BRAIN TUMORS

Multipronged Approach Takes Aim at Malignant Brain Tumors

Researchers and clinicians at UCLA are making progress in their efforts to find effective treatments for malignant brain tumors — in part through a strategy that recognizes multiple options are needed coupled with the ability to predict which therapies will most benefit each specific patient. “Thanks to our work in molecularly and genetically classifying these tumors, we have a better appreciation that there are different subtypes of the disease, and not all types can be treated equally,” explains Linda Liau, MD, PhD, director of the UCLA Brain Tumor Center.

Malignant gliomas, the most common of which is glioblastoma, are among the most lethal cancers and the second-leading cause of cancer death among young adults.

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UCLA Clinical Updates
Learn about the Latest Advances from UCLA

Adult Epilepsy Program
The recent introduction of two innovative surgical procedures at UCLA's Adult Epilepsy Program offers adults with debilitating seizures greater access to safe and effective treatments.

Improving Heart-Failure Management
The CardioMEMS HF System is the first implantable hemodynamic monitoring device for heart failure approved by the Food and Drug Administration.

UCLA Aortic Center
The UCLA Aortic Center offers a comprehensive slate of options for patients with all stages of aortic disease, from traditional open surgery to the latest minimally invasive repairs.

Catheterization Advances for Congenital Heart Disease
Minimally invasive catheter-based interventions are associated with less risk and easier recovery and now are considered the standard of care in treating all patients with congenital heart disease.

Targeting COPD
UCLA's Division of Pulmonary and Critical Care Medicine offers the latest treatments for COPD, including therapies available through clinical studies not offered at most centers.

UCLA Cystic Fibrosis Program
The Cystic Fibrosis Program at Mattel Children's Hospital UCLA offers comprehensive clinical care, research and educational support for infants, children, adolescents and adults with cystic fibrosis.

Early Kidney Disease Detection
A unique program in UCLA's Division of Pediatric Nephrology offers specialized care for children with renal and/or urinary-tract abnormalities beginning when an abnormality is detected in utero.

Full-Service HIV/AIDS Care, Education and Research
The Care-4-Families program at Mattel Children's Hospital UCLA provides a single point of contact and a broad spectrum of comprehensive, family-focused services for HIV-infected newborns, children, adolescents, pregnant women and mothers and HIV-exposed infants.

Continuing Medical Education: Save the Date

UCLA Brain Attack! '16 Stroke Symposium
When: Saturday, May 7, 2016
Where: UCLA Carnesale Commons
What: The UCLA Comprehensive Stroke Center presents the 21st annual UCLA Brain Attack! symposium, covering the practical, clinical aspects of stroke prevention, diagnosis and treatment. The course will include stroke risk factors, diagnostic testing and medical and interventional therapy.

This course is approved for AMA PRA Category 1 Credit.

Cost: $200 – Early Registration
$225 – Registration after Friday April 15, 2016
$150 – UC Faculty and Staff
Register: Go to cme.ucla.edu/courses and select “UCLA Brain Attack! '16 Symposium”

News from UCLA Health

How obstructive sleep apnea damages the brain
UCLA researchers have reported the first evidence that obstructive sleep apnea contributes to a breakdown of the blood-brain barrier that plays an important role in protecting brain tissue. The damage to the brain that can result from obstructive sleep apnea can lead to high blood pressure, depression, memory loss and anxiety, as well as contribute to stroke, diabetes, loss of testosterone and endocrine-related problems.

Department of Neurosurgery ranked No. 2
The UCLA Department of Neurosurgery ranks No. 2 in the nation in scholarly research, according to a paper published in the Journal of Neurosurgery that rated the academic publishing output of faculty at 103 American neurosurgical residency programs from 2009 to 2013.

Why children’s recovery times vary after traumatic brain injury
New research by UCLA scientists and colleagues suggests that damage to the fatty sheaths around the brain’s nerve fibers — and not the severity of the injury itself — explains why some youngsters bounce back quickly from traumatic brain injuries while others suffer devastating side effects for years.
UCLA Partnership Will Expand Rehab Services for Los Angeles

UCLA Health is partnering with Cedars-Sinai Medical Center to dramatically expand the availability of acute rehabilitation services in Los Angeles. The California Rehabilitation Institute, scheduled to open early next year, will be a freestanding, 138-bed acute rehab hospital in Century City that will more than triple the number of beds currently available for rehabilitation at the two facilities. In addition to the combined expertise of the two prominent healthcare organizations, the effort includes a managing partner, Select Medical, which treats more than 60,000 patients a day at its rehabilitation facilities around the country.

“This joint venture between UCLA Health and Cedars-Sinai will not only significantly expand the availability of rehabilitation services in the community, but through a consolidated, coordinated and experienced group working under the same roof, we will be able to achieve a level of quality and specialization of services that neither organization could have provided alone,” says David N. Alexander, MD, medical director of the California Rehabilitation Institute and UCLA's Neurological Rehabilitation and Research Unit.

Featuring the latest treatment protocols and equipment, along with 24-hour availability of medical care, the specialized rehabilitation hospital will have all private rooms, with a therapy gym on each floor. The institute will admit patients from both UCLA and Cedars-Sinai, as well as other hospitals and skilled-nursing facilities and, occasionally, directly from patients’ homes. About half of the patients will be recovering from neurological diagnoses, including stroke, traumatic brain injury, and spinal cord injury, Dr. Alexander says.

Patients at the facility will follow an intensive regimen, including treatment by various rehabilitation specialists each day. On-site staff and physical, occupational, speech and recreation therapists, as well as social workers, psychologists and neuropsychologists, will work with physicians to develop an individualized program designed to meet each patient’s rehabilitation goals while ensuring that any comorbid or concurrent medical problems are addressed.

“It is extremely important to have acute rehabilitation available to patients, and there has been a major unmet need,” Dr. Alexander says. “Hospital stays are shorter than in the past, and as improved therapies have become available, we are now seeing more people recover who would have otherwise remained more significantly impaired. These patients often need assistance to improve their mobility and their ability to perform basic daily activities. Acute rehabilitation improves recovery, reduces morbidity and mortality, increases the likelihood of home discharge and allows patients to become more independent.”
Progress is being made to treat malignant brain tumors using a strategy that combines multiple options with the ability to predict which therapies will most benefit specific patients. Next-generation sequencing techniques make it easier to identify molecular targets and direct patients to appropriate clinical trials.

STORY HIGHLIGHTS

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Next-generation sequencing techniques make it easier to identify molecular targets and direct patients to appropriate clinical trials.

The ability of glioblastoma to infiltrate and damage the surrounding brain makes it a particularly devastating tumor, in which complete surgical removal is impossible,” says Timothy Cloughesy, MD, director of the UCLA Neuro-Oncology Program at Ronald Reagan UCLA Medical Center. “It also is one of the most resistant tumors to radiation and chemotherapy. And because we don’t know how or what causes this tumor to develop, and it is detectable only when fully formed, we can’t prevent it or catch it early.”

Given the absence of a single effective therapy, UCLA’s efforts to change the outcomes of glioblastoma focus around evaluating and offering many promising therapies in clinical trials that approach killing or controlling the tumor from a variety of fundamental mechanisms. These include molecularly guided therapies — drugs that exploit information obtained by genetically profiling tumors then targeting specific molecular abnormalities found in a subgroup of patients; therapy that uses genes to deliver viruses to the tumor; and immune-based therapies, including tumor vaccines, to activate the patient’s native system against the cancer.

With next-generation sequencing techniques, it is now much easier to identify molecular targets than even a few years ago, Dr. Cloughesy notes. Nearly every patient’s tumor can be sent for sequencing, and then the patient can be assigned to a clinical trial based on the abnormalities found. “The drug companies are working with us to develop very focused agents,” Dr. Cloughesy says. “A drug might focus on a mutation found in only about 3 percent of glioblastomas, but if you can find something of great benefit for that small group of patients, that is significant. It’s a step toward personalized medicine.”

“Thanks to our work in molecularly and genetically classifying these tumors, we have a better appreciation that there are different subtypes of the disease, and not all types can be treated equally.”

The UCLA Neuro-Oncology Program offers trials of drugs that target various mutations of the epidermal growth factor receptor (EGFR), the most common glioblastoma abnormality. The program also has trials of compounds targeting IDH-mutated tumors, as well as drugs taking aim at tumors with molecular pathways that, when activated, are known to contribute to tumor growth and progression.

When brain-tumor researchers are asked about the most promising areas for future study, both genetic profiling and immunotherapy consistently top the list, Dr. Liau says. UCLA is at the forefront of both fields. UCLA’s immune-based therapies currently in clinical trials use treatments that enable the immune system to kill tumor cells by targeting factors, known as immune checkpoint inhibitors, which impede the immune system from successful tumor control. In addition, Dr. Liau and her colleagues developed the first dendritic cell (DC)-based vaccine, known as DCVax, for brain-tumor patients to be used in humans. “The problem with brain tumors is that, despite treatment, they tend to come back,” Dr. Liau says. “The promise of immunotherapy and vaccines is that they can hopefully prevent the cancer from returning.”

Malignant gliomas are among the most lethal cancers and the second-leading cause of cancer death among young adults.
Fifteen years ago, most experts believed it was not possible, because of the blood-brain barrier, for patients to mount an immune response to brain cancers. “We’ve found that these tumor vaccines can not only mount an immune response, but that a significant percentage of patients have had no recurrence for more than 10 years now, which for glioblastoma is very rare,” Dr. Liau says.

Currently, Dr. Liau and her colleagues at the UCLA Brain Tumor Center have begun to publish on genetic profiling and biomarkers to determine which patients are likely to fare well on immunotherapy. “Right now, we’re treating everyone the same way,” she says. “I am hopeful that in the next few years, we will have biomarkers that we can test either in the patient’s blood or via imaging. With these biomarkers, we will know in advance which patients will respond, and for those who won’t, we will work on other ways to treat the tumor.”

Many of the ongoing clinical trials for brain tumors grew out of studies that began at UCLA, which has a strong research base in each of the four major treatment targets: immunotherapy and tumor vaccines; alterations in cancer-cell metabolism; going after cancer stem cells to make them more sensitive to treatment; and taking aim at the IDH1 mutation, which is found in a subtype of glioblastomas and associated with significantly different tumor behavior.

“At UCLA, we are part of both a leading academic institution and a leading treatment center, and we have taken advantage of that by developing close working relationships along the continuum from the bench to the bedside,” Dr. Liau says. “Our basic scientists meet regularly to discuss what’s going on in the laboratories, and we share that information with the clinicians. This is particularly important in the brain tumor field, and it has been a key to our success in bringing new therapies to fruition.”
Neurocritical Care

ICU of the Future Improves Care for Neurocritical Patients

The emergence of neurocritical care as a recognized subspecialty over the last two decades has led to the development of comprehensive centers for neurological emergencies where significantly better outcomes can be achieved than from general intensive care units. Paul Vespa, MD, professor of neurosurgery and neurology at the David Geffen School of Medicine at UCLA and director of UCLA Health’s Neurocritical Care Program — which has received the center of excellence designation — discusses the state of the field.

How has neurocritical care evolved in recent years?

Neurocritical care has grown significantly as a subspecialty in the 21st century, with the development of professional certification, accreditation for neurocritical-care fellowship programs, and the recent recognition by the nonprofit medical quality watchdog Leapfrog Group that neurocritical-care specialists are essential for critically ill brain patients. We used to consider neurocritical care to be a postoperative ward where patients would go just to recover from surgery. They were treated like other critical-care patients with heart monitoring, and if they didn’t wake up it was just assumed the prognosis was poor and they were going to die. What has emerged is a brain-specific treatment for these patients. At programs such as ours, it has become critical care for the brain rather than critical care for the heart.

What do you mean by that?

While traditional critical care monitors the heart with an EKG, neurocritical care uses an EEG to monitor the brain. If we have a patient who is in a coma, for example, rather than focusing only on monitoring blood pressure, heart rate and cardiac arrhythmias, we will administer...
treatments to restore and enhance brain function, as well as controlling pressure inside of the brain and detecting and stopping seizures in the brain. Prior to this, critical care was more about monitoring blood pressure, heart rate and cardiac arrhythmias with these patients.

You and your colleagues helped to pioneer continuous EEG brain monitoring of patients in the neurointensive care unit.

That’s right. Starting in the late 1990s, we were the first to show that the brain can have silent, nonconvulsive seizure activity, and that these seizures lead to poor outcomes. That has created a whole field of monitoring the brain. Continuous EEG monitoring has become the standard of care in neuro ICUs. Now, when we treat patients, we adjust medications and surgical interventions based on what the brain needs rather than what the heart rhythm is, and we use continuous monitoring for that feedback.

In what other ways is the care at a center such as UCLA’s different for neurocritical patients?

Beyond the state-of-the-art technology, we provide around-the-clock monitoring and coverage by a neuro-intensivist. Too often, in facilities that don’t have neurocritical-care expertise, the approach is therapeutic nihilism — the feeling that “nothing is going to work and we should just stop.” In those circumstances, the treatment often is about preparing the family for death. We are optimistic that the brain can recover, we know how to enhance that recovery, and we are not looking to withdraw care when recovery is possible.

What types of patients should be referred to UCLA?

We are a center of excellence for neurological emergencies — especially for complicated cases — and we definitely want to encourage transfer of these patients. For any patients with brain trauma, brain hemorrhage, subarachnoid hemorrhage and other complex and serious brain injuries, the outcomes are going to be better at a comprehensive neurocritical-care center.

What is the future of neurocritical care?

That is something we are helping to define by creating technology and therapeutic approaches that are at the cutting edge and not generally available in hospitals. We have established what we call the ICU of the Future, which includes not only the service lines, but new technological and therapeutic approaches for monitoring the brain and delivering more personalized treatments for neurological emergencies. For example, we are using micro-dialysis, PET, MRI and other advanced imaging approaches in the ICU for improved continuous monitoring of patients. Our ICU of the Future is also employing telemedicine approaches, building on work that UCLA pioneered a decade ago to treat patients remotely with an ICU robot. Today, more than 1,500 robots are in U.S. hospitals, a significant number of them in ICUs. Our program uses the technology to deliver care for neurological emergencies at community hospitals via telemedicine, as well as employing a robot at UCLA’s neuro ICU to treat patients and supervise care overnight. We have basically created a human laboratory for studying every aspect of the comatose brain to determine how it can be fixed. We are using the latest and best technologies to treat patients today, as well as generating tomorrow’s therapies.
New Retrieval Device Shown to Be Major Benefit for Stroke Patients

A new device to remove obstructing blood clots represents a breakthrough in the treatment of acute ischemic stroke, according to Jeffrey Saver, MD, director of the UCLA Comprehensive Stroke Center. A multicenter clinical trial, headed by Dr. Saver, found that in patients with acute ischemic stroke — in which a clot blocks the blood supply to part of the brain — removing the clot with the stent retriever device, which was developed at UCLA, significantly reduced poststroke disability and increased the percentage of patients who were independent in their daily function after three months.

The device, called Solitaire, represents the first major advance in the treatment of acute ischemic stroke in 20 years — since the development of the clot-busting drug tPA, Dr. Saver says. He notes that approximately five-out-of-six strokes are ischemic; acute ischemic stroke is the second leading cause of death worldwide and the leading cause of adult disability. For years, the only proven treatment was tPA, but it provides only a modest benefit — when used up to four-and-a-half hours after the stroke’s onset, it dissolves the targeted clot between one-third and one-half of the time.

As a result, Dr. Saver explains, UCLA has spent the past two decades developing an alternative approach — mechanically attacking clots to pull them from occluded vessels. The first such device, the MERCI Coil Retriever, was invented at UCLA and cleared for use by the U.S. Food and Drug Administration in 2004. The MERCI device was shown to reopen arteries 60-to-65 percent of the time, but only fully reopening them one-fourth of the time, with modest impact on patient outcomes. “We needed newer-generation devices that would do a better job of opening arteries,” Dr. Saver says.

“...This is an ideal use of telemedicine because the exam needed to make decisions on the treatment of these patients is largely visual, the medical decision-making is complex, and there aren’t enough neurologists to go around.”
The Solitaire stent retriever, which entered clinical trials on the basis of preclinical research conducted by Reza Jahan, MD, a UCLA professor of radiology and a member of the UCLA Comprehensive Stroke Center, is such a device. Unlike the MERCI retriever — a helical-shaped coil designed to grab and pull the clots out of the blocked artery — Solitaire is a mesh-columned cage, with crossing struts that can expand and engage the clot at multiple points. "A neurointerventionalist physician goes up with a wire catheter inserted in the groin, deploys the columnar mesh stent into the clot, the mesh embeds in the clot, the neurointerventionalist pulls the retrievable stent out, and the clot comes with it, restoring blood flow," Dr. Saver says. "It’s like pulling the cork out of a wine bottle."

This has proved much more effective in pulling out clots, Dr. Saver notes, and it is also a significant advance over tPA alone. For patients with a large clot, tPA reopens vessels 25- to 30 percent of the time. In the multicenter study, the stent retriever device opened the artery 88 percent of the time, even when there was a large clot. Four other clinical trials published within the last year have shown similar results.

The advance has implications on regional systems of stroke care. "In the past, we have set these up so that patients were preferentially brought to primary stroke centers capable of giving intravenous tPA to chemically dissolve the clot," Dr. Saver says. "We need to evolve ambulance routing protocols to make sure that patients who will benefit from thrombectomy are brought to comprehensive stroke centers where there is the capability to perform this intervention, which requires a neurocatheter lab, neurointerventionalist physicians, and advanced postprocedural neurocritical care."

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**Telestroke Program Expands UCLA’s Expertise to Other Centers**

“Time is brain” is a common mantra in the stroke-treatment field, referring to the urgency of treating patients suffering from acute stroke — initially, in most cases, with the clot-busting drug tPA — before irreversible damage occurs. But in rural areas, and even many urban communities, hospitals that are otherwise capable of treating such patients may not have a neurologist — much less a neurologist with vascular training — available around the clock to go to the hospital and conduct the evaluation necessary before the drug can be administered.

The UCLA Telestroke Program addresses that concern by providing participating hospitals with 24/7 access to the expertise of the UCLA Comprehensive Stroke Center. “Many emergency room physicians are uncomfortable making a decision about thrombolytic therapy. They would much rather have a vascular neurologist helping them in making that determination,” says Latisha Katie Ali, MD, a vascular neurologist and director of UCLA’s Telestroke Program. “Through our televideo systems, we are able to conduct a visual examination, take a clinical history, review the neuroimaging and rapidly assess patients in a way that potentially changes their management.”

Hundreds of patients are seen remotely each year by UCLA Stroke Center experts through the program, which began in 2009 and currently has participation agreements with 23 hospitals throughout California. When emergency department physicians at these hospitals recognize a patient who may qualify, they contact the UCLA Telestroke Program and an expert reviews the case on a high-definition screen. “The technology is at the point where we can even zoom in enough to see changes in the pupil of the patients,” Dr. Ali says. “And to be able to interact with patients and their family members and see them for ourselves is much more effective than relying on a conversation with an ER physician.”

“This is an ideal use of telemedicine because the exam needed to make decisions on the treatment of these patients is largely visual, the medical decision-making is complex, and there aren’t enough neurologists to go around,” says Jeffrey Saver, MD, director of the UCLA Comprehensive Stroke Center. “This program provides much better access for patients in these emergency situations by enabling UCLA neurologists to make those judgments on demand.”
When ‘Time is Brain,’ Prompt Response Essential to Successful Stroke Treatment

As the first point of contact in quickly assessing and intervening with patients brought to the UCLA Comprehensive Stroke Center, the interventional neuroradiology team plays a key role in the success of UCLA’s stroke program.

When patients in Los Angeles appear to be suffering from acute stroke, emergency responders use the Los Angeles Prehospital Stroke Screen, a tool validated at UCLA, to identify those who should be transferred to the UCLA Comprehensive Stroke Center for potential interventional treatment. For patients who are routed to UCLA, the “brain attack” team is activated. After an initial rapid evaluation to determine whether the patient is suffering from an acute stroke as opposed to a stroke mimic, the team ensures that the patient is stable before further assessment using advanced imaging — either CT or MRI. If stroke intervention is indicated, the front-line treatment is medical, in the form of intravenous tissue plasminogen activator (tPA), a clot-busting drug that can be administered effectively up to four-and-a-half hours after an acute stroke.

If a patient shows blockage of a large vessel of the brain — most commonly the internal carotid...
artery, the middle cerebral artery or the basilar artery — he or she is taken to the angiography suite. There, assuming intravenous tPA hasn’t resolved the problem, the interventional neuroradiology team seeks to remove the clot. “This requires a large team that can respond quickly,” says Gary R. Duckwiler, MD, chief of the Division of Interventional Neuroradiology at UCLA. At all times, he notes, UCLA has a neurologist and interventional neuroradiologist on call, along with MR/CT techs, nurses and angiographic techs. “It is essential to have a system in place that will attend to the patient immediately and efficiently, because ‘time is brain,’” Dr. Duckwiler says. “We know that opening up blocked arteries as quickly as possible provides the best chance of recovery.”

The mainstay for removing clots and reopening vessels in patients with large occlusions that can’t be unblocked by tPA are devices that Dr. Duckwiler and his colleagues navigate, under X-ray guidance, through the artery of the groin, after an angiogram has identified the site of the blockage and the flow of blood to the brain. These stent-retriever devices are attached to a small wire and deployed through a catheter toward the brain vessels. “The devices are self-expanding,” Dr. Duckwiler says. “We place the device at the level of the clot, the stent retriever expands in the clot, the device captures it and then we pull it out in an effort to restore flow in the blood vessel.”

UCLA has been involved in developing the clot-removing technique from the beginning — the UCLA Division of Interventional Neuroradiology invented the first device approved by the U.S. Food and Drug Administration for use in opening up brain vessels in acute stroke, the MERCI retriever, and conducted the clinical trials that showed it improved outcomes for patients with large-vessel occlusions who fail to respond to medical therapy. “Our team has been involved in the advances in acute stroke care from the outset, both with medical and interventional therapies,” Dr. Duckwiler notes. The devices have improved significantly over the years, to the extent that Dr. Duckwiler and his colleagues are now able to successfully retrieve the blood clot in 80-to-90 percent of cases.

“It is essential to have a system in place that will attend to the patient immediately and efficiently, because ‘time is brain.’ We know that opening up blocked arteries as quickly as possible provides the best chance of recovery.”

Patients who are successfully treated also benefit from the full continuum of care offered by the UCLA Comprehensive Stroke Center, including the dedicated neurointensive team attending to patients in the neuro ICU, along with the specialists who work with patients during rehabilitation.

“Honing our practice over many years has made our team adept at getting patients assessed and treated quickly and successfully, in an environment where every aspect of care across the continuum is critical for overall patient recovery,” says Dr. Duckwiler. “This has contributed to significantly better overall outcomes, as demonstrated in multiple studies.”

If a patient shows blockage of a large vessel of the brain, he or she is taken to the angiography suite of the UCLA Comprehensive Stroke Center, where a neurologist and interventional neuroradiologist are always on call, along with MR/CT techs, nurses and angiographic techs.

One-Call Stroke Acceptance Line
For immediate acceptance of acute stroke transfers to UCLA, call (310) 825-0909 Press 1
For patients whose symptoms began in the past 12 hours with:
Brain hemorrhage • Subarachnoid hemorrhage • Brain trauma • Ischemic stroke
UCLA Physician Access Line

1-844-4UCLADR
(1-844-482-5237)

Be connected 24/7 with an appropriate UCLA physician to assist with questions about your patient’s care and referrals.

Please have the following information available:

• Phone number where you can be reached in 20 minutes (cell phone is recommended)
• Patient name
• Patient contact number (for possible follow-up appointments)

If the call is regarding an inpatient transfer, the following information also will be needed:

• Patient date of birth
• Current patient location (hospital and specific unit)
• Face sheet faxed to UCLA Health at 310-825-2700

For more information about the UCLA Physician Access Line, go to: uclahealth.org/p2p