Discovering new treatments is a top priority for all ALS researchers. Clinical trials are the endpoint, but long before that, drugs must be discovered and developed. It sounds simple, but in fact, it is one of the most challenging steps in forging new partnerships.

So what is the best way to find and develop new drugs that can be tested in clinical trials? That was the question that, in January 2008, brought together over 80 research scientists, neurologists, government officials, drug company CEOs and others, for a four-day research meeting "Accelerating ALS Research: Translating Basic Discoveries Into Therapies for ALS," sponsored by The ALS Association as part of its TREAT ALS initiative.

Collaboration among diverse groups is essential for progress in drug discovery and development for ALS, according to Lucie Bruijn, Ph.D., science director and vice president of The Association, and the TREAT ALS (Translational Research Advancing Therapy for ALS) initiative is a central part of that strategy.

“The purpose of TREAT ALS is to form academic and biotech partnerships to perform all the necessary but risky early-stage studies in drug development, to ultimately bring new therapies to patients," commented Dr. Bruijn. "Forums such as this meeting to share data and discuss strategy with such diverse expertise are critical to the success of the initiative and will continue to open up new opportunities for ALS research."

The wide-ranging discussions between diverse groups of professionals was unusual for a medical research meeting, where specialists so often talk only to those in their own narrow field. “It was unlike any other meeting I’ve been to,” said one participant.

Funding for the meeting was provided by the Association; the National Institute of Neurological Disorders and Stroke and The Office of Rare Diseases, National Institutes of Health; and The Linden Foundation in memory of Suzanne V.A. Kelsey.

Partners in Drug Discovery
“ALS is becoming a more attractive therapeutic target for large pharmaceutical companies,” according to Andrew Wood, Ph.D., CEO of Wyeth Research, due to the recent commercial success of a treatment for a rare metabolic disorder. Nonetheless, larger companies are still reluctant to fund the earliest stages of drug discovery and development, said Ross Stein, Ph.D., of Harvard Medical School, because of the high expense and high risk of failure.

Therefore, these riskier stages are still the province of academic researchers and small biotech companies. Throughout the conference, speakers made it clear that the more these smaller groups can do up front, the more likely it will be that a larger company will take an interest further down the development pipeline.

Funding for these high-risk efforts, therefore, will continue to come from private organizations such as The ALS Association, venture capitalists, and the federal government. The National Institute of Neurologic Diseases and Stroke (NINDS), a branch of the National Institutes of Health, is taking an interest in development of treatments for ALS, according to NINDS Director Story Landis, Ph.D., who said that ALS ranks high in NINDS goals “for where we can make a difference.” Partnerships between all these groups was a key theme of discussion.
The Best Targets in ALS

Drug discovery usually begins with identifying a “target”—something in a cell that the drug can interact with. In ALS, motor neurons are most affected, so researchers typically look for targets in these cells. The most common target is the protein superoxide dismutase 1 (SOD1). About 2% of all ALS cases are caused by mutations in the gene that encodes the SOD1 protein, and researchers have used mutant SOD1 to create animal models of the disease. Exactly how the mutant protein causes the disease is still unknown, however, making it more difficult to discover drugs in these models.

One characteristic of mutant SOD1 is that it forms clumps of proteins within neurons. Several groups are attempting to interrupt this process. Some are developing molecules that prevent two proteins from attaching to one another, while others are working on vaccines that would cling to the mutant protein and cause it to be broken down. Other groups are developing treatments to prevent the protein from forming in the first place, by silencing the mutant gene.

But SOD1 isn’t the only possible target. Some researchers have found that in ALS, transport is impaired down the long extensions of the motor neurons, called axons. Improving this transport may be beneficial. Others are targeting the immune system within the brain and spinal cord, since it appears that inflammation (caused by immune cells) worsens the disease. Still others are investigating how neurons handle toxic byproducts, and are attempting to find drugs that improve that ability.

Finally, because there may be no single best target in ALS, other researchers are focusing not on individual molecules or processes, but the overall health of neurons, and looking for compounds that protect them from harm.

Screening for Hits

With a target in hand, researchers then conduct a “drug screen.” In this step, thousands or even hundreds of thousands of chemical compounds are tested to see which, if any, has an effect on the target (e.g., which can prevent clumping of SOD1). An effective compound is called a “hit.” “On a difficult target, you need a half million compounds for a 50% chance of getting a hit,” said Chris Lipinski, Ph.D., one of the most respected chemists in the field of drug discovery.

Testing this number of compounds requires automation. While motor neurons are affected in ALS, they have not been used in most automated drug screens, because they have not been available in sufficient numbers. Stem cells are changing all that, according to Lee Rubin, Ph.D., of Harvard University. In his research, he isolates embryonic stem cells from normal or SOD1 mutant mice, and redirects them to make motor neurons, which can then be produced in abundance. New work indicates that reprogramming adult stem cells to become embryonic-like stem cells is also possible. This would allow the development of patient specific cell lines for drug screening. “It’s possible to contemplate making hundreds of cell lines for ALS,” he said, potentially individualized for drug screening in different types of disease. While not ready quite yet, this advance is likely to come very soon.

Once a hit is identified, it must be confirmed by replicating the experiment several times. Failure to replicate usually means the initial result was a “false positive,” and should not be pursued any further. It is a disheartening choice to abandon an initial hit, but this rigorous approach is one of the keys to an ultimately successful search, by avoiding costly research downstream on hits that don’t have the potential to move to the clinic.

Next, the compound must be modified in dozens or hundreds of different ways, to find a form that has the properties of a good drug: it is effective at a tolerable dose; it gets into the bloodstream and then into the brain and spinal cord; it can be safely metabolized and excreted; and it has few side effects. “Compounds that start out chemically intractable stay that way, with very few exceptions,” said Robert Pacifici, Ph.D., of the Cure Huntington’s Disease Initiative, meaning that even if a drug looks good in a cell-based screen, it may not have what it takes to make a good drug. The art of drug discovery is not only in finding leads, but in knowing which ones to pursue and develop.
With a drug candidate in hand, researchers can then test it in animal models, hoping it will not only slow the disease, but be safe and well tolerated as well. If the animal tests are a success, the drug can move on to clinical trials. The challenges of clinical trials in ALS are discussed more fully in http://www.als.org/research/article.cfm?id=1195 or full article http://www.als.org/research/event.cfm?id=1197.