Letter from the CEO

Are we any closer? What progress have we made? When are we going to find something? These are the questions that I get asked most. Perhaps you get them as well from your friends, your family, and others who want to know what is going on in the battle against ALS and what they can do to help.

This past year at the ALS Therapy Development Institute has been pivotal. Most importantly, we were able to follow-up on an exciting finding last year with a drug we called TDI-132/Gilenya® and announced in February of 2012 that we would be executing a clinical trial of it in ALS patients. This exciting announcement was followed by incredible outreach between families and the community to help fund this important Phase II clinical trial. I am pleased to report that the trial has been funded and will be completed in 2013. It is with great humility and cautious optimism that we take this step forward, and in advance I would like to recognize each of the people living with ALS who will participate in the trial for their heroism.

We are also excited to have continued to advance our important research collaboration with Biogen Idec and UCB Pharma on TDI-846 (CD40L). We are grateful to have such wonderful partners on that program, highlighted by the thoughtfulness of UCB’s Chief Medical Officer Iris Löw-Friedrich, M.D., Ph.D., who attended our 8th annual Leadership Summit, discussing directly with the patient community the important role that these types of collaborations play in moving potential treatments forward at big pharma. In addition at this year’s summit, we humbly recognized Dr. Theresa Stephan Hains, Rev. Bill Hassel, Eric Engdahl, Rob Tison, and Pete Frates with Leadership Awards. Finally, the following day, during an emotional second annual A White Coat Affair gala, it was my privilege to present Brit d’Arbeloff with our “Iron Horse Award”, in honor of our Institute’s founding partners.

It is also important to note we expanded our research institute in 2012, moving into a new 26,000 sq/ft space in Kendall Square. This was the first move for TDI in nearly 7 years, and with it, we more than doubled our in vivo screening facilities, added suites for cell-based research activities, and designated additional space for growth of the science team over the coming years. We need to continue to be innovative and out-front leading the effort to develop effective treatments for ALS patients today. Are we closer? Yes, we are, but now is not the time to celebrate the incremental steps. Now is the time to leverage this progress into larger and quicker leaps forward.

Thank you for your continued support. Without you, none of this would be possible.

Sincerely,

Steve Perrin, Ph.D.
CEO & Chief Scientific Officer
Announced the Launch of a Phase II Clinical Trial
ALS TDI announced its intent to launch a phase IIA clinical trial on TDI-132/Gilenya®, following our promising preclinical results showing positive outcomes on several disease measures in the SOD1 mouse model.

Expanded Research Facility in Cambridge
In March of 2012, we moved our research center into a 26,000 sq foot facility in the heart of Kendall Square in Cambridge. This is a 40% expansion from our previous home, adding 2.5 times the capacity in the animal facility and twice the lab space, allowing us to bring in house additional technologies and expertise—ultimately, allowing us to do more faster and take on more projects than ever before.

Renesensce, Neurotune & Gladstone Institutes Partnerships
We are working independently with these biotechnology companies to explore specific and very different approaches to treating ALS; to better develop models of disease, to test compounds that might have an effect on onset or progression, and to learn more about the neuromuscular junction’s role in disease course. We believe ALS is a complex disorder, and we partner strategically to achieve our mission.

10th Anniversary Tri-State Trek
The ALS TDI Tri-State Trek completed its 10th anniversary ride in 2012. This three-day, 270-mile event spanning three states started with 16 riders and has grown to over 400 participants, but the goal has always been the same: to end ALS. In its lifetime, the Tri-State Trek has raised $5.1 million for research at ALS TDI.

8th Annual Leadership Summit
The Ketchum Family - ALS has not slowed down Todd Ketchum, who was diagnosed with ALS in the fall of 2010 at 44 years old. Enjoying the outdoors, Todd and his wife Laura, along with their three sons, Toby, Sam, and Nevin, spend as much time as possible at their getaway in Tunbridge, Vermont. The Ketchum family, along with their close group of family and friends, have banded together to raise over $300,000 for the important research toward an effective treatment for ALS. Their passion for supporting ALS TDI goes beyond fundraising. The family represented us at the Red Sox 4-ALS game in May 2012, and their oldest son Sam interned alongside the scientists at ALS TDI who work hard every day for those battling ALS.

The Ketchum family is truly a part of the ALS TDI family and we could not continue our battle to end ALS without their tremendous support!

The Jaillet Family - Inspired by former Newton North classmate and founder of ALS TDI, Stephen Heywood, Michael Jaillet and his family started raising funds and awareness for ALS patients and for research through their foundation “MJ’s Army”.

Michael, diagnosed with ALS at age 43, along with his wife Libbi, and their three children, Mikey, AJ, and Katie, decided that the best place to donate research dollars was to the ALS TDI laboratory. TDI was built upon the commitment of families facing ALS. There is no better example of this commitment than that of the Jaillet family. In the past year, MJ’s Army has brought awareness to this devastating disease through 1,000 volunteered hours of service work, traveling to six cities, singing the national anthem at a Red Sox game, and hosting two fundraising events.

The Jaillet’s were so gracious to have shared their story in our annual appeal as an example of the effects of ALS on the entire family. Their story helped to bring in over $100,000 to the annual appeal in addition to their generous gift from MJ’s army of $30,000. We appreciate their courage and support to help us end ALS!
Six words: we should put this in patients. That is what we work toward each day at TDI. In the last two years, we have been fortunate to be able to say that twice. To make the statement a reality for PALS, we executed a fundraising campaign in 2012 to enable us to take this crucial next step.

TDI has always been a leader and innovator in the way that medical research is done. The ALS community has been a significant contributor to preclinical and clinical experiments on TDI 132/Gilenya®. Simply put, TDI-132/Gilenya® is going into ALS patients in 2013 because the community of supporters behind TDI accepted the challenge to make funding such a priority.

This unprecedented Phase IIA clinical trial will include 30 people living with ALS and will be completed during the first half of 2013. The goal of this small trial is two-fold. The primary objective is to determine whether or not TDI-132/Gilenya® can be given safely to ALS patients. The second goal is to investigate what effect the drug has on biomarkers of drug response accessible in the blood. The Institute is working closely with collaborators, including the drug’s maker, Novartis AG, on the design and execution of a larger Phase IIB clinical trial of TDI-132/Gilenya® which may begin enrollment in the early part of 2014.

Novartis first received FDA-approval to market fingolimod, an immunomodulating drug sold under the name Gilenya®, in 2010 for the treatment of multiple sclerosis. Gilenya® is thought to be able to modify how many certain cells, called lymphocytes, move around the body. It is thought that by reducing the number of circulating lymphocytes – through sequestration – will prevent them from contributing to the activation of the immune system, as well as neuroinflammation. Preclinical research of fingolimod, which became known internally as TDI-132, began at TDI in 2011, results of which in 2012 convinced the Institute to pursue clinical trial in ALS patients. These results were presented as part of a platform talk at the 23rd international research symposium of ALS/MND research held in Chicago in December 2012.

The ALS Therapy Development Institute has contracted the Northeast ALS Consortium to operate the clinical trial. Current enrollment sites include Massachusetts General Hospital in Boston; University of California, Irvine in Orange; Georgia Health Sciences University in Augusta; and Methodist Neurological Institute in Houston.
Phase IIa: Study Design

- Screening Period
  - ~60 Screened
  - 10 Subjects on Placebo
- On Active Treatment
  - 20 Subjects on 0.5 mg fingolimod
- Washout Period
  - 21 Days

Procedures performed at Post-Dose Hour 1, 2, 3, 4, 5, 6, 7 & 8

* Phase 2A Trial Site
The art of funding a clinical trial

Augie Nieto

To Augie Nieto, the word ‘leadership’ means something. Whether it has been as an entrepreneur, an innovator, a mentor, a board member, a chairman, a friend or a partner, the word “leader” carries significant weight to Nieto. When the FDA approved the clinical trial of TDI-132/Gilenya®, the Institute’s chairman showed leadership again.

But Augie and his wife Lynne are used to being the people that make important things happen. Through Augie’s Quest they have raised nearly $40 million for ALS research with the vast majority of it coming to ALS TDI. This funding helped propel the research that made the discoveries leading to the identification of Gilenya® as a candidate therapeutic for trial.

However, the Nietos went further this last year, providing a significant amount of funding without which TDI would not be able to execute this important trial.

“Seeing TDI-132 enter into clinical trial for ALS gives me hope that people living with ALS may soon be able to fight back.” That is what Augie Nieto said in a press release announcing that the FDA had approved the phase II clinical trial of TDI-132/Gilenya®.
Westphal Family

When the Westphal family grandchildren gathered to create their artistic collaboration, they strove to make something that would appeal to their grandparents. Here was the deal; whatever they made, their grandparents would purchase, but the kids had to donate their earnings to a cause of their choice.

The children were presented with information on a number of different non-profits, and by blind vote, they unanimously chose to donate their proceeds to ALS TDI, in honor of family friend, Corey Reich. The Westphal family has been generous supporters of the research at ALS TDI since Corey was diagnosed with the disease in 2007. This year, with the help of its youngest members, the Westphal Family donated $112,546 to the launch of the phase IIA trial of TDI-132/Gilenya®.

Lubbe Family

It’s not often that we are treated to the sight of a family of Easter Hedgehogs, but that’s exactly what nine-year-old Salli Lubbe offered to our science team as inspiration when they met to discuss the final data on TDI-132. And it worked.

Salli came into the lab with her parents, Klaus and Patti. Klaus had been a partner of ALS TDI for a number of years, as his company, BioXCell, has provided our team with monoclonal antibodies and recombinant proteins used in our research. BioXCell has also been a very generous sponsor of our A White Coat Affair gala since inception.

Patti had a pressing reason to visit the lab—her sister had been diagnosed with ALS. This lovely and generous family wanted to help launch ALS TDI’s first clinical trial. A few days after their visit to the lab, The Lubbe Family Foundation donated $100,000 to the launch of the phase IIA trial of TDI-132/Gilenya®.
Is it the right tool for the job?

The cause of ALS in the vast majority of cases remains a mystery. However, in the last 20 years, more than 20 genes have been linked to ALS. Most of these are considered to be causative (SOD1, etc); some are emerging as potentially playing a role in the rate of progression (ie: Eph4a). Some of the latest information suggests that in many cases, ALS is oligogenetic, where more than one of these “ALS genes” are found to be actors in some cases of ALS. Other times, research has suggested that a single gene alone can explain the vast majority of cases in a given country such as PRN1 in Finland or be nearly non-existent in a country such as C9orf72 mediated ALS cases in Japan. Combined, these new discoveries are now considered to explain as much as 20% of ALS cases worldwide.

While the discovery of genes associated with ALS has grown exponentially, their application as tools for drug development has been slow. This is becoming more important as new data clearly suggests that dysregulation of products of many of the familial ALS genes, such as SOD1, UBQLN2, TDP43, and C9orf72, are also dysregulated in sporadic cases of ALS. Using these genes to develop reliable models of neurodegeneration can accelerate drug target discovery and screening of potential treatments. The ALS Therapy Development Institute is seen as a leader in the characterization of emerging mouse models of ALS. Because relevant models of neurodegeneration are so central to treatment discovery in ALS, ALS TDI has embraced the challenging task of translating these genetic findings into tools for either target validation or drug screening. This past year, the Institute has advanced multiple models of aberrant TDP43 biology, a phenomenon that has been linked to both familial and sporadic cases of ALS.

Original publications describe various rodent models exploiting aberrant TDP43 biology presenting with a fatal ALS-like disease. However, there was significant heterogeneity in the survival phenotypes reported with some animals surviving more than twice as long as others. This type of phenotypic variability makes use of a model for target discovery and drug screening logistically impossible. This presented a serious hurdle, one that our Institute was uniquely positioned to tackle because of our scale and mouse model experience. We partnered with the Alzheimer’s Drug Development Foundation, the Association for Frontotemporal Degeneration, and the MDA, to characterize the first publically available transgenic mouse model of TDP43 mediated neurodegeneration - the Prp-A315T-TARDBP/Balo mouse developed by Robert Baloh, MD, PhD, and colleague at Washington University in St. Louis.
After breeding and analyzing nearly 1000 of these animals, ALS TDI and collaborators have determined that the Prp-A315T-TARDBp/Balo mouse model does not die of progressive voluntary muscle motor unit neurodegeneration, rather from an acute gastrointestinal dysfunction. The large scale evaluation of the model has made the system more predictable with an understanding the male mice undergo a more aggressive phenotype than females.

While the Prp-A315T-TARDBp/Balo mouse may not recapitulate motor neuron degeneration like what has been observed in ALS, it cannot be ruled out for study of generalized neurodegeneration. There is histopathological information to suggest that neuronal populations are damaged in these mice. Continued study of the model, its pathology, and gene expression analysis of pathways that are differentially expressed in its affected tissues might help to elucidate drug targets that could be generalized across neurodegenerative disorders, and conversely, those that are ALS specific.

Scientists at the Institute shared this and other data with colleagues worldwide at the 43rd annual Society for Neuroscience Meeting in New Orleans, the 23rd annual International ALS/MND Research Symposium in Chicago, and via webinars in 2012. The Institute remains undeterred in its effort to characterize additional models of ALS. It has in-licensed two additional models of TDP43 and is building its own model of TAF15 mutation mediated ALS in 2013. These new models are not simply tools for researchers in the lab, they are tools with potential to accelerate our mission; discover and develop effective treatments for ALS.
2012 Financial Review

For the fiscal year ending December 31, 2012, ALS TDI recognized just over $9.5 million in public support and revenue—the most growth in the last two years. This reflects the success of signature events like the 10th anniversary Tri-State Trek and 2nd annual A White Coat Affair gala, as well as the hundreds of grassroots fundraisers campaigning on behalf of our research. Together, they were able to raise the funds needed to sponsor the Phase IIA clinical trial of TDI-132/Gilenya® in ALS patients, a monumental milestone for the Institute. The trial is set to launch in 2013.

A full breakdown of our assets, liabilities, revenue, and expenses is below. For a complete copy of our IRS Form 990 or Independent Auditors Report, please visit our website at www.als.net or call us at 617.441.7200.

### Assets

#### Unrestricted Assets

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#### Restricted Assets

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**Net Assets EOY 2012** 4,781,558

### Liabilities & Net Assets

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**Total Liabilities & Net Assets** 7,256,370

### Public Support

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**Net Public** 9,512,367

### Expenses

#### Program

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**Total Program** 8,454,877

#### Support

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<td>Fundraising</td>
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**Total Support** 1,276,210

**Total Expenses** 9,731,087
Below is a graphical representation of revenue and expenses for the last three years, 2010-2012. As always, ALS TDI is committed to transparency in our research, in our fundraising, and in our financial information. We are proud of our continued achievement, year after year, to spend as much funding as possible every day on research toward our single mission: to end ALS. More information is available on our website at www.als.net.

### Financial Comparison 2010-2012

Below is a graphical representation of revenue and expenses for the last three years, 2010-2012. As always, ALS TDI is committed to transparency in our research, in our fundraising, and in our financial information. We are proud of our continued achievement, year after year, to spend as much funding as possible every day on research toward our single mission: to end ALS. More information is available on our website at www.als.net.

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>Total Spent</th>
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86 cents per dollar is spent on research.
“We need to continue to be innovative and out-front, leading the effort to develop effective treatments for ALS patients today. Are we closer? Yes, we are, but now is not the time to celebrate the incremental steps. Now is the time to leverage this progress into larger and quicker leaps forward.”

Steve Perrin, Ph.D.  
CEO & Chief Scientific Officer

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