annual report 2000

ALS THERAPY DEVELOPMENT FOUNDATION
As a nonprofit biotechnology company, the ALS Therapy Development Foundation works to fill the development gap in ALS, in order to transform useful information on ALS from a research paper to a concrete therapy.

Why a Nonprofit Biotech?

Traditionally, “disease nonprofits” operate to raise money that is then given out in grants to support research. Efficiency is evaluated by the ratio between fundraising costs and how much money is spent on research. Nonprofits like these often state with pride, “We are very efficient – we have less than fifteen percent overhead,” or, “We had a great year, we raised six million dollars.” This is so pervasive because the purpose of disease-based charities has been defined as philanthropic fundraising.

We challenge this definition. We are redefining the role of nonprofits fighting disease. We exist purely to develop treatments for the patients living with ALS today, not to raise money for research papers. We will have a great year when we have found a cocktail that arrests ALS. We had a good year during 2000 not because we increased our fundraising by more than 400 percent, but because we enabled the first human stem cell transplants in ALS, developed a process to rapidly test drugs for efficacy in ALS, and because we gave patients information to make decisions about their own treatments.

In the corporate world, biotechnology and pharmaceutical companies present themselves to the world by outlining their accomplishments in clinical development. Such companies have generated more than 95 percent of the new therapies available in the world today. Their shareholders demand the rapid, effective development of treatments because that is the only way the companies will make money and thrive. Unfortunately, these companies generally will not attack ALS because the “market” is not considered large enough.

As a nonprofit biotech we also have shareholders to whom we are responsible. My brother Stephen is one of them, as are the hundreds of patients we talk to regularly, and the rest of the 30,000 Americans who are presently living with ALS. Based on our relationships with our shareholders, we know that what they need now is the rapid, effective development of treatments for ALS. And this is what everyone at the Foundation takes responsibility for and strives to accomplish. Ultimately, we will be evaluated not by how much money we raise, but by how successfully we deliver treatments and information that help our shareholders.

James Allen Heywood, Director
**What We Do**

**FROM RESEARCH TO TREATMENTS**

Modeled after the best approaches used by commercial biotechnology companies, ALS Therapy Development Foundation has developed a process to rapidly screen drugs and therapies to determine how they will work to help ALS patients alive today.

Working within this process, the Foundation has become a new entity in therapy development: a nonprofit biotechnology company. For therapies to eventually reach ALS patients, a drug or therapy must go through several steps. These steps include:

- Collecting data supporting the therapy’s efficacy
- Proving the drug or therapy is manufactured consistently
- Proving through animal testing that the drug, human protocol and dose is safe and therapeutic

ALS-TDF works to identify both new and already-approved therapies efficacious in ALS using a quick, efficient system in the interest of ALS patients alive today. As a drug or therapy moves toward human treatment, it moves through the three phases outlined below:

1. **Research:** Research involves strategically reviewing information to identify different theories of the disease that will identify targets for treating or attacking ALS. The Foundation examines clinical studies and research papers already written on ALS, functional genomics and patient and doctor recommendations to identify therapy targets.

2. **Development:** Development includes **Targeting, Formulation, Validation and Preclinical studies.** This work requires a diverse, team-based approach with experts in formulation, chemistry and pharmacology. ALS-TDF has built its own team from these fields to accomplish these tasks – something traditionally undertaken at biotechs alone.

    **Targeting** involves testing or designing treatments against targets discovered in the research phase through assay screening, drug review and treatment design. The specific potential treatments developed must then go through **Formulation** to be tested and evaluated for human use. This involves studying stability, clearing time, bioavailability, blood-brain barrier permeability and approaches for delivering the drug to appropriate regions of the brain in safe, effective doses. After this work is completed, they are prioritized by potential benefit and moved forward to **Validation** where they are tested in the best animal models of the disease including the stroke model and SOD mouse.

    The therapies that appear effective in animal models have a significant potential to work in humans, and are moved into the Preclinical phase where safety, route of delivery, manufacturing and regulatory procedures are addressed so that the therapy can be moved to human use.

3. **Treatment:** If the therapy is safe and improves life expectancy in ALS animal models, it reaches the ultimate phase and goal of ALS-TDF – human **Treatment** for ALS patients alive today.

As the Foundation forges ahead in the unique approach to curing ALS patients, this process is continually reviewed and revised to work towards the most efficient procedure possible.
Identifying Viable Pathways for Treating ALS

Evaluating functional genomics studies done on ALS patients, ALS-TDF has identified strong inflammatory signatures in ALS patients. Based on that data, ALS-TDF began looking at the role of microglia in the brain and drugs that would work to prevent or stop the inflammation. In collaboration with leading researchers, ALS-TDF research staff began developing an IL13 assay, a microglial assay and the clodronate and cord blood transplant cocktail therapy, all projects which were moved to the Development phase during 2000.

During a human stem cell transplant treatment developed by the Foundation in 2000, ALS-TDF noticed that certain white blood cell markers are altered in ALS patients and began investigating their use in diagnosis and treatment. Based on this information, the Foundation developed a comprehensive theory of microglial activation as a key activator in ALS, and began collaborating with leaders in the microglial and immunology fields to develop a group of molecular targets for drugs to inactivate microglia. The information obtained through this treatment is potentially a significant finding that could impact how future stem cell treatments are implemented in ALS.

The Foundation contracted with NERAC, a professional database search company, to identify relevant patents, papers and scientific abstracts presented worldwide that relate to both ALS and associated theories of what might cause ALS. This search provides ALS-TDF with a larger breadth and scale of information than is typically available to an academic center. This richer information set improves the ability of ALS-TDF’s research staff to develop new theories of the disease and treatment targets.

“As a person suffering from ALS, I want to identify and work with an organization that can bring about results during my lifetime. I believe ALS-TDF is capable of bringing hope to the hopeless.”

Jesse Brown, Former U.S. Secretary of Veteran’s Affairs, ALS Patient

“People need to be aware that for so many out there the clock is ticking. ALS-TDF is unique because it realizes that time is an enemy. Therefore, they are aggressive at applying resources at the critical bottlenecks.”

Matt During, Professor of Neurosurgery and Director The CNS Gene Therapy Center at Thomas Jefferson Univ.
Development

Studying Targets for Efficacy & Safety for ALS

Thirty-five FDA-approved drugs were identified as ‘hits’ in the FDA 2000 project, conducted in collaboration with Dr. Steve Gullans at Harvard. Dr. Gullans used a hydrogen peroxide assay to distinguish drugs that have neuroprotective effects, which are now moving into the In-Vivo Screening Program.

- ALS-TDF has developed its own in-house In-Vivo Screening Program to test already-approved drugs for efficacy in ALS animal models. This is the largest single ALS In-Vivo Screening Program in the world. A key goal of the Foundation in 2001 is to get this program running at full capacity.

- ALS-TDF researchers began targeting drugs for the In-Vivo Screening Program that affect glutamate toxicity, neuroinflammation, mitochondrial function, antioxidants, immune modulation and growth factors. To choose the order to test these drugs, those that act on multiple pathways are prioritized higher on the screening list, along with drugs that are easily accessible and well-tolerated by humans. Through its prioritization of drugs the Foundation has identified key drug pathways that will hopefully be the most effective in attacking the disease.

- Six drugs from the FDA2000 Project have shown efficacy in preventing neuron death in multiple assay tests. These drugs have been put on the priority list for the In-Vivo Screening Program.

- An IL3 assay has been developed to see if any drugs might inhibit the expression of this gene. IL3 has been found to cause ALS if over-expressed in mice and is also associated with related inflammation. ALS-TDF began a process to try to quantify IL3 in ALS patient’s blood, cerebral spinal fluid and tissues.

- The Foundation began developing a microglial assay as well to evaluate drugs that would inactivate microglia. The Foundation is working on the microglial assay based on a theory that activated microglial cells are what is causing havoc in ALS patients’ spinal cord. This assay attempts to identify drugs that slow or shut down these cells completely, and then rebuild them.

- An extensive database of more than 200 drugs with potential efficacy for ALS has been developed by the ALS-TDF research team, including a priority list of 50 drugs. These drugs were gathered from FDA 2000 and Foundation research. They are moving into the In-Vivo Screening Program for animal testing to see how they might affect humans.
Clinical Development & Treatment

A research paper published last year presented findings that showed a drug called zVAD-FMK had efficacy in ALS. The Foundation immediately pursued this possibility and put the drug into animal testing, finding that the drug was too toxic for human use and was potentially lethal at the therapeutic dose. Though the result was disappointing, ALS-TDF was the only group to take responsibility for evaluating the drug’s possible immediate use for ALS patients.

The Foundation is now collaborating in the development of safer drugs that affect the same pathways. Though the drug itself failed, zVAD-FMK was instrumental in the decision to design a new version of the drug that is now awaiting formulation testing at the Foundation.

Another theory explored by the Foundation was glutamate toxicity, through the development of the Uptake Gene Therapy. This therapy was designed to replace EAAT2, a protein involved in the successful removal of glutamate from the extra-cellular space. The theory behind the therapy was strengthened by the discovery that when EAAT2 was over-expressed in SOD mice, ALS was delayed up to 400 percent. But initial tests of the gene therapy in SOD mice did not significantly alter survival, temporarily halting the project. ALS-TDF is working to improve the vector and/or change the target cells for treatment.

Three ALS patients received stem cell transplants using a protocol developed by the Foundation. Though the procedure was shown to be safe there was no clear benefit to the patients. The results also presented ALS-TDF with the challenge to find a way to produce the large number of cells necessary for additional treatments. Additionally, an intriguing signature in the patients’ blood was discovered that sent the program in a new direction.

In combination with other drugs, ALS-TDF believes a stem cell therapy can be therapeutic. Based on the results of these treatments, it was determined that further animal studies are necessary to design a more effective therapy. These studies began in 2000 and will be ongoing during 2001.

Clinical Development & Treatment

DRIVING THERAPIES FORWARD FOR USE BY ALS PATIENTS ALIVE TODAY

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Patients Are Our Shareholders

MEASURING SUCCESS IN LIVES, NOT DOLLARS

Karen and Fran Delaney

“The mission of the Foundation is driven by love, not profit. ALS-TDF reminds us of what it means to be part of humanity. They have given my family the greatest gift of all — hope. I believe that the people of ALS-TDF are the kind of people that make change a reality.”

Karen Delaney, Daughter of Fran Delaney

"Sometimes an act of great courage is required to change the status quo. ALS-TDF is that act of courage.”

Stephen Heywood

"ALS-TDF does not let distractions such as conventional thinking, profit or politics distract them from their goal. The Foundation's goal is clear, the motivation is pure and the passion is genuine. ALS-TDF brings innovative, open-minded thinking combined with a true sense of urgency that is a unique and positive influence in the fight against ALS.”

Fran Delaney - Vice President, Compaq Computer Corporation, ALS Patient
Patients are Our Shareholders

ALS Therapy Development Foundation exists to fill a gap in the existing health care system. Academic centers are not set up to complete repetitive and comprehensive tasks, and biotechnology companies pursue projects that will develop profits. Stepping into the crucial development phase, ALS-TDF became a new entity: a nonprofit biotechnology company.

At the core of this nonprofit biotech is the philosophy that patients are our shareholders. Any organization must measure its success in order to attain its goals, and the Foundation marks its success by gauging the degree to which ALS patients’ needs are met. As a nonprofit biotech, the profit potential is not measured in dollars, but in lives.

In 2001, ALS-TDF will continue its work for ALS patients in all its scientific work, including the full-scale expansion of the In-Vivo Screening Program and a new bioinformatics source for patients, researchers and doctors called “Neurobase.”

The Foundation expresses its sincere thanks to all those who have already chosen to invest in this unique, high-risk/high-reward venture called ALS Therapy Development Foundation. ALS-TDF investors stand apart because they have chosen to invest directly in therapy development for patients today. The stakes are high, but the potential outcome is greater than anything Wall Street has to offer – the lives of 30,000 ALS patients alive today and the 5,000 additional patients diagnosed every year.