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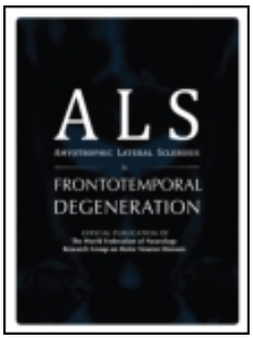

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: informahealthcare.com/journals/iafd20

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To cite this article: R. Robinson & L. I. Brujin (2013) Report on The ALS Association's drug discovery workshop, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 14:2, 81-84, DOI: 10.3109/21678421.2012.734519

To link to this article: https://doi.org/10.3109/21678421.2012.734519


Published online: 22 Oct 2012.


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Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2013; 14: 81–84

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REPORT

Report on The ALS Association's drug discovery workshop

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In early March 2012, over 120 researchers, drug developers, government officials, and clinicians came together in Washington D.C. for three days of discussions focused on advancing drug discovery for ALS. The workshop, hosted by The ALS Association, examined the barriers and opportunities for translating basic science discoveries into therapeutics, with special emphasis on biomarkers, alternative targets, and clinical trial development. Many researchers generously presented new and unpublished results, in keeping with the goal of the workshop of fostering discussion at the leading edge of ALS therapy development. The report below includes discussion of some work that had not yet undergone peer review at the time of presentation, and should be considered in that context.

In the keynote address, Chris Austin, Scientific Director for the National Center for Translational Therapeutics (NCTT) at the National Institutes of Health, placed the challenge for ALS within the context of rare or orphan diseases as a whole, of which over 6000 are known. Despite the identification of genes for two-thirds of these, treatments exist for fewer than 250 of them. The reasons are multiple, but a major one is the gulf between the work of basic researchers, who identify mechanisms and targets, and pharmaceutical companies, who alone have the resources to conduct large-scale clinical trials. That gap, often called the 'valley of death', is difficult to bridge, as the cost for bringing potential drugs forward rises steeply and the likelihood of success falls even more steeply in this zone. The NCTT has been designed to improve the odds of bridging that gap, by providing expertise in translational drug development, including chemical genomics, quantitative high-throughput screening, and preclinical development. More information is available at http://nctt.nih.gov.

Biomarkers

A key aspect of a successful development program is the availability of validated biomarkers that can be used in a clinical trial. Several speakers from the pharmaceutical industry noted that having a validated biomarker is a critical step in reducing the financial risk of a drug development program, since the biomarker allows the company to assess the likelihood of success of an agent much earlier in the development process. The ideal objective biomarker would supplement functional endpoints such as muscle strength or the ALS Functional Rating Scale. While both of these measures decline with disease progression, they may fluctuate, leading to the need for larger patient numbers and longer trials.

Two groups, taking two different approaches, presented their latest results at the meeting. Robert Bowser is looking for an ALS protein signature in the cerebrospinal fluid. He uses liquid chromatography and mass spectrometry to separate and identify CSF proteins, controlling for patient age, gender, site of onset, and other variables. By comparing patients to controls, he has found that the ratio of the levels of phosphorylated neurofilament heavy chain to complement C3 (pNFH/C3) identifies ALS patients with a sensitivity of 96% and a specificity of 90% (1). At the present time, the ratio is diagnostic, not prognostic, since longitudinal sampling has not been performed. He also reported preliminary evidence that the protease inhibitor cystatin C may help distinguish slow from fast progressors.

Rita Sattler, John Gerdes and Richard Bridges have collaborated on the development of a PET ligand that tags the EAAT2 glutamate transporter, which they are developing as a potential therapeutic biomarker for treatments that increase the level of the transporter. Severe loss of EAAT2 on astrocytes

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(Received 23 May 2012; accepted 24 September 2012)

ISSN 2167-8421 print/ISSN 2167-9223 online © 2013 Informa Healthcare
DOI: 10.3109/21678421.2012.734519

is seen in ALS patients, and in animal models transporter loss precedes symptom onset, leading to the hypothesis that its loss may hasten motor neuron death. Ceftriaxone a drug that increases EAAT2 and prolongs survival in animal models, has recently completed Phase III trials, but with no significant effect in patients. The PET ligand under development is given as a pro-drug to prevent peripheral glutamate overloading, and hydrolyzes to the active form after it crosses the blood-brain barrier. Work in the rat is completed, with testing in monkeys next. Safety testing is scheduled for later in 2012, and testing in patients as a biomarker as early as 2013.

John Trojanowski described the Alzheimer's Disease Neuroimaging Initiative (ADNI), currently in its eighth year. This public-private partnership combines neuroimaging with biological sample analysis to understand the natural history of the disease in detail, with the goal of improving clinical trials. A similar initiative in ALS would be extremely helpful, but concern was expressed that funding may be difficult to obtain for a rarer neurodegenerative disease like ALS.

A consensus emerged among the meeting participants that, despite the challenges, developing a set of biomarkers for ALS, especially for progression, is a critical and urgent need.

ALS disease mechanisms and targets

The discovery of the expanded hexanucleotide repeat in the *C9ORF72* gene, and the suggestion that it forms large RNA inclusions, has led to the question of whether this form of ALS might be similar to myotonic dystrophy, in which toxic RNA foci bind a transcription factor, leading to dysregulation in multiple cell types. A note of caution was offered by Bryan Traynor, one of the codiscoverers of the gene, however, who noted that the original data on inclusions have so far been difficult to replicate, calling their relevance into question: (since the meeting, additional data replicating the foci have been announced). A loss of function of the gene is also possible; the normal function of the gene is unknown.

Michael Strong described RNA metabolism as a large and potentially central focus in ALS etiology, given the RNA/DNA binding functions of both TDP-43 and FUS, but the nature of the involvement of RNA is still unknown. Knockdown of TDP-43 reduces activity of Rho GTPase, which interacts with cell-injury response factors. The loss of activity may be mediated by an effect on Rho-guanine nucleotide exchange factor (RGNEF). RGNEF interacts with mRNA of neurofilament light chain, but only in ALS lysates, and not controls (2). Novel RGNEF antibodies detect ALS pathology in motor neurons, suggesting another possible link in the pathway.

SOD1 aggregates, and how to prevent them, are a focus of two groups who presented their results at the meeting. Jeffrey Kelly introduced the session, describing that for the vast majority of the proteome, folding is biologically assisted. Chaperones help with folding, while proteasomes and the autophagy pathway dispose of misfolded or aggregated proteins. Kelly's group looks for small-molecule activators of protein homeostatic pathways. Since misfolding is common to most neurodegenerative diseases, it is possible that one drug could be applied to many diseases. The recent attempt to treat a peripheral misfolding disease, transthyretin amyloid cardiomyopathy, underscores the interest in protein misfolding as a therapeutic target, although the results from the trial were not conclusive enough to justify approval at this stage (3).

Al Sandrock gave an update on development of immunotherapy for misfolded SOD1 at Biogen-Idec. Quoting a recent study showing that 69% of the variance in patient survival in SOD1 familial ALS could be attributed to differences in aggregation propensity (4), he noted that the working hypothesis of the program is that misfolded SOD1, either mutant or oxidized wild-type, aggregates and causes motor neuron death. Therefore, antibodies to misfolded SOD1 may have the potential to reduce levels of toxic protein and slow disease progression. Several preclinical studies have been performed at Biogen-Idec, but evidence for changes in misfolded protein is still lacking, perhaps due to the use of models with more SOD1 than the antibodies can handle.

Jean-Pierre Julien reported that in his work with single-chain recombinant antibodies delivered intrathecally into SOD1 mice, antibody can be detected within three weeks of treatment, and treatment increases lifespan about 16 days, although with high variability. The mechanism of the effect is currently under study. In addition, he presented evidence that TDP-43 dysregulation in ALS can contribute to pathogenesis through activation of nuclear factor-kB (NF-kB) p65, a key molecule of the innate immune response. Inhibition of this pathway by Withaferin A treatment conferred protective effects in TDP-43 transgenic mouse models of ALS (5).

Jeffrey Rothstein reported that oligodendrocytes and their precursor cells, called NG2 cells, likely are major contributors to ALS. He reported unpublished results showing that deleting SOD1 from NG2 cells delays the onset of disease in mice and increases their survival, suggesting the potential efficacy of targeting therapy to the NG2 cells.

Pamela Shaw is investigating a stress-response pathway, called Nrf2-ARE, which drives expression of a large group of protective genes, including multiple antioxidant enzymes, and is down-regulated in SOD1 mice. A drug screen for small molecules to up-regulate the pathway led to identification of S[+] apomorphine, the enantiomer of an anti-parkinson drug, but without its dopaminergic activity. In unpublished work in mice, treatment led to better motor performance even late in the disease, but, for unknown reasons, no improvement in survival.

Other pathways being investigated include autophagy, axonal transport, neuroinflammation, and

neuron-to-neuron spread of protein misfolding. A key question for ALS drug development is how to prioritize targets, and engage industry in moving relevant therapeutics toward the clinic. This was identified as an important action item arising from the meeting.

Update on current trials

Clinical trials in ALS have increased in recent years in both number and quality. Factors contributing to this trend include the growth of the Northeast ALS (NEALS) consortium for clinical trials and training of investigators within it, a direct focus on translational drug development by non-profits including The ALS Association, and an increasing interest in the pharmaceutical sector to focus on rarer disorders. Merit Cudkowicz provided an overview of the current state of clinical trials in ALS, and suggested that the decision to move a drug to trial should not necessarily be dictated by results in animal models. Given the imperfection of the models, it may be justified to move to humans if a drug can be shown to be safe, that the proposed beneficial mechanism of the drug in ALS makes sense, and that the drug can hit the intended target in humans.

Frank Bennett at Isis Pharmaceuticals reported that the phase I trial of an antisense oligonucleotide that targets mutant SOD1 messenger RNA has been completed. The drug is delivered intrathecally, and is well tolerated, and no safety concerns have been identified. He also suggested that if the *C9ORF72* mutation causes a toxic gain of function, antisense targeting of the expansion could be therapeutic.

Douglas Kerr gave an overview and update of the ongoing development program of dexpramipexole at Biogen-Idec. This enantiomer of an anti-parkinson drug has little to no dopaminergic activity. It is thought to protect neurons against oxidative damage by stabilizing mitochondrial membranes. A phase II study of 102 early ALS patients suggested the drug may have a beneficial effect on disease progression and survival (6). A phase III trial has enrolled almost 1000 patients for treatment of up to 18 months, and is scheduled to be completed at the end of 2012.

Jesse Cedarbaum gave the group an update on CK2017357 being developed at Cytokinetics. The drug acts in fast skeletal muscle fibers to increase the sensitivity of the troponin complex to calcium. Binding of calcium to the troponin complex triggers muscle contraction, and the increased sensitivity causes a greater contraction for a given level of calcium. The largest effect is at the mid-range of effort, where most daily functions are performed. Single-dose studies have shown that the drug reduces fatigue and improves function in ALS patients (7).

Screening technologies

Multiple groups discussed their progress in developing drug screens for ALS. Wim Robberecht observes embryonic growth of motor neurons in zebrafish. Robberecht has found antisense molecules that rescue fish mutant for TDP-43, an RNA-binding protein that causes ALS and that is found in neuronal aggregates. The most effective antisense sequence targets EPHA4, a receptor in the ephrin system, an axonal guidance system for motor neurons during development and regrowth. Deletion of one copy of the gene for the receptor in SOD1 mice increased survival by 50%. A similar beneficial effect in fish can be induced with a small molecule that targets the receptor. The potential importance of the receptor as a target in ALS is also highlighted by the discovery that survival in ALS patients is inversely correlated with level of expression of the receptor, suggesting that reduction of EPHA4 receptor signaling may be therapeutic (8).

Steve Finkbeiner described a robotic arm his group has developed to carry cell plates from the incubator to the microscope, allowing precise repeatability and fully automated data acquisition. The system allows observation of individual cells over many hours, and is currently being employed to screen for compounds that affect the autophagy pathway.

Kevin Eggan reported on developments in induced pluripotent stem cell lines developed from ALS patients. His group currently has over 30 lines developed from genetically caused ALS, and more than 10 from sporadic cases. New lines from patients with the *C9ORF72* mutation are in progress. He noted that each line tends to be slightly different, in ways that pose some challenges for comparisons among them (9,10). In general, patient-derived cells are smaller and grow more slowly than those from controls. The unfolded protein response also differs between them. The NINDS has funded a consortium to develop iPS cells and to make them available to researchers, including for ALS (http://ccr.coriell.org/Sections/Collections/NINDS/?SsId=10).

The workshop highlighted the significant opportunities for the development of therapeutics for ALS, the increased interest from the pharmaceutical sector and the challenges and opportunities provided by an increasing number of potential targets of relevance in the disease. With increased investment into translational efforts, biomarker development and clinical trials for ALS, the potential of finding effective therapeutics is very promising.

Acknowledgements

The workshop was sponsored by The ALS Association; National Institutes of Neurological Disorders and Stroke; The ALS Society of Canada; The Office of Rare Diseases Research; Biogen-Idec; Knopp Biosciences; Bristol Myers Squibb; Pfizer; Isis Pharmaceuticals; and Cytokinetics.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Ganesalingam J, An J, Shaw CE, Shaw G, Lacomis D, Bowser R. Combination of neurofilament heavy chain and complement C3 as CSF biomarkers for ALS. J Neurochem. 2011;117:528–37.
2. Volkening K, Leystra-Lantz C, Strong MJ. Human low molecular weight neurofilament (NFL) mRNA interacts with a predicted p190RhoGEF homologue (RGNEF) in humans. Amyotroph Lateral Scler. 2010;11:97–103.
3. http://www.drugs.com/nda/tafamidis_120618.html. Viewed online 26 June, 2012.
4. Wang Q, Johnson JL, Agar NY, Agar JN. Protein aggregation and protein instability govern familial amyotrophic lateral sclerosis patient survival. PLoS Biol. 2008;6:e170.
5. Swarup V, Phaneuf D, Dupré N, Petri S, Strong M, Kriz J, Julien JP. Deregulation of TDP-43 in amyotrophic lateral sclerosis triggers nuclear factor κB-mediated pathogenic pathways. J Exp Med. 2011;208:2429–47.
6. Cudkowicz M, Bozik ME, Ingersoll EW, Miller R, Mitsumoto H, Shefner J, et al. The effects of dexpramipexole (KNS-760704) in individuals with amyotrophic lateral sclerosis. Nat Med. 2011;17:1652–6.
7. Shefner J, Cedarbaum JM, Cudkowicz ME, Maragakis N, Lee J, Jones D, et al. Safety, tolerability and pharmacodynamics of a skeletal muscle activator in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2012, May 16.
8. van Hoecke A, Schoonaert L, Lemmens R, Timmers M, Staats KA, Laird AS, et al. EPHA4 is a disease modifier of amyotrophic lateral sclerosis in animal models and in humans. Nat Med. 2012 Aug 26. doi: 10.1038/nm.2901. (Epub ahead of print)
9. Chaddah MR, Dickie BG, Lyall D, Marshall CJ, Sykes JB, Bruijn LI. Meeting report of the International Consortium of Stem Cell Networks' Workshop Towards Clinical Trials Using Stem Cells for Amyotrophic Lateral Sclerosis/Motor Neuron Disease. Amyotroph Lateral Scler. 2011;12:315–7. Epub 2011, Aug 3.
10. Bilican B, Serio A, Barmada SJ, Nishimura AL, Sullivan GJ, Carrasco M, et al. Mutant induced pluripotent stem cell lines recapitulate aspects of TDP-43 proteinopathies and reveal cell-specific vulnerability. Proc Natl Acad Sci U S A. 2012;109:5803–8. Epub 2012, Mar 26.