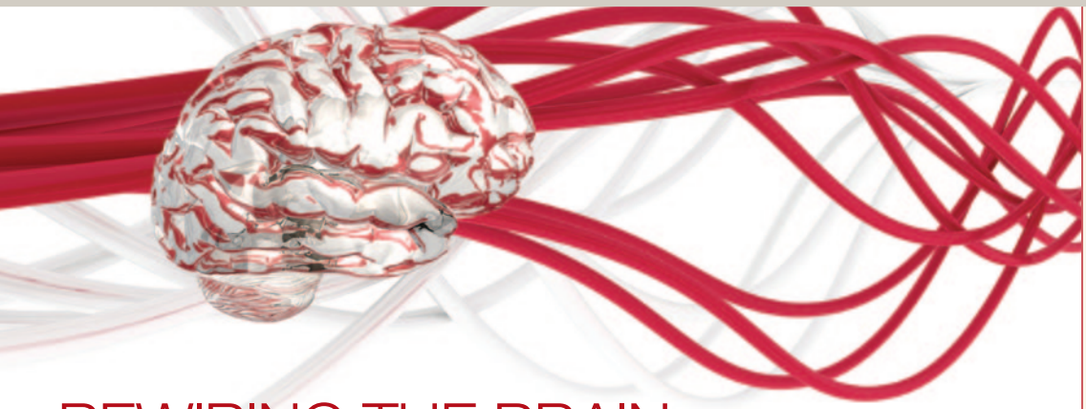
SUMMER 2012: ISSUE 2

NEURO-INNOVATION

News from the Stanford Neurology & Neurosurgery Departments

STANFORD HOSPITAL & CLINICS



INSIDE THIS ISSUE

REWIRING THE BRAIN: THREE DISCOVERIES TO WATCH

"Rewiring the Brain," a March symposium sponsored by Stanford Hospitals and Clinics and the School of Medicine, provided attendees with an opportunity to learn about emerging research in neuromodulation. This year we featured scientists who have taken a systems approach to cracking the neural code. Drawing from Stanford's expertise in clinical medicine, brain research and engineering, this conference provided attendees with a unique opportunity to exchange ideas and techniques with other experts in this increasingly interdisciplinary field. These researchers are using exciting new technologies to reverse-engineer brain circuitry, breaking down complex systems into simpler chemical and electrical processes, in order to gain a deeper understanding of the basic biologic underpinnings of human behavior.

For those of you who couldn't attend, here are three emerging technologies that inspired our thinking about research questions, collaborations and future clinical applications.

Frank M. Longo, MD, PhD
Chairman, Department of Neurology and Neurosciences

Gary K. Steinberg, MD, PhD
Chairman, Department of Neurosurgery

1 OPTOGENETICS TO OBSERVE BRAIN CIRCUITRY IN ACTION

Optogenetics allows researchers to genetically tag specific cells of living tissue, then turn biological process on and off with light pulses. Armed with this methodology, scientists can systematically identify distinct brain circuits that play important roles in sleep disorders, schizophrenia, Parkinson's disease and more. **Karl Deisseroth, MD, PhD**, associate professor of bioengineering and of psychiatry and behavioral sciences at Stanford, whose lab pioneered this technique, discussed recent animal studies where he is mapping the brain circuitry responsible for narcolepsy, depression, and addiction.

2 BRAIN PACEMAKERS TO MODULATE MOVEMENT DISORDERS

Helen Bronte-Stewart, MD, MSE, professor of neurology and neurological sciences and the director of the Stanford Movement Disorders Clinic, spoke about her research to identify abnormal patterns of basal ganglia electrical activity in movement disorders such as Parkinson's disease, tremor and dystonia. She is exploring ways to apply electrical stimulation through "brain pacemakers" to eliminate these debilitating arrhythmias. She also discussed new technology, which is being developed by companies like Medtronic and NeuroPace, where surgically implanted deep brain stimulation systems will be capable of monitoring and influencing brain activity.

3 TURNING THOUGHTS INTO ACTIONS WITH NEUROPROSTHETICS

Jaimie Henderson, MD, associate professor of neurosurgery at Stanford, gave an update on BrainGate2, a project that aims to develop technologies to restore the communication, mobility, and independence of people with neurologic disease, injury, or limb loss. Led by a multidisciplinary team at Brown University, Massachusetts General Hospital, Stanford University, and Providence VA Medical Center, the long-term goal is to create a system that literally turns thought into action with wireless brain sensors that allows impaired individuals to control external devices such as computers, wheelchairs and artificial limbs.

Even though many of these discoveries are years away from mainstream clinical application, we believe that keeping our clinicians and faculty abreast of these discoveries informs their practices and results in more innovative, progressive thinking about therapeutic approaches. ■

CHARTING THE COURSE TO A VACCINE FOR AGGRESSIVE BRAIN CANCERS

Glioblastoma, the most common and aggressive known brain cancer in adults, presents particular challenges: tumor excision can collaterally damage otherwise healthy brain structures while even infinitesimal remaining tumor cells can promote rapid tumor regrowth. Aggressive management that combines surgery, radiation and chemotherapy can bring serious side effects and is ineffective in the long term. As survival rates hover at 14 months after diagnosis, glioblastoma patients are in dire need of a safe and effective treatment to extend life expectancy.

Albert Wong, MD

The seminal discovery of the constitutively-active tumorigenic epidermal growth factor receptor EGFRvIII by Albert Wong, MD, professor of neurosurgery, springboarded his career-long effort to develop a vaccine for glioblastoma. This trailblazing work has lead to the following four national and international pre-clinical and clinical trials and offers hope to patients with glioblastoma.

The EGFRvIII vaccine Rindopepimut (CDX-10) advances to a Phase III trial

Last November Lawrence Recht, MD, and his Stanford team extended their collaboration with Celldex Therapeutics to a Phase III (ACT IV) clinical trial on the safety and efficacy of the EGFRvIII cancer vaccine Rindopepimut (CDX-10) in newly diagnosed EGFRvIII-positive glioblastoma patients. This worldwide effort expects to enroll up to 374 patients at over 150 centers.

Lawrence Recht, MD

Says Dr. Recht, professor of neurology and neurological sciences and principal investigator at Stanford, “This trial is the culmination of several years of preliminary study into the effectiveness of targeting this mutant receptor that is only expressed on cancer cells. These early studies all suggest that this vaccine is safe and effective. The current trial is the last step in moving this vaccine to general clinical use.”

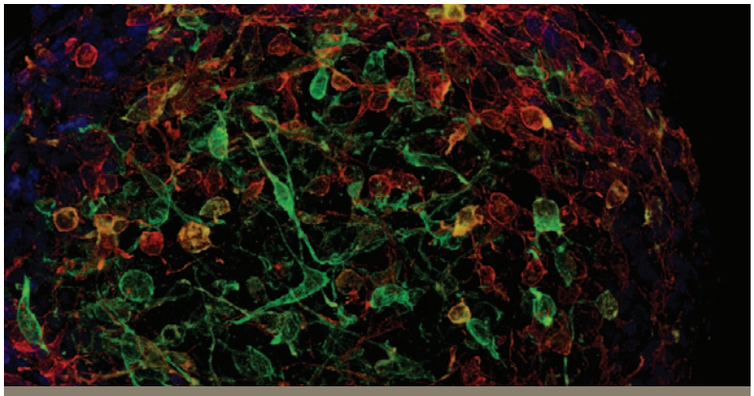
The encouraging Phase II trial (ACT III) of Rindopepimut involved 65 patients and 31 centers. Patients’ immune responses were robust, treatments were well tolerated and median overall survival improved from 15.2 to 24.6 months. See NCT01480479 at clinicaltrials.gov.

Improving outcomes for patients with recurrent glioblastoma

A groundbreaking clinical trial began April of 2012 for adults with recurrent glioblastoma. This phase II study, sponsored by Celldex Therapeutics, tests the anti-tumor activity of the Rindopepimut (CDX-110) vaccine in conjunction with Bevacizumab (Avastin). Says Gordon Li, MD, assistant professor of neurosurgery and principal investigator at Stanford, "Our hope is to improve the overall life expectancy and quality of life in patients diagnosed with this devastating disease." Multiple sites throughout the country will enroll 95 patients. See NCT01498328 at clinicaltrials.gov.

A bispecific antibody therapeutic that goes to the heart of glioblastoma tumors: cancer stem cells

Dr. Wong’s highly-targeted strategy to kill glioblastoma tumor cancer stem cells and to spare normal stem cells could dramatically extend long-term survival rates. He focuses on the exciting theory that glioblastoma originates from and is maintained by a small subset of cancer stem cells lurking within tissue.



The lack of co-localization of EGFRvIII (green) and wild-type EGFR (red) in glioblastoma strengthens the argument that EGFRvIII-positive cells are the relevant cancer stem cell population. Blue staining is DNA.

CD133, a marker on normal stem cells, is present in glioblastoma. If a cancer-specific gene alteration is also present, Dr. Wong reasoned, an antibody zeroing in on both markers could more precisely target cancer stem cells. His search revealed a tight association between cancer stem cells, CD133 and EGFRvIII. He developed a recombinant bispecific antibody, $BsAb^{EGFRvIII/CD133}$ to recognize these markers simultaneously. Remarkably, with BsAb injected into experimental mice, tumor formation is inhibited and survival rates are significantly increased. This research is at the pre-clinical stage. ▶

Hope for diffuse intrinsic pontine glioma—childhood DIPG


Gordon Li, MD

Despite relentless research and multiple clinical trials over two decades, childhood DIPG still produces dismal survival rates of 9-10 months. Determined to improve these statistics, Gordon Li, MD, is studying the potential of Rindopepimut (CDX-110) to attack DIPG. The lack of available DIPG tissue, however, has severely hampered the ability to establish a definitive role for EGFRvIII.

Dr. Li and colleagues at Stanford spent two years obtaining tissue from 11 pediatric DIPG tumors. Employing a highly specific antibody and other advanced techniques, they detected EGFRvIII in six of the eleven cases. In March these encouraging results were published in the *Journal of Neuro-Oncology*[1]. A Phase I clinical trial is now underway to test Rindopepimut (CDX-110) in children with newly diagnosed DIPG. See NCT01058850 at clinicaltrials.gov. ■

NEURO-ONCOLOGY PROGRAM UPDATE

Like all neuro-oncology programs, Stanford treats nervous-system tumors. But where Stanford's program differs from other institutions is in the team's approach to total patient care.


Stanford's neuro-oncology team treats the physical and sociological complications of cancer treatment, meeting weekly to discuss each patient's case.

The Stanford neuro-oncology team not only helps patients with the physical complications that cancer treatment can cause—neuropathy, seizures, radiation injury, metastases, debilitating headaches and paraneoplastic syndromes—it also assists them with the social, financial and mental challenges that can be just as devastating as the disease itself.

"We're more 'big picture' than other centers, crafting a personalized, comprehensive plan for each patient," said Lawrence Recht, MD, the director of the adult program.

At the heart of the program is a collaborative team of experts—in oncology, surgery, neurology, research, nursing, radiology, psychology, rehabilitation, and social work—that meets weekly to discuss each case.

"We put together patient plans that include a range of services, such as physical and cognitive therapy, psychological counseling, assistance with insurance and finances, and palliative care," said Seema Nagpal, MD, clinical assistant professor in neurology and neurological sciences.

"And above all, we prescribe hope and quality of life, because we've observed that our patients who feel better, live longer."

Stanford's neuro-oncology program offers a full range of treatment options that includes minimally invasive surgery, CyberKnife stereotactic radiosurgery (over 5,000 of procedures to date), and individualized immunotherapy and chemotherapy based on molecular analysis of tumors.

Griff Harsh, MD, director of Stanford neuro-oncology surgery and a pioneer of minimally invasive brain tumor surgery added, "As a team, we build on each other's expertise to improve what we can do for our patients."

This expertise translates into the most advanced care available, and the option for patients to participate in clinical trials testing a variety of vaccines, antibody therapies, radiation sensitizers and novel chemotherapy agents.

"If something cutting edge is going to be done, it's likely to be done here at Stanford," said Recht. ■

ALZHEIMER'S DISEASE: TARGETING TO TRANSLATION

Already a leader in bench-to-bedside research, Stanford's new Alzheimer's Translational Research Center leverages faculty expertise in Alzheimer's disease and related dementias in a collaborative effort to drive basic research as quickly as possible toward earlier diagnostics and more effective treatment. Frank Longo, MD, PhD—chair of the department of neurology and neurological sciences and the George E. and Lucy Becker professor of medicine—directs this new center.

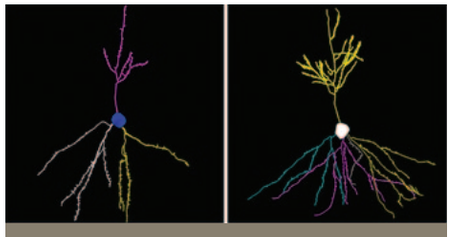
"The amazing richness of the neuroscience community at Stanford creates a powerful environment to translate newly found brain mechanisms into paradigm-shifting therapeutics."

Frank Longo, MD, PhD

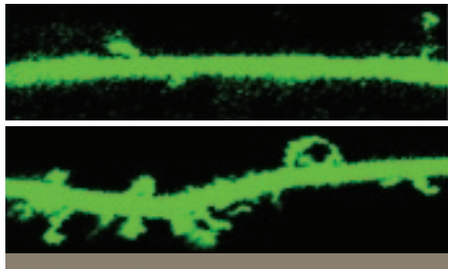
Small molecule therapeutics for Alzheimer's disease: When part is better than the whole

An exciting area of focus at the Alzheimer's Translational Research Center is small molecule therapeutics. Three laboratories are engaged in small molecule development to target Alzheimer's disease (AD) via neurotrophin, immune, and inflammatory pathways.

Neurotrophin Receptors

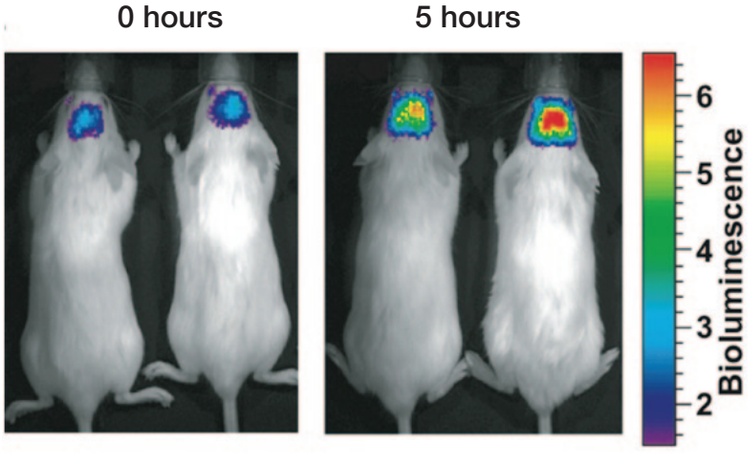


Small molecule rescue of hippocampal dendrites in AD mice.



Small molecule rescue of synaptic spines.

Several known neurotrophin growth factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), dictate whether new neurons live or die and therefore mediate synaptic plasticity and memory. Because these proteins cannot cross the blood–brain barrier, a major challenge in drug development for neuro-degenerative disorders is delivery to the brain.

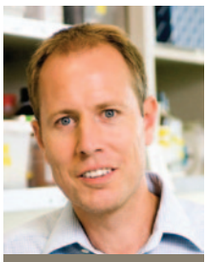


Bioluminescence imaging shows dose-dependent activation of TGF-beta signaling by a small molecule compound in the brain of transgenic reporter mice at 0 hrs (Left panel) vs. 5 hrs (Right panel; 5 vs. (L. mouse) 20 mg/kg (R. mouse)

Dr. Longo and his team, in collaboration with Steven Massa, MD, PhD, at UCSF, pioneered small-molecule drug-like compounds that both mimic key active domains of neurotrophin ligands and cross the blood–brain barrier. In the lab these small molecules modulate neurotrophin receptor function. Dr. Longo's team recently reported the first small molecule BDNF mimetic able to target the BDNF receptor TrkB with high affinity. In a rat model of traumatic brain injury, they demonstrated reductions in neurodegeneration and improved motor learning[1]. This BDNF compound and others in development show tremendous promise for several neurodegenerative diseases, including Alzheimer's, Parkinson's and Huntington's diseases. Current work funded by an NIH-NIA U01 grant is moving one lead compound toward human testing.

Immunology—a small molecule TGB-ß activator

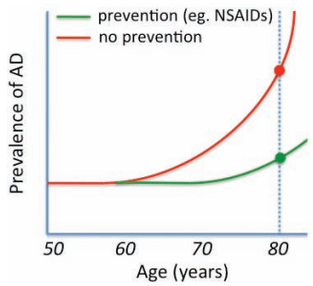
Focusing on another neurotrophic factor, Tony Wyss-Coray, PhD, professor of neurology and neurological sciences, and his team are developing a small-molecule drug capable of activating the brain's transforming growth factor-beta (TGF-ß) signaling pathway[2]. This approach is based on extensive studies from the Wyss-Coray ▶


Tony Wyss-Coray, PhD

lab pointing to a critical role of TGF- ß in neuronal survival, neurogenesis and cognition in animal models of neurodegeneration and AD[3].

Recent studies from the Wyss-Coray lab, funded by an NIH-NINDS U01 grant, show promising neuroprotective effects of a lead compound with TGF-ß activity in a model of acute neurodegeneration. Preclinical testing in a mouse model of AD is now underway. These studies, in close collaboration with the Longo lab, take advantage of the cutting-edge rodent behavioral facilities available to the Translational AD Center. Under the U01 grant, the pharmacology and toxicology of the identified lead compound is tested, in collaboration with SRI International, bringing the compound closer to a human clinical study.

Inflammation: The NSAIDs tip-off



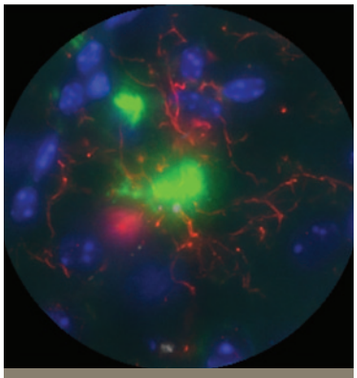
A hypothetical delay of just 5 years in the onset of AD would have a major impact in lowering the prevalence of AD. Several epidemiologic studies demonstrate a marked preventive effect of NSAIDs in healthy aging populations.

Preclinical development of AD is now believed to span years or even decades, with progressive increases in amyloid ß accumulation, tau phosphorylation and synaptic injury well underway before mild cognitive impairment (MCI) is diagnosed.

Research efforts focus most on treating patients with MCI or AD who are already symptomatic. As AD patients over 65 years old are expected to double over the next several decades, a fundamental shift to understanding the preclinical processes that lead to AD—and whether these could be targeted preventively—has taken on significant urgency.


Katrin Andreasson, MD

An important clue into mechanisms of AD prevention comes from epidemiological studies that demonstrate significant delaying effects of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen, on AD onset in normal aging populations[4-6]. NSAIDs inhibit inflammatory cyclooxygenase activity and prostaglandin production, which therefore points to an important role for cyclooxygenase enzymes and their prostaglandin products in the asymptomatic development of AD. Katrin Andreasson, MD, associate professor of neurology and neurological sciences, and her team, study and identify prostaglandin signaling pathways that function in preclinical development of AD in experimental models with genetic and pharmacologic strategies. Their overall goal is to understand—at a molecular, cellular and network level—what earliest events predispose patients to AD. Their translational goal is to target selected prostaglandin receptors with novel small molecules preventively and therapeutically in AD. While these therapeutic innovation programs have not yet reached the clinic, they serve to keep our team up to date on the pipeline of emerging therapies and trials. ■


An early amyloid plaque (green) surrounded by inflammatory microglia (red). Cell nuclei are labeled in blue.

MARK YOUR CALENDAR!

Join the Stanford Neurosciences faculty in beautiful San Francisco for this dynamic conference.

November 9-10, 2012
Location: JW Marriott
Union Square, San Francisco, CA

For more information visit: **cme.stanfordhospital.org**

NEW FACULTY

CIARA HARRAHER, MD, MPH

Clinical Assistant Professor, Neurosurgery
Stanford Neurosurgery Clinic
at Dominican Hospital

Dr. Harraher specializes in general neurosurgery with an interest in brain tumors, degenerative spine conditions and neurovascular disease. Her clinical epidemiology research interests include the surgical management of cerebral aneurysms, arteriovenous malformations and carotid stenosis.

RANDAL PEOPLES, MD

Clinical Associate Professor, Neurosurgery
Neurosurgery Clinic at St. Rose Hospital

General Adult and Pediatric Neurosurgeon, Medical Director of Stanford's first out-of-state outreach clinic in Las Vegas, Nevada. Special interest treating injuries of athletic performers, concussion, general spine and brain.

XINNAN WANG, PHD

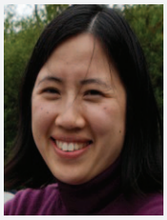
Assistant Professor of Neurosurgery

Dr. Wang researches how regulatory mechanisms control mitochondrial dynamics and function and the mechanisms by which even subtle perturbations of these processes may contribute to neurodegenerative disorders.

JOHN DAY, MD, PHD

Professor of Neurology and Neurological Sciences
Director, Neuromuscular Division and Clinics

Dr. Day coordinates comprehensive patient care involving basic, translational and clinical research. His translational research of peripheral nerves and muscle diseases focuses on underlying genetic defects and their molecular, cellular and clinically-significant consequences through investigation of patient specimens.



SUSY SHU-HSIN JENG, MD

Clinical Assistant Professor of Neurology
and Neurological Sciences

Dr. Jeng is a general child neurologist with a special interest in medical education.

YOON-JAE CHO, MD

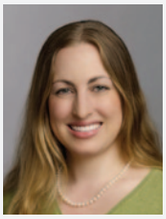
Assistant Professor of Neurology
and Neurosurgery

Dr. Cho is the Beirne Faculty Scholar in Pediatric Neuro-Oncology. His research focuses on identifying the important molecular mechanisms involved in brain cancer, searching for novel therapeutic targets and improving efficiency of clinical translation.

JORINA ELBERS, MD

Assistant Professor of Neurology and
Neurological Sciences

Dr. Elbers is a pediatric neurologist with specialty training in pediatric stroke. Her research interests include inflammatory vasculopathies and novel neuro-imaging techniques to study stroke and inflammation.



MICHELLE MONJE-DEISSEROTH, MD, PHD

Assistant Professor of Neurology and
Neurological Sciences

Dr. Monje-Deisseroth is a neurologist and neuro-oncologist. Her research focuses on the molecular and cellular mechanisms of postnatal neurodevelopment, with a special interest in the origins of pediatric brain tumors and consequences of cancer treatment.

JIN HYUNG LEE, PHD

Assistant Professor of Neurology and Neurological
Sciences and of Bioengineering (Acting)

Dr. Lee is an electrical engineer with a special interest in neuroscience. She studies large-scale circuit-level brain function using cutting-edge optogenetic functional magnetic resonance imaging technology (ofMRI).

STANFORD TO OPEN STATE-OF-THE-ART CLINICAL TRIALS CENTER

This fall Stanford will open the Jill and John Freidenrich Center for Translational Research, a 30,000 sq. ft. state-of-the-art facility for designing and conducting human-subject clinical trials, which is within walking distance of Stanford Hospital & Clinics and Lucile Packard Children's Hospital.

The Center features 27 patient stations, an infusion center, a sample collection lab, two phlebotomy rooms and an outdoor play area with a separate entrance for pediatric subjects. All the personnel required to manage the human side of clinical trials—nurses, nutritionists and psychologists—will be on hand. There will also be specialized rooms for informed consent discussions, remote observation, sleep studies and exercise physiology testing.

For questions about the following clinical trials, please contact our clinical trials research coordinator Maria Coburn at 650.736.9551 or **mcoburn@stanford.edu**

CLINICAL TRIALS

NEUROSURGERY

A Phase 1/2A Study of the Safety and Efficacy of Modified Stromal Cells (SB623) in Patients with Stable Ischemic Stroke
SB623 will be implanted into the peri-infarct region of the brain between 6-24 months after stroke.
PI: Gary K. Steinberg, MD, PhD
Sub-PI: Neil Schwartz, MD
(NCT01287936)

Familial Intracranial Aneurysm (FIA) Study
To explore genetic and environmental factors associated with the incidence of familial intracranial aneurysms. The study continues to enroll non-familial affected patients.
PI: Gary K. Steinberg, MD, PhD
(NCT00071565)

A Study of Patient Reported Outcomes After Stereotactic Radiosurgery for Trigeminal Neuralgia
PIs: Clara Y.H. Choi, MD, PhD and Scott G. Soltys, MD
(NCT01364285)

A Phase 1/2 Trial Assessing the Safety and Efficacy of Bilateral Intraputaminal and Intranigral Administration of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin [NTN]) in Subjects with Idiopathic Parkinson's Disease
PI: Jaimie Henderson, MD
(NCT00985517)

Radiosurgical Neuromodulation for Refractory Depression
Co-PIs: Hugh Brent Solvason, MD, PhD and John R. Adler, MD
(NCT01403441)

A Phase 1 Trial of Vorinostat Concurrent with Stereotactic Radiotherapy in Treatment of Brain Metastases from Non-Small Cell Lung Cancer
PI: Griff Harsh, MD
(NCT00946673)

A Study of Amifostine for Prevention of Facial Numbness in Patients Receiving Stereotactic Radiosurgery for Trigeminal Neuralgia
PIs: Clara Choi, MD, PhD and Scott Soltys, MD
(NCT01364259)

A Phase 1/2 Trial of Fractionated Stereotactic Radiosurgery to Treat Large Brain Metastases
To determine the optimal radiation dose.
PIs: Scott Soltys, MD and Clara Choi, MD, PhD
(NCT00928226)

Effects of Growth Hormone on Cognition and Cerebral Metabolism in Adults
To elucidate the effects of growth hormone replacement in patients with growth hormone deficiency on cognitive function using structural and functional neuroimaging and cognitive testing.
PI: Laurence Katznelson, MD
(NCT01007071)

A Phase II Study of Rindopepimut/GM-CSF in Patients with Relapsed EGFRvIII-Positive Glioblastoma
PI: Gordon Li, MD
(NCT01498328)

Progesterone for the Treatment of Traumatic Brain Injury (ProTECT III)
The ProTECT study will determine if intravenous (IV) progesterone, started within 4 hours of injury and given for a total of 96 hours, is more effective than placebo for treating victims of moderate to severe acute traumatic brain injury.
Stanford PI: Jim Quinn, MD
Sub-PIs: Marco Lee, MD and Christine Wijman, MD
(NCT00822900)

An International, Study of Rindopepimut/GM-CSF with Adjuvant Temozolomide in Patients with Newly Diagnosed, Surgically Resected, EGFRvIII-positive Glioblastoma (ACT IV)
PI: Lawrence Recht, MD
(NCT01480479)

A Phase 1/2 Trial of Temozolomide and Hypofractionated Radiotherapy in the Treatment of Supratentorial Glioblastoma Multiforme
To determine the safety and effectiveness of 1 week versus 6 weeks of hypofractionated radiotherapy in combination with temozolomide.
PIs: Scott G. Soltys, MD and Clara Choi, MD, PhD
(NCT01120639)

An Open Label, Multicenter, Single Arm Study of Pasireotide LAR in Patients with Rare Tumors of Neuroendocrine Origin
For patients with disease progression despite standard therapy or for whom no standard therapy is available.
PI: Laurence Katznelson, MD
(NCT00958841)

Investigation of DTI MRI as a Correlate to Pain Relief and Facial Numbness in Patients Following Stereotactic Radiosurgical Rhizotomy for Trigeminal Neuralgia
PIs: Clara Choi, MD, PhD and Scott Soltys, MD
(NCT01364272)

CyberKnife Radiosurgery and Quality of Life
Pain control and quality of life improvement after treatment with CyberKnife radiosurgery for spinal metastases.
PI: Steven Chang, MD
(NCT01163539)

NEUROLOGY

Population-based Studies of the Prevalence and Predisposing Factors of Peripheral Neuropathy
In collaboration with epidemiologists at UC Berkeley, the study investigates the potential environmental or occupational risk factors for peripheral neuropathy.
PI: Yuen So, MD, PhD

A Phase 2 Study of Verubulin with Radiation and Temozolomide for Adults with Newly Diagnosed Glioblastoma
PI: Lawrence Recht, MD
(NCT01285414)

A Phase 4 Study to Evaluate the Efficacy and Safety of Alglucosidase Alfa Produced at the 4000 L Scale for Pompe Disease
PI: John Day, MD, PhD
(NCT01526785)

Brain Networks in Neurodegenerative Diseases
To prospectively evaluate the application of FDG PET to aid in the diagnosis of Parkinson's disease and other atypical Parkinsonian syndromes.
PI: Kathleen Poston, MD, MS

Transient Ischemic Attack (TIA) Triage and Evaluation of Stroke Risk
PI: Gregory Albers, MD, Stanford University
(NCT01423201)

An Exploratory Study to Assess Two Doses of GSK2402968 in the Treatment of Ambulant Boys with Duchenne Muscular Dystrophy
PI: Yuen So, MD, PhD
(NCT01462292)

BrainGate2: Feasibility Study of an Intracortical Neural Interface System for Persons with Tetraplegia
PI: Jaimie Henderson, MD
(NCT00912041)

A Phase 2 Study of MEDI-575 (Monoclonal Antibody) in Adult Subjects with Recurrent Glioblastoma Multiforme
To evaluate the progression-free survival at 6 months in adult subjects treated with MEDI-575.
PI: Lawrence Recht, MD
(NCT01268566)

The Aging Brain: Risk for Dementia
This study will enroll older individuals with or without cognitive problems with the goal of determining which factors are most predictive developing dementia.
PI: Geoffrey Kerchner, MD, PhD

Microstructural Brain Imaging Using Ultra-High Field 7-Tesla MRI
This study aims to find the earliest structural changes corresponding to Alzheimer's disease and other neurodegenerative conditions and to correlate these changes with memory and other behavioral measures.
PI: Geoffrey Kerchner, MD, PhD

Resting-State Functional MRI for Diagnosing Alzheimer's Disease
The goal is to develop a resting-state functional connectivity biomarker able to detect signal in MCI and to distinguish AD from non-AD dementia at the single-patient level.
PI: Michael Greicius, MD, MPH

Phase 3 Study to Evaluate the Efficacy and Safety of Desmoteplase in Subjects with Acute Ischemic Stroke (DIAS-4)
PI: Maarten Lansberg, MD, PhD
(NCT00856661)

Prognosis of Critically Ill Neurological Patients
To determine how well health care providers can predict future neurological outcomes, if they differ in the prediction of outcome, and to assess outcomes of this patient population.
PI: Anna Finley-Caulfield, MD

Raloxifene for women with Alzheimer's disease
A multisite pilot randomized trial of raloxifene the treatment of women with Alzheimer's disease.
PI: Victor Henderson, MD, MS
(NCT00368459)

A Phase II Trial of MABT5102A on Brain Amyloid and Related Biomarkers in Patients with Mild to Moderate Alzheimer's Disease (BLAZE)
PI: Geoffrey Kerchner, MD, PhD

Diffusion Weighted Imaging Evaluation for Understanding Stroke Evolution Study-2: (DEFUSE-2)
To determine if MRI can help identify which patients ineligible for IV tPA therapy or who have failed IV tPA therapy should undergo an endovascular clot removal procedure.
PI: Gregory Albers, MD
(NCT01349946)

A Phase 1/2A Study of the Safety and Efficacy of Modified Stromal Cells (SB 623) in Patients with Stable Ischemic Stroke
SB623 will be implanted into the peri-infarct region of the brain between 6-24 months after stroke.
PI: Gary K. Steinberg, MD, PhD
Sub-PI: Neil Schwartz, MD

Diagnostic Utility of MRI in Intracerebral Hemorrhage
To measure the impact of state-of-the-art brain imaging technology on the diagnosis and treatment of patients with a spontaneous ICH to improve patient outcome.
PI: Christine Wijman, MD
(NCT00363662)

Pharmacodynamic Study of CK-2017357 in Patients with Generalized Myasthenia Gravis on Standard Therapy
PI: Yuen So, MD, PhD
(NCT01268280)

Prognostic Value of MRI and Biomarkers in Comatose Post-cardiac Arrest Patients (COMA)
To assess the value of state-of-the art brain imaging techniques (MRI), and blood tests in predicting outcome in these patients.
PI: Christine Wijman, MD

Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trial
A phase 3 study to determine if aspirin and clopidogrel together reduces the risk of stroke, heart attacks and other complications compared to aspirin alone.
PI: Gregory Albers, MD
(NCT00991029)

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-II
To determine the therapeutic benefit of intensive blood pressure reduction relative to standard treatment in acute intracerebral hemorrhage.
PI: Christine Wijman, MD
(NCT01176565)

Stroke Hyperglycemia Insulin Network Effort (SHINE) Trial
To determine safety and therapeutic benefit of treating hyperglycemic acute ischemic stroke patients with targeted glucose concentration (80mg/dL - 130 mg/dL).
PIs: James Quinn, MD and Christine Wijman, MD
(NCT01369069)

The Parkinson's Genetic Research Study (PaGeR)
PIs: Kathleen Poston, MD, MS and Rosalind Chuang, MD
(NCT01558479)

Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase 3 (CLEAR III)
To determine if EVD placement with low-dose rt-PA improves modified Rankin Scale scores at 6 months compared to subjects treated with EVD placement with placebo.
PI: Christine Wijman, MD
(NCT00784134)

Clinical and Genetic Characterization of Myotonic Dystrophy
PI: John Day, MD, PhD

CLINICAL TRIALS

NEUROLOGY *(continued)*

Safety and Efficacy Evaluation of Threshold Sound Conditioning by Conditioning-enhanced Hearing Aid
PI: Jaime Lopez, MD

NeuroThera® Efficacy and Safety Trial - 3 (NEST-3)
To assess the safety and efficacy of transcranial laser therapy (TLT) with the NeuroThera® Laser System for the treatment of acute ischemic stroke within 24 hrs of stroke onset.
PI: Gregory Albers, MD
(NCT01120301)

ACE-Seniors (Activities for Cognitive Enhancement of Seniors)
A randomized trail of healthy older adults to assess effects of innovative activities on remediation of age-related cognitive decline.
PI: Victor Henderson, MD, MS
(NCT01094509)

Insulin Resistance Intervention After Stroke Trial (IRIS)
To determine if pioglitazone will reduce the overall risk for fatal or nonfatal stroke or MI among non-diabetic men and women over age 44 years with insulin resistance and recent ischemic stroke or TIA.
PI: Maarten Lansberg, MD
(NCT00091949)

CRISP: A multi-center cohort study of acute stroke patients who are treated with endovascular therapy
The study is designed to determine optimal CT perfusion criteria to select patients for endovascular stroke treatment.
PI: Maarten Lansberg, MD, PhD

RADIOLOGY/NEURORADIOLOGY

Quantifying Collateral Perfusion in Cerebrovascular Disease
This study utilizes MRI to improve the detection and assessment of collateral blood vessels in patients with diseases of the brain, such as moyamoya disease and stroke.
PI: Greg Zaharchuk, MD, PhD
(NCT01419275)

NEUROIMMUNOLOGY

To Evaluate the Efficacy and Safety Of Ocrelizumab in Comparison to Interferon Beta-1a (Rebif) in Patients With Relapsing Multiple Sclerosis
PI: Jeffrey Dunn, MD
(NCT01412333)

JCV Antibody Program in Patients with Relapsing Multiple Sclerosis Receiving or Considering Treatment With Tysabri: STRATIFY-2
PI: Jeffrey Dunn, MD
(NCT01070836)

An Extension Protocol for Multiple Sclerosis Patients Who Participated in Previous Studies of Alemtuzumab
PI: Jeffrey Dunn, MD
(NCT00930553)

Biobank For MS And Other Demyelinating Diseases
To establish a large, longitudinal collection of high quality samples and data from subjects with MS, selected other demyelinating diseases as a shared resource to scientists researching the causes, sub-types, and biomarkers of MS and related demyelinating diseases.
PI: Jeffrey Dunn, MD
(NCT00445367)

To investigate the long term safety, tolerability, and efficacy of ACT-128800 (Ponesimod) in patients with relapsing remitting Multiple Sclerosis
PI: Jeffrey Dunn, MD
(NCT01093326)

Large-scale, Multi-disciplinary Sample and Data Repository for Multiple Sclerosis and Related Demyelinating Diseases
PI: Jeffrey Dunn, MD
(NCT00445367)

INTERVENTIONAL NEURORADIOLOGY

Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT)
This study is evaluating a new intracranial stent for intracranial stenosis.
PI: Michael P. Marks, MD

Intra-arterial Chemotherapy for Advanced Intraocular Retinoblastoma
This study is recruiting patients with inoperable tumors of the eye, specifically retinoblastoma. Patients will be treated with selective intra-arterial infusion of chemotherapy.
PIs: Jonathan W. Kim, MD and Huy M. Do, MD
(NCT01151748)

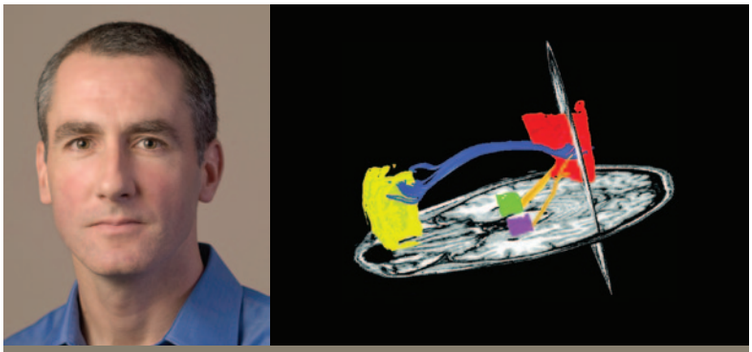
PEDIATRIC NEUROLOGY

A Phase I Study of Rindopepimut After Conventional Radiation in Children With Diffuse Intrinsic Pontine Gliomas
Safety and efficacy analysis of treating pediatric diffuse intrinsic pontine glioma patients with the EGFRvIII peptide vaccine after conventional radiation.
PI: Paul Fisher, MD
Sub-PIs: Albert J Wong, MD, Michael S.B. Edwards, MD, Michelle Monje-Deisseroth, MD, PhD and Gordon Li, MD
(NCT01058850)

Erlotinib Versus Oral Etoposide in Patients with Recurrent or Refractory Pediatric Ependymoma
PIs: Paul Fisher, MD, Sonia Partap, MD and Neysa Maria Marina
(NCT01032070)

Bevacizumab and Lapatinib in Children With Recurrent or Refractory Ependymoma
PI: Sonia Partap MD
Sub-PIs: Paul Graham Fisher, MD, Michelle Monje-Deisseroth, MD, PhD, Cynthia Campen, MD and Yoon-Jae Cho, MD
(NCT00883688)

NEW STRATEGIES AND TECHNOLOGIES FOR DIAGNOSIS, PREVENTION, AND TREATMENT



Michael Grecius, MD, discovered that one of the key memory networks degenerates early in Alzheimer patients.

The Stanford Center for Memory Disorders is dedicated to the fight against age-related cognitive decline. There are many different causes of memory loss, and an accurate diagnosis is essential to getting the best treatment. At the Center, our physicians lead an interdisciplinary team of health care professionals working together to provide the best possible diagnoses and treatment plans. Experts from the fields of neuropsychology, psychiatry, nursing, pharmacy, and genetic counseling collaborate closely with our behavioral and geriatric neurologists, allowing them to provide medical care that is both cutting edge and compassionate.

Located in the heart of Silicon Valley, the Stanford Center for Memory Disorders benefits from collaboration with leading experts in medical imaging, genomics, proteomics and stem cells. Because our Center physicians both care for patients and conduct research on memory disorders, patients benefit sooner from cutting-edge discoveries and knowledge about experimental treatment options. The Center's physician-researchers also have access to the Richard M. Lucas Center for Imaging, one of the premier centers in the world devoted to research in magnetic resonance imaging (MRI), spectroscopy (MRS) and CT imaging.

Promising areas of memory disorder research being conducted at the Center include:

BRAIN NETWORK MAPPING FOR DIAGNOSING COGNITIVE DISORDERS

Michael Greicius, MD, medical director of the Stanford Center for Memory Disorders and an assistant professor of neurology and neurological sciences, is using functional MRI with other imaging modalities to characterize neural networks in healthy adults and patients with neuropsychiatric disorders. His main research objective is to develop novel imaging biomarkers that will enhance the understanding, diagnosis, and treatment of Alzheimer's disease and related disorders. Recent work from Dr. Greicius' lab has shown that women are more susceptible than men to the main genetic risk factor for Alzheimer's disease. Ongoing genetic analyses with colleagues in biomedical informatics should help delineate some of the molecular causes behind this gender difference and identify potential new drug targets.

TREATMENT INTERVENTIONS FOR COGNITIVE DECLINE IN AGING AND DEMENTIA

Victor Henderson, MD, MS, is professor of neurology and neurological sciences and of health research and policy, where he directs the division of epidemiology. He studies risk factors for cognitive aging and dementia, and interventions to ameliorate cognitive decline. In a large 2.5-year randomized clinical trial among healthy older women, he and colleagues recently demonstrated selective cognitive benefit of soy isoflavone supplements. Currently, he is assessing effects of specific forms of physical activity and mental activity in healthy older adults as potential therapeutic interventions for age-related cognitive impairment.

USING ULTRA-HIGH FIELD MRI FOR DIAGNOSIS AND TRACKING OF ALZHEIMER'S DISEASE

Geoffrey Kerchner, MD, PhD, assistant professor of neurology and neurological sciences, uses ultra-high field MRI and other advanced neuro-imaging technologies to study how Alzheimer's disease and other age-related neurodegenerative illnesses affect the microscopic structure and circuitry of the brain. By revealing fine details of the living brain, equipment such as the 7-Tesla MRI allows neuro-imaging researchers the opportunity to observe, in living patients, disease-related anatomical changes previously observed only at autopsy. This imaging research may lead to better ways of diagnosing and tracking Alzheimer's disease. Dr. Kerchner also leads clinical trials of novel Alzheimer's disease therapeutics, including treatment with monoclonal antibodies directed against beta-amyloid, the main constituent of amyloid plaques.

IDENTIFYING BLOOD PROTEINS THAT AFFECT BRAIN AGING

Tony Wyss-Coray, PhD, professor of neurology and neurological sciences, is working to identify the dysfunctional immune responses that may contribute to the degradation of the aging brain and to the onset of Alzheimer's. He is also developing expanded blood-protein assays in a hunt for rejuvenating factors that may prove useful in treating dementia and, perhaps, slowing the aging process in older brains.

As the Center's research moves from bench to bedside, our staff is able to offer our patients a broader range of personalized treatment strategies, as well the coordinated care through Stanford Hospital's Aging Adult Services. ■

CASE STUDY: TREATING SEVERE NEUROMYELITIS OPTICA

SITUATION
Weakness in all four limbs, unilateral loss of vision, weight loss, problems with writing and memory.

STRATEGY
Plasmaphoresis, IVIG, high dose steroids, immune suppressant, and biologic therapy.

OUTCOME
After six months, regained walking and vision functions. Five years later, active and thriving in high school on a maintenance dose of prednisone.

Tatyana, a third-grader with a passion for hip-hop dancing, was nine years old when a school nurse noticed an unusual hitch in the girl's gait. She also complained of spine pain that caused her to walk with hunched shoulders. The nurse encouraged her parents to take their daughter to a pediatrician, who found no clinical signs of illness.

Over the summer, Tatyana's spine pain worsened. She lost weight between relapsing bouts of constipation and incontinence, and suffered from transient neurological problems, such as weakness in one leg, then the other. She lost vision in the center of her left eye. It got better, then she lost vision in her right eye.

By the fall of fourth grade, Tatyana was no longer able to walk. Specialists at her clinic performed a CT scan and spinal tap, which revealed severe nonspecific white matter lesions in the brain, spinal cord, and optic tracts. They diagnosed multiple sclerosis, a disease where immune factors in the blood attack a person's nerve cells. Tatyana was hospitalized and began monthly intravenous immunoglobulin (IVIG), which typically reduces inflammation and helps slow the progression of MS.

Unfortunately, IVIG only provided temporary relief to Tatyana, whose symptoms would flare between treatments. Her walking, writing and memory continued to decline.

"We were scared," said her mother, "Especially when a doctor told us that she might never walk again."

At that point Tatyana was referred to the Stanford Multiple Sclerosis Center and was assigned a medical team that included Jennifer Frankovich, MD, a pediatric rheumatologist at Lucile Packard Children's Hospital; Jeffrey Dunn, MD, Associate Director of the Center; and Keith P. Van Haren, MD, a pediatric neurologist at Packard Children's Hospital.

"Tatyana's flares were more severe than we see in a typical MS patient, so we began to suspect neuromyelitis optica (NMO), formerly called Devic's Disease," said Dunn. "Her optic neuritis, with vision loss moving from one eye to another, was an important clue."

In addition, her scans revealed lesions that were consistent with NMO. Further testing revealed NMO-IgG antibodies in her blood.

"As a team, we decided to take a more aggressive approach to end the inflammation and help reset Tatyana's immune system," said Frankovich.

The first step was plasmapheresis, where harmful auto-antibodies were removed from Tatyana's whole blood. Plasmapharesis was combined with high dose steroids, high dose IVIG, and an immune suppressant, called mycophenylate mofetil, that is frequently used in organ transplants. This forceful combination of medications was used for three months, and she made significant progress with this regimen. Within six months, she regained her eyesight and the ability to walk. Frankovich gradually weaned Tatyana off the plasmapharesis, the IVIG, then the steroids. After, she kept a close eye on Tatyana's immune system while on low dose steroids and mycophenylate. In the last year she was moved to solo therapy with a single infusion of Rituximab every 6 months and ongoing low-dose steroids.

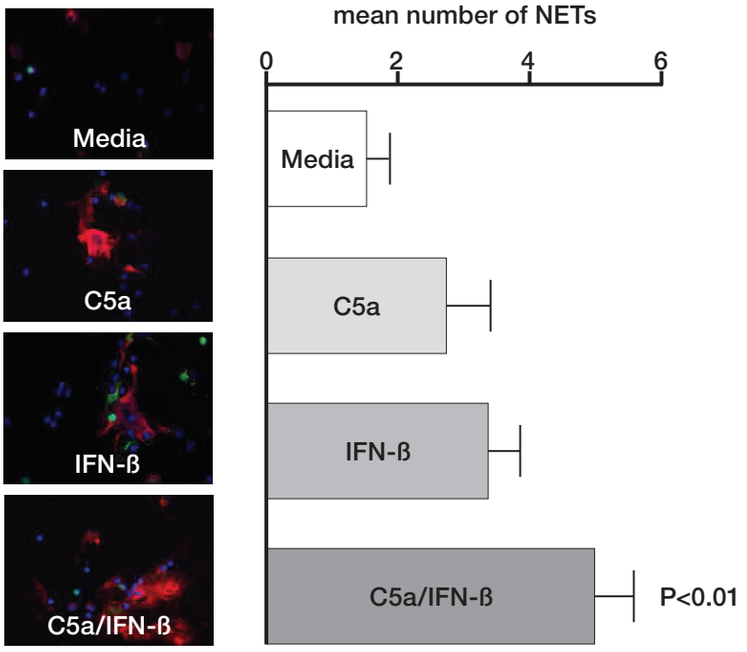
Today, five years after being told she might never walk again, Tatyana is getting As and Bs in high school, volunteering at a daycare center and taking a Zumba dance class. Though she has some numbness in her hands and some residual vision damage, she hasn't had a significant flare for the past few years, and she is healthy and happy.

"For severe life- or organ-threatening diseases, such as the case with Tatyana, we have found that the simultaneous use of multiple aggressive immune-modulating therapy is more likely to produce remission than using solo or sequential therapy," said Frankovich. "This approach is bold and requires diligent monitoring, but it results in more success stories than old single-therapy approaches." ■

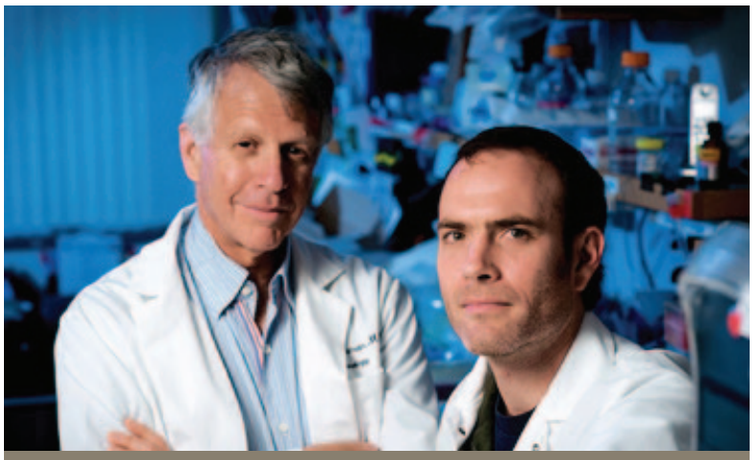
A TALE OF TWO DISEASES: TARGETED TREATMENT FOR NMO ON THE HORIZON

Neuromyelitis optica (NMO) is *not* relapsing-remitting multiple sclerosis (RRMS). Both of these neuro-inflammatory autoimmune diseases cause CNS demyelination but incorrect diagnoses of NMO as RRMS have led to treatments, such as ß-interferon, that unintentionally exacerbate NMO. The laboratory of Dr. Lawrence Steinman—George A. Zimmerman professor of neurology and neurological sciences, pediatrics, and genetics, and a respected expert in both NMO and RRMS—pioneers research into targeted therapies to mitigate neuronal damage in NMO patients.

Dr. Steinman's team, collaborating with researchers at Radboud University in the Netherlands, discovered an avenue for the first targeted treatment of NMO: neutrophil elastase inhibitors[1]. In this study T helper 17 (Th17) cells, already implicated in RRMS and its experimental autoimmune encephalomyelitis (EAE) mouse model, have taken center stage as data accumulate that NMO is itself a Th17-driven disease. Patients diagnosed with NMO had elevated levels of Th17 cytokines along with granulocyte chemokines, type 1 interferon and—notably—neutrophil elastase. The team showed that blocking neutrophil elastase ameliorated Th17-induced EAE.



Type I IFN synergizes with complement to release neutrophil elastase from neutrophils. Left: Neutrophil elastase (red), histone (green) and DNA (blue) in human neutrophil cultures stimulated with media, C5a, IFN-ß and C5a + IFN-ß. Right: Mean number of neutrophil extracellular traps (NETs) in neutrophil cultures of 4 controls stimulated with media, C5a, IFN-ß and C5a + IFN-ß.



Lawrence Steinman, MD *(left)* and Robert Axtell, MS, PhD *(right)*.

As neutrophils are short-lived first-line responders to inflammation, neutrophil elastase inhibition may prove most effective against acute NMO relapses. This treatment could also decrease the duration and dose of corticosteroid treatments, thus mitigating some of its serious side effects.

NMO is distinguished from RRMS by the presence of granulocytes and auto-antibodies against aquaporin in approximately 80 percent of patients. Seeking to improve the 30 to 50 percent effectiveness of ß-interferon in RRMS patients, Robert Axtell, PhD, a postdoctoral scholar in Dr. Steinman's lab, found differential expression of T cells in RRMS and its EAE model[2]. ß-interferon was effective in reducing EAE symptoms induced by T helper 1 (Th1) cells but exacerbated disease induced by Th17 cells. As Th17 may drive NMO, one explanation for the reduced effectiveness of ß-interferon is that RRMS statistics include misdiagnosed NMO patients.

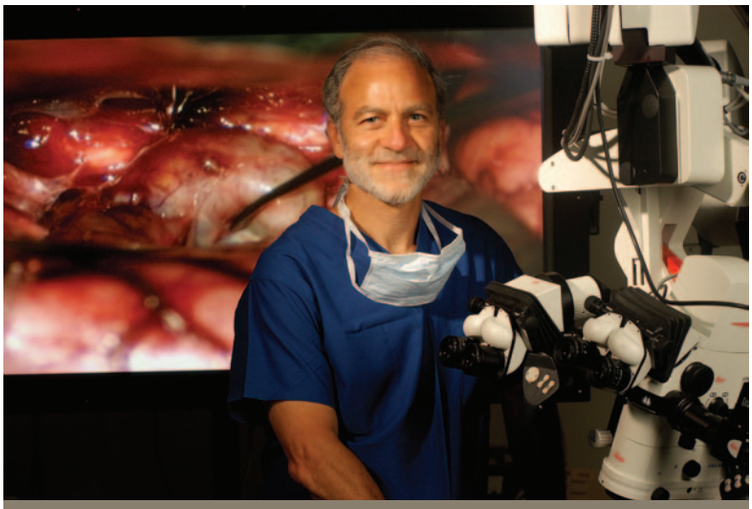
In a 2012 commentary Dr. Steinman describes the challenges of treating RRMS and NMO[3]. While targeted immune therapies exist for many immune-based diseases, including RRMS, care must be taken to choose the correct treatment at the correct time. As yet there are none approved for NMO, with treatment limited to systemic corticosteroids, plasmapheresis and immunosuppressive agents.

The elastase results add to the stockpile of known biomarkers for RRMS and help put accurate diagnosis and individually-tailored treatment for both RRMS and NMO clearly on the horizon.

The Guthy-Jackson Charitable Foundation, which supports efforts to prevent and cure NMO, recognizes Stanford as one of ten national centers of excellence for the diagnosis and treatment of NMO, and funds this research. ■

MYSTERY DIAGNOSIS: MOYAMOYA DISEASE

Among multiple centers of excellence at Stanford, the Moyamoya Center has a champion: Dr. Gary Steinberg. His vast experience with moyamoya and decades-long dedication to building a world-class treatment center has offered hundreds of moyamoya patients hope and a cure for this uncommon disease.



Dr. Gary Steinberg pioneered the technique of combined direct and indirect bypass surgery to maximize the long-term success of surgery for moyamoya patients.

Moyamoya, the cerebrovascular disease caused by progressive blockage of distal internal carotid arteries, was first discovered in Japan in the 1950s. Moyamoya loosely translates to "hazy puff of smoke," which describes the fragile collateral blood vessels generated in the brain's attempt to increase circulation at the occlusion. It has no known cause, although Stanford researchers are narrowing in on genetic and environmental risk factors. Historically thought of as an Asian disease, two-thirds of Stanford's patients have non-Asian heredity. An intriguing statistic Stanford neurosurgeons are studying is that approximately 70% of patients are female, which has led to a recent article in *Neurosurgery* by Khan et al on moyamoya's gender differences[1].

Symptom onset is often bimodal separated by decades, and can include stroke, TIA, headaches and/or seizures. Proper diagnosis is critical—and challenging. At Stanford, evaluation includes a neurological exam, neuropsychological testing and—to determine blood flow—digital subtraction angiography, Xenon CT and MRI, including perfusion studies.

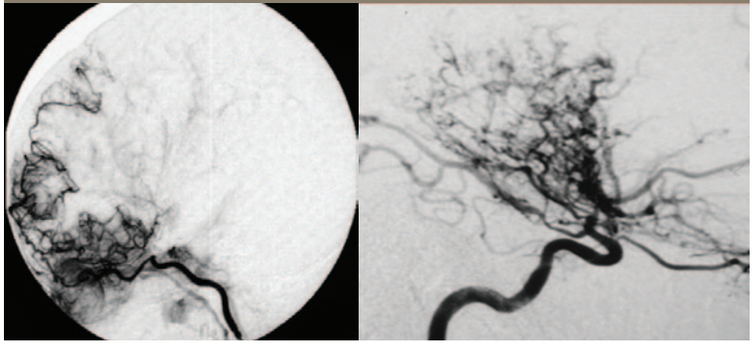
Complicating matters, moyamoya can be its sole manifestation or it can be associated with various conditions, such as neurofibromatosis, Down syndrome, sickle cell disease or primordial dwarfism. Many of these associated disorders lend credence to a genetic component for moyamoya.

Moyamoya diagnosis continues to evolve subtly. It is presently defined as a bilateral disease, whereas unilateral manifestation is considered by some to be syndromic even without other associated disorders. A frontier of diagnosis is where the disease spreads contralaterally after unilateral onset. In a retrospective study Dr. Steinberg, chairman of neurosurgery and Bernard and Ronni Lacroute–William Randolph Hearst professor of neurosurgery and the neurosciences, found that unilateral patients diagnosed with equivocal or mild contralateral disease were at increased risk of disease progression[2]. He considers ongoing reevaluation important to a patient's treatment regimen.

The mainstay treatment for moyamoya is surgical revascularization with direct, indirect or combined methods, including omental transposition. Dr. Steinberg pioneered the technique of combined direct and indirect bypass surgery; for every patient able to undergo direct bypass he also performs an indirect procedure to maximize optimal blood flow and long-term success of surgery. He has performed 948 bypass surgeries on 573 moyamoya patients aged 1 to 69 years from 46 states, Puerto Rico, the Virgin Islands and 16 countries, making Stanford the leading referral site in the United States and internationally.

A study of moyamoya patients who underwent revascularization surgery at Stanford from 1991–2008 concludes that revascularization surgery carries low risk, effectively prevents future ischemic events and improves quality of life[3]. Of 264 patients who underwent 450 revascularization procedures (mean follow-up of 4.9 years), surgical morbidity was 3.5% and mortality was 0.7% per treated hemisphere. Of 171 patients who presented with TIA, 91.8% were TIA free at 1 year and later. ▶

MRIs showing the profuse collateral network of vessels typically seen in moyamoya disease.



Cognitive decline in moyamoya patients is an important focus of Stanford researchers. Les Dorfman, MD, professor of neurology and neurological sciences and director of the Stanford Multiple Sclerosis Center, and his colleagues recently demonstrated that cognitive impairment can occur in the absence of a confounding factor such as ischemic stroke[4]. This impairment tends to strike executive functioning yet spare memory and intellect. Future research will help elucidate if moyamoya patients who undergo early revascularization surgery can retain or regain cognitive functioning.

To better understand the aberrant vasculature in moyamoya disease, Stanford scientists use array tomography—a breakthrough imaging technology developed by Stanford professor of molecular and cellular physiology Stephen Smith (see back cover)—to visualize changes in the brain's molecular architecture at extremely high resolution. Also underway is research examining the unique protein expression profiles of moyamoya vasculature, as well as extensive genetic sequencing of individuals with familial moyamoya disease. Another imminent report describes the discovery of multiple auto-antibodies in the serum of moyamoya patients. Taken together, these fundamental studies advance our knowledge of moyamoya and help guide us to better and timelier diagnoses and treatments. ■

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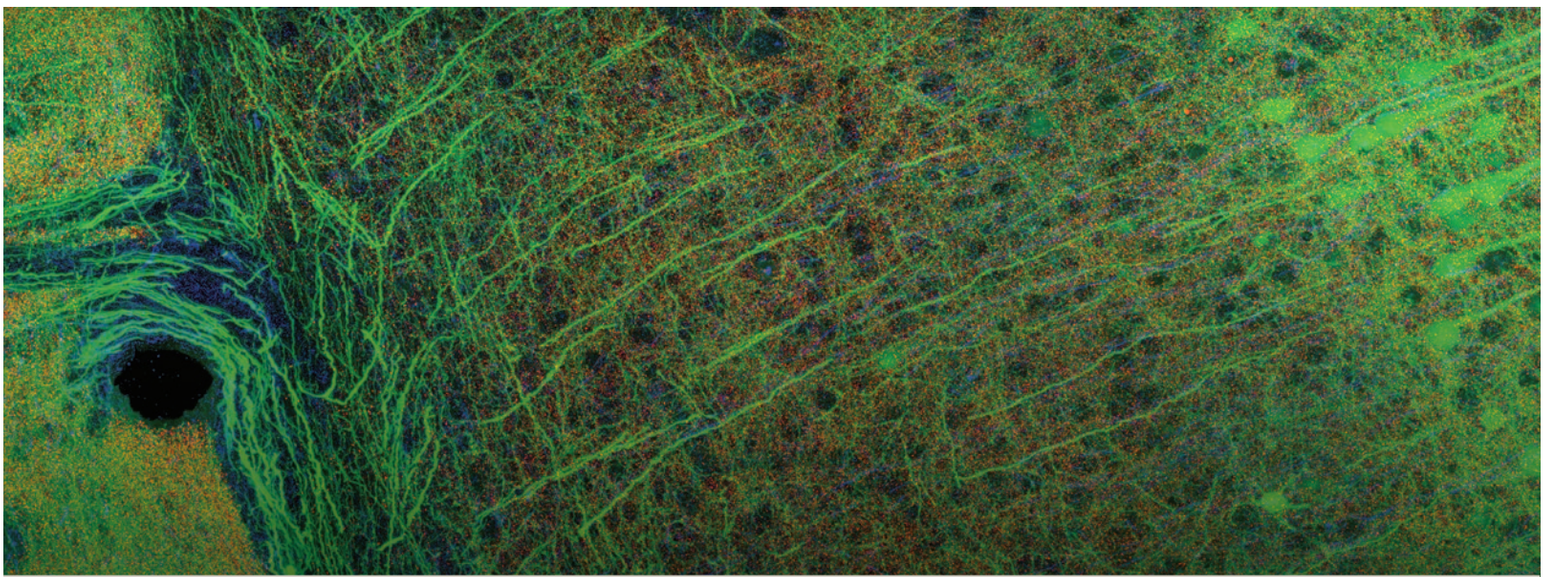

SUMMER 2012: ISSUE 2

NEURO-INNOVATION

News from the Stanford Neurology & Neurosurgery Departments

STANFORD
HOSPITAL & CLINICS

The beauty of a mouse cerebral cortex captured by Stephen Smith, PhD, Stanford professor of molecular and cellular physiology, with array tomography, an imaging method he co-invented.
To view a video: smithlab.stanford.edu