Preuss Laboratory Awarded Grant

Mark Israel MD, Kathleen M. Plant Distinguished Professor in the Department of Neurological Surgery and Director of the Preuss Laboratory for Molecular Neuro-Oncology in the Brain Tumor Research Center, has been awarded a grant of over $2 million to fund the development of animal models of brain tumors. Bill Weiss MD, PhD, Assistant Professor of Neurology and Pediatrics, is the coinvestigator participating in this work. This grant funds not only work to develop, characterize, and utilize mouse models of human brain tumors, but also participation of these UCSF investigators in the National Cancer Institute’s Mouse Models of Human Tumor Research Center, has been awarded a grant of over $2 million to fund the development of animal models of brain tumors. Bill Weiss MD, PhD, Assistant Professor of Neurology and Pediatrics, is the coinvestigator participating in this work. This grant funds not only work to develop, characterize, and utilize mouse models of human brain tumors, but also participation of these UCSF investigators in the National Cancer Institute’s Mouse Models of Human Tumor Research Center.

Gala Tribute to Michael Douglas Raises Funds for UCSF’s Brain Tumor Research Center

A benefit concert held at Davies Symphony Hall in honor of actor Michael Douglas helped raise $1.4 million to help fund the Michael Douglas Pediatric Brain Tumor Research Center at UCSF. The sold-out “Stars for Life” tribute was organized by Deborah Strobin and hosted by “Entertainment Tonight” star Mary Hart. Hart’s husband, Burt Sugarman, who underwent surgery for a brain tumor at UCSF nearly 10 years ago, was the impetus for Douglas’ becoming involved in fundraising for brain tumor research. Among the stars in attendance were Kirk Douglas, Danny DeVito, Paula Abdul, Genevieve Bujold, Sean and Robin Wright Penn, Karl Malden, and Sharon Stone. Broadway show tunes were sung by stage stars LeRoy Reams, Nancy Dussault, Karen Morrow, and Davis Gaines, and stand-up comedy was delivered by Ellen DeGeneres.

In welcoming the audience to this very special event, Mitchel Berger MD, Chairman of the Department of Neurological Surgery at UCSF and Director of the Brain Tumor Research Center (BTRC), and Charles Wilson MD, founder and former BTRC Director (1972-1997), thanked them for helping the BTRC to intensify its efforts in finding a cure for childhood brain tumors. Although brain tumors rank second only to leukemia as the most common cancer in children, enormous strides have been made toward curing leukemia, whereas the outlook for children with brain tumors is persistantly bleak. The BTRC’s team of basic scientists, clinical researchers, physicians,
As we enter a new century, there has never been a better time in science and translational medicine. Great new techniques are now available to us, such as gene sequencing and molecular biology methodologies, and vast research possibilities have opened up through the use of transgenic animal models. With these tools, it is at last realistic to pursue true bench-to-bedside translational research. During the past year, our neurosurgical faculty has made a commitment to bringing basic scientists to work with us—to rebuilding the department on a collaborative foundation strengthened by an underlying translational theme. The key to this new structure is translational research partnerships. We have designated many different neurosurgical research interests that are amenable to a translational approach. In each specific area, neurosurgeons trained in research are paired together with basic scientists in such a way that the clinical and basic science perspectives catalyze one another. New basic science faculty who have joined us in this partnership are introduced in this newsletter. In the Brain Tumor Research Center (BTRC), for example, the neuro-oncology research team pairs clinical trialists Mike Prados and Susan Chang with clinician researchers like Sandeep Kunwar, whose specialty is immunotoxin therapy for malignant brain tumors, and Kelly Nicholas, whose expertise lies in developing transgenic brain-tumor model systems. These BTRC clinician-researchers are likewise paired with basic scientists like Joe Costello, who is doing groundbreaking work in functional genomics. The developing cerebrovascular research team pairs neurosurgeon Michael Lawton with Julie Ellison, who has been recruited to direct the department’s Ischemia Research Program. Working in partnership, neurosurgeons Warwick Peacock and Nicholas Barbaro and basic scientist Scott Baraban are defining the biomedical basis of childhood epilepsy so as to develop better ways of treating it. Neurosurgeon Bill Rosenberg and biomechanical engineer Tony Keaveny on the UC Berkeley faculty have established the Neurospinal Biomechanics Research Program, investigating spinal biomechanics and patient-oriented outcomes studies as they apply to spinal disorders. Our commitment to translational research means partnerships between clinicians and basic scientists working together, meeting together as faculty within the same department, under the same leadership, with a united purpose. Having made this investment in a future of translational research, we are meeting the new millennium with confidence that it will reap rewards in better treatment for our patients.

—Mitchel S. Berger MD
Parkinsonism at Emory University. Currently, Dr. Starr is using human intraoperative data to investigate the pathophysiology of dystonia. In addition, he is supervising Neurosurgery resident Philip Theodosopouls MD in a study of the physiology and somatotopy of the human subthalamic nucleus in the parkinsonian state.

Dr. Starr's Selected Publications


Post-traumatic Inflammation May Contribute to Central Nervous System Pathogenesis and Recovery of Function

The recovery of function after traumatic brain and spinal-cord injury does not depend simply on the consequences of the initial mechanical destruction of tissue, but is also attributed to the evolution of complex secondary events that contribute to early as well as delayed cell injury. In the laboratory of Linda Noble PhD, Professor of Neurological Surgery and Director of the Program for Neurotrauma Research, experimental models of traumatic brain and spinal-cord injury in the rodent are used to study the early events that contribute to cell injury and impair functional recovery. The studies are focused on the role of the blood-brain and blood-spinal cord barriers in early pathogenesis after traumatic injury, the acute and chronic influences of...
inflammation on both injury and repair mechanisms, and the identification of those cellular defense mechanisms intrinsic to the brain and spinal cord that protect against secondary injury and may be essential for limiting the extent of cell injury. An established expert in the field of neurotrauma, Dr. Noble has done studies involving the development and refinement of experimental models of traumatic brain and spinal cord injury that mimic the human condition. These models have been used to study biological events that mediate cell injury and to assess the therapeutic efficacy of pharmacological interventions after injury.

In recent studies, Noble’s laboratory has showed that disruption of the blood-brain barrier induces the stress protein heme oxygenase in glia throughout the brain. Similarly, both traumatic brain and spinal-cord injury result in prominent induction of heme oxygenase in glia. Both pharmacologic and molecular strategies are now being used to test the hypothesis that this stress response is neuroprotective and may serve to limit the extent of progressive cell injury after trauma. Dr. Noble notes that there is evidence that post-traumatic inflammation may contribute to both central nervous system pathogenesis and recovery of function. Transgenic animals are providing essential models for better defining the role of inflammation in central nervous system injury.

Dr. Noble has served as Secretary and Vice President of the Neurotrauma Society and editor of the Neurotrauma Newsletter. She is a member of the editorial board for the Journal of Neurotrauma. Funded by the National Institutes of Health (NIH) to study trauma to the brain and spinal cord, she has served as a member and chair of the Neurology B1 study section of the National Institute of Neurological Disorders and Stroke, which recommends NIH funding for research projects involving the nervous system.

**Dr. Noble’s Selected Publications**


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**In the News...**

An article in *The New Yorker* and a forecast issue of the *British Medical Journal (BMJ)* have recently focused public esteem on former Neurological Surgery chairman Dr. Charles Wilson and his remarkable achievements. In *The Physical Genius* by *New Yorker* reporter Malcolm Gladwell, Wilson is portrayed as one of a handful of people—like cellist Yo-Yo Ma, basketball hero Michael Jordan, and ice hockey great Wayne Gretzky—that have a gift of sensing subtle patterns that gives them an affinity for translating thought into action. Gladwell creates a memorable portrait of Wilson as a neurosurgeon who is an archetype of that unique form of genius. Articles written by Wilson for the BMJ were of key interest at a major video press conference held in London in November, when the BMJ was one of 42 journals worldwide devoting a theme issue to the impact of new technologies on the future of medicine. Participating in the conference via audio link from California, Wilson elaborated on his articles, projecting the impact of medical technologies on the future of hospitals and the future use of sensors in medicine. He predicted that, while genomics will bring fundamental changes, vaccines will have the biggest impact, and sensors will transform health care, making laboratory testing, monitoring, pharmacologic dosing, and even surgery virtually a matter of home health care. Wilson continues to perform surgery and teach at UCSF, and is also a Director of the Institute for the Future. He performed his 3000th transsphenoidal operation to remove a pituitary tumor on June 22, 1999.


Charles B. Wilson MD, MSHA, DSc
Four Individuals Have Recently Joined Our Department.

Scott Baraban PhD has joined the faculty as an Assistant Professor in Residence. He has a PhD in Pharmacology from the University of Virginia and served as a postdoctoral fellow in the laboratory of Dr. Phil Schwarzkroin at the University of Washington, one of the preeminent epilepsy research labs in the world. Also, during this period, he was awarded a prestigious postdoctoral fellowship award from the American Epilepsy Society. He has most recently served as Assistant Professor at Case Western Reserve University in the Departments of Pediatrics and Neuroscience. Dr. Baraban comes to UCSF to join the efforts of the Department of Neurological Surgery and the Program in Biological Sciences and to develop an Epilepsy Research Program in Neurosurgery.

M. Kelly Nicholas MD PhD has recently joined the Neuro-Oncology Service with an appointment as Assistant Professor in Residence. During his training, Dr. Nicholas served a 3-year Neuro-Oncology fellowship at UCSF. He returns to UCSF from the University of Chicago. He has been actively involved in neuro-oncology research through clinical trials, evaluating new drugs and treatment strategies in adults with brain tumors, and in developing brain-tumor model systems. He recently became a Principal Investigator and Associate Member of the North American Brain Tumor Consortium.

Julie Ellison PhD is joining the faculty as an Assistant Professor in Residence. She completed her PhD in Anatomy and Cell Biology under the direction of Dr. Jean de Vellis at UCLA. In addition, she has served as a postdoctoral fellow in the laboratories of Dr. Hannah Kinney of the Department of Neurology at Harvard Medical School, Dr. Frank Sharp of the Department of Neurology at UCSF, and Dr. Linda Noble in Neurological Surgery at UCSF. Dr. Ellison was recruited to direct the Department's Ischemia Research Program.

Sandeep Kunwar MD PhD has been appointed Assistant Professor in Residence. He recently completed his neurosurgical residency here at UCSF. Dr. Kunwar came to UCSF with an interdepartmental neurobiology degree conferred with high distinction from the University of California, Berkeley. While in medical school, he received a Howard Hughes Medical Institute Fellowship and pursued research in neuro-oncology at the National Institutes of Health. He subsequently received a full scholarship from the Howard Hughes Medical Institute to complete his medical education at UCSF. While a resident, he received the Edwin Boldrey Basic Science Research Award as well as the Preuss Resident Research Award. Dr. Kunwar's specialty is malignant brain tumors and immunotoxins.

Joseph F. Costello PhD, who joins the faculty as Assistant Professor in Residence, has investigated the role of genetic and epigenetic alterations in the development of gliomas, the most common form of brain cancer in humans, by using a DNA fingerprinting technique called restriction landmark genomic scanning (RLGS). He first used RLGS technology to discover amplification of the gene encoding the cell-cycle regulator, cyclin-dependent kinase 6 (CDK6), in human brain tumors. This was the first discovery of CDK6 gene amplification in any human cancer. He is also addressing more general questions about the role of abnormal methylation in cancer and its effect on gene expression. In collaborative work he has showed that the aberrant methylation of CpG islands in several human cancers is not random and that the patterns of alteration are tumor-type specific.

Joseph Fike PhD was promoted to Professor in Residence in November 1999. He was recently awarded a 3-year National Institutes of Health grant to study radiation response of the subependyma.

Charles Wilson MD has been named to the Editorial Board of the Western Journal of Medicine and to the President's Council for Tulane University.
The study and its findings will be published in the journal *Nature Medicine* within the next few months. The results will also be presented at the upcoming AANS meeting in San Francisco in April, where Dr. Manley will receive the Synthes Head Injury Research Award. Special thanks are due to a number of people in the Department of Neurological Surgery, including Drs. Martin Holland, David McK-alip, and Grant Gauger, and Susan Eastwood. Work is currently underway to determine the role of aquaporins in the production and reabsorption of cerebrospinal fluid. In collaboration with Dr. Mitchel Berger, the role of aquaporins in brain tumor edema is also being explored.

At the meeting of the Western Neurosurgical Society in September, Praveen Mummaneni MD gave a platform presentation entitled, “Staged Radiosurgery for Large AVMs” and a poster presentation on “A New MRA Technique to Image Aneurysms of the Carotid Ring.” Dr. Mummaneni also presented a poster entitled, “Microsurgical Treatment of Tarlov’s Cysts” at the Congress of Neurological Surgeons in November 1999.

Matt Smyth MD gave a poster presentation on “The Poste-rior Interhemispheric Approach for Cerebrovascular Lesions” at the American Association of Neurological Surgeons Annual Meeting and at the 1999 Joint Section on Cerebrovascular Disease. This work was done with Michael Lawton MD, Chief of the Department’s Cerebrovascular Disorders Program.
In work on the analysis of outcomes within neurosurgery and spinal instability in particular, Dan has shown that posterior fixation with transarticular facet screws substantially reduces the odds of atlantoaxial non-union as compared to previous fixation techniques alone. Patients with instability due to trauma or rheumatoid arthritis benefit most from the procedure, and those with instability due to os odontoideum benefit least (3). Recently this mathematical technique for analysis of surgical outcomes, which Dan developed in collaboration with Dr. Kathleen Lamborn, was also applied to the results of odontoid screw fixation in a large series of patients from UCSF (4). His most recent paper, with former UCSF resident Paul Matz and Dr. Harold Rosegay, describes the history of the strain gauge, which was developed in 1946 to study the cause of syncope in airplane pilots, and the impact of this instrumentation on the measurement and reduction of increased intracranial pressure in patients with severe head injury (5). Dan also developed a technique using contrast-enhanced ultrasound to visualize ventriculoperitoneal shunt function in vitro.

Dan has been awarded a number of honors in recognition of his research. His work on chemopallidotomy merited the Resident Research Award from the Joint Section on Stereotactic and Functional Neurosurgery of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) in 1996. In 1998 he received the Resident Research Award from the Hydrocephalus Foundation at the Joint Section on Pediatric Neurosurgery of the AANS and CNS for his work with ultrasound. In 1998 he was also granted a Research Career Award from the NIH. In June 1999 he was presented the UCSF pediatric residents’ Special Appreciation Award in recognition of excellence in clinical care and commitment to teaching. Dan is the father of Max (age 7), Sam (age 3), Grace (age 1), and the husband of Becky.

References
1. Lieberman DM, Corthesy M-E, Cummins A, Oldfield EH: Reversal of experimental parkinsonism by using selective chemical ablation of the medial globus pallidus (GPM) to permanently reverse Parkinson syndrome in unilaterally parkinsonian macaques (1). In pursuing this work at UCSF, Dan, working with Dr. Nick Barbaro and others, has developed novel stereotactic techniques. Using this approach successfully in his studies of parkinsonism, Dan has obtained precision in isolating specific intracerebral targets within 1 mm in each dimension (2).

Using this approach successfully in his studies of parkinsonism, Lieberman has obtained precision in isolating specific intracerebral targets within 1 mm in each dimension.
Selected Recent Publications from the Department of Neurological Surgery


