Neurotrauma Research at the University of California, San Francisco Gets Back to BASICs

Brain and spinal cord injury affect close to two million people in the United States each year, causing permanent functional disabilities including paraplegia and quadriplegia. To better understand the mechanisms underlying neurological injury, neurotrauma surgeons and researchers at the University of California, San Francisco have formed the Brain and Spinal Injury Center (BASIC) — a joint collaboration between the departments of Neurological Surgery and Neurology. Both departments bring their particular areas of expertise to a multidisciplinary effort centered on translational research.

“There seem to be more scientists than clinicians studying trauma, so the connection is often lacking,” says Linda Noble-Haeusslein PhD, Co-Director of BASIC. “The feeling from scientists in the field is that it is difficult to bridge the gap between the lab and what is needed in the clinical setting.” The members of BASIC are in a unique position to bridge that gap. Their location at San Francisco General Hospital, a major Level I trauma center in northern California, enables them to see and treat a broad range of injuries. The presence of a strong clinical branch, which is often lacking at other trauma research institutions, allows bench scientists to work directly on the problems encountered daily by clinicians. Investigators are achieving this by incorporating what they know about human central nervous system injury into complex, clinically relevant animal models.

Geoffrey Manley MD, PhD, Co-Director of BASIC, uses a swine model to measure uptake and use of oxygen by brain tissue in order to better understand the metabolic consequences of hemorrhagic shock and the effects of resuscitation and alterations in ventilation. A large animal such as the swine is needed to realistically translate advances made in the laboratory into therapies for patients, and many medical devices first tested in swine are now used to treat humans in the ICU. “The clinical reality often refines the basic science question,” says Manley. “It is a continuum, and the transition is the most exciting part.”

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Hirose Y, Katayama M, Mirzoeva OK, Berger MS, Pieper RO. Akt down-regulation as a potential target for improving outcomes for patients with traumatic brain or spine injury.
Neurotrauma Research Gets Back to BASICS

While the swine model is useful for physiological and imaging studies of brain injury, the rodent model can be used to study the basic mechanisms of both brain and spinal cord injury. One particular advantage of the rodent model is that it can mimic both healthy and secondary damage. Primary damage refers to the initial mechanical damage that occurs with injury. Secondary damage (also known as auto-destruction) affects the penumbral zone — the boundary between irreversibly damaged and normal tissue — causing healthy tissue to die or lose function following primary injury. BASIC researchers have shown that secondary damage can result from an early inflammatory response. The open communication between the parenchymal and humeral compartments that occurs when the blood-spinal cord barrier is disrupted is important for central nervous system (CNS) injury research provides the gateway for overexuberant leukocytes to enter the CNS and break down tissue that would otherwise have remained unchanged. This process of the body unwittingly harming itself is known as inflammatory-mediated secondary tissue damage.

Adding to the complexity of the model, a cell can change its behavior depending on its location in the tissue and the time that has elapsed following initial injury. Noble-Haeusslein and her colleagues have recently used rodent models to study the role of matrix metalloproteases (MMP) in both the acutely and chronically injured spinal cord. They have shown that MMPs, a family of zinc- and calcium-requiring endopeptidases, play a different role in the acutely injured spinal cord than in wound healing. When the activity of MMP-9 was reduced in the acutely injured spinal cord, it resulted in stabilization of the blood-spinal cord barrier; however, the beneficial effects were lost if the MMP blockade was extended beyond the first 3 days after injury, implying that the function of MMP-9 has changed. Noble-Haeusslein’s goal is to develop therapeutic interventions that target these molecules’ temporal windows of expression. Further investigation into how MMPs interact with the injured spinal cord will allow researchers to use their contributions to leukocyte trafficking, angiogenesis, and remodeling of the extracellular matrix.

The members of BASIC recognize the importance not only of performing this much-needed research, but also of disseminating the results to the larger neurotrauma community. With this in mind, BASIC initiated the Northern California Neurotrauma Symposium in 2002 together with the University of California, Davis. The symposium has gained in popularity over the past few years and has become an annual event: “Often research is become so fragmented that we miss the overall picture,” says Noble-Haeusslein. “The symposium creates the opportunity to bring the focus back to improving the clinical condition.”

Marcus Ware MD, PhD was born and raised in Indiana, Mississippi. He attended public schools and balanced his education with interests in football, tennis, and working in his family’s dental laboratory. He attended college at Tougaloo College in Jackson, Mississippi where he majored in Chemistry. While in college, Ware became interested in molecular biology, and spent the nights and weekends of his sophomore year working in a laboratory at the University of Mississippi Medical Center, studying histone variants. He spent the following summers working in laboratories at the Massachusetts Institute of Technology (MIT) and the Upjohn Company.

Ware attended Harvard Medical School, where he was a student in the Harvard-MIT Health Sciences and Technology Program (HST) and the MD/PhD Program. While at Harvard, he worked in the laboratory of Christopher Walsh MD, PhD, studying molecular events in the development of the cerebral cortex. As part of his PhD thesis he identified mdab1, a gene required for proper cortical lamination. In addition, he also received the Harold Lombroso Biomedical Research Prize for his research into the dispersion of early cortical progenitors in the ferret cortex.

Ware was graduated from Harvard in 2000 and came to the University of California, San Francisco to become a resident in the Department of Neurological Surgery. His interest turned from the development of the cerebral cortex to the genetics and treatment of brain tumors. In 2003, he received the Mahaley Award for Excellence in Clinical Research from the American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Section on Tumors for his work with Michael McDermott MD on surgical resection and brachytherapy for recurrent atypical and malignant meningiomas. Last year, Ware obtained a National Research Service Award from the National Institutes of Health under the mentorship of Burt Feuerstein MD, PhD. With this grant, he studied copy-number alterations in gliomas using comparative genomic hybridization. Ware plans to pursue a career in academic neurosurgery with an emphasis on the treatment of brain tumors.


Burt Feuerstein MD, PhD. The role of 


The neurosurgical residency training program at the University of California, San Francisco (UCSF) is one of the largest and most prestigious in the country. One particular strength of the program is that residents are exposed to various subspecialties within neurosurgery, including pediatric neurosurgery. The UCSF pediatric neurosurgery service has been recognized for excellence in the treatment of brain tumors, spina bifida, and cerebrovascular diseases.

In July 2005, a pediatric neurosurgery rotation at Children’s Hospital and Research Center at Oakland (CHO) was added to the residency program. CHO is an independent, 205-bed children’s hospital that provides a unique training environment for pediatrics residents and subspecialists. It is Northern California’s only pediatric trauma center and possesses the region’s largest pediatric intensive care unit. The Division of Neurosurgery at CHO provides a full range of inpatient and outpatient services for infants, children, and adolescents with neurological disorders and has a close working relationship with the Department of Neurological Surgery at UCSF. The director of the new rotation is Peter Sun MD, who is Chief of the clinical neurosurgery service at CHO and a member of the clinical faculty at UCSF.

The addition of a rotation at CHO will expand the opportunities available for residents in the program. It will allow residents to gain from the unique strengths and advantages of the clinical service at CHO, including an active pediatric trauma service, a large craniosynostosis and craniofacial surgery program, and an expanding program in the management of spasticity and other functional disorders. Future plans for collaboration include the development of joint research programs that will build on the strengths of each institution.

In this issue, we feature part two of the Nursing Spotlight. Like the faculty, the nurses of the Department of Neurological Surgery have unique subspecialties, interests, and backgrounds. They have all developed specialized practices within the field of neurosurgery nursing, enabling them to provide expert care for patients who come to the University of California, San Francisco (UCSF).

Caroline Pearson RN, MS, CPNP received her BSN in 1991 from the University of Pennsylvania. After working for a year at Children’s Hospital Los Angeles, she moved to San Francisco and was hired as a staff nurse at UCSF. She worked in the pediatric medical and surgical units for five years before receiving her master’s degree at UCSF in 1999. Her specialty in pediatric neurosurgery staff as a Pediatric Nurse Practitioner in 2000, and currently works in both the outpatient and inpatient settings. She enjoys working in a complex, acute-care environment, and is especially interested in pain management and oncology. She is proud of the collaborative approach that the Department brings to the care of pediatric patients, and is directly involved with the Department’s multidisciplinary spina bifida and spasticity programs. Other areas of interest include pediatric pain management, complementary medicine, and the multicultural aspects of healthcare.

Maiann Ward RN, MS, NP received her BSN from the University of San Francisco in 1984, graduating with honors. In 1989 she became the Seizure Nurse Coordinator for the Neurosurgical Service, and has been a member of the clinically active Teaching and Research Center of UCSF since 1999. Since then she has held a dual role as Adult Nurse Practitioner and Clinical Nurse Specialist in the functional neurosurgery service. Ward’s primary areas of clinical and research interest are in neurological trauma and epilepsy.

Chris Ames MD
Ken Monson PhD
Donna Ferriero MD
S. Scott Panter PhD
John Fike PhD
Lawrence Pitts MD
Grant Gaugler MD
Marco Sorani PhD
Jialing Liu PhD
Philip Weinstein MD

Inna Belyaev RN was born in Russia and received her nursing degree in Odessa in 1972, with honors. After graduation, she worked as a nurse in the Odessa city hospital, first in orthopedics and neurological surgery, and then as the head nurse of the visiting nurse department before emigrating to the United States with her family. In 1979 Belyaev quickly learned English, passed her LVN exam in 1981, and passed her RN exam in 1983. She currently works as a clinical nurse in the UCSF Spine Center, assisting patients after they undergo complex spinal procedures such as artificial disk placement and fusion. She is looking forward to joining the Division of Neurosurgery at Children’s Hospital, where she can apply her extensive experience in neurological surgery.

Michele Meeker RN began her career in Philadelphia, working primarily with pediatric patients at the Children’s Hospital of Philadelphia pediatric trauma care unit. She received her BSN from San Francisco State University in 1990, after which she worked for eight years in the adult trauma intensive care unit at San Francisco General Hospital (SFGH). During that time she developed an interest in the treatment of traumatic brain injury, and in 1999 began working for the UCSF Department of Neurological Surgery at SFGH. Since then, she has worked closely with Geoffrey Manley MD, PhD and his colleagues at SFGH on clinical trials focused on improving treatment for patients who have suffered a traumatic brain injury. Meeker has also been involved with the design and coordination of a large prospective longitudinal clinical trial for patients with mild to moderate traumatic brain injury, funded by the Brain Trauma Foundation. Her career achievements include launching the first waiver-of-consent treatment study in San Francisco since the new federal and state regulations mandating community consent were implemented. She is very proud to work with the dedicated group of doctors, nurses, and researchers at SFGH.

Left: Peter Sun MD, Chief of the clinical neurosurgery service at Children’s Hospital and Research Center at Oakland (CHO); Right: Nader Sanai MD, the first resident from the Department of Neurological Surgery to participate in the new pediatric neurosurgery rotation at CHO.

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Christopher Ames MD, Assistant Professor of Neurological Surgery, has been appointed Co-Director of the Neurospinal Disorders Program in the Department of Neurological Surgery and Co-Director of the UCSF Spine Center. Ames has also performed the first L3-5 percutaneous fusion in California, using the AxiaLTF™ system. The system uses an advanced minimally-invasive technique to access the L3-5 vertebral bodies of the spine and enable lumbar fusion. For more information on the procedure visit www.Trans1inc.com.

Mitchell Berger MD, Kathleen M. Plant Distinguished Professor and Chairman of the Department of Neurological Surgery, has been invited to be the Scientific Program Chair of the 2006 American Association of Neurological Surgeons meeting.

Susan Chang MD, Professor and Co-Director of the Neurological Surgery Program in San Francisco, has ranked first in extramural funding awarded by the NIH to neurological surgery departments throughout the United States.

For the third straight year, the Department of Neurological Surgery at University of California, San Francisco has received first place in a Prospective Multicenter Study. This clinical research has also earned the Ronald Tasker Young Investigator Award for his clinical research on multiple sclerosis treatment for recurrent or refractory trigeminal neuralgia. This is a national award presented by the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Section on Pain. He will present his work at the annual meeting of the CNS in Boston in October of 2005.

Justin Smith MD, PhD, resident in the Department of Neurological Surgery, has been awarded the Ronald Tasker Young Investigator Award for his research on basic, translational, and clinical research. His research interests range from understanding the molecular causes of brain and spinal cord injury to improving clinical care for neurotrauma patients. He has recently defined a new molecular mechanism underlying cerebral edema that may lead to new treatments for this devastating consequence of brain injury. He is also considered an expert in the rapidly growing field of advanced neuro-monitoring. His work has been presented at numerous national and international meetings. He has been awarded the General Motors Trauma Research Award and the Synthes Head Injury Research Award. He is a member of the Executive Committee of the Joint Section on Trauma and Critical Care of the American Association of Neurological Surgeons and Congress of Neurological Surgeons, and serves as Co-Director of their Neurotrauma practical course. He is also a consultant for the Prehospital Guidelines Committee for the World Health Organization.

All of Manley's research has direct clinical relevance. Cerebral ischemia resulting in secondary brain damage is one of the major factors influencing outcome after severe brain injury. The ability to detect ischemia and intervene to protect the brain against its effects may result in reduced morbidity and mortality after trauma. The goal of Manley’s research in this clinical area is to determine if direct monitoring of brain tissue oxygenation and ischemic metabolites can better detect episodes of cerebral ischemia in patients with brain injury than current clinical monitoring techniques. Manley is also investigating brain oxygenation during hemorrhagic shock, metabolic monitoring of severely injured patients during resuscitation and critical care, and the role of aquaporin water channels in cerebral water transport.

Linda Noble-Haeusslein PhD is a Professor of Neurological Surgery at UCSF and Co-Director of BASIC. Her studies of neurotrauma have been funded by the National Institutes of Health for over 20 years. Noble-Haeusslein’s interest in trauma began when she was a physical therapist working closely with patients with spinal cord injuries. This clinical exposure served as the impetus to attend graduate school, where her studies addressed the complex interactions between damaged blood vessels and injured cells in the traumatized spinal cord. Her current research continues to reflect these interests, focusing on the dynamic interactions between inflammation, demyelination, and wound healing in the injured spinal cord, through ongoing collaborations with Zena Werb PhD and Steven Rosen PhD (Department of Anatomy). Alpa Trivedi PhD (Department of Neurological Surgery), Kimberly Topp PhD, PT (Department of Physical Therapy and Rehabilitation Science), and William Wherestone MD (Division of Emergency Medicine).

A second line of Noble-Haeusslein’s research addresses the unique vulnerability of the developing brain to traumatic injury — the leading cause of death and disability in children in the United States. Despite clear biological differences between the immature brain and the adult brain, therapies specifically tailored to children do not yet exist. Noble-Haeusslein’s laboratory has developed and characterized a murine model that mimics features seen in pediatric traumatic brain injury. From this experimental model, Noble-Haeusslein and colleagues have begun to learn how the developing brain responds to injury. Her collaborative studies with Donna Ferriero MD and John Fike PhD at UCSF and Jacob Raber PhD at Oregon Health and Science University suggest that the antioxidant status of the brain is a likely determinant of recovery after injury, and in fact may influence neurogenesis and the onset of cognitive deficits. Through the unique expertise of each of her collaborators and members of her laboratory (Catherine Price-Claus, Christine Cun, Clifft Hsu, Seong Koh, Justin Lee, Yong Lin, Nino Maida, Hovhannes Manvelyan, Andrea Olivas, Mathew Potts, Rama Pullela, Breset Walker, and Tomoko Sanyamaya), advances are being made to better understand how the brain and spinal cord respond to injury, the underlying mechanisms of repair, and the determinants of functional recovery. These studies serve as the foundation for developing therapies that are specifically tailored for patients with brain and spinal-cord injuries.