In 1999, ALS TDF set out to answer one question: What drugs and treatments should ALS patients take? By 2005, we evaluated more than 700 therapies and completed more than 250 mouse studies. In doing so, we built the most comprehensive program of its kind for any disease. When we started, we could not know where this journey would lead, but we expected to find promising leads from the existing research.

There are still ideas left to test, but for the most part, we did not find the answer we sought – a treatment that significantly modifies disease. What we did find lays out enormous challenges both for TDF and the entire field of translational research.

In our quest to look at every idea, our program tested more mice than all other ALS labs in the world combined. This effort included unsuccessful attempts to replicate the major animal studies that led to clinical trials.

In contrast to the studies published by other labs, our mouse study results have been essentially identical to the results of human clinical trials. This work demonstrates that much of what the field thought it knew about ALS therapies was false, and that drugs have been used on patients that never actually worked in the mouse. This year we will publish our findings in a paper that does not dwell on the problems, but outlines how to use higher standards to generate results with meaning.

TDF did not set out to raise the standards of translational research, but to find an answer to ALS. Given all we have learned, given the dwindling number of worthwhile treatments left to test, we must develop a new plan.

So now we commit to reaching a new goal.

This past year, TDF committed to developing the most comprehensive ALS research program ever conceived. Building on our world-class Therapeutic Development Program, TDF will use new tools and technologies to take apart ALS gene by gene, protein by protein, to understand it completely so we can stop it.

The Apollo Projects

In 1962 President John F. Kennedy announced his seminal plan to reach the moon – a journey of 239,900 miles. At the time, there were more questions about how to accomplish the mission than answers. Seven years later, Neil Armstrong took one small step for mankind. Today, such bold, brash ideas – reaching the moon, stopping ALS – have grown too rare.

We name our new research program, the TDF Apollo Projects, in honor of President Kennedy and the Apollo Program. Within seven years we plan to find a way to stop ALS. Like Kennedy, we do not know that this can be done. Like Kennedy, we intend to succeed.

Together our combined passion, history, and focused approach uniquely position TDF to lead.

Thank you,

Sincerely,

James Allen Heywood
d’Arbeloff Founding Director
“We choose to go to the moon...and do the other things, not because they are easy, but because they are hard, because that goal will serve to organize and measure the best of our energies and skills, because that challenge is one that we are willing to accept, one we are unwilling to postpone, and one which we intend to win...”

- President John F. Kennedy, 1962
The TDF Apollo Projects

2006 → 2011

The most comprehensive ALS research project ever conceived, the TDF Apollo Projects span every aspect of discovery research and therapeutic development.

Over the next seven years, TDF will build, expand and execute six projects that fill critical gaps across the entire spectrum of drug development in ALS — from discovery and validation of biological targets for drug treatment and the development of biomarkers, to the improvement of drug screening efforts and the execution of clinical investigations.

TDF’s Discovery Research Project will use profiling data to paint a detailed picture of gene and protein pathways specific to the ALS disease process. In parallel, we will seek to identify biomarkers, which can be used for diagnosing disease, tracking disease progression or evaluating the potential effectiveness of treatments.

Potential therapeutic targets will be prioritized through a large-scale bioinformatics platform. Promising leads will then be validated in animal models through genetic profiling. In concert, TDF will expand its drug screening capability, selecting therapies to test against those targets. TDF will then take the best therapeutic targets to clinical trial, in partnership with other organizations.

To support the research projects, a number of core facilities will be created or expanded. In particular, TDF plans to expand its Pipeline application to an open platform for use in evaluating and prioritizing potential therapies across disease.

Laying the Groundwork

TDF has completed a number of critical tasks in preparation for launching the TDF Apollo Projects.

> Developed a streamlined surgical process for allowing direct spinal delivery to the mouse in our animal studies.

> Published “Amyotrophic Lateral Sclerosis: A report on the state of research into the cause, cure and prevention of ALS.” Massachusetts Department of Public Health.

> Spun off biotechnology company ALSGEN, which is charged with discovering treatments for SOD1 familial ALS.

> Expanded and upgraded our laboratory to meet Biosafety Level 2 (BL2) guidelines.

> Launched the Gene Expression Core, which allows TDF to search for progression biomarkers and new therapeutic targets.

> Launched the Mass Spectrometry Core, which allows TDF to monitor drug levels attained in any tissue type.

> Launched the Histology and Microscopy Core, which allows TDF to monitor and track the cellular and protein alterations associated with disease state.

> Prepared two manuscripts on mouse model study design and intrathecal drug infusion.

Discovery Research

Which genes are expressed or altered in ALS versus non-ALS? Of those, which are most important?

Biomarker Development

What patterns of gene and protein expression changes can be used as diagnostic markers or to track disease progression?

Target Validation

Which altered genes are most promising as targets for therapeutic intervention with drugs or gene therapy?

Drug Screening

Which existing or developing drugs and other treatments have the greatest impact in slowing, arresting or stopping the disease?

Open Science

What happens when you publicly share all data realtime using an open informatics process and quality management system?

Clinical Trials

Which treatments work in humans?
The Mission

Stopping Disease

TDF’s Discovery Research Project will discover and profile all the molecular differences in ALS, resulting in a comprehensive, dynamic picture of how the disease operates in mice, humans and other models. This Project uses genomic, proteomic and bioinformatic technology platforms to identify and track fluctuations in gene and protein activity in the course of ALS. It will be implemented in a pathway modeling, publicly open informatics platform that will share a picture of ALS in real time with any researcher who wants to contribute.

Breaking Down ALS

Effective treatments require effective targets - molecular pathways the modification of which will impact disease. These can occur at all three fundamental biological levels in the cell.

DNA: HEREDITARY

RNA: MESSAGE

PROTEINS: STRUCTURES AND MACHINES

A NEW LOOK AT ALS ATROPHY:

By diagnosis, patients have already begun to experience atrophy and muscle loss as the large motor neurons begin to waste away and eventually die. TDF researchers are working to identify biomarkers, cellular components that allow the disease state to be detected and stopped much earlier.
To support the Apollo Projects, in 2005 TDF began building several research cores:

The Mass Spectrometry Core allows researchers to measure drug levels attained in any tissue type, crucial to validating targets.

The Gene Expression Core facilitates the discovery of biomarkers and new therapeutic targets. Gene expression profiling compares the genes expressed during disease progression in the ALS mouse and non-diseased mice.

The Microscopy Core allows the visualization of changes in tissue cells and proteins during disease progression and in response to therapeutics, to understand disease progress and monitor therapeutic efficacy. Using structured illumination and imaging software, we will attempt to reconstruct high resolution stacks and generate morphometric analyses of progression. This will allow the creation of a quantitative index for tracking the efficacy of treatments.

The Informatics Core is composed of three integrated tools that track all molecular, target, therapeutic, project and study results under a single platform that can share all information realtime. In essence, it allows TDF and the world’s researchers to see all molecular changes, relate them to targets, find drugs against those targets and then plan, track and execute the studies that will ultimately find effective treatments for ALS. The Informatics Core consists of a bioinformatics repository and analysis tool, the pipeline target and therapeutic development platform, and the LIMS system, which manages the laboratory operation.

“It is now possible to put on a glass ‘gene chip’ the size of a postage stamp the 42,000 genes that are the blueprint for a mouse. By mapping the progression of the disease, using gene chips, we can whittle those 42,000 genes down to a manageable number of pathways that can then be targeted with drugs, gene therapy, and gene silencing technologies.”

– Sean Scott, VP of Drug Development
Leaders In Action

Jon Blais

After receiving his ALS diagnosis, Jon Blais completed the 2005 Ironman Challenge in Kona, Hawaii and recently launched the War on ALS, which calls for multi-sport athletes to join the fight.

The Stafne Family

Scott Stafne and his wife Kirsten have committed to raising $100,000 for ALS research this year.

Mary Lou Krauseneck

Over the past five years, Mary Lou has inspired more than $1,000,000 in funding.

LEADERSHIP AWARDS 2005

“Twenty years from now you will be more disappointed by the things that you didn’t do than by the ones you did do. So throw off the bowlines. Sail away from the safe harbor. Catch the trade winds in your sails. Explore. Dream. Discover.” - Mark Twain

THE MARY LOU KRAUSENECK COURAGE AND LOVE AWARD:

Amy Whipple
Cousins Alex and Zoe Heywood have convinced their classmates to “trike” their way to more than $2,000 in funding for research.

The Friends for Faye group raised more than $500,000 in one year and won’t stop until an effective treatment is found.

“Do not let your fire go out, spark by irreplaceable spark, in the hopeless swamps of the approximate, the not-quite, the not-yet, the not-at-all. Do not let the hero in your soul perish, in lonely frustration for the life you deserved, but have never been able to reach. Check your road and the nature of your battle. The world you desire can be won, it exists, it is real, it is possible, it’s yours.”

- Ayn Rand

**The Stephen Heywood Patients Today Award:**
Joe Shambo & Matt Dowd

**The Fran Delaney Challenge and Respect Award:**
Faye Magneson

**The Stephen Milne Adventurous Spirit Award:**
Steve Lewis
Sports do not build character. They reveal it.”
- Haywood Hale Broun

Founded by PGA TOUR Pro Jeff Julian and golf legend Tom Watson and his caddy Bruce Edwards in 2003, Driving 4 Life has grown to be the premier fundraising program supporting ALS research through the game of golf.

D4L programs have raised more than $1 million a year for the past three years, marking a $3.5 million milestone in October 2005.

Thousands of golfers have participated in nearly 100 charity golf events since 2003 through the D4L Nationwide Event program.

D4L will grow the Signature Series from three to 20 events by 2009 through a unique partnership with the PGA TOUR and TPC Network.

“Facing challenges is what the game is all about.”
- Jeff Julian
# Financial Report 2005

## Assets

<table>
<thead>
<tr>
<th>Item</th>
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<td>Fixed Assets-Net</td>
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<td>Other Assets-Net</td>
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<td><strong>Total Assets</strong></td>
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## Liabilities and Net Assets

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<td>Net Assets</td>
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<td><strong>Total Liabilities and Net Assets</strong></td>
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## Support & Revenue

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<td>Contributions</td>
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<td>Grant Income</td>
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<td>Fundraising Events</td>
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<td>In-Kind Donations</td>
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<td>Interest, Dividends &amp; Gains/Losses</td>
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<td><strong>Total Income</strong></td>
<td><strong>3,509,483</strong></td>
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## Expenses

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<td>Research &amp; Development</td>
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<td>Patient Services</td>
<td>194,266</td>
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<td>Fundraising</td>
<td>374,219</td>
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<td>Management &amp; General</td>
<td>221,201</td>
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<td><strong>Total Expenses</strong></td>
<td><strong>3,735,019</strong></td>
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## Increase/(Decrease) in Net Assets

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<tr>
<td><strong>Increase/(Decrease) in Net Assets</strong></td>
<td><strong>(225,536)</strong></td>
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## Net Assets: Beginning of Year

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<td><strong>Net Assets: Beginning of Year</strong></td>
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## Net Assets: End of Year

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<tr>
<th>Item</th>
<th>Amount</th>
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<tbody>
<tr>
<td><strong>Net Assets: End of Year</strong></td>
<td><strong>468,476</strong></td>
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</tbody>
</table>

## Where the Money Comes From:

- Individual Contributions: 28%
- In-Kind Donations: 2%
- Grants: 15%
- Events: 55%

## Where the Money Goes:

- R&D: 79%
- Patient Services: 5%
- Fundraising: 10%
- Management & General: 6%
**MEMORIALS**

Gifts are made to ALS TDF in memory of a loved one upon their death. We express our sincere appreciation for these gifts made this year in memory of the following:

<table>
<thead>
<tr>
<th>Edward Abramson</th>
<th>John Farie</th>
<th>Karen Keefer</th>
<th>Al Munson</th>
<th>Roland Steben</th>
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<td>Jim Arey</td>
<td>Jeanne Fisher</td>
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<td>All of our Deceased Union</td>
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</table>

All of our Deceased Union
Brothers & Sisters
Brother of Janice Janson
Leadership Partners

In this battle against ALS, we have relied on the help, support, and passionate work of communities of people who share our mission. These people, scattered across the globe, have worked tirelessly this year to engage their communities in our fight against ALS. Our Leadership Partners bring essential support to the scientific team at ALS TDF with their actions, their drive, and their dollars.

Alan Inglis Fund
ALS Soccer Cup
Anthony Tucker Fund
Arrest ALS
Ben Heywood Effort
Bishop Fund
Blazeman’s War on ALS
Bryan and Mark Allain Fund
Carl Tanner Fund
Chris Martin Fund
Chris Stokos Fund
Christy Sloan Memorial Fund
Craig Cyr Golf Marathon
Darin Lilly Fund
David Dorfman Fund
David Eltschlager Fund
David Green Fund
Dean Adraktas Fund
Deane Jewell’s Team
DeeDee Fornengo Fund
Dennis Bourassa Fund
Dick Sanderson Fund
Donna Dake ALS Research Fund
Doug McGinness Fund
Elaine Leavitt Fund
Ellen Sutherland Fund
Elliot Macht Fund
NCPGA/AGA Father/Son Tournament
Frank Maynard Fund
Friends for Faye Fund
Friends of ALS TDF
Friends of Harry Gianneschi
Gloria Tourk Effort
Have a Heart
Herb Swartz Driving 4 Life Fund
HMS Host Golf Tournament
Hopkins Family Fund
Jack London Fund
Jack Orchard Effort
Jan Richardson Fund
Jane Goewey Fund
Jason Becker Fund
Jean Angel Fund
Jeff Julian Fund
Jeff Repetto Fund
Jeff Swanson Golf Marathon
Jeff Ureel Fund
Jennifer Nichols Fund
Stodard Family Fund
Jim and Susan Airey ALS Fund
Jim Fitzhenry Fund
Jim Raspanti Fund
Jim Sokiv Fund
Joe Shambo Fund
John Kary Drawdy Fund
Jon Russell Fund
Ken Melanson’s Quest for a Cure
LaMarche Fund
Larry Ellis Driving 4 Life Fund
Larry Manes Fund
Lee Blaskovich Fund
ALS TDF Palm Beach Fund
Luc Blais Fund
Maria Rychlik Fund
Marie Garratt Memorial Fund
Mary Jo Shippe Fund
Mary Lou Krauseneck Fund
Matt Dowd Fund
Melba Moeck Driving 4 Life Fund
Michael Donnelly Fund
Mike Aaronson Fund
Palley/Harfold Fund
Palguta’s Barracudas
Pam Barshack Fund
Paul Gerbick Fund
Peggy Lanza Fund
Peter’s Fund
PGA Tour Superstore World
Amateur Fund
Pittsburgh Families Effort
Randee Brown Fund
Richard M. Mott Effort
Robin Arnold Marathon Fund
Roby Molnar Swiss Fund
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- Franklin D. Roosevelt, 1932