For thousands of years, yeast has been an integral part of the lives of humans, providing bakers and brewers with the ability to produce a delicious array of bread, beer and wine. These days, in addition to yeast’s job unlocking culinary mysteries in vineyards and bakeries, it has been working in the laboratory to help unlock some of the mysteries of amyotrophic lateral sclerosis (ALS).

The baker’s yeast, known by its scientific name *Saccharomyces cerevisiae*, is a tiny single-celled organism that remarkably possesses most of the same basic cellular machinery as complicated neurons in our brain. At first it might seem crazy that yeast cells could help us learn anything about ALS, but it is worth pointing out that almost everything we now know about cancer started out from basic studies using yeast to learn how one yeast cell divides into two. Just a few months ago the Nobel Prize in Physiology or Medicine was awarded to a researcher who used yeast cells to figure out how proteins are shipped to different locations within the cell—some of the same principles that underlie how neurons in the brain communicate with each other. Therefore, let’s see what these simple, yet powerful yeast cells can teach us about ALS.

The RNA-binding protein TDP-43 was recently discovered to play a major role in ALS: it is mislocalized to cytoplasmic clumps in the degenerating motor neurons of most ALS patients (except those with SOD1 mutations), and mutations in the TDP-43 gene have been identified as a cause of rare familial and sporadic ALS cases. A yeast model has been developed to study what makes TDP-43 form aggregates in cells and what makes it kill those cells. Just like in neurons, TDP-43 also forms clumps in yeast cells when expressed at high levels. But unlike in neurons, where this...
Partnerships Continue to Lead to New Discoveries

This year has already seen numerous exciting publications increasing our understanding of how the most recently identified mutations in C9ORF72 lead to ALS. In addition, new genes and new potential causes underlying the disease are continually being identified. The most recent finding, the gene Matrin3, is also an RNA-binding protein. Many challenges remain, most importantly translating these findings into meaningful therapies. The Association is committed to finding a treatment and a cure through our partnerships with academia and industry and continuing to support a diverse but focused portfolio. Bringing new investigators into the fold through our Milton Safenowitz Post-Doctoral fellowship, encouraging clinician scientists to focus on ALS research, and supporting the TREAT ALS/NEALS (Northeast ALS Consortium) clinical trials network remain a key focus. Collaboration is important to making an impact in ALS research. The partnerships with industry, academia, government and funding organizations led to the success of bringing the first antisense trial for a neurological disorder into the clinic, which is detailed in an article in this publication. We are also becoming more and more aware that ALS is not one disease and individuals may respond very differently to treatment approaches. Efforts are underway to more effectively stratify ALS patients through biomarker discovery and induced pluripotent stem cell technologies.

Model systems, especially the mouse models for ALS, are often focused on as not being useful because they cannot predict clinical trial outcomes in people with ALS. In reality, the issue is much more complicated and failure in clinical trials cannot be blamed on the limitations of mouse models. Indeed, the mouse models have been extremely instructive in helping us tease out the time course of disease, the importance of glial cells in disease and in providing new potential targets to generate novel therapies. Clinical trial failures require us to think more carefully about the trial itself. Did we use the correct dose, did the drug that we are administering reach the target we identified, and if it did, did it affect the pathway we identified in the model systems to be important in disease? For this reason, The ALS Association, working closely with clinical and industry colleagues, is focusing on identifying biomarkers that will help answer these questions. So to go back to those model systems, a wide variety are in use, even simple yeast models as described by Dr. Gitler, and they all have their place in moving the field forward.

Finally I would like to acknowledge the vision and leadership of Dr. Jeremy Shefner, our current Sheila Essey Award recipient. His commitment to clinical research for ALS has been crucial in developing biomarkers for ALS, improving clinical trial design and facilitating numerous clinical trials through the TREAT ALS/NEALS network.

As we look forward to the research accomplishments for 2014, we reflect on the needs of those people living with ALS and feel even more committed to improving their lives and finding treatments and a cure for the disease.

–Lucie Bruijn, Ph.D., M.B.A.
From early in his career, Dr. Shefner developed expertise in electrodiagnostic medicine and brought that expertise to bear in developing motor unit number estimate (MUNE) as an objective biomarker to track ALS disease progression. MUNE is now in use in a number of ALS clinical trials, and the techniques he developed have become standard for its application in the field. “By developing new measures and refining others, Dr. Shefner has significantly improved the way ALS trials are performed worldwide,” said Orla Hardimann, M.D., Head of Academic Neurology at Trinity College, Dublin.

Dr. Shefner has been the principal investigator of numerous ALS trials, most recently of a skeletal muscle activator (Tirasemtiv, Cytokinetics) that increases muscle sensitivity to calcium release. This symptomatic therapy has been shown in initial trials to increase force output in the midrange of muscle activation, potentially aiding activities of daily living for people with ALS. A multinational double-blind phase 2 trial is currently underway, under Dr. Shefner’s leadership.

“Dr. Shefner has tirelessly devoted his career to the care of patients and families with ALS, and to developing new treatments for them,” said Dr. Cudkowicz. “It can safely be said that Dr. Shefner’s involvement has been one of the best things to happen to ALS therapeutic research. He is truly an extraordinary leader in every sense of the word.”

**RESOURCES**

- ALS mutations database
  [http://alsod.iop.kcl.ac.uk/index.aspx](http://alsod.iop.kcl.ac.uk/index.aspx)
- ALS Epidemiology
  [http://aces.stanford.edu/ForRes.html](http://aces.stanford.edu/ForRes.html)
- Coriell NINDS DNA repository
- SOD1 mutant rats, Taconic
  [http://www.taconic.com/2148](http://www.taconic.com/2148)
- Jackson Laboratories ALS Mouse Repository
- Control and SOD1 fibroblasts
- ALS Untangled
  [http://www.wfnals.org/alsu.html](http://www.wfnals.org/alsu.html)
- ALS Association Research Webinars
Antisense for ALS: Important New Treatment Strategy Advances

As the growing number of ALS genes attests, many cases of the disease begin with the expression of a mutant gene. Blocking that expression, therefore, stands out as a potentially definitive therapy, stopping the complex cascade of events leading to motor neuron death before it starts.

Antisense oligonucleotide (ASO) therapy has emerged as a highly promising approach for preventing expression of mutant genes in ALS. The ALS Association has taken the lead in supporting development of ASO therapy, beginning with early preclinical work providing proof of principle, and continuing through the first clinical trial of central delivery of ASOs in any neurologic condition. That trial, designed to test the safety and tolerability of the drug and establish the dosing requirements, was recently completed in people with ALS. Plans are underway to launch a treatment trial, possibly in 2015.

In the diagram to the right, we outline how antisense works and describe the state of progress in therapy development of ASOs for the treatment of two genetic forms of ALS.

Antisense oligonucleotides are short single-stranded DNA molecules that can be visualized as beads on a string. Once taken up inside of a cell—for example, a nerve cell—they can selectively target the molecular machinery that produces a protein such as superoxide dismutase (SOD1). Antisense does not correct the mutant gene, it is most commonly designed to reduce the harmful effects of a gain-of-function mutation. However, in some situations, it can increase production of a gene product, by overcoming splicing defects. This strategy is currently in development for treatment of spinal muscular atrophy, a pediatric motor neuron disease due to loss of function of the SMN (survival of motor neuron) protein.

What are Antisense Therapeutics?

ASOs used in therapeutic applications are chemically modified to resist degradation by cellular enzymes, thus prolonging their effect. Efficacy is based on exploitation of an ancient defense system that can prevent a virus from hijacking a cell’s molecular machinery (the RNAase pathway), and similar therapeutic strategies are under consideration. RNA interference, for example, using a double-stranded RNA delivered by a viral vector can also degrade the synthesis of a targeted protein, but “the prolonged activity of the RNase pathway from a single dose of ASO may offer significant advantages for a chronic disease such as ALS,” according to Don Cleveland, Ph.D., of the University of California at San Diego.
Antisense for ALS

Continued from page 4

Antisense for Mutant SOD1: From Animal Models to Clinical Trial

The mutant SOD1 gene accounts for about 20 percent of all familial ALS and up to two percent of all cases of ALS. The pioneering work of ALSA-supported researchers Dr. Cleveland and Richard Smith, M.D., at the Center for Neurologic Study, in conjunction with Isis Pharmaceuticals (Carlsbad, CA), developer of the ASOs, demonstrated the potential of using antisense in a rat model of SOD1-ALS. Treatment delayed the rate of disease progression by 37 percent when administered near the time of symptom onset. Further work went into scaling up the treatment, culminating in a first-in-human clinical trial, supported by The Association and led by Timothy Miller, M.D., Ph.D., of Washington University.

In that trial, patients were randomized to receive either placebo or an anti-SOD1 ASO, developed by Isis Pharmaceuticals and delivered by intrathecal infusion over 11.5 hours. Four cohorts of eight patients each (six active treatment, two placebo) were given escalating doses of drug, with safety assessed over a period of 28 days before commencing each new round. The frequency of adverse events was similar between active-treatment and placebo groups and were mainly related to the procedure. There were no dose-limiting toxic effects or safety or tolerability concerns. This initial trial did not include a measure of efficacy. Further development of the treatment strategy is underway, with assessment of newer oligonucleotide backbones and RNA targets.

Continued on page 7

Antisense for Mutant C9ORF72: A Major Target for ALS

Antisense therapy may have a bigger impact in the instance of C9ORF72-mediated ALS since it is responsible for approximately 40 percent of familial ALS and up to six percent of sporadic disease. Expansion of a repeated hexanucleotide region in the gene creates RNA transcripts containing hundreds or thousands of GGGGCC units. There are several hypothesized mechanisms of disease. The expanded RNA folds into three-dimensional structures that are thought to trap transcription factors, altering cell metabolism. The expansion is also translated in a non-standard fashion into aggregation-prone dipeptide “repeat-associated non ATG (RAN) translation products,” which may themselves trap other cell molecules. The mutation also reduces the quantity of normal C9ORF72 protein, whose function is unknown.

Continued on page 7

Antisense for ALS

TIMELINE cont.

1993
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2002

SOD1 gene mutation (chromosome 21) discovered in familial ALS
Trials using glutamate blocker riluzole begin

Don Cleveland, Ph.D.
Ludwig Institute
University of California, San Diego

Antisense for ALS

Continued from page 4

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Continued on page 7
aggregation process might take years or decades, in yeast TDP-43 forms clumps in a matter of a few hours, allowing experiments to be performed very rapidly. These studies have led to two important findings.

First, a small region towards the end of the protein was shown to be critical for TDP-43 aggregation and toxicity. Second, yeast cells revealed that ALS-causing mutations accelerate the rate of TDP-43 clumping, providing a mechanism by which they might cause disease. Importantly, others have confirmed these findings in multiple model systems, including mouse models, underscoring the power of the yeast system for providing disease-relevant insight.

The best feature of the yeast model system is the ability to perform unbiased genetic screens. We don’t know why TDP-43 aggregates in yeast (or in neurons) or why it is toxic, but we can ask the yeast cells to tell us the answer. We do this by performing a generic screen, where we search for yeast genes that can suppress or exacerbate TDP-43 aggregation and toxicity. In other words, can we find a yeast gene that when deleted or overexpressed allows the yeast cells to grow better even in the face of TDP-43 aggregates? The yeast genome is very well characterized and amenable to genetic manipulation. Methods are available to rapidly over express or knock out almost every gene. These experiments are inexpensive and fast—a single student in the laboratory can test every single yeast gene for an effect on TDP-43 in less than one month.

One gene that was discovered in a yeast screen for genes that could affect TDP-43 toxicity was the relative of a human gene called ataxin 2, which is known for its role in the neurodegenerative disease spinocerebellar ataxia 2, or SCA2. Increasing ataxin 2 levels worsened TDP-43 toxicity and decreasing ataxin 2 levels actually reduced toxicity. The ataxin 2 protein contains a repeated tract of the amino acid glutamine. Long expansions in the number of glutamines cause the SCA2 disease. Surprised on by the studies in yeast with TDP-43, the number of glutamines in this protein was examined in ALS patients and it was found that there was an increase in the length of the tract—not quite at the SCA2 disease level but longer than normal. These “intermediate-length” glutamine expansions in ataxin 2 are significantly associated with increased risk for ALS. Since these expansions are found in approximately five percent of ALS patients, they are now considered one of the more common genetic risk factors for ALS. Importantly, multiple independent laboratories from around the world have confirmed this association between ataxin 2 polyQ expansions and ALS. The discovery of a common genetic risk factor for ALS starting from a simple yeast screen highlights the utility of this model system and approach for gaining important insight with direct relevance to human disease.

In addition to yeast genetic screens uncovering disease mechanisms and new disease genes and risk factors, they have also unexpectedly revealed some novel concepts for therapeutic targets for ALS. One of the most effective genes at suppressing TDP-43 toxicity that emerged from the yeast screens was a gene called Dbr1, which encodes an enzyme that helps trim out sequences of genes called introns. In the absence of this enzyme, loops of introns accumulated in the cell and acted as a kind of decoy to sequester away TDP-43 aggregates from interfering with other important cellular RNAs and RNA-binding proteins. There is also a human version of this enzyme, which functions in the same way as the yeast one, raising the prospects of harnessing the enzymatic activity of Dbr1 as a new therapeutic target for combating ALS.

What’s next for yeast models in ALS research? The astonishing pace of new ALS disease gene discoveries in the last three years has invigorated ALS research with many new and promising avenues for future investigation. Simple experimental model systems, like yeast, will help to define how these new genes contribute to disease and how they might be targeted for therapies. For example, the discovery of mutations in the C9ORF72 gene as the most common cause of ALS represents a paradigm shift and intense effort is focused on understanding how C9ORF72 mutations cause disease. Yeast cells do not contain a gene related to C9ORF72 but they might be able to help out in other ways. The ALS-causing mutations in C9ORF72 produce fragments of RNA that accumulate in neurons and might be toxic. Perplexingly, non-standard translation products are also generated from the mutant C9ORF72 gene, and they themselves form aggregates that accumulate in the brain. Can yeast cells be engineered to express mutant C9ORF72 and test if these toxic RNAs and/or translation products accumulate? If so, rapid unbiased genetic and small molecule screens can be performed to discover both how they are produced, as well as methods for blocking their formation. The top leads from these screens can be tested in the numerous cellular and animal models for C9ORF72-ALS currently under development. Stay tuned.

Yeast Cells for ALS Research

Continued from page 1

The astonishing pace of new ALS disease gene discoveries in the last three years has invigorated ALS research...
Antisense for ALS

Continued from page 5

“The identification of the C9ORF72 gene mutation, and the likelihood that it causes a toxic gain of function, make it a promising candidate for treatment with antisense,” according to Lucie Bruijn, Ph.D., M.B.A., Chief Scientist for The ALS Association. The Association moved immediately to fund several research groups equipped to explore this therapeutic possibility.

Results from these studies have begun to emerge. Working in patient-derived induced pluripotent stem cells (iPSC) converted to motor neurons, several groups have shown that ASOs can reduce C9ORF72 pathology, including aggregation of RNA, aberrant binding of transcription factors, dysregulation of expression of other genes, susceptibility to glutamate excitotoxicity, and neuronal firing abnormalities. Not every abnormality responded to treatment—translation products remained unaffected, and newly discovered RNA aggregates made from the opposite strand of DNA (CCCCGG repeats) remained. However, the results are promising, and The ALS Association is facilitating the development of the technology with the aim of beginning a clinical trial as soon as it is safe and practicable.

ASOs are also being developed for use in spinal muscular atrophy, Huntington’s disease, Alzheimer’s disease (targeting tau protein), and myotonic dystrophy.

REFERENCES


Motor Neurons in a Dish: A State-of-the-Art Review

Understanding ALS requires studying the disease in multiple models, from individual cells to whole organisms. Among these, the most important is the study of individual motor neurons. The difficulty of growing large numbers of motor neurons has historically hindered such research. In a recently published state-of-the-art review, Brandi Davis-Dusenberry, Kevin Eggan and colleagues describe in detail how basic research in neuronal development provided the key insights that allow scientists to convert non-neuronal cells into neurons. They also outline the importance of quality control and use of cross-laboratory best practices in standardizing the motor neuron supply. Dr. Davis-Dusenberry is an ALS Association Milton Safenowitz Fellow.

Development of Motor Neurons in the Embryo

During early embryogenesis, a mixture of inhibitory and inductive signals triggers development of neural cells from ectodermal precursors. Key among these are inhibitors of bone morphogenetic protein, fibroblast growth factors and epidermal growth factors. Additional signals establish the rostrocaudal and dorsoventral axes. Reticinoic acid is principally responsible for caudalization of spinal cord neurons, leading to differentiation of primitive brain structures. Combinatorial expression of multiple transcription factors, including homeobox genes, causes motor neurons to arise from a subset of ventral spinal cord precursors. Further elaboration of this process gives rise to multiple anatomic (cervical, brachial, thoracic and lumbar) and functional (fast twitch, slow twitch and intrafusal) subtypes of motor neurons.

“The body of work describing the molecular underpinnings of motor neuron specification during development has enabled recapitulation of these signals in vitro for the ex vivo generation of motor neurons,” the authors point out, allowing generation of cells in numbers that would be impossible to obtain through direct culturing of embryonic tissue. “Continued integration of findings from developmental studies in model organisms and in vitro-derived motor neurons will allow a greater understanding of motor neuron specification, and as a consequence, further improve strategies to recapitulate motor neuron development in vitro.”

Motor Neurons from Stem Cells and Other Cells

These methods are now in wide use to generate abundant motor neurons from pluripotent stem cells (PSCs). PSCs can be isolated from preimplantation blastocysts, or created from fibroblasts (so-called induced PSCs, or iPSCs). Conversion of PSCs into motor neurons in vitro follows the in vivo developmental pathway, with timely addition of BMP inhibitors, growth factors, retinoic acid and other transcriptional regulators.

The field of stem cell biology has been moving at a lightning pace, and techniques for generating motor neurons have developed accordingly. Most recently, advances in understanding the signals controlling differentiation have led to “direct lineage conversion,” in which fibroblasts are converted directly to neurons without first becoming stem cells. In the mouse, this has even been performed in vivo, converting cardiac fibroblasts into cardiomyocytes to improve cardiovascular function. “It will be exciting to determine if a similar approach can be adopted in the nervous system to repair injuries and/or reverse neurodegenerative disease,” the authors note.

The authors propose four characteristics for evaluating motor neurons created through these methods. Cells should display motor neuron-specific markers, or even better, a full suite of gene changes evaluated with genome-wide transcription profiling. Cells should be electrically active, mimicking the firing activity of bona fide motor neurons in contact with a muscle. When cultured with muscle, they should form twitch, slow twitch and intrafusal subtypes of motor neurons.

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neuromuscular junctions, the special synapses at which the neuron contacts the muscle and controls contraction. Finally, they should be able to survive grafting into the spinal cord of a model animal, although this is so technically challenging that it may not be feasible in all situations.

The authors conclude, “We are optimistic that continued efforts to collaboratively establish best practices for motor neuron production, culture and evaluation in vitro will provide the keys to unlock novel therapeutic strategies for devastating neurological disorders, including ALS.”

HIGHLIGHTS FROM RECENT ALS RESEARCH

New Technique Generates ALS-Derived Muscle for Study

Muscle progenitor cells can be efficiently produced from either embryonic or induced pluripotent stem cells in culture, using a new combination of growth factors, according to new research. Researchers transformed iPSCs from two different people with familial forms of ALS; one caused by mutations in the SOD1 gene and the other by mutations in the VAPB gene. The technique may prove useful in studying the interaction between muscle and motor neurons. Loss of muscle-neuron contact is an early event in ALS pathogenesis.


TDP-43 Must Risk Misfolding to Function

TDP-43 protein must convert between alternative folded states as part of its normal RNA-binding function, and in so doing may misfold, according to recent work, an insight that may help tailor therapies designed to prevent misfolding. In this study researchers found that during the conversion between these states, TDP-43 entered an intermediate state in which it was at a high risk of becoming misfolded and losing its function, the first step in forming aggregates. The likelihood of misfolding was increased by cellular stresses known to be associated with ALS.


Preventing Stress Granule Formation May be Therapeutic

Inhibiting phosphorylation of a stress granule regulatory protein countered the effect of TDP-43 mutation in both flies and mammalian neurons bearing TDP-43 mutations, according to a new study. Mutation promotes formation of stress granules, structures that sequester mRNAs. The authors found that mutation increased phosphorylation of eIF2α, which promotes granule formation, and that inhibiting eIF2α phosphorylation mitigated TDP-43 toxicity. “These findings indicate that the dysfunction induced by prolonged stress granule formation might contribute directly to ALS and that compounds that mitigate this process may represent a novel therapeutic approach,” they concluded.


Unprecedented Details Reported of C9ORF72 Mutation’s Effects

Mutations in the C9ORF72 gene account for up to 40 percent of familial ALS and six percent of sporadic ALS. The mutation is an expansion of a six-nucleotide GGGGCC section of the gene, from as few as two units in the normal gene to hundreds to thousands. Much recent work has begun to elucidate the diverse pathologic consequences when the expansion is transcribed into RNA. Here, researchers found that the expansion folded into so-called G-quadruplexes, in which multiple guanines hydrogen-bond to form a three-dimensional loop, with the two cytosines linking successive guanine segments. The structures reduced the amount of protein that could be made from the gene, and trapped multiple cell proteins that are involved in controlling gene expression. “This important study gives us an unprecedented look at the effects of the C9ORF72 mutation,” said Dr. Bruijn. “It is now imperative that we follow up these observations with further work to clarify how these changes affect disease onset or progression. These insights will be critical in designing therapies to interrupt these processes.”


Focus on Astrocyte Toxicity in Motor Neuron Death

Two new studies strengthen the case that astrocytes play a key role in promoting motor neuron death. Meyer et al. developed a “rapid, highly reproducible method to convert adult human fibroblasts from living ALS patients to induced neuronal progenitor cells and subsequent differentiation into astrocytes (i-astrocytes).” In this model, they showed that coculture of i-astrocytes from familial ALS patients (SOD1 or C9ORF72), or from sporadic ALS patients, was toxic to motor neurons. Re et al. showed that astrocyte-induced motor neuron death occurred through a process of necroptosis, a type of programmed cell death involving specific signaling pathways.


Cell-to-cell Spread of Misfolded SOD1 Seen in Cell Model

Mutant SOD1 is responsible for 13 percent of familial ALS. Researchers showed that both misfolded mutant SOD1 protein and misfolded normal protein could be released by one cell and picked up by another cell, and that the uptake of misfolded protein could propagate the misfolding process from cell to cell. Cell-to-cell transmission could be reduced by antibodies against the SOD1 protein. “These results are intriguing, and potentially important in understanding the ALS disease process,” said Dr. Bruijn. “More work will need to be done to determine whether misfolded SOD1 does in fact move from cell to cell in humans, and whether this process contributes to the pattern of disease progression we see. Answering these important questions takes on new urgency with the publication of this study.”


High-Caloric Intake is Safe in ALS, Setting Stage to Test for Effect on Survival

Previous studies in ALS mice have shown that high-caloric intake is associated with increased survival, and ALS patients who are slightly obese tend to have longer survival. Now, researchers have shown that in people with ALS with a feeding tube in place, a high-calorie diet was safe over a five-month trial. “These encouraging results provide support for proceeding with a larger trial,” said Dr. Bruijn. “That trial will tell us whether this simple intervention can improve survival, an effect predicted from the animal model.”

Acknowledgement: Richard Robinson, Science Writer