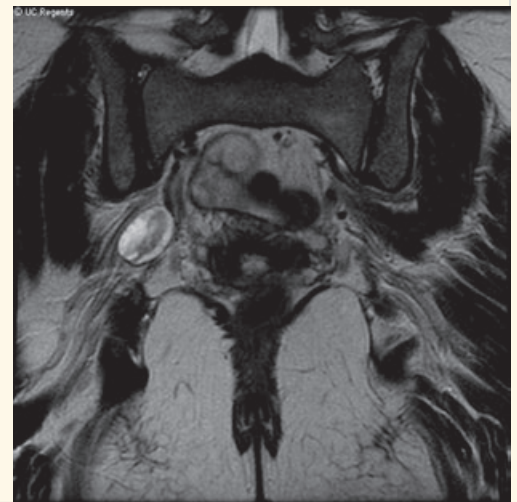
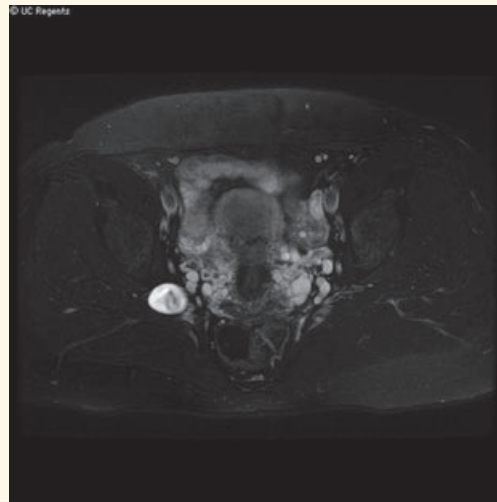
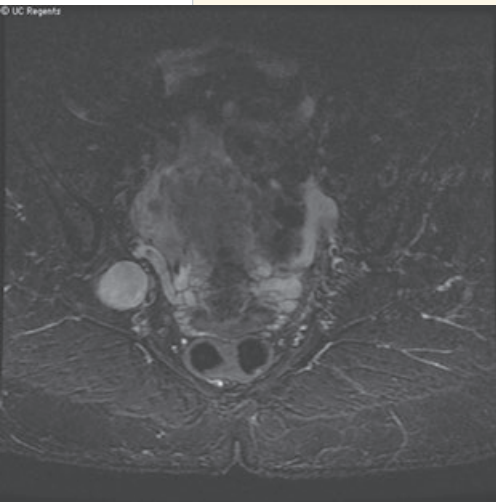
### Interdisciplinary Expertise Successfully Removes a Sciatic Notch Nerve Tumor

In the images below, UCSF neurological and colorectal surgeons collaborated on an abdominal surgical approach to resect a rare sciatic notch nerve tumor.

The patient was a middle-aged female who had experienced four years of right hip and buttock pain. In the six months prior to surgery, the pain had become progressively worse (in the 7-8/10 range), with tenderness at her right buttock

and occasional “electrical” shooting pains when changing positions. Lying down, sitting and standing for prolonged periods of time exacerbated her pain, and over-the-counter anti-inflammatories had been ineffective.

In the three months following the surgery, the patient reported pain relief and a return to her daily activities.





# Neurospinal Disorders

## The Value of Predictive Analytics for Complex Spine Surgeries

As the UCSF site director for the International Spine Study Group (ISSG), neurosurgeon Christopher Ames, MD, is at the center of a project to develop and test analytic models that predict complications, improvement and length of stay in candidates for complex spine surgeries. Such analytics could improve patient selection and counseling of patients and families, while also helping to determine proper length of stay and corresponding reimbursements.

Predictive modeling uses advanced computational methods to identify patterns in large data sets that can then be applied to individuals. In 2014, the ISSG began developing a number of different models that analyzed variables related to demographics, surgical data, quality of life and imaging.

In a study published in 2017 in the *Journal of Neurosurgery: Spine*, the ISSG was able to predict with 87 percent accuracy whether major or perioperative complications

would occur following adult spinal deformity surgery. In another study, published in 2016 in *Spine Deformity*, their model predicted with 86 percent accuracy either proximal junction failure or clinically significant proximal junctional kyphosis. Ames adds that because psychosocial factors are also an important consideration, it will be necessary to validate and standardize clinical outcome assessments that measure overall mental health and well-being.

“Building accurate predictive models is critical to prevent incentives for providers to withhold care in value-based care models and for us to be able to better counsel our patients on the risk-benefit of surgery and expectations for recovery,” says Ames. “These models also have powerful implications for a wide range of public health issues, ranging from health insurance to informed consent.”

“Building accurate predictive models is critical to prevent incentives for providers to withhold care in value-based care models and for us to be able to better counsel our patients on the risk-benefit of surgery and expectations for recovery.”

“Recovery time is considerably less using minimally invasive anterior and staged posterior surgery to correct spinal deformity.”

## Minimally Invasive Surgery Creates Options for Older Patients with Scoliosis

“Minimally invasive surgery enables us to correct significant scoliosis in older adults – a condition we are seeing with increased frequency in that population,” says UCSF neurosurgeon Dean Chou, MD.

In the past, complex deformity procedures were often considered off-limits for older adults, given the assumed risks of an invasive surgery. The refinement of a minimally invasive anterior procedure, which requires only a two- to three-inch incision, means that healthy patients up to age 80 can reasonably consider how such a procedure could positively affect their quality of life, says Chou.

“Recovery time is considerably less using minimally invasive anterior and staged posterior surgery to correct spinal deformity,” says UCSF neurosurgeon Praveen Mummaneni, MD. “There is less blood loss and less postoperative pain, and instead of spending a week in the ICU, these patients are mobilized early postoperatively. Moreover, instead of taking six months to recover, they might be back to normal activity within three months.”

Neurosurgeon Aaron Clark, MD, PhD, specializes in minimally invasive surgery for the spine. Minimally invasive operations can often be done as outpatient procedures at UCSF’s Mount Zion campus.

However, not all patients are candidates for minimally invasive correction of adult scoliosis. The minimally invasive spinal deformity (MISDEF) algorithm helps to select the appropriate surgical candidates. Chou and Mummaneni have published a number of papers documenting the outcomes and factors for success in this population, including:

Mummaneni PV, Shaffrey CI, Lenke LG, Park P, Wang MY, La Marca F, Smith JS, Mundis GM Jr, Okonkwo DO, Moal B, Fessler RG, Anand N, Uribe JS, Kanter AS, Akbarnia B, Fu KM; Minimally Invasive Surgery Section of the International Spine Study Group. The minimally invasive spinal deformity surgery algorithm: a reproducible rational framework for decision making in minimally invasive spinal deformity surgery. *Neurosurg Focus*. 2014;36(5):E6.

Uribe JS, Beckman J, Mummaneni PV, Okonkwo D, Nunley P, Wang MY, Mundis GM Jr, Park P, Eastlack R, Anand N, Kanter A, Lamarca F, Fessler R, Shaffrey CI, Lafage V, Chou D, Deviren V; MIS-ISSG Group. Does MIS surgery allow for shorter constructs in the surgical treatment of adult spinal deformity? *Neurosurgery*. 2017;80(3):489-497.

DiGiorgio AM, Edwards CS, Virk MS, Mummaneni PV, Chou D. Stereotactic navigation for the prepsaos oblique lateral lumbar interbody fusion: technical note and case series. *Neurosurg Focus*. 2017;43(2):E14.



## A Quality Outcomes Database for Spondylolisthesis

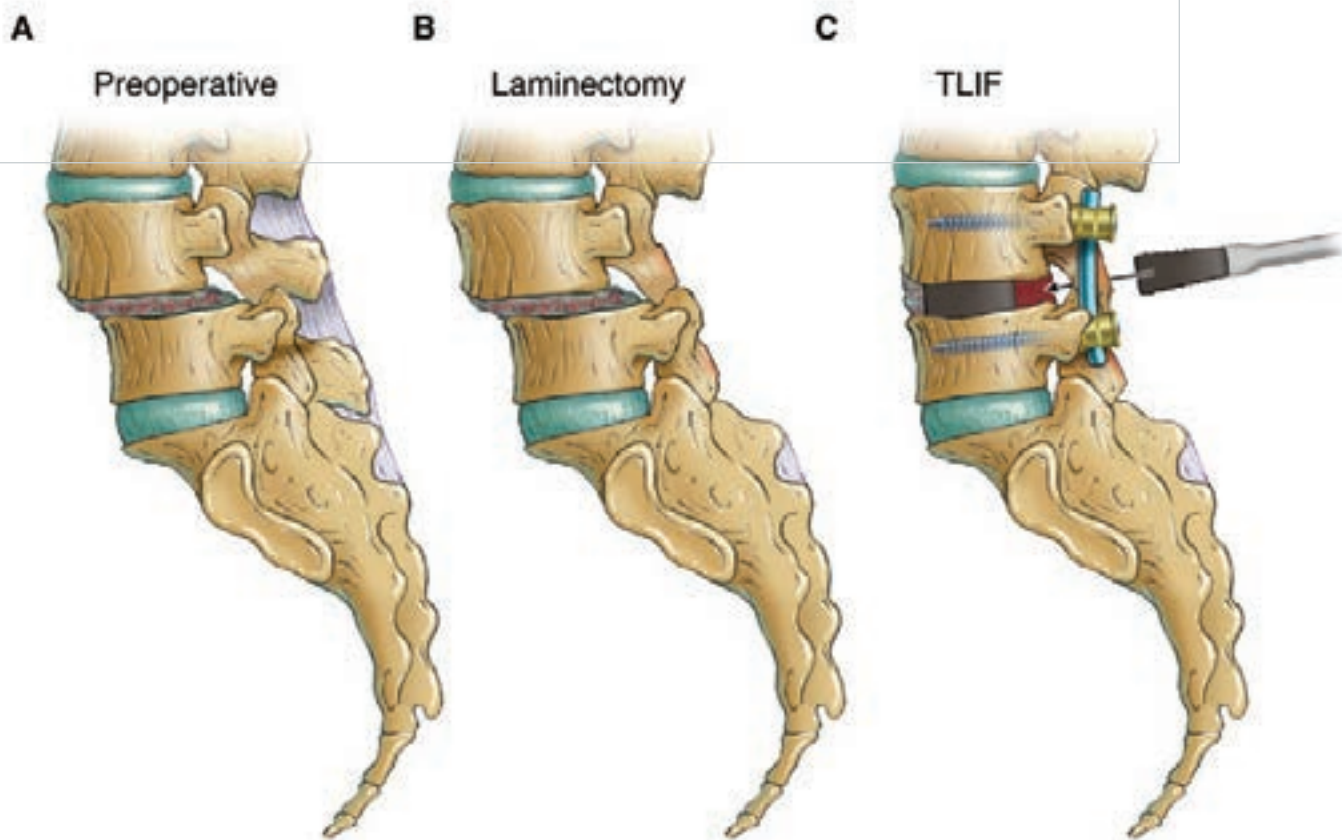
As advances in minimally invasive hardware, navigation systems and intraoperative CT scans make spinal decompression and/or fusion a very real possibility for increasing numbers of patients, it is important to understand how these changes affect patient selection. To that end, UCSF is one of the lead enrolling centers for a multicenter American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) spine section and NeuroPoint Alliance study trying to determine the factors that best identify the need for fusion in patients with spondylolisthesis.

In 2017, the research team for the study presented at a series of meetings throughout the country on topics that included:

- Lumbar Fusion Versus Laminectomy for Spondylolisthesis: Lessons Learned from the AANS/CNS Spine Section Study Group's Analysis of the N<sup>2</sup>QOD Registry
- Obesity Worsens Patient Reported Outcomes Following Surgery for Degenerative Lumbar Spondylolisthesis: An Analysis of the Quality Outcomes Database

Mummaneni PV, Bisson EF, Kerezoudis P, Glassman S, Foley K, Slotkin JR, Potts E, Shaffrey M, Shaffrey CI, Coric D, Knightly J, Park P, Fu KM, Devin CJ, Chotal S, Chan AK, Virk M, Asher AL, Bydon M. Minimally invasive versus open fusion for Grade I degenerative lumbar spondylolisthesis: analysis of the Quality Outcomes Database. *Neurosurg Focus*. 2017;43(2):E11.

(A) Artist illustration of degenerative L4-5 grade 1 spondylolisthesis. (B) Artist illustration depicts decompression-only surgery involving L4 and L5 decompressive laminectomies. (C) Artist illustration demonstrates an L4-5 transforaminal lumbar interbody fusion (TLIF), a surgical option that includes a fusion procedure in addition to decompression.







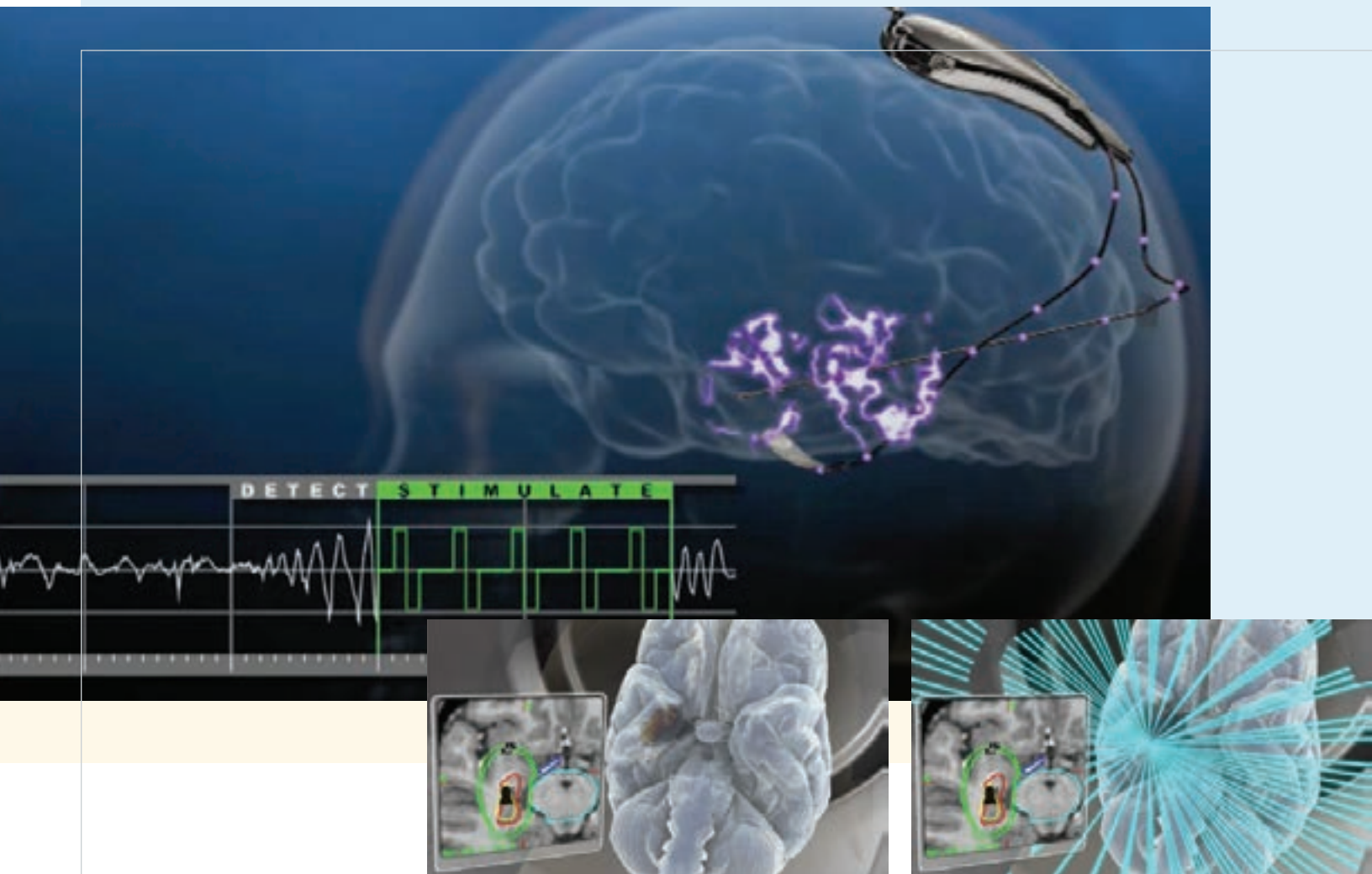
# Epilepsy

## Minimally Invasive Approaches Expand Use of Epilepsy Surgeries

When UCSF neurosurgeon Edward Chang, MD, co-edited the 2016 release of a book on minimally invasive epilepsy surgery, he hoped to make clear that patients with medically refractory epilepsy have a full menu of effective surgical options. Medically refractory patients make up about one-third of all epilepsy cases, and research has established that surgical interventions can significantly reduce seizure occurrence, thus reducing the corresponding morbidity, cognitive decline and premature death.

Surgery is particularly effective for patients with temporal lobe epilepsy. “For example, multiple studies have shown that surgical resection in patients with mesial temporal sclerosis can result in seizure-freedom rates up to 60 percent to 80 percent after two years, and up to 50 percent at 10 years following surgery,” says Chang. “Newer, minimally invasive procedures can offer similar benefits and, perhaps, garner more acceptance of surgery by

“Multiple studies have shown that surgical resection in patients with mesial temporal sclerosis can result in seizure-freedom rates up to 60 percent to 80 percent after two years, and up to 50 percent at 10 years following surgery.”



Above: Responsive neurostimulation uses a programmable device that senses abnormal electrical activity in the brain and delivers electrical stimulation to terminate seizures before a patient experiences symptoms. Below: Gamma Knife radiosurgery delivers finely focused beams of radiation to the area of the brain known to be causing seizures.

both patients and referring physicians, many of whom still are concerned about risk, despite numerous studies documenting relatively low morbidity for epilepsy surgery.”

The set of “minimally invasive” techniques spans open surgical procedures, ablative procedures, invasive monitoring and neuromodulation. “Together, they represent exciting and novel developments in epilepsy surgery aimed at minimizing the associated morbidities of surgical intervention while capitalizing on surgery’s potential benefits for patients with medically refractory epilepsy,” says Chang.

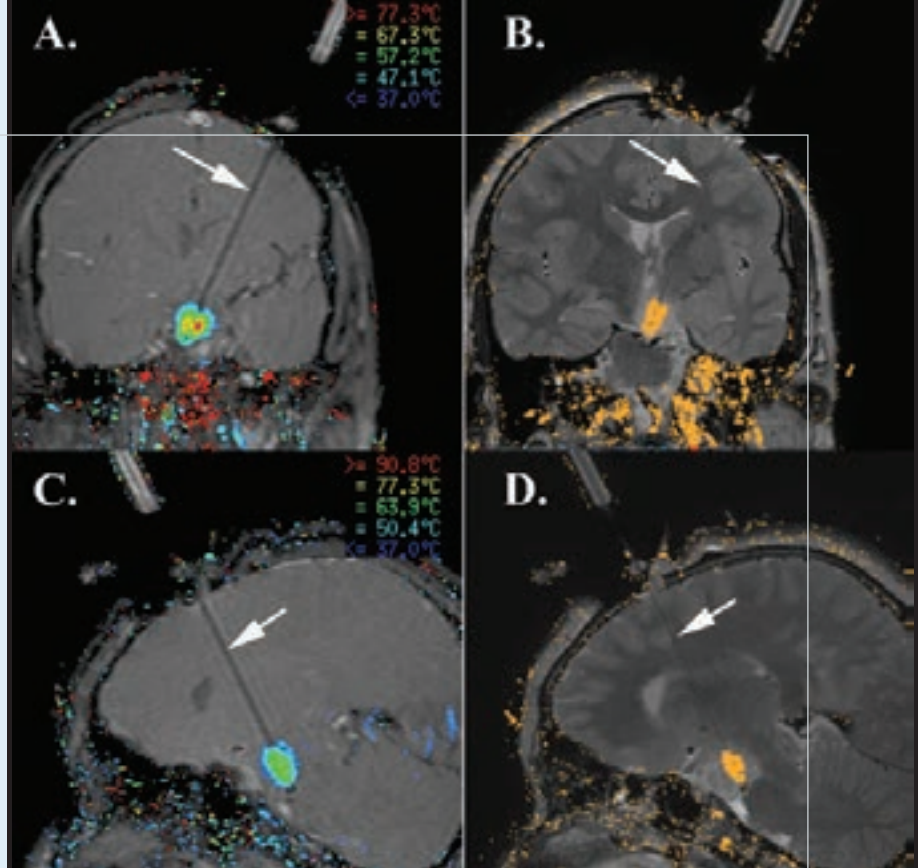
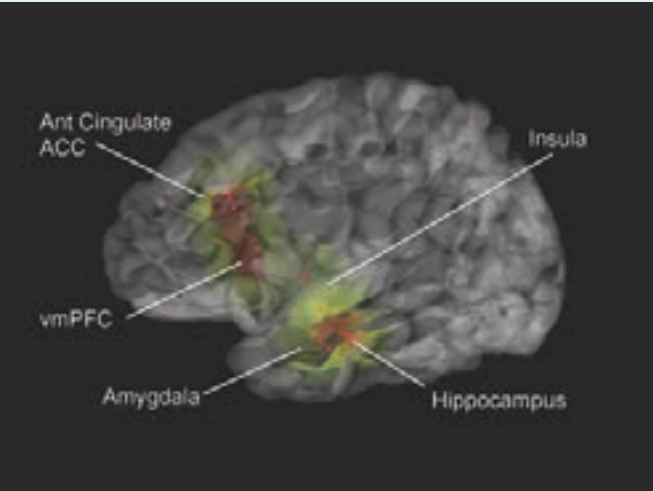
According to the National Association of Epilepsy Centers, UCSF completes more epilepsy surgeries than any other hospital or medical center in the West – a distinction made possible, in part, by experience with a number of these minimally invasive techniques.

That experience begins with the ability to pinpoint seizure activity prior to surgery. Stereoelectroencephalography plays a key role here, because precise implantation of electrodes yields recording of electrical seizure-related activity not possible using traditional recording methods. “It enables us to evaluate many patients for surgery who were once believed to be poor candidates,” says Chang.

Similarly, intraoperative brain mapping – pioneered at UCSF – identifies and avoids injury to sites of language, motor and sensory function, thus permitting the surgeon to remove focal points of epileptic activity to the maximum extent possible, while minimizing ill effects.

Once the locus of seizure activity is clear, says Chang, surgeons can offer patients a number of options tailored to the type and location of seizure activity. He notes:

Stereoelectroencephalography is a cutting-edge technology used to localize seizures and is less invasive than the standard subdural grid implantation.



Laser thermal ablation for epilepsy uses an MR-compatible laser fiber to heat and destroy small, well-defined areas of abnormal tissue.

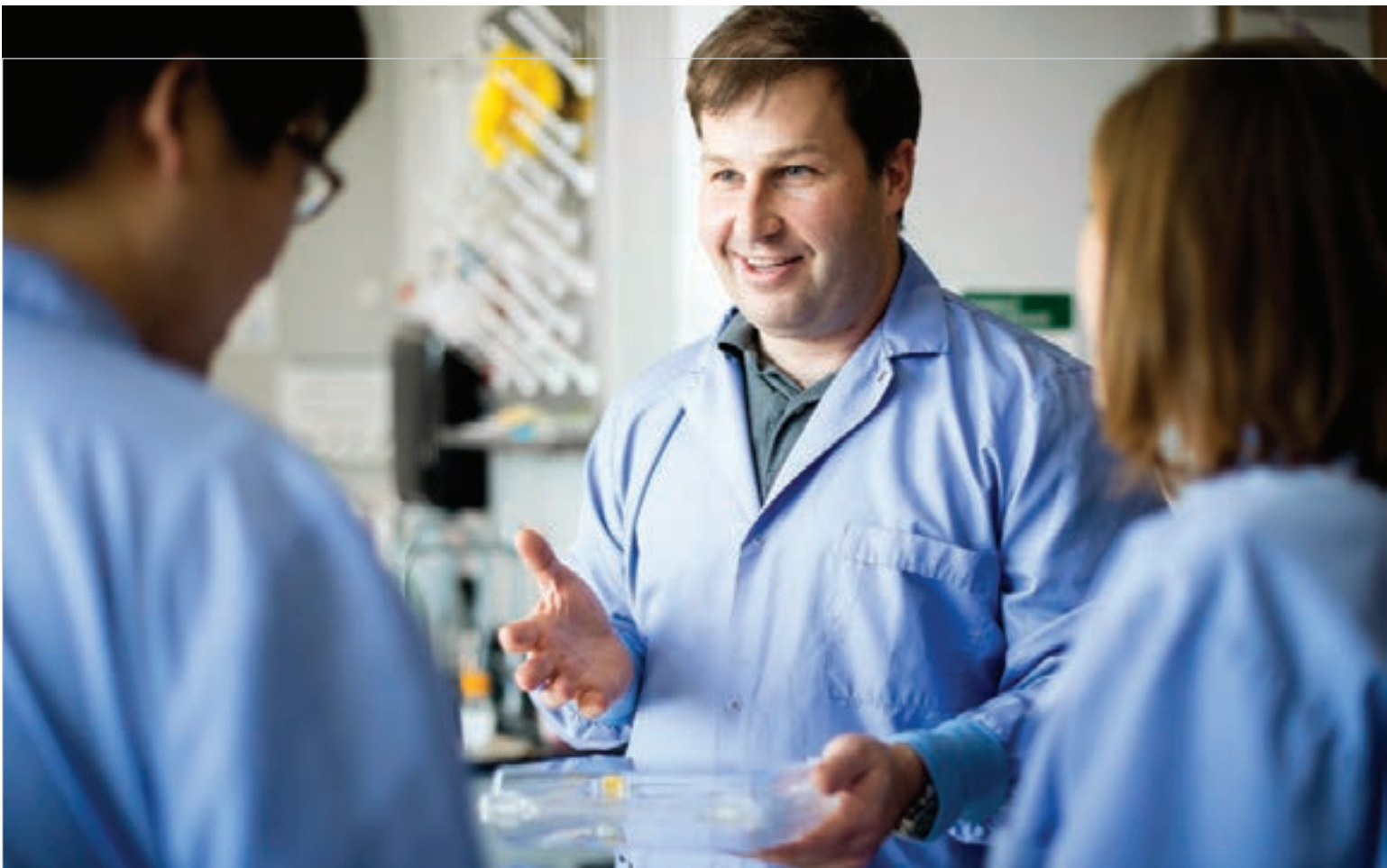
“There is increasing evidence that radiosurgery, ablation and neural stimulation approaches can approximate the same types of results as traditional open surgeries and, so, are very valuable options for long-suffering patients.”

- UCSF was the lead institution in the randomized, controlled Radiosurgery or Open Surgery for Epilepsy trial, which compared radiosurgery (focused radiation, Gamma Knife radiosurgery) with standard surgical care for temporal lobe epilepsy. The study concluded that radiosurgery is an effective treatment for temporal lobe epilepsy and is a viable option for properly selected patients.
- UCSF is also one of the few centers in the country with deep experience in MRI-guided laser interstitial thermotherapy, a technique in which surgeons use a small laser fiber to destroy a well-defined area of brain tissue that is causing seizures. The procedure leaves the surrounding tissue unharmed and is particularly effective for mesial temporal sclerosis and hypothalamic hamartoma.
- Finally, UCSF is among the world leaders in the use of responsive neurostimulation (RNS), in which an implantable device detects seizure-related electrical activity in the brain

and responds immediately by delivering imperceptible levels of electrical stimulation to prevent seizures before they start. “RNS works well for patients with seizures arising from more than one region in the brain, or from a region that can’t be safely removed by surgery,” says Chang. “Thanks to optimal patient selection, advanced surgical expertise and high-quality outpatient follow-up care, including a dedicated RNS clinic, our RNS patients have had an average seizure reduction of 80 percent. This surpasses the 48 percent to 66 percent seizure reduction reported in long-term clinical trials.”

He adds that while some questions remain about these minimally invasive procedures, “There is increasing evidence that radiosurgery, ablation and neural stimulation approaches can approximate the same types of results as traditional open surgeries and, so, are very valuable options for long-suffering patients.”





# Center for Neural Engineering and Prostheses

A collaboration between UCSF and UC Berkeley, the Center for Neural Engineering and Prostheses is a multidisciplinary effort aimed at conducting scientific research, developing neural prosthetic technology, efficiently translating this work into human clinical trials and training the next generation of neural engineers and technicians.

For this year's report, we speak with Loren Frank, PhD, whose work aims to understand how activity and plasticity in neural circuits underlie the making of memory, learning and the ability to use learned information to make decisions.



## Why study memory and learning?

We study memory because it's fundamental to who we are as human beings and to every decision we make in our daily lives – and when memory fails, as in Alzheimer's or other diseases, the consequences are devastating. Right now we can do very little to help people with those sorts of problems, in part because we don't know how the brain works, and it's hard to fix something if you don't know how it works.

## At this point, what do we know about how the brain forms and retrieves memories?

We've known for a while that memories are formed in the hippocampus, but the specific things that happen in the brain when a memory is formed and retrieved are only starting to become clear. One clue is that memory retrieval is fast – we can remember things in much less time than it took to form the memory in the first place.

That remarkable speed led us to focus on the activity of groups of neurons and to search for something fast that could be part of a memory. That worked. Our rat studies allowed us to see specific patterns of brain activity when memories are formed, and then to see those patterns “replayed” at high speed later, at times where memory retrieval could be happening. When we disrupted these patterns, it impaired rats' ability to recall and remember.

But we knew this was only one small part of the picture, because memories tie together things like smell and sight and sound and meaning, which are processed in different parts of the brain. The hippocampus helps create a web that brings activity patterns together across all parts of the brain. It's an incredibly complicated and distributed process. As we began to look at brain areas outside of the hippocampus, we found that when it looks as though the hippocampus is replaying a memory, the neurons in other parts of the brain seem to replay aspects of that memory as well.

These were exciting findings, but they also highlighted a fundamental limitation of our work. With traditional, hard-metal electrodes, we could record reasonably sized populations of neurons in one area of the brain at a time, but our tools were nowhere near good enough to track all of the activity across the brain that makes up a memory. That led us to a long-lasting collaboration with a group at Lawrence Livermore Labs. Together, we've built a whole new system that starts with soft, flexible recording devices – polymer probes – which avoid the damage and disruption of traditional electrodes and enable us to implant many more electrodes across many more regions of the brain and attain high-quality signals that pinpoint the activity of single neurons over long periods of time.

## What are the implications of this work for patient care?

There are many. One of the things these studies have helped us understand is that the brain does fundamentally different things at different times. By documenting how this works, we can devise new neurological therapies or tailor existing therapies more closely to the way our brain operates, so treatments can interact with the brain in real time, rather than just responding to one particular type of activity.

For example, in a collaboration with Dr. Yadong Huang, of the Gladstone Institute of Neurological Disease, we are working with mouse models to track how Alzheimer's disease disrupts memories. We believe this work could open the door to therapies where we could implant something in the brain that senses the disruptions and injects functional patterns of activity to restore the ability to make and retrieve memory.

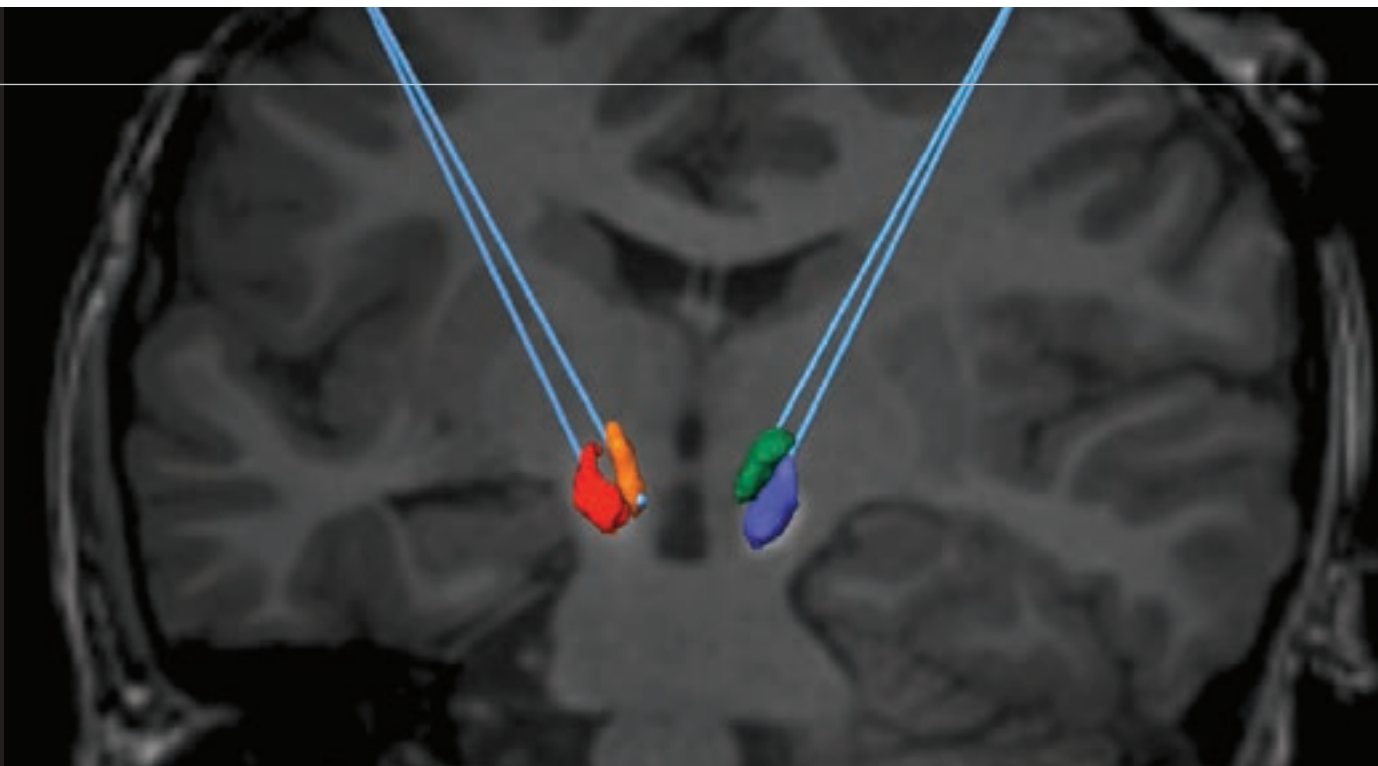
Of course, this raises important ethical questions about if and when such treatments would be acceptable. But if we can come up with a sound, ethical way to help the brain work better, this is worth pursuing when you consider the devastating suffering of patients with neurological or psychiatric diseases.

## Do the polymer probes you've developed have their own clinical implications?

In principle, with the right ethical safeguards, they could be used in humans to provide much greater resolution and understanding of both the surface and deeper structures of the brain.

With these types of projects in mind, we are currently working with Lawrence Livermore and Lawrence Berkeley Labs about how we might pull together all of this incredibly broad expertise on an ongoing basis for all three institutions. Perhaps in the long run, a patient could come in with a specific need, and a group of these experts could create a specialized device for the patient that helps him or her lead a more normal life. We're hoping to build something that would make that possible here in the Bay Area.





# Pediatric Neurosurgery

## Trial Opens for Convection-Enhanced Delivery for Diffuse Intrinsic Pontine Glioma

A recently opened phase I and early-efficacy study will test the use of convection-enhanced delivery (CED) of nanoliposomal irinotecan (nal-IRI), using real-time imaging with gadolinium for children with newly diagnosed diffuse intrinsic pontine glioma (DIPG). Treatment starts after completion of standard radiotherapy (within four to six weeks), with the intent to treat via CED every four to six weeks.

The trial aims to establish CED as a viable technology for children with DIPG and to determine the recommended phase II dose of nal-IRI.

CED uses a pressure gradient to distribute drugs via bulk flow of fluid through the interstitial space of tissues, and typically results in markedly improved distribution of infused therapeutics within the brain as compared to non-CED injections or the use of drug-eluting polymers, both of which depend mostly on diffusion for drug distribution. CED also obviates the challenges of systemic agents crossing the blood-brain barrier while minimizing systemic exposure and toxicity.

Nanoliposomes are microscopic phospholipid nanoparticles with a bilayered membrane structure that facilitate the administration of therapeutic agents. For the treatment of DIPG, nanoliposomes provide several advantages: (a) they prolong drug half-life and therefore increase exposure time of tumor cells to the drug, (b) they can be co-loaded with gadolinium, which allows real-time imaging and assessment of drug tumor distribution for each individual patient, and (c) they make co-loading or co-administration of several therapeutic agents possible, facilitating future multiagent therapy.

In prior work, the researchers have shown that CED of nanoliposomal irinotecan results in a significant survival benefit compared to intravenous delivery in a brain stem tumor in an animal model. In addition, it has also been shown that CED of nanoliposomal irinotecan leads to clinically significant target volume distributions in adult patients with glioblastoma.

## Pacific Pediatric Neuro-Oncology Consortium Clinical Trials

The Pacific Pediatric Neuro-Oncology Consortium (PNOC) is a network of 18 leading children's hospitals that was started by neuro-oncologists at UCSF's Pediatric Brain Center to accelerate the process of testing new therapies tailored to the cellular pathways or mutations of each child's specific

tumor. UCSF continues to lead PNOC, which offers rapid enrollment in clinical trials, in conjunction with the family-oriented care delivered by UCSF's team of dedicated physicians, nurses, social workers and neuropsychologists.

### Current Trials

#### • Newly diagnosed tumors

- Diffuse intrinsic pontine glioma (DIPG)
  - Molecular Profiling for Individualized Treatment Plan for DIPG (PNOC 003)
  - Convection Enhanced Delivery (CED) with Irinotecan Liposome Injection Using Real Time Imaging in Children with DIPG (PNOC 009)
  - H3.3K27M Peptide Vaccine for Children with Newly Diagnosed DIPG and Other Gliomas (PNOC 007)

#### • Recurrent disease

- Medulloblastoma and primitive neuroectodermal tumor (PNET)
  - Modified Measles Virus (MV-NIS) for Children and Young Adults with Recurrent Medulloblastoma or Recurrent Atypical Teratoid/Rhabdoid Tumors (ATRT; PNOC 005)
- Recurrent glioma
  - Safety, Phase 0, and Pilot Efficacy Study of Vemurafenib, an Oral Inhibitor of BRAFV600E, in Children and Young Adults with Recurrent/Refractory BRAFV600E- or BRAF Ins T Mutant Brain Tumors (PNOC 002)
  - Phase II Study of Everolimus for Recurrent or Progressive Low-Grade Gliomas in Children (PNOC 001)

#### • Trials studying novel neuroimaging techniques

- Pilot Study of Safety and Toxicity of Acquiring Hyperpolarized Carbon-13 Imaging in Children with Brain Tumors (PNOC 011)



## First Three Children Receive Gene Therapy Trial for AADC Deficiency

In a first-of-its-kind clinical trial for patients aged 5 to 18 years old, researchers at UCSF have infused adeno-associated viral vector carrying the aromatic L-amino acid decarboxylase (AADC) gene (AAV2-AADC) into the putamen of three children with AADC deficiency, a rare genetic disorder. By increasing the expression of AADC in the brain, physicians hope to reduce symptom severity and improve quality of life for these children, who suffer from symptoms that include developmental delay, autonomic dysfunction, cognitive disabilities and severe movement disorders resembling dystonia or Parkinson's disease.

The current trial's use of convection-enhanced delivery is enabling coverage of a larger volume of brain tissue than can be achieved with direct injection; the procedure is visualized in real time on intraoperative MR images to ensure that the correct dose covers the target area.

While a trial of the AAV2-AADC gene therapy for adults with Parkinson's disease has shown encouraging results (see page 32), "The target in the pediatric trial is different," says Nalin Gupta, MD, PhD, the trial's principal investigator. "We will follow these patients carefully, over an extended period of time to determine long-term efficacy."



## Advances in the Treatment of Hypothalamic Hamartoma

For patients with hypothalamic hamartoma, pediatric neurosurgeons at UCSF have completed six laser interstitial thermotherapy (LITT) treatments using real-time, intraoperative MRI. Hypothalamic hamartoma is a rare epilepsy characterized by spells of involuntary laughter with interval irritability and depressed mood.

In LITT, surgeons use a very small laser fiber to destroy a well-defined area of abnormal brain tissue causing seizures, leaving the surrounding tissue unharmed.

“In addition, the intraoperative MRI system we use is important because it eliminates the need for using a head frame in children. It also allows us to monitor each electrode as it is placed into the brain, while other techniques require trips back and forth from the operating room to the scanner,” says UCSF neurosurgeon Kurtis Auguste, MD. “The software directs us with submillimeter precision, in real time, so we can float a wire to the middle of the hamartoma and make on-the-fly adjustments as needed.”



## Responsive Neurostimulation for Teens and Children with Epilepsy

The UCSF Department of Neurological Surgery is a world leader in the use of responsive neurostimulation (RNS). Now, the department has begun pioneering use of this technology in children, with the help of a close, collaborative relationship with NeuroPace, a Silicon Valley company that developed, refines and manufactures RNS technology.

The RNS system is particularly well suited for patients with seizures arising from more than one region in the brain, or from a region that cannot be safely removed by surgery. Success depends on precise placement of electrodes in the brain – first to map seizure activity and then to place the device itself – and on personalized device programming. Our outstanding outcomes in adults result from optimal patient selection, advanced surgical expertise and high-quality outpatient follow-up care, including a dedicated RNS clinic, among the first of its kind in the nation.

The UCSF pediatric team recently initiated a series of RNS implantations in children, with the hope of eventually adapting the technology to very young children in need. While the device awaits FDA approval for children, UCSF is one of the few centers in the country testing it in the pediatric setting, which poses some unique surgical challenges.

“We are working on retrospective surveys of children’s skulls to help engineers tailor individual devices and screws that we can safely anchor to a child’s skull, which is quite thin compared to an adult’s,” says UCSF pediatric neurosurgeon and Director of the UCSF Pediatric Epilepsy Surgery Program Kurtis Auguste, MD. “In addition, precise neuroimaging has been essential for completing these procedures in young people. I hope by the end of my career that we can move away from removing brain tissue and be able to lay down a precise lattice of electrodes to successfully modulate seizure activity.”

“We hope to determine if the thalamus is a more effective DBS target for these patients, to understand why some kids with secondary dystonia respond and others don’t and to see if we can establish unbiased quality-of-life markers for the success of these procedures.”

## Clinical Trial Seeks to Improve Efficacy of DBS for Secondary Dystonia

Deep brain stimulation (DBS) is quite effective in the treatment of primary dystonia, but for secondary dystonia – which has a variety of causes, including perinatal injuries (cerebral palsy), central nervous system infections, traumatic brain injuries and metabolic, neurodegenerative and mitochondrial conditions – DBS results have been, at best, mixed. Researchers do understand, however, that younger age at the time of surgery (less than 21 years old) and shorter symptom duration are predictive factors for a good postoperative outcome.

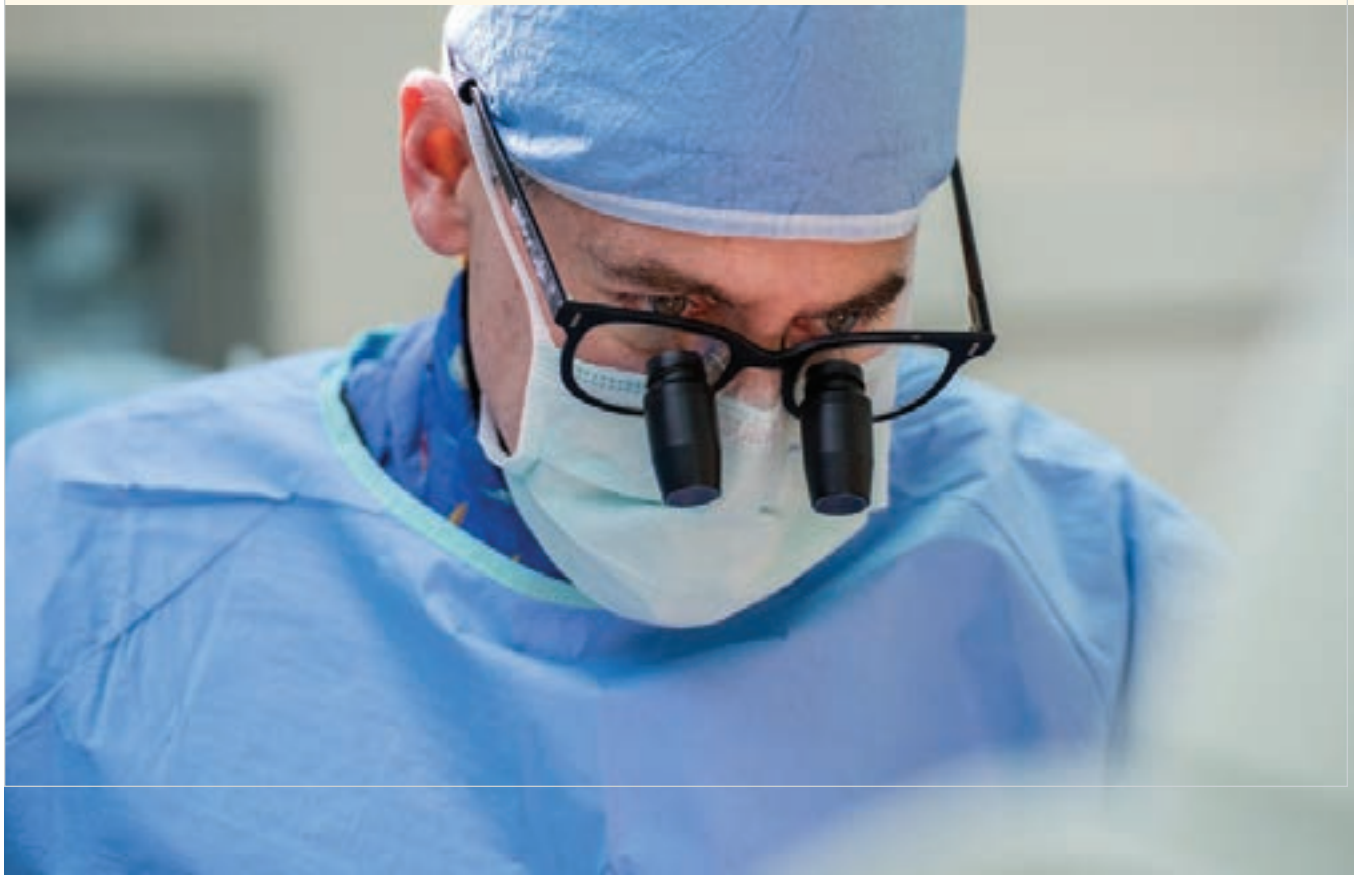
That’s why pediatric neurologist and movement disorders expert Amy Viehoveer, MD, PhD – part of an expanding pediatric movement disorders clinical team at UCSF – is leading a clinical trial that will blend DBS advances with insights from 30- to 40-year-old research in an attempt to extend the effective reach of DBS and ease the considerable suffering of her young patients.

The older research, completed before the development of DBS technology, showed that creating small holes in the thalamus effectively reduced movement disorder symptoms,

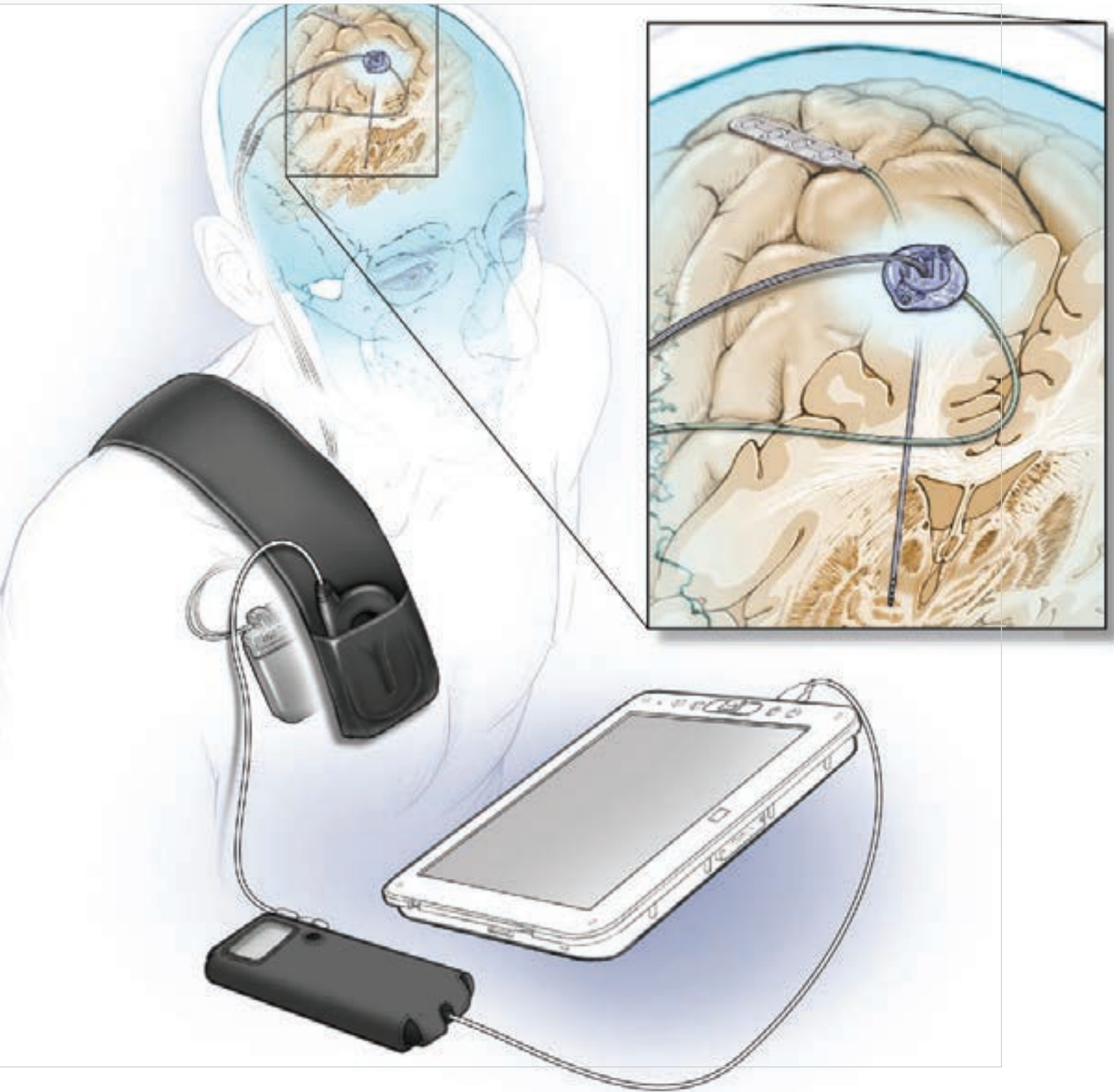
but that the side effects were unacceptable. Researchers theorize, however, that the symptom reduction in the older studies occurred because pathways in the globus pallidus and cerebellum are associated with the disruptive circuitry involved in secondary dystonia – and both pathways lead to the thalamus. In response, a few clinical sites have begun targeting the thalamus with DBS even though this is not an FDA-approved target for DBS systems. But Viehoveer believes hers is the first clinical study trying to systematically gather quality data to help guide patient selection for the procedure in children, teens and young adults.

“We hope to determine if the thalamus is a more effective DBS target for these patients, to understand why some kids with secondary dystonia respond and others don’t and to see if we can establish unbiased quality-of-life markers for the success of these procedures,” says Viehoveer. She notes that typical quality-of-life markers do not fit neatly with what many patients and families consider genuine improvement for patients with dystonia.

UCSF neurosurgeon Philip Starr, MD, PhD, is a leading expert in deep brain stimulation for adult and pediatric movement disorders.



# Movement Disorders



A closed-loop stimulation system for Parkinson's disease delivers electrical stimulation only when it detects abnormal brain signals associated with the onset of symptoms.



“The system responds in real time to changing brain signals, much like responsive neurostimulation for epilepsy.”

## Trial to Test Closed-Loop Brain Stimulation for Parkinson’s Disease

In early 2018, a research team at UCSF will begin enrollment for a clinical trial aimed at improving deep brain stimulation (DBS) for Parkinson’s disease by incorporating a closed-loop stimulation system. The trial is funded by a new UH3 grant from the National Institutes of Health’s Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative.

“The system responds in real time to changing brain signals, much like responsive neurostimulation for epilepsy,” says UCSF neurosurgeon Philip Starr, MD, PhD. “The device is algorithm-driven and will auto-adjust when it detects changes. We and others have completed some in-clinic testing, but until this trial, no one has completed a long-term ambulatory trial of this method.”

In the trial, during DBS surgery, surgeons will place an additional electrode over the motor cortex, looking for personalized signatures in each patient’s brain rhythms. Once the surgeons have identified the signatures, patients will go home with the implanted closed-loop system. The study will use its results to define the technical characteristics required for the design of future DBS devices in the hope that these systems can both simplify the therapy and make it more effective. For the former, it could avert laborious trial-and-error manual programming by clinicians associated with DBS today. For the latter, the closed-loop system should be more sensitive to changing brain needs, including modulating down when stimulation becomes less necessary, thereby reducing adverse effects.

“Most people think of Parkinson’s as a movement disorder, but it is in fact a neuropsychiatric disorder that includes problems with mood, thinking, anxiety, impulsivity and even a form of addiction to medication known as dopamine dysregulation syndrome.”

## Cortical Stimulation for Depression and Anxiety in Parkinson’s Disease

Neurosurgeons at UCSF have begun studying the use of cortical stimulation to treat depression and anxiety in patients with Parkinson’s disease.

The project is part of a \$26 million, multi-institutional research program funded by the Defense Advanced Research Projects Agency (DARPA), a major partner in support of former President Barack Obama’s BRAIN Initiative, under the agency’s Systems-Based Neurotechnology for Emerging Therapies (SUBNETS) program. The umbrella study employs advanced technology to characterize human brain networks more broadly and to better understand and treat a range of common debilitating psychiatric disorders, focusing first on anxiety disorders and major depression.

The overall strategy has been first to identify brain-signaling pathways specifically associated with anxiety and depression, then to develop devices to provide precise stimulation therapies that guide 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.

UCSF neurosurgeon Philip Starr, MD, PhD, a member of the team that regularly treats Parkinson’s patients with deep brain stimulation implants, says, “Most people think of Parkinson’s as a movement disorder, but it is in fact a neuropsychiatric disorder that includes problems with mood, thinking, anxiety, impulsivity and even a form of addiction to medication known as dopamine dysregulation syndrome. These symptoms are as fundamental a part of the disorder as slow movement or tremor.”

Moreover, Starr says, the psychiatric symptoms of Parkinson’s disease wax and wane, so the recordings, which will be made by high-resolution devices resting directly on patients’ brains, should reveal in detail how brain activity changes when patients enter a depressed or anxious state, data that have been unobtainable before recent technological advances. Because these data are so valuable and so challenging to obtain, all recordings – stripped of patients’ identities – will be deposited in accessible databases for the use of other researchers.



Paul Larson, MD, and Alastair Martin, PhD, with a ClearPoint SmartFrame device – part of a system they helped develop that allows deep brain stimulation leads and drug-delivery catheters to be implanted under real-time visualization inside an MRI unit.

## Interim Results of Phase Ib Gene Therapy Trial for Advanced Parkinson's Disease

An ongoing clinical trial at UCSF for advanced Parkinson's disease is evaluating the use of gene therapy to increase the brain's production of amino acid decarboxylase (AADC), an enzyme that converts oral levodopa into dopamine. Oral levodopa is the most common medication to treat the symptoms of Parkinson's disease. Having a steady availability of AADC in the brain with this one-time treatment could allow patients to improve their sensitivity to oral levodopa, thereby reducing their dependence on the medication, with the potential to improve their motor symptoms and quality of life.

The trial uses real-time MRI to monitor infusion of the gene therapy vector into the putamen, overcoming the limitations of drug-delivery technology used in previous trials. For the 15 patients enrolled in the study, the UCSF team was able to successfully make adjustments in the position of the infusion catheter or increase the volume if the infusion was not covering a sufficient area of the putamen. The majority of patients were able to return home within two days of completing surgery.

The first five patients in the study (cohort 1) received a dose of 450 microliters, while the other 10 (five each in cohorts 2 and 3) received up to 900 microliters. After six months, positron-emission tomography (PET) scanning showed an increase in the conversion of oral levodopa to dopamine in both groups, but there was more dopamine in the brains of

patients who received the higher volumes. Although follow-up is still ongoing, five subjects in cohort 1 and three in cohort 2 have completed 12-month follow-up evaluations. At 12 months, daily levodopa equivalents were reduced an average of 10 percent for cohort 1 and 35 percent for cohort 2. Time without troublesome dyskinesias, as recorded in motor diaries, increased by 1.6 hours in cohort 1 and 4.1 hours in cohort 2.

"This was a small phase Ib safety and tolerability trial in 15 patients, so while these results are encouraging, we have to be cautious in extrapolating them too broadly," says the study's principal investigator at UCSF, Paul Larson, MD. Interim results of the study were presented at the 2017 annual scientific meetings of the American Association of Neurological Surgeons and the American Academy of Neurology. A second phase Ib study, which is introducing a posterior approach to catheter placement, began in August 2017 and is being funded by Voyager Therapeutics.

"It's important to recognize that this work and many of the advances in CED and gene therapy are informed by the preclinical work in nonhuman primates in [UCSF researcher] Krystof Bankiewicz's lab," says Larson. "He developed the basic science techniques being used in the trial and has primates eight to nine years out [that] are still producing the enzyme.... I believe gene therapy is the key to ultimately finding a cure for Parkinson's disease."

# Vascular Neurosurgery

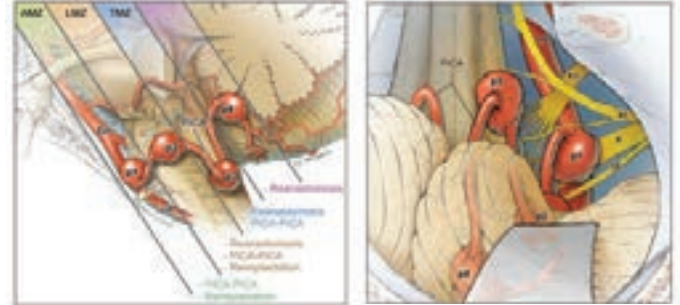
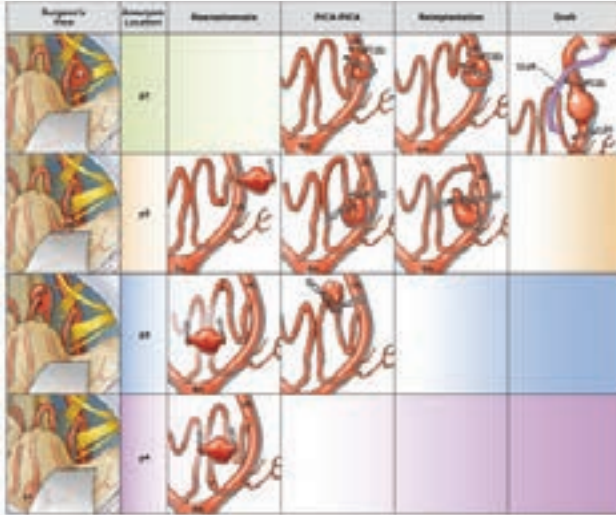


Figure from: Abl A, McDougall CM, Breshears JD, Lawton MT. Intracranial-to-intracranial bypass for posterior inferior cerebellar artery aneurysms: options, technical challenges, and results in 35 patients. *J Neurosurg.* 2016;124(5):1275-1286.

## Seeking the Best Approaches for Cerebrovascular Disorders

The return to UCSF of Chief of Vascular Neurosurgery Adib Abl, MD, who also directs the Cerebrovascular Disorders Program, means that patients can take advantage of his surgical and endovascular expertise, as well as his relentless drive to find better treatment alternatives.

Abl completed a fellowship in open vascular neurosurgery at UCSF under Michael Lawton, MD, before eventually becoming director of cerebrovascular surgery at the University of Arkansas for Medical Sciences College of Medicine. He returned to UCSF in 2017.

His role is multifaceted but includes his multidisciplinary, collaborative work at the UCSF Center for Stroke and Cerebrovascular Disease, where all surgical management of cerebrovascular disorders is coordinated. The center – which involves more than 30 specialists, including neurosurgeons, neurologists and interventional neuroradiologists – is the leading referral center for cerebrovascular disease in Northern California, caring for more than 300 aneurysm patients and more than 75 arteriovenous malformation (AVM) patients annually.

“We’re able to consider both endovascular and surgical approaches for every patient, and decide what’s going to give them the best outcome,” says Abl. “An endovascular procedure that allows the patient to go home the next day is a great option when we can offer it, but for some lesions it makes more sense to provide a more permanent solution with open surgery.”

When lesions are too complex for endovascular approaches – or when they fail such approaches – the center’s high volumes make it ideally suited to complete complex surgical procedures, such as skull base approaches for brain stem or posterior fossa AVMs and cavernous malformations or bypass procedures for aneurysms that fail clipping. “The solution ultimately has to be tailored to the type of lesion and its location, nuances of the pathology, and the age and preferences of the patient,” says Abl.

As for his constant search for better treatments, an example is the paper Abl published in December 2016 in *Operative Neurosurgery*, which drew on his own clinical experience to explore a better way to complete surgery for many intracranial pathologies. Typically, surgeons place these patients in sitting, lateral or prone positions for the supracerebellar infratentorial (SCIT) approach. Abl believed there might be a way to leverage the advantages of these positions while averting their disadvantages, which include surgeon discomfort and fatigue in protracted surgeries, as well as the risk of venous air emboli.

After testing a few alternative positions, Abl and his co-investigators concluded: “The [gravity-dependent] supine lateral SCIT approach allows natural cerebellar relaxation via gravity without the need for lumbar drainage and is a novel, straightforward operative technique with inherent advantages over the prone, lateral decubitus, and sitting positions.”

“We’re able to consider both endovascular and surgical approaches for every patient, and decide what’s going to give them the best outcome.”





Chief of Vascular Neurosurgery Adib Abila, MD, removes a giant internal carotid artery aneurysm.

## New Research Education Center

With the aim of creating a powerful, real-time teaching tool, the UCSF Department of Neurological Surgery has invested in a 3-D, high-definition videoconference room that receives direct, real-time streaming from the operating room.

“The investment we’ve made in fiber-optic cable to directly stream to a 3-D conference room where the picture appears on a full wall panel means people have an extraordinary opportunity

to view a procedure happening in real time,” says UCSF vascular neurosurgeon Adib Abila, MD. “It gives our residents a better understanding of the anatomy of neurosurgery, and ultimately, we could host courses or conferences that take advantage of being able to witness these live surgical presentations with remarkable clarity.”

# Community Outreach

The UCSF Neurological Surgery Community Extension Program provides neurosurgical clinics throughout the Bay Area, partnering with community hospitals and physicians to provide world-class specialty care closer to home and allowing for coordinated care with the patient’s local health care team.

“We recognize that one of our patients’ greatest needs around the time of surgery is their local support network of friends and family,” says Tarun Arora, MD, director of the program. “Providing care directly in a patient’s community is the best way to ensure that network is available to the patient. If other medical problems come up, easy access

and open communication with other doctors who already know the patient well can lead to faster diagnosis and management of these problems.”

By placing UCSF neurosurgeons in the community setting, the program enables them to more quickly address serious neurological diseases, which often improves outcomes. The full-time faculty in Marin, Napa and Oakland also perform surgery at UCSF Medical Center for patients with complex disorders who may need a full range of specialists or access to an advanced technology.

“Referring providers get to know us personally and can call on us at a moment’s notice,” says Arora. “When they do so, they know that their patients will get the best specialty care possible.”



## Adult Neurosurgery Clinics

- Marin General Hospital, Marin
- Queen of the Valley Medical Center, Napa
- Highland Hospital, Oakland

## Pediatric Neurosurgery Clinic

- Good Samaritan Hospital, San Jose



## New Internship Program Introduces Young Teens to Health Care Careers

For nearly 10 years, Jessica Van Tuyl has worked at the nonprofit Oasis for Girls. The organization, which serves over 150 young women of color each year, provides a variety of life and career development programs to under-resourced neighborhoods in San Francisco.

“Many of our girls want to go into medical careers,” explains Van Tuyl, “but often lack the opportunity to explore the diverse career paths that health care encompasses.”

This year, the UCSF Department of Neurological Surgery, LinkedIn and Oasis for Girls teamed up to address this specific need. Together, they launched the GROW internship – a program providing interns with unique access to a variety of roles in the UCSF medical system.

On August 8, San Francisco teenagers Theresa Cruz, Nelsey Garcia, Hannah Ma and Kelly Ye became the first graduates of the new GROW internship program. Paired with mentors across UCSF’s Department of Neurological Surgery, the young women were exposed to a variety of health care careers.

For most of the interns, the highlight of the eight-week program was a visit to the operating room, where they observed pediatric neurosurgeon Kurtis Auguste, MD, performing surgery on an 11-month-old infant. The successful operation involved the surgical insertion of a shunt (a thin tube) to drain excess liquid from the patient’s brain.

Some people might feel squeamish about watching brain surgery, but the girls were fascinated. To them, the entire day was memorable and exciting down to the last detail – from wearing scrubs to experiencing “the smell of a real hospital.”

The GROW internship also featured rotations with nonmedical staff in UCSF’s Department of Neurological Surgery. By highlighting health care careers beyond the well-known physician and nursing professions, the program exposed the teens to the myriad of roles required to keep a hospital running.

For all the interns, learning important job and administrative skills was a tangible outcome that they were able to include on their brand-new LinkedIn profiles. From using Microsoft PowerPoint and Excel to composing professional emails, the teens were continually gaining the experience necessary to thrive in a professional environment.

Van Tuyl hopes to expand the GROW internship program in future years, with the ultimate goal of empowering young women with both the skills and the confidence to build their future careers. For Ye, an aspiring surgeon and 16-year-old high school senior, the internship program did just that: “It really inspired me to keep going even though there is so much schooling.”

“Many of our girls want to go into medical careers, but often lack the opportunity to explore the diverse career paths that health care encompasses.”

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