



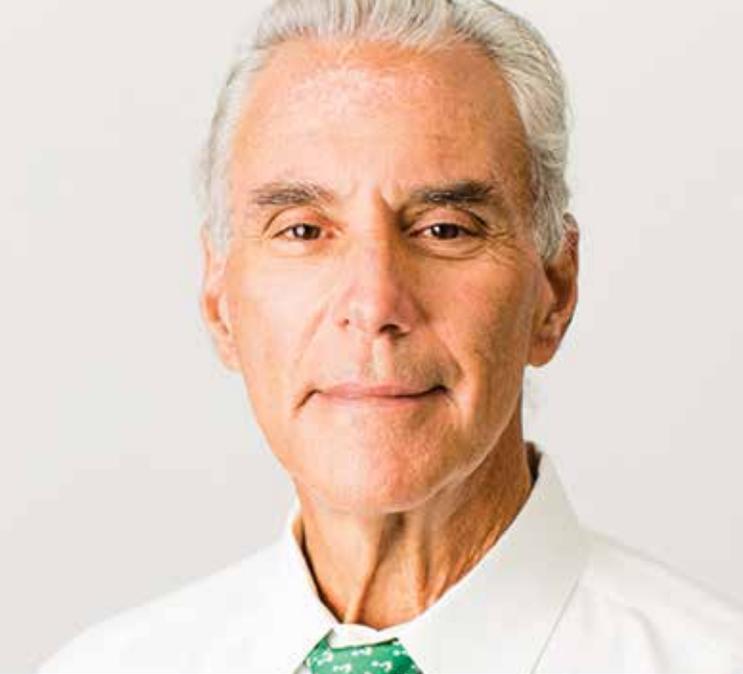
UCSF Neurological Surgery



2018 Annual Report

UCSF

University of California
San Francisco



Contents

Dear Colleague:

This year UCSF was ranked among the top three neurosurgery and neurology programs in the nation by U.S. News & World Report's 2018-19 survey of Best Hospitals. UCSF Medical Center was also ranked the best hospital in California and sixth nationwide. Our Department also continues to receive the highest amount of NIH funding of any academic neurosurgery program in the nation and our neurosurgery residency program is ranked #1 by Doximity for program reputation.

We also continue to expand our services throughout the Bay Area, with UCSF adult neurosurgery available in Marin, Napa and Oakland to provide easy coordination with local physicians and convenient access for patients in those areas. We have also recently partnered with John Muir Health to offer neurosurgery evaluations at the new Berkeley Outpatient Center, a center for primary and specialty care serving patients in the East Bay.

I hope you enjoy reading about the clinical and research highlights from our Department in 2018. I am very proud of the achievements we have made this year in advancing the field of neurosurgery and, as always, would like to thank you for allowing us to partner with you in the care of your patients.

Mitchel S. Berger, MD

Professor and Chair

Department of Neurological Surgery

Berthold and Belle N. Guggenheimer Endowed Chair

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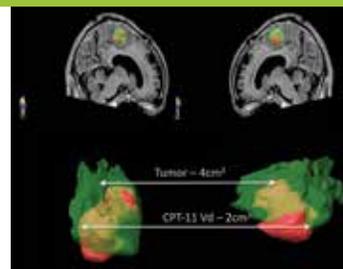
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Brain Tumor Center

Clockwise from top: A modified poliovirus is being used in a new clinical trial for recurrent glioblastoma; Nicholas Butowski, MD; Convection-enhanced delivery ensures better delivery of therapeutic agents to brain tumors.



New Trials Build on Promising Polio Vaccine, Convection-Enhanced Delivery

The UCSF Brain Tumor Center is one of four sites in the country testing a modified version of a poliovirus that had encouraging results against glioblastoma (GBM) in a recent phase I clinical trial. In a study published in the *New England Journal of Medicine*, researchers from Duke University found that nearly 21 percent of recurrent GBM patients treated with the experimental modified virus were alive after three years, compared with 4 percent of patients with similar tumors who received standard therapies. Moreover, the findings indicated that patients who didn't do as well in the initial study may do better with the modified dose being used at UCSF and the three other sites, according to neuro-oncologist Nicholas Butowski, MD, who is co-leading the UCSF arm with neurosurgeons Manish Aghi, MD, PhD and Mitchel Berger, MD.

In the trial, physicians infuse an oncolytic, genetically modified form of polio into patients' tumors through a surgically implanted catheter, in an effort to prompt the immune system to target GBM cells. Half of the patients will receive the study

virus only; the other half will also receive a course of the chemotherapy lomustine, which will begin eight weeks after the one-time polio treatment.

To be eligible for the trial, patients must have a recurrent tumor, located in an area that is amenable to convection-enhanced delivery. "We will enroll 31 in each arm, and we hope that by this time next year, we will have some preliminary indications of how the therapy is working," says Butowski.

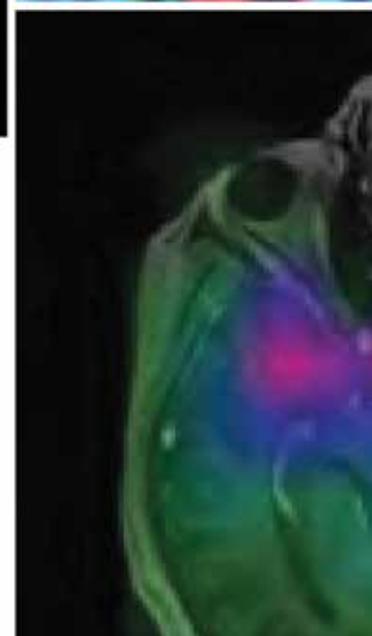
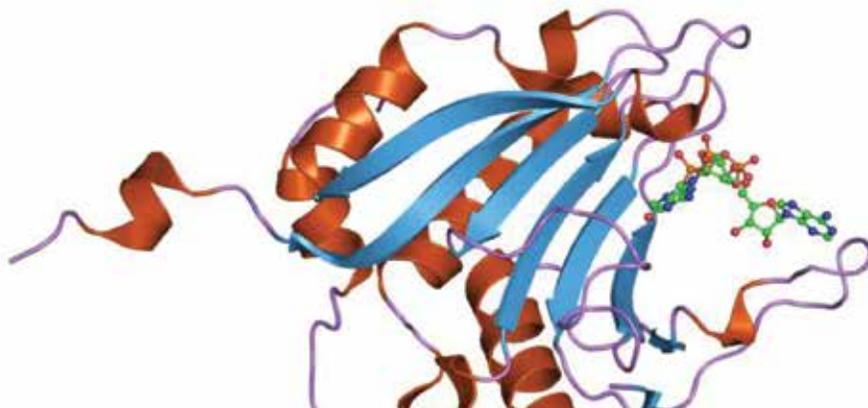
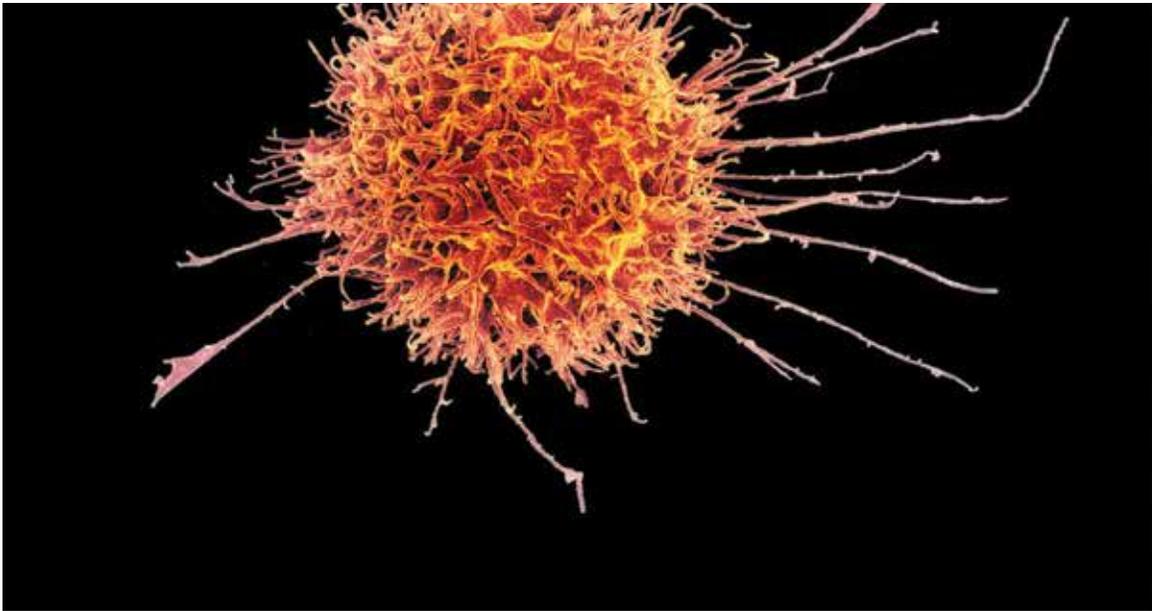
Butowski and Aghi are also leading a next-phase trial for GBM using convection-enhanced delivery of nanoliposomal irinotecan. "We now have greater flexibility to alter the dose – to increase the volume by as much as a factor of 17, so we can get the right amount of drug to fit the shape and size of the patient's tumor," says Butowski. 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.

With SPOR Funding Renewed, Four Projects Take Center Stage

In 2018, the UCSF Department of Neurological Surgery successfully secured renewal of National Cancer Institute funding for a Specialized Program of Research Excellence (SPOR) in brain cancer. Department Chair Mitchel Berger, MD, is the program's principal investigator, and four innovative projects will advance various aspects of diagnosis and treatment.

Blood Immunomethylomic Markers of Outcome in Glioblastoma Patients: By developing and testing a powerful method for immune profiling, discovered at UCSF, that is based on unique immune cell DNA methylation fingerprints, this project aims to help clinicians and patients better understand prognoses, avoid unnecessary interventions and improve risk stratification for future clinical trials. Led by John Wiencke, PhD, Annette Molinaro, PhD, and Jennifer Clarke, MD, the research team will assess immune status in a cohort of patients with newly diagnosed GBM from initial diagnosis through surgery, radiation and chemotherapy; evaluate the prognostic value of methylation-generated immune profiles and other factors in GBM patient survival and progression; and test how this information influences clinical decision making.

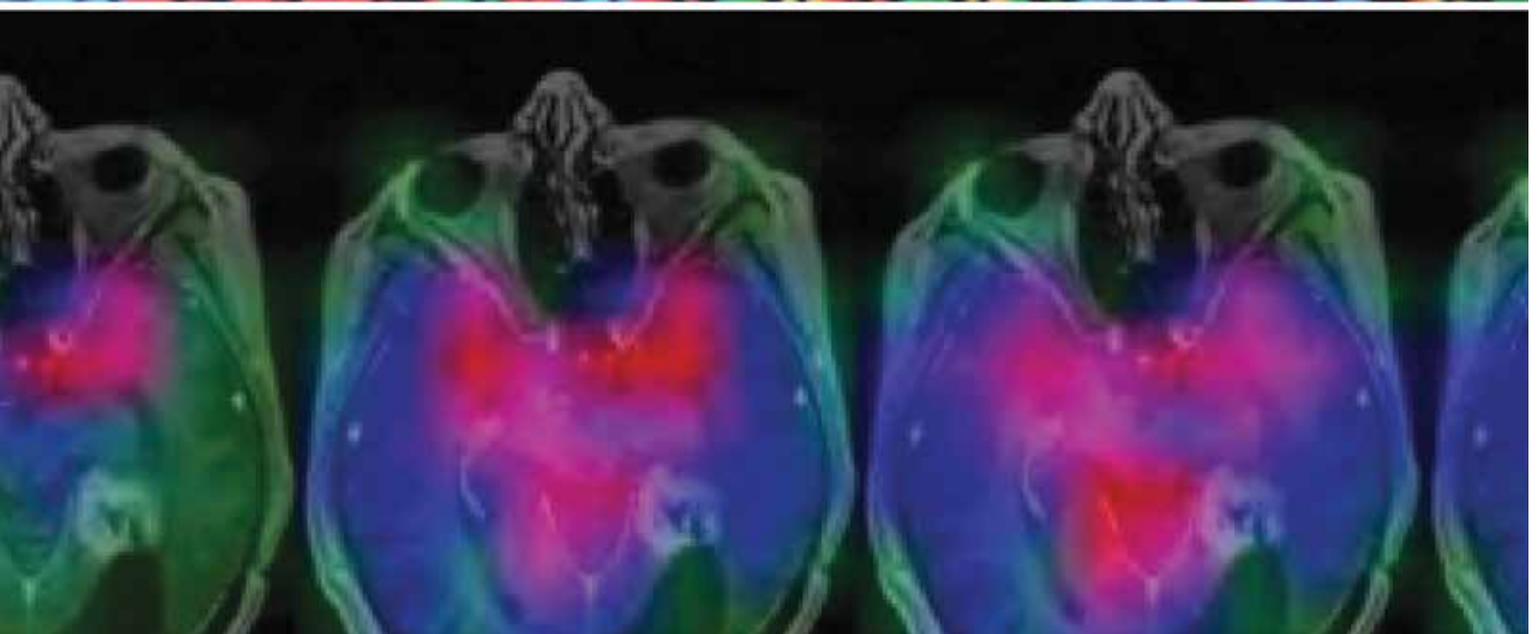
Monitoring Metabolism in GBM Using Hyperpolarized C-13 Imaging and H-1 MRSI: Led by Sarah Nelson, PhD, and Susan Chang, MD, the objective of this project is to combine hyperpolarized C-13 imaging and H-1 magnetic resonance spectroscopic imaging (MRSI) data to detect differences in dynamic and steady-state metabolism in an effort to improve evaluation of treatment response in patients with GBM. The research team will apply these two metabolic imaging strategies to patients with newly diagnosed GBM before and after radiation therapy to determine whether they improve the definition of residual tumor and to target locations for tissue sampling in patients undergoing surgery for suspected recurrence, to validate H-1 and C-13 parameters as markers of recurrent tumor versus treatment-related effects. The team will also obtain metabolic imaging from patients suspected of having recurrent GBM being treated with standard-of-care therapies to test the hypothesis that the lactate-to-pyruvate ratio will be an earlier indicator of response than the choline-to-N-acetylaspartate index.



A New Therapeutic Target for TERT Promoter

Mutant Glioma: Joseph Costello, PhD, and Mitchel Berger, MD, lead this project, which will develop GA-binding protein (GABP) transcription factor as a therapeutic target to reverse the immortality of tumors harboring a mutant telomerase reverse transcriptase (TERT) promoter. TERT promoter mutations are present in more than 80 percent of GBM and oligodendroglioma, and are believed to play a role in overcoming the body's natural barriers to cancer cell proliferation by reactivating TERT expression. The UCSF Brain Tumor Center's discovery that GABP – a single ubiquitously expressed transcription factor – uniquely binds to the mutant TERT promoter and drives TERT reactivation in TERT promoter-mutant glioma and other cancers offers promise for a powerful new therapeutic target. This project will determine if the mutant TERT promoter is uniformly present throughout each tumor, and if GABPb1L modulation leads to tumor cell death while sparing normal cells.

Targeting 4EBP1 on GBM: Led by William Weiss, MD, PhD, and Nicholas Butowski, MD, this project aims to develop a new class of drugs for clinical use by evaluating a clinical 4EBP1 inhibitor, and providing a precision medicine path forward for a clinical trial in patients with GBM. In both published and preliminary data, the team has identified the mTOR target 4EBP1 as a robust biomarker for therapeutic response – findings that re-established mTOR as a central target in GBM treatment and traced the failure of existing drugs to incomplete and/or nondurable inhibition of mTORC1. Since then, the research team has identified and tested a new class of 4EBP1 inhibitors that potently block 4EBP1 in GBM in vivo, leading to robust improvement in survival in preclinical orthotopic models of GBM. This project will develop this class of drugs for clinical use by defining the optimal glioma subpopulation for clinical trials using inhibitors of 4EBP1, optimizing the efficacy of 4EBP1 inhibitors for clinical development and designing and conducting a phase IB clinical trial with the clinical agent Rev1 in pathway-activated recurrent GBM.





Caregiver Program Expands

Established in 2013, UCSF's Neuro-Oncology Gordon Murray Caregiver Program – which gives loved ones the resources they need to ease the responsibility of caregiving – continues to grow. Among its activities, the program supports the Milton Marks Neuro-Oncology Family Camp, a monthly caregiver support group and an annual caregiver retreat.

The 2018 caregiver retreat at the Parnassus campus was titled Fostering Resilience through Creativity and Community and drew 31 caregivers. It included educational seminars on the caregiver's role, neuroanatomy, stress management and values-based living. Participants also engaged in mini support groups with specific foci, and could take part in such activities as massage, music therapy and mindfulness meditation. "It can be isolating to take care of a brain tumor patient, and our retreat is a wonderful day of support, nourishment and community," says Susan Chang, MD.

“It can be isolating to take care of a brain tumor patient, and our retreat is a wonderful day of support, nourishment and community.” – Susan Chang, MD

Specialized Support for Survivors of Brain Cancer

As brain tumor treatments have advanced, the survivor community has grown. In response – and with help and support from a longtime patient, caregivers, the UCSF Helen Diller Family Comprehensive Cancer Center and the Silicon Valley Community Foundation – the UCSF Department of Neurological Surgery has instituted its first program for brain cancer survivors: the Sheri Sobrato Brisson Brain Cancer Survivor Program.

Because brain tumors can have lasting effects on a survivor's ability to work and interact with others, the new survivorship program provides adult survivors with the

necessary support and clinical care to address lingering neurocognitive concerns. A team of specialists, including a neuropsychologist, assesses the survivor's needs and devises an individualized plan to help improve any language, motor or cognitive impairments caused by the brain tumor or its treatment. The goal is to enhance the care of patients with brain tumors through a collaborative, multidimensional approach focused on optimizing cognitive rehabilitation and improving every patient's quality of life.

A Glioma Precision Medicine Program

Thanks to a generous contribution from a private donor, the UCSF Brain Tumor Center has launched five cutting-edge projects that explore bold avenues to potentially advance treatment for malignant glioma:

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|---|---|--|
| <ul style="list-style-type: none"> • Matching drug combinations to patients' individual genetic profiles in a pilot clinical trial | <ul style="list-style-type: none"> • A new therapy for targeting TERT promoter mutations in cancer cells | <ul style="list-style-type: none"> • Immunotherapy using CAR T cells to recognize and kill glioma cells |
| <ul style="list-style-type: none"> • Convection-enhanced delivery of a viral gene therapy | <ul style="list-style-type: none"> • Leveraging data science to link clinical outcomes with genomics and imaging characteristics | |

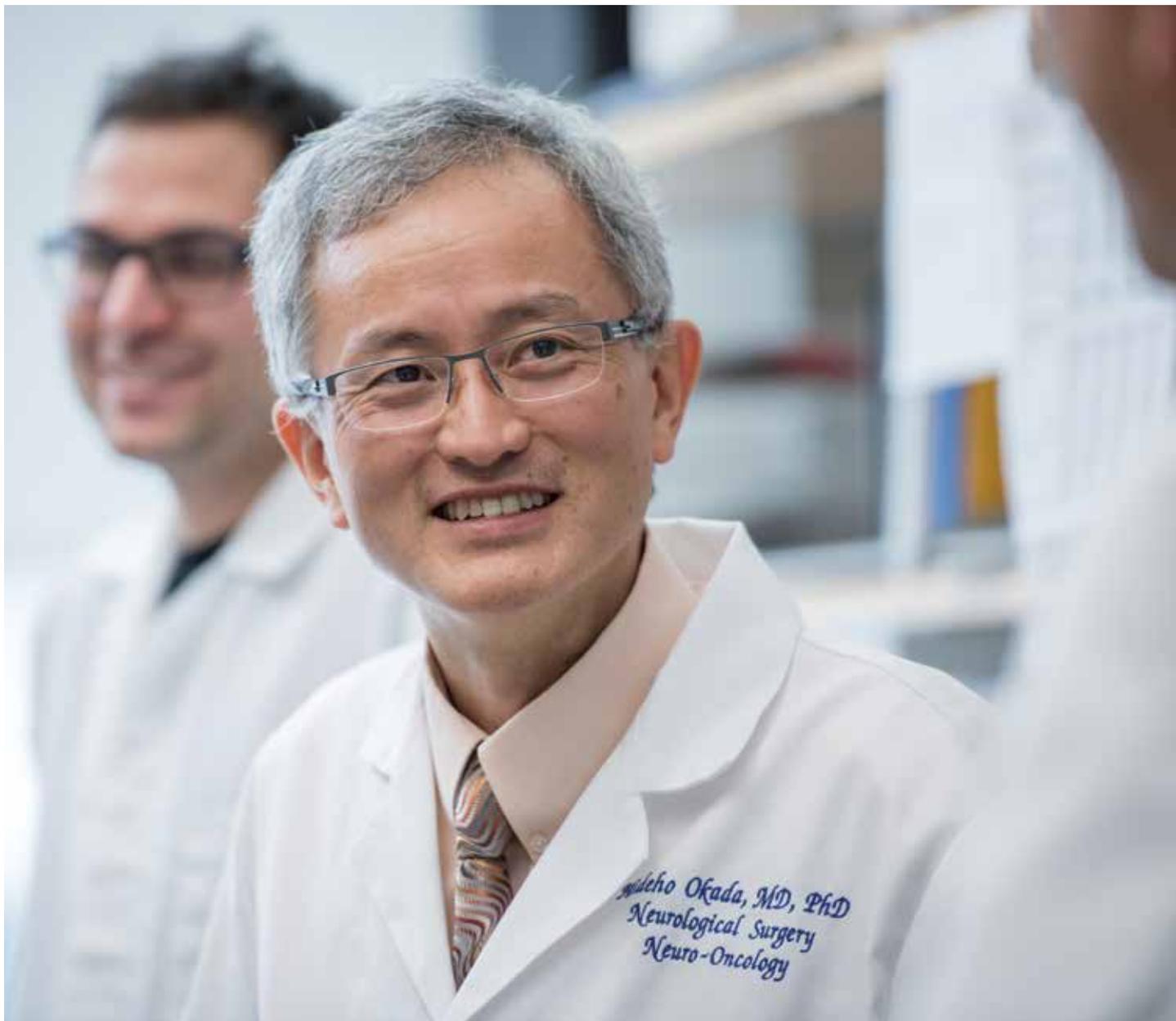
Discovery Opens Door for New DIPG Therapies

This year, the lab of Hideho Okada, MD, PhD, discovered a novel neoantigen that could be a promising therapeutic target in more than 70 percent of patients with diffuse intrinsic pontine glioma (DIPG). The study appeared in the *Journal of Experimental Medicine*.¹

DIPGs are the leading cause of cancer-related mortality in children, with median survival of less than one year. Okada's team found that T-cell receptor (TCR)-transduced T-cells efficiently killed glioma cells that contain an antigen that occurs in about 70 percent of DIPGs; the T-cells significantly

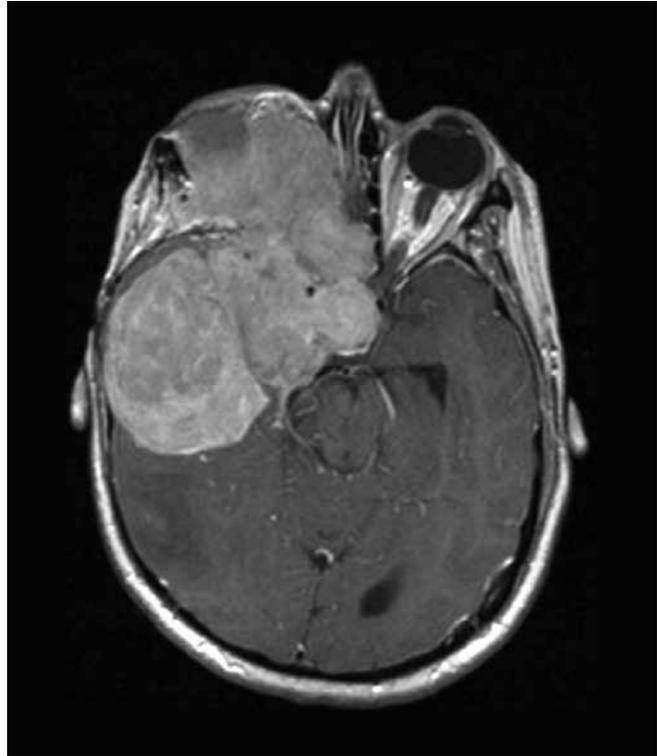
suppressed the progression of glioma xenografts in mice. Moreover, because assays suggested the absence of known human proteins sharing the key amino acid residues required for recognition by the TCR, Okada is hopeful that TCR-transduced T-cells can be safely used in patients.

"Tumor heterogeneity is one of the toughest challenges we face in treating many tumors, but we find this antigen is very uniform throughout DIPGs, which makes it a very attractive target for developing a T-cell-based therapy," says Okada.



Aggressive Meningiomas Linked to a Single Gene

A milestone effort to define the molecular profile of aggressive meningioma identified FOXM1 as a key transcription factor driving proliferation and recurrence. A group of investigators led by David R. Raleigh, MD, PhD, examined 280 human meningioma samples collected by UCSF neurosurgeons between 1990 and 2015. Using an array of techniques, including RNA sequencing, whole exome sequencing, DNA methylation profiling, tissue microarrays and targeted gene expression profiling, Raleigh found that heightened activation of the FOXM1 gene was the unifying factor between aggressive meningiomas in both men and women, in older and younger patients and in meningiomas arising in different parts of the brain. The gene's activation seems to be an important driver of both newly diagnosed tumors and recurrence following treatment. This finding could help clinicians distinguish earlier between aggressive meningiomas and those more responsive to treatment.



UCSF Neurological Surgery Chair Wins Prestigious Award

Mitchel S. Berger, MD, Chair of Neurological Surgery, received the Fedor Krause Medal for Excellence from the German Society of Neurosurgery at the organization's annual meeting in Muenster, Germany. Berger was also selected for the 20th Annual Labatt Brain Tumor Research Centre Academic Lectureship at the University of Toronto. These awards recognized his pioneering work in awake surgery and brain mapping that have drastically minimized morbidity associated with glioma resection.

Michael W. McDermott Honored with Endowed Professorship

UCSF neurosurgeon Michael W. McDermott, MD, has long been a global leader in advancing the treatment of meningiomas. This August, McDermott was appointed the Wolfe Family Endowed Professor in Meningioma Research, honoring his career-long dedication to improving patient care and developing innovative therapies for these tumors. McDermott also leads the UCSF Wolfe Meningioma Program Project, which brings together clinicians and scientists in studies of epidemiology, molecular genomics and novel therapeutics.





Shawn Hervey-Jumper, MD (right), specializes in awake brain mapping to preserve language and cognitive function for patients with brain tumors.

Awake Mapping Research Could Clarify Treatment Choices

The research program of neurosurgeon Shawn Hervey-Jumper, MD, is deeply influenced by his patients' struggles to understand how treatment will affect their quality of life. This is especially important, he says, given that we now know molecular markers that indicate a brain tumor patient's likely prognosis, and 70 percent of surviving patients experience cognitive dysfunction that leads to reduced quality of life.

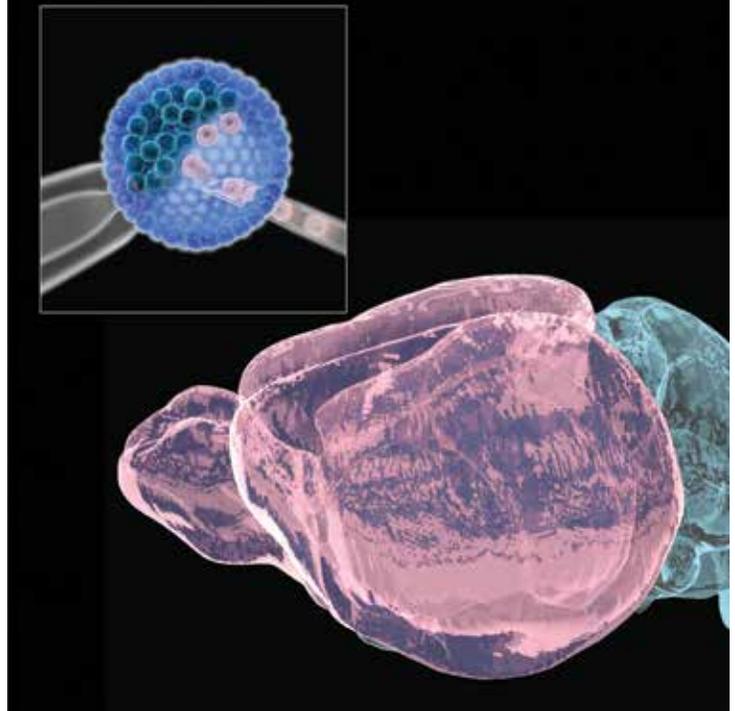
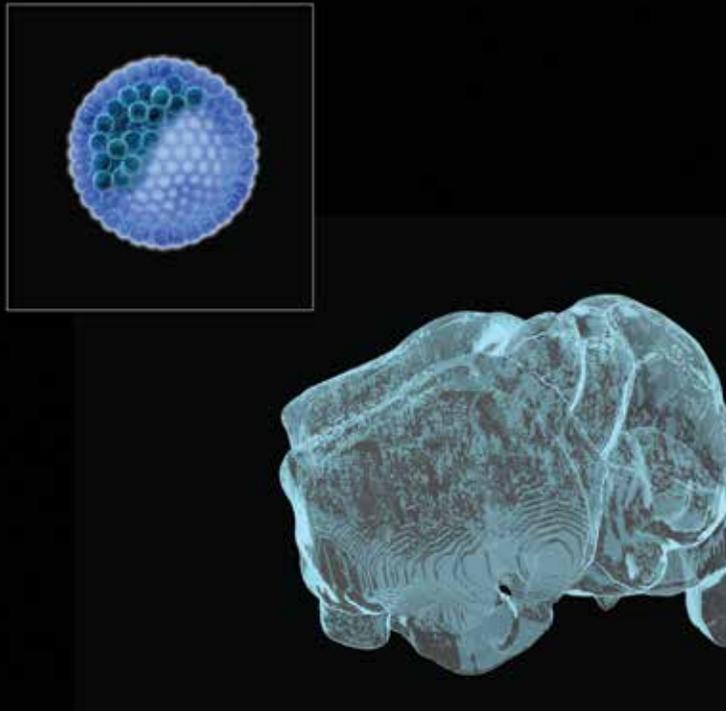
Hervey-Jumper's research, therefore, aims to understand the mechanisms by which gliomas disturb functional language and cognitive networks. A 2017 Robert Wood Johnson Foundation Harold Amos Scholar and recipient of a UCSF Brain SPORE Career Development award, Hervey-Jumper says that better understanding of why a significant percentage of gliomas remain functionally relevant could have an important impact on decisions about what to remove during surgery, as well as patients' subsequent treatment.

To that end, Hervey-Jumper tests patients' language and cognitive function prior to surgery. Then, during awake surgeries, he uses magnetoencephalography (MEG) or electrocorticography (ECoG) to more closely measure areas of functional connectivity within patient gliomas. He grows glioma cells for experiments in his laboratory to better understand how functionally connected glioma cells grow. And postsurgery, Hervey-Jumper follows participating patients regularly by testing their cognition and language abilities. His initial work has indicated more synaptogenic activity in areas of high connectivity.

"As we develop this, I am hoping we can better explain to patients the risks of their operations and make more informed choices about the options we pursue and when these options should be considered," he says.

"I am hoping we can better explain to patients the risks of their operations and make more informed choices about the options we pursue and when these options should be considered"

– Shawn Harvey-Jumper, MD



Building a Patchwork Brain to Study Neurological Disease

Scientists at UCSF and Boston Children's Hospital have developed a new technique for making mice with brains that combine the genetics of two different mouse strains.

The authors aim to use this technique to learn more about how brain cancers form, and about how genetic alterations in different parts of the brain impact diseases such as autism or schizophrenia. They developed a new and improved mouse "chimera" by clearing out a space in the developing brains of early-stage mouse embryos, enabling cells derived from other mice to grow there instead.

To scientists who study how mammals develop through embryogenesis and beyond, a chimera is a genetically retooled mouse combining cells from different mice. Chimeras are used to sort out key questions about how organs emerge and function over time and how genes behave differently in different parts of an animal.

In the brain, for instance, researchers might want to ask whether a specific gene variant that has been linked to schizophrenia plays different roles in "executive" regions of the brain's prefrontal cortex versus deeper, more primal brain regions. However, with conventional methods many complex steps, including mouse breeding, are required to get answers about how specific genes and proteins act in different parts of the brain.

The researchers, led by Bjoern Schwer, MD, PhD, assistant professor of neurological surgery at UCSF, and Fred Alt, PhD, who directs the Program in Cellular and Molecular Medicine at Boston Children's, developed a new mouse strain in which cells that form key brain structures were programmed to poison themselves with a bacterial toxin during the earliest stages of brain development. The death of these cells left space for injected embryonic stem cells from another mouse to regrow the missing brain structures, resulting in a mouse in which different parts of the brain can have totally distinct genetics.

Schwer and Alt, who are co-senior authors of a paper published in *Nature* detailing the new technique, believe their new technique will speed new discoveries to help understand human brain maladies.²

"Mice with embryonic-stem-cell-derived brain regions are indistinguishable from normal mice in memory and learning tasks," says Schwer, who is a member of the UCSF Weill Institute for Neurosciences and the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF. "Now we can use embryonic stem cells to reliably generate key structures of the brain, arguably the most complex organ in vertebrates."

With the technique, called neural blastocyst complementation, researchers can routinely make one or more genetic alterations in embryonic stem cells and directly observe their effects in the brain, according to Schwer.

Alt, who is a Howard Hughes Medical Institute (HMMI) investigator, invented blastocyst complementation earlier to study the development of T and B lymphocytes in the immune system, but until now nobody had made it work to generate brain structures.

"We think of this strategy as a completely new platform for neurobiologists to study every aspect of the brain," Alt says, "from basic knowledge of which genes control brain development to potentially finding new gene therapies for brain cancers and psychiatric disorders."

This article was written by Jeff Norris and first appeared on UCSF News October 10, 2018.

Research Supplies Targeted Treatment Options for Inoperable Brain Tumors

One of the things that make brain tumors especially lethal is the fact that they are often inoperable due to their location. New research led by pathologist David Solomon, MD, PhD, provides much-needed targeted treatment options for patients whose tumors cannot be surgically removed.

Using tumor genome sequencing, Solomon identified the first potential targeted drug to treat chordoid gliomas, a rare type of brain cancer that develops within the third ventricle, a fluid-filled pocket that helps cushion the brain. In the study, published in *Nature Communications*, Solomon's team sequenced the genomes of 13 chordoid glioma tumors and identified a single mutation in one gene, *PRKCA*, that was consistent across all

13 samples. *PRKCA* is part of the MAP kinase pathway, which is turned off in normal brain cells, but the mutation activates the MAP kinase pathway, causing the cells to divide dangerously and form a tumor.³

Because the MAP kinase pathway is so commonly implicated in cancer, drugs that target it are already available and approved by the Food and Drug Administration (FDA). The researchers tested trametinib, a drug used to treat melanoma, on brain cells with the *PRKCA* mutation and found that the drug effectively stopped tumor growth in cells carrying the mutation. Solomon is now working with neuro-oncologists at UCSF Medical Center to set up a nationwide clinical trial for patients with chordoid gliomas.

Dramatic New Findings on Neurogenesis

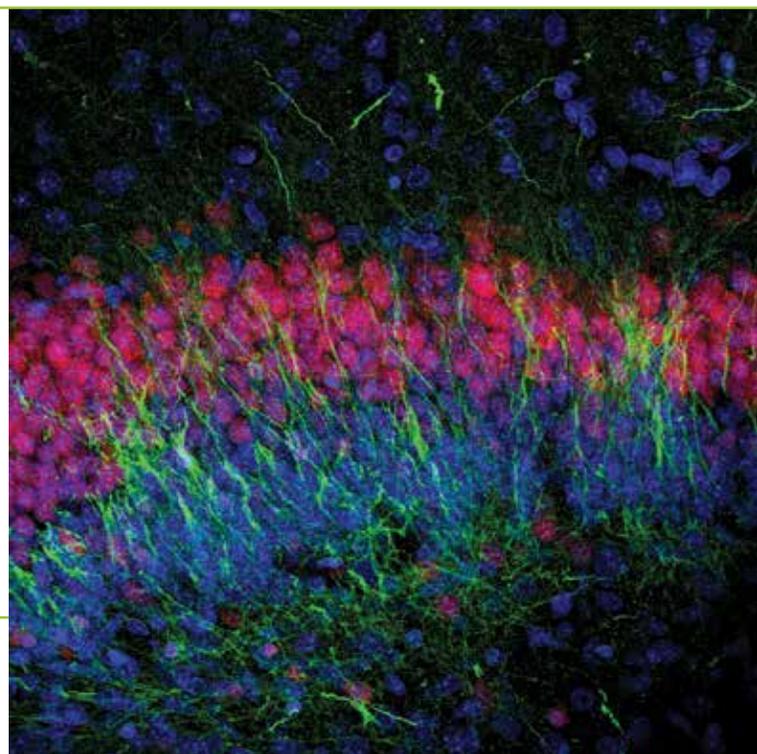
In two new articles – one in *Cell Stem Cell* and the other in *Nature* – the UCSF Brain Tumor Center lab of neuroscientist Arturo Alvarez-Buylla, PhD, called into question long-standing beliefs about the brain's ability to regenerate.

In the first study, the team found that neural stem cells do not divide asymmetrically as previously believed and that only about 20 percent to 30 percent self-renew, a process that occurs maybe two or three times before these cells differentiate and the stem cell population eventually becomes depleted.⁴

In the second, the scientists showed that in the human hippocampus, neurogenesis declines throughout childhood and is undetectable in adults.⁵ “We find that if neurogenesis occurs in the adult hippocampus in humans, it is an extremely rare phenomenon, raising questions about its contribution to brain repair or normal brain function,” says Alvarez-Buylla.

Human hippocampus at birth.

Credit: Arturo Alvarez-Buylla, PhD



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Pituitary Disorders

Neurosurgeon Philip Theodosopoulos, MD, and otolaryngologist Jose Gurrola, MD, provide collaborative, multidisciplinary care to patients with pituitary disorders.

The California Center for Pituitary Disorders Continues to Grow

In 2017, the California Center for Pituitary Disorders at UCSF expanded its patient volumes to 264 cases, making it one of the busiest centers of its kind in the United States. The growth in the number of cases has continued in 2018.

The center provides both surgical and medical management of all pituitary disorders, including pituitary and parasellar tumors, inflammatory conditions and hormonal conditions.

By adding more surgeons, and through close collaboration with the UCSF Department of Otolaryngology – Head and Neck Surgery, the center has also expanded its use of minimally invasive endonasal surgery, which enables surgeons to see further into the sinonasal and parasellar sinuses than they can with a standard microsurgical approach. The endonasal approach is especially useful for more invasive lesions that are suspected of spreading to other areas of the sinuses.

Pediatric Pituitary Program

Pituitary disorders in children are rare medical conditions that are best treated by a multidisciplinary group of specialists. At UCSF, pediatric patients with pituitary disorders are treated in a state-of-the-art children's hospital where they can receive care from physicians with in-depth understanding of how pituitary disorders affect this age group. Some of the more common pituitary disorders seen in children include pituitary tumors

(such as prolactinomas), craniopharyngiomas and Rathke's cleft cysts. Pituitary dysfunction caused by the growth of abnormal masses can result in loss of normal growth, or failure to progress through puberty. Other common consequences include visual loss and a buildup of cerebrospinal fluid (hydrocephalus).

Understanding Atypical Pituitary Adenomas

Scientists have long struggled to definitively characterize tumors known as atypical pituitary adenomas, which make up about 10 percent of all pituitary tumors. According to neurosurgeon Manish Aghi, MD, PhD, difficulty in defining these tumors is problematic, because some believe such tumors might indicate malignant tumor growth elsewhere and require more careful monitoring than the majority of pituitary tumors. That's why, in the *Journal of Neurosurgery*, Aghi was lead author of a widely read case series on the topic.¹

"We wanted to start a dialog that could help us do a better job of understanding the significance of these tumors," says Aghi. His article concluded, "When compared with nonatypical pituitary adenomas, atypical adenomas are more likely to present in younger patients at a larger size, are more often hormonally hypersecretory, and are associated with earlier

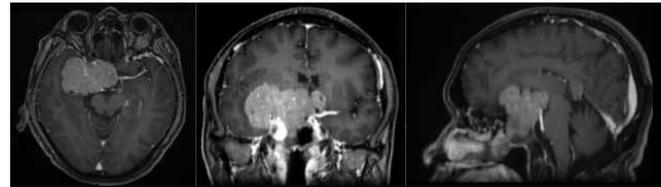
recurrence. These features lend credence to atypical pituitary adenomas being a distinct clinical entity in addition to a discrete pathological diagnosis."

"The article got an enormous response because shortly before publication, the WHO [World Health Organization] eliminated the category, and we suspect people became concerned that would make it harder to advance understanding of how best to treat these tumors," says Aghi. "We believe it's part of our job to convince the WHO that this is a worthy category, which could mean expanding our series. We need to be able to identify the worst 10 percent of pituitary tumors, not because we want to frighten patients, but to ensure we properly monitor them and do necessary follow-up scans."

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Right: MRI T1 post-contrast sequences (from left to right: axial, coronal, sagittal) of a 51-year-old man with recurrent pituitary adenoma. **Below:** Manish Aghi, MD, PhD, and Ivan El-Sayed, MD, perform endoscopic transsphenoidal surgery for a pituitary tumor.





Brain and Spinal Injury Center (BASIC)

Human stem cell-derived neuron. *Credit: Aditi Deshpande, PhD.*

Primate Study Shows Promise for Repairing Spinal Cord Injuries

A diverse team of neuroscientists and surgeons – largely from UC campuses, including UCSF – has successfully grafted human neural progenitor cells (NPCs) into rhesus monkeys with spinal cord injuries. The grafts grew hundreds of thousands of human axons and synapses, resulting in improved forelimb function in the monkeys. The findings, published in *Nature Medicine*, are a significant step in translating earlier work in rodents closer to human clinical trials aimed at repairing paralyzing spinal cord injuries.¹

Derived from an 8-week-old human embryonic spinal cord, the NPCs contained active growth programs that supported robust axon extension and seemed insensitive to inhibitors present in the adult central nervous system, including myelin. As the grafts grew over a nine-month period, they expressed key neural markers and sent hundreds of thousands of axons through the injury site to undamaged cells and tissue on the other side. Within months, the monkeys began to display partial recovery of movement in their affected forelimbs and, for the first known time in a primate model, regenerated corticospinal axons, which are essential for voluntary movement in humans.

“Functional improvement was limited, but we believe might improve with more time and more active rehabilitation,” says co-author Michael Beattie, PhD, director of research at the Brain and Spinal Injury Center (BASIC) at UCSF. “This highly complex translational project shows the value of collaborative research across UC campuses with unique facilities.” BASIC’s Jacqueline Bresnahan, PhD, and Adam Ferguson, PhD, were also co-authors of the study.

The research team has now secured an additional multisite, National Institutes of Health (NIH) R01 grant to test a preclinical model that will determine whether the approach is worth bringing to a human clinical trial. A UCSF team will lead one arm of the grant, which will try to address questions about whether the approach could spur tumor growth over time. The team will follow the transplanted animals for 18 months.

“This highly complex translational project shows the value of collaborative research across UC campuses with unique facilities.” – Michael Beattie, PhD

Study Finds Inadequate Treatment for Concussion Patients

A nationwide study led by scientists at UCSF and the University of Southern California found that more than half of the patients seen at top-level trauma centers may fall off the radar shortly after diagnosis, jeopardizing treatments for the long-term effects of concussion, or mild traumatic brain injury (TBI), which include increased risk for neurodegenerative disease, such as Parkinson's and dementia, as well as psychiatric disorders.

Between 3 million and 5 million Americans suffer TBIs each year, but of the 831 patients in the study treated in hospital emergency departments for concussion, or mild TBI, only 44 percent saw a physician or other medical provider within three months, the scientists report. The study appeared in *JAMA Network Open*.²

"This is a public health crisis that is being overlooked," says Geoffrey Manley, MD, PhD, one of the study's authors, who is also the principal investigator of a study called Transforming

Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI), which has collected and analyzed clinical data on close to 3,000 traumatic brain injury patients from 18 top-level trauma centers nationwide. The data were an important component of the study. "If physicians did not follow up on patients in the emergency department with diabetes and heart disease, there would be accusations of malpractice. For too many patients, concussion is being treated as a minor injury."

He adds that because concussion research has focused on athletes, ordinary people and physicians may not be as attuned as they should be to concussion risks. He says half of concussion patients are discharged without being warned about possible follow-up symptoms – a particularly prevalent concern among the homeless and the incarcerated.



UCSF-led Consortium to Receive \$3.45 Million from NFL to Study Traumatic Brain Injury

The National Football League (NFL) has awarded more than \$3.45 million to a UCSF-led research consortium tasked with identifying the causes, risk factors, biomarkers and prognoses for patients with traumatic brain injury, as well as breaking the deadlock in the development of effective treatments.

The grant, from the NFL's *Play Smart. Play Safe* initiative, is directed to the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study, which has collected and analyzed clinical data from TBI patients at 18 level 1 trauma centers nationwide.

The \$3,454,080 grant, which will be divided between UCSF and 17 study sites, will help fund a follow-on study, TRACK-TBI Longitudinal (TRACK-TBI LONG), that aims to advance the understanding of TBI by tracking patients over several years. Investigators from UCSF and the other study sites will compare TBI patients with two control groups: the patients' uninjured friends and family members, and patients with orthopedic injury but no brain trauma. Data will be collected on brain imaging, blood-based biomarkers and outcome assessments of psychological health, physical recovery and functional status.



Protecting astronauts from harmful radiation will be key to making deep space exploration possible.

Susanna Rosi, PhD

Deep Space Radiation Treatment Reboots Brain's Immune System

The lab of UCSF neuroscientist Susanna Rosi, PhD, director of neurocognitive research in the UCSF BASIC, has identified the first potential treatment for the brain damage caused by exposure to cosmic rays – a drug that prevents memory impairment in mice exposed to simulated space radiation. The study was published in *Scientific Reports*.³

As space travel becomes increasingly common, humans venturing beyond the Earth's protective magnetic fields will be exposed to levels of cosmic radiation estimated to be 1,000 times higher than what we experience on Earth. Protecting astronauts from this harmful radiation will be key to making deep space exploration possible.

In this collaborative study, Rosi – who has conducted NASA-funded research for the past four years to understand how deep space radiation may affect astronauts' brains – exposed

the mice to a dose of radiation comparable to what they might experience in deep space. Beginning a week later, some of the mice were treated for 15 days with PLX5622, a drug that the Rosi lab had previously shown to prevent cognitive deficits in a mouse model of cancer radiation therapy when administered prior to irradiation of the brain. The treated mice performed like healthy mice on a subsequent memory task, while the untreated mice did not. And when the researchers examined the animals' brains, the brains of untreated mice had lost significant numbers of synapses, while the brains of treated mice appeared normal. The authors hypothesize that by forcing the brain to replace irritable, radiation-exposed microglia with new, healthy microglia, the drug had allowed the animals to avoid the cognitive consequences of radiation.

Bench to Bedside: Advancing the Treatment of Spinal Cord Injury

At Priscilla Chan and Mark Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG), neurosurgeon Sanjay Dhall, MD, is leading an effort that is changing emergent treatment of spinal cord injury (SCI). The effort – rooted in BASIC research and the Canadian Multicentre CSF Monitoring and Biomarker Study (CAMPER), a clinical trial for which UCSF is the only site in the United States – is demonstrating that patients can recover from spinal cord injuries for which there was once little hope of recovery.

Three pieces of research underlie the new treatment approach. First, BASIC researchers developed a scale that found early MRI is a strong predictor of spinal cord recovery. At ZSFG, the early imaging is combined with what Dhall calls ultra-early treatment, also rooted in BASIC research that found getting appropriate patients to the operating room within 12 hours of injury leads to dramatically better outcomes than those for patients who undergo surgery between 12 and 24 hours of their injury. The third research finding, published in *Neurology*, demonstrated that maintaining spinal cord perfusion pressure (SCPP) above 50 mm Hg is a strong predictor of improved neurologic recovery and can provide useful information to guide the hemodynamic management of patients with acute SCI.⁴

This led to protocols at ZSFG in which clinicians treat spinal cord injury like a surgical emergency. A team – emergency physician, anesthesiologist, neurologist, neurosurgeon and radiologist – mobilizes when an SCI patient is on the way to the hospital. If a rapid evaluation deems it necessary, the patient is rushed to the MRI machine, an effort that has cut time to MRI to 15 minutes. In turn, clinicians have cut mean time to surgery to just under 11 hours. And they have personalized care after surgery, so they are better managing blood flow and oxygen postoperatively through the new protocol using SCPP.

“In international databases, the likelihood of recovery from spinal cord injury hovers around 20 percent,” says Dhall. “With implementation of aggressive management, our improvement rate is 89 percent, and if we get them to surgery within 12 hours, we get more than one or 1.5 points of improvement, compared to half a point in other cases. What excites me most about this is that SCI has been seen as irreversible; now we know even the worst injuries can be helped.”

Sanjay Dhall, MD, associate professor of neurological surgery, and director of Spinal Neurotrauma at Zuckerberg San Francisco General Hospital (ZSFGH), explains his patient's injury and treatment with a model of the vertebra.





An Open Data Commons for Spinal Cord Injury and Beyond

This year the BASIC team fully launched the first multi-stakeholder, large-scale data-sharing initiative in spinal cord injury research: the Open Data Commons for Spinal Cord Injury (ODC-SCI.org), funded by the Craig H. Neilsen Foundation with endorsements from the NIH, the Department of Veterans Affairs (VA) and nonprofits. This effort is being co-led by UCSF principal investigator Adam Ferguson, PhD, and a steering committee composed of international spinal cord injury thought leaders, including UCSF BASIC's Michael Beattie, PhD, and Jacqueline Bresnahan, PhD.

The BASIC team also recently received funding to extend this model to traumatic brain injury (TBI), with Ferguson, Beattie, Bresnahan, and Susanna Rosi, PhD, as co-principal investigators. One of five awards granted nationally by the Translational Outcomes Project in Neurotrauma (TOP-NT) (UG3/UH3) funding program from the National Institute of Neurological Disorders and Stroke (NINDS), the effort will focus on early biomarker discovery in preclinical TBI. The same team also received an award from the VA to focus on chronic TBI data science.

Applying Artificial Intelligence to Better Understand TBI and Spinal Cord Injury

BASIC neuroscientist Adam Ferguson, PhD, is using artificial intelligence to better understand spinal cord and traumatic brain injuries. Ferguson and his BASIC colleagues applied machine learning techniques to pull a clearer answer from large amounts of data derived from three rat studies aimed at identifying the best possible therapies for traumatic brain injury (TBI).

The researchers developed a machine learning algorithm that performed a number of functions to overcome factors that often confound scientists in these types of studies. For one, it enabled the researchers to identify what characteristics best indicated that a rat was better; characteristics that included lesion size, motor ability, memory capacity and others. That created a score, which enabled the team to measure and rank the possible combinations from the three therapies tested in the previous studies.

In a paper published in *Scientific Reports*, Ferguson – working with UCSF BASIC's Jenny Haefeli, PhD, and Jialing Liu, PhD, and UCSF neurologists Ray Swanson, MD, and Steve Massa, MD, PhD – found that coadministration of the anti-inflammatory agent minocycline and the molecule LM11A-31 was the best drug regimen to promote recovery following TBI.⁵ The team also found that waiting until at least a week after injury to initiate physical therapy enhanced recovery from injury. “The machine learning was a way to rapidly make our way through the complexity to find an important answer that was there – but hidden – in the data,” says Ferguson.

Geoffrey T. Manley Honored with Endowed Professorship

On December 6, 2018, UCSF neurosurgeon Geoffrey T. Manley, MD, PhD was appointed the Margaret Liu Endowed Professor in Traumatic Brain Injury. This endowment is generously funded by Margaret Liu Collins, in recognition of Dr. Manley's career-long commitment to advancing the field of neurotrauma research and ultimately improving care for patients with traumatic brain injury.



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Pain and Peripheral Nerve Disorders

“We are turning to this approach more and more, because the procedure is less invasive.” – Line Jacques, MD

Human Nerve Allograft Is Less Invasive

In January 2017, a 23-year-old right-handed male was cleaning a knife when it slipped out of his hand and lodged itself behind his knee. Over the next year, he suffered from numbness and tingling in the lateral part of his left leg and shin and experienced difficulty walking due to foot drop and pain.

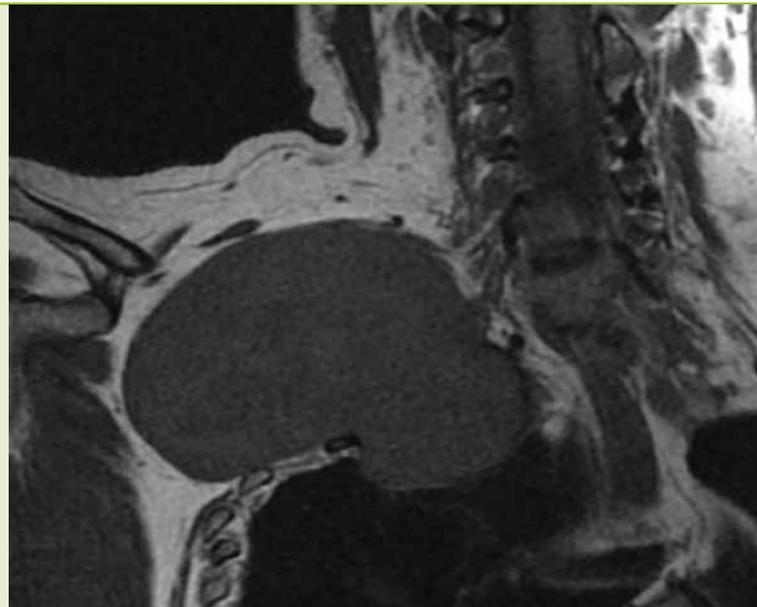
After evaluation, Line Jacques, MD, chief of peripheral nerve and pain surgery, chose to use a processed human nerve allograft to address these conditions. Postsurgery, the young man returned to normal activities within a week.

“We are turning to this approach more and more, because the procedure is less invasive,” says Jacques. “There is no need to harvest a sural nerve, and so we avoid both a scar and a second site of surgery.”

Improved Surgical Approaches for Peripheral Nerve Tumors

To remove tumors arising from peripheral nerves that run between the plexus and thorax, UCSF cardiothoracic surgeons and neurosurgeons have forged an innovative collaboration in which they simultaneously complete a sternotomy and brachial plexus surgery.

This approach was recently performed to remove a tumor (image at right) in a 31-year-old woman with a history of neurofibromatosis type 1, who also – due to a posterior instrumented fusion for severe scoliosis – had a long history of right arm numbness and tingling as well as paroxysmal episodes of spasticity in her upper extremity. After surgery, the woman resumed physical therapy and was able to go back to work a month later.





UCSF Neurosurgical Resident Wins CNS Award

UCSF resident Kunal Raygor, MD, won the William H. Sweet Young Investigator Award from the Congress of Neurological Surgeons (CNS) for a study examining the outcomes of patients with trigeminal neuralgia whose pain recurred after initial treatment with stereotactic radiosurgery (SRS). Raygor and his colleagues found that patients who received microvascular decompression after failed SRS had longer duration of pain relief than those who received repeat SRS. In the group that received repeat SRS, sensory changes following treatment were predictive of better pain control.



A 3-D Model for Teaching Brachial Plexus Surgery

Brachial plexus surgery aimed at removing tumors and repairing damaged nerves is a complex procedure, one that has traditionally been a challenge to teach. That's why the UCSF Department of Neurological Surgery is developing a 3-dimensional (3-D) model for teaching brachial plexus surgery to both residents and community neurosurgeons.

"Understanding both the anatomy and the surgery itself on a 3-D model will enable us to be more successful at understanding tumor location and the relationship of the tumor with the brachial plexus and vessels, especially when tumors extend into the chest," says Line Jacques, MD.



Neurospinal Disorders

Neurosurgeons Catherine Miller, MD, and Praveen Mummaneni, MD, perform an awake transforaminal interbody fusion for a patient with degenerative spondylolisthesis.

First Awake Spine Fusions on the West Coast Performed at UCSF

Praveen Mummaneni, MD, became one of the first neurospinal surgeons in the western United States to complete awake decompression and fusion procedures. The novel procedure is characterized by an Enhanced Recovery After Surgery (ERAS) protocol, newly tailored to spine surgery; close collaboration between UCSF neurosurgeons and anesthesiologists; a presurgical liposomal injection of the nonopioid pain medication bupivacaine, the effects of which last between six and eight hours postsurgery; the latest generation of percutaneous screws and expandable cages; and patients going home on oral pain medication, with recovery time as little as three

days. Properly selected patients even have the option of going home the same day. “For people who have difficulty emerging from medical anesthesia, we offer these surgeries for decompressions and fusions to relieve herniated disks, lumbar spinal stenosis and spondylolisthesis,” says Mummaneni. “Usually we can get patients home in 24 hours, and sometimes we can get them home the same day and back to work shortly after. For now, this approach is limited to one-level procedures and patients with BMIs [body mass indexes] under 35, but with more experience, the inclusion criteria will expand.”



Awake Spine Surgery Videos

Watch Dr. Mummaneni discuss awake surgery treatment options and case studies on UCSF's MedConnection at medconnection.ucsfhealth.org/neurosurgery



Motion-Preserving Techniques

Lee Tan, MD, brings a broad perspective to spine surgery, having trained in both neurospinal and orthopaedic surgical procedures while completing a fellowship at Columbia University Irving Medical Center. Tan is especially expert in the use of motion-preserving techniques for cervical spine surgeries

that avert fusions. He says, “For patients with one- to two-level disk disease, these techniques put less stress on adjacent levels, thereby allowing for a normal range of motion and reducing the risk of disease in the future.”

“These techniques put less stress on adjacent levels, thereby allowing for a normal range of motion and reducing the risk of disease in the future.” – Lee Tan, MD

Minimally Invasive Spine Surgery

Procedures for Scoliosis: Neurosurgeons at the UCSF Spine Center continue to test more minimally invasive (MI) approaches for the treatment of all scoliosis. “Of late, where appropriate, we go through the side and just treat the painful levels, not the entire scoliosis. There is less blood loss, less morbidity and high levels of patient satisfaction,” says neurosurgeon Dean Chou, MD.

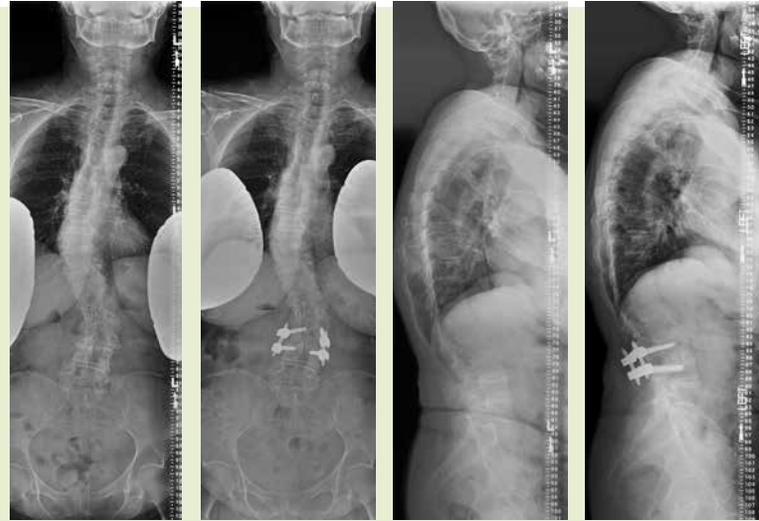
After treating and tracking more than 100 patients, the group presented its results at the 2018 North American Spine Society meeting. “We believe this is something to offer patients who can’t tolerate a larger surgery,” says Chou. In addition, as part of a Neurosurgery Clinics of North America publication focused on spinal deformity, Mummaneni and Chou co-authored a chapter that described a new algorithm to define when MI spine surgery is appropriate.

Single-Position Anterior-Posterior Surgery: UCSF neurospinal surgeon Aaron Clark, MD, PhD, is one of a small group nationwide testing the use of MI single-position anterior-posterior surgery for patients who need fusion or reconstruction and who have mild to moderate deformity, degenerative disk disease or spondylolisthesis. “We used to begin with patients in a lateral or supine position, and we would flip them into a prone position, but now we can do both lateral and posterior in a single position, which improves operative efficiency,” says Clark.

He says the newer techniques are made possible by new types of instrumentation that allow surgeons to complete posterior screw placement in bottom levels while patients are in a lateral position, as well as by an intraoperative CT scan and spinal navigation. “That improves our accuracy and may expose both patients and staff to less radiation exposure, because we don’t need as many X-rays,” says Clark.

Limited Fusions for Adult Scoliosis

Traditionally, surgical approaches for treatment of adult scoliosis have involved fusions at 8-10 levels of the spine – major surgery, associated with numerous complications. However, at the 2018 American Association of Neurological Surgeons (AANS) Annual Scientific Meeting, neurosurgeon Dean Chou, MD, presented a study that showed older patients in pain may not need such extensive surgery. If the pain is largely limited to leg pain and the patient is well balanced, a UCSF study of 50-80 patients showed that doing as few as two levels can often address the pain concerns.¹



A UCSF study showed that fusing as few as two levels can address pain concerns for patients with scoliosis.

Dean Chou, MD



Risk Outcome Calculators for Adult Deformity

Working with colleagues across the globe, this year neurosurgeon Christopher Ames, MD, co-founded Global Spine Analytics, a research organization that develops risk, outcome and cost calculators for adult spinal deformity and scoliosis treatment. A coalition of 35 surgeons and 17 sites across North America and Europe, the organization is already testing real-time, preoperative risk and outcome prediction software in participating surgeon offices. “During an office visit, the

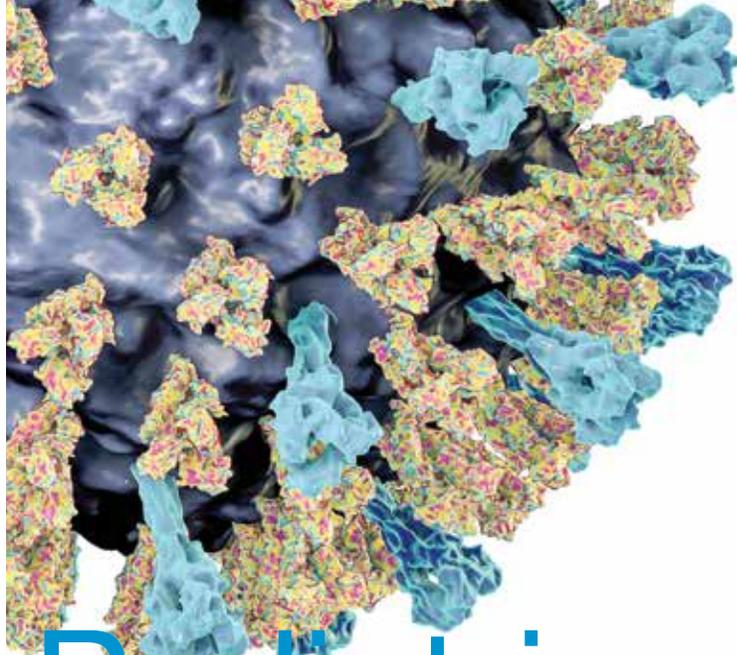
software predicts the risk of complications and readmissions, as well as clinically important improvements tailored to each patient, center and surgeon,” says Ames. “And we can rerun the predictions based on various surgical options before we finalize the surgical plan. I’m already doing this, and patients love it.” Ames expects that after the testing phase and any workflow adjustments are complete, the coalition will provide access to the software for all spinal deformity surgeons.

Joseph Osorio, MD, PhD, and Christopher Ames, MD, perform surgery for a rare thoracolumbar variant of Scheuermann’s Kyphosis.



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Pediatric Neurosurgery

A modified measles virus is being used to target recurrent medulloblastoma.

Can a Measles Virus Treat Medulloblastoma in Children?

Medulloblastoma (MB) is the most common malignant brain tumor in children. Of the four MB subtypes, group 3 tumors have the worst prognosis, with a five-year survival rate approaching zero. “Those who do survive face severe, lifelong debilitating sequelae from the radiation therapy used in standard treatment,” says pediatric neurosurgeon Corey Raffel, MD, PhD.

In a hopeful sign, the last few years have demonstrated that oncolytic measles virus (MV) could be effective against MB tumors in immunodeficient animal models, but these models do not allow examination of the effect of the immune system on MV therapy. To address this concern, Raffel’s lab has developed a unique mouse medulloblastoma cell line that is infected by MV, allows replication of MV, forms group 3 MB-like tumors in the brain of immune-competent mice and is effectively killed by MV, with a complete response in 60 percent of MV-treated mice, according to a study published in *Neuro-Oncology*.¹

“We hypothesize that the combination of MV therapy and immune checkpoint inhibition – which has already been proven effective in some cases – will be synergistic in the treatment of MB tumors,” says Raffel. Now he is part of a UCSF team in the Pacific Pediatric Neuro-Oncology Consortium (PNOC) that has initiated a phase I clinical trial to study the safety of a modified MV in children and young adults with recurrent medulloblastoma or atypical teratoid rhabdoid tumor (ATRT). In cases where radiation and chemotherapy have failed, trial participants will receive measles virus into the recurrent tumor in the brain and/or into the fluid space around the brain and spinal cord, depending on tumor location.

“As we demonstrate safety, we will treat children with progressively increasing numbers of viral particles to determine how much virus we can give without causing intolerable side effects,” says Raffel. “We are hoping that this study will lead to additional trials to demonstrate the efficacy of measles virus in the treatment of medulloblastoma.”

Virtual Reality Aids Surgical Planning, Patient Communication

In November 2017, UCSF Benioff Children's Hospital became the first stand-alone children's hospital to acquire the Precision Virtual Reality visualization platform. This advanced technology provides neurosurgeons with an inside-out view of the anatomy and pathology of their patients' complex neurologic conditions for surgical planning. At the same time, the technology enables patients and families to visualize their own anatomy and better understand their conditions, so they can better participate in shared decision making about their treatment plan.

The 360-degree model that virtual reality (VR) creates is based on each patient's CT and MRI scans. Wearing immersive goggles, the physician and patient can, together, tour the patient's anatomy prior to surgery. In addition, says pediatric

neurosurgeon Kurtis Auguste, MD, the models are useful for intraoperative visualization and navigation during complex surgical procedures.

"VR is a giant leap forward in translating a rigidly two-dimensional world into the volumetric, 360-degree, three-dimensional surgical world," says Auguste. "Its immersive nature closely mimics what we encounter in the operating room. Seeing structures and anatomic relationships that were not readily apparent in two dimensions allows me to rehearse entire surgical sequences ahead of time in 3-D, making this a powerful tool to best prepare for the toughest neurosurgical procedures.... And the way it allows me to take patients and families on a guided tour through their own anatomy is a game changer for communication and for alleviating their anxiety."

"VR is a giant leap forward in translating a rigidly two-dimensional world into the volumetric, 360-degree, three-dimensional surgical world."

– Kurtis Auguste, MD



New Precision Medicine Trial for Pediatric Brain Tumors

A new clinical trial led by Sabine Mueller, MD, PhD, is testing personalized drug cocktails based on the genetic profiles of children with malignant brain tumors. The trial will be offered through the Pacific Pediatric Neuro-Oncology Consortium (PNOC) and will treat up to 44 children and young adults. Patients will be enrolled at UCSF Benioff Children's Hospital San Francisco and other sites in the 18-hospital PNOC network, which is tasked with translating new findings in cancer biology to more effective therapies. The drug cocktails will be developed with up to four therapies specifically targeted to the child's tumor. Each will be screened using the UCSF 500 Cancer Gene Panel, which flags the most common cancer genetic mutations; as well as RNA sequencing and whole-genome and whole-exome sequencing for all DNA and genes. "We have learned a lot about the molecular makeup of high-grade gliomas in recent years and we recognize that their heterogeneity means that a blanket treatment approach fails to reach most patients," says Mueller. "We hope that this personalized strategy may lead the way to life-saving treatments for children with high-grade gliomas, as well as other treatment-resistant brain tumors."

Single-Level Selective Dorsal Rhizotomy Shown to Be Effective Treatment for Spastic Cerebral Palsy

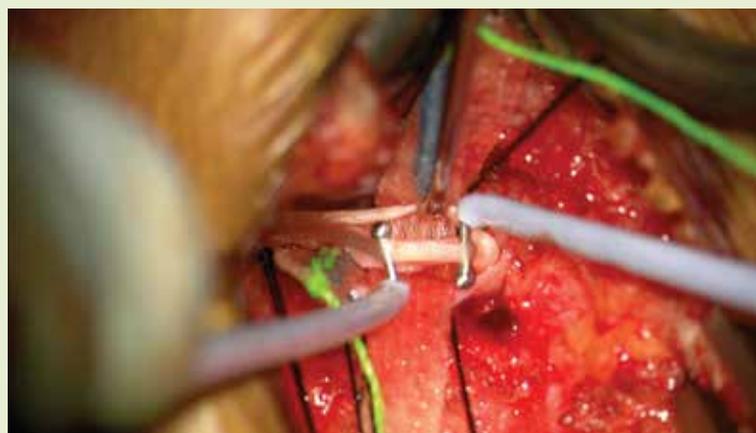
At UCSF Benioff Children's Hospitals, a combination of surgical expertise in selective dorsal rhizotomy and intensive rehabilitation at the nationally recognized UCSF Pediatric Physical Medicine and Rehabilitation Clinic has proven an effective approach for achieving tone reduction in patients with spastic cerebral palsy.

"Cerebral palsy is the most common childhood disability, and spastic cerebral palsy is the most common form," says pediatric neurosurgeon Lauren Ostling, MD. "Tone reduction for spastic diplegic and quadriplegic patients is extremely important for maximizing function, decreasing pain and improving ease of care – and it may delay or eliminate the need for some orthopedic interventions."

Ostling says that selective dorsal rhizotomy is an important option for tone reduction because the advantages include a long-term, permanent reduction in tone through a single procedure, avoidance of complications associated with intrathecal baclofen pumps and lack of side effects associated with oral medications used for spasticity.

At UCSF, the procedure involves a single-level laminoplasty centered over the conus medullaris. Surgeons isolate the dorsal sensory roots from the ventral motor roots based on visualization and neurophysiologic stimulation thresholds and then divide the dorsal roots into rootlets and section them based on neurophysiologic monitoring criteria.

"Sectioning of these rootlets decreases the stimulation of the alpha motor unit, thus decreasing spasticity," says Ostling. "And the single-level laminoplasty has less risk of future spinal deformity than a multilevel procedure and appears to lead to a faster, less painful recovery, which allows patients to begin their intensive rehab as soon as possible."



Top: Intraoperative view of the conus from a single level laminoplasty.

Bottom: Stimulation of a dorsal rootlet that has been isolated from a larger dorsal root.

"Tone reduction for spastic diplegic and quadriplegic patients is extremely important for maximizing function, decreasing pain and improving ease of care."

– Lauren Ostling, MD

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Movement Disorders



In a study of gene therapy for Parkinson's disease, infusions of the therapy into the brain are directed by real-time MRI visualization.

AADC Trial Moves to Phase II, Using New Delivery Technique

After completing a phase IB trial, which evaluated the use of gene therapy to increase the brain's production of aromatic L-amino acid decarboxylase (AADC) to improve treatment for advanced Parkinson's disease, neurosurgeon Paul Larson, MD, is co-leading the phase II version of the trial.

In this next phase of investigation, the research team will use a more efficient surgical approach for infusing the gene therapy vector into the putamen. "Rather than making two or three penetrations through the brain to deposit the therapy in different locations, we will use a single penetration from the back of the head and place the infusion cannula along the length of the putamen," says Larson. As with phase IB, this phase of the trial will continue to use real-time MRI to monitor infusion of the gene therapy vector.

Oral levodopa is the most common medication to treat the symptoms of Parkinson's disease. Increasing the level 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 safety profile during phase I was excellent, and in phase II we are expanding to nine surgical and 23 enrolling sites, including UCSF Medical Center and the San Francisco VA Health Care System," says Larson.



“We believe our device provides a more reliable signal than devices that record brain activity in the basal ganglia.”

– Philip Starr, MD, PhD

First Demonstration of Adaptive DBS Shows Promise

With publication in the *Journal of Neural Engineering*, Philip Starr, MD, PhD, led a team that demonstrated the real-world feasibility of adaptive, or closed-loop, deep brain stimulation (DBS).¹ “Our study followed two patients with Parkinson’s disease using a fully implanted neural prosthesis that uses brain sensing to control stimulation amplitude,” says Starr. In short-term, in-clinic testing, the approach realized substantial energy savings without compromising therapeutic efficacy.

The device is different from traditional DBS devices because it can both monitor and modulate brain activity. The research team implanted an electrode over the primary motor cortex, a part of the brain critical for normal movement. The signals from the electrode then fed into a computer program embedded

in the device, which determined whether and how much to stimulate the brain. For the Starr lab’s study, the researchers used a cortical narrowband gamma oscillation related to dyskinesia (uncontrolled movements) to decrease stimulation voltage when gamma oscillatory activity was high, indicating dyskinesia, and increase stimulation voltage when oscillatory activity was low.

“This is the first demonstration of adaptive DBS in Parkinson’s disease using a fully implanted device and neural sensing,” wrote Starr. “By receiving feedback from the motor cortex, far from the stimulation source, we believe our device provides a more reliable signal than devices that record brain activity in the basal ganglia.”

Breakthrough Approach for AADC Deficiency

In a remarkable study, UCSF researcher Krystof Bankiewicz, MD, PhD, used convection-based delivery of a gene therapy to successfully treat patients with the rare disorder known as aromatic L-amino acid decarboxylase (AADC) deficiency. The therapy has received orphan drug designation from the United States Food and Drug Administration (FDA) and is under consideration for regenerative medicine advanced therapy designation. The approach, says Bankiewicz, is also proof-of-concept for treatment of numerous other genetic disorders.

AADC deficiency is a rare, inherited disorder that appears in the first year of life. Children with the condition may have severe developmental delays, weak muscle tone, problems moving and uncontrollable movements of the arms and legs. The disease is caused by a genetic defect in the AADC enzyme, which makes chemical messengers that are essential for the brain to work properly. “Because the disease is caused by a profound loss of functional AADC, gene replacement has been seen as one of the most desirable and potentially transformative candidate therapies,” says Bankiewicz.

In the study – pediatric neurosurgeon Nalin Gupta, MD, PhD, was the lead surgeon – researchers used an MRI-guided navigational system with submillimeter precision

to deliver recombinant adeno-associated virus serotype 2 vector encoding human AADC (AAV2-hAADC) to the ventral tegmental area and substantia nigra pars compacta of AADC-deficient children. The idea was that such an approach would substantially rescue dopamine and serotonin biosynthesis to improve the patients’ quality of life.

That seems to be precisely what happened. The afflicted children, who in some cases could not even successfully stand, progressed rapidly after the one-time treatment and, with physical therapy, were walking within six months of the infusion.

The concept and delivery system is nearly identical to what researchers are using in the phase II AADC trial for Parkinson’s disease described on the previous page. “In my mind, this approach is appropriate for treating many different genetic disorders; we just have to know the gene correction,” says Bankiewicz, who has already published a paper describing this approach for Alzheimer’s disease, for which he expects to start a clinical trial in 2019.



Fellowship-Trained Surgeon Expands Capacity

Neurosurgeon and former UCSF resident and fellow Doris Wang, MD, PhD, has joined the movement disorders team, significantly expanding the group's capacity to treat patients with Parkinson's disease and other movement disorders using neuromodulation and ablative procedures. In addition to her work at UCSF Medical Center at Mount Zion and the San Francisco VA Health Care System, Wang will also conduct outreach clinics in Fresno, in collaboration with UCSF Fresno neurologists.

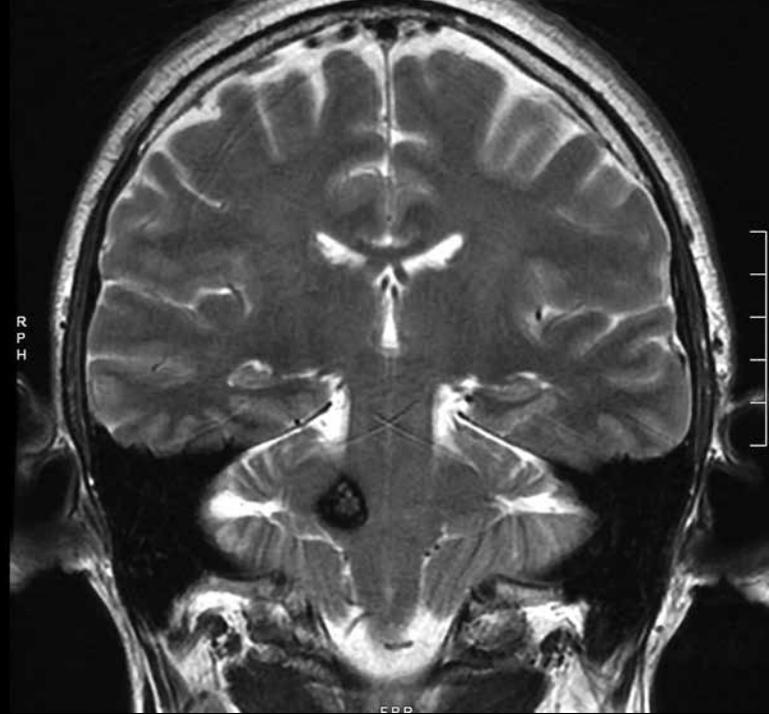
During her fellowship in stereotactic and functional neurosurgery, Wang studied human network physiology of movement disorders, and her research focuses on the neural architecture of human motor skill learning using an implanted, bidirectional deep brain stimulation (DBS) device. She aims to develop targeted, closed-loop therapies to restore motor skill learning in patients with brain diseases and injuries.

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A coronal MRI shows a cavernous malformation of the brainstem in the right pons.



Vascular Neurosurgery

UCSF Named Clinical Center of Excellence for Cerebral Cavernous Malformation

On June 2, 2018, the Angioma Alliance named UCSF a Clinical Center of Excellence in Cerebral Cavernous Malformation (CCM). UCSF is the only institution in California, and one of only six in the nation, to earn this designation, which recognizes centers that provide high-quality interdisciplinary care for adult and pediatric patients with both sporadic and familial cerebral cavernous malformation. The standard of care at the centers is expected to meet or exceed the consensus guidelines recognized by the Angioma Alliance Scientific Advisory Board.

Led by Chief of Vascular Neurosurgery Adib Abl, MD, and Nerissa Ko, MD, the UCSF Clinical Center of Excellence in CCM includes a coordinated team of nationally recognized experts from multiple specialties with extensive experience in CCM. UCSF is also home to an active clinical research program in cerebrovascular malformations through the UCSF Center for Cerebrovascular Research.

All designated centers:

- Have at least six core faculty in neurosurgery, neurology, epileptology, neuroradiology and genetics and have two additional specialty physicians with CCM expertise in any of the following disciplines: pediatric neurology, pediatric neurosurgery, dermatology or neuro-ophthalmology.
- Maintain an active clinical research program with a history of publications and must have one active internal review board (IRB)-approved CCM research project.

- Host at least one grand rounds per year.
- Organize at least one patient education event annually.
- See at least 50 CCM patients per year.
- Possess cutting-edge MRI technology, which allows for better diagnosis and follow-up care.



Rare Cerebrovascular Disorders Relatively Common at UCSF

According to vascular and endovascular neurosurgeon Adib Abl, MD, chief of vascular neurosurgery, in 2018 his team saw growing volumes for brain arteriovenous malformations (AVMs), basilar artery aneurysms and spinal vascular malformations, all relatively rare disorders.

“Basilar aneurysms are the deepest of all aneurysms, and we’ve treated more than 15 in the past year, some with surgery, some with an endovascular approach,” says Abl, who in addition to his neurological surgery training is also fellowship-trained in open vascular neurosurgery. “We also regularly perform surgeries for spinal vascular malformations, including cavernous angiomas of the spine, arteriovascular malformations and fistulae.”

In addition, says Abl, the vascular neurosurgery group has been gaining valuable experience with a new device for minimally invasive, endoscopic evacuation of hemorrhagic strokes not caused by aneurysms or AVMs. “To treat many of these bleeds, we used to perform an indirect surgical decompression, which involved removing a large portion of the skull on one side,” he says. “This device enables us to go directly after a clot in the brain with a minimal opening and a one- to two-inch-long incision, shortening the amount of time patients spend in the ICU and the hospital.”

Adib Abl, Chief of Vascular Neurosurgery

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Chief of Vascular Neurosurgery Adib Abl, MD, and nurse practitioner Marlene Burt give a neurological exam to Sharon Hardy six months after she underwent surgery for an aneurysm at UCSF Medical Center.



Edward Chang, MD, implants a responsive neurostimulation system in a patient with epilepsy.

Epilepsy



Study Finds Responsive Neurostimulation Can Help Predict Seizure Activity

According to a study in *Nature Communications*, monthly cycles of brain activity can help predict when seizures in patients with epilepsy will occur next, giving physicians a new tool for helping patients with epilepsy.¹

The authors – Vikram Rao, MD, and Edward Chang, MD, from the UCSF departments of neurology and neurological surgery – analyzed the brain activity of 37 patients who had an implanted NeuroPace responsive neurostimulation system at UCSF. The approach, which is typically reserved for patients who do not respond to medication and are not eligible for resective surgery, uses the neurostimulator to monitor interictal epileptiform activity (IEA) to detect when a seizure is about to begin and stimulates the brain using an electrical pulse to halt the seizure.

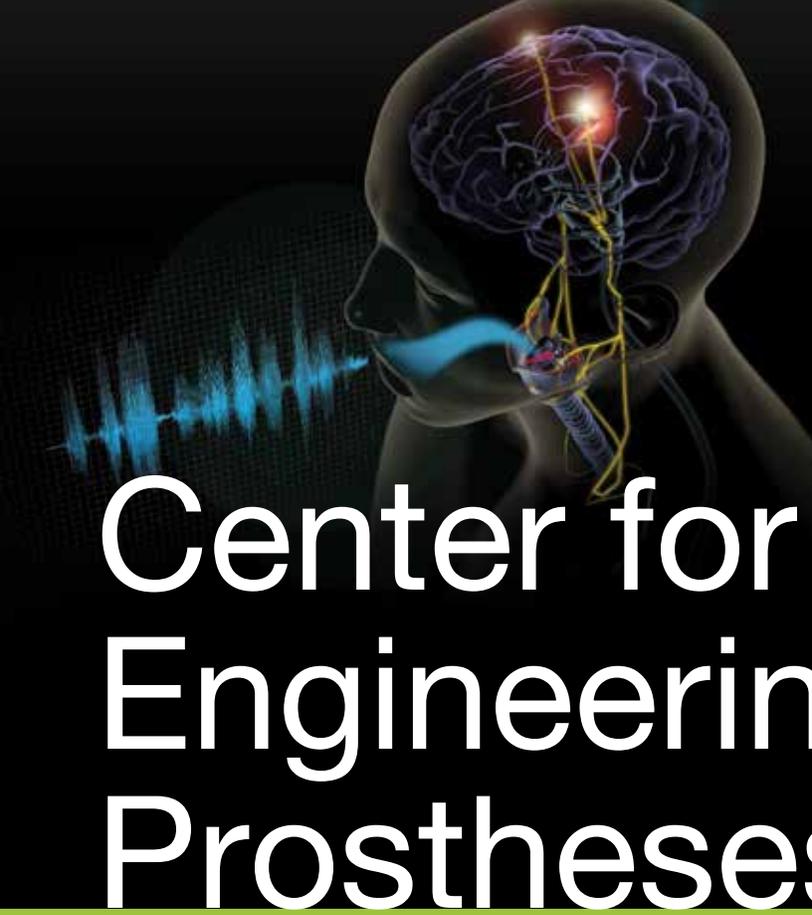
In the study, over the course of many years, the device monitored multidien (multiday) seizure cycles, which are most commonly 20-30 days in duration. Such cycles, wrote the

research team, “are robust and relatively stable for up to 10 years in men and women.” The study showed, for the first time, that seizures tend to occur during the rising phase of multidien IEA rhythms, thus providing a novel biomarker for determining relative seizure risk.

Because of the length of time patients were in the study – one patient participated for more than 10 years – the researchers saw patterns of brain activity they had never observed before. “Knowing the risk of a seemingly random event is helpful to living your life and modifying your behavior,” says Rao. “If I could tell you there’s a 90 percent chance of thunderstorms, you’d probably do something different, like pack an umbrella or cancel the trip to the beach. Whereas if there’s 100 percent chance of sunshine, that’d be helpful to know, too.”

Reference

1. Baud MO, Kleen JK, Mirro EA, Andrechak JC, King-Stephens D, Chang EF, Rao VR. Multi-day rhythms modulate seizure risk in epilepsy. *Nat Commun*. 2018;9(1):88.



Center for Neural Engineering and Prostheses

How the Brain Makes Intelligible Speech

A study by scientists at the Center for Neural Engineering and Prostheses – a joint project of neuroscientists at UCSF and engineers at UC Berkeley – reveals how human beings engage the dozens of muscles that shape our breath into the sounds that form words and sentences.¹ According to neurosurgeon and senior author Edward Chang, MD, the findings could ultimately help engineers create brain implants that monitor neural activity related to speech production and translate the signals into synthetic spoken language for people unable to speak.

Published in *Neuron*, the study used direct cortical recordings from the human sensorimotor cortex while participants spoke natural sentences that included sounds spanning the entire English phonetic inventory to reveal how the brain's speech centers are organized. Doctoral degree candidate Josh Chartier

and Gopala K. Anumanchipalli, PhD, researchers in the Chang lab, led the study in collaboration with linguist Keith Johnson, PhD, of UC Berkeley. After placing electrocorticography (ECoG) electrodes over a region of ventral sensorimotor cortex that is a key center of speech production, the researchers had five volunteers awaiting epilepsy surgery read aloud a collection of 460 natural sentences designed to capture a comprehensive collection of American English articulations.

The ECoG mapping ultimately revealed that the brain's speech centers are organized more according to the physical needs of the vocal tract as it produces speech than by how speech sounds. One example: the mouth might form what are typically understood as identical sounds differently, depending on the vowels that follow.

Reference

1. Chartier J, Anumanchipalli GK, Johnson K, Chang EF. Encoding of articulatory kinematic trajectories in human speech sensorimotor cortex. *Neuron*. 2018;98(5):1042-1054.e4.



Community Extension

Steady Expansion Extends Neurosurgical Expertise to Surrounding Communities

“Over the last seven and a half years, we have steadily grown our ability to bring UCSF neurosurgery experts into communities throughout the greater Bay Area,” says UCSF neurosurgeon Tarun Arora, MD, the department’s director of community extension. “In 2018, we had a number of exciting developments all aimed at collaborating with physicians closer to each patient’s home.”

At Marin General Hospital, for example, Catherine Miller, MD – a neurosurgeon who recently completed a complex spine surgery fellowship with Praveen Mummaneni, MD – became the third UCSF faculty member at the facility. “In addition,

we’re building on our tumor and radiosurgery program at Marin General, including expanding access to clinical trials and other specialized services,” says Arora.

The department also has faculty practicing at Saint Francis Memorial Hospital in San Francisco, Queen of the Valley Medical Center in Napa, Highland Hospital in Oakland, and the newly opened John Muir Health/UCSF Health Berkeley Outpatient Center. The latter center services patients in Berkeley, Oakland, Emeryville and the surrounding areas, who now have access to a range of top primary and specialty care doctors – including neurological surgeons – as well as urgent care and other health care services under one roof.

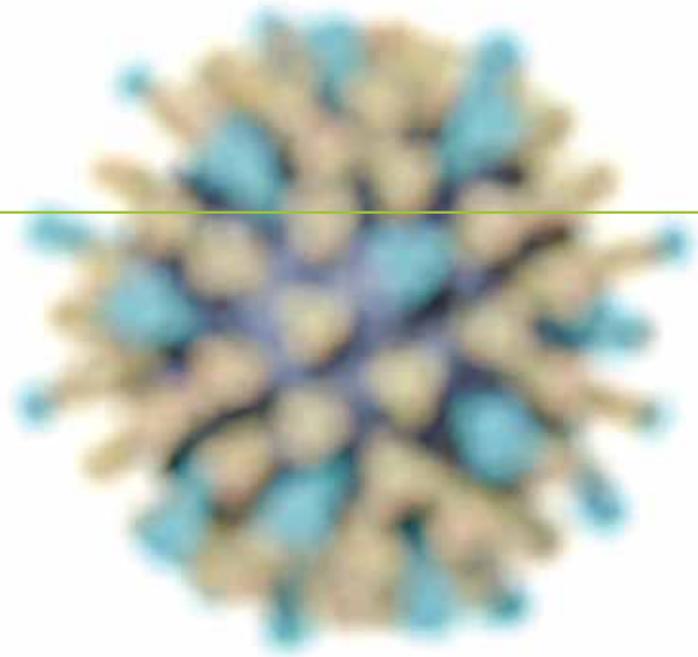
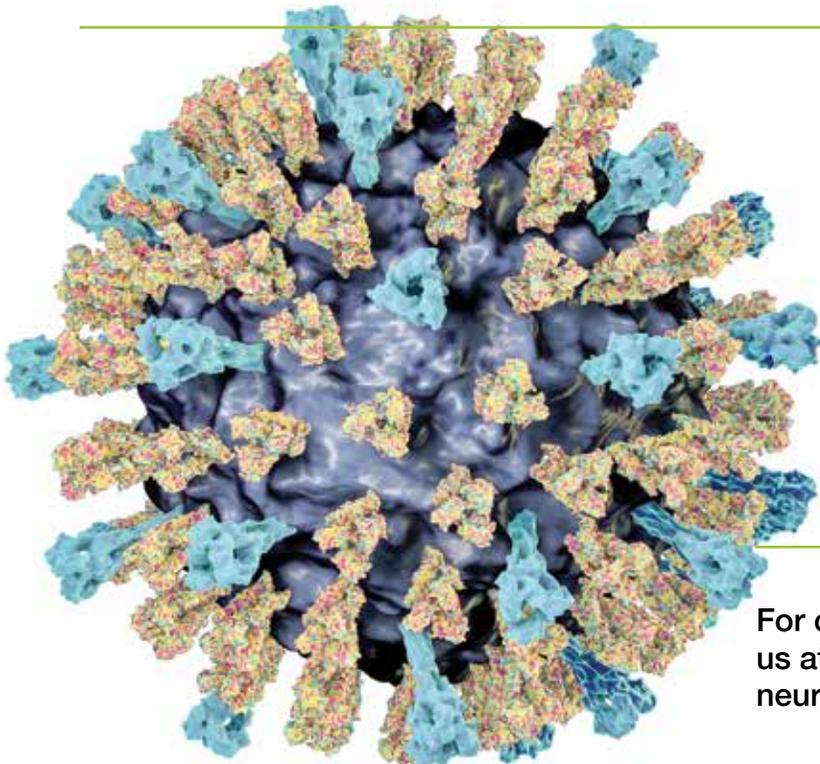
“We have steadily grown our ability to bring UCSF neurosurgery experts into communities throughout the greater Bay Area” – Taron Arora, MD

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