volume 8 number 5 | ucsf department of neurological surgery

neurosurgery news

Stem Cell Therapy for Brain Tumors Speeds towards Investigational New Drug Application

The California Institute for Regenerative Medicine (CIRM) has awarded a grant of over $19 million to advance stem-cell-based strategies for treating glioblastoma – the most aggressive form of primary brain tumor. The objective of the grant is to file an investigational new drug (IND) application with the U.S. Food and Drug Administration within four years, driving a stem-cell-associated therapy towards clinical trial in 2015. The studies will be led by Mitchel S. Berger MD, chair of the UCSF Department of Neurological Surgery and director of the UCSF Brain Tumor Research Center, and includes collaborators at the Ludwig Institute for Cancer Research at the University of California, San Diego; the Burnham Institute for Medical Research; the University of California, Los Angeles; and the Salk Institute. The overall goal of the project is to genetically engineer stem cells that deliver therapeutic agents to selectively kill glioblastoma cells. The concept is based on the research team's discovery that stem cells naturally home to brain tumor cells. If the product of this research is approved by the FDA, it would be tested first in patients with recurrent glioblastoma.

The Stem Cells

Stem cells were first observed to home to tumor cells in 1995 when a team at the Harvard Institutes of Medicine, led by Evan Snyder PhD, injected neural stem cells into a rodent model of glioma. They were looking to prove that stem cells could migrate within the adult brain and potentially be used for delivering therapeutic gene products. "We saw that stem cells could spread widely and that the presence of disease changed their migration patterns in the brain," says Snyder, currently professor at the Burnham Institute and co-investigator for the CIRM project. How and why stem cells track brain tumor cells is not well understood and remains an active area of investigation. "There are three main reasons this could be happening," says Snyder. "The first is that tumors may produce chemo-attractants that stem cells follow. Second, stem cells follow damage in the brain, possibly to repair these areas. And finally, because stem cells and tumor cells are basically two sides of the same coin, they may simply be responding to similar cues."

Regardless of the mechanism, their ability to selectively home to tumor cells has made stem cells an attractive delivery vehicle for anti-tumor drugs. Preliminary studies have shown that neural stem cells injected into glioblastoma can spread throughout a tumor mass, but stop at the interface with normal brain except where brain tumor cells are infiltrating normal parenchyma, in which case neural stem cells follow the migrating tumor cells. The UCSF-led team hopes to take advantage of this finding to allow the stem cells to deliver drug only to the tumor cells, avoiding harm to normal tissue – a major drawback associated with current therapeutic regimens. "It's really an evolution of viral gene therapy," says Elizabeth Read MD, adjunct professor of laboratory medicine at UCSF and consultant for the project. "The efficacy of gene therapy has been limited because of distribution. Stem cells may be a better delivery vehicle."

During the first six months of the new project, the team will be evaluating three types of stem cells to determine which will be the most effective vector: mesenchymal stem cells (derived from adult bone marrow); adult neural stem cells (derived from adult neurosurgical patients); and fetal neural stem cells (derived from fetal brain tissue). There is little consensus regarding which stem cell type is the best candidate for drug delivery in the brain, and a head-to-head comparison, being done for the first time in these studies, could

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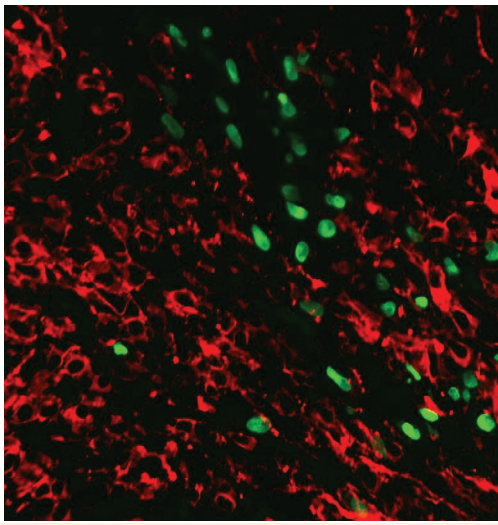
Mesenchymal stem cells (green) injected directly into intracranial tumor show ability to disseminate/migrate within tumor (red).



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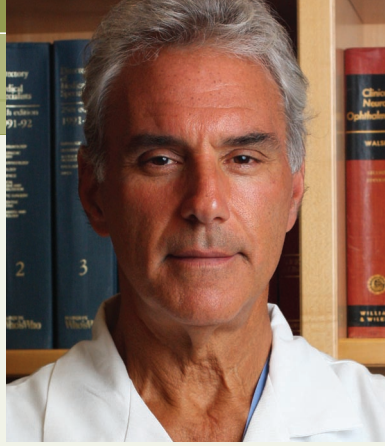

The "California Stem Cell Research and Cures" ballot initiative, passed in November of 2004 by California voters, radically changed the landscape of stem cell research in the United States. It established the California Institute of Regenerative Medicine (CIRM) to allocate funding across the full range of stem cell research at a time when federal funding had all but grinded to a halt. As a result, top stem cell scientists were recruited to universities and biotechnology companies throughout California, allowing the state to move into a position where it could be competitive with other areas of the world, while maintaining rigorous standards for safety and ethics.

A core priority of CIRM is to promote collaboration between "competing" institutions by funding projects that bring together the best researchers from across the state. I am pleased to announce that a team led by the Department of Neurological Surgery at UCSF has recently been granted over $19 million to develop a stem cell therapy for brain tumor patients that will move into clinical trials by 2015 (see page 1). Our collaborators for this research are located at the Ludwig Institute for Cancer Research at the University of California, San Diego; the Burnham Institute for Medical Research; the University of California, Los Angeles; and the Salk Institute. Without the legislation established in California, this kind of multi-center, translational stem cell research would not be possible. CIRM has a unique ability to fund projects with less preliminary data than would be required by the National Institutes of Health, and the Disease Team Awards are mechanisms to support high-risk research for the patients most in need of new treatments.

The stem cell product being developed by our team will first be tested in patients with recurrent glioblastoma, the most lethal type of brain tumor. Glioblastoma is highly resistant to current therapies, including chemotherapy and radiation, and survival expectations at recurrence are measured in weeks to months. Clearly there is an urgent, unmet need to improve treatment options for these patients.

To have reached a point where we are ready to conduct clinical trials of stem cell therapies in humans is a remarkable feat. Currently two Neurological Surgery faculty members, David Rowitch MD, PhD and Nalin Gupta MD, PhD, chief of pediatric neurosurgery, are involved in a phase I clinical trial of neural stem cells for Pelizaeus-Merzbacher Disease, a rare condition affecting children that makes them unable to form myelin. The study, sponsored by Stem Cells Inc., is the first clinical trial involving stem cells for this disease and only the second clinical trial using human neural stem cells in humans in the United States. As a phase I study, the primary goal is to ensure the safety of the therapy, but investigators will also be using MRI scans to search for evidence of new myelin formation.

At UCSF, we are fortunate to work in an environment that emphasizes the importance of translational research, and the science being performed as a result of the CIRM Disease Team Award mechanism especially highlights the feedback loop between product development, preclinical evaluation, and clinical application. These experiments are about discovery and illustrate that translational research is not a linear procedure, but rather a dynamic process. The types of interactions that drive translational research thrive best under conditions where clinicians and scientists work in close proximity, and UCSF continues to build the infrastructure essential to creating those conditions. This year, we will open the doors of the Regneration Medicine Building, which will house the Eli and Edythe Broad Program in Regeneration Medicine, and by 2012 a Neuroscience Institute will be completed on the Mission Bay campus. With this commitment and support from CIRM and the community, UCSF is at the forefront of beginning to realize the potential of stem cell therapy.

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Kathleen M. Plant
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Director, Brain Tumor
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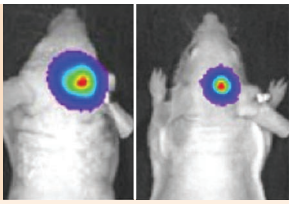

Bioluminescence images of a mouse model of brain tumor. The area covered by the colored halo is proportional to the amount of tumor. An untreated mouse (left) exhibits more tumor than a mouse treated with a chemotherapeutic agent (right).

Stem Cell Therapy for Brain Tumors Speeds towards Investigational New Drug Application

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settle the debate. Fetal neural stem cells do not carry the pluripotent characteristics of embryonic stem cells, but may be the frontrunner for these experiments because the simple fact of their youth makes them more robust and responsive than adult stem cells. The cell type used in the project's subsequent experiments will ultimately be chosen based on longevity in brain tumor homing, biodistribution, pharmacokinetic profile, and proliferative capacity.

To account for the possibility that the stem cells may give rise to new undifferentiated cells in the brain and form tumors, they will be engineered with a suicide gene that can be activated once the drug has been delivered to the tumor cells and an anti-tumor effect is seen. It would also be activated if patients were to show signs of clinical deterioration.

The Drugs

In the next phase of the project, investigators will select the optimal tumor-killing agent with which to arm the stem cells. Currently under consideration are tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and the enzyme cytosine deaminase (CD). TRAIL is a secreted, soluble protein that interacts with death receptor 4, frequently found on glioblastoma cells, to become activated and induce apoptosis. It has long been studied in animal models of tumors and has been a promising candidate for targeted cancer therapy. Although TRAIL has a high therapeutic index for tumor, there is variable expression of death receptor 4 across individual glioblastoma samples. To account for this variability, investigators will test both high and low expression of death receptor 4 in an animal model to test the sensitivity of the drug. "Direct cell killing may be the most effective way to kill the tumor," says Snyder. "The specificity of TRAIL may also be more desirable than a therapy that causes off-target effects."

Evidence from other preclinical studies makes an equally enticing argument for using CD. The enzyme converts the non-toxic prodrug 5-fluorocytosine (5-FC) into cytotoxic 5-fluorouracil (5-FU), which is efficacious for killing tumor cells in animal models. It can cross the blood-brain barrier and incorporates into the DNA of cancer cells, causing damage that is difficult for the cells to repair. "One potential advantage of CD over TRAIL is that a broader range of tumor types may show sensitivity," says C. David James PhD, professor of neurosurgery at UCSF and co-investigator for the grant.

The Delivery

Whether or not the therapy will be successful in combating brain tumors largely depends on whether or not the drug reaches tumor cells in sufficient quantities and if the stem cells are able to track satellite tumor cells that remain after surgery. These satellite cells contribute to the recurrence of glioblastoma and a critical aim of this study is to eradicate them. A variety of delivery methods will be examined in an intracranial, xenograft mouse model of glioma, including intracarotid injections and direct intratumoral injections. The stem cells will be tagged with luciferase – a fluorescent molecule that allows the cells to be easily identified – so that investigators can follow the distribution of the vectors. The bioluminescent imaging techniques to visualize the migration of the cells were developed by Dr. Snyder and colleagues while at Harvard University, and are now being used at UCSF.

The primary goal of the work is to ensure the safety of the therapy, and specifically to ensure that the stem cells do not begin to divide and become tumorigenic. A secondary goal is to observe how much the experimental tumors respond. These preclinical studies may also give the investigators clues as to whether a second or third dose might be needed, and when these would need to be administered to human patients during clinical trials.

For more about the project, visit: http://neurosurgery.ucsf.edu/index.php/research_BTRC_CIRM.html

For more about CIRM and the Disease Team Awards, visit: http://www.cirm.ca.gov/

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Isaac Yang MD completed his neurosurgical residency in June, 2010 after serving as chief resident in the UCSF Department of Neurological Surgery. Originally from Lodi, California, Dr. Yang's interest in neurobiology began as an undergraduate at UC Berkeley where he earned an undergraduate degree with a double major in Molecular and Cell Biology, emphasis Neurobiology, and Social Welfare, emphasis Sociology, with highest honors and Phi Beta Kappa. He then attended the UCLA School of Medicine where he graduated with AOA honors, the Dean's Outstanding Thesis Award, and the Lasky Memorial Research Award.

As a neurosurgery resident at UCSF, with Andrew Parsa MD, PhD, Dr. Yang help to characterize the natural history of vestibular schwannoma and the important prognostic factors that affect radiosurgery and microsurgical treatment of these lesions. With Nicholas Barbaro MD, he detailed the role of radiosurgery for medically resistant epilepsy. With Michael Lawton MD, Dr. Yang documented the complex surgical technique of creating aneurysm clip tubes utilizing fenestrated aneurysm clips. With Manish Aghi MD, PhD, he published in *Nature Reviews Clinical Oncology* the recent advances in imaging technology that can distinguish treatment effect from tumor recurrence after anti-VEGF therapy. Most recently, in collaboration with Drs. Barbaro and Parsa, Dr. Yang reported the improved seizure control outcomes for early intervention with microsurgery in adult patients with ganglioglioma tumors.

Dr. Yang's principal research goals are to investigate novel applications of immunotherapy to malignant human gliomas. In 2008, Dr. Yang completed a postdoctoral research fellowship in the UCSF Brain Tumor Research Center laboratory of Dr. Parsa. With support from an NIH National Research Service Award Fellowship, he analyzed the immunologic profile of human glioblastoma patients to study the correlation of immunologic markers and infiltrate with patient outcome. He was subsequently awarded the Congress of Neurological Surgeons Dandy Research Fellowship to pursue his research in glioblastoma immunology.

While a resident at UCSF, Dr. Yang's clinical and research efforts have been recognized with the American Association of Neurological Surgeons Leksell Award, the American Academy of Neurological

residents' publications

Chang EF, Edwards E, Nagarajan SS, Fogelson N, Dalal SS, Canolty RT, Kirsch HE, Barbaro NM, Knight RT. Cortical spatio-temporal dynamics underlying phonological target detection in humans [published online ahead of print May 13, 2010]. J Cogn Neurosci. doi:10.1162/jocn.2010.21466.

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Yin D, **Richardson RM,** Fiandaca MS, Bringas J, Forsayeth J, Berger MS, Bankiewicz KS. Cannula placement for effective convection-enhanced delivery in the nonhuman primate thalamus and brainstem: implications for clinical delivery of therapeutics [published online ahead of print Apr 2, 2010]. J Neurosurg. doi: 10.3171/2010.2.JNS091744.

and Orthopedic Surgeons Resident Research Award, the Edwin Boldrey Award from the San Francisco Neurological Society, the American Association of Neurological Surgeons Integra Brain Tumor Award, the Kaiser Award from the San Francisco Neurological Society, a UCSF Translational Scientist Training Research Grant, and the UCSF Department of Neurological Surgery's Howard Nafzigger Resident of the Year Award and Susan Eastwood Memorial Award for best resident publication. He was also the only resident at UCSF to receive the 2010 UCSF Medical Center Exceptional Physician Award.

Dr. Yang also has a dedicated passion to teaching and has served as a teacher and mentor at the UCSF School of Medicine, San Francisco State University, and UC Berkeley. He has been honored with the American Medical Student Association Golden Scalpel Award, Distinguished Mentor Award, the Golden Apple (twice), the American College of Surgeons National Resident Teaching Finalist Award, and the UCSF School of Medicine Outstanding Teaching Award.

Dr. Yang is dedicated to improving the care and treatment of patients with brain tumors and feels deeply indebted to all of his teachers and mentors who have guided him on this path. After residency, he will continue his passion for academic neurosurgery, brain tumor research, and skull base tumors as a faculty member in the Department of Neurosurgery at the UCLA Geffen School of Medicine.

C. David James obtained his PhD in Biomedical Sciences from Wright State University, Dayton, Ohio in 1986. He subsequently trained as a post-doctoral fellow at the Ludwig Institute for Cancer Research, Montreal, with Webster Cavenee PhD, from 1986 to 1989. During his post-doctoral training he developed an interest in the genetics and molecular biology of central nervous system (CNS) tumors, which have served as the primary focus of his research for 25 years. His first independent position was as a Senior Staff Investigator in the Department of Neurosurgery at Henry Ford Hospital in Detroit, MI, where he was a key contributor in launching the institution's first program in neuro-oncology research.

In 1991, Dr. James relocated to Emory University as a faculty member in the Department of Neurosurgery, and, as before, helped initiate a program in neuro-oncology research. In 1996, he accepted a faculty position in the Department of Laboratory Medicine and Pathology at the Mayo Clinic in Rochester, MN, where he was promoted to Professor in 2001. During his tenure at Mayo (1996 to 2006), Dr. James' research leadership was of fundamental importance to establishing neuro-oncology as a premier program in the Mayo Comprehensive Cancer Center, and the Center was awarded a Specialized Program of Research Excellence grant from the National Cancer Institute in 2004. In 2006, Dr. James joined the faculty of the UCSF Department of Neurological Surgery and Brain Tumor Research Center, where he serves as the Center's Associate Director.

In addition to his independent and programmatic research efforts, which utilize CNS tumor genetic information for testing therapeutic hypotheses in rodent models, Dr. James is a member of the editorial boards for the *International Journal of Oncology, Clinical Cancer Research,* and he is a Senior Editor for the journal *Neuro-Oncology.* Dr. James served as the Basic Science Director for the Society for Neuro-Oncology from 1999 to 2001, and is a current member of the Scientific Advisory Committees for the Pediatric Brain Tumor Foundation and the National Brain Tumor Society. In addition to these activities, he has served on numerous review committees for the National Institutes of Health (NIH), including his current membership with the Clinical Neuroimmunology and Brain Tumors Study Section.

Dr. James' research has been continuously supported by the NIH since 1991, and he has authored more than 120 peer-reviewed research publications, among which he is best known for his seminal contributions involving genetic alterations that are associated with CNS tumor development.

selected publications

Dinca EB, Lu K, Sarkaria J, Pieper RO, Prados MD, Haas-Kogan D, VandenBerg SR, Berger MS, **James CD.** p53 Small Molecule Inhibitor Enhances Temozolomide Cytotoxic Activity against Intracranial Glioblastoma Xenografts. Cancer Res 2008;68:10034-39.

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Michaud K, Solomon DA, Oermann E, Kim J-S, Zhong W-Z, Prados MD, Ozawa T, **James CD,** Waldman T. Pharmacologic inhibition of cdk4/6 arrests the growth of glioblastoma multiforme intracranial xenografts. Cancer Res 2010;70:3228-38.

Manish Aghi MD, PhD, assistant professor of neurological surgery, will be principal investigator on the upcoming Phase I clinical trial "A Phase 1 Ascending Dose Trial of the Safety and Tolerability of Toca 511 in Patients with Recurrent GBM," which will be performed at UCSF and will study non-replicating retroviruses for the treatment of recurrent glioblastoma.

Mitchel S. Berger MD, Kathleen M. Plant distinguished professor and chair of neurological surgery has been elected Vice President of the American Association of Neurological Surgeons. He has also been appointed to serve on the new National Football League Head, Neck and Spine Medical Committee. The committee replaces the Mild Traumatic Brain Injury Committee and will focus on health and safety for NFL players. Dr. Berger will particularly be focused on retired players' issues.

Michael S. Beattie PhD, professor of neurological surgery, and **Geoffrey Manley MD, PhD,** professor of neurological surgery, have been awarded over $1.1 million by the Department of Defense Spinal Cord Injury Research Program to develop preclinical models of cases of combined head and spinal cord injury. They will partner with Graham Creasey MD at the VA Health Service Palo Alto. Other investigators from the UCSF Brain and Spinal Injury Center include **Jacqueline Bresnahan PhD** and **Adam Ferguson PhD.**

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

Rebecca Ihrie PhD, postdoctoral fellow in the laboratory of Arturo Alvarez-Buylla PhD, has been awarded the American Association for Cancer Research–National Brain Tumor Society Fellowship, in memory of Bonnie Brooks. Dr. Ihrie received this award for her project entitled "Developing a Novel Model of Pediatric Glioblastoma." Two AACR–NBTS awards are given nationally each year.

Claudia Petritsch PhD, assistant adjunct professor of neurological surgery, has been awarded the American Brain Tumor Association Research Discovery Grant for her project "Asymmetry-Defective Oligodendroglial Progenitors as Potential Origin of High-Grade Oligodendroglioma."

Andrew Parsa MD, PhD, associate professor of neurological surgery and Reza and Georgianna Khatib endowed chair in Skull Base Tumor Surgery, was recognized with the Journal of Neuro-Oncology Award given by the Joint Section on Tumors of the American Association of Neurological Surgeons. He was also given the Most Dedicated Mentor Award under the Pathways to Careers in Clinical and Translational Research (PACCTR) Program at UCSF, and was a UCSF School of Medicine Kaiser Teaching Award Nominee.

Michael Prados MD, professor and Charles B. Wilson endowed chair of neurological surgery, is the principal investigator of a new project funded by the Ben and Catherine Ivy Foundation to develop a brain tumor clinical trials consortium of 5 major institutions across the United States. The main objective of the consortium will be to perform small, enriched-patient clinical trials in patients with recurrent GBM who are scheduled for repeat surgery to screen promising molecularly targeted agents and to validate drug distribution, pharmacokinetics, and pharmacodynamics in tumor tissue. Another objective will be to create a virtual tissue bank to prospectively identify patient subgroups who will be candidates for clinical trials done at time of tumor recurrence.

Philip Starr MD, PhD, professor and Dolores Cakebread endowed chair of neurological surgery, has been granted an R01 award from the NIH to study cortical and basal ganglia local field potentials in human movement disorders.

Michael E. Sughrue MD, resident in the Department of Neurological Surgery, was recognized with the Ronald L. Bittner Award for best neuro-oncology abstract by the American Association for Neurological Surgeons.

Isaac Yang MD, recent chief resident in the Department of Neurological Surgery, has been honored with several recent awards, including the American Association of Neurological Surgeons Integra Foundation Brain Tumor Award; the San Francisco Neurological Society Edwin F. Boldrey Award for Basic Science Research; the UCSF Clinical & Translational Science Resident Research Award; and the American Medical Student Association Golden Scalpel Award. He received the Susan Eastwood Memorial Award for best resident publication and the Howard Nafzigger Resident of the Year Award, both from the Department of Neurological Surgery. Dr. Yang was also the only resident to receive the UCSF Medical Center Exceptional Physician Award in 2010.

In Memoriam

The Department of Neurological Surgery honors the memory of two distinguished colleagues who passed away this year. **Harold Rosegay MD,** known affectionately as the Colonel by his residents, joined the faculty of the UCSF Department of Neurological Surgery in 1972. He was honored consistently over the years as both a pre-eminent neurosurgeon and revered teacher, receiving several prestigious awards, including the Resident Teaching Award in Neurosurgery virtually every year until the award was named for him. In 1998, Dr. Rosegay's residents and colleagues expressed their admiration and their gratitude for his guidance by dedicating a library named in his honor to carry on his legacy as a neurosurgeon, teacher, scientist, and scholar. Following retirement, Dr. Rosegay was named Professor Emeritus and pursued his research interests in the history of neurological surgery.

Byron Cone Pevehouse MD earned his MD from Baylor Medical School in 1952, and performed his neurosurgical residency training at UCSF from 1954 to 1958. Dr. Pevehouse served as the Chief of Neurosurgical Services for UCSF at San Francisco General Hospital and Chief of Pediatric Neurosurgery at the UC Medical Center for many years. In 1967, he was appointed Chairman of the Department of Neurological Surgery at University of Pacific-Presbyterian Medical Center, serving in this position for 23 years. Dr. Pevehouse served nationally as President of the American Association of Neurological Surgeons and the Society of Neurological Surgeons, and was founder of the neurosurgical resident matching program. He served as a major advocate of medical malpractice regulation legislation in California and neurosurgical Medicare billing code reform in Washington, D.C. We celebrate the lives of these extraordinary physicians who will be greatly missed but fondly remembered.

New Faculty

The Department of Neurological Surgery at UCSF is pleased to welcome five new members to our faculty. **Michael Huang MD,** specializing in skull base and cerebrovascular surgery, will join the Neurosurgery clinical faculty as an assistant clinical professor in August, 2010. Dr. Huang has recently completed a skull base and cerebrovascular fellowship at the University of South Florida.

Adam Ferguson PhD, former postdoctoral fellow, has become an assistant adjunct professor of neurological surgery and joins the investigators of the UCSF Brain and Spinal Injury Center.

Edward F. Chang MD, former resident in the Department, will join the faculty as an assistant professor. His clinical practice will focus on brain tumors, epilepsy, and movement disorders, and he will also serve as director of our forthcoming Center for Neural Engineering.

Vincent Wang MD, PhD, former resident in the Department, will join the faculty as a clinical instructor at our outreach clinics at Saint Francis Hospital, St. Mary's Hospital, Chinese Hospital, and Marin General Hospital.

Finally, we are pleased to be brining on board two speicialists in neuropathology, **Joanna Phillips PhD** and **Arie Perry PhD.**

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selected recent publications from the department of neurological surgery

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