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Dear Dr. Porter:

On behalf of the Myasthenia Gravis Foundation of America (MGFA) and its Medical/Scientific Advisory Board (MSAB), we have responded to the questions posed in the National Institute of Neurological Disorders and Stroke (NINDS) “Blue Sky” Initiative as they relate to myasthenia gravis (MG) and disorders of neuromuscular transmission.

The MGFA appreciates the opportunity to provide input to NINDS' long-term strategic planning effort. Because MG is a relatively rare disease that does not garner great attention from the national health authorities or public policy makers, the undertaking of basic, translational and clinical research poses great challenges. Therefore, assisting the NINDS to focus its sights toward future research that could enhance the diagnosis and treatment of people with MG is particularly significant to our organization.

1) What will the neuroscience research landscape look like?

The MGFA hopes to establish a national/international Research Network in the next 5-10 years. The network would consist of medical centers with established expertise in care of patients with neuromuscular disease that submit clinical information in a standardized fashion to a data coordinating center. The network then functions to organize retrospective and prospective studies in the area of comparative outcomes, best practices, financial costs of myasthenia gravis, and infrastructure for research studies requiring biological samples, including biomarker discovery.

The MGFA already has established an alliance with the American Academy of Neurology to fund a research fellowship to encourage young neurology investigators to enter the field. The NIH/NINDS could provide seed support for development of other alliances in the field, including the first established Research Network for MG, along the lines provided for Parkinson Disease and other neurological disorders.

2) What challenges and opportunities can we expect?

Considerable opportunity exists to facilitate communication among scientists (basic, translational and clinical), the public. There is a need for continued support of basic research in immunology and autoimmunity, much of which can be provided through NIH channels including NINDS.
Considerable challenges to research also exist. MG and other disorders of the neuromuscular junction are relatively rare diseases and have been largely neglected by national health authorities and the pharmaceutical industry, increasing the challenges of carrying out basic, translational and clinical research in this field. Clearly, funding for basic/translational research programs in neuromuscular disease, in general, is limited. Recent initiatives by the NINDS have created programs promoting basic and translational research in neuromuscular disease in an attempt to address this deficit, but these are predominantly targeted to the muscular dystrophies. Similar programs establishing rare disorders networks and centers of excellence are needed for autoimmune neuromuscular diseases, and MG in particular.

For clinical trials, multi-center trials are often needed to enroll adequate numbers of patients for study, increasing their cost and complexity. While randomized controlled trials (RCTs) are the most powerful tool for assessing questions of therapeutic efficacy, and properly designed RCTs minimize selection bias and ensure the homogeneity of the comparison groups, there are significant limitations of RCTs in MG and other rare disorders. Many neuromuscular diseases are so uncommon that collecting sufficient numbers of patients to answer even simple questions regarding therapeutic interventions with mild or even moderate effects is often difficult. Meeting regulatory requirements for an approved indication of a therapeutic agent in neuromuscular disease is therefore often a challenge. In addition, there may be a wide phenotypic variability in patients with particular neuromuscular diagnoses, and the rate of progression and, in some cases, fluctuating nature of disease, make it difficult to establish sufficiently stable, homogeneous study cohorts. Finally, rates of improvement in patients treated with placebo can often be quite high. These issues have come into focus with two recently published RCTs examining the efficacy of mycophenolate mofetil (MMF) in MG (Muscle Study Group, 2008; Sanders et al, 2008).

These challenges highlight the need for new approaches to the study of these diseases that will yield clinically useful information substantiating the effectiveness of various treatments and providing guidelines for their effective use. Such approaches might include, but are not limited to, longitudinal studies, retrospective studies and comparison studies. However, a prerequisite for these types of studies is the development of standardized protocols, outcome measures, and common standards for diagnosis and care of patients. A step towards achieving this goal would be the establishment of national and international patient databases. Without validated outcome measures, consensus on standards of care and diagnosis, and uniform patient databases, setting up trials of the most promising therapies will continue to be exceedingly difficult.

3) What scientific and technological advances could revolutionize basic and clinical neuroscience?

Over the last 12 months, the MSAB has proposed the following areas for study to advance both basic and clinical understanding of MG, with the goal of improving patient outcomes.

a) Etiology: What is the basic cause of the disease? Define genetic and environmental factors.

b) Detection/early diagnosis: Although most patients can be diagnosed relatively early there are some who remain difficult to diagnose and some in whom there is uncertainty regarding the diagnosis. Can more sensitive and more specific methods of diagnosis be developed? Can we educate physicians and the public better to identify MG? Would earlier diagnosis lead to improved treatment?

c) Genetics of MG:
   1. Genome-wide association study (this is in development)
   2. Other approaches
   3. Proteomic evaluation

d) Enhance understanding and application of current treatment of MG: This step includes application of drugs developed for use in other diseases and assessment of established therapy including mycophenolate mofetil (MMF), tacrolimus (FK 506), rituximab, anti-TNF agents (etanercept), and further study of a promising antisense oligonucleotid,
Monarsen. Furthermore, are there particular combinations of treatments that will lead to the best responses?
Plasma Exchange and IVIg are remarkably effective treatment options but they are difficult to administer and they are extremely expensive. Is there a way to provide these treatments in an easier, safer, and less expensive format? Can we establish exactly why IVIg works in MG? Is immunoabsorption, a more specific approach than plasma exchange geared to only remove known-to-be pathogenic antibodies in the disease, a potential approach?

e) Thymus: How exactly does the thymus gland promote the production of acetylcholine receptor antibodies? Are we scientifically certain about the role of thymectomy in treating this disorder? The thymus is abnormal in MG. Does the type or degree of abnormality predict the clinical course of MG or optimal treatment?
f) New therapeutic targets need to be identified for MG, with the goal of improved treatment responses and fewer adverse events. Areas proposed for further study include complement inhibition and dendritic cells/antigen presenting cells.
g) New strategies for treatment include development of potential vaccine therapies:
   - Vaccines
     - Give AChR or synthetic AChR
     - Mucosal or subcutaneous
     - Effective in experimental MG
   - T-cell vaccines
     - Already in clinical trials in MS and rheumatoid arthritis
     - Effective in experimental MG
     - Induce antibodies that target the T cell receptor
   - Antigen-specific tolerance
     - Immune regulatory cells (T cells, B cells, Dendritic cells)
     - Regulatory antibodies
h) Quality of life aspects: Develop better strategies to improve quality of life and develop rigorous research methods to study quality of life in MG.
i) Collateral effects of MG: sleep disorders, cognition, stress relationships, associated medical conditions.

4) How can NINDS best contribute within the broader neuroscience research enterprise?
There is considerable opportunity for NINDS to facilitate communication among scientists (basic, translational and clinical), the public. There is a need for continued support of basic research in immunology and autoimmunity, much of which can be provided through NIH channels including NINDS. For instance, the understanding of MG pathogenesis and development of therapeutics cannot be achieved by focused research studies of MG alone, but also require broad understanding of the immune system, a pursuit the NIH can support. Certainly, enhanced communication among scientists working in different but parallel fields of study could help move this forward.

Basic and translational scientific research carried out in the area of MG and related disorders is reliant upon the availability of high-quality biomaterials (DNA, white blood cells, antibodies, and thymic and muscle tissue), while clinical trials rely on the availability of suitable patient cohorts. For new treatments to make their way into clinical practice for patients affected with these disorders, it is essential that access to these resources is facilitated between and among different investigators. As noted above, the establishment of biobanks and the introduction of large patient databases for MG can facilitate this important requirement for future research. These sorts of resources are beginning to become available in other neuromuscular diseases through the efforts of the NINDS and the MDA, but are largely nonexistent for MG.

Funding to address many of these issues and the specific areas listed under question 3 would also help move the overall neuroscience research enterprise forward. For instance funding for items a, b, c, f, g, h, i are those we would expect the NINDS to have considerable interest in from a funding standpoint.
5) What ethical, legal and social issues related to neuroscience research will emerge?

There is growing attention to the role chronic diseases play on quality of life, and these measures are being utilized more and more in clinical outcome studies. Genome-wide association studies will likely raise ethical/legal issues in the future as they relate to diseases not traditionally falling under the hereditary banner, including myasthenia gravis and other acquired disorders of neuromuscular transmission (Lambert-Eaton myasthenic syndrome). MG is a relatively rare disease that does not garner great attention from the pharmaceutical industry. However, many medications approved for other immune-mediated disorders have been found to be useful in MG. Ethical and social issues could arise if restraints are placed on use of off-label agents as part of ongoing reform efforts to reduce the cost of health-care delivery.

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