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Forum

Progressive MS Alliance Industry Forum: Maximizing Collective Impact To Enable Drug Development

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The Progressive MS Alliance Industry Forum describes a new approach to address barriers to developing treatments for progressive multiple sclerosis (MS). This innovative model promises to facilitate robust collaboration between industry, academia, and patient organizations and accelerate research towards the overarching goal of developing safe and effective treatments for progressive MS.

Although significant progress has been made in the understanding and treatment of relapsing-remitting MS, the same cannot be said for the progressive (primary and secondary) forms of the disease. Of the more than 2.3 million people worldwide living with multiple sclerosis, more than 1 million live with a progressive form. These individuals and their care partners are faced with the challenging reality that there are still no effective treatments for progressive MS. Consequently, people with MS are demanding a renewed focus on progressive MS and are urging relevant stakeholders to work together to maximize their collective impact on developing new treatments for this devastating form of the disease.

For the first time in their collective histories, the organizations committed to the welfare of people living with MS have decided to work together to promote innovation and scientific progress regardless of geographic boundaries. The initial commitment of MS Societies will be €22 million over the next 4 years to sustain a long-term Progressive MS Research Program. The collaboration, formally known as the International Progressive MS Alliance (www.progressivemsalliance.org/), was established in 2012 with the express call to expedite the development of disease-modifying and symptoms-management therapies for people living with progressive MS. Within this framework, collaboration with the pharmaceutical and biotechnology industry is a crucial element to address this significant challenge.

Patients with Progressive MS Need Innovative Therapies

In Europe, the burden of brain disorders was estimated at €798 billion in 2010 and is growing [1]. The rest of the world faces similar challenges. The market for disease-modifying drugs is clearly very large. However, for chronic degenerative disorders, such as Alzheimer's and Parkinson's diseases, and for progressive forms of MS, the process of discovery and validation of pathogenetic treatments has almost completely failed, despite decades of research. After many years of industry divestment from these areas, some companies are beginning to reinvest, suggesting that neuroscience drug discovery and development may be poised for a renaissance (https://lifescivc.com/2016/02/are-we-poised-for-a-neuroscience-research-renaissance-maybe).

Despite these positive developments, people with progressive MS still lack disease-modifying treatments [2–4]. The pharmaceutical sector has concentrated its efforts and investments on the development of anti-inflammatory and immunomodulatory drugs, and on less-risky relapsing-remitting MS studies where the development and regulatory paths are better defined [5,6]. One key reason for the lack of advancement is the

absence of a fundamental understanding of the pathophysiology of disease progression, and this has prevented significant progress that could lead to treatment [7]. For progressive MS, R&D tools are unproven or do not exist. With this backdrop, drug developers must take significant risks upfront and perform large clinical trials, exposing a large number of patients to treatment without knowing the probability of being successful.

Pivotal Phase III clinical trials of disease-modifying agents in progressive MS have been long, extraordinarily expensive, and almost always unsuccessful [8]. A recent study with ocrelizumab in primary progressive MS found that B cell targeting had a significant effect on confirmed disease progression, providing some hope for people with progressive disease, especially those with active inflammation who are treated early in their disease course [9]. However, anti-inflammatory drugs that target the adaptive immune system, such as ocrelizumab, likely do not target the core pathophysiology underlying neurodegeneration, and are thus limited in their potential to affect neurodegeneration resulting from prior inflammatory lesions. Therefore, people living with progressive MS need new innovative neuroprotective and neuroreparative therapies to target ongoing neurodegenerative processes.

Given the challenges presented, the Alliance recognizes that, for progressive MS research to be successful and have a more substantial clinical impact in modifying disease progression, a new multi-stakeholder collaborative model is needed.

Progressive MS Alliance Industry Forum

In 2014 the Progressive MS Alliance established the Industry Forum to enable ongoing collaboration between the pharmaceutical and biotechnology industry and the academic and patient organizations addressing progressive MS. Industry collaborators are companies, organizations, and individuals with a shared interest in new and innovative treatments for progressive MS. The original collaborating companies include Biogen, EMD Serono, Genentech, a member of Roche, Novartis AG, Sanofi Genzyme, and Teva. The active engagement of pharmaceutical companies to this call to action illustrated the shared interest with the academic and patient communities in finding solutions for people living with this devastating form of the disease.

Governance

In the past decade, stakeholders within the healthcare ecosystem have launched collaborative efforts between academia and industry in an attempt to help neuroscience deliver innovation and stimulate new treatment development. However, many of these initiatives are governed and driven by industry and academia, and the relevance of this model has been recently commented [10]. Historically, patients and their advocacy organizations were involved solely as supporters rather than initiators or partners for translational initiatives. Today, patient organizations bring a sense of urgency, focus, and mission to research that aims to transcend obstacles to discovery and development [11].

A key difference of the Progressive MS Alliance Industry Forum initiative from most academic/industry partnerships is that MS patient advocacy organizations are at the center of the collaboration, ensuring progress towards the goals of the Alliance. Oversight is provided by the Executive Committee of the Alliance, a body composed of the CEOs of the MS Societies providing financial support for the Alliance. The scientific direction of the Alliance is overseen by its Scientific Steering Committee, consisting of scientific experts and people living with MS from 12 different countries, which reports to the Executive Committee. The Industry Forum is an advisory group to the Scientific Steering Committee and is composed primarily of R&D representatives from Industry together with representation from people with MS, academia, and MS patient advocacy organizations. The Industry Forum is co-chaired by one academic representative of the Scientific Steering Committee and one representative from a collaborating company.

As an advisory group of the Scientific Steering Committee, the Industry Forum serves the essential role of ensuring that the perspective of those responsible for, and with expertise in, the development of new therapies is a constant consideration throughout the research strategy of the Alliance. The objective of the Forum is to remove barriers and create an environment conducive to open discussions, with the sole purpose of developing safe and effective treatments. Further, the governance structure under the leadership of global MS advocacy organizations fosters collaboration and a patient-centered approach to drug discovery and development [12].

Strategy: Revitalizing Innovation in Progressive MS and Creating Networks of Excellence

Leaders from industry have been engaged since the outset of the development of the Alliance's research strategy. In 2012, the Alliance identified key priority areas for research [13]. These areas represent opportunities where concerted research efforts could provide significant impact in overcoming the current barriers in developing effective treatments for progressive MS (Table 1). In 2014 the Alliance committed to providing sustainable, long-term research funding to address these areas. The launch of the Alliance research funding initiatives demonstrates the global commitment by patient organizations, academia, and industry to speed solutions in progressive MS.

Furthermore, the leadership of the Industry Forum and Alliance has identified additional gaps that must be addressed to make progress in the development of innovative treatments and to de-risk drug discovery and development. These gaps include standardized drug-discovery tools

Table 1. The Progressive MS Alliance: Research Priorities

(i)	Drug-discovery programs that identify and validate molecular and cellular targets and/or phenotypes, and screen and characterize drug candidates, which may be either repurposed or first-in-human drugs.
(ii)	Design and run smaller, faster trials to enable clinical proof-of-concept, for example testing new outcome measures or biomarkers of progression that could shorten development time for therapies for progressive MS.
(iii)	Conduct trials to test agents and rehabilitation treatments using new and existing outcome measures. With better trial designs, more life-changing treatment choices will be available to people faster.
(iv)	Develop and evaluate new therapies and rehabilitation to manage symptoms. People will have greater access to effective rehabilitation and symptomatic treatments that improve their daily quality of life.

and improved patient selection and stratification in clinical trials and monitoring disease progression.

To start addressing these gaps, the Industry Forum has identified two initial areas of precompetitive collaboration opportunity: translational pathophysiology and data sharing. The successful design of therapies for progressive MS requires significant advances in the understanding of the complex mechanisms underlying disease progression to identify new targets and translate research findings into therapies. In 2015, a critical appraisal of the translational potential of current basic scientific pathophysiological knowledge was performed in conjunction with industry representatives [14]. Precompetitive collaboration on translational pathophysiology will enable a concerted effort to prioritize pathogenetic mechanisms and to standardize relevant drug-discovery tools.

Data sharing, although raising complex challenges [15], has been recognized as a priority by the Industry Forum. A better understanding of the natural history of the progressive phase of the disease with both retrospective and prospective studies, bridged with already ongoing research efforts in the same direction, is fundamental, as is the creation or consolidation of clinical trial datasets and networks for the validation of new treatments. Precompetitive collaboration in this area will enable the MS community to refine diagnosis, improve patient selection and stratification in clinical trials, and monitor disease progression, with the ultimate goal of improving prediction of efficacy and safety of innovative treatments for progressive MS.

Progressive MS Alliance Industry Forum Challenge

Moving forward to fulfill the mission of the Progressive MS Alliance we should embrace the unique opportunity to fully advance the science of multi-stakeholder collaborations [16]. In this case, collective impact is a much broader concept than how research outcomes have traditionally been measured. Successful outcomes and metrics will need to be identified that reflect the shared efforts of the Alliance and the Industry Forum, and it will be necessary to develop a relevant infrastructure to support this work. Establishing clear goals and a strong foundation will ensure that all stakeholders remain engaged and thus enable the collaborative model of the Industry Forum to be fully realized and meet the needs of people living with progressive MS.

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