



# BRAIN ACTIVITY

ACADEMIC AND RESEARCH NEWS

VOLUME 4 NUMBER 2

## IN THIS ISSUE . . .

. . . we focus on innovative treatment for and research on movement disorders, from deep brain stimulation – one of the most effective treatments for Parkinson's disease – to finding new targets in the brain to control Parkinson's disease and motor disorders affecting the aging brain.



## NEW CENTER TREATS PARKINSON'S DISEASE AND OTHER MOVEMENT DISORDERS

Parkinson's disease is a slowly progressive disorder caused by the degeneration of brain cells that produce the neurotransmitter dopamine. It affects as many as 1.5 million Americans, according to The National Parkinson Foundation, which estimates that approximately 50,000 new cases are diagnosed each year.

Deep-brain stimulation (DBS) is one of the most effective treatments for Parkinson's disease, and the San Francisco Veterans Affairs Medical Center (SFVAMC) has become a leader in this form of therapy. Recently, UCSF Neurosurgeon **Philip Starr MD PhD** and researcher **Robert Turner PhD** (see page 3) were among the Parkinson's disease specialists at the SFVAMC receiving \$5 million from the Department of Veterans Affairs to establish the San Francisco Parkinson's Disease Research, Education, and Clinical Center (PADRECC).

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*PADRECC program members from left to right, first row (seated): Paul Larson MD, neurosurgeon; Philip Theodosopoulos MD, neurosurgery resident; Philip Starr MD PhD, PADRECC Associate Clinical Director and SFVAMC Chief of Neurosurgery; William Marks Jr. MD, PADRECC Director and neurologist; Anthony Mosely MD, neurology fellow. Second row: Fely Lopez, program assistant; Sandra Shefrin MD, neurologist; Mathew Mori, staff research associate; Susan Heath RN MSN, Associate Director for Clinical Care and clinical nurse specialist; John Walker PhD, neuropsychologist. Third row: Gary Abrams MD, neurologist and Associate Director for Education and Evaluation; Lori Anzaldo, program manager; Johannes Rothlind PhD, clinical psychologist. Missing from the photograph: Chadwick Christine MD, neurologist; Heidi Clay RN, neurosurgery clinical nurse specialist; Marsha Melnick PhD, physical therapist. Photo: Edgardo Caballero, VAMC Photographer*



## LOOKING TO THE FUTURE

Whereas treatment for movement disorders – like Parkinson's disease, spasmodic torticollis, or tremor – was once exclusively medical, technologies are evolving that permit remarkable improvement for patients who are treated surgically. In planning the Department's future course, it seemed to me that we should take a new approach to these problems in partnership with our colleagues in Neurology, Neuroradiology, and Rehabilitation Medicine. Our efforts are meeting with success.

With a grant of \$5 million from the Department of Veterans Affairs, we have built a center at the San Francisco Veterans Affairs Medical Center – one of a consortium of six Parkinson's Disease Research, Education, and Clinical Centers (PADRECCs) nationwide – under the direction of neurologist William J. Marks Jr. MD with neurosurgeon Philip Starr MD PhD. The SFVAMC is a leader in one of the most effective treatments for Parkinson's disease – deep-brain stimulation. Phil Starr, Bill Marks, Paul Larson MD, SFVAMC Assistant Chief of Neurological Surgery, and their team now treat patients from VA Hospitals across the country and also patients in our Parkinson's Disease Referral Center at Moffit Hospital. For more than 100 veterans so far treated with deep-brain stimulators, the results are highly encouraging.

A grant of \$500,000 per year for 5 years from Medtronic Inc. will go toward finding new targets in the brain to control Parkinson's disease and motor disorders affecting the aging brain. Translational research in our Department is a partnership effort of clinicians and basic scientists collaborating to develop new clinical therapies from findings made in the laboratory. Krys Bankiewicz PhD and Robert Turner PhD are at the forefront of research to control movement disorders. Dr. Bankiewicz focuses on convection-enhanced delivery of molecules and viral vectors into the brain, with the goal of infusing medications directly into brain or, conceivably, delivering molecules to replace depleted neurons. Dr. Turner's focus is defining the role of frontal cortex and basal ganglia in motor control, quantitatively defining brain areas that produce optimal therapeutic effects in response to stimulation for movement disorders and evaluating pallidal surgery as therapy for dystonia.

All movement disorders are targets for our work during the next 5 years. In consultation with our clinicians, our scientists will model movement disorders in the laboratory, and together we will find new approaches to the abatement of these debilitating conditions.

Mitchel S. Berger MD  
Professor and Chairman

## PARKINSON'S DISEASE AND OTHER MOVEMENT DISORDERS

*Continued from page 1*

Together with UCSF neurologist William J. Marks Jr. MD, who is Director of the new PADRECC, and the SFVAMC and UCSF DBS team, Dr. Starr has treated more than 250 patients with DBS. Drs. Marks and Starr are conducting a randomized study comparing therapy with deep-brain stimulation at two different brain targets – the globus pallidus and the subthalamic nucleus. They are assisted by UCSF neurologist Chadwick Christine MD, UCSF neurosurgery clinical nurse specialist Heidi Clay RN, SFVAMC clinical nurse specialist Susan Heath RN MSN, UCSF physical therapist Marsha Melnick PhD, and UCSF neuropsychologist John Walker PhD.

PADRECC investigators, including UCSF neurosurgeon **Paul S. Larson MD** and neurologist Sandra Shefrin MD, are participating in a multicenter VA study designed to expand on the efforts of the San Francisco DBS study by investigating the efficacy of pallidal and subthalamic nucleus DBS in patients with advanced Parkinson's disease whose symptoms are inadequately controlled by pharmacotherapy. Patients will be randomly assigned to one of the surgical arms (either bilateral pallidal or subthalamic DBS) or to the best medical management. The first outcome measure of the study, assessed at 6 months, will be the amount of daily good-quality motor function experienced by patients in the surgical arm versus the medical arm of the study. Patients in the medical treatment group will then undergo DBS surgery, with random assignment to either of the brain targets for the therapy. Postoperative outcomes for the pallidal and subthalamic nucleus groups will be assessed during 2 years of follow-up review to determine the efficacy of the treatments and the relative merits of the two targets for DBS.

Deep-brain stimulation of the globus pallidus or subthalamic nucleus is effective in treating all of the primary motor features of Parkinson's disease, and sometimes allows for significant reductions in medication doses. In deep-brain stimulation, small electrodes are surgically implanted in the thalamus and connected to a pacemaker-like device implanted under the skin of the patient's chest, just below the collarbone. The device delivers continuous, high-frequency electrical stimulation to the brain via the implanted electrodes, which helps "rebalance" the control messages in the brain, thereby suppressing tremor. Deep-brain stimulation has the added advantages of being adjustable, reversible, and not destructive to brain tissue.

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## Gene Therapy for Parkinson's Disease



Dopamine deficiency causes the main symptoms of Parkinson's disease: slowing of emotional and voluntary movement, muscular rigidity, postural abnormality, and tremor. L-dopa (L-3,4-hydroxy phenylalanine) therapy is initially successful in many patients, but L-dopa needs aromatic L-amino acid decarboxylase (AADC) to convert it to dopamine. As the disease progresses, the cells that store AADC are lost, which causes patients to become resistant to L-dopa treatment.

**Krys Bankiewicz MD PhD**, Associate Professor of Neurological Surgery and Principal Investigator, Neurological Surgery Research Centers, and his colleagues recently found that the transfer of the gene that codes for AADC into the striatum of the brain restores the L-dopa-to-dopamine conversion to normal levels. They are now developing the therapy for future clinical trials. According to Bankiewicz, "Gene transfer technology offers the possibility of achieving prolonged delivery of proteins into specific areas of the CNS, although at the moment, gene transfer does require brain surgery." Several enzymes are involved in the synthesis of dopamine, and a successful gene therapy strategy to restore endogenous dopamine production would involve transduction of several genes.

Bankiewicz's approach is to transfer only the gene for AADC, the enzyme that completes the last step in the pathway that converts L-dopa to dopamine. He notes that, "With disease progression, there is a severe loss of dopamine terminals in the striatum. The enzyme AADC is concentrated in these terminals and is therefore also reduced." After successful AADC gene transfer, subsequently administered exogenous L-dopa should then be converted to the functional neurotransmitter and could improve symptoms. Bankiewicz adds that because the cells that express the AADC gene following gene transfer are not affected by Parkinson's disease, levels of AADC should not be affected by the ongoing disease process.

## Investigating the Relation Between Brain Dysfunction and Movement Disorders



Research in the laboratory of **Robert Turner PhD**, Assistant Professor of Neurological Surgery and Principal Investigator, Neurological Surgery Research Centers, is directed toward understanding the relationship between brain dysfunctions, like those in Parkinson's disease and dystonia, and the variety of movement impairments involved. Skillful and flexible control of a limb depends on dynamic interactions among neurons distributed across many brain regions. The frontal cortex and basal ganglia are key regions in this process. When the normal interactions between these areas are disrupted, as in Parkinson's disease, disorders of movement result.

One approach being used to understand the relationship between brain dysfunction and movement disorders is to correlate the firing patterns of single neurons, recorded in awake subjects as they perform movement tasks, with measures of motor performance or impairment. Dr. Turner's current research addresses the question of whether the basal ganglia serve as a kind of "teacher" to the cortex for the learning of new motor skills. This hypothesis is being tested by observing the effects of lesions or high-frequency stimulation in the internal globus pallidus (the primary output nucleus of the basal ganglia) on an animal's ability to learn new motor skills. The results of this project will have special clinical relevance because lesions or high frequency stimulation in the internal globus pallidus are used regularly as neurosurgical therapies for Parkinson's disease. It is therefore important to understand whether these therapies might have an undesirable effect on a patient's ability to learn new skills. This project will also assess the effects of the pallidal lesions on neuronal activity in the motor-related frontal cortical areas. How the lesion-related changes in cortical activity correlate with changes in task performance will provide insights into normal roles of the basal ganglia in regulating cortical activity.

*Continued on page 4*

Together with neurosurgeon **Philip Starr MD PhD**, Dr. Turner is studying the task-related activity of neurons in the globus pallidus and subthalamic nucleus of patients who are undergoing stereotactic surgery for movement disorders. Patients perform behavioral tasks designed to dissociate various frontal lobe functions, such as limb motor control, oculomotor control, orofacial movement, and working memory. Results from this study will provide insights into the functional organization of basal ganglia circuits in humans, which in turn should improve the targeting of specific functional circuits for neurosurgical treatments. Turner and Starr are also investigating the roles of the basal ganglia in focal dystonia. Finally, in collaboration with neurosurgeons and neurologists at Emory and Dartmouth Universities, Dr. Turner is using positron emission tomography to study the abnormalities in brain activity that are associated with Parkinson's disease and how those abnormalities change following neurosurgical treatments such as pallidal lesioning or high-frequency stimulation.

#### Dr. Turner's Selected Publications

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#### Dr. Bankiewicz's Selected Publications

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## NEW FACULTY APPOINTED

We are pleased to welcome four new faculty members to the Department.

**Arturo Alvarez-Buylla PhD**, who comes to UCSF from Rockefeller University, has an international reputation for his work in developmental neuroscience and stem-cell neurobiology research. His principal interests are in the assembly of the brain, brain tumors and repair, and the ontogeny and phylogeny of behavior. Professor Alvarez-Buylla holds the Stephen Muss Endowed Chair in Neurological Surgery and is a Principal Investigator with the Neurological Surgery Research Centers.

**Gabriele Bergers PhD** has joined the Department and Brain Tumor Research Center as Assistant Professor. Her work focuses on the role of angiogenesis as a critical factor in tumor development and progression. She has made major contributions to the understanding of additional mechanisms of the angiogenic switch in endogenous tumors of transgenic mice, such as the RipTag mice, which develop pancreatic islet carcinomas in a multi-step pathway. She has collaborated with Dr. Judah Folkman at Children's Hospital, Boston to translate these studies into experimental therapeutic approaches and preclinical trials that reflect different stages of disease progression. She was the first to publish data that angiogenesis inhibitors may prove most efficacious when they are targeted to specific stages of cancer.

**Natalie Compagnone PhD** has been appointed Assistant Professor in the Department of Neurological Surgery to direct the Laboratory for Spinal Cord Development and Regeneration. Her primary interest is in the organization of structures and the role of biological molecules in this process. Her laboratory is studying the role of neurosteroids in the cellular and molecular events leading to cytoarchitectural organization of the developing neural tube and brain. The aim is to use a mouse model to translate this knowledge into a therapeutic approach for treating spinal cord and brain injury.

**Jialing Liu PhD** has been appointed Assistant Professor in the Department. Her research interest is in uncovering the mechanisms mediating functional recovery and neural plasticity following cerebral ischemia. She has been funded by the National Institutes of Health to support her research.

# PEDIATRIC NEUROSURGERY NEWS

## IMPROVED SURGICAL OPTIONS FOR CHILDREN WITH EPILEPSY

At UCSF, comprehensive treatment for children with medically intractable seizures brings together several specialties, including child neurology, neurosurgery, neuropsychology, and rehabilitation medicine. Recent advances in functional imaging and intraoperative mapping have led to a far better understanding of each patient's seizure type and have improved the safety of resective surgery.

The initial evaluation, directed by Dr. Vincent Gibbons, a pediatric epileptologist with the Division of Child Neurology at UCSF, and other members of his division, involves a detailed history of the patient's seizures, a prolonged inpatient video-EEG recording, a detailed magnetic resonance imaging (MRI) study, and neuropsychological testing. A critical factor that determines whether a child may benefit from resective surgery is whether a specific focus in the brain is responsible for seizure onset. This may require further functional and localizing tests (*see box*).

Resection of epileptic foci is limited by the proximity of eloquent cortex. Intraoperative techniques used at UCSF to identify and avoid injury to those cortical areas include detailed direct cortical recordings with implanted brain electrodes, sometimes lasting several days; craniotomy with the patient awake to permit mapping of speech centers before resection begins; and direct motor mapping in conjunction with functional MRI. These techniques enable the neuro-



surgeon to tailor cortical resections so as to maximize the possibility of seizure control while incurring minimal deficits. Other surgical procedures that are targeted toward specific forms of epilepsy are selective or gross temporal lobectomy, hemispherectomy, corpus callosotomy, and subpial resections.

The future may lie with procedures that permit physiologic control of seizures by direct brain stimulation. The first generation of these procedures is vagus nerve stimula-

tion (VNS) with the Cyberonics NeuroCybernetic Prosthesis (NCP®) System. Unlike other types of epilepsy surgery, surgical implantation of the NCP System does not involve the brain. The VNS generator and lead are implanted in the chest and neck. The generator, similar to a cardiac pacemaker, works to synchronize brain activity, to prevent and terminate seizures that are difficult to treat because they cannot be localized to a particular focus. Several patients have been treated with this system at UCSF.

The Northern California Comprehensive Epilepsy Center, which is located at UCSF, has facilities for the comprehensive evaluation and management of children who have seizures. The surgical team consists of **Nalin Gupta MD, Mitchel Berger MD, Victor Perry MD, and Warwick Peacock MD.** To reach the pediatric neurosurgeons, call 415-353-7500. The Northern California Comprehensive Epilepsy Center can be reached at 415-476-6337.

### Newer Technologies Used in the Evaluation of Epilepsy

**Single Photon Emission Computed Tomography (SPECT):** an imaging technique used especially for qualitative measures of regional cerebral perfusion. It is similar to positron emission tomography (PET) in using the photons emitted by the agency of a radioactive tracer to create an image, but has supplanted PET in the functional evaluation of pediatric candidates for epilepsy surgery.

**Functional Magnetic Resonance Imaging (fMRI):** an imaging technique based on noninvasive detection of small regions of increased cerebral blood flow through decreases in deoxyhemoglobin concentration. Its use is no longer limited to awake and fully cooperative patients, thereby increasing its role in evaluating pediatric epilepsy.

**Proton Magnetic Resonance Spectroscopy (MRS):** a noninvasive technique similar to magnetic resonance imaging that uses compounds containing N-acetylaspartate, creatine, and phosphocreatine. Added to routine imaging, MRS studies provide important lateralizing information, especially in evaluating temporal lobe epilepsy.

**Magnetoencephalography (MEG):** a noninvasive technique for localizing and characterizing the electrical activity of the central nervous system by measuring the associated magnetic fields emanating from the brain. MEG permits the activity of the brain to be measured in real time, rather than as a still image. It has many of the advantages of PET and fMRI, but far better temporal resolution. MEG has an important role in the presurgical evaluation of pediatric patients, for whom placement and monitoring of subdural or depth electrodes and intensive EEG monitoring are especially difficult.

# NEUROSURGERY

## notes

**Mitchel S. Berger MD** was the 2002 William S. Keith Lecturer in Neurosurgery at the University of Toronto. During his 3-day visit, he spoke about: Molecular-Based Profiling and Outcome Prediction of Gliomas, Current Management of Glial Tumors: Making Slow but Steady Progress, and Manuscript Writing in Neurosurgery: Helpful Hints. The Keith Lecturer traditionally helps to adjudicate the competition for the Thomas P. Morley Neurosurgical Resident Prize.

**Gabriele Bergers PhD** has received the Kimmel Scholar Award, a substantial financial award given to selected promising scientists engaged in cancer research who are at an early stage of their career. The Sidney Kimmel Foundation for Cancer Research principally supports the research programs of accomplished young cancer researchers emphasizing basic research, the rapid translation of basic science concepts into potential therapeutic applications, and clinical research with innovative treatment strategies. Dr. Bergers' research focus is on the investigation of angiogenesis and tumor invasion.

**Charles B. Wilson MD DSc MSHA** was honored by the Pituitary Network Association as the first recipient of the Gentle Giant Award, the highest honor bestowed by the PNA, for his contributions and dedication to the field of pituitary medicine. The Pituitary Network Association is an international nonprofit organization for patients with pituitary tumors and disorders, their families, and the physicians and health care providers who treat them. It is the world's largest and fastest growing patient volunteer organization devoted to the treatment and cure of pituitary disorders.

**Cornelia von Koch MD PhD**, a fourth-year resident in Neurological Surgery, has been selected as a Neurosurgery Research and Education Foundation Research Fellow by the American Association of Neurological Surgeons.

The following faculty currently hold Endowed Chairs in the Department of Neurological Surgery. We are grateful to the generous donors who make this honor possible.

**Michael T. Lawton MD**

Tong Po Kan Endowed Chair in Neurological Surgery

**Arturo Alvarez-Buylla PhD**

Stephen Muss Endowed Chair in Neurological Surgery

**Nalin Gupta MD PhD**

Dennis Bruce Dettmer Endowed Chair in Pediatric Neurological Surgery

**Russell Pieper PhD**

Suzanne Marie Haderle and Robert Vincent Haderle Endowed Chair in Molecular Neuro-Oncology

**Michael Prados MD**

Charles B. Wilson MD Endowed Chair in Neurological Surgery

**Dennis Deen PhD**

Berthold and Belle N. Guggenhime Endowed Chair in Neurological Surgery

### Grandmothers . . .

*A grandmother is a lady who has no little children of her own.*

*She likes other people's.*

*Grandmothers don't have to do anything except be there.*

*They are old, so they shouldn't play hard or run.*

*It's enough if they drive us to the market and have a lot of dimes ready.*

*When they take us for walks, they slow down for poet-things,  
like pretty leaves and caterpillars.*

*They never say "hurry up."*

*Grandmothers don't have to be smart –*

*only answer questions like,*

*"Why isn't God married?" and "How come dogs chase cats?"*

*When they read to us, they don't skip, or mind if we ask for the same story over again.*

*Everybody should try to have a grandmother – especially if you don't have TV,  
because they are the only grownups who have time.*

– Mary Louise Rosegay

Mary Louise Rosegay and Professor Emeritus of Neurological Surgery Dr. Harold Rosegay have been friends and mentors to the residents of the UCSF Department of Neurological Surgery for many years. After Mrs. Rosegay died on 26 October 2000, Dr. Rosegay discovered this poem, which we share with the many people at UCSF who cherish her memory.

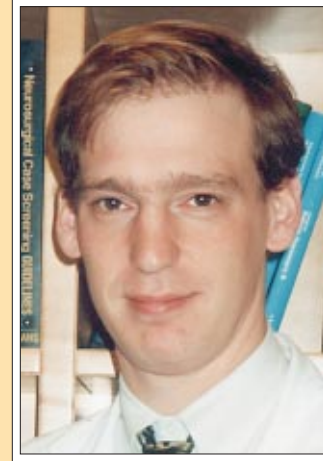
**Philip V. Theodosopoulos MD**



**Philip V. Theodosopoulos MD** has had a variety of interests over the past 6 years. His interest in Parkinson's disease and movement disorders led him to study the physiology of the human subthalamic nucleus and the globus pallidus internus with neurosurgeon **Philip Starr MD PhD**, analyzing intraoperative recordings from the subthalamic nucleus in order to determine the somatotopic arrangement of the nucleus. His strong interest in outcomes in neurosurgery resulted in collaborations with neuro-oncologists **Susan Chang MD** and **Michael Prados MD**, assessing the effect of adjuvant chemotherapy in the treatment of recurrent gliomas and the efficacy of temozolomide in the treatment of recurrent malignant gliomas. It also led him to develop a predictive model for pain recurrence following posterior fossa exploration for trigeminal neuralgia, based on the outcomes of over 600 patients operated on by **Charles Wilson MD**. He has correlated magnetic resonance spectroscopy and pathology results for newly diagnosed brain lesions and currently is reviewing the results of surgical treatment of giant intracranial meningiomas with neurosurgeon **Michael McDermott MD**.

A graduate of the Massachusetts Institute of Technology, Dr. Theodosopoulos received his MD from Stanford University School of Medicine, where he won the Dean's award for Distinguished Research in Neurobiology. Completing his residency in June 2002, Theodosopoulos will pursue fellowship training in skull base/vascular surgery with Dr. Arthur Day at the University of Florida. He plans to pursue an academic career in the fields of skull base surgery and neuro-oncology, with a special emphasis on clinical trial development and outcomes studies.

**Steven G. Ojemann MD**



**Steven G. Ojemann MD**, a graduate of the University of Washington cum laude and with College Honors, received a Bachelor of Science degree in Cell and Molecular Biology and a Bachelor of Arts degree in Political Science. As an undergraduate, Dr. Ojemann received the Robert A. Dahl award to the Outstanding Scholar in Political Science. He received his MD from the University of California, Los Angeles in 1996, and was elected to the Alpha Omega Alpha medical honor society. During his residency, Dr. Ojemann has worked with **Charles D. Yingling PhD** and **Mitchel Berger MD**, showing that the use of multichannel electromyography (EMG) recording improves the sensitivity of electrical stimulation mapping techniques for identifying the brain's motor pathways during tumor surgery. In a recently published study of malignant meningiomas with **Michael McDermott MD**, **Penny Sneed MD**, **David Larson MD PhD**, and other Gamma-Knife Radiosurgery (GKS) faculty, he showed that GKS was therapeutically effective for these lesions, and that tumor control relates to tumor size and the patient's age. He has received a National Research Service Award from the National Institutes of Health to study, under **Philip Starr MD PhD**, the physiologic properties of neurons in the basal ganglia as they relate to speech and language. Dr. Ojemann completes his residency in the summer of 2002, and will join the faculty in the Department of Neurosurgery at the University of Colorado next fall, where he will serve as the Chief of Stereotactic and Functional Neurosurgery.



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**– Selected Recent Publications from the Department of Neurological Surgery –**

**Auguste KI, Quinones-Hinojosa A, Lawton MT.** The tandem bypass: subclavian artery-to-middle cerebral artery bypass with dacron and saphenous vein grafts. Technical case report. *Surg Neurol* 2001;56:164-9.

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