Recent advances in both the diagnosis and treatment of multiple sclerosis (MS) have made a considerable difference for patients suffering from the disease.

"In many cases, we can significantly delay profound disability – and we are working on reversing the disease," says neurologist Ari Green, MD, medical director of the UCSF Multiple Sclerosis Center, which sees nearly 6,000 patients each year and recently centralized its operations at the medical center’s Mission Bay campus.

(continued on page 6)
Transforming Care to Restore Patients’ Lives

At an academic medical center like UCSF, where we participate in and witness remarkable research efforts, it is hard not to become excited by what we may soon be able to offer the suffering patients and families we see every day. This issue of Neuroscience at UCSF Medical Center highlights some of the innovative clinical approaches that are on the horizon, and that are already transforming prospects for the patients we care for today.

For those wrestling with multiple sclerosis, we made important progress in developing and testing new therapies against inflammation, and in clinician-friendly, patient-friendly mobile tools for predicting the best treatment for individual patients. We have also begun a groundbreaking clinical trial that we believe has a good chance of achieving repair – remyelination – of multiple sclerosis scars, which means potentially reversing disability.

For brain tumors, our robust and balanced clinical trial program includes a number of trials aimed at preventing recurrence of glioblastoma and low-grade gliomas, which are also advancing the ideal of precision medicine. This goes hand in hand with the introduction of an exciting new Brain Tumor Immunotherapy Center, which is devising a new generation of brain cancer vaccines to work concurrently with existing treatment regimens.

Our new satellite clinic and telemedicine approach for amyotrophic lateral sclerosis (ALS) means that families and patients who often struggle to get necessary treatment will have it much more readily available to them than it has been in the past. Similarly, our collaborative UCSF Bay Area Concussion and Brain Injury Program builds on the seminal work of UCSF clinicians and researchers who are advancing the diagnosis and treatment of traumatic brain injury.

Even individually, these are important advances that have a direct impact on the patients we share with all of you in the community. Taken together, they demonstrate the power of collaboration and, because we see these patients every day, the fierce urgency of now.

Stephen L. Hauser, MD
Robert A. Fishman Distinguished Professor and Chair
UCSF Department of Neurology

Refining Diagnoses Can Improve Outcomes for Traumatic Brain Injuries

When the UCSF Bay Area Concussion and Brain Injury Program opened its doors last year, it was building on the work of UCSF clinicians and researchers changing the diagnosis and treatment of traumatic brain injury (TBI).

Neurosurgeon Geoffrey Manley, MD, PhD, is at the center of much of that work. In addition to his clinical work, Manley leads a team of US researchers at more than 20 institutions who are participating in the International Initiative for Traumatic Brain Injury Research (InTBIR), a collaborative effort for which the NIH is awarding $18.8 million over five years.

The work, says Manley, will validate new diagnostic tools and better stratify patients with TBI, which affects about 1.7 million people each year in the US. “As we translate the research into clinical tools, clinicians will have better methods for treating their concussion patients,” says Manley.

Changing the Gold Standard

One important advance is the recognition that computed tomography (CT) scans are no longer the gold standard for a TBI diagnosis, says Manley, whose clinical TBI program – one of the first of its kind in the country – was recently recertified by The Joint Commission.

“In the past, when there were no observable findings on a CT scan, patients received a nebulous classification of mild TBI or concussion; too often, they
were misclassified as not having a brain injury,” says Manley. “We’ve shown that cutting-edge MRI imaging identifies lesions associated with poorer outcomes that a CT scan does not pick up.”

**Today’s Dilemma**

Despite these types of advances, says Manley, “Many are still unaware of the new procedures, and care is not yet standardized.”

One place it is standardized is at the UCSF Bay Area Concussion and Brain Injury Program, located at the UCSF Orthopaedic Institute at Mission Bay. There, Manley sees patients along with other nationally recognized experts in:

- Sports medicine
- Physical medicine and rehabilitation
- Neuropsychology
- Neuroradiology
- Neurology
- Neurosurgery
- Physical therapy

“The multidisciplinary nature and accumulated experience is critical,” says Manley. “If you have a head injury, you want access to the people peeling back the onion on a problem for which evidence-based research and consensus is just emerging.”

For more information, contact Dr. Manley at (415) 353-1915.

**Enhancing Care and Prevention in Professional Sports**

UCSF Chair of Neurological Surgery Mitchel Berger, MD, serves on the National Football League’s Head, Neck and Spine Medical Committee, a panel charged with reducing the risk of head injuries to players. The committee has made its mark in a number of areas, including:

- **Rule Changes**: The committee advised moving kick-offs from the 30- to the 35-yard line. “The subsequent decrease in kickoff returns has reduced concussions on kickoffs by about 50 percent,” says Berger.

- **Improved Diagnoses**: The NFL and GE Healthcare have awarded grants for imaging techniques that can better define and diagnose concussion. UCSF neuroradiologist Esther Yuh, MD, PhD, was among the first grantees.

- **Enhanced Discovery**: “An independent sideline physician now examines players when a suspected concussion occurs,” says Berger.

- **More Rigorous Return-to-Play Guidelines**: “Following concussion, players now have to pass six rigorous stages before they can return to play,” says Berger.

For more information, contact Dr. Berger at (415) 353-1915.
New Generation of Vaccines Aim to Prevent Brain Cancer Recurrence

The nearly inevitable recurrence of brain cancer after initial treatment has long been one of the most significant problems with which neurosurgeons and neuro-oncologists wrestle. Having taken on the search for a solution, newly arrived UCSF neurosurgeon Hideho Okada, MD, PhD, believes that physicians may soon have a new tool in the armamentarium.

Okada spearheads the new Brain Tumor Immunotherapy Center (BTIC) at UCSF Medical Center, which is offering multiple lines of cancer immunotherapy clinical trials. He is principal investigator on two of those trials: one for low-grade glioma, as well as an entirely novel personalized vaccine for glioblastoma.

**Low-Grade Glioma Vaccines**

For low-grade glioma, the BTIC is initiating a group of trials aimed at helping patients at any stage of the disease, from initial diagnosis through post-treatment analysis of any remaining disease. “Our goal is to make all of these complementary, so any low-grade glioma patient can find an available clinical trial,” says Okada.

The trial on which Okada is the principal investigator deploys a vaccine derived from glioblastoma tissue. “Because a majority of low-grade glioma cases recur as high-grade glioma, the vaccine is not only therapeutic [to reduce the margins left after resection], but also prophylactic in that we expect it to create immunity against the high-grade glioma,” he says.

The side effects are transient flulike symptoms, such as low-grade fever, fatigue and headache, which typically disappear within 24 to 48 hours and are usually manageable with acetaminophen. Okada adds that despite its origins, there has been no indication that the vaccine promotes cancer progression.

While initial tests have been promising, Okada cautions that even if the trials show good results, use of the vaccine requires close collaboration with neuro-oncologists, because the vaccine is just one part of a comprehensive treatment plan.

**Precision Medicine Vaccine for Glioblastoma**

The second trial – the personalized vaccine for glioblastoma – is a collaboration with a German biotech company that is conducting trials in Europe. Okada will be pursuing the only North American version of the trial, and he and his collaborators are currently finalizing the clinical protocols.

This vaccine employs high-throughput gene sequencing to personalize the molecular makeup of the vaccine.

“Until recently, the cost and time for gene sequencing of each patient was prohibitive,” says Okada. “But now we can integrate cutting-edge technologies in high-throughput sequencing and molecular immunology to bring the cost and time down and make the vaccine more effective.”

In the proposed trial, after resected tissue is used to analyze the genes, each patient will receive an on-demand, tailor-made vaccine aimed at preventing recurrence as part of a comprehensive treatment plan. “We are moving ahead with the US approval process and have secured some funding,” says Okada. “I am excited by the prospects.”

For more information, contact Dr. Okada at (415) 353-7500.
Multidisciplinary clinics such as ours at UCSF Medical Center improve the quality of life for people with ALS [amyotrophic lateral sclerosis] and prolong survival, but it can be very difficult for families to travel extended distances to come to these clinics,” says Catherine Lomen-Hoerth, MD, PhD, medical director of the ALS Treatment and Research Center at UCSF.

In recognition of the struggles these families face, the UCSF ALS Center – one of only 34 ALS Association-certified Centers of Excellence nationwide – is expanding its support for the community of people facing ALS, often referred to as Lou Gehrig’s disease. In partnership with The ALS Association Golden West Chapter, the UCSF ALS Center now offers direct service through a new satellite clinic in Santa Rosa. This is the second satellite clinic for UCSF; the first opened in 2005 in Monterey, as part of an effort to meet the needs of the southern Bay Area and Central Coast ALS community.

In addition, for those who can’t get to these clinics regularly, the UCSF Department of Neurology is launching a pilot program in telemedicine technology, which will eventually allow people with ALS throughout California to access the center’s services from their homes.

Meeting Patients’ and Families’ Needs

“ALS remains a devastating disease,” says Lomen-Hoerth, who follows about 375 patients with the condition. “The average life expectancy is two to five years from diagnosis; there is no known cause, no cure; and in the later stages of the disease, the annual costs for home care, coupled with the cost of necessary equipment, can exceed $200,000 per year.”

But, she says, expert care from teams of health care professionals with expertise in managing ALS and arranging the social support families require can ease the burden. Patients also benefit from research in progress at places like the ALS Treatment and Research Center at UCSF, which brings together experts that include:

- Neurologists
- Nurses
- Respiratory therapists
- Speech pathologists
- Nutritionists
- Physical therapists
- Occupational therapists
- Social workers

Teleneurology Extends the Reach

The telemedicine program is a pilot project that uses videoconferencing for clinical consultations with any resident of California who has a computer with a camera.

“Our telemedicine approach, the new satellite clinic and the support from The ALS Association Golden West Chapter not only greatly increases access to care for people who are living with ALS, but actually dramatically reimagines our traditional model in a way that could be replicable for other ALS clinics and for other diseases,” says Lomen-Hoerth. “These are critical services that many families desperately need.”

For more information, contact Dr. Lomen-Hoerth at (415) 353-2122.
The Age of Therapeutics
The introduction of four new therapeutics in the past few years has nearly doubled the available medications, says Green.

“The addition of these new disease-modifying therapies allows us to tailor therapies to our individual patients better than we could in the past,” he says.

In turn, Green and Chan used a high-throughput assay for identifying molecules that can stimulate the oligodendrocytes with limited toxicity and side effects – and then showed they could achieve remyelination in both the lab and in animal models.

One compound they identified was an existing drug with a good safety record. They have received FDA approval for a phase II clinical trial that would test this drug in the treatment of MS. Patients who enroll will have evidence of demyelination without axonal death; good candidates are those who’ve had an optic neuritis in the last five years.

“This is the brave new world of repair therapeutics in neurodegenerative disease,” says Green. “The beauty of this approach is that we’re catalyzing the brain’s endogenous capacity for repair. … The substrate is there; we just have to give the needed push.”

For more information, contact Dr. Green at (415) 353-2069.
Clinical Trial Program Gives Brain Tumor Patients New Options

Because clinical trials offer hope to patients for whom standard treatments are inadequate, an academic medical center like UCSF must maintain a robust clinical trial program, says Nicholas Butowski, MD, director of translational research for the UCSF division of neuro-oncology and a member of the renowned Brain Tumor Research Center at UCSF.

An expert in novel therapeutic approaches to brain tumors and a co-investigator on the National Cancer Institute-supported North American Brain Tumor Consortium clinical trials, Butowski says not only is the clinical trials program at the UCSF Brain Tumor Research Center funded and supported by the NIH, but it also facilitates investigator-initiated trials and close relationships with industry.

“We are balanced here,” he says. “We have 20 different preclinical labs, feeding into a robust translational program that includes phase I, phase II and phase III trials.” The trials range from new cytotoxic protocols and molecularly targeted drugs to immunotherapy. Many of the trials include quality-of-life and neurocognitive components.

“Currently, we are especially focused on two challenges: drug delivery and the enhancement of molecules, including oxygen-carrying molecules that can improve the efficacy of radiation and traditional chemotherapy,” says Butowski.

Taking Sharp Aim at Glioblastoma

Butowski points to one novel phase I trial that constitutes a multipronged attack on recurrent glioblastoma.

One prong has investigators forgoing systemic chemotherapy to inject the medication directly into the glioblastoma via convection-enhanced delivery in the operating room. The approach addresses the long-standing problem of getting systemic therapies across the blood-brain barrier and places the therapy directly on the tumor site.

A second prong employs real-time MRI to guide catheter placement. “This allows even more precise delivery, assures we cover the entire tumor – and if we are missing the target, we can correct that in the moment,” says Butowski.

Finally, the trial addresses patients’ innate resistance to chemotherapy by modifying the drug with a topoisomerase inhibitor in a nanoliposomal form to ease movement through the brain and enable the medication to stay longer in the spot where it’s been injected.

If the phase I trial demonstrates safety, in phase II Butowski expects to incorporate more computer modeling throughout the process. The modeling, he says, can account for anatomy and physics to predict placement barriers. Moreover, the researchers will be able to gauge the accuracy of the original predictions, which will enable the computer to recalibrate and more accurately predict catheter placement for individual patients moving ahead.

“No one has ever tried to use an MRI scanner and computer modeling to correct for placement problems in the human brain,” says Butowski. “We believe this will be safer and more effective for patients.”

For more information, contact Dr. Butowski at (415) 353-2966.
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CME Courses
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