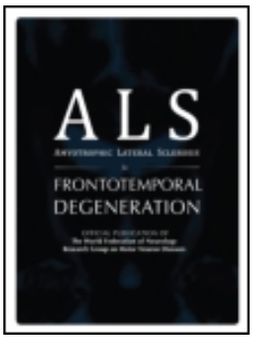

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

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ORIGINAL ARTICLE

Funding agencies and disease organizations: Resources and recommendations to facilitate ALS clinical research

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Abstract

Ten groups presented their perspectives on facilitating clinical research in ALS including four federal agencies, four disease organizations, one foundation and one advocacy group. The federal agencies (National Institute of Neurological Disorders and Stroke, National Institute of Environmental Health Sciences, Office of Rare Diseases Research, Department of Defense) encourage fostering a team approach between pre-clinical and clinical research investigators, coordinating with patient groups in the early phases of clinical studies, enhancing private and public partnerships, and investigating the interplay between genetic susceptibility and environmental exposure. The disease organizations (Muscular Dystrophy Association, ALS Association, ALS Society of Canada, and the Motor Neurone Disease Association UK) support fellowship training programs to develop ALS clinician scientists, and encourage work on the epidemiology of ALS, on genetic and epigenetic mechanisms that are relevant to ALS pathogenesis, on developing ALS registries and biobanks, and building bridges of collaboration among study groups. The Foundation supports innovative projects, including stem-cell research, and Patient Advocacy is committed to supporting excellence in ALS research and patient care, and believes strongly in enhancing communication between patients and members of the research community.

Key words: *ALS, funding agencies, patient voluntary organizations*

Introduction

Federal agencies, disease organizations, foundations and patient advocacy groups all play crucial roles in promoting clinical and patient oriented research to advance our understanding of the pathogenesis of ALS and ultimately to help identify specific causes of the disease. In this paper we report on the presentations made at the International ALS Conference by representatives of these groups.

National Institute of Neurological Disorders and Stroke (NINDS)

Given current budgetary constraints, limited resources and the rarity of ALS, the leadership at NINDS stresses the importance of setting priorities and believes that it is crucial for every study to achieve its fullest potential. NINDS emphasizes the necessity of applying vigorous scientific standards whenever discoveries move from pre-clinical research toward the clinic. It is important to note that the consortium statement has changed and improved how clinical trials are being conducted. It was developed by the international editors of biomedical journals and it requires that each subject entering into a trial is accounted for so that there is no bias in the reporting. It also required that the methods to minimize bias, such as randomization and blinding, are stated explicitly.

The web site clinicaltrials.gov is often used by patients and physicians to search for clinical trials,

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and it has another important role to accomplish – to bring transparency into clinical trials. Clinical trials must be registered so that the public understands what they did and did not achieve. Because reporting is subject to publication bias, it is important to be able to ascertain if certain experiments in the clinical arena have been carried out and whether the outcomes were positive or negative. Such an approach would also be helpful regarding studies in the pre-clinical arena.

Given finite patient numbers and limited resources, NINDS feels there are only a few opportunities for efficacy trials (phase III) that typically require multiple sites, and often international efforts. They require many hundreds, even thousands, of patients. Therefore it is vital to set priorities in the exploratory trial arena – in phase IB, phase II trials – and make optimum use of biomarkers that lead to clear go/no-go decisions.

NINDS proposes creating links between pre-clinical and clinical research programs, to bridge pre-clinical and clinical research early on through multidisciplinary teams. An example is fostering a team approach among pre-clinical and clinical research investigators so that the compound being studied, the route of administration, and the dose selected for trial are readily translatable from the pre-clinical to the clinical stage. Biomarkers that are used in pre-clinical experiments may have the potential to provide an early read-out when the study reaches the clinical stage. NINDS believes that it will be necessary to develop a better understanding of how the outcomes in pre-clinical models relate to the human phenotype. Finally, it is essential to consider the regulatory pathway early on in the development of a clinical study – selecting, in phase II of a study, for example, an outcome measure that is accepted by the regulatory agencies.

It is helpful to leverage partnerships and bring the research community together, by sharing data standards and SOPs: making data available online so the research community can see how information is collected; coordinating internationally so that the ability to perform meta-analysis is enhanced; and developing a universal consent form that allows for sharing of data and specimens. The overwhelming majority of patients consent to give a blood sample, a skin biopsy and a CSF sample because they hope the sample will be made available to scientists and advance research. It is also important to coordinate with patient groups early on, to encourage dialogue between patients and study investigators, and to enhance private and public partnerships in ways that go beyond being a site in a clinical trial; to participate, for example, in biomarker initiatives and outcome measure validation.

National Institute of Environmental Health Sciences, NIEHS

The NIEHS is a part of the NIH located in North Carolina within Research Triangle Park, which allows access to multiple universities and resources. The mission of this organization is to support research encompassing the effect of environmental exposures on human health. Environmental exposures include heavy metals, industrial chemicals, agricultural chemicals, air pollutants, and ozone; and exclude self-induced exposures such as alcohol consumption, high-fat diet, smoking, and infectious diseases unless combined with environmental exposures. The NIEHS believes that a complex interplay between genetic susceptibility and environmental exposure (both multifactorial) is likely to be important in the pathogenesis of ALS; and that the brain's high metabolic rate coupled with its low concentration of antioxidants makes it very susceptible to oxidative stress. Regarding possible causative factors in ALS, the mission of the NIEHS is to study exposure to chemicals (such as formaldehyde, cassava toxins and cyanobacteria); support work using G93A mice expressing human SOD1 exposed to methylmercury, which emerges as a risk factor in these mice for ALS; support the multicenter ALS cohort study of oxidative stress and disease progression; and explore the effect of variation in genes of xenobiotic response proteins in ALS. Additional topics of interest are genetic epidemiology of ALS in Veterans, environmentally sensitive genes in motor neuron degeneration, and the role of heavy metals in ALS. Although funding is limited, the NIEHS encourages investigators to apply for funding and to contact staff members not only to discuss research ideas but also for advice on how to navigate the NIH system.

Office of Rare Diseases Research (ORDR)

The ORDR encourages members of the ALS community to apply for a Rare Diseases Consortium Research grant, as ALS certainly meets the criteria and requirements for funding. These grants are cooperative agreements of type U54. The requirements include having three disease types in the area, conducting longitudinal or natural history studies, carrying out clinical trials – usually phase I or II, but occasionally phase III, having close relationships with patient advocacy groups, incorporating a training component, and having at least one pilot study. From 2003 to 2009, the ORDR had 10 consortia and now it has grown to a total of 19. This includes seven that are neurological, such as the Clinical Investigation of Neurologic Channelopathies (CINCH) Consortium, the Spinocerebellar Ataxia Consortium, Hereditary Neuropathy Consortium, Dystonia Coalition, Autonomic Rare Diseases Clinical Research Consortium, the Lysosomal Disease Network and a Brain Vascular Malformation consortium. The type of coordination and cooperation that occurs in the rare disease consortia is likely to be very helpful in bringing together the multiple disciplines of the ALS community.

Department of Defense

The Department of Defense (DOD) is involved in ALS research because the ALS Advocacy community went to Congress and demanded monies to focus specifically on ALS research. The DOD program is very small, but that allows it to be nimble, and it has been proud to fund a number of ALS researchers. The DOD has focused its small portfolio on therapy development, which meshes appropriately with NINDS because it has focused on more basic research and on clinical trials which DOD cannot afford. The DOD has offered two mechanisms in the past, both focused on drug development – a Therapeutic Idea Award that emphasizes innovation, and a Therapeutic Development Award, which is a larger award, of 1.5 million dollars. These awards are intended to support preclinical therapy development efforts. For fiscal year '12, DOD cannot offer the research community a funding mechanism at the present time, but in the future, should funds become available, DOD might be able to address some of the issues that have been raised at the meeting, e.g. increasing the opportunities for basic scientists and clinicians to work together on the development of new models that would illuminate the pathogenesis of ALS.

Muscular Dystrophy Association (MDA)

In terms of investigator initiated studies, along the lines of the NIH model, the MDA has about 75 different multi-year projects currently funded, which total about $25 million. The MDA also has a robust translational research program that is designed to absorb some of the risks inherent in the early stages of drug development research. The MDA also funds a clinical research network, and fellowship training programs. One of the important missions of the MDA is to increase the number of ALS researchers, specifically clinician scientists. There are two flagship training programs: 1) The Clinical Research Training Grant is typically given to Fellows of neuromuscular study to spend dedicated time doing clinical research; 2) The Development Grant is typically given to senior post-doctorate scientists – MDs or MD, PhDs – who can then set up their own research laboratories. The MDA would welcome high quality applications for these training awards. The MDA enthusiastically appeals to all potential mentors to identify promising candidates and apply for these awards to help in the establishment of the next generation of ALS researchers and clinician scientists. The MDA also fosters information exchange and collaborations through sponsorship of national conferences and symposia.

ALS Association (ALSA)

The Association drew attention to a number of presentations made at the meeting that were particularly noteworthy and have generated excitement in the field of ALS research. Macklis's work to deepen understanding of the molecular controls over corticospinal and corticobulbar motor neurons and to utilize developing neurons to repair and rebuild complex motor neuronal circuitry in the mammalian brain, holds great promise for ALS research. Ravits's compelling studies suggesting that the process of degeneration in ALS is focally triggered and anatomically propagating over time is important to pursue with experimental studies. Henderson's work describing how MMP-9 knockout SOD1 mice have an attenuated form of the disease, leads to the very interesting possibility that MMP-9 could become a candidate target in future efforts to treat ALS more effectively. It is likely that, in the future, clinical trial research will begin to explore whether there are specific ALS phenotypes that are more or less likely to respond in clinical studies. ALSA embraces taking lessons from animal models of ALS and applying them to human studies; a case in point is the high-fat, high-calorie diet trial designed to test the hypothesis, suggested by observational studies and studies in mice, that a high-fat and/or high-calorie diet can significantly increase survival in ALS. Although they are expensive and challenging, ALSA has supported and is enthusiastic about continuing to support epidemiological studies; it is important to standardize these studies through ACES and through EURALS etc., and it would be helpful to partner with other funding agencies. Understanding genetic and epigenetic mechanisms are clearly critical to ALS research and are most worthy of support.

ALSA is excited about improving the recruitment of patients who are under-represented into clinical studies, and of funding the best science, appreciating that along with being innovative, funded projects might entail some risk. ALSA encourages partnerships with government agencies and other funding organizations, and seeks to bring the best researchers together working on innovative projects to move the field forward to fruitful outcomes.

ALS Society of Canada

The ALS Society of Canada believes in the importance of following up on interesting epidemiological observations such as the possible role of lead toxicity and head trauma in the pathogenesis of ALS, and the concept that intrauterine testosterone levels might affect motor neuronal function in adult life. Also noted was the importance of following through on biomarker studies – developing pathways for the most interesting biomarker candidates to be further investigated and validated so that they become useful to clinical research.

Other ideas discussed during the meeting bearing on epidemiology, genetics, and study methodologies were of great interest to the ALS Society of Canada: 1) the importance of considering how environmental factors might contribute not only to

the death of motor neurons, but to the process of degeneration that underlies progression of the disease; 2) pursuing the study of genes and proteins that are part of the epigenetic/non-coding RNA network associated with known familial ALS (FALS) genes; and 3) bringing epidemiologists together with basic scientists to validate epidemiological hits and trying to identify mechanisms of disease pathogenesis.

ALS Canada is a strong supporter of resources and infrastructure. The organization believes in the importance of biobanking, developing ALS registries and building bridges of collaboration between study groups to harmonize the research enterprise and move the field forward.

Motor Neurone Disease Association UK

The Motor Neurone Disease Association (MNDA) is the sole national charity in England, Wales and Northern Ireland that provides people with MND the care and support they need, as well as promoting research into causes, treatments and, ultimately, a cure for this devastating condition. As a leading research funder, the Association has invested £20 million in research over the past decade and currently supports a portfolio of 45 projects: infrastructure activity such as DNA banking; basic and clinical science initiatives aimed at understanding disease pathogenesis and identifying therapeutic targets; and healthcare research aimed at improving the evidence base that is required to underpin multidisciplinary care practice and enhance patient survival and quality of life. The MNDA also plays a prominent role in facilitating the international research effort, through encouraging 'open access' to new data/publications and through its role as organizers of the International Symposium on ALS/MND, the world's premier annual meeting on the disease.

The Association is also committed to ensuring that everyone with MND receives the best care, achieves the highest quality of life possible and dies with dignity. This includes supporting the caregivers and family as well as those with the disease, through financial support, information provision and helping to reduce the isolation that can accompany a diagnosis of MND. In addition to funding a network of 19 care centers providing high standards of multidisciplinary care, MNDA provides a range of information resources and training opportunities for health and social care professionals, accompanied by local and national influencing of statutory health and social care service provision. In pursuit of their goals, MNDA appreciates the value of collaboration and is committed to creating opportunities to work in partnership with others, nationally and internationally, to achieve their objectives and ultimate vision of a world free of motor neuron disease.

Judith and Jean Pape Adams Charitable Foundation

The Judith and Jean Pape Adams Charitable Foundation was founded about eight years ago upon the death of Jean Pape Adams, who died of ALS. A primary purpose of the Foundation is to support research in discovering the causes of and finding a cure for ALS. The Foundation is eager to support innovative projects, including stem-cell research; it has already supported two human stem-cell research trials in ALS. The chair of the Foundation's ALS Advisory committee (DC) – a physician-immunologist-scientist for 50 years, now retired – observed that the field of ALS today is very much like the field of immunology he joined 50 years ago. At that time, systemic lupus erythematosus (SLE) was treated as one disease, as also were lymphomas. Looking back at 50 years of immunology in the fields of lupus and lymphoma one observes that breakthroughs came as both disorders were phenotyped clinically and experimentally. First, it was realized that lupus was actually two diseases – a cutaneous form, and a systemic illness with a subacute form. The early iteration of genome-wide association studies – HLA typing – showed that the three types of lupus were associated with three completely different HLA types. A crucial observation that illuminated the genetics of lupus was the realization that patients with thrombocytopenia or nephropathy had different genetic profiles from those who had neither complication, and that African-Americans had a very different genetic profile from Asians or Caucasians. Based on such observations, the first FDA approved drug for the treatment of lupus in 58 years – which commenced marketing about six months ago – is having a major impact on this disease in Caucasians and Asians; it is not effective in the African-American population. In hindsight, our deeper understanding of SLE and how to treat it was revealed principally by genetics and gene expression studies. Similarly, in non-Hodgkin's lymphoma, 50 years ago, lymphoma was lymphoma; then categorization was somewhat refined into Hodgkin's and non-Hodgkin's lymphoma, followed by decades spent on subdividing non-Hodgkin's lymphoma. At the present time, there are 11 types of lymphoma and nine of them have five-year survival rates of better than 80%. For two of them – multiple myeloma and mantle cell lymphoma – little progress has been made in treatment. Our understanding of lymphomas and advances in the field unfolded because of the work of good clinicians, carefully parsing and phenotyping the disease, creating clinical subdivisions among the patient population, and finally developing treatments, effective in many, but still not all. It is likely that ALS – although manifesting as one disease – may not be one disease, and may have many different etiologies. Members of the foundation recommend that those engaged in ALS research seek clinical distinctions among

patients with ALS and, from those observations, it is hoped that better understanding of the genetics of ALS will ensue, and that more effective treatments of ALS might follow.

Patient Advocacy

Mr. Monti's eldest son was diagnosed 16 years ago with ALS at age 28 years and died five years later. Ever since this tragic event, Mr. Monti – a nuclear engineer by education and training – has been highly active for ALS Patient Advocacy. He expressed his deep appreciation to the conference organizers and participants for their tireless efforts in "going after the disease", and articulated his abiding commitment to ALS research.

The Advocacy group recognizes the enormity, complexity, and seriousness of the problems posed by ALS; and acknowledges how the disease can overwhelm anyone, and the research community, and how grateful patients and families are that the intense research and clinical efforts continue undiminished. From their vantage point, patient advocates suggest four principles that might prove helpful in ALS research: 1) to ensure uniformity of data collection for ALS registries – so that all data collection conforms to the same set of standards; 2) to consider applying a method used in engineering to better understand the complexities of ALS research, e.g. failure analysis can be used to determine why a study or research endeavor might have been unproductive; 3) to develop a language that speaks to the laity, to communicate with ordinary people as clearly as possible, the nature of the problem and the needs of the research community: with a common language, the group believes individuals will understand why it is important to fund a given project and they will be motivated to become research advocates, and help move the field forward; and finally 4) to ensure that patient advocates encourage ALS physicians to report their cases and strive to develop a National ALS registry.