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EDITORIAL

The Evolving Landscape of Motor Neuron Disease Therapeutics

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Editorial

What has become increasingly appreciated by scientists and clinicians is that therapeutics for amyotrophic lateral sclerosis (ALS) will likely be targeted to a number of different disease-relevant pathways, much like we have seen in the oncological sciences. It is no longer a widely held belief that a single pathogenic cascade can account for the clinical and pathological features of this heterogeneous disease. With this in mind, the field of ALS therapeutics has entered an exciting time for creative ideas regarding mechanisms of disease and targeted therapeutics. In the last decade, the development of new preclinical models and systems based on human cells (induced pluripotent cell lines) derived from actual patients has dramatically expanded the possibilities of candidate cellular targets for new drugs. This is especially true as we are increasingly appreciating genotype/phenotype correlations as new ALS genes are being discovered. In this issue of *Neurotherapeutics*, our contributors explore some of the more recent discoveries relating to motor neuron cell death and discuss how these discoveries may translate to novel ALS therapeutics.

Discoveries about nuclear pore dysfunction as a core mechanism, not only for ALS but for a number of neurodegenerative diseases, serve as an important foundation for our understanding of molecular trafficking. Importantly, this pathway may be an initiating pathophysiology in sporadic ALS and may be the cause (or one cause) for TDP43 dysfunction–common to almost all ALS. As Spead et al. [1] discuss in their review of the topic, we have already come to see early therapeutic strategies that can repair underlying nuclear pore complex defects as well as aberrant nucleocytoplasmic shuttling of important RNA binding proteins–believed to be at the heart of many, if not most, forms of ALS. As one will see from the other reviews, targeting this disease initiating event may become an important target for effective interventions.

Hayes and Kalab [2] review the importance of a central player in sporadic ALS, TDP-43, whose loss from normal nuclear localization and accumulation/aggregation in the cytoplasm in ALS is believed to represent one of the underpinnings of the disease. This is one of the most intensely studied proteins in ALS, and its role as a guardian of the transcriptome is now well established. While the exact mechanism(s) by which TDP43 mislocalization causes disease remains a topic of intense research, it is attracting attention as a target for therapeutics. With this in mind, there are a number of clinical trials targeting the TDP-43 proteinopathy in ALS through a variety of mechanisms led by attempts to accelerate the clearance of cytoplasmic TDP-43 aggregates by inducing autophagy. The authors speculate on the enormous potential opportunities for modulating this critical protein in the context of all forms of ALS and also balance their enthusiasm by discussing a number of the preclinical and clinical challenges that remain.

As Li et al. [3] detail, it has long been proposed that ALS is caused, at least in part, by an infectious source, but attempts to reproduce virally mediated infections that initiate disease have not been reliably demonstrated. However, the authors highlight the fascinating biology behind human endogenous retroviruses (HERV) and specifically HERV-K activation in ALS. These are a family of endogenous retroviruses existing in the genome that become reactivated in disease. The authors highlight two groundbreaking studies, the first of which identified HERV-K in ALS patients and the second showing that expression of the HERV-K envelope protein under a neuronal promoter could induce a motor neuron syndrome in mice. These observations, and contributions by other investigators, have spawned thoughts about potential therapeutics that include antiretroviral drugs, antisense oligonucleotides, shRNA, and antibodies that may also target the envelope protein. Of course, clinical therapies alone

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do not truly prove or disprove a basic hypothesis–but this research for the first time is truly spawning novel approaches to ALS therapy by employing rigorously designed clinical trials.

Metabolic dysfunction as either an etiology or consequence of ALS pathobiology remains one of the most well studied, reproducible, and potentially targetable pathways for the disease. Nelson and Trotti [4] review the fundamental defects in neuronal and glial metabolism that may contribute to the disease and, importantly, offer a discussion of how these observations have translated to clinical efforts at restoring energy balance.

Extracellular vesicles (EV), whose contents vary but include RNA and proteins, are released by a number of different cell types under both physiological as well as pathological conditions. In their review of EV in ALS, Kim et al. [5] detail the composition of this broad family of membrane-bound vesicles. Importantly, isolation of EV from blood, saliva, urine, and cerebrospinal fluid has revealed their potential utility as biomarkers of disease from a diverse cellular origin. Extracellular vesicles secreted from various CNS cell types, including neurons and glia, have also been studied as novel pathways of intercellular communication in the CNS. The authors speculate that misfolded proteins, thought to be a pathophysiological mechanism of ALS, are associated with EV and have the capacity to be transferred between cell types of the CNS–thus providing a potential mechanism for disease spread. The pathological spread of neurodegeneration in ALS is well known clinically and although quite variable, has long demanded a creative mechanistic hypothesis. One such hypothesis may center around the release of these EV. Thus, the study of EV may yield both a diagnostic biomarker of ALS pathobiology as well as a target for curbing the spread of disease throughout the neuraxis.

Decades of research have been focused on the cell soma as the locus of dysfunction in ALS with axon loss and distal denervation as a secondary byproduct of failure at the soma. Work by a number of investigators, as reviewed by one of the leaders in the field of axon biology, Coleman [6], has challenged this notion and firmly placed established axon dysfunction and distal denervation as an important target for early ALS therapeutic intervention. Is axon dysfunction the first step in the injury to motor neurons, or a downstream event? Regardless of that hypothesis, the development of the understanding of SARM1-related pathways and targeted therapies is certainly going to avail ALS patients of new opportunities for therapy. The review focuses on the emerging role of SARM-1, an "axon killer," in ALS and the therapeutic opportunities being built around its biology.

Perhaps no new field of therapeutics has generated as much enthusiasm as the development of antisense oligonucleotides (ASO) for targeting genetic forms of ALS. Twenty-five years after the discovery of the first ALS gene, SOD1, ASOs targeting this protein are now showing promise for this patient population. Boros et al. [7] share insights into the development of ASOs that include ASO design, the extensive preclinical package showing target engagement, toxicity studies, and efficacy measurements that resulted in the design of early phase clinical trials for SOD1 ASOs in ALS. They also appear to be one of the fastest approaches for the development of highly specific drugs–with the translation from pathway discovery to actual trials measured in a handful of years rather than decades!

Capitalizing on an evolving sophistication in methods for gene modulation, Meijboom and Brown [8], who themselves have shown important advances in the delivery of gene therapies to ALS patients, discuss the ever-increasing number of ALS-related genes being targeted. In addition to ASO strategies, they highlight other RNA-based therapeutics including small activating RNAs, and AIMers (short chemically modified oligonucleotides that direct A-I editing of endogenous transcripts). They also recap how viral vector deliveries of these gene therapies may change the future of ALS therapeutics. These are exciting new therapeutic modalities and questions remain. Are they the future of therapeutic targets? Will they be safe? Will they be affordable? These and many more scientific and practical questions lie ahead for these modalities. This review begins to reveal the many possibilities.

Finally, therapeutic development is incomplete without appropriate clinical trial design. The field of ALS therapeutics has a long history of failures at the clinical trial stage. The reasons for this are likely multifactorial including underpowered studies, absence of patient stratification by genotype and/or phenotype, a paucity of biomarkers of disease, and outcome measures that may be insensitive to subtle but important influences of these therapies. Fournier [9] details new measures for the assessment of meaningful clinical outcomes in ALS including her own work developing a new Rasch-Built Overall ALS Disability Scale (ROADS) that was designed to overcome the psychometric limitations of the widely used ALS Functional Rating Scale-Revised (ALSFRS-R). She also highlights new biofluid biomarkers, like neurofilament, that will likely see increased visibility as the specifics of their sensitivity and specificity in the disease are revealed. Importantly, she also discusses the often-overlooked challenges of diversity, equity, and inclusion in clinical trial design.

These ideas and approaches likely herald the next 5–10 years of challenges and changes in ALS clinical research. Regardless of how well designed or interesting the preclinical science is executed, it is the final step, the clinical trial, that finally tests the hypothesis. Improvements in that final experiment are critical to future successes for patients. There are additional scientific and clinical issues not tackled in this issue that certainly require scientific investigations and review: What accounts for the combination of ALS and

frontotemporal dementia (FTD) in selected gene mutations (e.g. C9orf72)? What accounts for cell-specific injury in ALS, and can an understanding of that biology help develop better drugs? Why does it take decades for the manifestation of clinical disease? Are there better approaches (specific biomarkers) to assure early patient identification in drug trials?

Taken together, this issue focusing on motor neuron disease provides a broad perspective of new and well-established hypotheses regarding ALS pathobiology with insights into some of the novel therapeutics now at the fore of the field. While it is clear that these new approaches present challenges with regard to the timing and methods of delivery, the breadth of targetable pathways offers continued opportunities for success.

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Required Author Forms Disclosure forms provided by the author are available with the online version of this article.

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