The Forbes Norris MDA/ALS Research Center

Forbes Norris ALS Center News

SPRING | SUMMER 2003

From the Desk of Robert G. Miller, M.D.

All of us at the Forbes Norris ALS Center are committed to finding a cause and cure for ALS. I want to share our excitement on the development of several new approaches.

Clinical Trials

The Norris ALS Center is engaged in three major goals to fight ALS. 1) Better understanding of the mechanisms for why motor nerve cells become sick; 2) Developing better therapeutics to benefit the quality of life for our patients; and 3) Developing markers to monitor disease progression and improve clinical trials efficiency.

A major advance has been the National Institutes of Health (NIH) entry into the funding of clinical trials and studies in ALS. NIH funded specialized screening studies of currently available drugs to identify possible promising compounds. NIH also recently funded new clinical trials to evaluate the efficacy of creatine, insulin-like growth factor-1 (IGF-1), and minocycline to determine their effectiveness as therapies for ALS.

• Please see the Research Agenda section of this newsletter for a listing of our current clinical trials

Patient Care Projects

In the last few years, we have experienced a dramatic rise in "evidence-based practice guidelines" applications improving management of ALS. Published in 1999, the "ALS Practice Parameters," an American Academy of Neurology landmark project has had a tremendous impact on raising the standard of ALS care throughout North America and Europe and more recently Japan. It is the template for application of future research to the management of ALS.

For the last six years I have been privileged to direct the North American ALS C.A.R.E. Database, the largest database available for learning about ALS from a patient and caregiver prospective. With almost 5,000 patients enrolled from more than 100 centers in North America, health care professionals have learned many valuable lessons, which they are able to apply in their day-to-day patient assessments.

An additional area of importance is the Cochrane Collaboration, a global network of healthcare professionals. The Collaboration is committed to a thorough and rigorous examination of the available published evidence on various therapies and the publication of systematic reviews designed to establish a benchmark for therapeutics.

Comprehensive Clinical Care Team

No discussion about the Norris ALS Center would be complete without acknowledging the tremendous breath and depth of expertise in the Comprehensive Clinical Care Team, headed by Deborah Gelinas, M.D. She has assembled one of the best multidisciplinary teams available providing comprehensive multifaceted care for our ALS patients.

Dr. Gelinas, in conjunction with Mary Abood, Ph.D., has recently conducted a pilot study of the effects of Marinol in ALS. She reported on the study's early positive results at the recent International ALS/MND Scientific Symposium held in Melbourne, Australia.

Robert G. Miller, M.D.
Norris ALS Center Director

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THE FORBES NORRIS MDA/ALS RESEARCH CENTER

RESEARCH AGENDA

Working in all aspects of basis science and clinical research, including clinical drug trials, is an important part of fighting and winning the war against ALS. Participation in research is a difficult personal medical decision. If you are interested in participating in any of our current clinical research studies, please contact our **Research Nurse, Jason Mass at (415) 600–3967**.

Research Trials at the Norris ALS Center:

Minocycline Study — Testing the possible benefit of minocycline, an antibiotic and caspase enzyme inhibitor in controlling programmed cell death, which is regulated by caspase enzymes.

Insulin Like Growth Factor-I (IGF-I) Study — Evaluate the effects of IGF-l on the progression of muscle weakness.

Creatine Study — Testing whether treatment with creatine results in increased and sustained muscle strength in addition to the possibility of slowing progressive muscle deterioration.

Magnetic Resonance Study — Measuring the concentrations of several chemicals in the brain help us understand the possible causes of ALS including the role of abnormal glutamate levels in the brain. Glutamate may serve as a reliable indicator of specific impairments in early detection and evaluation of new drug therapies.

On-going Studies:

Exercise Study — Measures the effects of regular exercise on muscle strength, endurance and mood and quality of life.

"ALS Care" Database — North American voluntary patient care database serves as a tool to help us better understand clinical practices for ALS patient care and the relationship between medical practices and clinical outcomes.

Studies Scheduled to Start Soon:

Herbal Dietary Supplement Study — Evaluate the nutritional effects on patients with excessive saliva monitoring symptoms and daily activities.

Mathews ALS Family Fund Update

We reported in the last Norris Center Newsletter on the inspired gift initiated by the Marshall Mathews Family exclusively for Patient Services at the Forbes Norris ALS Center. We have received a commitment of $230,000, part of which is being used to hire a new Nurse Case Manager to supplement the tireless work of Patty O'Connor, who alone has been managing our patient load for five years.

Unlike funds for research or clinical trials, sufficient revenue for critical patient services are very difficult to secure. Their necessity is reflected in the improved quality of life throughout the course of the disease for all of our patients, which is not seen in the usual medical setting.

If you would like to contribute to the Mathews ALS Family Fund send your contribution directly to the Norris ALS Center, or call Dee Norris at (415) 600-3608. Please designate the "Mathews ALS Fund" on your check.

New Arrivals at the Clinic:

Speech Pathologist Amy Roman, our communication and swallowing expert, gave birth to a healthy baby girl, Julia, born February 14th, a little valentine. While Amy is on maternity leave, Tiffany Mahoney will be our Speech Pathologist specialist. Congratulations Amy, her husband Roger, and welcome Julia!

New Phone Number Prefix at the Norris Center

All the telephone prefixes at the Norris Center have changed to 600. So when you give us a call, just change the old prefix 923 with 600.

ALS BASIC SCIENCE RESEARCH

Exciting investigative work in the causes of ALS is underway in the laboratories of Drs. Nancy Lee, Mary Abood, and Jian Liu here at the Norris ALS Center.

Meet the Senior ALS Basic Science Research staff

Nancy M. Lee, Ph.D.
Senior Research Scientist

Dr. Lee's professional experience began in Austin at the University of Texas in 1963. She continued to develop her work as a research biochemist, research pharmacologist, and a professor of pharmacology at the Universities of California and Minnesota. She joined California Pacific Medical Center's Research Institute as a senior research molecular biologist in 1995.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that is usually fatal within two or three years after onset. Before death, the patient suffers progressive loss of muscular function, essentially becoming a prisoner of his or her own body. The cause of ALS is not known, however, a small proportion of cases are hereditary, and of these, 10 - 20% result from a mutation in the gene for superoxide dismutase (SOD), which functions in the metabolism of free radicals in the body. Laboratory mice with this mutation develop a disease similar to ALS, and are a useful model for studying the disease. If the molecular pathologies underlying ALS can be unraveled, it may be possible ultimately to halt or even reverse progression of the disease by targeting these processes.

Our approach has been to examine mutant mice at a very early age, before detectable morphological or behavioral symptoms develop. Our rationale is that changes that occur in the earliest stages are likely to be causative of the disease, whereas later changes may be the residual from the progressive degeneration of the nervous system. Detection and characterization of these earliest molecular changes would allow us to design therapeutic interventions to either block or slow down progression in people, thus halting or reversing the nervous system degenerative process.

This strategy is not only logical and feasible; it has been used in other diseases, such as diabetes. For instance, insulin has been used for the last 50 years to ease the ravages of diabetes and has saved millions of lives, yet we still do not have a cure for diabetes. We have also analyzed the expression of a number of genes in ALS that function in such processes such as oxidative stress, metabolism of glutamate, as well as "immuno-surveillance" by glial cells. All of these genes have been implicated in ALS by other studies, but their role in disease progression is not known. We found that many of these genes were altered in animals where symptoms had appeared, but only a handful of these genes were also altered in animals prior to the development of symptoms. Our results suggest that we can identify those molecular changes that play an important role in the earliest initial ALS development. At the same time, we may be able to rule out and exclude certain other molecular pathologies. This ongoing work will allow therapeutic approaches to focus on the most promising molecular targets.

Our goal is to help ALS patients lead independent productive lives, even in the absence of an immediate cure. Intelligent designs of therapeutic intervention at the earliest possible stage of ALS might prevent much of the bodily function deterioration that occurs at the later stages of the disease, not only prolonging life, but also greatly improving their quality of life. Preventing disease progression to the point where patients are able to continue taking care of themselves would represent an enormous medical breakthrough.

Mary Abood, Ph.D.
Research Scientist

Dr. Abood joined the research staff at the Forbes Norris ALS Research Center in 1999. With over fifteen years of research experience, Dr. Abood has worked at the Pritzker Laboratory at Stanford University and as a tenured Associate Professor at Virginia Commonwealth University in Richmond, Virginia. While completing her Ph.D. in Pharmacology at the University of California San

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Francisco in 1986, Dr. Abood developed an intense interest in drug toxicology and drug dependence. Doing research with synthetic and plant-derived chemicals know as cannabinoids, which are found in Cannabis Sativa, commonly known as marijuana, Dr. Abood discovered that cannabinoids modulate or tone down glutamate neurotransmission, which has been implicated as one of the leading causes of motor neuron death in ALS. Thus, her journey in ALS research began.

Dr. Abood's laboratory is making dramatic progress towards understanding the role of cannabinoids and their receptors in ALS. They have found that the cannabinoid, *tetrahydrocannabidiol (THC)*, reduced the rate of decline in motor function and increased survival (by 5%) in the transgenic SOD-1 ALS mouse model. Importantly, THC was found to be effective when administered after the onset of signs of disease; it is the first compound demonstrated to be effective *after* disease onset in the mouse model. The significance of this finding is amplified when one considers that pre-clinical testing of most compounds has demonstrated efficacy only when administered before disease onset and most of these compounds have shown no benefit in clinical trials. This is very important because it shows us that this class of compounds may provide a new template for designing new ALS drugs for treatment.

Jian Liu, Ph.D.
Associate Research Scientist

We welcome the newest addition to our research team; Dr. Jian Liu joined Norris ALS Center in January from San Diego. She is devoting her energies to an improved understanding of ALS by studying cell death mechanisms in ALS.

Dr. Liu did her postdoctoral training with Dr. Don W. Cleveland at UCSD, where she has spent the last several years studying specially bred ALS rodent models. She received her Ph.D. in Neurosciences from Washington University, St. Louis, Missouri.

At the Norris ALS Center, Jian Liu will focus her ALS research on animal models, studying the involvement of mitochondria, the energy-generating machinery in our cells. Many studies, including her work, have led scientists to the recognition that mitochondria are important targets in ALS. By understanding how mitochondria are damaged and what the detrimental consequences are, Dr. Liu hopes to find and design drugs that can target specific mitochondria malfunction. The ultimate goal of her research is not only to better understand ALS disease, but also to find compounds that will have a beneficial effect on the devastating effects of ALS.

Upcoming Events

Ask the ALS Experts
Update on ALS Basic Science/Clinical Research
Saturday, May 17, 2003; 1:00 – 4:00 pm
Miyako Radisson Hotel
Post Street, San Francisco
For more information call (415) 673–7500

All Star ALS Gala Event
Saturday, June 7, 2003
Atherton
For information call (415) 392-2572

Ask the ALS National Experts
Saturday, October 18, 2003
Location TBA
Local and National Experts

The Forbes Norris Award

Each year the International ALS/MND Alliance, hosts of the International ALS/MND Symposium, is honored to present the Forbes Norris Award to the physician/scientist nominated by his ALS colleagues as exemplifying "care and compassion in the study and management of ALS." The 2002 award was presented to Professor Vianney DeJong, of the Netherlands, who was not in attendance. However, Dee Norris read the proclamation and will fly to the Netherlands to present this prestigious award to Prof. DeJong at a later date.

The Humanitarian Award

This award was inaugurated by the International ALS/MND Alliance in 2000 to recognize non-scientific contribution to the fight against ALS/MND. We are extremely proud that the winner of the 2002 award was our own star, Dee Holden Norris, Advisory Director Forbes Norris ALS Center.

News Report:
International Symposium on ALS/MND in Melbourne

Last November over 450 scientists, clinical workers, and other leaders in the field of ALS/MND gathered in Melbourne, Australia to hear the latest clinical and scientific research developments in ALS. This annual meeting, held in a different world location each year, reveals the level of studies in progress looking at the mechanisms of cellular death in motor neurons, as well as the validity of successful clinical interventions and observations to improve the quality of life for those who must live with ALS.

The symposium began with America's Dr. Merit Cudkowicz, giving an overview of all recent clinical trials: the successes, failures and those in progress, the difficulties, the problems, and recommendations for future trials.

Of significant interest were reports on cognitive and neuropsychological changes in ALS. These papers verified what has been anecdotally reported for years, but only now have been significantly documented. This new clinical perception should aid in diagnostic awareness and management plans for clinicians everywhere.

Testifying to the importance of the role that non-invasive ventilation and percutaneous gastrostomy (PEG) plays in modern ALS management, several papers gave comprehensive overviews of these clinical interventions and their advantageous use in clinical care, especially when introduced early.

The increased understanding of the significant role genetics play in ALS was highlighted by an update from Dr. Robert Brown identifying a new gene segment linked to familial ALS found on Chromosome 16. This important burgeoning field has spawned a heightened awareness of the need for appropriate early genetic counseling and the role that pre-symptomatic gene testing and follow-up can and should play in ALS families with a disease history.

Several significant studies reported from Australia, Canada, Italy, and the United Kingdom, revealed the increased interest worldwide in "Quality of Life" issues and the important role in the effectiveness and overall treatment protocol of palliative care. Other papers discussed the search for disease progression markers and different indicators for accurate respiratory status and better management.

The most controversial presentations in the science sessions had to do with stem cells. A paper from Italy on a pilot project injecting mesenchymal stem cells directly into the spinal cord created much heated discussion. Other reports on stems cells were by Dr. Jeffrey Rothstein, who gave an overview of current research status. It is clear that many unknowns remain which scientists are just beginning to unravel and a better understanding is needed before the use of these cells can be introduced as a potential therapy.

This challenging and thought provoking symposia presented the most up-to-date, state-of-the-art summary of all that is current in ALS research and treatment.

Next year's meeting will be held in Milan, Italy.

California Pacific Medical Center

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The Gift of Giving

The Forbes Norris MDA/ALS Research Center is totally dependent upon private donations to support its patient services programs. It is supported, in part by the support of generous donors for ALS to the California Pacific Medical Center Foundation.

For more information on the Foundation or on ways you may give to the Forbes Norris MDA/ALS Research Center to support their services, please call Dee Norris at (415) 600-3608.

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