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STANFORD
MEDICINE

STANFORD DEPARTMENT OF NEUROSURGERY

# Stanford Neurosurgery

## Fusing Neuroscience to New Therapies for Patients

***Can Stem Cells Save Our Memories?***

***Testing a Vaccine for Brain Tumors***

Induced Pluripotent Stem Cells (iPS cells)
engineered from the skin cells of a Parkinson's Disease patient.
Dr. Theo Palmer, Director of Stanford Neurosurgery's Neural
Stem Cell Program, searches for answers to the neuropathology
of Parkinson's Disease in his quest for a cure *(pages: 17-20)*.

# Department of Neurosurgery
# Stanford University School of Medicine

## *Table of Contents:*






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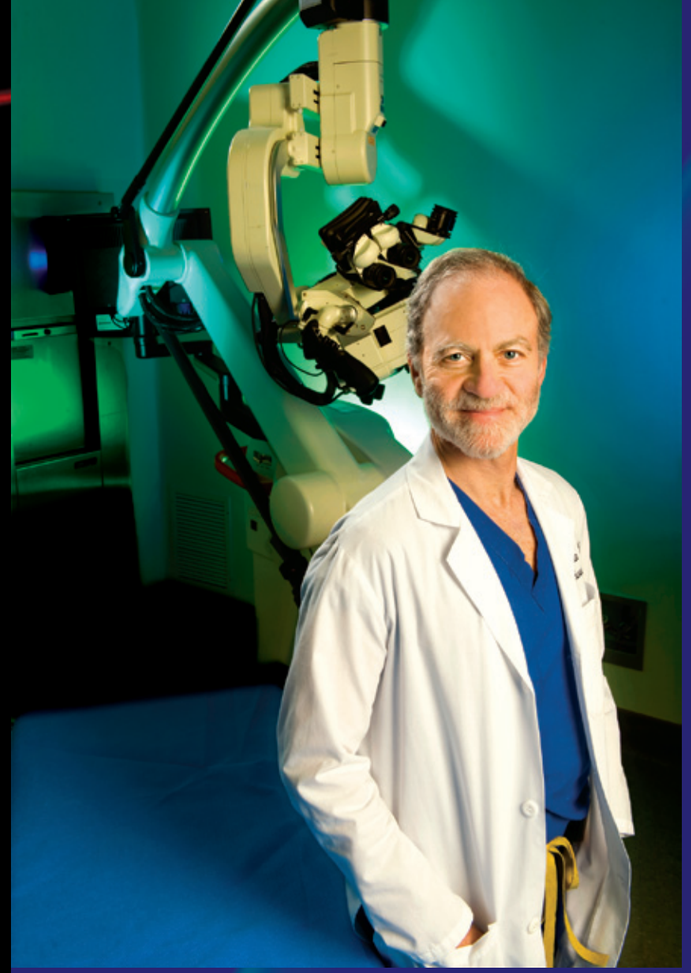
STANFORD
SCHOOL OF MEDICINE
*Stanford University Medical Center*

# Message *from the* Chairman:

"As physicians, we rely on proven strategies to treat the whole patient ... and as scientists, we rely on our powers of observation and creativity to penetrate the unanswered mysteries in our field ... and we do this as deeply as our technologies and our imaginations will take us - down to the microscopic stem cell."

*Gary K. Steinberg, M.D., Ph.D.*



## *Dear Friends and Colleagues:*

Over the last decade, Stanford Neurosurgery has gained world recognition for its advanced clinical care, scientific research and technological inventions. We have cultivated an environment of collaboration and creativity that facilitates the rapid translation of discoveries pioneered in our laboratories and clinics into new therapies for patients.

We are leaders in the emerging frontiers of Neuroregeneration and Neurorestoration, which seek novel methods for repairing damaged cells and circuits in the brain and spinal cord after injury. Utilizing advances in precise imaging techniques, molecular biology, computer technology, neurophysiology and other basic sciences, and by partnering with the Stanford Institute for Neuro-Innovation and Translational Neurosciences, we are developing new strategies to restore neurological function. These include brain and spinal cord stimulation, stem cell transplantation, tissue engineering, micro-pumps that deliver therapeutic drugs and molecules, and exciting brain-computer interface technology as future Neuroprosthetics.

Our utilization of minimally invasive therapies such as endovascular, endoscopic, percutaneous and radiosurgical techniques are also improving patient outcomes. In addition, our research support has grown to over $10 million dollars annually, placing us among the top Neurosurgery programs nationally for NIH funding alone. We also gratefully thank our many donors who have generously supported our success.

We are especially proud of our educational programs that train the visionary surgeons and scientists of the future. Our residents and fellows routinely become leaders in academic neurosurgery and research both nationally and abroad. Finally, we strive to promote knowledge and understanding amongst our colleagues and friends of the pathomechanisms underlying neurologic disease, so that we may work together to better serve our patients.

Sincerely,

Gary K. Steinberg, M.D., Ph.D.



# Stanford impacts Stroke disability

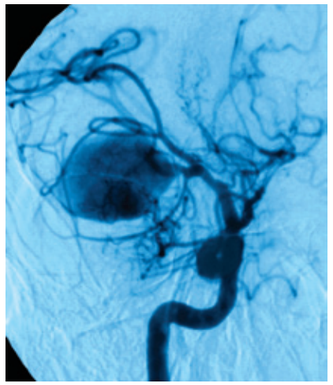
## *Through a collaborative approach to Research and Intervention*

Stroke affects about 795,000 individuals annually in the United States (one occurs every 40 seconds). It is the third leading cause of death and the number one cause of disability. Stroke risk increases with age, and for each decade after 55 that risk doubles. More than 4 million people have survived a stroke or brain attack in this country and are living with some form of neurological impairment or disability. The severity of disability for 75% of stroke survivors is enough to limit their employability. The overall economic impact of stroke exceeds $45 billion annually in the U.S. alone.

Eighty-seven percent of strokes are due to ischemia: a reduction or sudden interruption of blood supply to the brain caused mainly by a thrombus (locally occurring blood clot), or an embolus (blood clot from elsewhere in the body that travels to a brain artery). The most common origin of emboli is the heart, linking stroke with heart disease. In either case, the absence of blood flow starves the brain of oxygen and glucose triggering a cascade of devastating molecular reactions at the cellular level leading to brain damage or stroke. Depending on the length of time the blockage remains and the brain region in which it occurs, permanent disability or death may follow.

The other 13% of strokes are due to hemorrhage from a ruptured blood vessel in the brain. It is estimated that 1 in 15 people will develop a brain aneurysm in their lifetime. Brain aneurysms can occur in people of all ages, but are most commonly detected in those aged 35 to 60. Ruptured aneurysms account for 30,000 hemorrhagic strokes per year in the U.S. 50% of these patients will die within 30 days of their brain bleeds. Other causes of hemorrhagic stroke include hypertension, AVMs, cavernous malformations, and rare abnormal vessel diseases such as Moyamoya.

Given the prevalence, social and economic burdens, along with the health care challenges that stroke presents, Stanford clinicians and research scientists are devoting considerable talent and resources to understanding stroke's pathophysiology and optimal treatments. The Stanford Neurosurgery Department works closely with the Department of Neurology and the Division of Interventional Neuroradiology, coordinated with the Stanford Stroke Center to sponsor research studies, clinical trials, community outreach, education, prevention and therapeutic innovations all aimed at improving patients' outcomes from stroke. New therapies include clot busting drugs, less invasive endovascular procedures, special microsurgical techniques and neuroregeneration.



# Cerebrovascular Neurosurgery

Stanford is an international referral center for complex neurovascular disorders of the brain and spinal cord. A multidisciplinary team consisting of neurosurgeons, interventional neuroradiologists, stroke neurologists and radiation oncologists collaborate closely to design individualized treatment plans combining optimal therapies for each patient's unique needs. These may include microsurgery, endovascular surgery, or radiosurgery in any combination, depending on the lesion's size, location, anatomical features and the patient's medical condition.

Over the last two decades, the neurovascular team has treated over 2,500 aneurysms and more than 2,000 vascular malformations (AVMs, cavernous malformations and AV fistulas) making it one of largest quaternary referral centers in the nation for highly specialized surgeries and minimally invasive endovascular and radiation therapies. Occlusive cerebrovascular lesions like carotid artery stenosis and Moyamoya disease are also a significant part of Stanford's case volume. Patients from all over the world are drawn to Stanford for revascularization bypass surgeries for Moyamoya disease - a rare disorder where blood vessels in the brain either clot off causing ischemic strokes or bleed leading to brain damage and loss of neurological function. The Stanford vascular team's success with these disorders is aided by technological advances in neuro-imaging, surgical navigation, intra-operative brain monitoring, and new less invasive surgical techniques to accurately target and treat even the most complex cerebrovascular diseases.

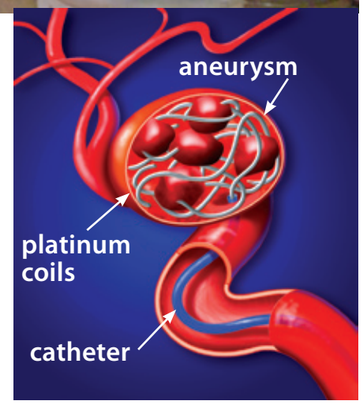
Working closely with endovascular specialists Dr. Michael Marks and Dr. Huy Do in Interventional Neuroradiology, Stanford's cerebrovascular team is helping patients with neurovascular conditions including aneurysms, AVMs, carotid artery stenosis and ischemic stroke using the most efficacious and least invasive techniques available to treat their vascular diseases.

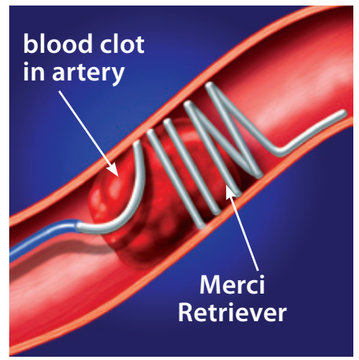
Dr. Michael Marks (left ) and Dr. Robert Dodd (right) perform an endovascular treatment at Stanford Hospital.

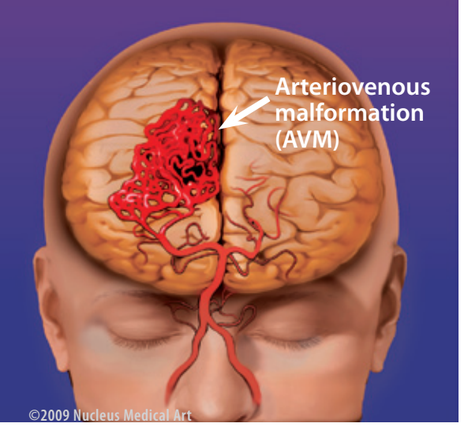
**Robert L. Dodd, M.D., Ph.D.**
Assistant Professor, Neurosurgery and Radiology

Trained as both a cerebrovascular surgeon and an endovascular neurointerventionalist, Dr. Robert Dodd represents the future trend for treating aneurysms, AVMs and arterio-venous fistulae (AVFs) with less invasive endovascular techniques that are safer for patients and shorten recovery times. In the last year, Dr. Dodd and his colleagues in Interventional Neuroradiology treated 48% of the 248 aneurysm cases at Stanford with detachable coils. These are injected into the aneurysm via a catheter that enters the groin and is then navigated up to the brain aneurysm from inside the arteries. The coils clot off the aneurysm from the inside to prevent future ruptures that could cause hemorrhage and stroke. Endovascular embolization of AVMs using a "super-glue" or liquid adhesive is often performed to facilitate subsequent therapies with microsurgery or radiosurgery. Brain and spinal cord AVFs can usually be cured by this technique alone.

Patients with acute ischemic stroke are also benefiting from endovascular therapies. Blood clots that plug up the brain's arterial blood supply causing transient ischemic attacks (TIAs) or strokes can now be mechanically removed with a tiny device called a Concentric Merci Retriever. Using the same method described above through a catheter, a corkscrew type device can pierce the blood clot allowing the skilled neurointerventionalist to then pull it out and restore normal blood flow. In the last year, 30 of these emergency thromboembolectomies were successfully performed using this technique along with the Penumbra Suction Catheter, which also safely removes blood clots.





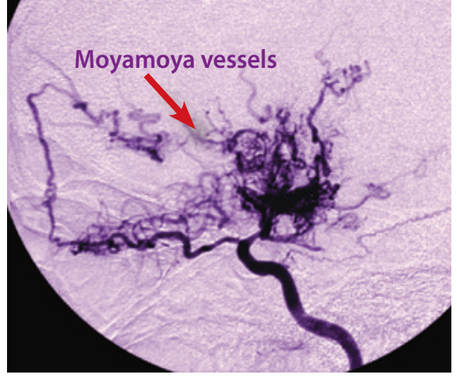

## Steven D. Chang, M.D.

Robert C. and Jeannette Powell Professor in the Neurosciences
Professor, Neurosurgery
Co-Director, Stanford CyberKnife Program

With extensive experience in both cerebrovascular surgery and stereotactic radiosurgery, Dr. Steven Chang is uniquely qualified to treat intracranial and intraspinal AVMs (arteriovenous malformations). These congenital vascular lesions are composed of fragile blood vessels and cause significant morbidity and mortality from hemorrhage, progressive neurologic deficits, seizures and intractable headaches. Over the last 2 decades the Stanford AVM Program has treated over 2000 patients referred from worldwide with AVMs involving the central nervous system, the majority of which are large, deeply located in the brain, and involve eloquent or critical brain regions, rendering these AVMs particularly challenging. The success of the Stanford AVM Program in achieving excellent clinical outcomes is the use of multimodality therapy, including combinations of endovascular embolization, stereotactic radiosurgery (such as CyberKnife) and microsurgery.

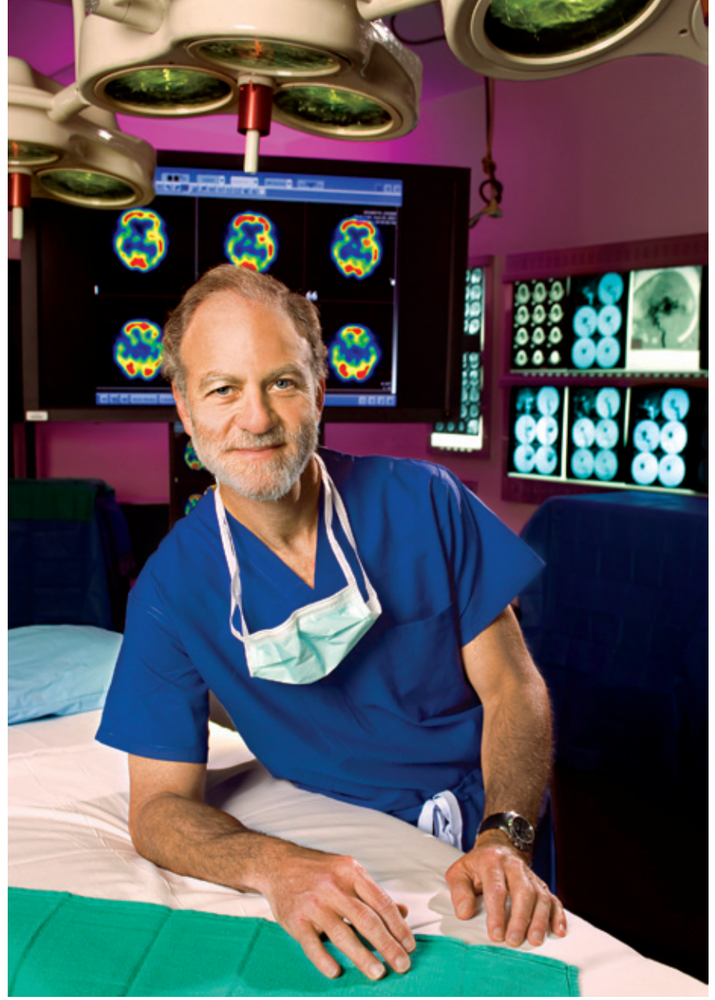
Dr. Chang has published his AVM clinical work widely and has been invited to present at scientific meetings internationally. His current research investigates the genetics and proteomics of intracranial AVMs by identifying serum biomarkers and specific genes that predict obliteration response and bleeding risk following radiosurgery. He is also exploring the use of fractionated radiosurgery (multiple sessions utilizing lower doses) and radiosensitizers to enhance the effectiveness and safety of AVM treatment. Dr. Chang performs microsurgery on patients with other vascular disorders such as intracranial aneurysms, dural arteriovenous fistulas (AVFs) and cavernous malformations. He is also developing new surgical and medical treatments for patients with intracerebral hematomas. He is currently Topic Reviews Editor for the medical journal, *Neurosurgery.*






One the rarest forms of occlusive cerebrovascular disorders encountered in neurosurgery is Moyamoya disease. Fragile blood vessels proliferate around a blocked artery in an attempt to bypass an occlusion and their appearance on a cerebral angiogram resembles a "puff of smoke" or "Moyamoya," a term coined by a Japanese team who first described the disease. It can affect both children and adults usually with symptoms of TIAs, strokes, headaches and seizures. There is currently no drug treatment for Moyamoya disease and surgery is aimed at bypassing the blockage with another artery to restore normal blood flow. Dr. Gary Steinberg has performed over 700 of these revascularization procedures for Moyamoya making his case experience with this disease one of the largest in the world.

Other neurovascular conditions treated surgically by Dr. Steinberg include: intracranial aneurysms, AVMs, brain stem and other deep seated cavernous malformations, carotid artery disease and various types of occlusive vascular disease. Tissue engineering, neurogenesis and angiogenesis - facilitating the brain's ability to grow new neurons and blood vessels - are the focus of Dr. Steinberg's research efforts. His laboratory seeks to determine how transplanted neural stem cells can assist the process of repairing the damaged brain after a stroke. Dr. Steinberg's research group recently received a $20 million grant from the California Institute of Regenerative Medicine (CIRM) to translate this stem



## Gary K. Steinberg, M.D., Ph.D.

Bernard & Ronni Lacroute-William Randolph Hearst Professor of Neurosurgery and the Neurosciences
Chairman, Neurosurgery
Director, Stanford Institute for Neuro-Innovation and Translational Neurosciences

cell transplant technology from the laboratory into a phase I clinical trial in stroke patients within the next four years.

In addition to serving as Neurosurgery's Department Chairman, Dr. Steinberg performs several other leadership roles at Stanford. He is also Co-Director and founder of the Stanford Stroke Center (one of the first Stroke Centers in the nation) and is Director of the Stanford Institute for Neuro-Innovation and Translational Neurosciences: a unique consortium of neuroscientists, clinicians and specialists from other scholarly disciplines, all dedicated to expanding the current knowledge base and research opportunities aimed at understanding the human mind, brain, and nervous system. Ultimately, the goal is to transform new discoveries into life saving therapies for patients.

# Cerebrovascular Research

## Protecting brain cells from **Death by Stroke**

**Pak H. Chan, Ph.D.**
James R. Doty Professor in Neurosurgery and the Neurosciences
Vice Chair and Director, Neurosurgery Research

During ischemic stroke, brain trauma, and some other neurodegenerative diseases like Alzheimer's, a convergence of molecular signals instructs brain neurons to live or die. Dr. Pak Chan and his colleagues are studying ways to direct the signals' activity towards survival to preserve vital brain function. Dr. Chan has been a pioneer in stroke and brain injury research. He was the first scientist to use transgenic animals containing special genes that make key proteins to explore oxidative stress in neuronal death and survival. He discovered a number of important detrimental pathways that cause death of neurons, astrocytes and cerebral blood vessels after stroke, related to dysfunction of mitochondria and critical genes, and to DNA damage. These breakthrough studies have uncovered molecular targets for pharmacological therapeutic interventions against stroke.

A primary focus is to overexpress a naturally occurring antioxidant protein called superoxide dismutase (SOD), which can block the harmful reactive oxygen radicals and protect the brain against stroke. Currently, Dr. Chan is also investigating signaling pathways that promote survival of brain tissue and methods of translating this knowledge into clinical therapies.

Dr. Chan has received many grants and awards from the National Institutes of Health (NIH) and the American Heart Association, including an NIH Jacob Javits Neuroscience Investigator Award. In 2008, Dr. Chan received the Thomas Willis Award from the American Stroke Association, the highest honor bestowed on a stroke scientist internationally.

# Preventing Brain Hemorrhages by Understanding the Blood-Brain Barrier

Nearly 80% of strokes are due to the abrupt occlusion of a cerebral artery by a clot. Restoring the cerebral blood flow (reperfusion) early, either by pharmacological agents (e.g., tissue plasminogen activator, tPA) or by mechanical clot removal, can salvage 'at risk' brain tissue, thereby limiting neurological disability. Reperfusion strategies have proved to be the most effective therapies for stroke treatment. However, ischemia and early reperfusion can cause blood-brain barrier injury, leading to cerebral edema and/or devastating brain hemorrhages, which are associated with extremely high rates of morbidity and mortality. These complications, along with a narrow therapeutic window, significantly limit the benefits of currently approved stroke therapies.

Despite the clinical importance of reperfusion injury, little is known about its pathophysiology, primarily due to the lack of adequate animal models allowing its investigation. There is clear evidence that the underlying ischemia reperfusion injury mechanisms involve excess production of reactive oxygen species (free radicals), which are generated soon after vessel occlusion and also in later stages of infarct development. Vascular cells are the first targets of free radical-induced injury during reperfusion, so we have developed a unique animal model that allows us to investigate reperfusion-induced vascular injury and secondary brain damage. By genetically manipulating the level of key antioxidants in the brain, we have been able to identify some of the vascular molecular targets of reactive oxygen species as well as to evaluate therapeutic strategies aimed at preventing reperfusion-related brain hemorrhage and edema. Knowledge obtained from these basic science discoveries are currently being translated into potentially effective and safe neuroprotective strategies against stroke.


**Carolina M. Maier, Ph.D.**
Senior Scientist, Neurosurgery



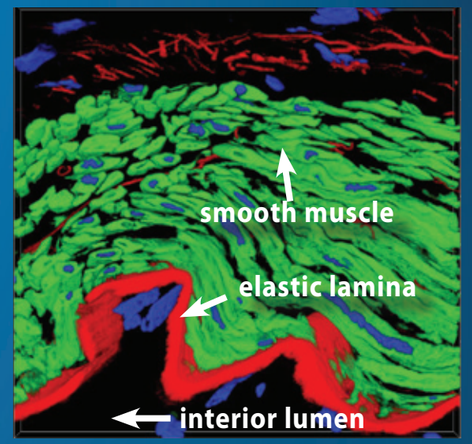
# Stanford Moyamoya Center Research

## Defining the Molecular and Genetic Defects of Moyamoya Blood Vessels

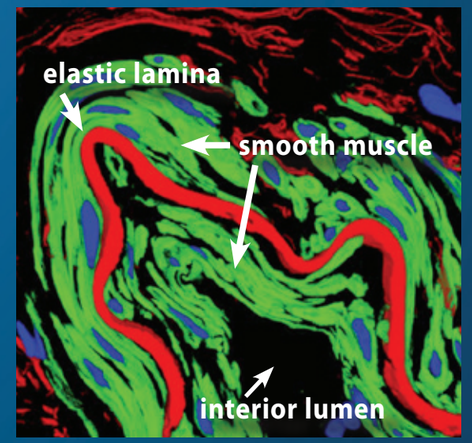
Stanford is one of the largest referral centers for Moyamoya disease in the world. Moyamoya occurs when arteries at the base of the brain progressively narrow, resulting in restricted blood flow and ultimately complete blockage, causing ischemic stroke. Compensatory proliferation of collateral Moyamoya vessels in the brain are highly susceptible to hemorrhage. Both this ischemia and hemorrhage lead to significant morbidity and mortality. The Stanford Moyamoya Center is currently conducting research focused on the underlying genetic basis and molecular mechanisms of the disease. Approximately 10 percent of cases are familial, and prior genetic studies have identified some general chromosomal regions that are involved.

The Stanford Moyamoya Center in collaboration with Dianna Milewicz, M.D., Ph.D., Professor and Director of Medical Genetics at University of Texas, Houston, have discovered mutations in a single gene (MYH11) that lead to Moyamoya. This gene is responsible for making beta myosin heavy chain, a component of smooth muscle in arteries. By studying blood DNA from 182 Moyamoya patients as compared to normal controls, the research team found that some Moyamoya patients had unique mutations in the MYH11 gene. Since it is known that smooth muscle overgrowth is responsible for the occlusion of brain arteries in Moyamoya disease, the team is investigating how the gene mutation causes the abnormality.

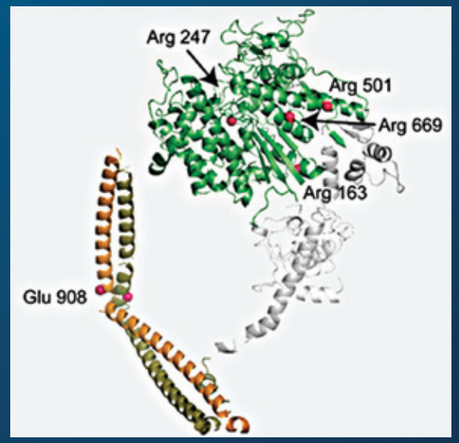
Using a new imaging technology called array tomography (upper and center right) developed by Stephen Smith, Ph.D., Professor of Molecular and Cellular Physiology at Stanford, the Moyamoya team has identified structural changes in the cerebral arteries of Moyamoya patients. The arterial smooth muscle cells (green layers) migrate past the elastic lamina (red layer) to the interior of the vessel, potentially leading to occlusion. Other research projects are seeking to illuminate clinical and blood flow parameters that predict the disease's natural history, as well as the role of endothelial stem cells in promoting angiogenesis.




*above:* Normal cerebral artery




*above:* Moyamoya cerebral artery




Beta myosin heavy chain protein with MYH11 mutations

**Marion S. Buckwalter, M.D., Ph.D.**
Assistant Professor, Neurology and Neurosurgery

## Why do younger brains exhibit greater *plasticity* for Stroke Recovery?

The brain's ability to repair itself after a stroke is known as "brain plasticity." Younger brains possess greater plasticity than older ones. Unfortunately, the vast majority of strokes occur in older patients. Dr. Marion Buckwalter's work as a clinical neurologist fuels her desire to develop new therapies to help her patients recover from stroke. Understanding the differences between younger and older brain plasticity could offer revealing insights into new methods of advancing a cure for stroke.

Patients usually seek medical help for stroke shortly after they experience problems like paralysis or numbness, or difficulty speaking or thinking. During the onset of symptoms, two processes accelerate: inflammation and the regenerative response. It is also these two processes that are likely modulated by age, and therefore influence the brain's potential to recover from a stroke.

Inflammation, when it is unchecked, can lead to further brain damage. Dr. Buckwalter and colleagues study a factor called "transforming growth factor beta (TGF-beta)." This is a substance that is produced after brain injury that can either activate or suppress the immune system. Dr. Buckwalter is investigating how TGF-beta stimulates the immune system to control recovery.

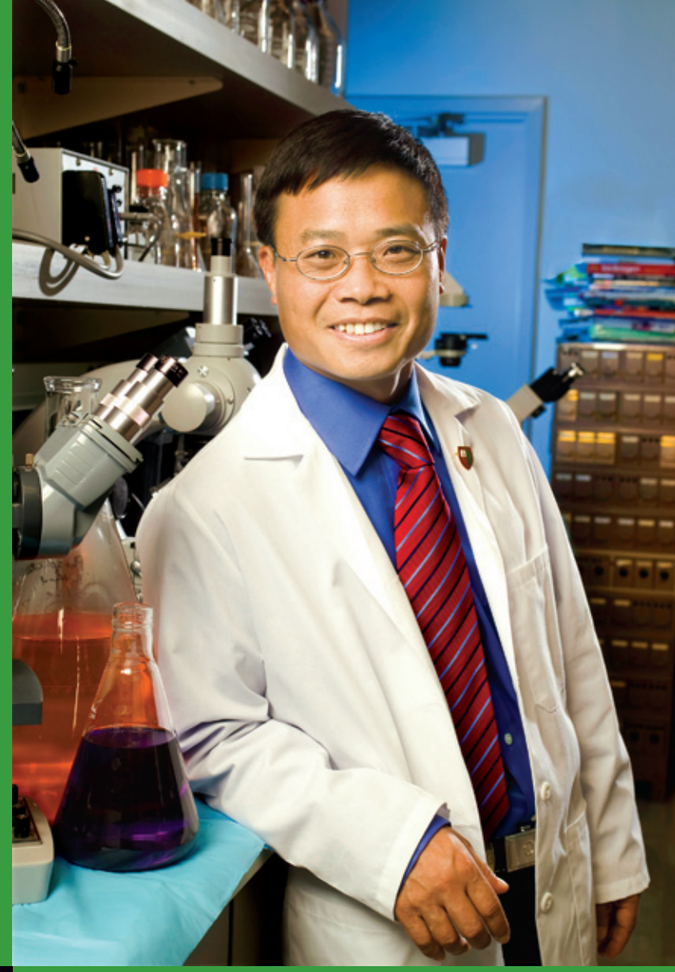
Neurotrophins are ideal candidates to mediate how the regenerative response works after stroke. These are secreted proteins that prevent nerve cells from dying and help brain cells form new connections. Dr. Buckwalter's team is testing the therapeutic effect of administering drugs that mimic neurotrophins developed by Stanford Neurology Department Chairman and Professor, Dr. Frank Longo, on stroke recovery. To help answer these questions, Dr. Buckwalter and her collaborators are using advanced technology to image and study the brain's complex regenerative response to stroke in laboratory models.

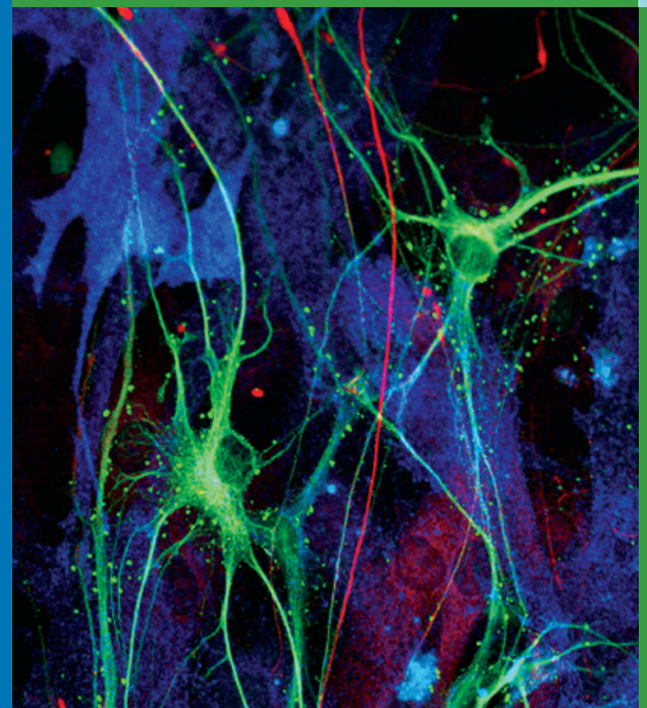


## Conditioning the brain to Survive Stroke

**Heng Zhao, Ph.D.**
Assistant Professor, Neurosurgery

Ischemic stroke is caused by the blockage of an artery in the brain. Ironically, a large part of the damage from stroke is caused by the subsequent restoration of blood flow, which is termed "reperfusion." Dr. Heng Zhao is studying an intriguing phenomenon that protects the brain from this damage when reperfusion is interrupted for several short intervals, a process called "postconditioning." Since reperfusion unleashes a torrent of hazards to the brain (inflammation, reactive oxygen species and direct damage to brain cells), Dr. Zhao's research team is intensively investigating what brain cell survival pathways are activated by postconditioning, with the goal of finding new drug targets for stroke therapies.





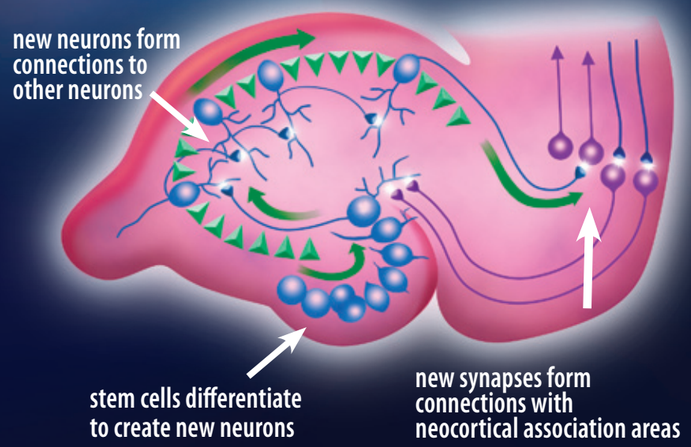
There is another form of conditioning, called "ischemic cerebral preconditioning," in which a very small stroke is intentionally induced to confer protection when a subsequent, much larger stroke is predicted to occur. Dr. Zhao and colleagues are exploring the use of a form of preconditioning called "remote ischemic preconditioning," which as the name implies, interrupts blood flow in a peripheral artery. By performing the procedure in a non-vital area (such as a limb), the degree of risk is profoundly reduced, but the robust protection against cerebral ischemia is still achieved. In addition to pioneering this new experimental therapy, Dr. Zhao is identifying specific protective factors that may be transferred to the brain by remote preconditioning.


# Can stem cells save *our memories?*

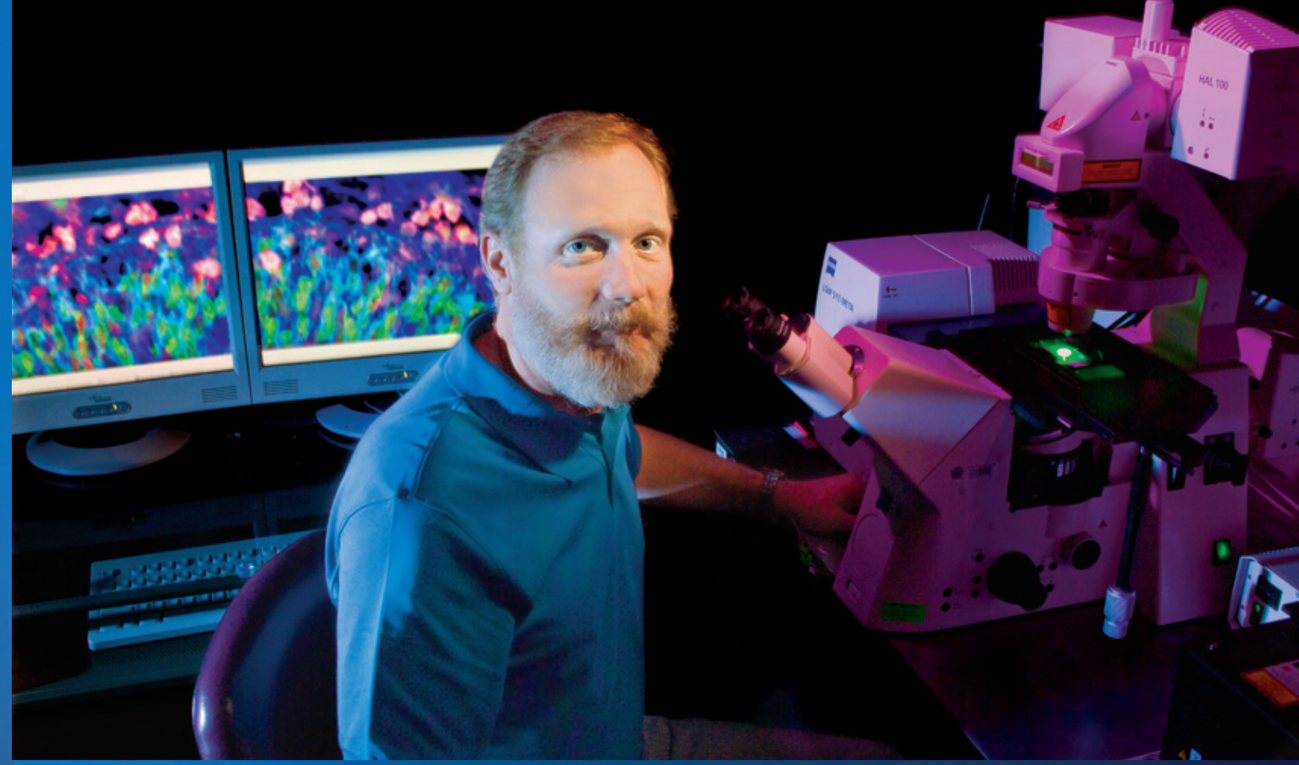
NEURAL STEM CELLS are responsible for building the complex neural networks of the central nervous system during development and their task continues in the adult, where they maintain and repair the brain as it ages. In most brain regions, adult stem cell activity is limited to replacing accessory cells. The neurons that make up the circuitry of the brain are not replaced. The hippocampal formation is an exception. In this region of the brain, stem cells continuously generate replacement neurons for circuits that are directly responsible for encoding new memories. This is one of only two adult brain regions that routinely produce new neurons (a process termed "neurogenesis").

Studies in adult neurogenesis at Stanford initially led Dr. Theo Palmer to the pioneering discovery that neurogenesis is exquisitely sensitive to immune signaling and tissue inflammation. Virtually every injury or disease process in the brain causes inflammation and when the immune system is activated, stem cells cease making new neurons. Dr. Palmer has found that controlling inflammation can enhance neurogenesis and restore memory function after brain injury from trauma, infection and radiation damage.

## Neurogenesis in the Hippocampus





**Theo Palmer, Ph.D.**
Associate Professor, Neurosurgery
Director, Neural Stem Cell Program

## Stem Cells May Show Promise for Parkinson's Disease & Psychiatric Disorders

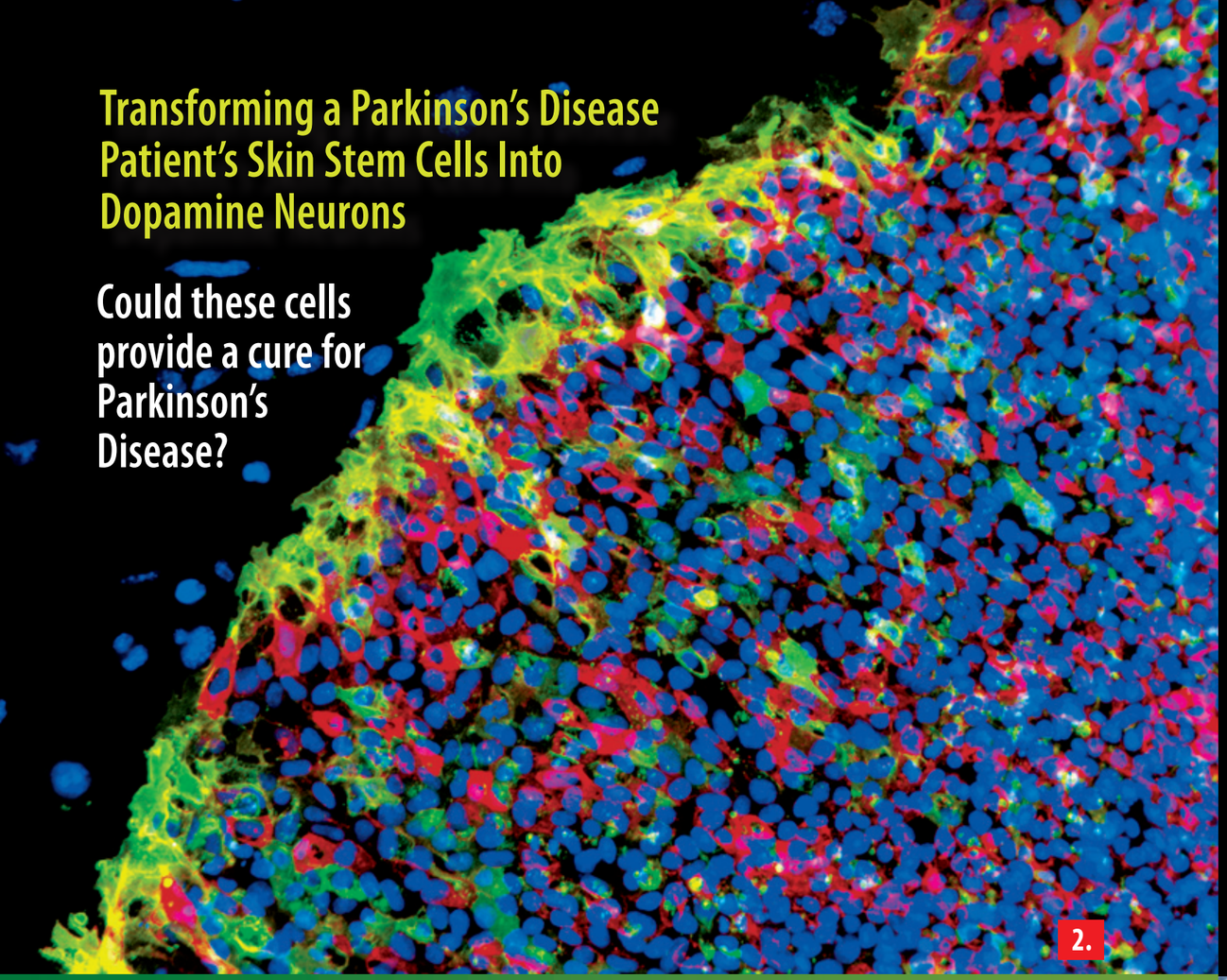
In one application, children who undergo radiation treatment for brain cancer often experience cognitive decline later in life. Dr. Palmer and his team found that when they modeled this condition in the laboratory, stem cells were severely impaired in their ability to generate new neurons. Surprisingly, they discovered that this malfunction in neurogenesis was due to brain inflammation caused by the radiation treatments and could be reversed with simple therapy using nonsteroidal anti-inflammatory drugs like indomethacin.

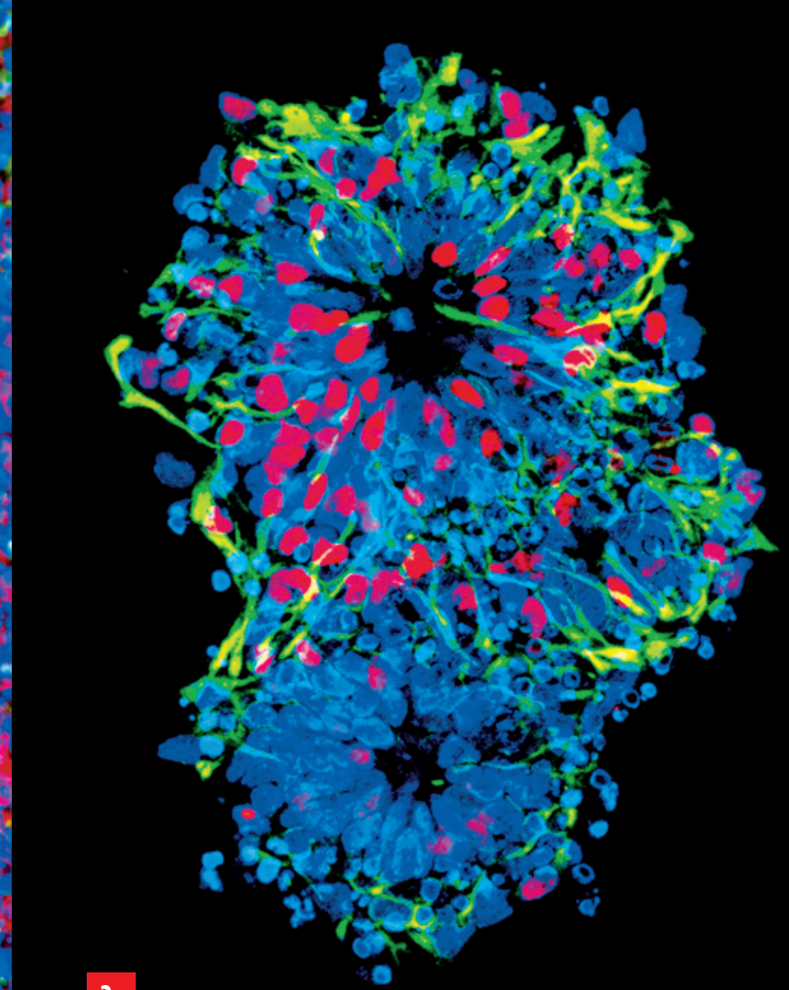
Dr. Palmer is also investigating the interaction between immune signaling and stem cell activity within the fetal brain during development. Infections and illness during pregnancy have long been linked to later autism and schizophrenia in the child, yet the reasons for this linkage are poorly understood. Members of the Palmer laboratory have found that maternal immune signaling during pregnancy disrupts neural stem cell activity in the developing brain and that simple interventions to quiet maternal immune signaling can prevent detrimental alterations in the fetal brain.

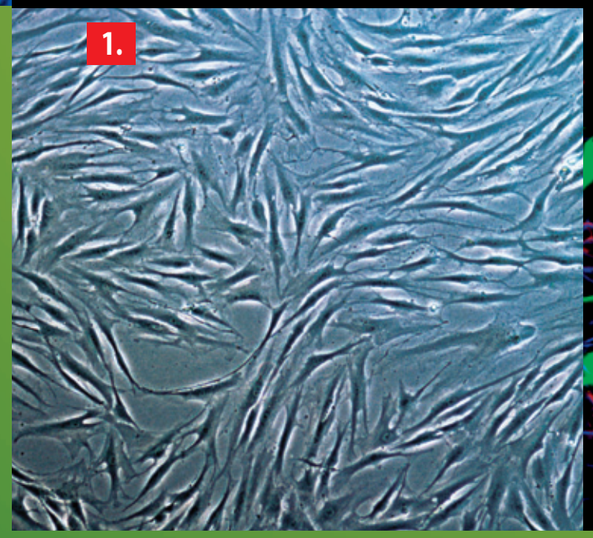
Immune signaling is equally important for neural stem cell function at the end of life and stem cell technology is also being used to develop treatments for aging-related diseases such as Parkinson's disease (PD). PD is caused by the degeneration of neurons that control movement. The degenerative process is accompanied by widespread tissue inflammation that worsens the degenerative process and may hinder attempts to use stem cell transplants to replace lost neurons. Together with Dr. Renee Reijo Pera in the Stanford Stem Cell Institute and Department of Obstetrics and Gynecology, Dr. Palmer is generating induced pluripotent stem cells (iPScells) from skin cells of PD patients. These iPS cells can be coaxed to become neurons in a Petri dish and these diseased neurons are now being used by Dr. Palmer to test drugs for their ability to slow or stop the disease. iPS cells are also being used to create normal functioning neurons that can be transplanted to replace degenerated neurons and reverse the Parkinson's symptoms. Dr. Palmer's novel exploration of the interaction between the immune system and stem cell biology paves the way towards therapies that target neural stem cells at each stage of life, from prenatal development, thorough childhood and into old age.

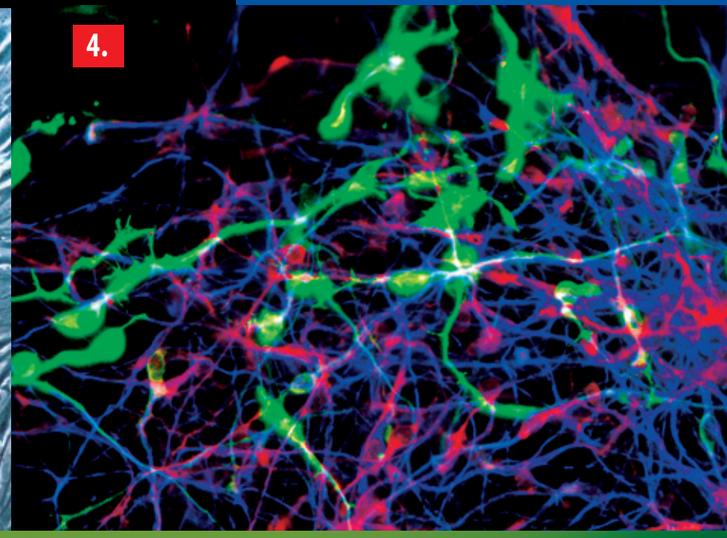
# Transforming a Parkinson's Disease Patient's Skin Stem Cells Into Dopamine Neurons

## Could these cells provide a cure for Parkinson's Disease?




**1. Skin Cells of Parkinson's Disease Patient:** Light microscope image of dermal fibroblasts from a Parkinson's Disease patient with a triplication of the SNCA gene. These fibroblasts were reprogrammed to become iPS cells.

**2. Induced Pluripotent Stem Cells (iPS cells):** Immunofluorescence image of iPS cells derived from fibroblasts in image 1. DAPI, in blue, highlights all the cell nuclei. SSEA3, in green, and TRA160, in red, are markers of pluripotency.

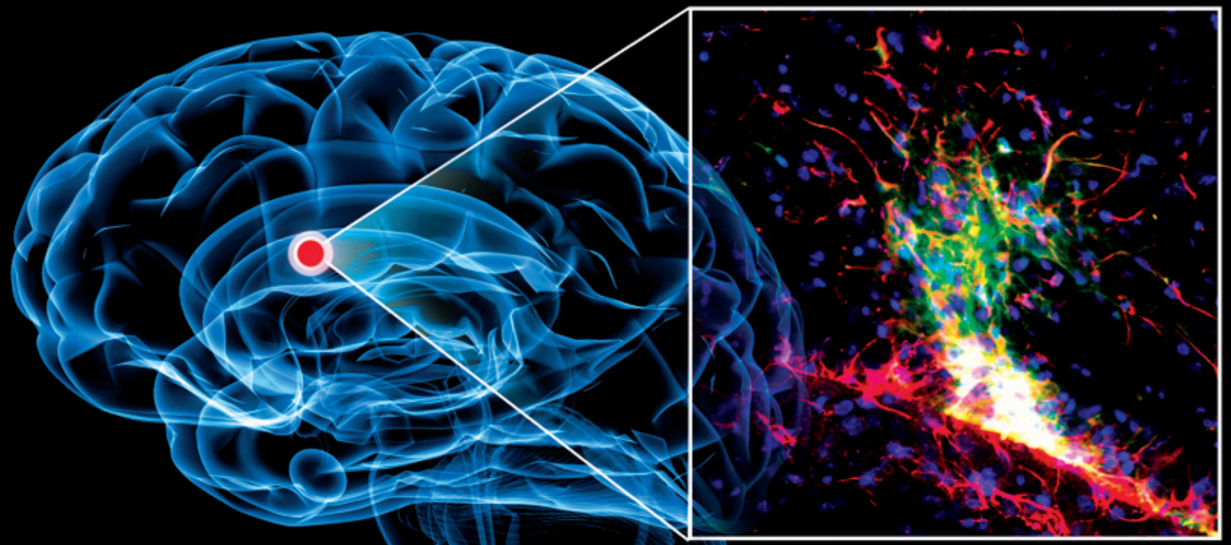
**3. Human Neural Progenitor Cells (Rosettes):** This image shows iPS cells that are in the process of becoming neurons. At this stage they are neural progenitor cells (the cells that become neurons) arranged in characteristic flower looking formation termed rosettes. DAPI, in blue, highlights all the cell nuclei. Nestin, in green, labels neural progenitors. Otx2, in red, labels a subpopulation of neural progenitors that can become midbrain dopamine neurons.

**4. PD iPS-Derived Dopamine Neurons:** This image shows iPS cells that have differentiated into neurons. Double cortin, in red, and beta-III tubulin, in blue, are structural proteins in neurons. Tyrosine hydroxylase, in green, is an enzyme required for the production of dopamine, and is present in all dopaminergic neurons. Since these neurons were derived from a patient with a gene mutation which is believed to cause PD, these neurons also have that mutation, and are being used to study what goes wrong in PD.

It is often difficult to study human specific neurobiology and neuropathology due to technical and ethical issues surrounding sample collection from human subjects. It would be preferable, and indeed, easier to grow appropriate human tissues in-vitro to perform these experiments. Embryonic stem cells are capable of differentiating into every cell type in the human body, but still have significant ethical problems surrounding their collection and derivation. Induced pluripotent stem cells (iPS cells) are largely similar to embryonic stem cells in their ability to differentiate into all the different cells of the human body, while alleviating the destruction of human embryos which typically accompanies embryonic stem cell derivation. Presumably, almost any cell type can be reprogrammed into an iPS cell – including many that are easily obtained with little risk and discomfort such as dermal fibroblasts (skin cells).

The derivation of many iPS cell lines from individuals with known disease phenotypes will allow the creation of very powerful models of human disease. Parkinson's Disease (PD) is a human disease which does not naturally occur in other animals, making it difficult to study in non-human tissue. Dr. Theo Palmer and his collaborators have recently begun creating iPS cell lines from individuals with mutations known to be involved in PD such as a triplication of the alpha-synuclein gene (SNCA). SNCA is highly expressed in the brain, and triplication of this gene results in even higher expression of the protein within cells. The mechanism by which this overexpression of SNCA causes selective degeneration of midbrain dopamine neurons is still unknown. Dr. Palmer hopes to gain insights into the mechanisms of Parkinson's Disease by studying these new iPS cell derived dopamine neurons in his ongoing research.

Images courtesy of Branden Cord from Dr. Theo Palmer's Lab; Ha Nam Nguyen and Blake Byers from Dr. Renee Reijo Pera's Lab



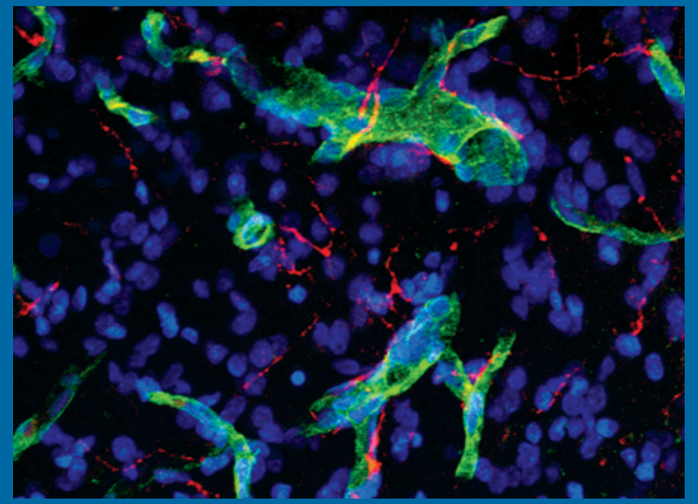
*(above:)* Transplanted stem cells (green) migrating towards blood vessels in stroke-damaged brain.

# Designing Stem Cells For Transplantation

Marcel M. Daadi, Ph.D.
Senior Scientist, Neurosurgery

Embryonic stem cells have the enormous potential to form any cell type in the body. In order to harness this potential for neurorestorative therapies, Senior Scientist Marcel Daadi has developed a method to direct human embryonic stem cells to form only neural stem cells - cells solely dedicated to building neurons and other important brain cells, glia. Using this novel technique, Dr. Daadi can produce neural cells that are homogeneous and stable enough to be grown for use in the clinic for transplantation. A clinical trial using these cells in stroke patients is currently being planned and they also have the potential to treat neurodegenerative diseases such as Parkinson's.

Dr. Daadi and colleagues have demonstrated that these neural stem cells can improve functional recovery when they are transplanted one week after stroke in a laboratory model. The neural stem cells migrated toward the stroke and differentiated into fully functional neurons as well as glia. Most importantly, Dr. Daadi's technique overcame a major barrier to the safe use of embryonic stem cells: the transplanted cells did not give rise to tumors.



*(above:)* Human neural progenitor cells (red) are found in close proximity to blood vessels (green).

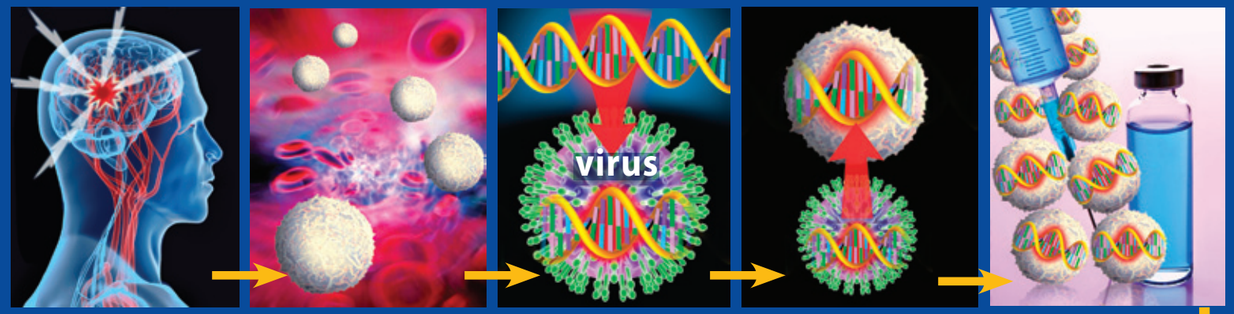
# Stem Cells Assist the Brain's Natural Repair Process *After a* Stroke

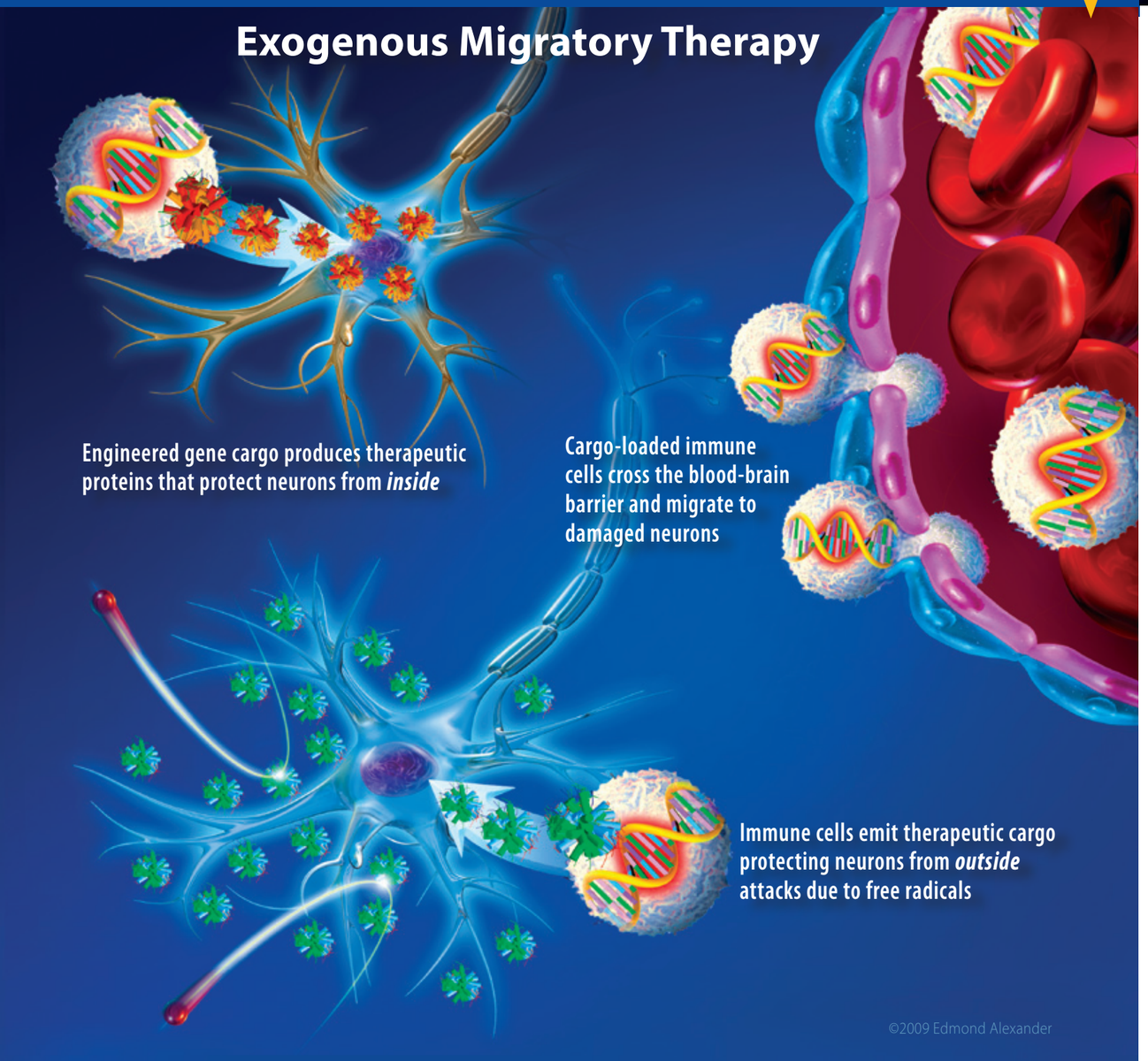
Tonya M. Bliss, Ph.D.
Senior Scientist, Neurosurgery

Most of the current therapies for stroke strive to stop or slow damage to the brain and must be administered within hours of the event. Dr. Tonya Bliss is exploring stem cell transplantation to repair the brain long after the stroke event, offering hope to a larger population of stroke patients.

Dr. Bliss and colleagues have discovered that stem cells transplanted a week after ischemic stroke can improve recovery in a laboratory model. The goal of their research is to understand how this improvement occurs. Dr. Bliss' work has demonstrated that the transplanted cells produce factors such as vascular endothelial growth factor (VEGF) that enhance the brain's endogenous repair mechanisms by altering nerve connectivity and promoting blood vessel growth to ultimately produce neurological recovery. Once these factors are identified, then stem cells can be custom engineered to produce more of the repair factors and thus increase their efficacy.

The interaction between the transplanted stem cells and the injured brain is a two-way street, with the local environment of the stroke having a major effect on how the stem cells behave. Because the stroke milieu changes over time, another focus of Dr. Bliss' research is to determine an optimal window of time for stem cell transplantation to occur. Her work is another example of how basic research can lead to vital therapies for patients.




# Can Neurons Be Saved From STRESS?

**Robert M. Sapolsky, Ph.D.**
John A. and Cynthia Fry Gunn Professor,
Biology, Neurology and Neurosurgery

Few Westerners are likely to die of scarlet fever, malaria or dysentery. Instead, we live well enough and long enough to suffer diseases of slow accumulation of damage; critically most diseases of the Westernized lifestyle can be caused or worsened by *stress*. For more than 20 years, Dr. Robert Sapolsky's resarch has explored one piece of this story, namely the fact that stress and a class of stress hormones (glucocorticoids) can damage the nervous system. His lab investigates how such damage occurs, its relevance to a number of neurological and psychiatric disorders, and the development of novel therapeutic strategies.

Dr. Sapolsky's work also includes the creation of a unique immune cell-based gene therapy for brain injuries resulting from strokes, seizures, or damage from chronic stress that is both non-invasive and injury-specific, called ***Exogenous Migratory Therapy (EMT)***. Gene therapy is a promising form of treatment for acute brain injury where the brain damage is exacerbated by the accompanying cascade of inflammatory assaults. The clinical application of gene therapy is hindered however, by the difficulty of gene transport to the brain, which is restricted by a protective layer known as the blood-brain barrier (BBB). Previous delivery strategies have been severely limited, either by their high degree of invasiveness, or lack of injury-specificity, resulting in adverse side effects. Overcoming these obstacles is a primary research objective of Dr. Sapolsky's lab group.

Drawing from our knowledge of the inflammatory response to brain injury, Dr. Sapolsky's ***Exogenous Migratory Therapy*** strategy, brought to fruition by Dr. Nathan Manley, a post-doctoral fellow in the lab, targets vulnerable neurons through the use of injury-responsive immune cells. These 'cellular EMTs' rapidly migrate to damaged tissue in the brain through the bloodstream and selectively cross the BBB in response to inflammatory signals present at the injury site. Temporary collection and removal of these immune cells from the circulation allows them to be retrovirally-loaded with a specially designed gene cargo propagated in the laboratory. Afterwards, these immune cells are reintroduced whereby the gene-loaded cells migrate or home directly to damaged brain neurons and release their therapeutic cargo (proteins emitted from the gene) that facilitates neuronal recovery. Another novel feature of EMT is its dual action approach through delivery of cargo that protect neurons from the inside as well as from the outside, neutralizing damaging attacks from free radicals.

Dr. Sapolsky is also widely respected for his 25 years of research on baboon behavior and stress related disease that he conducts annually in the Serengeti of East Africa. He has authored several critically acclaimed books including "Why Zebras Don't Get Ulcers," and "A Primate's Memoir," which won the Royal Society Prize for Science Books. He has received many academic accolades including the prestigious MacArthur Fellowship "Genius Grant." In 2007, he was honored with the John P. McGovern Award for Behavioral Science from the American Association for the Advancement of Science. His laboratory research is funded by the National Institutes of Health (NIH).

# Pediatric Neurosurgery

Any serious illness that befalls a child causes enormous emotional and physical strain, both for the child and the family. Neurosurgical problems in the pediatric age group are often difficult and complex. The Lucile Packard Children's Hospital (LPCH) Pediatric Neurosurgery Program provides individualized care for infants to young adults and encompasses the full range of neurosurgical disorders affecting a child's brain or spinal cord. Dr. Michael Edwards at Stanford leads the dedicated pediatric team consisting of neurosurgeons, anesthesiologists and specialized nurses. In 2009, LPCH was ranked by U.S. News and World Report as the best pediatric hospital in the Bay Area for neurosurgery and amongst the top 10 institutions overall nationally. The Pediatric Neurosurgery Program at Stanford has earned a national reputation for delivering the highest standard of family-focused care. This is due to the Neurosurgery team's clinical expertise integrated with neuroscientists, and professional support from an array of specialists including pediatric therapists, and on site child education and recreation therapy.

Pioneering work in new minimally invasive neurosurgery techniques such as neuroendoscopy, sophisticated image guidance, and intraoperative imaging techniques, which is supported by cutting edge technology including the advanced 3-Tesla MRI scanner which provides detailed fiber tract mapping and imaging of critical functions (the only facility of its kind in Northern California), gives the program an advantage in efficiency of diagnosis and in developing lower risk surgical treatments. The newly established Ford Family Surgery Center at LPCH is the most advanced surgical facility in the country designed exclusively for pediatrics, allowing the pediatric neurosurgical team to tackle even the most formidable of diseases and conditions.



Taking a family-centered approach by providing special care and support to children and parents while facing challenging neurological conditions

**Michael S.B. Edwards, M.D.**
Lucile Packard Professor of Neurosurgery and Pediatrics
Vice Chair, Pediatric Neurosurgery
Co-Director, Children's Brain Tumor Center

## Treating Childhood Diseases of the Brain and Spine from Malignant Tumors to Head Trauma and Prenatal Abnormalities

Childhood malignancies of the central nervous system continue to be one of the most common cancers that afflict children. As Director of Stanford's Pediatric Neurosurgery Program, Dr. Michael Edwards has established an exceptional service and is recognized by his peers as one of the country's most respected pediatric neurosurgeons. Dr. Edwards specializes in the advanced microsurgical treatment of all forms of benign and malignant central nervous system tumors. These include gliomas and medulloblastomas, brain stem gliomas, astrocytomas, pituitary tumors, and pineal region tumors. Minimally invasive techniques are preferred, allowing for miniature exposures of the brain and spinal cord. Endoscopic neurosurgical techniques and advanced targeting methods such as intraoperative neuroimaging, brain mapping, and monitoring are used to enhance tumor removal while minimizing risks to the patient. LPCH was also the first hospital in the nation to offer CyberKnife Radiosurgery for pediatric brain tumors, a non-invasive technique that utilizes high doses of precisely controlled radiation to treat brain and spine tumors. The clinical Neuro-Oncology Program headed by Dr. Paul G. Fisher and Dr. Edwards offers state-of-the-art treatment for newly diagnosed and recurrent CNS tumors. Many of these novel therapies are offered to patients through enrollment into clinical trials including institutional protocols, as well as participation in the Children's Oncology Group (COG).

### Mapping Epilepsy in the Brain to Assist Surgery

Children with medically intractable epilepsy are jointly managed by Dr. Edwards and his team of specialists in cooperation with the pediatric epilepsy group, led by Dr. Donald Olson based at the Stanford Comprehensive Epilepsy Center (SCEC) and LPCH. The new neuroimaging center dedicated to pediatric imaging uses the high field 3 Tesla MRI incorporating functional MRI, diffusion tensor imaging and white matter tractography, along with magnetoencephalography (MEG), Phase II intracranial monitoring and functional mapping to study critical brain regions and their connections prior to surgery.

Head trauma is the leading cause of death in the United States in children over one year of age, and brain and spinal cord injury accounts for more than 80% of them. Pediatric brain injuries carry a high emotional, psychosocial and economic impact because these patients often have comparatively long hospital stays with demanding systemic complications from their injuries. Dr. Edwards and the pediatric team are highly trained to diagnose and treat all forms of neurologic trauma.

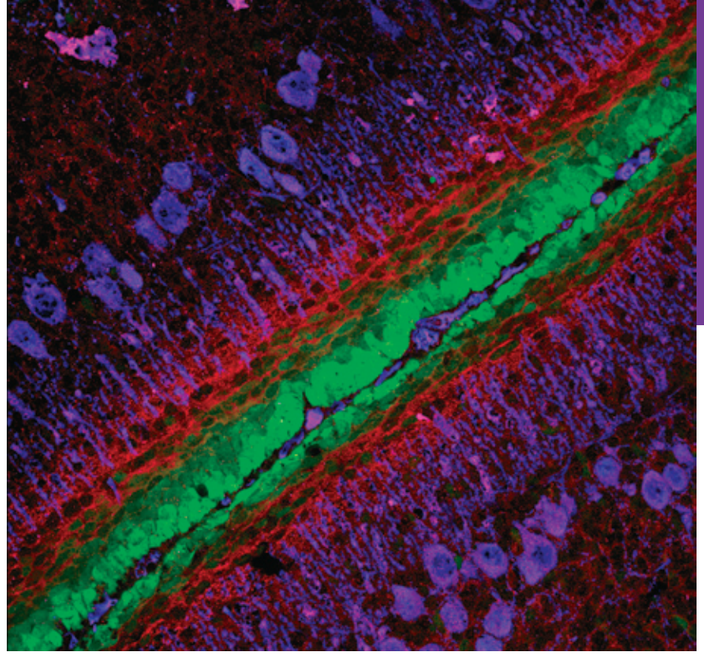
In addition, the Multidisciplinary Prenatal Diagnostic Program at LPCH combines the expertise of Perinatology, Neonatology, Obstetrics, Genetics, in utero MRI Imaging, and Pediatric Neurosurgery to provide consultation and treatment to mothers and families who are diagnosed with an in utero CNS abnormality.

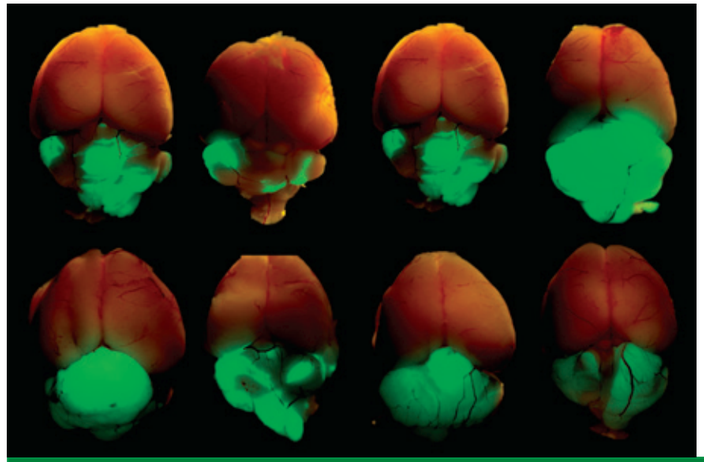
## Raphael Guzman, M.D.
Assistant Professor, Neurosurgery and Pediatrics

Dr. Raphael Guzman completed sub-specialty training in both cerebrovascular and pediatric neurosurgery. Pediatric cerebrovascular conditions are a major part of Dr. Guzman's special interests including: arteriovenous malformations, intracranial aneurysms and Moyamoya disease. All are managed in an interdisciplinary setting involving the Stanford Stroke Center, Interventional Neuroradiology, the CyberKnife Radiosurgery Center and the Stanford Moyamoya Center.

Craniosynostosis is a rare pediatric condition in which the skull bones of an infant's head fuse too early causing craniofacial asymmetry and problems for the growing brain. Dr. Guzman and his team are partnering with plastic craniofacial surgeons, geneticists, and specialist nurses to lead the Stanford Craniofacial Anomalies (CFA) Center at Lucile Packard Children's Hospital (LPCH). Advanced surgical techniques developed at Stanford and LPCH are used to recontour the skull, relieving pressure and correcting deformities. Drs. Guzman and Edwards are also investigating the role of mutations in genes encoding fibroblast growth factors and the transcription factors TWIST and MSX2 in dura mater as the causative factors in craniosynostosis. Strong collaborations between the clinic and the laboratory have made Stanford's cranio-facial reconstructive services among the best in the nation. Deformities as seen in Syndromic Synostosis (Crouzon, Apert's and Pfeiffer), as well as fronto-nasal dysplasia syndromes are often referred to the pediatric team at Stanford from throughout the larger community for their renowned expertise and success in correcting this condition.
Dr. Guzman's research into stem cell therapy has received support from government and charity groups, offering hope in the future for the cellular repair of neurologic disease. Dr. Guzman was recently nominated as the Bechtel Faculty Scholar in Translational Pediatric Medicine to advance research into neonatal ischemia and potential stem cell related therapies. The regeneration of white matter injury in the developing brain might be of special importance. The research in Dr. Guzman's lab focuses on the development of minimally invasive methods to deliver stem cells to the brain. The goal is to study the effect of neural stem cells on white matter repair after hypoxia-ischemia. A combination of basic science and translational research with the application of in vivo molecular imaging will hopefully facilitate the next step of moving his research efforts from the laboratory into effective patient therapies.







# Stanford Center for Children's Brain Tumors

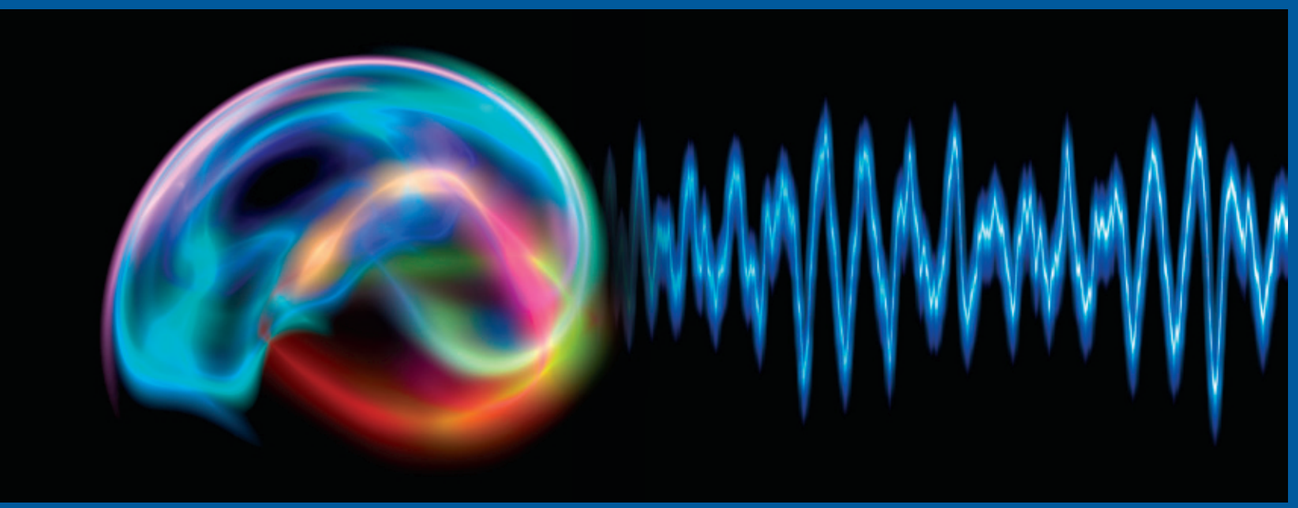
The Center for Children's Brain Tumors (CCBT) was established in 2004 with generous funding from the Price, Listwin, and Chambers families to better comprehend pediatric brain tumors by facilitating collaboration between basic science researchers, neuro-oncology and pediatric neurosurgery. Directing the center are pediatric neurosurgeon Michael Edwards, M.D., developmental biologist Matthew Scott, Ph.D., and pediatric neurologist/ neuro-oncologist Paul Fisher, M.D. Each specialist brings unique expertise to the comprehension of brain tumor biology. The center draws upon the burgeoning fields of genomics and proteomics, stem cell research, structural biology, chemical biology, computer imaging and high-throughput screening strategies. Issues that inhibit the advancement of pediatric brain tumor care are also being studied along with finding a cure. The CCBT's ultimate mission is to safely transform scientific discovery into effective new therapies for patients.

## *Unlocking* the Genetic Code for Medulloblastoma Brain Tumors

One exciting example of the several ongoing research projects sponsored by the CCBT includes Dr. Matthew Scott and colleagues who discovered in 1996 that mutations in the Hedgehog receptor gene PATCHED *(top image)* affected normal development of the cerebellar granule layer precursor cells (green) and resulted in the formation of medulloblastoma tumors. They then genetically engineered a mouse model of the disease by constructing a mutant patched1 mouse model *(bottom image)*. Present avenues of research will apply genome sequencing of mouse medulloblastoma tumor tissue compared to adjacent non-tumor normal cerebellum. The second phase will include similar sequencing in human medulloblastoma and cerebellum. The third phase will be to monitor the progression of tumors by examining early pre-tumors for genetic lesions. In collaboration with Chris Contag, Ph.D. and the Molecular Imaging Program at Stanford (MIPS), the pediatric neurosurgery team is evaluating the feasibility of improving medulloblastoma tumor resections by labeling the cells with novel peptides and using a hand-held confocal microscope to visualize residual cells at the tumor margin.

# Functional
## *Neurosurgery*

*Modulating Neuronal Firing in the Brain and Spinal Cord*



*(Above:)* Dr. Jaimie Henderson performing a Deep Brain Stimulation (DBS) procedure in Stanford Hospital O.R.

**Reaching for a glass on the dinner table, turning the page of a book, or saying "hello" to a loved one - all these actions are produced by amazingly integrated systems of nerves that work so seamlessly we take them for granted until there is a breakdown in communication. Malfunctions can result in seriously disabling symptoms such as tremors, uncontrollable spasms, seizures, loss of muscle control or chronic pain. Functional neurosurgery strives to alleviate miscommunications in the nervous system to restore normal neurological function.**

**Stanford's Functional Neurosurgery Program excels in both treatment and research for a variety of chronic neurological disorders. Many of these conditions have traditionally been treated by destruction of the malfunctioning brain areas. However, the main focus of the Stanford Functional Neurosurgery Program is the use of nondestructive techniques to modulate nervous system function (neuromodulation). Examples of neuromodulation therapies include deep brain stimulation (DBS), spinal cord stimulation, peripheral nerve stimulation, and the use of pumps to deliver small quantities of chemicals such as drugs for cancer pain, or other therapeutic agents like stem cells or viruses for gene therapy.**

**Jaimie M. Henderson, M.D.**
Robert and Ruth Halperin Faculty Scholar
Associate Professor, Neurosurgery
Director, Stereotactic and Functional Neurosurgery

Dr. Jaimie Henderson is one of the world's foremost experts in the use of image-guided surgical techniques for functional neurosurgical procedures such as the placement of deep brain stimulators (DBS) to treat movement disorders, pain, epilepsy, and psychiatric diseases.

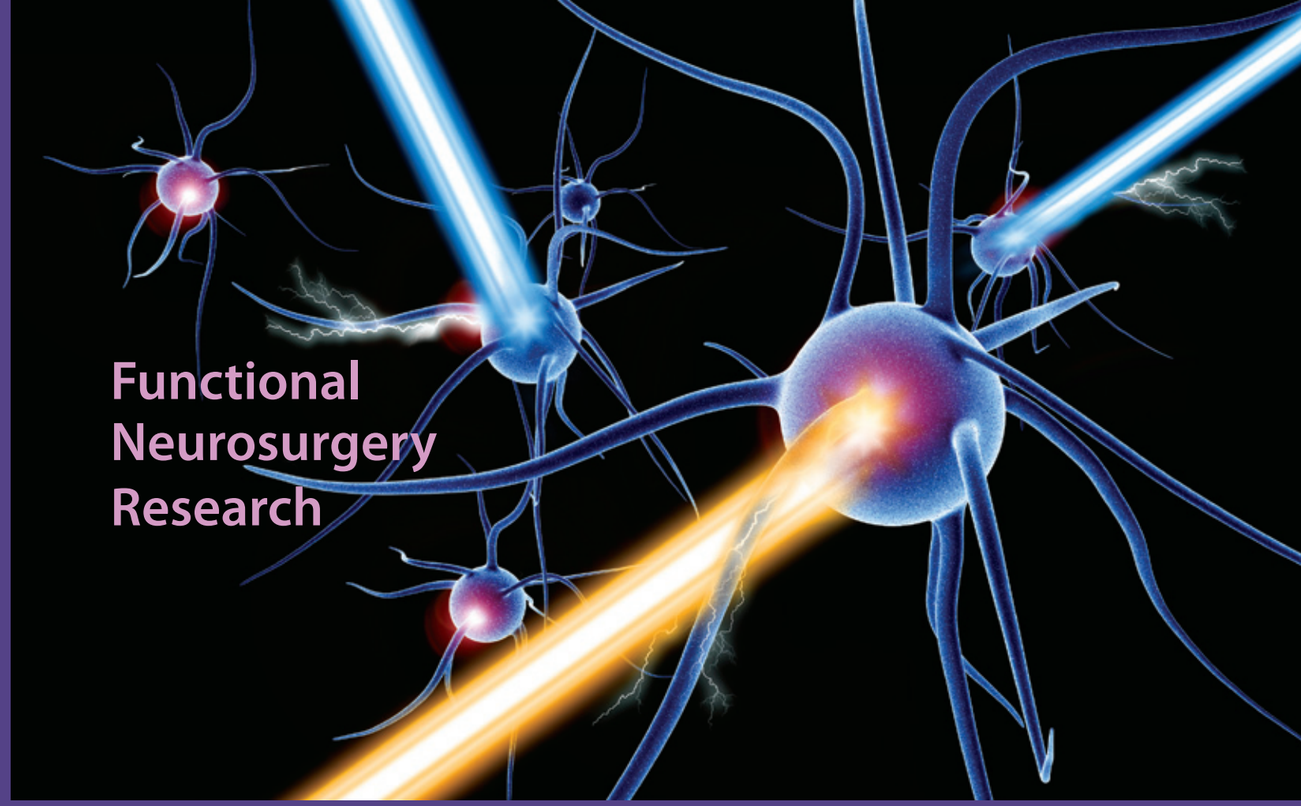
DBS uses tiny electrodes to deliver small pulses of electric current to areas of the brain such as the subthalamic nucleus in Parkinson's patients. The electrical impulses block the abnormal firing of neurons that cause Parkinson's symptoms such as tremors, rigidity, slowed movement and problems walking. The electrodes are guided with sub-millimeter accuracy to a precise location in the brain using a frameless stereotactic procedure pioneered by Dr. Henderson. The electrodes remain implanted and are connected to a battery operated stimulator installed under the skin of the chest. The system is then custom programmed to act like a pacemaker regulating the brain's electrical firing of neuronal activity.

Dr. Henderson and his colleagues in Stanford Neurology recently completed a clinical study of DBS for the treatment of medically refractory epilepsy, a form of the neurological condition unresponsive to antiepileptic drugs. The study was positive and will now go forward to the Food and Drug Administration (FDA) for further analysis in clinical trials. Negotiations are also underway to begin clinical trials of DBS for intractable depression and obsessive-compulsive disorder.

Another approach to neuromodulation is to actually engineer neurons in a circuit to produce inhibitory signals. Dr. Henderson is one of the investigators in a multi-center trial of gene therapy for Parkinson's treatment, introducing the GAD gene into subthalamic nucleus neurons with an adeno-associated viral vector, thus producing inhibition in this area which is overactive in Parkinson's disease.

As current President of the North American Neuromodulation Society, Dr. Henderson is leading policy efforts at state and national levels to ensure access to neuromodulation technologies for patients with severe chronic neurologic disease.





# Functional Neurosurgery Research

## Optogenetics: *Using* Light *Beams to Turn Nerve Cells On and Off*

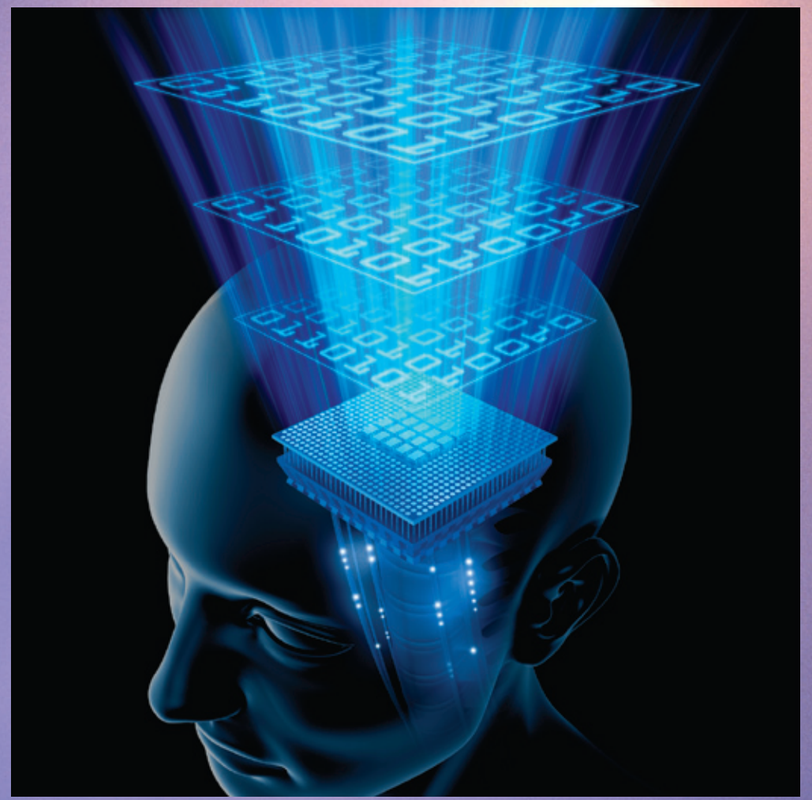
Dr. Henderson is spearheading a translational research project ultimately aimed towards patient applications in collaboration with Dr. Karl Deisseroth from Stanford Bioengineering and Psychiatry Departments, utilizing a revolutionary technique called Optogenetics invented by Dr. Deisseroth's research group. Optogenetics uses microscopic beams of light to switch individual brain neurons on and off.

Brain neurons specialize in their function and harmonize with one another much like different musical instruments in an orchestra. The genius of optogenetics is that it can target very specific groups of neurons in a circuit to fine tune overactive or underactive neurons by using fiberoptic micro-lasers to stimulate or inhibit their functions. Optogenetics renders neurons responsive to light by inserting a gene harvested from ancient algae or primitive bacteria that produce light sensitive ion channels capable of turning the neuron's activity on by a blue light wavelength or off with a yellow light. This elegant avenue of modulating neuronal performance has the potential to be much more nuanced and precise than traditional DBS in fine tuning and correcting abnormal neuronal firing. Ultimately, this technique may offer significant therapeutic benefits for Parkinson's disease and psychiatric disorders such as depression, to restore normal brain function.

Drs. Henderson's and Deisseroth's findings using optogenetics in animal models of Parkinson's disease have demonstrated positive results and were published recently in the prestigious journal, *Science*.

# Brain-Computer *Interface*

## *Offering paralyzed patients mind control of movement*



## *Functional Neurosurgery's Vision for Future Translational Therapies*

Paralysis results from interruption of the normal connections between the brain and muscles. Dr. Henderson is collaborating with Dr. Krishna Shenoy in Stanford's Department of Electrical Engineering, who designs high-performance neural prosthetic systems which are also known as brain-computer interfaces, to bring these systems out of the laboratory and into the clinic to help patients with paralysis. A 100-microelectrode recording array (4 x 4 mm in size) is implanted on the brain's premotor cortex to transmit information to a computer that decodes neural activity into output signals. These output signals are then programmed to move computer cursors or prosthetic devices (artificial limbs), restoring function to paralyzed patients and even possibly re-activating paralyzed muscles.

The goal of this ambitious research program is to devise a brain-computer interface that could be plugged in through a standard USB port to allow a paralyzed patient to move a computer mouse or mechanical arm using brain signals alone. Plans are underway to perform the first implants in patients paralyzed from Amyotrophic Lateral Sclerosis (ALS), Lou Gehrig's disease, in 2010.

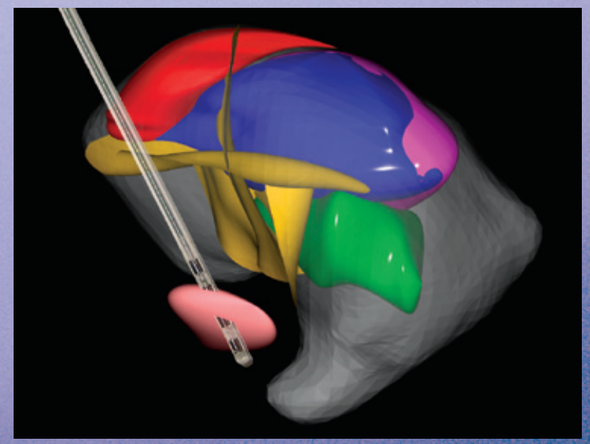


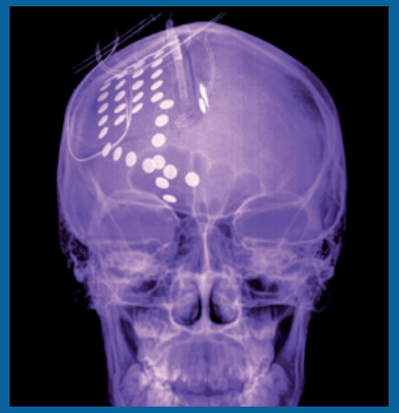
**Hong Yu, M.D.**
Assistant Professor, Neurosurgery

A recent new arrival to Stanford Neurosurgery, Dr. HongYu's clinical specialty in functional neurosurgery includes the treatment of movement disorders, epilepsy, and pain. She is especially interested in expanding the application of DBS to eating disorders and obesity. These pathologies bridge the psychiatric or limbic disorders with the autonomic nervous system, which controls eating.

Dr. Yu has helped develop a new automated image processing algorithm that creates brain atlas mapping for functional neurosurgery targets on MRI. This becomes especially useful when targets are not "visible" to the naked eye, or are poorly delineated by intraoperative electrophysiology recordings. The use of this brain atlas will not only facilitate target localization, but also streamline the entire DBS implantation process, making it more accessible and conducive to uniform outcomes at medical centers in diverse locations.

Dr. Yu was recently honored with awards for her research from the Southern Neurosurgical Society and the American Society for Stereotactic and Functional Neurosurgery.





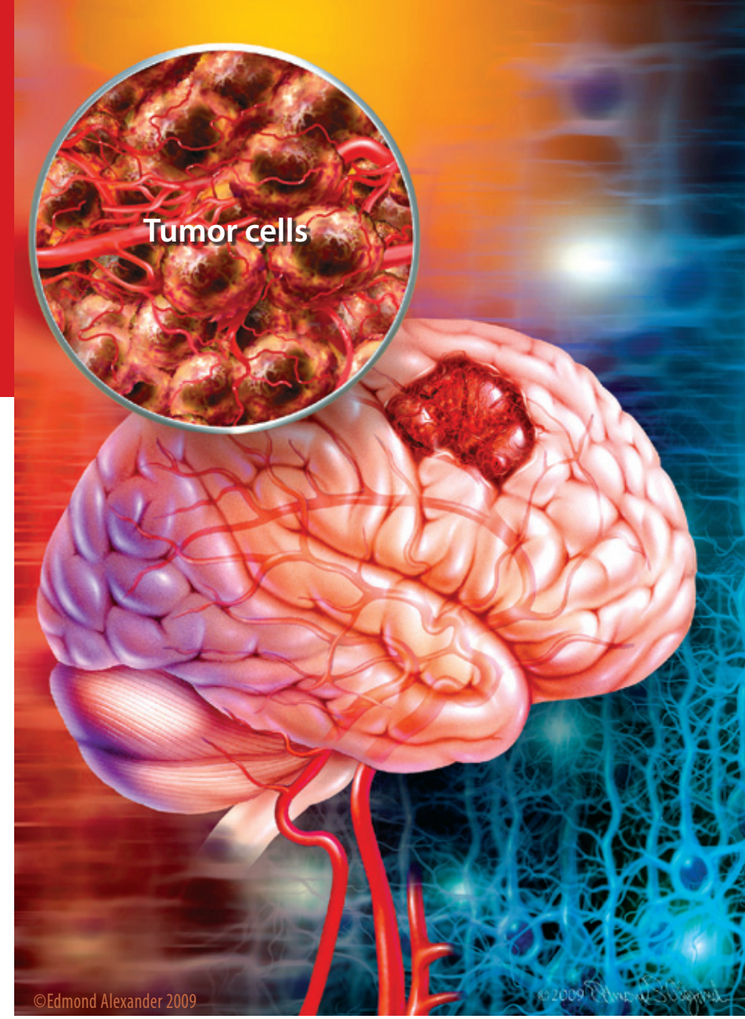
**Lawrence M. Shuer, M.D.**
Professor, Neurosurgery
Vice Chair, Neurosurgery Quality Assurance
Associate Dean for Graduate Medical Education

Dr. Lawrence Shuer's Functional Neurosurgery interests include epilepsy resistant to maximal medical management, where surgery is necessary to treat the patient's symptoms. In conjunction with Stanford epilepsy neurologists, Dr. Shuer places electrode grids on the brain to accurately map the location of seizure foci at surgery and on the epilepsy monitoring patient unit. This information is then analyzed to determine which diseased brain areas are inciting the seizures, thus requiring microsurgical resection. Preoperative functional MRI data and intraoperative stimulation of brain structures in conscious patients identify critical brain regions to facilitate removal of epileptic tissue with minimal risk. Dr. Shuer utilizes vagus nerve stimulation in the neck as an alternative therapy for difficult to control seizures in epilepsy patients.

In addition, Dr. Shuer is an expert in treating the disabling form of facial pain known as trigeminal neuralgia (tic douloreaux) with microvascular decompression and percutaneous rhizotomy.

Dr. Shuer is currently serving as Associate Dean for Graduate Medical Education at Stanford University School of Medicine and as Vice Chair of Quality Assurance in Neurosurgery. He has performed many other leadership roles during his career including a term as Chief of Staff at Stanford Hospital and Clinics from 1996 to 2008. He is also actively involved in the training and mentoring of residents, interns, and medical students in the field of neurological surgery.

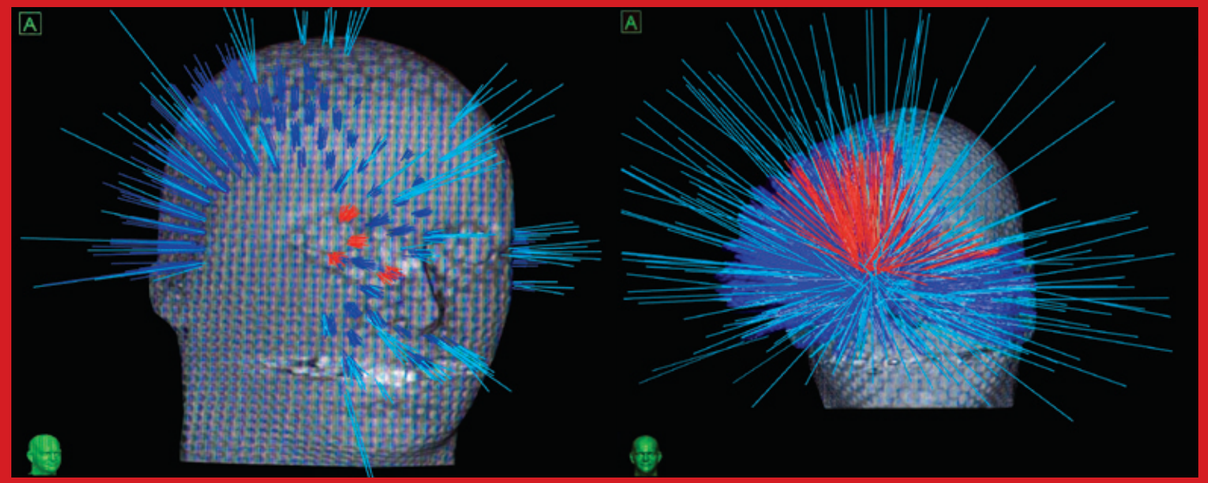
# Stanford Brain Tumor Center




According to the American Brain Tumor Association, more than 150,000 people in the U.S. are diagnosed with a new brain tumor each year. This includes primary brain tumors (those that arise in the brain) and metastatic brain tumors that spread from cancer elsewhere in the body. Seventy-five percent of brain tumors are benign, with the remainder being malignant. The survival rate for patients with a malignant brain tumor is 32%. Benign brain tumors can often be treated successfully and sometimes cured.

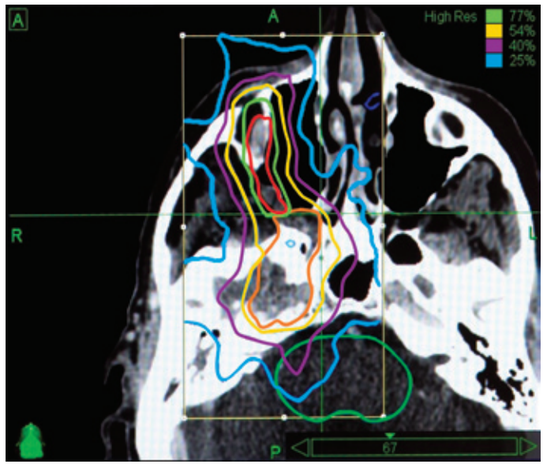
The Stanford Brain Tumor Center includes a number of neurosurgical faculty and combines multidisciplinary clinical care and a strong research program to facilitate rapid transfer of basic scientific findings into clinical protocols for patients with tumors of the brain, skull base and spine. The Brain Tumor Center is also an important component of the Stanford Cancer Center, designated by the National Cancer Institute as a certified Comprehensive Cancer Center (one of only 39 nationally). Diseases treated in the center include both benign and malignant tumors of the brain and spine in adults and children. Targeted pathologies include primary brain tumors (such as gliomas, craniopharyngiomas, germ cell tumors and lymphomas), metastatic tumors, and tumors of the skull base (including meningiomas, pituitary adenomas, and acoustic neuromas). Minimally invasive therapies, such as radiosurgery, are a particular strength of the Neurosurgery Department. Studies of innovative treatments currently underway include an immune vaccine for recurrent glioblastoma, fractionated radiosurgery for acoustic neuromas, timozodamide for adult malignant gliomas, oxygenation agents as radiosensitizers, and combination chemotherapy for pediatric tumors.

Basic science research efforts within the Neurosurgery Department include investigation of the regulatory mechanism of tumor angiogenesis, tumor angiogenesis as a target for gene therapy, immunotherapy, therapy involving insertion of tumor suppressor genes, tumor cell invasion, stem cell origin for brain tumors, and the application of gene chips to enable molecular characterization of brain tumors.



# Robotic Radiosurgery with CyberKnife

## Targeting brain tumors with unprecedented accuracy to give high dose radiation therapy safely




**John R. Adler, Jr., M.D.**
Dorothy and TK Chan Professor of Neurosurgery
Vice Chair, Neurosurgery Innovation and Technology

Dr. John Adler's passion is developing minimally invasive methods for treating brain and spinal cord disorders by utilizing computerized image guidance and radiosurgery technologies. He is best known for having pioneered the field of image-guided radiation, starting with his invention of the CyberKnife. This robotic instrument enables very high doses of therapeutic radiation to be uniquely delivered to tumors with pinpoint sub-millimeter accuracy, thereby sparing surrounding normal brain tissue from the damaging effects of radiation. CyberKnife radiosurgery is particularly advantageous for treating surgically inaccessible tumors in deep or sensitive brain locations that typically control critical neurologic functions, such as language, vision or motor control. Another unique feature of the outpatient CyberKnife is that is does not require placement of a rigid skull frame, rendering the procedure much more comfortable for the patient than conventional radiosurgical procedures. This characteristic gives the CyberKnife system a distinct advantage for treating a broad range of tumors throughout the body, in addition to the brain.

Today more than 80,000 patients have undergone radiosurgery using the Cyberknife in over 180 medical centers throughout the world. In 2006, Stanford was the first institution to add a second CyberKnife radiosurgery system dedicated, in co-operation with the Stanford Comprehensive Cancer Center, to pediatrics and non-neurologic conditions. Dr. Adler has initiated various CyberKnife procedures including radiosurgical ablation of large cerebral metastases, skull base meningiomas, acoustic neuromas, pituitary

adenomas and tumors adjacent to the optic nerves, as well as treatment of trigeminal neuralgia (chronic, severe facial pain), obsessive compulsive disorders, spinal tumors and spinal arteriovenous malformations. Meanwhile, the FDA recently approved clinical trials at Stanford to investigate the treatment of intractable depression with CyberKnife radiomodulation. In the past, Dr. Adler also spearheaded clinical applications for the treatment of several non-neurosurgical diseases such as prostate, lung and pancreas tumors. He is now leading the technology development to treat atrial fibrillation (a heart arrhythmia that causes many strokes) with CyberKnife radiosurgery. He attracts patients for CyberKnife therapy worldwide.

Dr. Adler also co-directs the Stanford Institute for Neuro-Innovation and Translational Neurosciences' Innovation Fellowship Program that nurtures other scientists and inventors in the creation of novel therapeutic technologies in neuroscience.

**Steven D. Chang, M.D.**
Robert C. and Jeannette Powell Professor in the Neurosciences
Professor, Neurosurgery
Co-Director, Stanford CyberKnife Program

## Expanding Applications for CyberKnife Radiation Therapy

As Co-Director of the Stanford CyberKnife Radiosurgery Program since 2003, Dr. Steven Chang has been instrumental in the program's phenomenal success in achieving an international reputation for its innovation, outstanding clinical care and rigorous academic standards. The Stanford CyberKnife Radiosurgery team consists of neurosurgeons, radiation oncologists including Co-Director, Dr. Iris Gibbs, and physicists working collaboratively to treat neurological disorders. Dr. Chang's research attempts to define new indications and rigorously assess clinical outcomes for patients with skull base tumors including acoustic neuromas and craniopharyngiomas, brain metastases, nasopharyngeal cancers and spinal tumors treated with radiosurgery. An important recent study analyzed the cost-utility of CyberKnife therapy for metastatic spinal tumors. In 2008, Dr. Chang was the first to treat a cardiac sarcoma (heart cancer) with CyberKnife radiosurgery. Due to his extensive experience with radiosurgery, Dr. Chang has been invited to organize and lecture at stereotactic radiosurgery symposia around the world. In addition to his expertise in radiosurgery treatment, Dr. Chang has a vigorous clinical practice performing microsurgical resection of brain tumors such as gliomas, meningiomas, acoustic neuromas and vascular lesions. He routinely demonstrates his surgical skills by obtaining outstanding clinical results in patients harboring the most challenging brain tumors.

Dr. Chang is also a prolific academic researcher publishing more than 200 manuscripts and book chapters, primarily related to the radiosurgical treatment of brain tumors. He directs the Stanford Radiosurgery Fellowship Program that has trained many neurosurgeons who have become faculty members at leading academic medical institutions. As a testament to Dr. Chang's scholarly and clinical work, he recently became the youngest faculty member in Neurosurgery to receive a Stanford University Endowed Chair, the highest honor bestowed on a professor.



**Clara Y. Choi, M.D., Ph.D.**
Assistant Professor, Neurosurgery
Director, CyberKnife Radiosurgery Research Program

## Radiosurgery Research

Dr. Clara Choi currently serves as the Director of Stanford's Radiosurgery Research Program. She completed special training as part of the NIH supported Medical Scientist Training Program, obtaining both her M.D. and Ph.D. in Biological Chemistry. Her additional education and certification as a Radiation Oncologist makes Dr. Choi the ideal leader for pursuing new avenues of CyberKnife and radiosurgery research. Various radiosurgery studies are underway aimed at understanding the tolerance of normal tissues to the high dose of radiation utilized in radiosurgery. Particularly promising areas of investigation include the use of a radio-protectant and high resolution neuro-imaging to improve pain control and decrease the adverse effects following radiosurgery treatment of trigeminal neuralgia (intractable, lancinating facial pain); radiosurgery divided into multiple lower dose fractions combined with chemotherapy for treating malig-nant gliomas (primary brain tumors); use of a novel drug (histone deacetylase inhibitor) in conjunction with radiosurgery to treat brain metastases from lung cancer; and radiosurgery for treatment of spinal metastatic lesions.

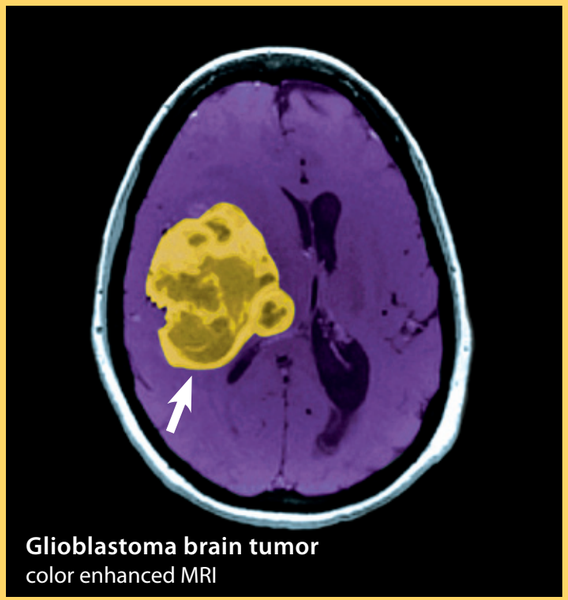
Dr. Choi has received several research awards from the Radiological Society of North America and the American Society for Therapeutic Radiology and Oncology, related to her inventive molecular imaging of key interactions between critical proteins and gene mutations affecting brain tumor patients.

As part of her current research grant awarded by the National Comprehensive Cancer Network (NCCN), she is exploring the efficacy of the anti-cancer agent vorinostat in combination with chemotherapy and/or radiation therapy in selected locally advanced non-metastatic cancers. These include non-small cell lung cancer, head and neck cancer, pancreatic adenocarcinoma, and brain metastases from a solid tumor with particular emphasis on lung cancer.

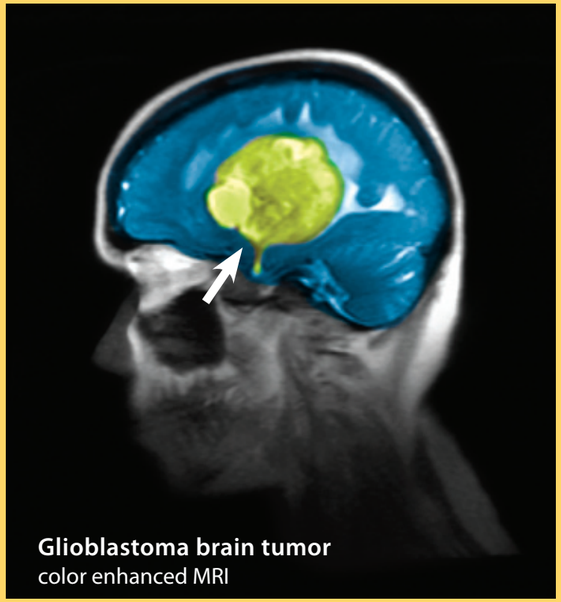
Dr. Robert Lieberson recently joined the Stanford CyberKnife team as a Clinical Assistant Professor. His education includes a neurosurgery residency and neuro-oncology fellowship at Stanford, as well as specialized training in radiosurgery. He is currently investigating the use of CyberKnife radiosurgery to treat paragangliomas (a benign tumor) of the skull base and spine, and facet back pain (a leading cause of disability), with very encouraging preliminary results for both conditions. Dr. Lieberson also participates in Stanford Neurosurgery community outreach, as a spine and neurotrauma surgeon at Santa Clara Valley Medical Center and Sequoia Hospital.

**Robert E. Lieberson, M.D.**
**Assistant Professor, Neurosurgery**

# Brain Tumor Research



**Glioblastoma brain tumor**
color enhanced MRI



**Glioblastoma brain tumor**
color enhanced MRI

## Testing a vaccine against the deadliest of brain tumors:

# Glioblastoma

## By altering a protein EGFRvIII, the immune system can be taught to destroy tumor cells

**Albert J.Wong, M.D.**
**Professor, Neurosurgery**

Glioblastoma is the most deadly of all brain tumors. Without therapy, patients usually die within 3 months of diagnosis. Available treatments are mainly palliative, extending survival time to an average of one year. This is because glioblastoma tumors are highly resistant to both chemotherapy and radiation in addition to their tendency to grow very rapidly in the brain, causing progressively severe neurological deficits and cognitive impairment.

Dr. Albert Wong has developed a groundbreaking immunotherapy vaccine that has more than doubled survival rates in Phase II/III clinical trials being conducted at over 20 academic institutions around the nation. The vaccine directs the patient's own immune system to attack and kill glioblastoma cells while leaving healthy cells intact.

Dr. Wong discovered an altered protein called EGFRvIII that is present in 60% of all glioblastomas. His team found that this particular abnormal protein causes the uncontrolled growth seen in glioblastomas, making it an ideal target for cancer therapy. Patients are immunized with a short version of EGFRvIII that is specific to glioblastoma cells. Their immune systems then recognize the cancer cells as foreign invaders, prompting t-cells to attack and destroy them while leaving normal cells unaffected.

The EGFRvIII vaccine will also be tested in pediatric brainstem gliomas, a particularly destructive tumor that invariably kills children within one year, where very few advances have been made in improving survival. Dr. Wong's team has found that this tumor also expresses the EGFRvIII protein. A Phase I clinical trial will commence in 2010 that has been funded by the National Institutes of Health.

Another approach being pursued by Dr. Wong's team that holds promise for glioblastoma treatment utilizes bivalent antibodies. Antibodies normally recognize only one protein and have been shown to be effective therapies against cancer (e.g., Herceptin and Avastin). By using gene splicing, Dr. Wong's team created an antibody that recognizes EGFRvIII (glioblastomas) and CD133, a protein on stem cells. This dual-specific antibody is designed to target an elusive population, the glioblastoma stem cell, which is believed to be the most vital target for an effective glioblastoma therapy.

The future expansion of research on EGFRvIII by Dr. Wong and his colleagues may be applicable to a very different class of diseases that include Alzheimer's and Parkinson's. The death of nerve cells in these diseases is often the result of an error in protein production. Certain "misfolded" proteins that are produced erroneously accumulate and eventually cause cell death. Dr. Wong's team has found that cells making a truncated version of EGFRvIII surprisingly turn on a pathway that is a protective response against misfolded proteins, and cell death is prevented. This may lead to a therapy that will halt the effects of neurodegeneration in Alzheimer's and Parkinson's diseases.

# Isolating Cancer Stem Cells for *Destruction*

**Stephen L. Skirboll, M.D.**
Assistant Professor, Neurosurgery
Chief, Neurosurgery, Veterans Affairs Palo Alto Health Care System

Dr. Stephen Skirboll's research seeks to determine the identity of stem cells that cause brain tumors in order to target them for therapy. Because these stem cells are rare, finding them is a major challenge requiring new technologies. Dr. Skirboll and his Stanford colleagues are using two powerful approaches to isolate the stem cells that cause glioblastomas, an aggressive form of brain cancer. The first approach uses an array of antibodies to capture the cancer stem cells from a tumor. The captured cells are then cultured on the array; if the antibody recognizes a self-renewing stem cell, the cells will grow on the spot where those antibodies were on the array. From this, Dr. Skirboll can glean a "signature" of cell surface proteins that are present on the cancer cells. In the future, researchers will use this cell surface signature to isolate and target the cancer stem cells for destruction.

Another strategy to treat brain cancer is to rob the stem cells of their ability to self renew or multiply. Dr. Skirboll is collaborating with Scripps Research Institute to screen tens of thousands of drug-like compounds that can cause glioma stem cells to differentiate and lose their ability to divide. This therapy can halt the aggressive growth of glioblastomas and transform them into more benign tumors that can be treated successfully.

As the Chief of the Neurosurgery Section at the Veterans Affairs Palo Alto Health Care System (VAPAHCS), Dr. Skirboll understands the urgent need for new imaging technology that would enable the complete removal of difficult brain tumors with minimal impact on normal surrounding tissue. His team is developing new agents that can specifically identify glioblastoma cells during surgery. These agents will offer clinicians a powerful tool to improve the accuracy of tumor removal during surgery, lessening the possibility that the cancer may recur in the future.




# Making Cancer Cells *Vulnerable* to Chemotherapy

**Marina Holgado-Madruga, M.D., Ph.D.**
Instructor, Neurosurgery

The cells that comprise the brain are quite interactive, coordinating tissue growth and repair via a complex system of molecules that are released by one cell and then taken up by another. Once a cell receives a signal from another, a cascade of intracellular events occurs that interprets the signal, affecting subsequent cell activity. Dr. Marina Holgado-Madruga is studying the signaling cascades that instruct cancer cells to either proliferate or die. The ultimate goal of her research is to identify drug targets that can sensitize cancer cells to chemotherapy, making these treatments more effective.

Chemotherapy kills cancer cells in part by creating reactive oxygen species (ROS), which destroy the cell. Simultaneously, however, the cancer cell is also receiving signals from other external factors such as the receptor tyrosine kinases to thrive and proliferate. Dr. Holgado-Madruga and colleagues seek to tip the balance towards cell death by manipulating a protein, called Gab1, which integrates opposing sets of instructions to live and die. Her research has shown that Gab1 integrates the survival or death pathways by interacting with specific protein partners.

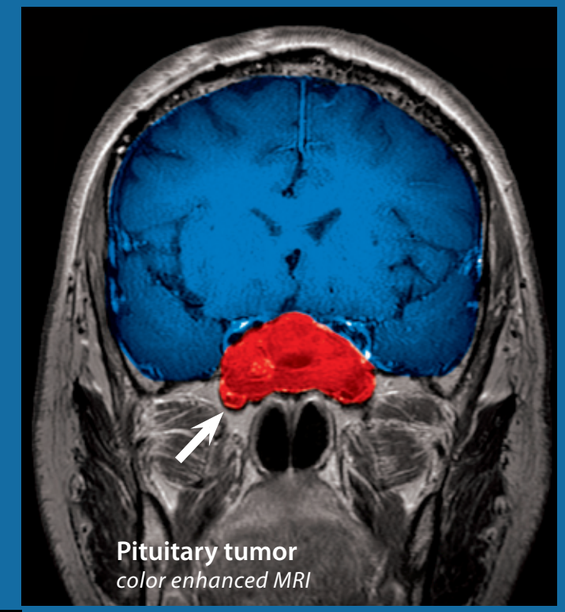
Dr. Holgado-Madruga and her team are investigating molecules as possible future therapies that will bind to Gab1 in cancer cells to favor the death pathway over the survival one. The team is utilizing advanced imaging techniques, genetics, and high throughput technologies to accomplish the challenging goal of making cancer cells more susceptible to treatment.

# Stanford Pituitary Center and Skull Base Tumor Program

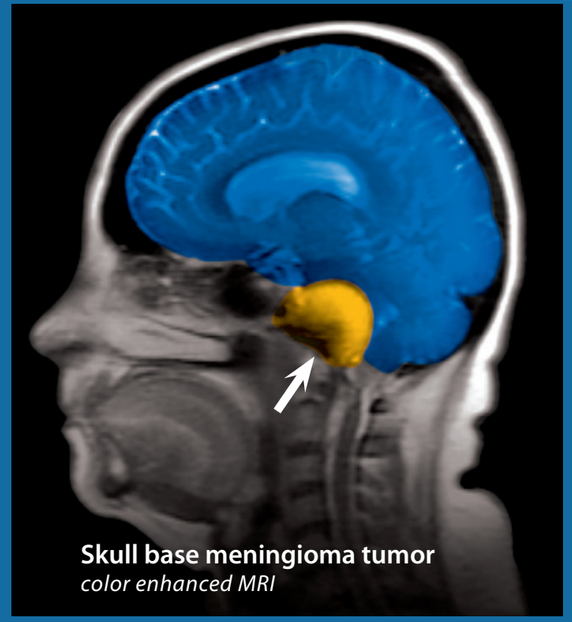
Stanford Neurosurgery Pituitary Team *(from left)* Drs. Robert Dodd, Laurence Katznelson, and Griff Harsh performing a group consultation in Stanford's Pituitary Clinic.

## Stanford Specialists Utilize a Team Approach to Diagnose and Treat Skull Base and Pituitary Tumors

The pituitary gland is a pea-sized organ situated near the center of the skull base. It is sometimes called the master hormonal gland as it orchestrates many bodily functions through the secretion of numerous hormones. Tumors arising from this gland account for about 10% of all brain tumors. Because of the central role of the pituitary in governing the body, pituitary disorders can cause a wide spectrum of symptoms, not only hormonal but also compressive, from the pressure effects of the tumor on surrounding critical neurological structures, such as the optic apparatus. An accurate diagnosis can be extremely difficult as a pituitary tumor may mimic other disorders and specialist referral is often delayed with deleterious consequences, such as blindness.



**Pituitary tumor**
*color enhanced MRI*



**Skull base meningioma tumor**
*color enhanced MRI*

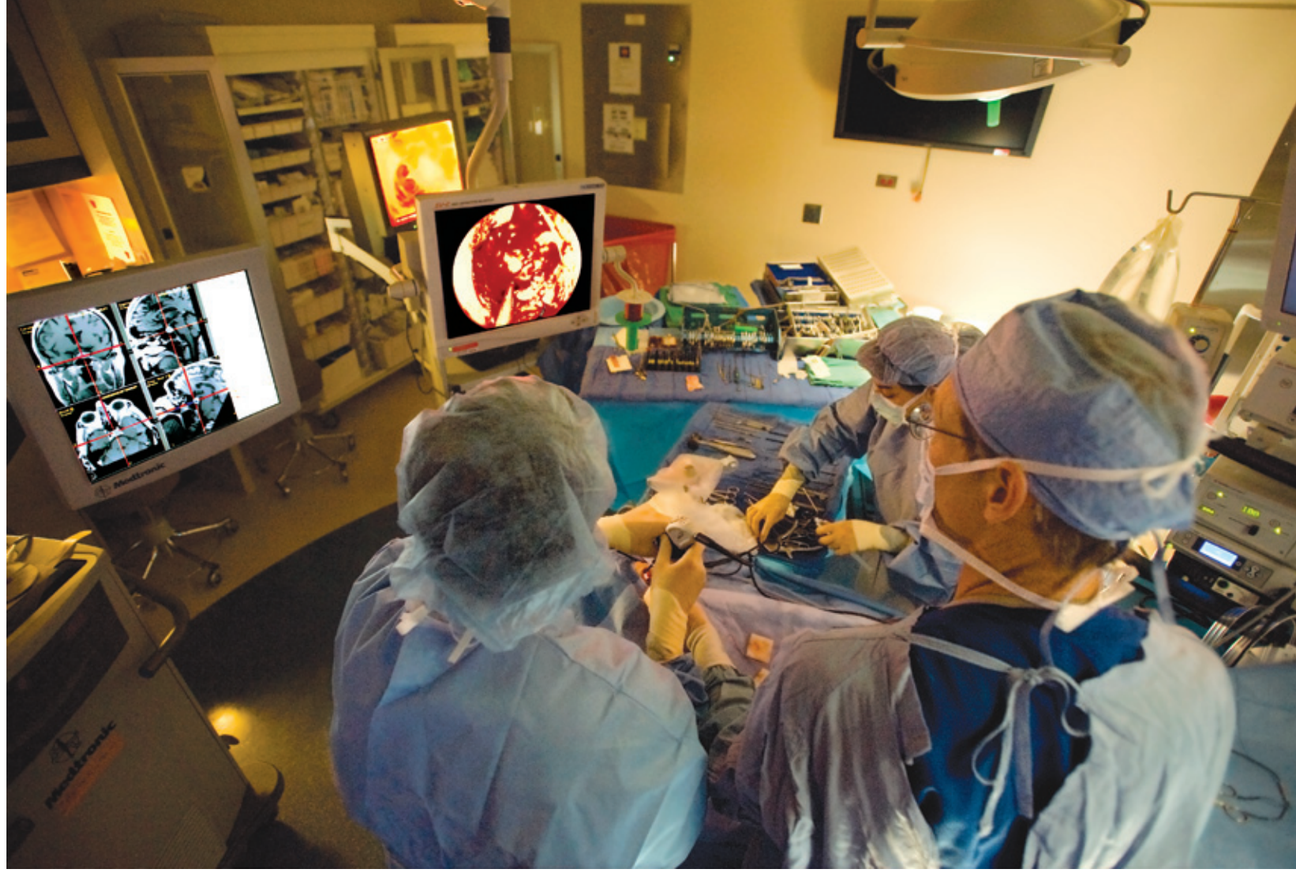
Stanford's pituitary team of neurosurgeons, neuroendocrinologists and specialist nurses is dedicated to the comprehensive evaluation, diagnosis and treatment of the full spectrum of pituitary disorders. Under the leadership of Dr. Griff Harsh, as Surgical Director, and Dr. Laurence Katznelson, as Medical Director, patients are cared for in an interdisciplinary approach with the latest treatment modalities, including neuroendoscopic surgery, stereotactic radiosurgery and medical therapies. A single center with simultaneous access to both surgical and medical specialists appropriately addresses the complexity of the problems faced by patients and their families with pituitary disorders and facilitates the development of an individualized treatment plan.

# Accessing Pituitary Tumors Through the Nose with Endoscopy and Computer Image Guidance

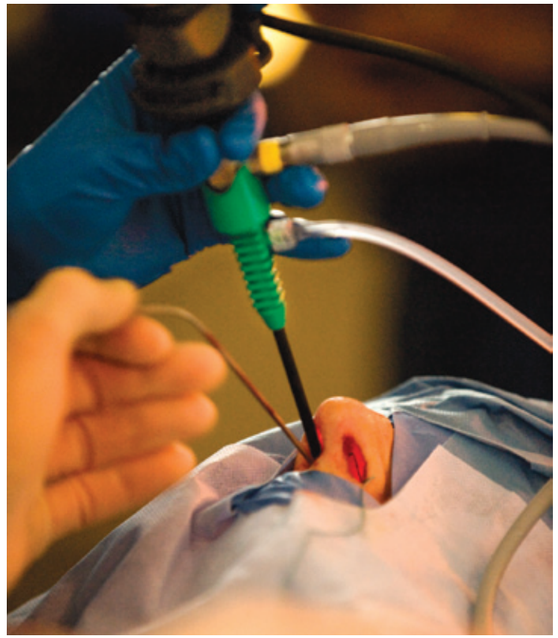

**Griffith R. Harsh IV, M.D.**
Professor, Neurosurgery
Vice Chair, Neurosurgery Education
Surgical Director, Stanford Pituitary Center
Program Director, Neurosurgery Resident Training

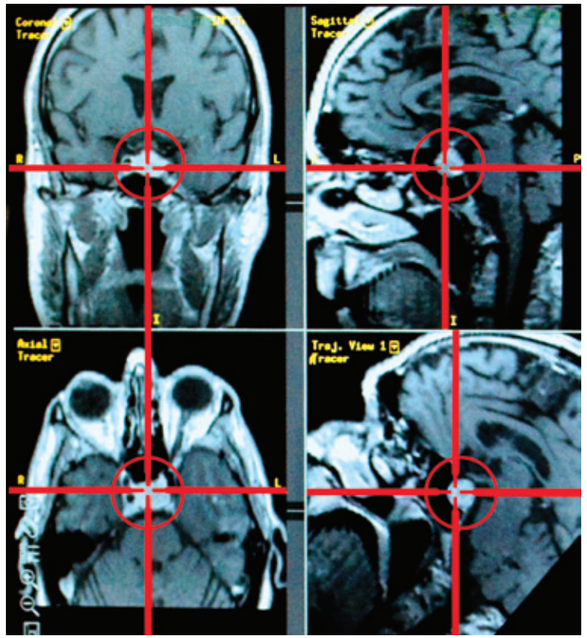

Although the pituitary gland lies near the center of the head, pituitary tumors are readily accessed through the nostrils and associated nasal air sinuses without skin incisions. A panoramic view of the region of the pituitary gland can be obtained using an endoscopic endonasal transsphenoidal approach. The superb visualization of normal and pathologic anatomy permits tumor removal with low risk to surrounding critical neural and vascular structures. The Stanford Pituitary Center has vast experience with neuroendoscopic surgical approaches to the brain and pituitary gland.

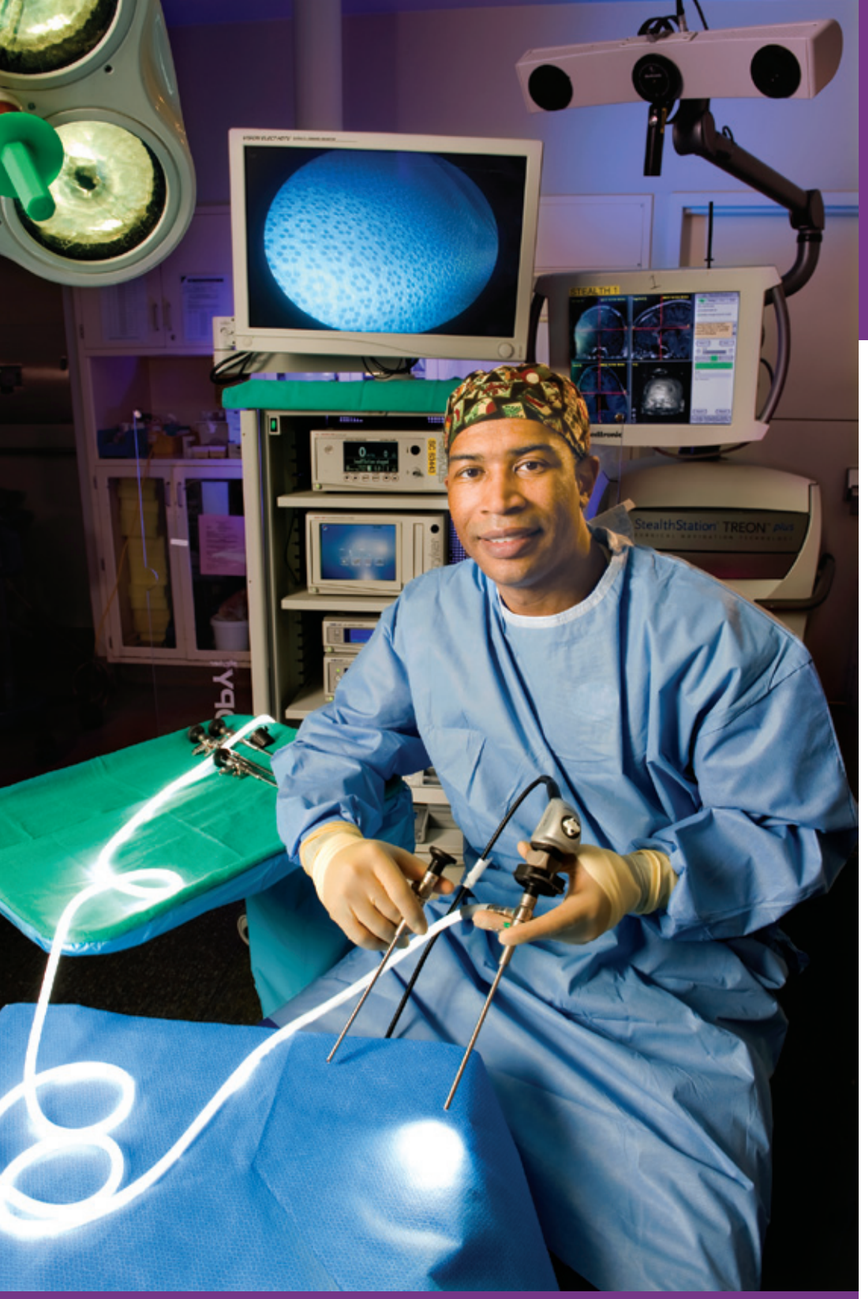
In addition to serving as Surgical Director of the Stanford Pituitary Center, Dr. Griff Harsh is also the Surgical Director of the Stanford Brain Tumor Center, overseeing one of the country's largest brain tumor programs in the treatment of both benign and malignant brain tumors. As the lead skull base neurosurgeon, he collaborates with world-renowned surgeons from the Stanford Department of Otolaryngology. This skull base surgery team has accumulated a vast experience with highly complex skull base and pituitary tumors referred to Stanford from throughout the world. Vestibular schwannomas (acoustic neuromas), craniopharyngiomas, chordomas, skull base meningiomas, and other tumors are routinely treated by a multidisciplinary team that selects the optimal comprehensive treatment plan for each patient's individual needs. Where appropriate, Dr. Harsh, who is also highly experienced at stereotactic radiosurgery, treats patients at the Stanford CyberKnife Center. Stanford neurosurgeons utilize world class facilities and equipment including intraoperative image-guidance and continuous neurological monitoring to ensure high surgical precision and optimal surgical outcome, even in the most complex cases. Surgery with the patient awake is performed when necessary to allow safe removal of tumors adjacent to or within eloquent areas of the brain. Patients are cared for in state-of-the-art intensive care and dedicated hospital units and receive counseling and support before, during, and after treatment from a team of specialist therapists dedicated to achieving the best outcome for every patient.



*(above:)* Dr. Griff Harsh performs endonasal transsphenoidal surgery on a pituitary tumor patient.
*(below left:)* Endoscopic resection of pituitary tumor through the nose. *(below right:)* Computer image guidance system.








**Robert L. Dodd, M.D., Ph.D.**
Assistant Professor, Neurosurgery and Radiology

*The improved visualization and targeting of tumors with endoscopes allows neurosurgeons to perform more precise excisions in critical brain regions*

Endoscopic neurosurgery has revolutionized the treatment of many neurological conditions, such as tumors arising from the pituitary gland and from within ventricles of the brain. The slim instrument allows minimally invasive access to the brain and enhances visibility of the tumor and surrounding structures. Angled endoscopes help the neurosurgeon to look around corners that are otherwise obscured with conventional approaches, thereby maximizing the chances of a complete excision of the tumor.

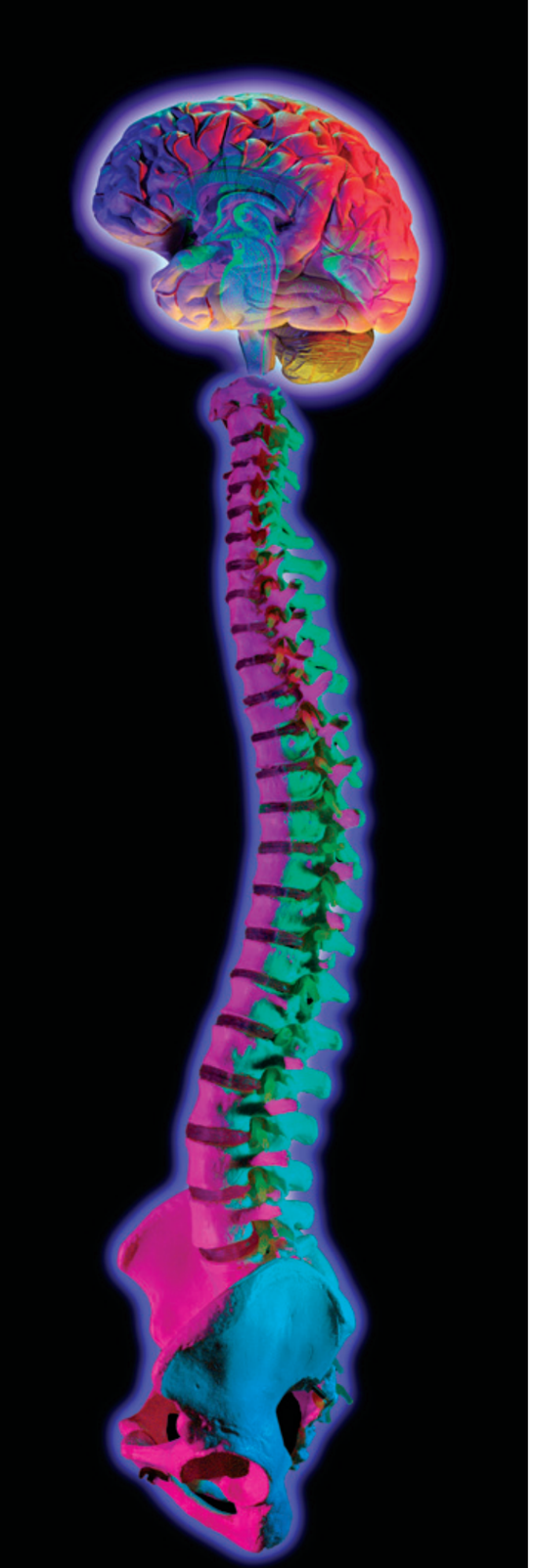
Dr. Robert Dodd has trained with the world's leading neuroendoscopists. He is an integral member of the Stanford Pituitary Center and routinely treats pituitary tumors using the endonasal transsphenoidal approach. Requiring no skin incision, patients are kept hospitalized typically for less than 48 hours without the discomfort of nasal packs. Ventricular tumors, such as colloid cysts, meningiomas, and other benign or malignant tumors, may also be approached endoscopically when appropriate, bringing the advantages of a minimal skin incision, faster recovery, shorter hospital stay, and earlier return to normal life for the patient. The endoscopic field continues to evolve, and Stanford has been at the forefront of developing new endoscopic technologies to obtain higher definition images in 3-dimensions. These advances will permit better visualization of difficult tumors and more effective treatments for complex cases in the future.




**Laurence Katznelson, M.D.**
Professor, Neurosurgery and Medicine
Medical Director, Stanford Pituitary Center
Director, Endocrinology Fellowship Training Progam

Dr. Laurence Katznelson is the Medical Director of the Stanford Pituitary Center and an international expert in the medical treatment of pituitary disorders. As many pituitary disorders are effectively treated without surgery, patients are carefully selected for a range of medical and drug therapies and monitored closely during and after their treatments. Pituitary tumors are often benign overgrowths that secrete excessive amounts of hormones. These are known as secretory tumors. They may also, however, grow to a size where surrounding neurological structures, such as the optic nerves, are compressed causing visual problems and even blindness. The Stanford Pituitary Center cares for patients with any pituitary disorder, ranging from prolactinomas and non-secretory adenomas, to other rarer benign and malignant tumors. Patients with acromegaly, growth hormone deficiency, Cushing's disease, and other hormonal diseases are evaluated jointly by the multidisciplinary team.

Through the participation of several multicenter, randomized, blinded clinical trials, Dr. Katznelson has also been actively involved in looking at ways to improve existing treatments and to assess the safety and efficacy of newer generations of drugs for the treatment of patients with pituitary diseases, such as acromegaly and Cushing's disease. He is also currently researching the effects of brain injury on pituitary function with emphasis on the impact of hypopituitarism on rehabilitation. Another novel research investigation of Dr. Katznelson's involves studying the effects of neuroendocrine factors, such as growth hormone and glucocorticoids on neurocognitive function.



# NeuroSpine

Spinal cord disorders can be caused by injury, congenital deformities, tumors, infections, disease, or the degenerative effects of aging. As a principal site of the central nervous system and the control center of the musculoskeletal system in conjuction with the brain, any pain or loss of function in this area can lead to devastating consequences in a patient's quality of life and independence. The Stanford NeuroSpine team treats the full spectrum of neurospine disorders including back and neck pain, spinal stenosis, tumors, osteoporotic fractures, spine trauma, spondyolisthesis (slipped spine), peripheral nerve injury, herniated discs, degenerative spine disease, and Chiari and vascular malformations. The team provides superior patient care by applying and developing the latest surgical techniques, such as motion-sparing technologies, endoscopic spinal surgery, minimally invasive techniques, and CyberKnife radiosurgery.


**Jon Park, M.D.**
Associate Professor, Neurosurgery
Director, Spine Neurosurgery and the NeuroSpine Center

As Director of Comprehensive Spine Neurosurgery at Stanford, Dr. Jon Park emphasizes spine treatments that are the most effective while also decreasing healing time for patients. The most valuable technique to accomplish this is minimally invasive surgery. Conventional open approaches to spinal surgery require prolonged general anesthesia, long periods of hospitalization and increased recovery time. Minimally invasive surgeries take advantage of recent advances in video endoscopy, image guidance, robotic assistance, and special surgical instruments to access and repair the spine through small portals. As a result, patients leave the hospital sooner and recover faster. Under Dr. Park's direction, Stanford Neurosurgery has pioneered the use of minimally invasive surgery and applies it to spinal tumor resection, complex spine reconstruction and peripheral nerve reconstruction.

Dr. Park's clinical expertise encompasses many aspects of spine pathology including tumors, the use of new technologies to reconstruct damaged spines, endoscopic sympathectomy (which treats a variety of symptoms in the sympathetic nervous system such as excessive sweating of the feet and hands), repair of fractures from vertebrae weakened by osteoporosis and compression fractures using kyphoplasty and vertebroplasty, surgery for spine trauma, and vertebral disc replacement.

Dr. Park's research is conducted in the NeuroSpine Center and focuses on developing spinal devices and implants for non-fusion spinal stabilization, as well as prosthetic artificial discs. His research lab is also investigating biological regeneration of the spinal nerves and discs utilizing stem cells and growth factors that will offer new hope to patients suffering from spine disorders in the future.

## Stanford's NeuroSpine Surgeons Help Patients Return to Active Lifestyles Early

With more than 20 years of experience, Dr. Lawrence Shuer's clinical expertise in spine neurosurgery centers on the repair of neurological and structural damage from degenerative diseases such as lumbar and cervical spondylosis, where the intervertebral discs degenerate or become thin and rupture. Dr. Shuer treats intraspinal tumors both inside the spinal cord and those pressing from the outside on nerves and the cord. One of his clinical specialties is the evaluation and treatment of Chiari malformations with syringomyelia (spinal cord cysts). He has collaborated with the National Aeronautics and Space Administration (NASA) on neuro-anatomical studies of the spine, as well as non-invasive monitoring of changes in intracranial pressure. In addition, Dr. Shuer has also helped develop a novel method of treating fungal meningitis, a deadly infection that causes swelling around the spine and brain.

**Lawrence M. Shuer, M.D.**
Professor, Neurosurgery
Vice-Chair, Neurosurgery Quality Assurance
Associate Dean for Graduate Medical Education

## Utilizing Less Invasive Treatment Options for Pain and Degenerative Disease

**Stefan A. Mindea, M.D.**
Assistant Professor, Neurosurgery
Director, Minimally Invasive NeuroSpine Surgery

Dr. Stefan Mindea's expertise centers on treating a wide range of primary and metastatic spinal tumors in addition to complex spinal reconstruction and vertebroplasty/kyphoplasty. Dr. Mindea's contribution to Stanford's oncology repertoire involves performing a novel surgical procedure called "en bloc spondylectomy," a procedure performed at only a select group of hospitals around the world. This procedure involves removing an entire segment of the spine infiltrated with tumor in one piece (i.e. "en bloc") rather than in a piecemeal fashion, thus increasing the likelihood of complete tumor removal and cure. In conjunction with utilizing advanced laser technology to accomplish tumor resection, Dr. Mindea strives to offer patients the safest and most technically advanced means of treating their spinal tumor or metastasis. As part of Stanford's multidisciplinary approach to treating spinal tumors, Dr. Mindea also works with the Radiation Oncology department to treat smaller tumors with CyberKnife, an outpatient procedure in which a robotic device delivers tiny precisely guided beams of stereotactic radiation to eradicate spinal tumors.

In addition, Dr. Mindea also provides patients with emerging non-fusion based solutions to varying spinal disorders by incorporating sophisticated technology for the treatment of cervical and lumbar disc herniations/bulges, spinal stenosis, scoliosis, deformity, and osteoporotic vertebral fractures. Dr. Mindea also collaborates extensively with spinal surgeons and biomedical engineers across the country and holds numerous provisional patents for new spinal devices. He is a committed surgeon educator and frequently trains other spine surgeons at national workshops on the techniques of minimally invasive spinal surgery and artificial disc surgery.

# Stanford Partnership for Spinal Cord Injury and Repair

*Advancing Spinal Cord Stimulation & Neuroprosthetics*


**Spinal cord injury affects several million people worldwide, including many young people injured in accidents, those affected by multiple sclerosis, and older people with arthritis who suffer a fall. The economic impact of traumatic spinal cord injury alone exceeds $9.7 billion annually in the United States. Our mission in the Stanford Partnership for Spinal Cord Injury and Repair is to advance knowledge of the mechanisms underlying injury and diseases of the spinal cord and to accelerate development of novel methods of repair. The Partnership is also focused on strategies to restore function after spinal cord injury and to translate new discoveries into therapies that improve the quality of life for people who suffer from spinal cord dysfunction. Basic scientists and clinicians from the Department of Neurosurgery at Stanford, the Veterans Affairs Palo Alto Health Care System and Santa Clara Valley Medical Center have partnered with colleagues across disciplines to harness the abundance of talent that exists locally and collaborate on special research projects to help patients with spinal cord injury return to as normal a life as possible.**



## Microelectronic implants help paralyzed patients regain bladder control

Dr. Graham Creasey works with patients paralyzed from spinal cord injuries, and he has learned that the desire to regain control of the ability to use the bathroom or to cough to clear one's lungs can take precedence over the desire to regain other functions such as walking. By developing new electronic devices, called "neural prostheses," that can interact with the patient's nervous system, Dr. Creasey has helped patients like Amanda Boxtel (right) to regain a simple, yet essential, body function: bladder control. Amanda is paralyzed from the waist down from a traumatic skiing accident that damaged her spinal cord. Today, her quality of life is significantly improved by this simple neural prosthetic device.

Since nerves communicate by electrical impulses, the function of some damaged nerves can be restored by connecting microelectronic devices to provide the missing signals by electrical stimulation of other nerves. Like pacemakers, these devices are usually implanted surgically under the skin. They can be connected to peripheral nerves or nerve roots to restore useful movement to paralyzed muscles after spinal cord injury. The key to advancing these techniques has been the creation of safe, stable connections between microelectronic devices and human nerve tissue. Microscopic electrodes created by the silicon chip


**Graham H. Creasey, M.D.**
Paralyzed Veterans of America Professor of Spinal Cord Injury Medicine
Professor, Neurosurgery
Director, Spinal Cord Injury Program, Veterans Affairs Palo Alto Health Care System,
Clinical Director, Stanford Partnership for Spinal Cord Injury and Repair

industry now allow these neural interfaces to be accomplished at the level of single cells. This opens up the possibility of connecting computing systems directly to the central nervous system.

Drawing on Stanford's strengths in engineering and stem cell biology, Dr. Creasey is also directing the Stanford Partnership for Spinal Cord Injury and Repair Program's clinical initiatives with colleagues in neurosurgery and other disciplines to explore stem cell transplantation and other therapies aimed at promoting neurorestoration in the damaged spinal cord, ultimately to regain control of limbs and to restore feeling.

# NeuroSpine Research

## *Stimulating Regenerative Disc Cell Growth to Repair Herniated Discs*

As a member of the NeuroSpine Center, Dr. Judith Murovic is developing a regenerative therapy for repairing herniated discs. The goal of her research is to tailor a therapy to a particular patient by growing their own disc cells in a Petri dish and testing growth factors called bone morphogenic proteins for their ability to make new disc cells grow. The most efficient factor is then injected into the cavity of the herniated disc to stimulate regenerative growth in the patient's disc cells.

Ultimately, the techniques Dr. Murovic is developing may be applied to a more ambitious goal, to grow an entire disc from a patient's disc cells as a replacement. Patient's cells that were removed during surgery can be grown in the presence of growth factors on a three dimensional matrix that will allow them to form the structure of a new intact intervertebral disc in the shape of the original damaged disc.

Dr. Murovic also studies the biomechanical properties of spine instrumentation systems and artificial discs, as well as tracking their outcomes when used in a clinical setting.

**Judith A. Murovic, M.D.**
Clinical Instructor, Neurosurgery



**Maxwell Boakye, M.D.**
Assistant Professor, Neurosurgery
Director, Neurosurgery Outcomes Research

The nervous system exhibits plasticity or potential to modify its structure and physiology as a result of injury or experience. The extent of plasticity may be related to behavioral outcomes after injury. Dr. Max Boakye is the Director of the Neural Plasticity Laboratory and the Section of Outcomes Research. The Neural Plasticity Laboratory focuses on using innovative state-of-the-art multimodal techniques such as functional magnetic resonance imaging and transcranial magnetic stimulation to understand neural plasticity and recovery after brain and spinal cord injury. There are several ongoing studies of brain and spinal cord plasticity after nervous system damage and on the role of genetic polymorphisms in mediating plasticity and recovery. Dr. Boakye is developing techniques to induce long-lasting plasticity in the spinal cord in order to resume function after injury. This work involves collaborations with Dr. Jenny Kiratli and Dr. Vandana Punj at the VA Palo Alto SCI center and Dr. Tamara Bushnik, Dr. Steve McKenna and Dr. Akshat Shah of the Santa Clara Valley SCI center. The research in Dr. Boakye's lab is currently supported by a Veterans Administration Merit Grant.

The Neurosurgery Section of Outcomes Research studies complication rates and outcomes after various neurosurgical disorders. Ongoing studies include development of predictive and risk stratification models of adverse outcome and mortality after spinal surgery in elderly patients using a variety of techniques including artificial neural networks, and classification and regression tree modeling. Other projects include evaluation of the impact of resident participation in neurosurgical disorders, and comparative and cost effectiveness of new neurosurgical technologies and procedures. Dr. Boakye was the principal investigator of a study evaluating the efficacy of CyberKnife radiosurgery for the treatment of facetogenic back pain.

Dr. Boakye specializes in general neurosurgery, spinal neurosurgery and spinal cord injury. He has extensive expertise in complex spinal surgery involving degenerative diseases of the spine, spinal tumors, spinal deformity such as scoliosis, and minimally invasive spinal surgery. His practice incorporates the latest techniques in complex spinal neurosurgery and serves primarily the veterans population at the VA Palo Alto Health Care System. He is also a consultant neurosurgeon at the Palo Alto VA Spinal Cord Injury center where he advises numerous SCI physicians.

# *Neuro*Trauma

## *Stanford's Level I Trauma Center & Life Flight Emergency Transport*


*Each Support Stanford's*

## Traumatic Brain Injury Program

### Providing State-of-the-Art Acute Interventions and Transport for NeuroTrauma Patients

An estimated 5.3 million Americans, or more than 2% of the U.S. population, are currently living with disabilities resulting from traumatic brain injuries (TBIs). Nearly 2 million new TBIs occur each year in this country. Of these, 70% require an emergency department visit, 34% result in hospitalization, and 3.8% lead to death. Traumatic brain injury is a national health problem affecting 200,000 new victims annually. In addition, another 1.7 million people will suffer *mild* TBIs, such as brain concussions. The detrimental cumulative effect on neuro-psychological function and brain pathology following repetitive concussions is now being recognized, with important implications for many sports and athletes. The annual economic cost of TBIs in the U.S. alone is approximately $80 billion.

The Stanford Traumatic Brain Injury Program delivers state-of-the art Neuro-Intensive care for acutely brain injured patients at Stanford, Santa Clara Valley Medical Center (SCVMC) and the Veterans Affairs Palo Alto Health Care System (VAPHCS), with SCVMC and VAPHCS providing nationally recognized Centers of Excellence for brain trauma rehabilitation. New methods are being developed to monitor severe brain injury using cerebral oxygenation and perfusion monitors, as well as microdialysis and chemical analysis of brain tissue, cerebrospinal fluid and blood. Brain imaging techniques such as magnetic resonance (MR) and diffusion tensor imaging (DTI) are also utilized. Current research is identifying specific blood biomarkers that predict future neurological and psychological sequelae following mild and severe brain trauma, allowing earlier targeted intervention. Another major effort is underway to improve the outcome from this devastating condition by applying therapeutic advances pioneered at Stanford such as mild brain hypothermia for patients and investigating new pharmacologic treatments as part of NIH supported clinical trials.

**Odette A. Harris, M.D., M.P.H.**
Associate Professor, Neurosurgery
Director, Traumatic Brain Injury Program
Associate Chief of Staff, Polytrauma, Veterans Affairs Palo Alto Health Care System

As Associate Chief of Staff for Polytrauma at the Veterans Affairs Palo Alto Health Care System (VAPAHCS), Dr. Odette Harris oversees the clinical, research and educational programs related to traumatic brain injuries. The injuries of men and women who have recently served in U.S. military operations differ from those sustained during previous conflicts in both their type and complications. Today's soldiers often suffer multiple wounds, with a very high incidence of traumatic brain injury. As a result, the U.S. government has designated the VAPAHCS as one of four specialized VA Polytrauma Centers in the country along with over 100 rehabilitation sites across the U.S.

Dr. Harris is also Director of Stanford's Traumatic Brain Injury Program. She implements and streamlines current treatment algorithms aimed at improving the outcomes of this growing population. The goal is specific not only to mortality, but to enhancing functional outcomes. Dr. Harris collaborates with colleagues in Surgical Trauma, Neuro-Critical Care, Nursing, Rehabilitation and related specialties.

In addition to her training as a neurosurgeon, Dr. Harris also completed a Masters of Public Health in Epidemiology from UC Berkeley. Her research has focused on improving functional outcomes following traumatic brain injury. She has received numerous awards for her neurotrauma research including the prestigious Van Wagenen Fellowship, the Synthes Award for the AANS/CNS Section on Neurotrauma and Critical Care, the Research Award from the Western Neurosurgical Society and the Adam Williams Traumatic Brain Injury Institute Grant. She has lectured throughout the country and is a co-author of the AANS/Brain Trauma Foundation "Guidelines for the Management of Severe Traumatic Brain Injury," to define current standard of care therapies. Her research includes identifying unique blood protein markers that may predict long term neurologic and psychological deficits following traumatic brain injuries. She is a co-investigator on the NIH sponsored Pro-TECT III trial, and co-investigator on the NIH sponsored Neurologic Emergencies Treatment Trials Southeastern Collaborative Network.



# Community Outreach:
## Extending Stanford's High Quality Patient Care Across the Bay Area

**Roland A. Torres, M.D.**
Associate Professor, Neurosurgery
Acting Chief, Neurosurgery, Santa Clara Valley Medical Center

Dr. Roland Torres is currently Acting Chief of Neurosurgery at Santa Clara Valley Medical Center (SCVMC) in San Jose, where he leads a neurosurgical team that delivers specialized care to Santa Clara County residents who suffer from neurosurgical disease and injury. Many of these patients are admitted with brain and spinal cord trauma, Dr. Torres' area of expertise. He received special training in head injury and completed a fellowship in complex spine surgery. Dr. Torres is a nationally recognized neurotrauma and neurocritical care expert, actively engaged with the AANS/CNS Section on Neurotrauma and Critical Care. He is often invited to moderate scientific symposia and is one of few neurosurgeons in the U.S. certified as an Advanced Trauma Life Support instructor.

Dr. Torres' clinical research aims to deliver the most advanced care for patients with severe traumatic brain and spinal cord injuries. Dr. Torres is a co-investigator in the National Institutes of Health (NIH) multi-center Neurological Emergencies Treatment Trials (NETT) Network at Stanford. He is working closely with industry and currently developing several innovative monitoring technologies, including cerebral oxygenation and cerebral blood flow monitoring for brain and spinal cord injury. He is also studying the effects of anticoagulant medications on the trauma patient. Dr. Torres collaborates with a full array of surgical subspecialty divisions at SCVMC, a major American College of Surgeons (ACS) Level I Trauma Center and shares close working relationships with community neurosurgeons and emergency room physicians. He was a 2008 Stanford Faculty Fellow.

# Stanford Neurosurgeons Engage Local Communities and the World, Spreading Hope, Education, and Research Opportunities

## Jason I. Lifshutz, M.D.
Assistant Professor, Neurosurgery

Dr. Jason Lifshutz has been serving the San Jose community since 2005 by providing essential neurosurgical care. After finishing his neurosurgical residency at Loma Linda University, including a postdoctoral research fellowship in Spinal Cord Injury at UC Irvine, he completed a 2 year clinical fellowship in Spine Surgery at the Medical College of Wisconsin. Dr. Lifshutz is an expert in minimally invasive spine surgery, as well as in complex instrumentation and stabilization of the spine in patients with degenerative disease or traumatic injury. He delivers general neurosurgical services and is a member of the Neuroscience teams at Good Samaritan Hospital, Santa Clara Valley Medical Center, El Camino Hospital in Los Gatos, and O'Connor Hospital. Dr. Lifshutz is highly regarded by his colleagues in the community.

## Edward Rustamzadeh, M.D., Ph.D.
Assistant Professor, Neurosurgery

Dr. Edward Rustamzadeh practices neurosurgery primarily in the San Jose region, including O'Connor Hospital, Good Samaritan Hospital, and El Camino Hospitals in Los Gatos and Mountain View. While at the University of Minnesota completing his neurosurgical residency training, Dr. Rustamzadeh also obtained a Ph.D. in the Department of Biophysical Sciences and Medical Physics, performing his doctoral research on immunotoxin therapy for brain tumors. He received further specialized fellowship training in epilepsy surgery and spinal reconstruction surgery. He has received grants from the National Institutes of Health (NIH), the American Heart Association and Alpha Omega Alpha, and has published both peer reviewed articles and book chapters regarding his research. Dr. Rustamzadeh works with other community neurosurgeons and primary care physicians to deliver critical neurosurgical care to the Silicon Valley region. His clinical interests include degenerative spine disease and deformity, minimally invasive spine surgery and brain tumors.



## James R. Doty, M.D.
Professor, Neurosurgery
Director, Center for Compassion and Altruism Research and Education,
Director, Neurosciences Institute at El Camino Hospital

Dr. James Doty is an expert in minimally invasive and complex spine surgery and was one of the first surgeons to embrace stereotactic radiosurgery utilizing the CyberKnife, a technology invented at Stanford that uses precisely focused beams of radiation to treat tumors, vascular malformations and chronic pain disorders of the brain and spinal cord, as well as tumors of the chest, abdomen and pelvis. He is Director of the Neurosciences Institute at El Camino Hospital, where he is primarily based, with a focus on providing neurosurgical and clinical neuroscience care to the community. Dr. Doty has extensive experience in the surgical and medical management of spine disorders, including herniated discs, degenerative disease, tumors and traumatic injuries such as fractures and dislocations. He has published his clinical research in the areas of spinal disease and stereotactic radiosurgery. He is also an entrepreneur and has developed several technologies for treating spinal disorders, as well as participating in protocols assessing new neurosurgical devices.

As a philanthropist, Dr. Doty has contributed major gifts to a number of universities and charitable organizations, including the establishment of an Endowed Professorship in the Department of Neurosurgery for a neuroscientist. More recently, he has become deeply interested in understanding the neural basis of compassion and altruism.

*(left:)* Dr. Gary Steinberg, *(center:)* His Holiness the Dalai Lama, *(right:)* Dr. James Doty.

He is the founder and Director of the Center for Compassion and Altruism Research and Education (CCARE), a key program in the Stanford Institute for Neuro-Innovation and Translational Neurosciences (SINTN), whose mission is to scientifically study the neural, mental and social basis of compassion and altruistic behavior, and explore rigorous training exercises through which individuals and societies can learn these behaviors. Towards this goal, CCARE will employ a multidisciplinary approach to create a community of scholars, including neuroscientists performing human brain imaging, cognitive psychologists, neuroeconomists, contemplative scholars, and philosophers. The Dalai Lama is intimately engaged with CCARE.

# At Santa Clara Valley Medical Center, Neurosurgery's Education and Training Outreach Benefits Local Patients and Future Clinicians

**Marco Lee, M.D., Ph.D.**
Assistant Professor, Neurosurgery
Director, Surgical Neuro-Oncology,
Santa Clara Valley Medical Center

Dr. Marco Lee is the Director of Surgical Neuro-oncology at the Santa Clara Valley Medical Center (SCVMC). He completed his neurosurgery residency in Oxford and Edinburgh. He also acquired subspecialty fellowship training in skull base/cerebrovascular surgery and radiosurgery at Stanford. Dr. Lee is a fellow of both the Royal Colleges of Surgeons of England and Ireland, and he is also a board certified neurosurgeon from the Royal College of Surgeons. He was a Medical Research Council research fellow and studied neural gene therapy for his Ph.D. thesis at Oxford. He continues his research on brain tumor stem cells, advanced neurovascular monitoring and radiosurgery of brain and spinal diseases in collaboration with leading research groups at Stanford. His clinical interests beyond general neurosurgery include operative and radiosurgical treatment of skull base tumors, pituitary disease and cerebrovascular lesions. Dr. Lee also has a passion for training residents and students and teaches regularly at Stanford, SCVMC and at international neurosurgical workshops.



# Neurosurgery Nurses

**Stanford's Team of Neurosurgery Nurses.** *(from left:)* Jodette Carrillo CNS, PNP, Bonnie Taft CPNP, Michelle Klesczewski MSN,NP, Traci Hornbeck MSN, PA-C, Teresa Bell-Stephens RN, CNRN, Olivia Chu MSN, NP, Ami Lombardi MSN, NP, Candice Osuga Lin RN, MSN, ACNP, Alison Kerr RN, MSN, Lisa Martini MSN, NP, Kathleen Biederman RN, Mary Marcellus RN. *(Nurses not present include:)* Melissa Ballard ACNP, Elizabeth Lee MSN, NP, Cortney Moore MSN, NP, Carol Barch MSN, ACNP, CNRN, Joli Vavao MSN, ACNP, CPNP, and Elizabeth Colglazier CPNP.

Stanford's neurosurgery nurses are key contributors to the outstanding clinical care and academic achievement that are the hallmarks of the Neurosurgery Department. Working in close partnership with Stanford physicians as nurse practitioners, physician assistants and nurse coordinators, neurosurgery nurses provide essential guidance, education and advocacy, to patients and their families as they navigate the diagnostic procedures, treatment modalities, and follow-up visits that are involved in the course of most Stanford patients' highly detailed and specialized care. Advanced training and certification in the neurosciences from professional organizations such as the American Association of Neuroscience Nurses is fostered and encouraged. Stanford nurses also participate in clinical research projects, publishing or co-authoring articles describing their areas of investigation in major academic medical journals. In addition, some nurses partner with Stanford's world renowned physicians by enrolling patients in NIH sponsored clinical trials, gathering and processing outcomes data, and delivering presentations to colleagues at national and international neurosurgical conferences. Neurosurgery's dedicated nurses also routinely organize and speak at local community seminars for other health professionals and the public at large, thus making a valuable contribution to Stanford's outreach and educational missions.

# Neurosurgery Education and Training


## Several Recent Graduates and Current Residents from Stanford Neurosurgery's Education and Training Program

*(from left)* Jenny Zou, M.D., Ph.D.: 2009 graduate; currently Assistant Professor of Neurosurgery at Mt. Sinai School of Medicine, New York. Justin Massengale, M.D.: 2008 graduate; 2009 Clinical Instructor; currently Assistant Professor of Neurosurgery, Boston University School of Medicine. Marco Lee, M.D., Ph.D.: 2008-9 Clinical Instructor; currently Assistant Professor of Neurosurgery, Stanford University School of Medicine. Sam Cheshier, M.D., Ph.D.: 2008 graduate; 2008-9 Van Wagenen fellow, Lund, Sweden; currently Pediatric Neurosurgery fellow, University of Toronto. Chirag Patil, M.D., M.S.E: 2010 graduate; 2010 Assistant Professor of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles. Nandan Lad, M.D., Ph.D.: current resident. Justin Santerelli, M.D.: current resident. Ashley Grosvenor, M.D.: current resident.

Since 1961, when Dr. John Hanbery, the first Head of the Stanford Neurosurgery Division, established the Neurosurgery Residency Program, education and training have been critical components of our academic excellence. The Resident Training Program is designed to produce clinically outstanding academic neurosurgeons who will become innovative leaders in this rapidly expanding field. It involves five clinical years and two years of dedicated research. We currently admit two or three new residents per year.

Residents can participate in over 3,500 neurosurgical operations annually in the Stanford program. Specific neurosurgical subspecialty rotations are performed in cerebrovascular/endovascular, brain and pituitary tumors, spine, pediatric, trauma, functional (movement disorders, epilepsy, pain), radiosurgery, and general neurosurgery at Stanford University Medical Center, Lucile Packard Children's Hospital, the Veterans Affairs Palo Alto Health Care System, and Santa Clara Valley Medical Center. Rotations on neurology, neuroradiology, neuropathology and ICU are also part of the curriculum. Strong emphasis is placed on honing diagnostic acumen, expanding the neurosurgical, neuroscience and medical knowledge base, refining communication and personal interaction skills, and developing expertise in microsurgical techniques, endoscopy, spine stabilization instrumentation, and computer guided stereotaxis. Interaction between residents and faculty is fostered in the operating arena, patient wards, clinics, teaching sessions, and seminars; and through individual mentoring.

Residents participate in clinical and research teaching conferences within each subspecialty, weekly Grand Rounds, and monthly Difficult Case Conference. In Difficult Case Conference, residents analyze clinical case scenarios in a group forum. In addition, prominent neurosurgeons from other academic centers are invited two to three times a month to teach our trainees as Visiting Professors.

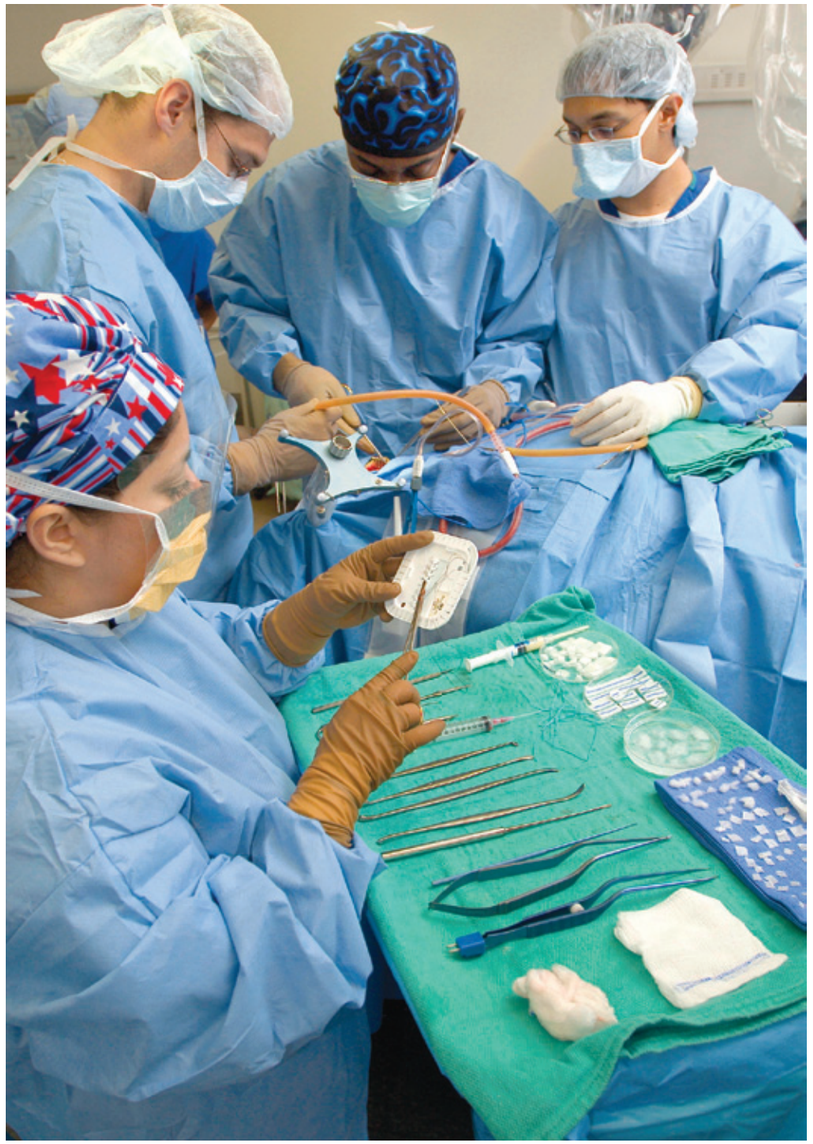
Two full time residency years are dedicated to research. This may be conducted in science departments throughout Stanford University and even at other institutions. Possible research activities include laboratory experimentation, a Bio-design fellowship, a clinical fellowship, or Masters Degree programs in Epidemiology and Public Health. At the conclusion of their training, our residents are exceptionally knowledgeable about neurosurgery and the neurosciences, experienced in patient management, proficient technically, compassionate in patient care, and able to critically evaluate neurosurgical basic research and clinical techniques. Many of our residents receive highly competitive grants to support their research,

# Neurosurgical Expertise and Academic Scholarship are Nurtured in Stanford's Educational Programs

including those from the NIH (National Research Service Award), AANS Neurosurgery Research and Education Foundation, Congress of Neurological Surgeons, Christopher Reeves Paralysis Foundation and the Giannini Family Foundation. The Department was also recently awarded an NIH R25 Resident Training Grant. Two of our recent residents received the prestigious AANS Van Wagenen Fellowship, awarded to one graduating neurosurgical resident nationally each year. Approximately two-thirds of our graduating residents are recruited to academic neurosurgical faculty positions around the country.

Medical students are encouraged to take rotations on the neurosurgical service as part of their clinical neuroscience requirement and as sub-interns. Many Stanford medical students also participate in neurosurgical research as part of their scholarly concentration, Medical Scholars Program, or a Ph.D. program. Each year, several graduating medical students choose to pursue neurosurgical residencies. Numerous Stanford undergraduate students take advantage of research opportunities in Neurosurgical laboratories for their Honor theses.

In addition, the Stanford Department of Neurosurgery offers 1-2 year postdoctoral clinical fellowships in Cerebrovascular Surgery, Spine Surgery, Stereotactic Radiosurgery, Functional Neurosurgery, Pediatric Neurosurgery, and 1-3 year postdoctoral research fellowships in our Neurosurgical laboratories. Many postdoctoral fellows have become faculty members at leading academic institutions throughout the world.



Residents and Fellows are assisting in one of 3,500 neurosurgery operations performed each year in the Stanford Neurosurgery training program.

Dr. Griff Harsh *(above center)* became Program Director of Stanford Neurosurgery Residency Training in 2004, and under his leadership the program has more than doubled in size. He encourages a thoughtful, data driven, and patient-responsive approach to the management of illness from neurosurgery residents, while also nurturing their academic facilities for research, writing and public speaking.

Dr. Gary Steinberg *(above center)* leads resident trainees though a vascular case in the Stanford Hospital OR.

# Thank You to Our Donors

## for Their Generous Support

## In Appreciation

Gary K. Steinberg, M.D., Ph.D., and the faculty of the Department of Neurosurgery gratefully acknowledge the following individuals, organizations, and foundations whose gifts have totaled $10,000 or more over the last fourteen years. This list represents many different interests including private gifts, research grants, scholarship funds, endowed professorships, and bequests. We regret that space limitations do not allow us to include the name of every donor. Each and every gift is most appreciated and has contributed to the life-saving mission of the department.

## Thank you for making our work possible

American Association of Neurological Surgeons
American Brain Tumor Association
American Heart Association
Anonymous (5)
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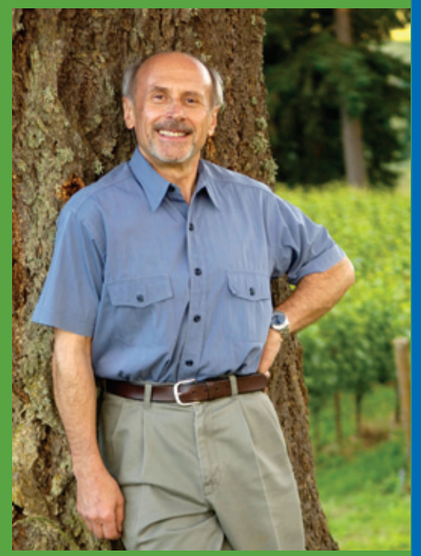
United Spinal Association
The Estate of William E. Walsh
Paula Zappettini

# *Insights From Some of Our Contributors*

## Ronni Lacroute and Bernard Lacroute

WHEN RONNI LACROUTE suffered a devastating hemorrhage from a cerebral vascular malformation she was referred to the Department of Neurosurgery at Stanford. Recognizing the severity of her condition, Dr. Gary Steinberg scheduled immediate surgery. "He saved my life," Ronni recalls. "He was the most gentle, kind doctor I had ever met. When I came out of surgery, he was holding my hand." This experience motivated the Lacroutes to support the department in perpetuity through an endowed professorship. In addition, they continue to support research in neuroregeneration, research critical to our understanding of how to repair the nervous system and restore neurologic function. "I am very enthusiastic about this work and feel it must be funded," says Bernard. "This research is invaluable."



## Dorothy and Thye King Chan

AN ENDOWED CHAIR IS the highest academic award that the university can bestow upon a faculty member, becoming an enduring tribute to the donor's belief in academic excellence and social responsibility. After a life-changing family experience at Stanford University Medical Center, the Chans established the Dorothy and Thye King Chan Professorship in Neurosurgery as a reflection of their gratitude to Stanford for the treatment and research conducted here. Dr. John Adler is the inaugural holder of the professorship. "Not only did Dr. Adler perform life-saving surgery, but he supported us during many challenging days as we kept a vigil at the bedside," said Dorothy.

"Having come all the way from Singapore, this was especially meaningful to us."

*Photos: Bay* Area Event Photography

# *Together, we improve patients' lives ...*

## Stephen Hearst, William Randolph Hearst Foundation

SUPPORT FROM THE WILLIAM RANDOLPH HEARST Foundation has been instrumental in the evolution of the Department of Neurosurgery into a world-class academic medicine enterprise, renowned for its clinical, educational, and research contributions. "The Hearst Foundations understand the opportunity and responsibility to make a critical difference in many areas – including human health," said Stephen Hearst. "I was introduced to Gary Steinberg in the 1990s and was incredibly impressed with what he saw as possible in the future. Much of what Gary envisioned back then has become the way things are done today. The gift to establish an endowed professorship was of special importance to my sister who was very grateful for the care she received at Stanford. Gifts to support medical research are an example of the Foundations' commitment to accelerate innovative solutions to complex problems."

# *... and advance the science of neurosurgery*

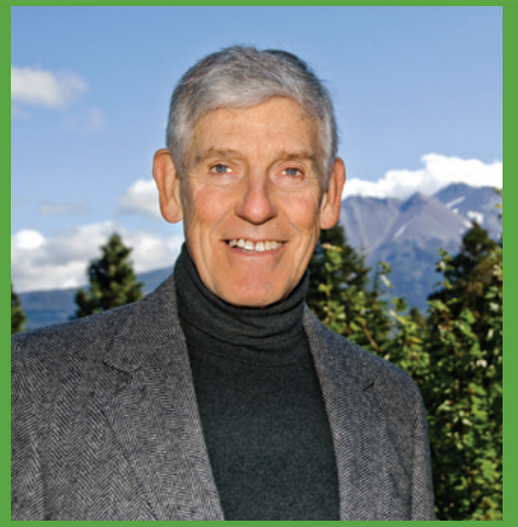


*photo:* Linda Sue Runnels

## John B. Runnels, M.D.

JOHN "JACK" RUNNELS, M.D., spent 8 years at Stanford training to be a neurosurgeon where he was profoundly influenced by mentors John Hanbery and James Golden. "I left Stanford as the best neurosurgeon I could be," said Dr. Runnels. "I also left with a life-long love of teaching which is why I have chosen to support the training and education of neurosurgeons at Stanford." Now retired, his career included clinical and teaching responsibilities at a number of respected institutions. "It costs more than a million dollars to train a neurosurgeon. I can think of no better legacy to my profession than to help prepare future generations to better serve patients and their communities."

# How You Can Help Us Grow

## Join Our Team and Make a Difference

PHILANTHROPY which supports the most creative ideas of our clinicians, researchers, and students offers a deeply rewarding experience for donors and recipients. Expendable gifts address a specific need, providing critical resources for continuing the department's legacy of innovation and excellence in teaching, research, and patient care. Endowed funds provide a legacy, forever connecting the name of the donor—or someone the donor wishes to honor—with Stanford and the cause they care about. For more information about how you can support the work of the Department of Neurosurgery, please contact:


Lorraine S. Alexander
Senior Director of Development
650.234.0613
email:
lalexander@stanford.edu


## In Memoriam

The Department of Neurosurgery acknowledges the many friends and alumni who have contributed to the John and Shirley Hanbery Scholars Fund and the John W. Hanbery Memorial Fund. Both honor the memory of John W. Hanbery, M.D., who served as Chief of the Division of Neurosurgery from 1964 to 1989 and laid the groundwork for department status. His legacy lives on in the department's programs and the many neurosurgeons he trained, who now train others. His mentees include currently serving Stanford professors, John R. Adler, M.D.; Lawrence M. Shuer, M.D.; and Gary K. Steinberg, M.D., Ph.D.

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# Recent Neurosurgery Publications

## Brain Tumors, Pituitary Tumors & CyberKnife Radiosurgery

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# Recent Neurosurgery Publications

## Spine & Peripheral Nerve

**Endoscopic Microdiscectomy,**
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GK Klute, C Kantor, C Darrouzet, H Wild, S Wilkinson, S Iveljic, GH Creasey. *Journal of Rehabilitation Research and Development 46(3): 293-304, 2009.*

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SP Lad, CG Patil, EM Lad, MG Hayden, M Boakye. *Surgical Neurology 71:580-4, 2009.*

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**NANS training requirements for spinal cord stimulation devices: Selection, implantation, and follow-up.**
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**National trends in spinal arteriovenous malformations.**
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**Lower thoracic spinal cord stimulation to restore cough in patients with spinal cord injury: results of a National Institutes of Health-Sponsored clinical trial. Part II: clinical outcomes.**
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PS Kalanithi, CG Patil, M Boakye. *Spine* 34:1963-9, 2009.

**Fracture-related thoracic kyphotic deformity correction by single-stage posterolateral vertebrectomy with circumferential reconstruction and stabilization: outcome in 30 cases.**
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# Recent Neurosurgery Publications

## Functional Neurosurgery (Movement Disorders, Pain, Epilepsy & Depression)

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in J Verhaagen and J McDonald (eds): *Handbook of Clinical Neurology, Volume on Spinal Cord Trauma.* GH Creasey, London: Martin Dunitz, Taylor & Francis Group, 2010 (in press).

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**Neuromuscular electrical stimulation in spinal cord injury,**
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**NANS training requirements for spinal cord stimulation devices: Selection, implantation, and follow-up.**
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V Gradinaru, M Mogri, KR Thompson, JM Henderson, K Deisseroth. *Science 324:354-9, 2009.*

**Lower thoracic spinal cord stimulation to restore cough in patients with spinal cord injury: results of a National Institutes of Health-Sponsored clinical trial. Part II: clinical outcomes.**
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H Yu, JS Neimat. *Neurotherapeautics 5:26-36, 2008.*

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# Recent Neurosurgery Publications

## Traumatic Brain Injury

**Discrete cerebral hypothermia in the management of traumatic brain injury: A randomized control trial.**
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## Additional Research Topics

**The stressed CNS: When glucocorticoids aggravate inflammation.**
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K Chao, L Katznelson. *Journal of Neurosurgery 109:889-92, 2008.*

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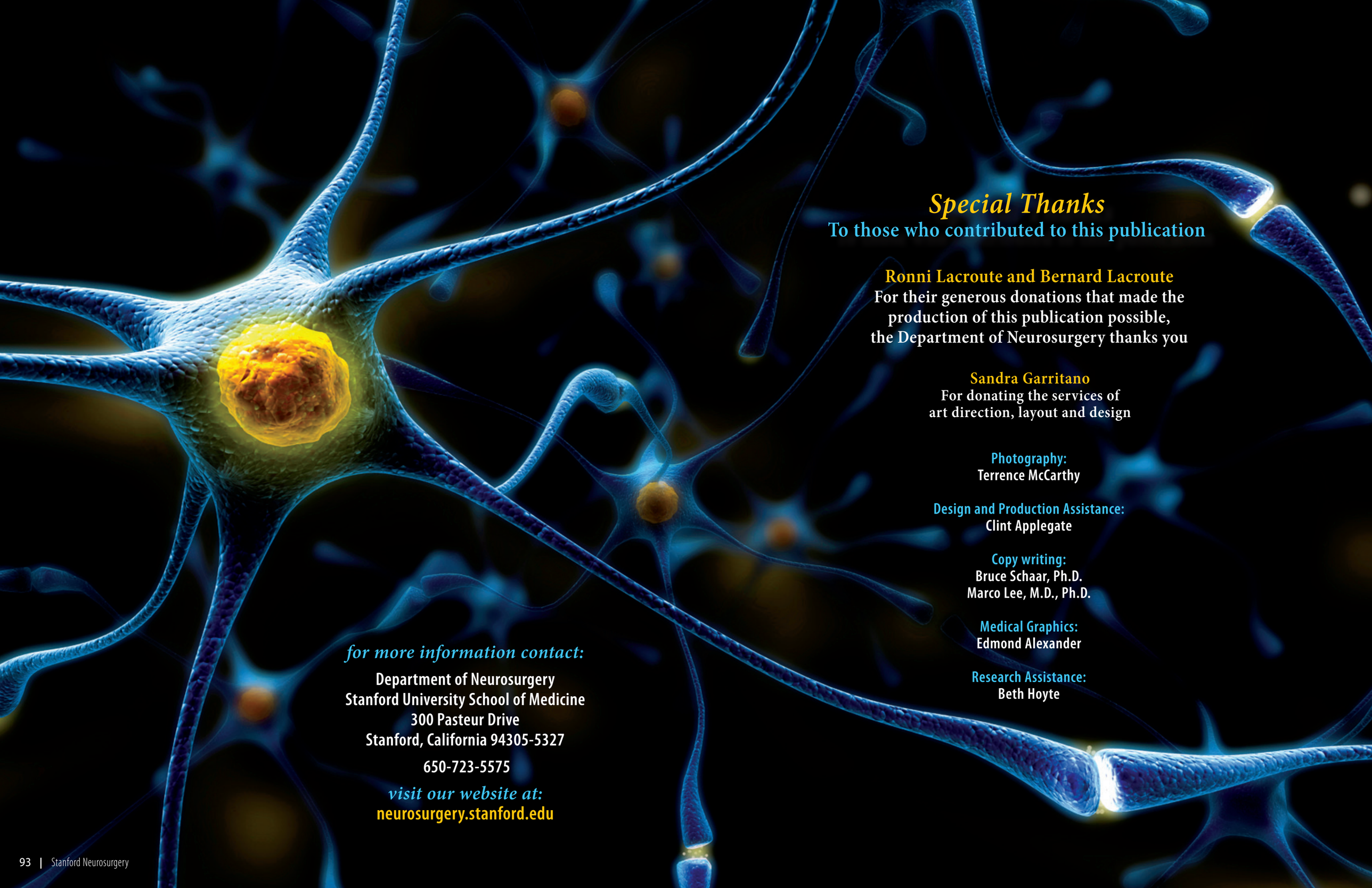

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