IMAGING DISEASE MECHANISMS IN PEOPLE WITH ALS

By Nazem Atassi, M.D.
Associate Director, Neurological Clinical Research Institute (NCRI) at Massachusetts General Hospital, Assistant Professor of Neurology at Harvard Medical School

Our ALS imaging research is focused on understanding the mechanisms of ALS and designing efficient clinical trials by building advanced human imaging platforms.

ALS drug development faces many challenges that result in very high failure rates of tested therapies. Unfortunately, most ALS therapies that show encouraging results in the lab do not translate into effective treatments for people with ALS. One of the biggest challenges in ALS drug development is the lack of a mechanistic readout of drug efficacy in patients at early phases of clinical drug development. Our team at Mass General Hospital (MGH) is laser-focused on building these needed imaging mechanistic platforms.

We are currently developing multiple positron emission tomography (PET) imaging platforms to measure key mechanistic pathways in people with ALS including inflammation, glutamate toxicity and epigenetics.

**Imaging Inflammation in People With ALS**

Our research shows increased PBR28 uptake in the motor cortices and brainstem in people with ALS. We also show that the anatomical distribution of increased PBR28 uptake corresponds to ALS clinical presentation; for example, people with limb-onset weakness had higher PBR28 uptake in the motor cortices and patients with bulbar-onset weakness had higher PBR28 uptake in the brainstem (Figure 1). Furthermore, higher PBR28 uptake was strongly correlated with worse functional status measured by ALSFRS-R and worse pathological reflexes. [Atassi N et al. Neuroimage. 2215]

We are now testing the same technology using a novel tracer called GE180 as part of the TRACK ALS project that is funded by The ALS Association and ALS Finding a Cure Foundation. GE180 has a longer half-life and is available in commercial cassettes. This would allow us to scale up this imaging platform to multicenter studies and clinical trials.

In addition, we are now taking this technology to a critical new level by studying inflammation in people who carry an ALS gene but don’t have any of the clinical symptoms of ALS. This will allow us to measure the pre-clinical pathological changes in the brain in people who are at risk of developing ALS. (Continued on page 8)
NEW MODEL SYSTEMS, EMERGING DISEASE PATHWAYS AND IMAGING TOOLS HELP ACCELERATE DRUG DISCOVERY AND DEVELOPMENT FOR ALS

By Lucie Bruijn, Ph.D., M.B.A.
Chief Scientist
The ALS Association

This year marks the second anniversary of the ALS Ice Bucket Challenge, and with the resulting increased awareness and resources for ALS research, significant advances are being made, including the discovery of new genes such as NEK1 and C21orf2. As the discovery of additional genes associated with ALS continues to grow, disease pathways are emerging that can be targeted to develop new therapeutic approaches. These opportunities have escalated the number of industry and academic partnerships in drug development for ALS.

Alongside research progress, clinical trials for ALS are either about to start, in progress or completed and awaiting review of results. Cytokinetik announced completion of enrollment this summer of their phase III trial testing a fast skeletal muscle troponin activator to increase muscle strength and respiratory function. Results from the Arimoclomol trial, targeting SOD1 misfolding, are anticipated later this year. Researchers in California received FDA approval for a combination cell gene-therapy approach, entering the clinic for safety testing in the New Year.

Several new mouse models are emerging including those expressing ALS-associated mutations in ubiquilin and profilin genes. These models mimic many important aspects of the human disease including motor neuron loss, muscle weakness, accumulations of mutant protein and TDP43 (present in almost all cases of the human disease).

Finally, I would like to recognize this year’s recipients of the Milton Safenowitz Postdoctoral Fellowship for ALS Research to encourage and facilitate promising young scientists to enter the ALS field. The Safenowitz family, through the Greater New York Chapter of The ALS Association, founded this award program in memory of Mr. Safenowitz, who died of ALS in 1998. Fellows work with a senior mentor and receive extensive exposure to the ALS research community by attending meetings and delivering presentations about their exciting work. The 2016 fellowship award recipients include the following:

- Tiffany Todd, Ph.D.
  Mayo Clinic Jacksonville; Jacksonville, Fla.
  Modeling selective vulnerability and disease-specific functions in mice by the comparison of C9orf72 repeat models to a novel disease control

  Disease-related repeat expansions of C9orf72 in ALS and another neurodegenerative disease, spinocerebellar ataxia type 36 (SCA36), are likely a source of toxicity in neurons. Dr. Todd, under the mentorship of Dr. Leonard Petrucelli, aims to compare these two repeats using mouse models in order to understand why certain neurons respond differently to each repeat paving the way to ALS treatments.
  “I am excited to see what insights this comparison study will give into the mechanisms underlying ALS and how the knowledge gained from this study will influence future research and therapeutic development.”

- Vicente Valenzuela, Ph.D.
  University of Chile; Santiago, Chile
  Gene therapy to attenuate ER stress alterations in ALS

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MILTON SAFENOWITZ POSTDOCTORAL FELLOWSHIPS

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TIMELINE


French neurologist Jean-Martin Charcot identifies ALS
DNA structure solved
Nerve growth factor (NGF) identified—protective, growth promoting factor for nerve cells
SOD1 enzyme identified
Programmed cell death in motor neurons demonstrated
The ALS Association funds study of inherited motor neuron disease
Genes for muscular dystrophy identified
The ALS Association funds search for a common genetic link to ALS
Congress declares the 1990s the “Decade of the Brain”
Growth factor CNTF is found to increase survival of motor neurons
Researchers link familial ALS to chromosome 21
The ALS Association begins workshops
Glutamate transporter shown to be defective in ALS
Growth factor BDNF found to increase survival of motor neurons
Therapeutic gene silencing holds great promise as a clinical strategy to treat ALS. Dr. Godinho, under the guidance of Robert Brown, M.D., Ph.D., synthesized a novel gene silencing strategy to silence both SOD1 and C9orf72 that exhibits efficient uptake in neurons. He plans to validate and test the efficiency of this strategy in the brain and spinal cord of established ALS mouse models, leading the way to develop effective drugs to treat ALS.

“I am deeply honored and truly grateful to have been selected as a fellowship recipient, and believe my work will contribute to the development of adequate therapeutic gene silencing platforms that may have profound impact on the treatment of ALS.”

Amanda Gleixner, Ph.D.
University of Pittsburgh; Pittsburgh, Pa.

Linking impaired nucleocytoplasmic trafficking in C9orf72 ALS to altered nuclear pore complex O-linked N-acetylglucosamine (O-GlcNAc) posttranslational modifications

Deficits in nucleocytoplasmic trafficking have been observed in C9orf72-associated ALS, but why this occurs in disease is unknown. Dr. Gleixner, under the mentorship of Christopher Donnelly, Ph.D., will explore the link between impaired nucleocytoplasmic trafficking in C9orf72 ALS and alterations in the nuclear pore complex, specifically by modulating O-GlcNAcylation of nucleoporins.

“The generous support from the Milton Safenowitz Postdoctoral Fellowship will allow me to investigate the nuclear pore complex (NPC) in patient tissue and motor neurons derived from induced pluripotent stem cells.”

Sergey Stavisky, Ph.D.
Stanford University; Stanford, Calif.

Clinically-useful brain-machine interface control of a robotic prosthetic arm by people with ALS

Assistive technology offers people living with ALS prolonged independence in their daily activities. Dr. Stavisky, under the guidance of Jamie Henderson, M.D., will develop and optimize a clinically useful brain-machine interface control of a robotic prosthetic arm and hand for people living with ALS.

“The focus of my work could restore patients’ ability to move their own muscles, improving the quality of life of people with ALS, while other ongoing research advances towards treating the disease itself.”

Jeanne E. McKeon, Ph.D.
University of Massachusetts Medical School; Worcester, Mass.

Disruption of actin dynamics as a pathogenic mechanism in ALS

Mutations in profilin I (PFN1) cause one type of familial ALS that is important in regulating actin dynamics. Dr. McKeon, under the mentorship of Daryl Bosco, Ph.D., will study the alteration of actin dynamics and actin-dependent cellular processes as a pathogenic mechanism of ALS.

“I am very grateful for research support from The ALS Association which will help me yield critical insight into pathogenic mechanisms and druggable targets in the more common form of the disease.”

The ALS Association holds scientific workshop on “Environmental Factors and Gene Susceptibility.”

Assing aggressive search for new ALS genes funded by The ALS Association.

Scientists complete map of mouse genome.

Agency of Toxic Substances and Disease Registry awards five grants focused on ALS.

The ALS Association/NINDS collaborative effort begins screening drugs.

The ALS Association co-sponsors workshop on high-throughput drug screening with NINDS.

NINDS issues first ever RFA (request for applications) specifically for ALS research.

A transgenic rat is designed, efforts start on fly model.

Attention turns to support cells of nerve tissue to find role in ALS.

Inflammation on and programmed cell death gather research interest.

ALS2 gene (alsin protein) linked to juvenile ALS.

The ALS Association/NINDS collaborative effort begins screening drugs.
The genetic conservation between humans and mice, ease of animal husbandry, and the technologies available to manipulate the mouse genome all have propelled the mouse as the premier mammalian model organism to study disease. Over the years, single gene, loss of function "knock-outs" in the mouse genome all have propelled the technologies available to manipulate each gene represents an important piece of the puzzle in the development of therapeutics. For many years, causative genes for ALS were unknown and it was only in 1993 when familial ALS population, indeed a significant proportion of familial ALS cases have been classified as familial in nature, meaning simply that there is a heritable component that can be traced within a family pedigree. The identification of these genes and subsequent understanding of how they function can help researchers identify: Associations and gain of function mutations in a time dependent and tissue specific manner. The number of mouse models in the ALS bucket was accumulating at a rapid pace. In 2011, excitement grew in the ALS research community when the elusive genetic mutation in ALS families was discovered to be a hexanucleotide repeat expansion in a gene called C9orf72. The genetic mutation represented an astounding 40% of all familial ALS cases. The C9orf72 mutation created a whole new challenge in ALS mouse models. The repeat was isolated from patient cells, but the engineering of the repeats in mice was challenging, as the repeat often contracted in the cloning process prior to microinjection. A number of labs have reported the creation of transgenic animals carrying the hexanucleotide (GGGCGG) repeat. Each published the presence of repeat-associated non-ATG (RAN) translation, RNA foci and RAN translation products in the brain-a similar pathology seen in people living with ALS. At traditional knock-outs and overexpressing transgenes, researchers were now employing the use of conditional and inducible systems to introduce both loss of function and gain of function mutations in a time dependent and tissue specific manner. The number of mouse models in the ALS bucket was accumulating at a rapid pace. In 2011, excitement grew in the ALS research community when the elusive genetic mutation in ALS families was discovered to be a hexanucleotide repeat expansion in a gene called C9orf72. The genetic mutation represented an astounding 40% of all familial ALS cases. The C9orf72 mutation created a whole new challenge in ALS mouse models. The repeat was isolated from patient cells, but the engineering of the repeats in mice was challenging, as the repeat often contracted in the cloning process prior to microinjection. A number of labs have reported the creation of transgenic animals carrying the hexanucleotide (GGGCGG) repeat. Each published the presence of repeat-associated non-ATG (RAN) translation, RNA foci and RAN translation products in the brain-a similar pathology seen in people living with ALS. At traditional knock-outs and overexpressing transgenes, researchers were now employing the use of conditional and inducible systems to introduce both loss of function and gain of function mutations in a time dependent and tissue specific manner.
least one lab has reported gross physiological abnormalities and paralysis in a subset of animals. These C9orf72 models represent the first generation of C9orf72 and already hold great potential for evaluating therapeutics targeting the repeat expansion.

Another Faucet
Genetic mutations in ALS have traditionally been identified through linkage analysis. With advances in genome sequencing, a new path forward has emerged. Genome sequencing of large numbers of people with ALS is a strategy now employed by a number of groups. These “big data” sets provide us not only with new causative genes in ALS, but also a catalog of rare variants and allow us to explore the role of noncoding and intergenic genetic variation in the pathogenesis of motor neuron degeneration. Already, new genes such as TBK1, TUBA4A, NEK1, and CHCHD10 have been identified using this approach and our knowledge of genetic variants in ALS patients is increasing exponentially! This sets the stage for a personalized medicine approach to ALS, where therapies identified as being helpful would not be a treatment for all ALS, but tailored to the specific mutation harbored by the patient.

Coupled with the identification of new causative genes in ALS are major advances in genome editing technologies allowing us to genetically engineer mice at an unprecedented rate. The CRISPR/Cas9 system allows researchers to reproduce pathogenic mutations found in humans in animal models. The simplicity of technique even affords introduction of the same mutation in different genetic backgrounds (i.e. different mouse strains) at once. The reduced time and cost associated with the CRISPR/Cas9 system, along with the veritable ease of technology, streamlines production of these mouse models.

Sharing the Wealth
The ALS genetic landscape is changing dramatically. Our knowledge of the genetic variants and the ability to quickly engineer the mouse models has the potential to rapidly increase our understanding of the pathophysiology and disease mechanisms of ALS. The Jackson Laboratory (JAX) is committed to making these emerging ALS mouse models available to the scientific community. In 2010, The ALS Association, the ALS Therapy Alliance and the Tow Foundation provided the funding necessary to initiate the ALS Mouse Model Resource at JAX. The role of the repository was to import and distribute mouse models provided by ALS investigators. This ensures adequate commercial supply and equal accessibility of models to all investigators; an important factor in maximizing the potential of the models as agents of therapeutic discovery. This is especially true for new and emerging models, where unlimited and equal access will lead to the most efficient characterization. Today, JAX is not only distributing mouse models of ALS but also collaborating with scientists and clinicians to leverage the genetic engineering, reproductive sciences and scaled breeding facilities to engineer these new ALS models at JAX. In doing so, they put the animals in the hands of ALS researchers more quickly and complete the second site validation of disease relevant phenotypes. With this full bucket of resources at the disposal, effective therapeutics can become a closer reality for ALS patients.

References

| Stem cells generated from ALS patients | Discovery of DFP6 in two genome-wide association studies in ALS |
| Mutations in TDP-43 linked to familial and sporadic ALS | Induced Pluripotent Stem Cell Technology opens up new avenues for ALS |
| Identification of new gene linked to familial ALS, fused in Sarcoma (FUS) on Chromosome 16 | First patients enrolled for antisense and stem cell trials in U.S. |
| Ubiquitin-2 discovery: C9orf72 discovery | The ALS Association hosts 2nd Drug Discovery Workshop for ALS September |
| Identification of CYRAN translated peptide | First human antisense trial published—approach safe in people with ALS |
| Mutations in Matrin 3 identified, linked to ALS | New studies shed light on TDP-43 disease mechanism |
| C9orf72 repeat expansion mutations—disease mechanisms begin to unfold | Antisense clinical trial for SOD1 started |

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**RESOURCES**

**ALS Mutations Database**
http://alsod.iop.kcl.ac.uk/home.aspx

**ALS IPS Cell Lines**
http://cedars-sinai.edu/Research/Research-Cores/Induced-PluripotentStem-Cell-Core/-ALS-iPSC-Lines.aspx

**ALS Epidemiology**
http://aces.stanford.edu/ForRes.html

**SODI Mutant Rats, Taconic**
http://www.taconic.com/rat-model/sod1-rat

**Jackson Laboratories ALS Mouse Repository**
https://www.jax.org/search?q=ALS+mouse+repository

**ALS Mouse Model Summary**
http://www.alsod.iop.kcl.ac.uk/home.aspx

**ALS Association Research Webinars**
http://www.alzforum.org/research-webinars.html

**ALS Research Forum**
http://www.alsresearchforum.org/
GENES AND DISEASE MECHANISMS: C9ORF72

This year has seen major progress in understanding the consequences of the C9orf72 expansion mutation, the most common genetic cause of ALS and frontotemporal dementia (FTD). New work has also begun to reveal the normal function of the protein, which may be important for understanding the full effects of the gene mutation, and for predicting the effect of shutting down the gene through antisense therapy or other means.

New Mouse Models Display ALS-like and FTD-like Phenotypes

Two groups of researchers, both funded by the ALS Association, developed mouse models of the expansion (carrying up to 500 GGGGCC units, versus fewer than 30 in the normal gene), using a bacterial artificial chromosome (BAC) as a vector for the gene. In addition to the entire gene, the BAC can carry the gene’s promoter and other regulatory regions, increasing the fidelity of the resulting mouse model. Both models developed the full range of pathology seen in people with the mutation, including accumulation of RNA known as “foci,” which form from the expansion, and dipeptide repeat proteins (DRPs), which are transcribed from the expanded RNA. Both models also developed behavioral symptoms and neuronal degeneration; the model created by Lui et al. also displayed motor impairment. Jiang et al. also showed that antisense oligonucleotides directed against the mutant RNA reduced both foci and DRPs, and mitigated anxiety-like behaviors. The work strengthens the case that antisense treatment against the mutation, which is currently in development, may be therapeutic in ALS patients.

Pathogenic Mechanisms of Mutant C9orf72

The expansion in the C9orf72 gene produces both RNA foci and dipeptide repeat proteins. Evidence is accumulating that each may contribute to pathogenesis, through different mechanisms. Zhang et al. show that one of the DRPs, poly(glycine-arginine), forms aggregates that sequester both HR23 proteins, involved in proteasomal degradation, and proteins that mediate nuclear transport. Similar sequestration was seen in patient samples. Conlon et al. explored the consequences of higher-order folding of the expanded RNA transcribed from the gene. Previous work has shown the RNA forms so-called G quadruplex structures, which can bind proteins. They found that these structures primarily bound the splicing factor hnRNP H, which led to dysregulation of splicing of multiple transcripts in brains of patients with the C9orf72 mutation. And Lopez-Gonzalez et al. showed that there was an increase in the level of DNA damage in cells derived from C9orf72 patients, and that DRPs caused DNA damage in normal cells, suggesting that the proteins were directly responsible for the damage seen in ALS cells. The damage was associated with reduction in mitochondrial protein synthesis, leading to oxidative stress. Reduction in oxidative stress reduced the DNA damage.

Wild-type C9orf72 Protein Regulates Autophagy

Several new studies show that the normal C9orf72 protein helps regulate autophagy, a cellular protostasis pathway important for degrading aggregates and organelles. Webster, Smith and colleagues used RNA interference to reduce C9orf72 expression, leading to a reduction in the number of autophagosomes compared to control after treatment with an autophagy trigger. They showed that the protein interacts with the ULK1 complex, which is required for the initiation of autophagy, and that the protein binds directly to Rabla, which is necessary for ULK1 translocation to the phagophore. The results may explain the reduction in autophagy seen in C9orf72 ALS patients, whose levels of un-mutated C9orf72 protein are below normal.

Meanwhile, Yang and colleagues showed that the normal C9orf72 protein is part of a multiprotein complex that includes the autophagy regulator ATG101 and a protein of previously unknown function, Smith-Magenis syndrome chromosomal region candidate gene 8 (SMCR8). Knockout of either C9orf72 or Smcr8 led to a reduction in autophagy, indicating a codependence in their interaction with ULK1.


Free: http://elifesciences.org/content/5/35/1656.long

An Alternative to Antisense

While antisense therapy against the repeat expansion looks promising, it may require targeting both the sense strand of DNA, and its complement, the antisense strand, since both strands are transcribed and both lead to RNA foci and DRP production. An alternative explored by Kramer et al. is to target the transcription elongation factor Sp4, a protein required for transcribing repetitive DNA. Knocking down the protein in cell culture suppressed production of mutant transcripts, reducing both foci and DRPs, suggesting it may be a valuable strategy for therapy development.


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Optineurin Suppresses Necroptosis

Optineurin mutation is a rare cause of ALS, but a recent study suggests optineurin may be involved in ALS pathogenesis more widely. Previous work by the authors of the new paper had shown that loss of optineurin sensitizes cells to death by necroptosis, a form of programmed cell death distinct from apoptosis. In the new study, Ito et al. show that optineurin normally promotes the degradation of a pro-necroptosis protein called RIPK1. Loss of optineurin allows RIPK1 to trigger inflammation and necroptosis specifically in oligodendrocytes, leading to loss of myelin and neuronal dysfunction. Because optineurin binds ubiquitin, which is found in protein aggregates in multiple neurodegenerative diseases, including ALS, suggesting ubiquitinated protein aggregates may induce a functional optineurin deficiency and may contribute to neurodegeneration far beyond cases of optineurin mutation.


Whole-genome Sequencing Identifies NEK1 and Other Risk Genes

In recent years, whole-genome sequencing has emerged as a new standard in the search for risk genes. International consortia involving scores of laboratories in dozens of countries have brought the tools of “big data” to bear on the understanding of the genetic architecture of ALS, and the discovery of new genes. In a study of over 15,000 patients and over 25,000 matched controls, van Rheenen et al. established evidence that ALS is a complex trait, with multiple genes contributing to risk in individual cases. In a separate study that combined whole-genome analysis of more than 1,000 patients with analysis of variants in a small isolated population, Kenna et al. found that loss-of-function variants in the gene NEK1 occurred in almost 3% of ALS cases. NEK1 is involved in microtubule stability and related functions of the human disease. They show that mice expressing mutant profilin 1, a rare cause of ALS, develop weakness beginning at 350 days and become paralyzed at 421 days. Expression in motor neurons led to motor neuron degeneration in the spinal cord, with presymptomatic axonal degeneration, cytoskeletal disorganization and relatively late development of ubiquitin-positive protein aggregates. In addition to its value in understanding profilin-linked ALS, this new model progressive neurodegeneration may allow identification of cellular-level commonalities between profilin- and SOD1-based ALS, which may provide clues to new targets for therapies.


Epidemiology

The national ALS Registry, maintained by the Centers for Disease Control, has provided an update on the prevalence of ALS in the United States, combining data from national health databases and the online patient portal. The total number of cases in 2012 was 14,713 and in 2013 was 15,908, giving U.S. prevalence rates of 4.7 and 5.0 per 100,000, respectively. Using published incidence studies, and publicly available population data and expected growth, Arthur et al. calculate that the total number of ALS cases worldwide will grow by almost 70% in 25 years, largely due to aging of the world population, with the largest increases expected in developing nations. In the world as a whole, the number of ALS cases will increase from 222,801 in 2015 to 376,674 in 2040, they predict.


Free https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5150534/

Profilin 1 Mouse Replicates Multiple Aspects of ALS

To date, only the SOD1 mutant mouse has replicated the major features of human ALS: degeneration of motor neurons, progressive weakness, and early death. In a new study, Yang et al. present a new model that also displays these features, as well as cellular pathology reminiscent of the natural disease. They show that mice expressing mutant profilin 1, a rare cause of ALS, develop weakness beginning at 350 days and become paralyzed at 421 days. Expression in motor neurons led to motor neuron degeneration in the spinal cord, with presymptomatic axonal degeneration, cytoskeletal disorganization and relatively late development of ubiquitin-positive protein aggregates. In addition to its value in understanding profilin-linked ALS, this new model progressive neurodegeneration may allow identification of cellular-level commonalities between profilin- and SOD1-based ALS, which may provide clues to new targets for therapies.

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(CONTINUED FROM PAGE 1)

By Nazem Atassi, M.D.

This information will be extremely important to understand all forms of ALS (genetic and non-genetic).

Imaging Glutamate Toxicity in People With ALS

Our team is now building a new imaging platform using GE-179 PET tracer to measure NMDA excitotoxicity in people with ALS. NMDA is activated by glutamate, which is the major excitatory neurotransmitter in the Central Nervous System (CNS).

While it normally plays important roles as a neurotransmitter, increased glutamate concentrations can be toxic to neurons (a phenomenon known as excitotoxicity). Increased levels of glutamate have been found in the cerebrospinal fluid of people with ALS and glutamate excitotoxicity is considered one of the main mechanisms leading to motor neuron degeneration in ALS. Of relevance to ALS therapeutics, riluzole, the only FDA-approved medication for ALS, is thought to reduce glutamate levels, thus reducing glutamate signaling and excitotoxicity. This study will generate important preliminary data about the feasibility and value of imaging NMDA receptor activity in people with ALS, which would have major applications in measuring the biological activity of candidate ALS therapies that target the excitotoxicity pathway. Ultimately, such mechanism-based biomarkers will increase our understanding of disease mechanisms and accelerate the pace of ALS drug development. This project is funded by The ALS Association, ALS Finding a Cure and the ALS ONE foundation.

Imaging Epigenetics in People With ALS

The histone deacetylases (HDAC) are naturally occurring enzymes that regulate gene transcription and are implicated in ALS pathophysiology. ALS animal models and postmortem tissue show increased expression of certain subtypes of HDACs. Martinostat is a novel tracer which was developed at Mass General Hospital (MGH) and allows noninvasive quantification of HDAC expression in people (Figure 2) [Insights into epigenetics through human HDAC PET imaging. Science Translational Medicine. 2016]. We are now launching this exciting program and soon we will start enrolling in this study.

Mechanism-based imaging research has direct and tangible impact on the lives of ALS patients and their families in two main ways:

I. Understand the Causes of ALS in Patients

The study of ALS mechanisms used to be limited to pathological and animal studies in the lab. We are now at a point in history where we have advanced imaging technologies that allow us to study ALS causes in patients, and this is the core focus of our research. These advanced imaging technologies will open the window to study mechanisms such as inflammation, excitotoxicity and epigenetics in patients who suffer from ALS, and immediately translate these discoveries to effective treatments for ALS patients.

II. Accelerate the Pace of ALS Drug Discovery

ALS drug development used to rely solely on clinical outcomes which require designing very large and inefficient clinical trials. Our imaging team is currently building an exciting and diverse pipeline of mechanistic imaging platforms to be used as specific readouts of drug efficacy in many efficient ALS clinical trials. Similar imaging pipelines allowed the multiple sclerosis (MS) field to develop many successful and effective treatments that were approved in the past 10 years. Our goal is to replicate the MS successes in ALS by building imaging tools that are available for researchers and companies around the world in order to accelerate drug discoveries for ALS patients. This is already happening with the launch of three ALS clinical trials (Ibudilast, RN560, AMX0035) that are all using our imaging technologies within less than a year of our initial publication in 2015.

Please visit The ALS Association’s new research web pages at ALSA.org/research to learn more about our global research program to find treatments and a cure for the disease.