Neural Repair After Stroke and Spinal Cord Injury: 
New Insights Yield Promising Strategies

To what extent can there be life after a stroke or spinal cord injury? Researchers in the UCLA Department of Neurology are learning much about the recovery process that takes place in the brain in these instances, and are moving toward new strategies that could dramatically improve the lives of future brain-injured patients.

Surgical Strategy for Spinal Cord Injury
Spinal cord injury affects between 250,000 and 400,000 people in the United States. Approximately 11,000 people sustain such injuries each year. These individuals, more than half of whom are under the age of 30, suffer partial or complete loss of sensation and function below the injury site. But great strides are being made in laboratories such as that of Leif A. Havton, M.D., Ph.D., associate professor in the Department of Neurology, that could lead to strategies for neural repair after such injuries.

S. Thomas Carmichael, M.D., Ph.D., assistant professor in the Department of Neurology and Leif A. Havton, M.D., Ph.D., associate professor in the Department of Neurology

Dr. Havton’s research team has focused on an understudied form of spinal cord injury that affects the lowest portion of the spinal cord, called the conus medullaris; and the associated nerve roots known as the cauda equina. The two structures are injured together in approximately 20 percent of spinal cord injuries, including many motor vehicle accidents, traumatic falls, and sports injuries. Victims typically lose motor control of the legs, experience sensory loss, and lose control of bladder, bowel, and reproductive functions.

“These are devastating injuries that most commonly affect young males,” says Dr. Havton. “Often, these patients develop a very difficult-to-treat form of pain, and sadly, there are no current treatments to reverse these effects.”

But Dr. Havton and colleagues have developed laboratory models that mimic the symptoms of patients with these injuries, enabling them to test in rats a strategy for surgically reconnecting the spinal cord to its nerve roots. The results of their “root implantation” surgery have been very encouraging. Dr. Havton’s team has shown that the procedure can rescue nerve cells that would otherwise be at risk of dying.

Axons—the nerve-cell fibers that carry messages to other cells—have grown from the nerve cells in the spinal cord out to the periphery. These new trajectories can also create new contacts in both the bladder and the sphincters that control the lower urinary tract, helping the rodents to regain bladder function. The root surgery also appears to reduce pain from the injury.

“We hope that this strategy in some form will be part of new treatments for patients with these injuries,” says Dr. Havton. He has begun discussions with surgical colleagues about the feasibility of moving the technique from the laboratory to a human clinical trial.

Exploiting the Initial Post-Stroke Repair Process
Only heart disease and cancer kill more Americans each year than stroke, in which blood vessels carrying oxygen and other nutrients to the brain are blocked or burst. For the more than 5 million stroke survivors, a major concern is the cognitive and physical impairment that typically results from the brain cells that are affected by the attack. “Compared to other organs and nerves in the body, the brain doesn’t repair and regenerate very well, especially in the adult,” says S. Thomas Carmichael, M.D., Ph.D., assistant professor in the Department of Neurology.
These same circumstances are now and significant new treatments to provide hopeful time for providing practical and incremental process. Individuals and small groups of highly motivated members of society have examined this process closely and, bringing experiences from other domains such as the business world, have questioned whether this should be the only means by which to advance our knowledge of neurologic disorders and their treatment. These groups are developing alternative funding sources for targeted research projects aimed at hastening the pace of delivering practical treatments to patients with a wide range of neurologic disorders. Unlike venture capitalists who seek large financial gains for relatively small investments, such philanthropists seek to reduce the time required to deliver novel and effective treatments to patients, in the most cost efficient manner possible. This is accomplished by reducing overhead and the requirement to prepare massive research proposals, frequent progress reports and extensive publication of results. Instead, research success is judged by the timeliness and quality of experimental results that lead to additional insights and shorten the time between laboratory experimentation and clinical relevance. Further, these individuals are sophisticated and understand that medical research is not the same as engineering. In the latter situation, twice as much money can often produce a result in half of the time. Research does not work that way. Its name alone is indicative of the unpredictable outcome of a given experiment – “re-search” to look again. Nevertheless, these philanthropists recognize that if there are 50 plausible hypotheses about a given neurological illness, exploring all 50 in parallel will be 50 times faster than exploring them serially.

In the UCLA Department of Neurology, we have had the opportunity to develop just such a program with Dr. Miriam and Sheldon Adelson through their medical research foundation. They are committed to solving neurological problems associated with nerve injury and neural repair. They chose a global solution. With the able leadership of Bruce Dobkin, M.D., in our department, a group of expert scientists and clinicians from around the world have been assembled to tackle this problem and to develop a consortium of integrated projects focused on data sharing and expedited results. I am happy to report that this group is now formally commissioned and funded through the Adelson Medical Research Foundation and results of the first round of research experiences by the participants, many of whom are in our department, were reported last fall.

This is but one example of how individuals outside of the field of neurology and medicine can have a dramatic effect on the direction of the field and its important products. One person, one family, one group can, have and always will make a difference.

John Mazziotta, M.D., Ph.D.
Chair, Department of Neurology
Stark Professor of Neurology
In recent years, there has been a growing appreciation of the association between resistance to the effects of insulin, a hormone that helps people metabolize sugar, and the risk of Alzheimer’s disease (AD). Specifically, it has been observed that elevated levels of insulin in the blood of AD patients placed them at greater risk for the development of disease. Exactly how this occurs is not yet certain, but it has been observed that insulin can increase the release of Abeta, the toxic molecule from the brain thought to trigger AD. Moreover, this molecule is broken down by an insulin-degrading enzyme – an enzyme that also helps to degrade insulin. Therefore, the presence of increased levels of insulin may compete with the toxic molecule for the action of this enzyme, causing less Abeta to be broken down.

Whatever the mechanism, preliminary studies of rosiglitazone, an insulin-sensitizing medication used for the treatment of diabetes, have yielded promising results in persons with AD. In a small study of persons with either early AD or an isolated memory problem suggesting even earlier AD (mild cognitive impairment, or MCI), persons treated with rosiglitazone had better cognitive functioning after six months. A larger study demonstrated that a subset of patients with a specific genetic marker associated with the risk of AD who were treated with rosiglitazone performed better on a cognitive test after 24 weeks than did those given a placebo.

The UCLA Kagan Alzheimer’s Disease Treatment Development Program is committed to helping to find more effective treatments for the devastating disorder. Researchers in the program are engaged in multiple studies, either developed at UCLA or in collaboration with other centers through the National Institutes of Health or the pharmaceutical industry. The AD studies include two of rosiglitazone. One involves enrolling persons with MCI to verify and further elaborate the effects of rosiglitazone in this population. The second will enroll persons with AD to analyze the effect of genetic sub-type. For more information about these studies or others involving AD or MCI, please call (310) 794-6191.

The achievement is particularly noteworthy, Dr. Mazziotta notes, because, although most scientists believe that opportunities for progress and advances in human health have never been more promising, NIH’s growth has been reduced in recent years as the federal budget for biomedical research has tightened.

Dr. Mazziotta stresses that NIH tends to fund incremental, low-risk approaches, and that private philanthropy from the UCLA Neurology Partners in Discovery continues to be needed more than ever to enable researchers to test sound scientific hypotheses that are less conservative, but often are needed to move the field forward in significant leaps rather than small steps.

“We are on the threshold of a new era in neurology therapies because of all of the basic science insights we have gained in recent years,” says Dr. Mazziotta. “With our top-ranked position in NIH funding, augmented by contributions from our generous and loyal Partners in Discovery, we are well positioned to deliver practical new treatments for patients.”
Marilyn Hilton MS Achievement Center Helps People with MS Live Better Lives

Ongoing research at UCLA and other institutions provides hope of an eventual cure for multiple sclerosis (MS), a chronic, disabling disease of the central nervous system. But in the absence of a cure, the UCLA Department of Neurology continues to also focus on offering the best clinical services to help MS patients manage their disease. The Marilyn Hilton MS Achievement Center (MSAC) at UCLA provides an important part of that package – wellness services for individuals with MS that complement the medical management of their disease.

MSAC was established in 2001 as a partnership between the Department and the National MS Society to create an innovative new resource for those living with MS. The collaboration was a result of the vision and years of effort by leaders including Drs. Robert Collins and Bruce Dobkin at UCLA; Dr. Leon LeBuffe and Denise Nowack at the Southern California chapter of the National MS Society; and Mr. Steve Hilton and the Hilton family. More than 300 people have been served by the center’s programs, which include:

The Day Program. MSAC’s Day Program is a place where people with MS go one day each week to work on physical, emotional and recreational wellness goals through customized activities designed to help them live well with the disease. The aim is to provide the tools to assist members in improving and/or stabilizing function, enhancing emotional well-being and increasing independence, in a setting of shared support and acceptance.

The program is geared toward people who have been living with MS for a period of time and are facing multiple life challenges related to MS. They may have difficulty because of symptoms in areas including mobility, emotional health and cognition. Program components include yoga, art therapy, fitness (strengthening, stretching, cardiovascular), health education, physical and occupational therapy assessment, recreation therapy, nutrition, adaptive computing and cognitive stimulation classes.

Members have reported important functional improvements as a result of their work at the center, including the ability to function more independently at home; improved mobility and balance; decreased fatigue, depression and pain; and an overall sense of empowerment. “I have made so many changes for the better,” says one patient. “I am more independent, more able to do things for myself.”

Living Well. The MS Achievement Center also offers “Living Well,” a program specifically designed to meet the needs of those persons recently diagnosed with MS. The program, held in the evening to accommodate people who are working full-time or are in school, consists of 12 weekly three-hour sessions. It is led by an MS-specialist professional team that includes a neurologist, clinical nurse specialist, physical therapist, personal trainer, psychologist, counselor, dietitian, occupational therapist, speech pathologist and recreation therapist. Over the course of the 12-week program, participants have the opportunity to:
• Develop a comprehensive personal fitness and nutrition program
• Understand and better manage MS symptoms, including fatigue and stress
• Develop emotional and spiritual health practices for living well with MS
• Increase their ability to cope with the diagnosis and the unpredictability of MS
• Meet others with MS and develop a support network

Participants have found the program tremendously beneficial, and formal evaluations have shown statistically significant self-reported changes in increased global health, exercise/physical activity, eating/nutritional habits, self-efficacy, wellness coping skills, psychological well-being, and spirituality, along with reductions in fatigue and anxiety.

LEAP. The Lifestyle Education and Assessment Program (LEAP), the center’s newest program, is a one-day experience that provides a comprehensive multidisciplinary evaluation of neurologic and functional status by the center’s team of health care professionals. It is targeted for individuals living with MS in outlying communities who lack access to MS specialty care. The goals of LEAP are to assess each individual’s unique needs, identify areas for potential improvement, and establish a plan for interventions that can be implemented in the patient’s home community. Both the MS patient and his or her physician are provided with a complete report based on the team’s findings.

The Marilyn Hilton MS Achievement Center at UCLA is committed to the goals of its parent organizations, the UCLA Department of Neurology and the Southern California Chapter of the National MS Society: to provide state-of-the-art research, education and care and to end the devastating effects of MS for individuals with MS and their families. Many of the MSAC programs are being replicated at the Eric Small Centers for Optimal Living in other locations in Southern California. Additionally, the MSAC is developing ways to extend its reach via the WWW: Wellness Without Walls initiative, which will use videoconferencing, distance learning, and teleconferencing technology to serve an even broader community.

The MSAC also plans to continue to expand some of its other initiatives, including an aquatic exercise program, fall prevention workshops, and its annual professional education conference for health care professionals who work with persons with MS.

Anyone interested in learning more about the Marilyn Hilton MS Achievement Center or taking a tour of the facility is invited to contact Executive Director Stephanie Fisher at ssfisher@mednet.ucla.edu or (310) 267-4071.
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**donor recognition**

Dr. Miriam and Sheldon G. Adelson, through the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation, have created the Adelson Program in Neural Repair and Rehabilitation (APNRR). The APNRR aims to translate basic science discoveries into treatments for paralysis and loss of sensation in people who suffer from neurological diseases such as stroke, traumatic spinal cord and brain injury, multiple sclerosis, peripheral neuropathy and other neurological diseases. The Adelsons’ goal is for the APNRR to contribute to finding solutions for neurological diseases and disabilities and create a more efficient and creative production line for translational research from bench to bedside.

Drs. Bruce Dobkin and John Mazziotta from UCLA’s Department of Neurology collaborate with scientists from UC San Diego, Cornell, Johns Hopkins, Harvard, Rochester, Rockefeller, and the Weizmann Institute as well as others to formulate strategies and create collaborations to help drive the search for biological cures for neurological diseases. From the initial meeting, after the first round of collaborative research proposals were reviewed and graded by all attendees the APNRR provided funding of more than $7 million for 30 scientists, who contributed 40 proposals.

The APNRR is a multidisciplinary, multi-institutional collaboration-based model, which is highly unusual in the field of medical research. The Foundation and the APNRR aim to increase the effectiveness of medical research in finding better solutions to medical problems.

For more on the APNRR, see page 7.

**kudos**

John C. Mazziotta, M.D., Ph.D., chair of the Department of Neurology and director of the Ahmanson-Lovelace Brain Mapping Center, has been named as a new member to the prestigious Institute of Medicine of the National Academies. Dr. Mazziotta chairs one of the largest neurology departments in the United States, which last year achieved the distinguished position of being first in NIH research funding. An expert in brain imaging, he established the first Brain Mapping Center at UCLA that includes all of the methods available to study human brain structure and function. He is the principal investigator of the International Consortium for Brain Mapping, whose goal is to develop the first atlas of the human brain that will include behavioral, demographic, imaging and genetic data from 7,000 subjects.

Liana Apostolova, M.D., received the prestigious Paul B. Beeson Career Development Award in Aging. This award, co-funded by the National Institute of Aging and private foundations, is given to promising young investigators who show great potential and whose research and leadership are enhancing the health and quality of life for the elderly. Dr. Apostolova’s research project uses magnetic resonance imaging data of subjects diagnosed with mild cognitive impairment to identify Alzheimer’s disease before it has inflicted Alzheimer’s dementia. Identifying mild impairment enables initiation of therapeutic interventions in the earliest stages, maximizing their impact.

David B. Teplow, Ph.D., received a $7.9 million grant from the National Institute on Aging to support his ongoing pursuit to finding solutions for Alzheimer’s disease. This national investigation into how brain proteins stick together abnormally to cause Alzheimer’s involves an interdisciplinary team of leading investigators in the fields of chemistry, physics, molecular biology and neurology from UCLA, MIT, UC Santa Barbara and Boston University. “We look forward to using this support to advance our efforts to understand the pathologic mechanisms of Alzheimer’s disease,” Dr. Teplow said, “and to develop a new class of therapeutic agents attacking what we believe to be the seminal toxic moiety in the disorder.”

Claude Wasterlain, M.D., was awarded the Pierre Gloor Award of the American Clinical Neurophysiology Society at the society’s annual meeting in Chicago, where he also gave a lecture on the mechanisms responsible for the transition from single seizures to status epilepticus. The Pierre Gloor Award is given for “outstanding contributions to clinical neurophysiology research.” Dr. Wasterlain received the award for contributing to the understanding of status epilepticus – a condition in which seizures are uncontrolled and continuous – and its complications.

For more on the APNRR, see page 7.
Dr. Alon Y. Avidan, the new associate director of the UCLA Sleep Disorders Center, has developed a national expertise in sleep disorders in the older person, conducting important research on the topic. Dr. Avidan received his Bachelor of Science degree in Biology from UCLA, then attended medical school at the George Washington University School of Medicine and Health Sciences in Washington, DC, where he also obtained a Master of Public Health. He subsequently completed his neurology residency at the Georgetown University Medical Center, where he was chief resident. After residency, he completed a fellowship in clinical neurophysiology and sleep disorders at the Cleveland Clinic Foundation.

In 1999, Dr. Avidan joined the Department of Neurology at the University of Michigan as assistant professor, director of the Sleep Disorders Clinic and chair of the Resident Education Committee. There, he was principal investigator of a National Heart, Lung & Blood Institute, NIH, Sleep Academic Award that helped him develop a number of educational modules for teaching sleep topics.

At UCLA’s Sleep Disorders Center, Dr. Avidan plans to continue his research in geriatric sleep medicine and to examine the neurocognitive consequences of sleep deprivation among physicians in training. His clinical interests include management of sleep-disordered breathing, movement disorders of sleep, circadian rhythm disorders, insomnia and hypersomnia. As director of the center’s outpatient clinic, Dr. Avidan plans to enhance the clinical services and continue his contributions in sleep disorders.

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assistant professor in the Department of Neurology.

But in recent years, Dr. Carmichael notes, stroke researchers have learned about an initial process of repair following a stroke, in which brain cells are able to sprout new connections and even generate new neurons, with the activity taking place in the brain regions that are important to post-stroke recovery of function. “We didn’t think the adult brain was capable of anything like this until the last 5-6 years,” says Dr. Carmichael.

Seizing on these findings, his laboratory is trying to understand the molecular processes behind these phenomena. Dr. Carmichael’s team has homed in on the genes and neurons that are involved, postulating that amplifying the genetic activity that stimulates the new connections and brain cell production will enhance the recovery process. “By identifying the entire gene expression pattern of a regenerating neuron – what does a grown-up nerve cell need to turn on in order to sprout a new connection – we can identify and activate the control points,” Dr. Carmichael explains.

His group has identified proteins that appear to restrict the formation of new connections, and has found that these proteins are different in older adults than in young adults – an important observation given that most experimental models of stroke involve young animals. “If we really want to understand how the brains of stroke patients repair and how we might enhance that process, we have to more closely examine the process in aged animals,” Dr. Carmichael notes.

By studying older animal models, Dr. Carmichael and colleagues found that the two proteins – ephrin-A5 and myelin-associated glycoprotein – are in a position to hinder the recovery process. “As we identify the proteins in the brain that block the formation of new neurons and connections, we will also start to find the major control points in the cells that turn on that process,” Dr. Carmichael says. Within a few years, he predicts, this may lead to new drugs that can improve recovery following a stroke.

The recognition that neural recovery, however small, takes place in the adult brain after most central nervous system injuries has spurred a stepped-up effort that places the field of neurorepair at the threshold of dramatic gains, Dr. Carmichael says. The urgency of this effort has never been greater. “As the population ages, the incidence of stroke is expected to substantially increase,” Dr. Carmichael notes. “This is going to leave a large number of disabled survivors, and a growing clinical need to improve functional recovery.”

Rehab Program Seeks to Optimize Functional Recovery

In the UCLA Neurological Rehabilitation and Research Program, there is a growing focus on the development of “end-user” strategies to optimize functional recovery.

On the one hand, this means finding the best ways to train patients in regaining their physical and cognitive abilities using the parts of their nervous system that were not affected.
by the injury. This can have a dual effect. “While we’re training patients in tasks such as walking or using their hands better, we’re also driving intrinsic mechanisms in the nervous system – molecules and pathways that are associated with that learning skill – which helps to make stronger connections between nerve cells that come to represent the actions that are being learned,” says Bruce H. Dobkin, M.D., the program’s director. At the same time, Dr. Dobkin explains, this training lays the groundwork for research that will be needed after biological interventions are developed. “Any new treatment will be implemented on what is essentially a new nervous system,” he says, “and if we are adding connections to that system, those connections may not be effective until they’re trained. If, for example, cells are implanted that increase the excitability of an area of the brain, we need to commandeer those new cells into a network that does something useful.” Dr. Dobkin’s research team is currently studying strategies in the laboratory with this goal in mind.

“All neurorepair interventions will have to be linked to a rehabilitation approach that maximizes functional recovery,” Dr. Dobkin explains. Functional magnetic resonance imaging enables the researchers to monitor whether the goals of exciting certain areas of the brain to help the nervous system adapt through training are being achieved.

Much progress has been made recently at the basic level, and that is paving the way for major advances in neurorepair, Dr. Dobkin adds. “We now know that we can drive motor-skills learning by monitoring how the brain is evolving as those skills are being learned,” he says. “We can better understand which pathways make important contributions to that relearning after the brain or spinal cord have been injured. In addition, any brain or spinal cord injury leads to changes in the area surrounding the injury – a re-expression of genes and molecules that hadn’t been expressed, most likely, since embryogenesis. There is, in a sense, an intrinsic system that is trying to fix things, and one of our goals is to prolong and amplify that natural repair system.”

Supporting “Out of the Box” Studies

A new program is providing generous funding for teams of basic and clinical scientists from UCLA and other institutions who are taking an innovative approach to research into neural repair and rehabilitation.

The Miriam and Sheldon Adelson Program in Neural Repair and Rehabilitation (APNRR), established last year by the founders of the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation in consultation with the UCLA Department of Neurology, promotes basic and clinical research to better understand and manipulate the biology of damage and repair to neurons and axons within the brain, spinal cord, and peripheral nerves.

The program’s goal is to lessen the disabilities of patients who suffer the loss of movement and sensation from injury and disease. But more than that, APNRR aims to create a culture of basic science discovery, evaluation, and clinical application built on experiences of outstanding scientists who are not bound by the search for a cure for a single disease. Unlike traditionally funded research approaches, the program will develop collaborations among basic and clinical scientists to discover and apply fundamental insights into the common denominators of damage and repair, particularly for central and peripheral cell signaling, axonal regeneration, myelination and targeting.

“As a scientific activity, it often takes many people working together on particular aspects of neural repair and rehabilitation to get anywhere,” says Bruce Dobkin, M.D., professor of neurology at UCLA and director of the APNRR. “But research that combines basic science and the translation of that basic science into human therapies is not generally well funded by the National Institutes of Health. That’s one of the reasons we developed this program.”

APNRR grantees must work within the framework of the program’s collaborative research model. The program hopes to create a more efficient system of translating research from the laboratory to the clinic by funding outstanding scientists who are willing to pool their knowledge and ideas and openly collaborate across the necessary range of disciplines. APNRR investigators currently span 30 laboratories at 12 universities. Investigators are encouraged to take risks in their research agendas – a contrast to the incremental studies favored by most granting institutions. To encourage true peer review, grant applications are brief and focused, and are reviewed by all members of the consortium of investigators. Approximately 40 interactive proposals were funded for the first year at a total of more than $7 million.

“The APNRR has given researchers at UCLA and the other institutions tremendous freedom to work together and think outside the box,” says Dr. Dobkin. “Members of the consortium are very excited to be funded for this kind of creative, collaborative work across neurological diseases that cause serious disability.”
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