Recent Studies Open New Pathways for Hope

Promising new discoveries provide new opportunities for ALS research. The identification of mutations in the protein TDP-43 linked to some cases of sporadic and familial ALS confirm that this protein is directly involved in the disease process. This enables the development of new model systems for ALS, crucial not only to understanding disease mechanism but important as tools for drug development. There is an increasing interest in the academic and biotech sector to develop therapies for ALS. One of the limitations has been the focus on one animal model, the G93A SOD1 transgenic mice, representing only a small percentage of the disease.

The discovery of variations in the gene DPP6, that controls an enzyme found mostly in the brain and associated with spinal cord injury in rats, in two different studies and populations provides early evidence that the whole genome association studies have the potential to uncover gene changes linked to sporadic ALS. Recent advances in stem cell technology provide opportunities to develop cell lines from people with ALS so that we can more closely mimic the human disease in the laboratory.

As highlighted in this issue’s article titled “New Treatments for ALS 2008” on pages 4 and 5, there are many challenges to clinical trials for ALS, but with a growing number of potential compounds for the disease and networks to move trials forward, we are better positioned now to bring potential therapies to patients. Through the growing interest in translational efforts, there is an increasing interaction between clinicians, research scientists and the industry and an enthusiasm to move research from the lab to the clinic.

It is indeed a promising time for researchers to be focused on ALS research, and with commitment and collaboration, we look forward to new therapeutic approaches for people with ALS.

- Lucie Bruijn, Ph.D.

Robberecht honored with Essey Award

The ALS Association joins the American Academy of Neurology in presenting the 2008 Sheila Essey Award for ALS Research to Wim Robberecht, M.D., during the Academy’s 60th Annual meeting in Chicago, April 12-18, 2008.

Robberecht, Chairman of the Department of Neurology, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium is a highly respected clinician and researcher in the ALS field. His research aims to contribute to the understanding of the disease mechanism of ALS and to the development of a treatment for this disorder. To this end, the clinical team he directs is actively involved in clinical trials, genetics of ALS and epidemiology. In addition, his team provides multi-disciplinary care for ALS patients.

His laboratory has used in vitro cultures of motor neurons and glial cells to determine the role of excitotoxic and calcium-mediated motor neuron death, the involvement of heat shock proteins in neurodegeneration and the biology of vascular endothelial growth factor (VEGF) in ALS. More recently his laboratory has focused on using a zebrafish model for ALS and has observed some interesting early changes in axon outgrowth that may be exploited to develop a novel screen for ALS.

“Our work on excitotoxicity, VEGF and glial...”

- Lucie Bruijn, Ph.D.
Essey Award cont.

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cells will hopefully contribute to the understanding of the sporadic form of ALS accounting for the majority of ALS patients. In addition, the genetic screen of the zebrafish model we recently developed may complement the results obtained in human studies. Such combined approach of basic and clinical research is, at least in my mind, what is needed in order to advance the understanding and treatment of ALS. The participation of ALS patients in molecular, genetic and therapeutic studies is pivotal.” commented Robberecht.

“As clinician and research scientist, Robberecht has contributed significantly to the ALS field, and his leadership and collaborative approach to research efforts are invaluable to the ALS community,” commented Lucie Bruijn, Ph.D.

The $25,000 prize honors the memory of Sheila Essey and was made possible through the generosity of the Essey Family Fund. Past recipients have often used the funds to support research of promising young scientists on their teams.

Clinician Scientist Receives Award

The ALS Association and the American Academy of Neurology (AAN) are pleased to announce that Alice S. Chen-Plotkin, M.D., from the University of Pennsylvania School of Medicine, Philadelphia, PA, is this year’s recipient for the AAN/ALS Association Clinician Scientist Development Award as part of TREAT ALS (Translational Research Advancing Therapy for ALS). The purpose of the award is to recruit talented and promising young clinicians to the ALS research field, who propose innovative clinical research, and to foster their development to make significant contributions to ALS clinical research. Dr. Chen-Plotkin’s study will focus on the suggested role of TDP-43 in regulating the expression of genes.

TDP-43 (TAR DNA binding protein 43) has been previously identified as a major component of the “inclusions,” or protein clumps, found in the motor neurons of ALS patients. Scientists have recently identified mutations in the gene encoding TDP-43 linked to familial and sporadic ALS confirming that in at least some cases of ALS TDP-43 is integral to the disease process. “We hope that by understanding the genome-wide expression of genes in ALS and the contribution of TDP-43 to regulating this process, we can find early clues to the causes of disease. This, in turn, might lead to the development of effective therapies,” commented Dr. Chen-Plotkin. “I feel extremely honored to be receiving the AAN/ALS Foundation Clinician Scientist Development Award. Not only does it provide crucial support for my research, but it also serves as a vote of confidence and, as such, is very encouraging to a fledgling neurologist-neuroscientist.”

Opportunities for Drug Discovery in ALS cont.

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effects of mutant superoxide dismutase 1 (SOD1), and the protein aggregation it causes. SOD1 mutations account for 20% of familial ALS, or about 2% of all ALS cases. Efforts are also underway to develop a vaccine against the mutant protein, to stabilize it in its normal form, and to silence it with antisense. But SOD1 is only a small part of the ALS picture, and targeting it is only part of the solution, speakers agreed. Other potential targets include improving axonal transport, rescuing mitochondria, and reducing neuroinflammation. Drug screens for each of these targets are contemplated.

High-throughput screening requires fast and simple assays, which are best done in individual cells not whole animals. New developments in stem cells will soon allow rapid production of billions of human motor neurons, perfect for the task (mouse neurons can already be made in such abundance). Partnering between academic researchers, who have identified potential targets, and biotech companies with expertise in central nervous system drug development will improve the chances of success by drawing on the specialized strengths of each group, Dr. Bruijn said.

Clinical trials are the goal of all this effort, of course. The full picture of ALS clinical trials is covered elsewhere in this issue, in a special article by Merit Cudkowicz, M.D., of Massachusetts General Hospital.

TO KEEP CURRENT with the ALS field, read the monthly journal news reports at www.alsa.org under the research tab.

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In vitro culture of motor neurons (red) and glial cells (green) derived from the G-93A SOD1 mouse model. – Image courtesy of Wim Robberecht

Alice S. Chen-Plotkin, M.D.