International Progressive MS Alliance Convenes Stakeholders to Consider Challenges and Next Steps at Second Scientific Congress

Research on progressive MS is advancing, with the first modest treatment success recently reported and more paths opening for understanding what’s driving the disease, but with many challenges remaining. That was the take-home message from the International Progressive MS Alliance’s Second Scientific Congress, where more than 200 researchers and supporters gathered in San Francisco in May to review research progress, challenges and next steps to speed the development of therapies for progressive MS. The conference, which moved from describing the underlying mechanisms of progression to issues around the design and delivery of clinical trials, was sponsored by the MS organizations of the Alliance, with additional support from the Conrad N. Hilton Foundation and other Alliance supporters.

“The landscape has changed dramatically since the Alliance was formed four years ago,” noted Alliance Scientific Steering Committee Chair Professor Alan J. Thompson (University College London, UK), “with increased awareness within the research community as well as significant growth in organizations participating as Alliance partners.” (Read more in the Alliance’s 2015 Progress Report.)

WHAT’S DRIVING PROGRESSION? MORE CLUES EMERGE

Although it is not clear what causes MS, headway is being made toward understanding how the damage done to the nervous system leads to the loss of nerve cells and progressive disability.

• Where does MS hit? Dr. Jeroen Geurts (VU University Medical Center, Netherlands) showed evidence that MS damage begins early, and there are differences in where MS lesions (damaged areas) occur depending on the type of MS a person has. For example, people with progressive MS are more likely to have lesions in the spinal cord than people with relapsing MS. He noted that advanced imaging techniques are enabling a more detailed picture of lesions in the brain’s white matter (where the nerve’s wires are concentrated) and gray matter (where the nerve cell bodies are concentrated) and emphasized the importance of interconnecting networks between brain areas in both the development of disability and as a potential mechanism for recovery.
• **Cascade of events** — Dr. Manuel Friese (University Medical Center Hamburg-Eppendorf, Germany) noted the series of events triggered by chronic inflammation in MS and may contribute to nerve degeneration. When nerve signal-enhancing myelin is damaged, nerve axons can respond by redistributing pores called ion channels along the stripped areas to facilitate nerve signaling. This increases energy demand and may lead to an overload of calcium and sodium entering the axon, contributing to degeneration. These channels, he noted, are prime candidates for new therapies aimed at protecting the nerves, citing amiloride, an old diuretic (or “water pill”) being repurposed and tested in MS for its ability to block a specific type of channel.

• **Energy crisis** — Another damaging event is malfunction of mitochondria, the tiny power houses inside axons and nerve cell bodies, reducing the energy output needed to keep nerve cells alive. During a “poster session” that featured data from researchers who had received Allian Challenge Awards, Drs. Jack van Horssen (VU University Medical Center, Netherlands) and Don Mahad (University of Edinburgh, UK) showed findings of mitochondrial malfunction. Preliminary work in mice testing identified possible solutions to fix or prevent this problem.

• **Meningeal inflammation** — Abnormal clusters have been identified in tissues that cover the brain and spinal cord, called the meninges, especially in progressive MS. These clusters have been linked to gray matter lesions and a more severe course of MS. A Challenge Award poster, presented by Dr. Pavan Bhargava, reporting research by a team led by Dr. Peter Calabresi (Johns Hopkins University, US) described a clinical trial underway that targets meningeal inflammation with rituximab given directly into the spinal fluid (intrathecally). So far the team has not found any severe adverse effects. A related poster by Drs. Richard Reynolds, Roberta Magliozzi (Imperial College London, UK), Massimiliano Calabrese (University of Verona, Italy) and team reported on proteins found in the spinal fluid and linked them to advanced brain MRI scans. They found messenger proteins suggestive of meningeal inflammation in people with the most severe damage, and hope to further validate these as a tool for predicting who might need aggressive therapy.

“**The profile of progressive MS has risen enormously, and the number of papers and meetings focusing on progressive MS has doubled or tripled — it’s now center stage.**”

– Dr. Alan Thompson (UK), University College London

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REPAIR AND RECOVERY

The brain naturally reacts to the damage of MS in a number of ways, such as by repairing nerve-insulating myelin, and by compensating for damage through reorganization and plasticity, where other parts of the brain take over. Participants noted that these recovery mechanisms may be enhanced to improve function in MS.

• **Stimulating self-repair** — Dr. Jonah Chan (University of California, San Francisco, US) described innovative research through which a team identified the allergy medication clemastine as a possible therapy to drive immature myelin-making cells, which reside all over the brain, to repair myelin in MS. The team has clarified the molecular target that seems to be stimulating repair, and conducted a successful early trial of clemastine. This research should help refine this approach as a possible treatment strategy for restoring myelin in MS.

• **Improving memory** — Dr. Nancy Chiaravalloti (Kessler Foundation Research Center, US) described the problem of cognitive impairment faced by many people with MS. The team has had success with the “modified story memory technique,” which teaches people to learn new information by visualizing a narrative or context for words being memorized. They also showed that this technique had increased areas of brain activity after training, suggesting brain reorganization.

• **Finite capacity** — Some participants noted that progressive disability becomes apparent after the brain’s normal strategies for compensating for damage are no longer completely effective. Dr. Francesco Mori (Università Tor Vergata, Italy) reviewed the impact of exercise and other approaches to increasing brain plasticity and rewiring, noting that it is not known how far brain plasticity can be pushed and at what point this ability is reduced in people with progressive MS.

CLINICAL TRIALS: HOW TO PUSH FORWARD?

Despite the first positive results from a large-scale clinical trial in primary progressive MS (announced in fall 2015 from a trial of ocrelizumab), many agreed that more successes are needed to change the lives of people living with progressive MS.

“Collaboration is key… The treatment will come from the efforts of a large network of people.”

— Dr. Catherine Lubetzki (France), Pierre and Marie Curie University and Sapêtrière Hospital
• **Lessons from previous trials** —
Drs. Xavier Montalban (Hospital Universitari Vall d’Hebron, Spain) and Jerry Wolinsky (University of Texas Health Sciences Center, US) reviewed characteristics of participants who were involved in clinical trials that failed to show effectiveness in progressive MS, compared to the ocrelizumab trial. Informal analyses of some trials suggest that people with progressive MS who had higher levels of inflammatory activity (seen on MRI) at the beginning of the trials were more likely to benefit from treatments that helped people with relapsing MS. However, since clinical trials lump together people with high and low levels of inflammation, they showed no average benefit overall. This suggests that some people who have progressive MS and MRI-detected inflammation may benefit from some available disease-modifying therapies, and holds lessons for the design and planning of future clinical trials.

• **Betting on a winner** — Large clinical trials that lead to marketing applications are expensive and take years, so there is an urgent need for a readout that shows early success or failure of a potential therapy for progressive MS. “The primary challenge is that there is no established way to determine quickly whether a new therapeutic approach is working in a proof-of-concept, phase 2 [short and small] clinical trial” in progressive MS, noted Dr. Per Soelberg Sorensen (University of Copenhagen, Denmark). Several presentations focused on strategies to find such a readout using advanced imaging techniques and predictive biomarkers in spinal fluid or blood.

• **Designing better trials** — There was also discussion around the need for better trial designs that can speed the development of therapies. One example given was the UK’s **MS-SMART** trial in secondary progressive MS, which uses a so-called ‘adaptive’ design, which starts by comparing three different therapies and then narrows down to the best choice more quickly than traditional, separately conducted trials.

• **Industry collaboration** — Dr. Giancarlo Comi (Scientific Institute San Raffaele, Italy) introduced a session involving the Alliance’s **Industry Forum**. Participants noted that previous barriers to collaborations between academic researchers and industry in the “pre-competitive space” are breaking down. “Collaboration is key,” echoed Dr. Catherine Lubetzki (Pierre and Marie Curie University and Sapétrière Hospital, France). “The treatment will come from the efforts of a large network of people.” Among themes discussed were the importance of identifying

> “You have answered the call and that must surely give people with progressive MS hope.”

— Mr. Alexis Donelly (Ireland; pictured above, center), Scientific Steering Committee Member
therapy targets through basic research, the need for sharing data from trials, and the need for sensitive clinical trial outcome measures that can prove a therapy is slowing, stopping or reversing progressive MS.

EMERGING OPPORTUNITIES / NEW HORIZONS

• **Learning from other diseases** — Dr. Jeffrey Cummings (Cleveland Clinic Lou Ruvo Center for Brain Health, US) noted that both MS and Alzheimer’s disease involve inflammation and neurodegeneration. There is now a way to detect Alzheimer’s 15 years before symptoms arise. Such a predictive biomarker for MS would open up the door to preventing MS and progression. Dr. Cummings remarked that researchers in both fields are learning valuable lessons from each other, and it’s possible that therapies designed to protect against degeneration are being sought for Alzheimer’s disease may also benefit people with progressive MS.

• **High-tech data and tools** — Introducing a session on new horizons, Dr. Bill Carroll (MS Research Australia) said, “There are huge amounts of data being accumulated. Data has gravity… it speeds scientific discovery and decision making.” For example, there are many studies that collect long-term data about people with MS. Dr. Paul Matthews (Imperial College London, UK) noted that these types of “cohort” studies can be used to answer big questions about progressive MS. There are approaches being taken in other diseases where data is being shared on open platforms that can be mined by outside researchers to speed progress. In MS, work is underway by several researchers and organizations to understand how to best take advantage of this data to maximize impact for people with progressive MS. Dr. Atul Butte (University of California, San Francisco, US) described several publically available platforms of raw data from research of different medical conditions. His team is mining this open-access data to detect unforeseen patterns, providing new clues to biomarkers and disease predictors. He noted that this approach could be used to make new discoveries in progressive MS.

• **Clues provided by high-tech gene studies** — Dr. Philip De Jager (Brigham and Women’s Hospital, US) described opportunities for understanding the influence of genes in MS, reviewing the work of the 20-group worldwide collaboration of the International MS Genetics Consortium. Of the more than 200 genes that appear to be involved in influencing the risk of getting MS, they have not seen differences in progressive versus relapsing forms. But they are mining data further to identify biological pathways that could be disrupted to stop progression.
Dr. Robert Fox (Cleveland Clinic, US), who was lead author of the Alliance’s first scientific paper that outlined challenges and priorities, summarized key outcomes from the meeting. “I think there has been a lot of progress,” noting the many new opportunities identified during the meeting, and the need to keep the focus on key challenges, such as the need for better disease models, understanding what drives progressive MS, finding biomarkers, designing and conducting better trials, and developing new therapies and rehabilitation strategies to address symptoms.

“What an amazing team you are producing,” noted Caroline Sincock, from Glasgow Scotland, one of the new Alliance Scientific Steering Committee members who lives with secondary progressive MS. “You are not shying away from the hard questions. This gives us not just hope, but progress. For that we are eternally grateful.”

“Having a loved one with progressive MS means watching them lose function and freedom over time. I look forward to telling people living with progressive MS about everything I’ve heard this week, which will be the first good news they have heard in a long time.”

– Mr. Jonathan Strum, pictured speaking, (US), Scientific Steering Committee Member

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