Scientific Congress Focuses on Mechanisms Driving MS Progression and How to Stop Them

The *International Progressive MS Alliance* brought together its leadership, funded researchers and other key stakeholders to Vienna, Austria in June for its Fourth Scientific Congress. The purpose was to assess the Alliance’s investments in untested ideas to advance understanding of mechanisms that drive progression. Lack of advancement in this area has hindered development of better treatments for people living with progressive MS. The findings presented will help inform future Alliance strategies and investments to accelerate progress in achieving the Alliance’s overall mission to end MS progression.

Seventeen research teams received €75,000 pilot investments, called Challenges in Progressive MS Awards, and presented results to date and plans for next steps. They shared findings in short presentations, displayed scientific posters, and engaged in panel discussions with audience input. Sessions were organized by the Scientific Meeting Planning Team with oversight from the Meeting Co-Chairs Drs. Ruth Ann Marrie (University of Manitoba, Canada) and Robert Fox (Cleveland Clinic Foundation, United States).

The Challenge Awards are just one of several research funding programs supporting the Alliance’s *Global Research Agenda*. In opening remarks, Ms. Vanessa Fanning, Chair of the Alliance’s People Affected by MS Engagement Coordination Team, offered how the viewpoints of people with MS influence research priorities and help researchers understand barriers to patient participation. Members of this Team were part of panel discussions throughout the Congress.
MECHANISMS OF MS PROGRESSION

Dr. Tanja Kuhlmann (University of Münster, Germany) provided an overview describing an emerging concept: MS is a continuous disease process that is influenced by several different underlying mechanisms of nervous system injury, counter-balanced by the body’s ability to repair or compensate for that injury. (This concept was outlined in a recently published paper.)

She noted that MS progression independent of relapses (referred to as “PIRA”) is driven by persisting inflammation that can be localized to specific spots (lesions) or can also be diffuse across the brain and spinal cord. This persisting inflammation (also called compartmentalized inflammation) can cause damage to nerve-insulating myelin, and also the nerve wires (axons) and nerve cells. It can also inhibit the brain’s store of repair cells (oligodendrocyte precursor cells — OPCs) from moving into injured areas and commencing myelin regeneration.

There has been a recent focus on the difference between MS brain (and spinal cord) lesions related to relapses and lesions that are chronic and slowly expanding. These chronic lesions are now called mixed inactive/active lesions since only their outer rims appear to be actively engaged in tissue damage and their interiors are dormant. Mixed lesions don’t show signs of myelin repair, and their edges, or rims, inhibit OPC repair functions. The rims are thought to contain microglia, which are immune cells that reside in the brain. Microglia can play both helpful and harmful roles, depending on circumstances. Some mixed lesion rims contain iron that can be seen on MRI, and these iron rims have been linked to worse MS progression.

Dr. Kuhlmann noted that further understanding of the underlying mechanisms and cells driving MS progression will help identify new targets for treatments. Recipients of Challenges in Progressive MS Awards who presented during this session included:

**Exploring iron rims:** Dr. Simon Hametner (Medical University of Vienna, Austria) studied lesions with iron rims (as described by Dr. Kuhlmann), noting that almost half of the mixed active/inactive lesions seen in MS have iron rims, and they can appear even early in the course of MS.

- The iron is taken up by microglia, and his team explored how the iron is accumulated by an immune-related protein called CD163.
- They used tissues and MRI from people with progressive MS, along with genetic profiles, to gather evidence of the link between CD163 and MS severity.
- They suggest that the iron comes from hemoglobin, a component of blood. They were unable to find a gene that made people more prone to developing iron rim lesions.
- Going forward, they plan to identify one or more molecules that are actually causing tissue damage in these lesions and discover what is preventing myelin repair in these lesions.

**Origins of nerve loss:** A team led by Dr. Jennifer Gommerman (University of Toronto, Canada) used Alliance funding to focus on a deep region of the brain called the hippocampus to determine how damage may occur that affects cognitive function in people with progressive MS.

- Previous studies have shown that damage to the hippocampus, an area known to be important in cognitive function, may affect connections between nerve cells.
- Dr. Gommerman’s team has been studying how a specific part of the immune system known as “complement” may be linked to nerve loss. The team identified a component of this complement system, C3, as a likely culprit, actively breaking nerve connections in the hippocampus.
- They plan to further explore how this malfunction of the immune system occurs and whether there are ways to target C3 to ultimately slow, stop, or prevent progression of nerve injury and cognitive problems in MS.
Dr. Hans Lassmann (Medical University of Vienna, Austria) gave an overview on the types of nervous system damage that can occur in MS and possible underlying mechanisms. He noted that myelin loss in the cortex — the outer “gray matter” of the brain where nerve cells reside — is unique to MS and can happen early in its course and accumulate over time.

Dr. Lassmann discussed the challenges of protecting the nervous system in MS. There are several clinical trials of neuroprotective agents underway, including lipoic acid, BTK inhibitors, and statins. Given the complex underpinnings of progression and tissue damage, he noted the importance of discovering whether there is a dominant pathway that leads to tissue damage. This would enable better targeting of that pathway to slow or stop injury and progression. Challenge Award projects shared during this session included:

**(Nature’s way of protecting nerves):** A team led by Dr. Don Mahad (University of Edinburgh, United Kingdom) investigated a natural response that can protect nerves after myelin loss, and ways to promote it to stop progressive disability in MS.

- This natural protective response (“axonal response of mitochondria to demyelination,” or ARMD) in nerve cells occurs after the loss of myelin. In ARMD, the energy producing powerhouses of cells (mitochondria) move from the nerve cell body to the axon to locally increase energy production. This feeds the axon in attempt to keep it healthy after myelin is lost.

- The team explored ARMD in several mouse models and in brain tissue samples. It appears that ARMD varies according to the degree of myelin loss. They plan to further explore how ARMD responses to myelin loss change over time, how these responses vary according to the type of nerve, and how responses are different when lost myelin is no longer adequately restored.

- There are several agents that can boost ARMD to protect the vulnerable axons in mice. At least one, the diabetes drug pioglitazone, is now in early trials involving people with MS.

- The team wants to continue investigating ARMD and other protective mechanisms to understand when and how axons may be protected in MS.

**Calming harmful astrocytes:** A team led by Dr. Laura Airas (University of Turku, Finland) tested a potential therapy for blocking destructive activity by brain cells called astrocytes.

- Astrocytes normally conduct housekeeping and supportive activities for other brain cells, but they have also been implicated in the loss of nerve cells in progressive MS.

- A specific docking site, or signaling receptor (A2AR), has been found to be increased in astrocytes located near MS brain lesions in people with advanced secondary progressive MS, but not in relapsing MS.

- The team found that potential therapies that block A2AR’s function can protect nerve cells in a cell culture system that models the pathology of progressive MS. They also identified a marker seen with positron emission scanning (PET) that enables them to trace A2AR activity in the brain.

- They are now planning to use this marker as an outcome measure in an early clinical trial as one way to monitor the effectiveness of a therapy that blocks A2AR in progressive MS.
Dr. Robin Franklin (Altos Labs, Cambridge Institute, United Kingdom)

Dr. Franklin gave an overview of efforts to regenerate myelin. Research suggests that natural myelin repair and other regenerative processes in the body slow with aging, and aging coincides with progressive phases of MS. He noted that OPCs, which would normally conduct much of the needed regeneration of myelin, also diminish with aging, showing less ability to multiply and to specialize into mature myelin-making oligodendrocytes.

Dr. Franklin noted that many of the potential myelin repair strategies identified with lab screening platforms don’t perform well in older animals, and by implication, older people. The good news is that several approaches have been identified that can reverse the effects of aging on OPCs. These include fasting, which is not a practical solution. Another is the diabetes treatment metformin. In rodent models, metformin has been shown to reverse age-related blockage to myelin repair. This drug is currently in clinical trials in combination with myelin repair agents.

Challenge Award recipients who presented during this session included:

Myelin regeneration and microglia:
Dr. Anne Desmazieres (Sorbonne Université, France) presented results from a collaboration with Dr. Bernard Zalc that focused on the gaps between myelin sheaths along axons, called Nodes of Ranvier. These nodes help speed nerve conduction.

- Using novel models and advanced technologies, they explored interactions between microglia and nerve fibers that affect electrical conduction of nerve cells and myelin formation.
- They found that myelin loss alters the structure of the Nodes of Ranvier, and that nerve electrical activity could encourage reorganization of these structures, with involvement of microglia. Nerve activity also increased the tendency for microglia to act in ways that promoted myelin regeneration.
- The team plans to further dissect mechanisms that control myelin formation to develop novel strategies to promote myelin repair.

The role of MicroRNAs in myelin loss:
Dr. María Muñoz-San Martin (Royal College of Surgeons in Ireland) presented results and future plans for developing a therapy for primary progressive MS, which shows less inflammation than other types of MS and is thought to involve destructive factors beyond inflammation.

- This team investigated the role of a small fragment — called a microRNA — that appears to be involved in myelin damage.
- They used lab models to tease out the role of one microRNA with the goal of designing compounds that may inhibit its function to prevent myelin damage.
- If continued study confirms that blocking a specific microRNA is therapeutically effective in rodent MS models, it could ultimately lead to the development and testing of a targeted therapy created specifically to stop progression of disability for people with primary progressive MS.

Myelin abnormalities: Dr. Antonio Luchicchi (Amsterdam University Medical Center, The Netherlands) and team have been exploring whether the interaction between myelin and the axon it coats might be altered in MS, leading to progression.

- This team found that brain tissue in people with progressive MS sometimes has “blisters” where the myelin is detached from axons, and these blisters can be found in brain regions where there are no signs of MS immune attacks against myelin.
- They explored myelin blisters using a recently developed imaging tool to study brain tissue. This enabled them to begin to define the biochemical interactions that may be leading to myelin blisters and whether the interactions can be blocked as a therapeutic strategy.
- They plan to continue this line of study to discover when and where in the brain blistering occurs and how it relates to the evolution of MS lesions and progression.
Dr. Cristina Granziera (University of Basel, Switzerland) gave an overview of research on biomarkers of MS progression. Biomarkers are usually indicators of current or future disease activity — such as a blood test that measures cholesterol (the marker) to predict risk of heart disease (future disease). There is a need for better biomarkers that can detect MS progression, rapidly measure treatment impacts in clinical trials, and predict an individual’s course and response to therapy.

Given the importance of microglia in chronic lesions, Dr. Granziera noted progress in ways to detect their presence. Recent advances using PET (advanced imaging) have promise, and with further validation could be used in clinical trials as an indicator that a therapy is working. Many fluid biomarkers have also been identified as having potential. Those furthest along in research include blood (serum) and spinal fluid levels of neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP).

NfL is a fragment of debris that enters the spinal fluid and blood when axons are damaged and GFAP is related to damage to astrocytes. Both complement each other for monitoring treatment responses and disease progression. Essential information about how the changing levels of these molecules should be interpreted by doctors and people with MS is still missing. Challenge Award recipients who presented during this session included:

**Developing NfL and GFAP as biomarkers:**
Dr. David Leppert (University Hospital Basel, Switzerland) and colleagues have been working on a way to detect NfL and GFAP in the blood to better enable their use in the clinic.
- The team has found a way to tag NfL with harmless levels of radioactivity so that low concentrations can be easily detected.
- They worked with lab models of MS-like disease to better understand the relationship between nerve and astrocyte damage and the appearance of NfL and GFAP in the spinal fluid and blood over an extended time frame.
- They have found that combining NfL and GFAP measures may be the best biomarker to predict progression in the absence of relapses.
- Going forward, the team hopes to further understand normal values of GFAP and potentially identify other markers related to progression.

**Novel biomarker may predict future disease course:** A team led by Dr. An Goris (University of Leuven, Belgium) has been using advanced statistical methods to detect which of many types of microglia are most responsible for nerve injury and progression.
- They have narrowed in on a marker called CHIT1 that identifies microglia that are active at the edges of chronic MS brain lesions. Now they plan to identify additional markers that may more sensitively identify these specific microglia and whose presence may predict nerve damage and progression early in the disease course.
- Having predictive tools may promote better treatment decisions early enough to slow or prevent future disease activity and progression.
INPUT FROM INDUSTRY

The meeting included a panel discussion among members of the Alliance’s Industry Forum moderated by Dr. Xavier Montalban (CEMCAT Catalan Multiple Sclerosis Center, Spain). The Forum is Co-Chaired by Dr. Florian von Raison (Novartis Pharma AG, France) and Dr. Marco Salvetti (Sapienza University of Rome, Italy). Industry representatives can collaborate on shared goals in this pre-competitive environment to drive novel drug discovery and research development in progressive MS. Some discussion included:

• The need for better clinical trial designs to speed the identification of promising approaches to treating progressive MS
• Opportunities to test novel outcome measures of progression that incorporate digital wearables and predictive biomarkers in phase 2 trials
• The need to engage drug regulators in the evolving understanding of MS as a continuum which is not necessarily in line with current labels of types of disease, as well as acceptance of more informative outcome measures

WRAP UPS

Dr. Salvetti provided a summary of presentations from the first day and emphasized the need for more models that reflect the underlying mechanisms of MS progression. He noted that we can learn from other diseases since there are likely common mechanisms that underlie nerve degeneration across disorders.

Dr. Anne Cross (Washington University in St. Louis, United States) offered reflections on dogma that was formerly considered fact about MS that turned out not to be true — such as that axons are spared from damage. She noted the importance of keeping open minds and allowing serendipity to help drive advances for people with MS.

NEXT STEPS

With their preliminary findings in hand, many of the Challenge Award recipients have applied for larger follow-on funding to pursue their ideas further. It will be the task of the Alliance’s Scientific Steering Committee and other experts, including people living with MS, to determine which to prioritize for further investment.
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