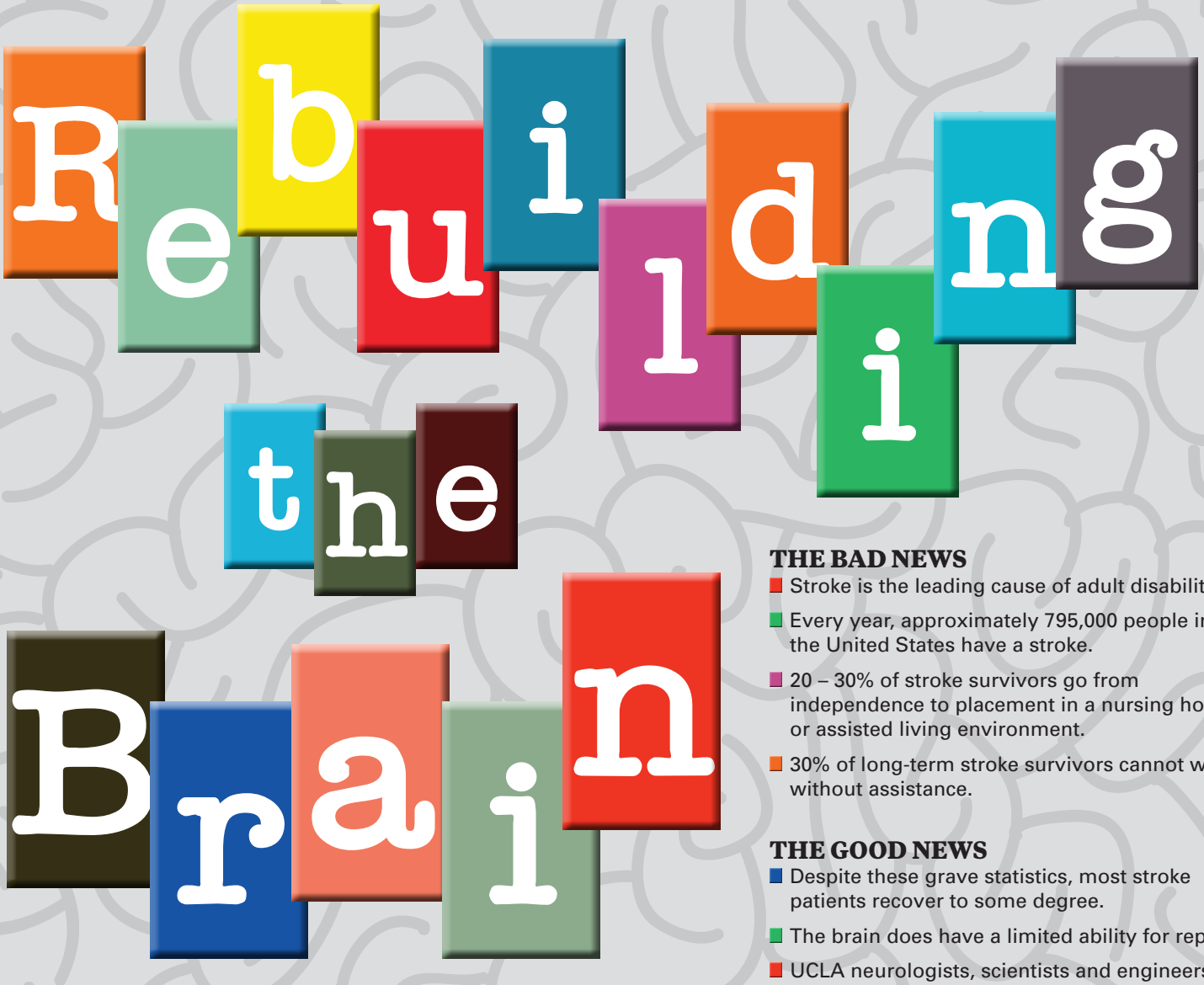
Winter 2014

UCLA Department of Neurology

Partners *in* Discovery



THE BAD NEWS

- Stroke is the leading cause of adult disability.
- Every year, approximately 795,000 people in the United States have a stroke.
- 20 – 30% of stroke survivors go from independence to placement in a nursing home or assisted living environment.
- 30% of long-term stroke survivors cannot walk without assistance.

THE GOOD NEWS

- Despite these grave statistics, most stroke patients recover to some degree.
- The brain does have a limited ability for repair.
- UCLA neurologists, scientists and engineers are making exciting advances in neural repair after stroke.

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UCLA

Chair's Column

John C. Mazziotta, M.D., Ph.D.
Chair, Department of Neurology
Stark Professor of Neurology
David Geffen School of Medicine at UCLA

"I am constantly amazed and energized by the courage shown by patients and their families when facing these tough disorders and their resilience in optimizing their quality of life through the maximum treatments available to them."

Disorders of the nervous system are tough problems. They are tough scientifically because they are very complicated and their root causes have proven to be quite illusive and possibly multi-factorial. These disorders are also tough on patients, their families and friends. The toll of neurological disease is typically played out over a chronic course spanning not just years but decades and, sometimes, entire lifetimes.

By and large, most individuals with neurological disease accept it and continue to contribute significantly to their own lives, their families and to society. Despite the fact that they have an added burden, many--if not most--excel. Some obvious public examples include Franklin Roosevelt, Steven Hawkings, Anne Romney, and many others.

The same sort of resilience also is manifested by our faculty and trainees who toil every day to try to find insights that will produce a better understanding and, ultimately, safer and improved treatments and cures for these disorders. They work under substantial stress to try to obtain funding for research in an economic climate that has become much more harsh in recent years. Success in such endeavors requires extremely long hours, hard work and dedication. Many sacrifice their own compensation for the good of their laboratory efforts and the opportunity to make significant progress.

This issue of our newsletter describes a number of programs where resilience, both on the part of the investigators and the patients, is testimony to their ability to persevere in difficult conditions. I am proud to be associated with both groups and admire them for everything they do every day.

ART OF THE BRAIN
UCLA NEURO-ONCOLOGY PROGRAM

Celebrates 15th Annual Gala "The Art of Healing with Family Traditions"

On September 27, 2014, Art of the Brain celebrated its 15th anniversary with a gala themed, "The Art of Survival – Honoring Our First Responders." The brainchild of co-founder Judi Kaufman, international community activist and brain cancer survivor, Art of the Brain is a patient-driven organization dedicated to raising money for the UCLA Neuro-Oncology Program's brain cancer research, under the direction of Dr. Timothy Cloughesy. The anniversary gala was held in UCLA's Schoenberg Auditorium and Courtyard and featured a festival of gourmet food and wine, along with special performances and a special exhibit of artists paired with brain cancer survivors to express the survivors' stories in various art mediums.

"We celebrate the talent and zest for life of the courageous men and women facing brain cancer and we pay tribute to the unforgettable individuals we have sadly lost," said a radiant Kaufman (center), here flanked by Dr. Cloughesy (left) and Dr. John Mazziotta, Chair of the UCLA Department of Neurology (right). The Johnny Mercer Foundation and Jennifer and Robert Lopata were the event's lead sponsors.

Photo: Tonya Wise

Memory Loss Associated With Alzheimer's Reversed For First Time

Dale E. Bredesen, M.D.

Director, Mary S. Easton Center for Alzheimer's Disease Research at UCLA

Director of Alzheimer's Disease Program

Director of Neurodegenerative Disease Research, David Geffen School of Medicine at UCLA

Since it was first described over 100 years ago, Alzheimer's disease has been without an effective treatment. That may finally be about to change. In the first, small study of a novel, personalized and comprehensive program to reverse memory loss, most of the participants displayed subjective or objective improvement in their memories beginning within three to six months.

The study was conducted by Dr. Dale Bredesen, Director of the Mary S. Easton Center for Alzheimer's Disease Research at UCLA. It is the first study to suggest that memory loss in patients may be reversed — and improvement sustained — using a complex, 36-point therapeutic program that involves comprehensive diet changes, brain stimulation, exercise, sleep optimization, specific pharmaceuticals and vitamins, and multiple additional steps that affect brain chemistry.

Due to memory issues, six patients in the study had discontinued working or had been struggling at their jobs at the time they joined the study; all were able to return to their jobs or continue working with improved performance, and their improvements have been sustained. (The patient in treatment the longest has been receiving the therapy for two-and-a-half years.)

This small study included patients with memory loss associated with Alzheimer's disease, amnestic mild cognitive impairment or subjective cognitive impairment (in which the patient reports cognitive problems). One patient who had been diagnosed with late stage Alzheimer's did not improve. It is important to note, this program focuses on patients with early stage Alzheimer's disease and memory impairment.

The findings are published in the current online edition of the journal *Aging*.

Dr. Bredesen, the paper's author, said the findings are "very encouraging," but he added that the results are anecdotal, and a more extensive, controlled clinical trial is needed.

No single drug has been found to stop or even slow the progression of Alzheimer's, and current therapies have only had modest effects on symptoms. "In the past decade alone, hundreds of clinical trials have been conducted for Alzheimer's, without success, at an aggregate cost of over $1 billion," said Bredesen.

Although other chronic illnesses such as cardiovascular disease, cancer and HIV have been improved through the use of combination therapies, comprehensive combination therapies have not been explored for Alzheimer's and other memory disorders. However, over the past few decades, genetic and biochemical research has revealed an extensive network of molecular interactions involved in the development of Alzheimer's disease.

"That suggested that a broader-based therapeutic approach, rather than a single drug that aims at a single target, may be feasible and potentially more effective for the treatment of cognitive decline due to Alzheimer's," Bredesen said.

The uniform failure of drug trials in Alzheimer's influenced Bredesen's desire to better understand the fundamental nature of the disease. His laboratory has found evidence that Alzheimer's stems from an imbalance in nerve cell signaling. In the normal brain, specific signals foster nerve connections and memory making, while balancing signals support memory loss, allowing irrelevant information to be forgotten. But in people with Alzheimer's, the balance of these opposing signals is disturbed, nerve connections are suppressed and memories are lost.

That finding is contrary to the popular belief that Alzheimer's is caused by the accumulation of sticky plaques in the brain. Bredesen believes the amyloid beta peptide, the source of the plaques, has a normal function in the brain, as part of a larger set of molecules that promote signals that cause nerve connections to lapse. Thus, the increase in the peptide that occurs in Alzheimer's shifts the balance in favor of memory loss.

As a result, Dr. Bredesen thought that, rather than a single targeted agent, the solution might be a multiple-component system approach, in line with the approach for other chronic illnesses.

"The existing Alzheimer's drugs affect a single target, but Alzheimer's disease is more complex. Imagine having a roof with 36 holes in it, and your drug patched one hole very well," he said. "The drug may have worked, and a single hole may have been fixed, but you still have 35 other leaks, and so the underlying process may not be affected much."

Bredesen's approach is personalized to the patient, based on extensive testing to determine what is affecting the brain's plasticity signaling network. In the case of one patient, therapy consisted of some, but not all, of the components of Bredesen's program, including:

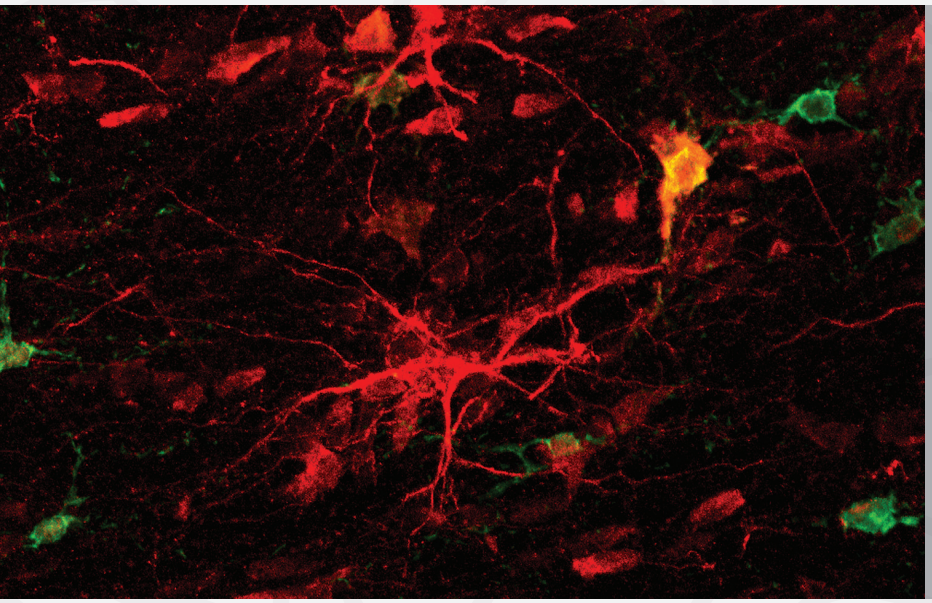
- eliminating all simple carbohydrates, gluten and processed food from her diet, and eating more vegetables, fruits and non-farmed fish meditating twice a day and beginning yoga to reduce stress
- sleeping seven to eight hours per night, up from four to five
- taking melatonin, methylcobalamin, vitamin D3, fish oil and coenzyme Q10 each day
- optimizing oral hygiene using an electric flosser and electric toothbrush
- reinstating hormone replacement therapy, which had previously been discontinued
- fasting for a minimum of 12 hours between dinner and breakfast, and for a minimum of three hours between dinner and bedtime
- exercising for a minimum of 30 minutes, four to six days per week

Bredesen said the program's downsides are its complexity and that the burden falls on patients and caregivers to follow it. In the study, none of the patients was able to stick to the entire protocol. Their most common complaints were the diet and lifestyle changes, and having to take multiple pills each day.

The good news, though, said Bredesen, are the side effects: "It is noteworthy that the major side effects of this therapeutic system are improved health and an improved body mass index, a stark contrast to the side effects of many drugs."

The results suggest that memory loss may be reversed and improvement sustained with the therapeutic program, but Bredesen cautioned that the results need to be replicated. Research funding is needed to continue these types of studies. We are very hopeful with our initial results.

"The current, anecdotal results require a larger trial, not only to confirm or refute the results reported here, but also to address key questions raised, such as the degree of improvement that can be achieved routinely, how late in the course of cognitive decline reversal can be effected, whether such an approach may be effective in patients with familial Alzheimer's disease, and last, how long improvement can be sustained," he said.



Pre-clinical model of stroke: red areas are cells in the brain that form the insulation for its connections (oligodendrocytes); green areas are cells from an adult progenitor (stem cell) normally present in the brain; and yellow area indicates cells that have newly turned from a stem cell into a mature insulating cell in response to the stroke.

Continued from Cover

While occupational therapy and physical therapy are physical-medicine approaches to neurorehabilitation, no current drug therapy exists to promote neural repair after any brain injury. Enter Dr. S. Thomas Carmichael, Professor and Vice Chair for Research and Programs in the UCLA Department of Neurology, Co-Director of the UCLA Broad Stem Cell Research Center, and a leading international expert on brain repair after stroke. Dr. Carmichael has both active laboratory and clinical interests in stroke and rehabilitation—especially in how the brain repairs from injury. His lab studies the molecular and cellular mechanisms of neural repair after stroke and other forms of brain injury with the goal to identify the mechanisms of recovery after stroke.

"We study the cells and molecules that begin to repair the brain after stroke, and how these are limited or incomplete," he says. "A neural repair program is the basic science of regenerative medicine for the brain. We focus on molecular systems and mechanisms of neural repair that might provide for new therapies to promote recovery after stroke. The next step is to apply the new therapeutics for functional recovery in patients."

Carmichael's lab takes a systems biology (computational and bioinformatics analyses of complex biological components—in this case, molecules) approach to the research. "By combining molecular, genetic, cellular and behavioral studies into a systems biology approach to neural repair, we hope to identify new molecular pathways for stroke recovery." The focus of Carmichael's research is on the process of axonal spouting and neural stem cell responses after stroke, as well as on neural stem cell transplantation (see sidebar). He aims to pioneer molecular neurorehabilitation: the delivery of specific molecules that promote brain repair and recovery. "This goal has relevance to stroke and beyond," he says, "as conditions of traumatic brain injury, Alzheimer's and Parkinson's diseases, and multiple sclerosis all are characterized by brain injury and only limited neural repair."

Dr. Carmichael is co-author, with Drs. Andrew N. Clarkson, Ben S. Huang, Sarah E. MacIsaac, and Istvan Mody, of landmark studies that appeared in the journal Nature in 2010 and molecular profiling of molecules that activate new connections in the brain in subsequent years in similarly high-profile journals. They were the first to define the role of brain excitability in tissue recovery, the action of specific brain circuits, and the development of a new pharmacology for neural repair after stroke. "These study results opened a window on how the injured brain functions and generated a more integrative research approach," Carmichael says. "This emerging research approach defines the new connections that grow in the brain after stroke and lead to recovery, identifies how activity in these circuits controls their formation, and then identifies the molecules that trigger this growth program."

In a specific example, after stroke the brain turns on molecular systems that control initial damage but then stay active in later weeks and limit recovery. Dr. Carmichael and his colleagues identified treatments that can modify these systems so that they still actively limit the initial damage, but then are stopped, so that brain recovery occurs to a greater degree.

Recovery means literally learning to move again. Clinical evidence indicates that there is a benefit to forcing the impaired arm or leg to move more during stroke recovery. Current neurorehabilitation therapy utilizes this kind of

patterned behavioral activity, e.g., using the injured arm to perform daily functions such as combing the hair and brushing teeth. The big question for Carmichael is whether this activity triggers new circuits to form in the brain and, if so, whether the molecules that induce these circuits can be identified. "First, we have to determine how this patterned activity alters brain circuitry and then identify the molecules that are active in producing these new circuits," he explains. "Once we have these molecules in hand, we can then develop drugs that stimulate them. We are more than halfway there in this process, as we have identified that the clinical process of overusing an affected limb after stroke does trigger new connections to form in the brain, and these connections are induce by novel molecular pathways."

Following the concept that recovery means learning to move again, Carmichael and his collaborators at UCLA studied molecules that are active in learning, in order to evaluate their role in stroke recovery. The group determined that CREB, which has a well documented role in memory formation in the brain, has a potent effect in promoting recovery. "We turned CREB on inside a small group of neurons after stroke in a specific, movement-related brain area, and found that this could promote full recovery in a stroke model. This defines not only a specific molecule that promotes recovery, but also that this molecule is powerful enough in its effect that it can induce recovery even when activated in a small number of brain circuits," says Carmichael.

"In essence, turning CREB on after stroke rewires the brain. It takes the limited amount of plasticity that is triggered by stroke and amplifies it." An understanding of the neuronal properties that activate brain plasticity is important for the development of new treatments.

"In total, our work has identified several key molecular pathways, such as CREB, that promote or enhance brain repair, but we're still seven to ten years away from taking these basic discoveries and developing new drugs for them," he says. "The next 10 years will be very exciting. The current findings have put us on a course to develop new drugs to promote plasticity and recovery after stroke."

Stem Cell Therapy in Stroke Recovery

There have been tremendous advances in neuroplasticity and neurorepair over the last 15 years and new research programs are applying basic science discoveries toward human therapies. The effect of stem cells on recovery after stroke is being tested at UCLA. Dr. Carmichael has received a grant from the California Institute for Regenerative Medicine (CIRM) to develop tissue bioengineering systems for a stem cell therapy to treat stroke that seeks to circumvent the inability of most stem cell therapies to survive and repair the injured brain. These studies work with adult-derived stem cells (termed induced pluripotent stem cells).

"Stem cell therapies do produce recovery in preclinical models of stroke. However, the major bottleneck is that most of the stem cells die when they are transplanted in the brain," Carmichael says.

He and his team in the Department of Neurology are collaborating with bioengineers and stem cell biologists to use tissue-engineering approaches to enhance the survival of the stem cells when they are transplanted. This team includes Drs. Tatiana Segura and William Lowry. The multidisciplinary group has developed biopolymer-based hydrogels—gels made of natural body proteins—in the form of pouches to house the stem cells for transplantation into the brain.

According to Carmichael, stem cells like to be in a particular microenvironment and they happen to like blood vessels. The stroke cavity is normally a hostile site for stem cell transplantation. It is inflamed and lacks blood flow, and most transplanted cells die when placed into it. However, because it is a cavity that can accept a large-volume transplant and is directly adjacent to a major site of neural repair in stroke, it is an ideal site for stem cell transplantation.

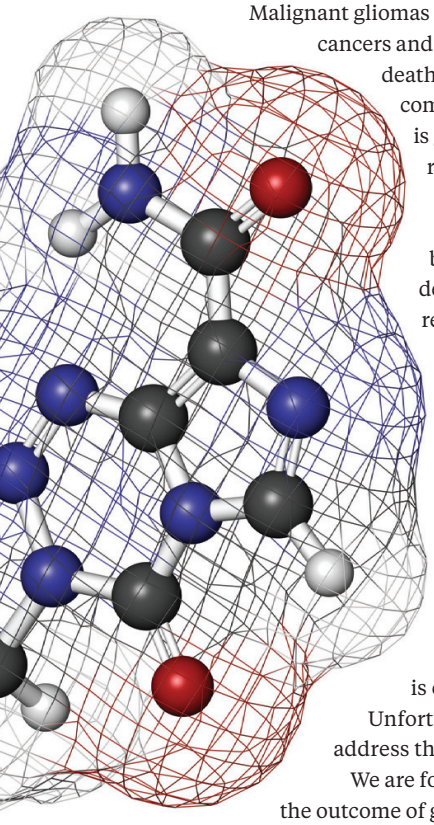
Carmichael and his team have shown that the biopolymer hydrogels, which provide an ability to link functionally important molecules for stem cell survival, allow stem cells to be transplanted directly into the stroke cavity by creating a pro-growth matrix where the stem cells feel at home. "The gel creates its own niche in the cavity," Carmichael says, "and in the preclinical model, this allowed the stem cells to survive and thrive in the brain." This bioengineering approach provides a direct pathway for translation to patients in future studies.

UCLA NEURO-ONCOLOGY PROGRAM:

MEETING THE CHALLENGE OF GLIOBLASTOMA

by Timothy Cloughesy, M.D., Director, UCLA Neuro-Oncology Program

"The UCLA Neuro-Oncology program has committed to evaluating numerous well designed and cutting-edge clinical trials that approach killing the tumor or controlling it through a variety of mechanisms."



Malignant gliomas are among the most lethal of human cancers and the second leading cause of cancer deaths among young adults. The most common of the malignant gliomas is glioblastoma. Although this is a relatively rare tumor, compared to lung, breast and prostate cancer, its ability to infiltrate and damage the surrounding brain makes it a particularly devastating tumor. Complete surgical removal is impossible.

Glioblastoma also is one of the most resistant tumors to radiation and chemotherapy, which accounts, in part, for the poor survivorship rates. What's more, while the best way to treat any cancer is either to prevent it or catch it early, this approach is unavailable to glioblastoma patients at present. We do not know how or what causes this tumor to form and the tumor is only detectable when fully formed. Unfortunately, this means that we can only address the tumor once it is identified.

We are focusing all of our efforts on changing the outcome of glioblastoma. The UCLA Neuro-Oncology program has committed to evaluating numerous well designed and cutting-edge clinical trials that approach killing the tumor or controlling it through a variety of mechanisms. These include: molecularly guided small-molecule and antibody-targeted therapy, gene transfer therapy with viruses, and immune- based therapies utilizing antibodies to release the native inhibitory effects of the immune system preventing tumor cell kill and control. We offer these trials to any and all patients with glioblastoma with the goal of rapidly defining which populations will achieve the best possible results. We work to refine and improve these results toward a cure.

UCLA CLINICAL TRIALS

UCLA MOLECULARLY GUIDED TRIALS

Our goal is to identify a molecular target in the brain tumor that is responsible for the growth and progression of the tumor and then to treat it with a specific inhibitor.

Target:

- EGFR: This is the most common molecular abnormality in glioblastoma, present in more than 50 percent of patients. Currently, the following molecularly guided trials are being offered to patients with EGFR-mutated tumors:
- Neratinib: Small molecule targeting amplified EGFR-recurrent malignant glioma
- AMG595: Antibody drug conjugate against EGFR vIII-recurrent malignant glioma
- IDH1 and IDH2: These molecular abnormalities are common in lower grade gliomas, seen predominantly in young adults. Currently the following molecularly guided trials are being offered to patients with IDH-mutated tumors:
- AG120 and AG221: Small molecule targeting IDH mutated recurrent malignant glioma
- FGFR: This is a rare but very targetable mutated receptor in glioblastoma.
- BGJ398: Small molecule targeting FGFR mutated recurrent malignant gliomas
- Other Targets: Many tumors have commonly activated molecular pathways leading to growth and progression. Although not directly mutated, these pathways can be targeted to slow or stop tumor progression. The following agents are used either alone or in combination to treat glioblastoma:
- GDC0084: Small molecule targeting PI3k/TOR Kinase in recurrent malignant gliomas
- MLN0128: Small molecule targeting TOR Kinsase in surgically accessible recurrent malignant gliomas
- AMG386: Antibody against Tie2 and used with bevacizumab in recurrent malignant gliomas.

UCLA GENE TRANSFER THERAPY

This form of clinical trial utilizes genetically engineered viruses to infect and deliver a gene of choice to the tumor that will cause it to die or become susceptible to death from another treatment.

Gene-transferred Cytosine deaminase:

- Toca 511: replication competent retrovirus transferring cytosine deaminase to recurrent malignant glioma cells to create susceptibility to orally administered 5FC

UCLA IMMUNE-BASED THERAPIES

These trials use therapies that allow the immune system to kill tumor cells by releasing factors , called Immune Check-Point Inhibitors, which inhibit the immune system from successful tumor control. UCLA offers the following immune-based therapies:

- Nivolumab and Ipilimumab: These are antibodies against PD-1 and CTLA-4 that release the inhibitory effects of the immune system to attack malignant glioma.

Meet Our Fellows

Maisha Tamar Robinson, M.D., M.S.

Pictured here on The Great Wall of China:
Dr. Nuriya Robinson (left) sister of **Dr. Maisha Tamar Robinson** (right)

UCLA Neurology Fellow Maisha Robinson, whose focus is neuro-palliative care, is all about faith, hope and healing, and has been since childhood in Memphis, Tennessee, where her father is a full-time pastor as well as an internist who works in public health. Her mother, who has had a career in hospital administration, is co-pastor of the church. Her parents' backgrounds in medicine and ministry clearly inspired Dr. Robinson and her identical twin sister, who is an OB/GYN in global and women's health in Chicago and sub-Saharan Africa.

It was during residency at the Mayo Clinic in Minnesota that Dr. Robinson became interested in pursuing a career in neuro-palliative care. "There was an evident, yet frequently unmet need to focus on comfort and function throughout the stages of chronic, neurological disease," she says.

After completing a one-year hospice and palliative medicine fellowship at Memorial Sloan Kettering Cancer Center, where she managed symptoms of terminally ill patients and learned the principles of end-of-life care, Dr. Robinson completed a neurohospitalist fellowship at Mayo Clinic Florida, prior to coming to UCLA. She began a Health Services Research Fellowship through the Robert Wood Johnson Foundation Clinical Scholars Program in 2013, and chose UCLA because of what she felt she could learn from Dr. Barbara Vickrey, whose work focuses on improved patient health outcomes.

One project explores strategies to improve end-of-life care-planning among African Americans. "I'm partnering with churches in L.A. to develop an intervention to improve end-of-life care planning in an effort to reduce healthcare disparities at the end of life in a cohort of people who are at high risk for stroke, dementia, and other neurological diseases," Dr. Robinson says. "We need to promote the concept of 'dying well'—to make it relatable and to present it in an acceptable way."

Dr. Robinson's current clinical work is in ALS, and she enjoys UCLA's multidisciplinary effort, from physicians, occupational and physical therapists to dieticians and social workers. She believes that the medical community and family members make a difference at the end of life. "I try to identify the legacy people wish to leave behind as their family comes together in support. People are so appreciative—that's what motivates me."

The Power of Philanthropy

Steven C. Gordon Family Chair in Parkinson's Disease Research

From left: UCLA Chancellor Gene Block; Dr. John Mazziotta, chairman of the Department of Neurology; Mr. Steven Gordon and Dr. Carlos Portera-Cailliau

"Philanthropy was part of my upbringing. I grew up watching my mother make five-dollar gifts to whoever needed them," says Steven Gordon, whose family foundation—The Steven C. Gordon Family Foundation—has pledged a gift to the Department of Neurology in the David Geffen School of Medicine at UCLA to establish the **Steven C. Gordon Family Chair in Parkinson's Disease Research**. The Gordon family graciously made the donation in memory of Steven Gordon's father, Benjamin Gordon, who was afflicted with Parkinson's disease.

Carlos Portera-Cailliau, M.D., Ph.D., professor in the Movement Disorders Program in the Department of Neurology, has been selected as the inaugural chair holder. This important philanthropic contribution will provide long-term teaching and research support for distinguished faculty in the Department of Neurology.

What areas inspire Gordon's philanthropic passion? "We support childhood and adult education, and medical research in areas where we've lost friends," Gordon says. "I enjoy making sure today's geniuses have the opportunity to see their research come through."

Gordon believes philanthropy has always been a good investment, "even if it's just feeling good about what you did. If you're lucky enough to be given more than you need, you want to be sure that you can say you did something good with it."

According to Gordon, his decisions about giving happen quickly. "I follow my heart, and I'm almost always influenced by the events around me."

The Department of Neurology celebrated the Gordon family's gift and Dr. Portera-Cailliau's appointment on May 19, 2014 with both Mr. Gordon and Dr. Portera-Cailliau in attendance, along with their families and friends.

Volunteer Faculty

Philip Ente, M.D.

Dr. Ente and his wife Angela

Dr. Philip Ente didn't begin his career as a neurologist. A graduate of the University of Pennsylvania, he was a neuroscientist whose specialty was how brain cells process odors. He traveled to Paris to study with an expert in taste and smell, and in the process developed connections with great chefs. Eventually, he was able to work at Maison Troisgros, one of France's finest restaurants.

While in France, he was advised to get out of the field due to anticipated funding problems. Thus, he wound up in medical school at the University of Paris, while continuing to work in cuisine and science. After finding that the advice he received was correct, he entered a residency program in neurology at Hahnemann Medical College, now Drexel University College of Medicine. After completing his residency and fellowship, he went into academic medicine at Jefferson Medical College, now Sidney Kimmel Medical College.

Subsequently, Dr. Ente moved to California—in particular, the Santa Ynez Valley (think wine)—where he set up a private practice in general neurology. To maintain his connection to academia, he became a volunteer faculty member at UCLA. While dining at the French restaurant L'Orangerie in Los Angeles, he encountered a waiter with whom he had briefly crossed paths in France. When Dr. Ente explained to the waiter that he had previously worked at Troisgros, the owner of the restaurant came over and immediately offered him a job . This led to dual-purpose trips to Los Angeles: to combine teaching at UCLA with a day of working in the restaurant.

"I enjoy teaching residents, so I don't mind driving monthly to teach residents in clinic," Dr. Ente says. "I specialize in general clinical neurology and I like to help the residents use their skills to diagnose brain illnesses. It's important to teach them to use their minds using their five senses and intellect—not to only rely on machines. I want them to think, to look at a patient and process what they're seeing."

He gives a great example of what can happen when a patient isn't assessed accurately. "I was called into the hospital to see a mildly demented patient who was in isolation due to infection. All the tests were inconclusive. It turns out that the patient was deaf, but because all the medical staff were wearing masks in isolation he couldn't read lips. They just run tests and don't consider the whole person."

Dr. Ente maintains his private neurology practice, and still lectures occasionally on the neurology of wine.

Why I Do This

Christian Herrmann, Jr., M.D.

Professor Emeritus of Neurology
David Geffen School of Medicine at UCLA

" I've seen tremendous development in medicine. After all, I came into it before sulfa drugs and penicillin."

Dr. Christian Herrmann, Jr., has spent a lifetime connecting things, starting with the old-fashioned plug he used to connect his mother's curling iron when he was a boy in Lansing, Michigan. "I was always interested in electricity," he says. "I was a stagehand in junior high and I did the Christmas lighting for my church when I was a teenager. I devised a system to move the Star of Bethlehem from the back to the front of the church ahead of the Wise Men."

It is no wonder, then, that Dr. Herrmann became a specialist in electroencephalograpy (EEG), the recording of electrical activity along the scalp to measure the voltage fluctuations from ionic current flows within the neurons of the brain. He also specialized in the care of patients with myasthenia gravis, a chronic autoimmune neuromuscular disease characterized by varying degrees of weakness of the skeletal (voluntary) muscles of the body.

In 1941, Dr. Herrmann entered medical school at the University of Michigan, where he was inspired by one of his neuroanatomy professors, Elizabeth Caroline Crosby, who became the first woman to receive full professorship at the University of Michigan Medical School and was the third author of the classic textbook, The Comparative Anatomy of the Nervous System of Vertebrates. He remembers her as "humble but knowledgeable."

While Dr. Herrmann was in medical school, his cousin (who later became a successful gasteroenterologist) was diagnosed with multiple sclerosis and Dr. Herrmann's interest in the nervous system intensified. "This was the part of medicine that interested me and it needed some help." Plus, the EEG and the electrocardiogram (EKG) were evolving," he explains.

On December 11th of that year, the United States entered World War II and Dr. Herrmann's medical education was sped up. "Medical schools ran year-round. The Army and the Navy both had medical programs. I was called back into the Navy and was sent to the Naval Medical Center San Diego, where I had to serve for two years. In July of 1944, I graduated from medical school and I had an internship and completed part of my medical residency at Henry Ford Hospital in Detroit, MI ." he says.

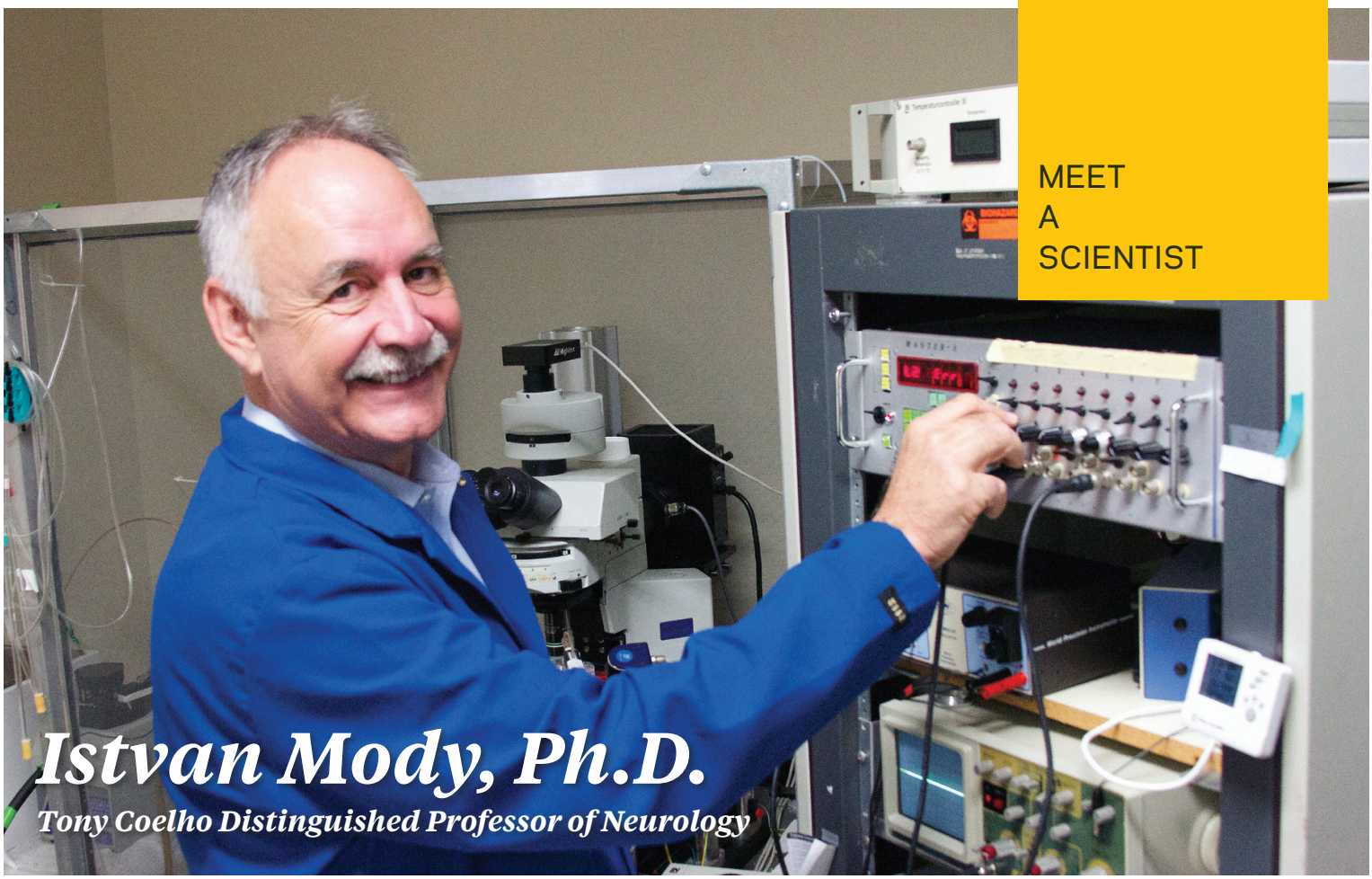
After the war, Dr. Herrmann was accepted for residency at the Neurologic Institute of New York at Presbyterian Hospital. He trained under Dr. Houston Merrit, one of the pre-eminent academic neurologists of his day and dean of the Columbia University College of Physicians and Surgeons from 1958 to 1970.

"Dr. Paul Hoefer from Vienna was on our faculty. He opened one of the first electroencephalography (EEG) laboratories in the U.S. to study the diagnostic value of brain waves," Dr. Herrmann says. "I read EEGs at night. It was the time of iron lungs and polio and myasthenia gravis. I slept in an adjacent room to take care of these patients."

In 1951, UCLA was establishing a division of neurology. Dr. Augustus Rose was the first chief and when Dr. Herrmann came to UCLA in 1954, he was the second faculty member. In Dr. Herrmann's book, *History of Neurology* at UCLA, he recounts that he traveled to Harbor Hospital on a number of occasions to make rounds with medical residents. (Harbor General Hospital, now UCLA-Harbor Medical Center, began as the station hospital at the Los Angeles port of Embarkation and was sold by the U.S. Army as war surplus to the Los Angeles County Department of Charities. Harbor General Hospital opened one month later and in 1951 affiliated with the University of California as a teaching hospital for the UCLA School of Medicine.) Dr. Herrmann recalls that the rounds took place in barracks and that the trip from Westwood to Torrance was even more arduous in those days before the freeway than it is now.

"The UCLA hospital in Westwood hadn't opened; they used Wadsworth (now the VA West Los Angeles Medical Center) and a small research area in a building at the VA. Marion Davies, actress and friend of UCLA, owned a block of land at Olympic and Barrington on which was a pediatric hospital that was given to the UCLA Department of Pediatrics. Neurology was allowed to have space there for an EEG laboratory if we would do EEGs on children. Neurology also had a clinic in that building."

Dr. Herrmann, who still comes to campus weekly to do credentialing and to share his knowledge with the Department's trainees, has been at UCLA for 60 years. "I've seen tremendous development in medicine," he says. "After all, I came into it before sulfa drugs and penicillin." A conference room in the Reed Neurological Research Building at UCLA is named for this learned and caring neurologist who has treated thousands of patients and mentored hundreds of residents, fellows, and medical students. His contributions to medical education in the UCLA Department of Neurology are legendary.



MEET
A
SCIENTIST

Istvan Mody, Ph.D.

Tony Coelho Distinguished Professor of Neurology

"It is so easy to be doing creative endeavors in software, or to come up with a design for an Apple app. But the brain is the ultimate challenge,"

"It is so easy to be doing creative endeavors in software, or to come up with a design for an Apple app. But the brain is the ultimate challenge," says Dr. Istvan Mody, who has been at UCLA since 1995.

Dr. Mody's research focuses on communication between nerve cells in the brain: synaptic transmission. "Our quest is to understand how long-term alterations in the excitability of nerve cells and circuits are responsible for offsetting the frail balance between excitation and inhibition," he says. In layman's terms, tipping this balance—either acutely or chronically—results in the nervous system showing signs of abnormal activity leading to specific neurological and psychiatric disorders, such as epilepsy, Alzheimer's disease, schizophrenia, or depression.

His primary research is to study how inhibition works in the brain. "Eighty percent of the nerve cells in the brain are excitatory and 20 percent of them are inhibitory; the latter do 80 percent of the job," Dr. Mody says. "These inhibitory cells are like a telephone switchboard, grouping cells into circuits." Basically, when the balance between excitation and inhibition is disrupted, cells start to behave abnormally, leading to certain brain disorders. "When the brain experiences deficits in inhibitory cell function; network connectivity suffers. Abnormal connectivity is a characteristic of brain disorders," he explains.

"In both the healthy and the diseased brain our aim is to study and understand synaptic transmission, the fundamental means of communication between nerve cells in a circuit. In addition to receptors found at the synapse, many receptors are scattered over the entire surface of the neurons, and these we call extrasynaptic receptors. Their activation by low levels of ambient neurotransmittors found in the space surrounding the cells is very important for certain brain functions. Our present research focuses on scientific models of epilepsy, Huntington's disease, stress, alcoholism, premenstrual dysphoric disorder (PMDD), and postpartum depression. We also record from human brain tissue surgically removed for the treatment of epilepsies," Dr. Mody says. "We utilize many experimental approaches. Studying the fundamental mechanisms responsible for the altered synapses and circuits will lead to novel therapies for a number of devastating neurological and psychiatric disorders."

The Mody Lab studies the process of how epilepsy develops in the normal brain. According to Dr. Mody, there are many causes of epilepsies. "Some people develop epilepsy after a head injury, for instance, and some don't. We want to find biomarkers that will help us determine who will develop epilepsy and who will not. Presently, we suspect that some very high-frequency neuronal oscillations—after an insult to the brain—are instrumental in converting a normal brain to an epileptic brain," he says.

With respect to Alzheimer's disease, Dr. Mody's lab uses a scientific model to determine if abnormally heightened neuronal activity is responsible for the release of the amyloid beta protein that is a key event in the early development of the disease. "Can we dampen the excitability and halt the progression of the disease? Will we be able to use this as a therapeutic intervention in the future?" These are questions he hopes to answer.

Dr. Mody believes science is all about "the discovery of new things. All this basic research will help us to cure disease," he says.

Crusading for Brain Cancer Research

Cranium Crusaders, an organization that raises awareness and support for brain cancer research, held its eighth annual fundraiser in Long Beach on September 18th. Cris Zavaleta and Cindy Atkinson, who met at UCLA where their late husbands, Hank Zavaleta and Tom Atkinson, were being treated for brain cancer, founded the organization. Both men had been diagnosed with glioblastoma multiforme, the most common and aggressive malignant primary brain tumor. Sadly, the women lost their husbands to the disease, but a friendship and shared desire to find a cure were born.

The "Cranium Crusaders" have raised more than $450,000 over the years. All of these funds have been dedicated to the brain cancer research of Dr. Timothy Cloughesy.

From left: Cris Zavaleta, UCLA's Dr. Timothy Cloughesy, and Cindy Atkinson

Race Car Driver John Paul, Jr., Honored at Race to End Huntington's Disease

Legendary race car driver, John Paul, Jr., was honored at a special fundraiser at the Sebring International Raceway in Sebring, Florida. The event was hosted by Historic Sportscar Racing, Ltd., to raise money for Huntington's disease (HD) research at UCLA. John, who retired from professional racing in 2001 after noticing that the telemetry of a car he was testing did not match what he thought his feet were doing in the car, is now a passionate advocate for HD research. During the event, lead singer of AC/DC, Brian Johnson, and drivers Brian Redman, Dorsey Schroeder, Hurley Haywood, Jim Pace, John Fergus, Rob Dyson and Roger Mandeville raced a Porsche 935 JLP HD1. Thanks to John, his fans, and the motorsports community, generous proceeds were directed to HD clinician researcher Dr. Susan Perlman, Director of the UCLA Huntington's Disease Center.

Pedal for a Cause

The 3rd Annual Tour de Pier, scheduled for May 17, 2015, is a unique fundraising event that brings one of the hottest indoor fitness activities – spinning – to the gorgeous outdoors of the iconic Manhattan Beach Pier. Whether you're a solo rider or a team, the fundraising minimum for each bike is $500. Tour de Pier benefits three outstanding charities, one of which is the Uncle Kory Foundation, a Neuro-Oncology Program donor. The Uncle Kory Foundation (UKF) is a non-profit, tax exempt 501(c)(3) organization inspired by the life of Kory Lewis Hunter. The UKF is dedicated to funding brain cancer research, specifically Glioblastoma. For more information, visit TourDePier.com.

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In Memoriam

The Department of Neurology is sad to report the passing of a very supportive donor.

Arthur E. Schramm

The UCLA Department of Neurology was saddened by the loss of Arthur E. Schramm, 72, attorney and longtime senior executive with shopping center owner and developer Westfield Group. Mr. Schramm died March 18, 2014 at his home in Los Angeles, California. His business successes were significant, but so were his community endeavors. While Mr. Schramm served on other boards, he was especially committed to the battle against Multiple Sclerosis. He served on The National MS Society Board Southern California Chapter and recently helped found the Tom Sherak MS HOPE Foundation (www.mshopefoundation.com).

A talented attorney noted for his wisdom, innate knowledge of the retail real estate industry and legal expertise, Mr. Schramm was born in Flushing, New York and grew up on Long Island. Survivors include his wife of 48 years, Britta Schramm; two children, including Kimberle Schramm of Los Angeles; and Katrina Schramm-Dorsey of Stamford, Connecticut; son-in-law Riccardo Conti of Los Angeles, and six grandchildren.

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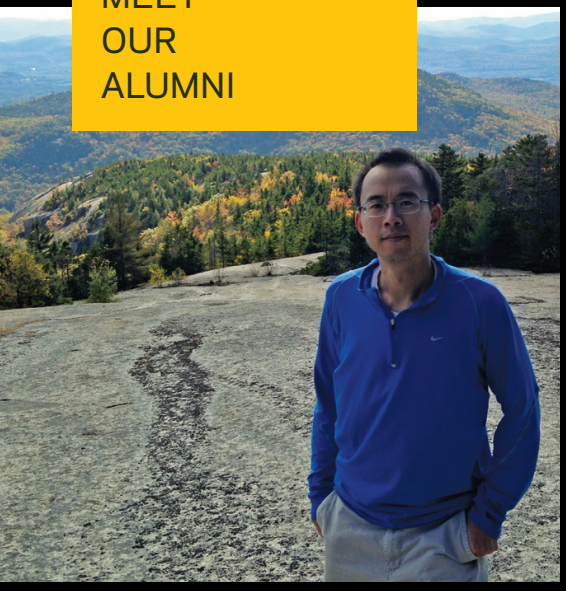

Michael G. Ho, M.D.

Alumni of the UCLA Department of Neurology utilize their training in a variety of different ways. While many treat patients, others apply their expertise to research and academic medicine.

It was Dr. Michael Ho's medical school experience with neurological patients at UCSF that inspired him to specialize in neurology. "The neuro patients were the most fascinating, plus the field is so promising. There are so many new medications, technologies and therapies—the new developments are very exciting."

Dr. Ho is a neurohospitalist with subspecialty in epilepsy who currently practices in Boston, Mass. After graduating from UCSF Medical School in 2008, he chose UCLA for his residency because he felt it offered the best training. "UCLA has fantastic faculty, plus a three-hospital system for training, so you get different faculty and see diverse patient populations. In real life, you will encounter all types of patient groups, such as in Olive View and the West L.A. VA, and the three different hospitals prepare you for real-life medicine," he says. "With the county hospital experience, you got more ownership of patients and more control so there was the perfect balance of supervision and autonomy for patient care at UCLA. I currently work mainly at Carney Hospital in Boston, which is an affiliated teaching hospital of Tufts School of Medicine, and it has a county-type patient population, so I am really grateful to have trained at a place like UCLA, which prepared me for this experience."

"I really appreciate the resources and easy accessibility of mentors at UCLA. I did a research poster for the American Academy of Neurology with Dr. Jeff Saver in stroke, who was a fantastic clinician research mentor and learned EEGs with Dr. Jason Soss in epilepsy, to name just a few of the wonderful mentors. Dr. Mazziotta was incredibly helpful for career mentorship and finding jobs, even after I completed the program," Dr. Ho says.

Dr. Ho left Los Angeles to complete a fellowship in epilepsy at Massachusetts General Hospital in 2013. He has been practicing medicine in the Boston area for three years, and serves on the Neurology faculty of Tufts University Medical School.

No stranger to New England, Dr. Ho graduated from Yale University with a major in Biochemistry. He completed his undergraduate studies at Yale University.

"L.A. is home, though," says Dr. Ho. "I grew up there and I hope to end up there."