Eighty scientists and clinicians from around the world were convened in Boston in early March by the International Progressive MS Alliance (Alliance) to discuss what is known and not known about the chain of events and mechanisms (known as “pathogenesis”) leading to progressive MS, which is characterized by the gradual loss of function. This is a key priority research area for the Alliance because unearthing details of these events will identify critical pathways that could be targeted by new therapies aimed at stopping progression and restoring function for the estimated 1 million people who live with a progressive form of MS. Over the course of two days, experts from diverse fields discussed many different aspects of progressive MS, including:

**HOW MAY IMMUNE CELLS BE INVOLVED IN MS DAMAGE AND PROGRESSION?**

The cause of MS is still unknown, but the damage MS does to the nervous system is being better mapped. Attendees discussed the latest ideas about biological events leading to the loss of nerve cells — considered a key driver of progressive disability.

- **Microglia: bad, good, or both?** The brain has its own resident immune cells, called microglia, that can become activated to contribute to the inflammation and nerve damage that occur in MS. Dr. Marco Prinz (University of Freiburg – Germany) discussed the possible role of microglia in MS progression, but also their beneficial activities such as removing debris and stimulating myelin repair. Understanding these roles could lead to ways to ramp up their good activities and inhibit the bad ones.
• What is the role of “meningeal” inflammation in progression? Dr. Francisca Aloisi (Italian Institute of Health – Italy) discussed abnormal clusters of immune B cells within tissues (called the meninges) that cover the brain and spinal cord and which have been noted largely in progressive, but also relapsing MS. The Alliance is funding several studies to understand and attempt to treat meningeal inflammation in MS, which may be involved in driving disease activity and progression.

• What else do B cells do? Besides their presence as clusters in the meninges, Dr. Amit Bar-Or (McGill University – Canada) discussed other ways that B cells may stimulate MS immune attacks both early and later in the disease course, and release destructive antibodies and other substances toxic to brain tissues.

“This is uncharted territory and it’s rather daunting, but we are committed to finding solutions for progressive MS”

– Dr. Alan Thompson, Chair of the Alliance Scientific Steering Committee

There is also new evidence that some B cells can regulate and turn off immune activity, so strategies that target all types of B cells may kill the good with the bad.

• What comes first, nervous system abnormality or immune attacks? This question, posed by Dr. Peter Stys (University of Calgary - Canada), was meant to challenge assumptions that the first or initiating event in MS is an autoimmune attack, versus an initiating abnormality in the nervous system that later stimulates immune attacks. This question – which doesn’t yet have a definitive answer – requires researchers to think in new ways to find breakthrough solutions for people with progressive MS.

WHAT OTHER FORCES DRIVE PROGRESSION?

• Are the power generators of nerve cells (mitochondria) at fault? Dr. Don Mahad (University of Edinburgh – United Kingdom) described research suggesting that when the myelin coating on nerve fibers is injured in MS, mitochondria inside the nerves may malfunction and become unable to produce energy needed to keep nerve cells alive. If this holds true, finding ways to support mitochondria may protect nerve cells from harm and help prevent progression.

• How might fatty substances be involved? Lipids (fats) have been hard to study, but Dr. Peter Calabresi (Johns Hopkins University – USA) described new technologies to examine their role in MS. Nerve-insulating myelin is about 80% lipids, and sometimes these and other lipids may be converted to toxic substances called ceramides. Some ceramides have been shown to be at abnormally high levels in secondary-progressive MS, and so may represent a new target for therapy.

• How do brain cells called astrocytes contribute? Astrocytes play many different roles, explained Dr. Samuel Ludwin (Queen’s University - Canada). They form the brain’s structural scaffolding and the web-like
blood-brain barrier which breaks down to let a flood of immune cells into the nervous system during MS attacks. Astrocytes create the scarring found in MS brain lesions, and can release factors that can either promote myelin repair or inhibit it. Dr. Aiden Haghiakia (Ruhr-University – Germany) explained that people who have the MS-like disease neuromyelitis optica (NMO) do not experience long-term progression, speculating that it may have to do with the lack of astrocyte activity in NMO. Knowing how and when to block or stimulate astrocyte activities may be another key to slowing progression and restoring function.

**APPROACHES TO REPAIRING THE DAMAGE**

The possibility of myelin repair is no longer science fiction, and several clinical trials are testing myelin repair strategies.

> “We’ve established more clarity around the questions in progressive MS that will help us substantially going forward”
> – Meeting Co-Chair Dr. Robert Fox

- **How does myelin regrow?** Dr. Robert Miller (George Washington University - USA) noted that there are two key sources of myelin-making cells in the adult brain: the mature cells (oligodendrocytes) that wrap myelin around nerve fibers and can be damaged in MS, and immature versions of those cells which are held in reserve in several areas of the brain. He suggested that stimulating both mature and immature myelin-making cells would be a possible strategy for repair, and explained that using a combination of therapies will likely be needed to combat some of the multiple factors involved in myelin damage.

- **Which stem cells may be useful for MS repair?** Turning a person’s skin cells into stem cells (called induced pluripotent stem cells) capable of repair is getting closer to a reality, reported Dr. Gianvito Martino (San Raffaele Scientific Institute – Italy). Transplanting these cells into mice creates conditions that turn off inflammation, promote oligodendrocyte survival and stimulate myelin repair. He cautioned that in some circumstances these cells can also cause tumors, stressing the need for additional research. In addition, his team has grown these cells in the lab to create “MS in a dish” as a potential means of screening therapies that may protect against damage or stimulate repair.

**CAN HIGH TECHNOLOGY SPEED THE SEARCH FOR THERAPIES?**

Several speakers discussed ways that emerging technologies and large-scale research databases are enabling new approaches to visualize complex webs of interactions that lead to disease and progression, and the pathways that may represent strategic targets for therapeutics.

- **Are there drugs on the shelf that would benefit progressive MS?** Dr. Sergio Baranzini (University of California, San Francisco - USA) showed high-tech possibilities for finding hidden links and potential benefits of known drugs that might be repurposed to treat progressive MS. Dr. Luke Lairson (California Institute for Biomedical Research – USA) discussed a screening technique they used to search for drugs that could stimulate myelin repair. The team is now refining an allergy drug to amplify its repair activity.


**Which pathologic mechanisms are most relevant?** Among the different mechanisms that sustain disease progression, Dr. Andrea Califano (Columbia University – USA) described a path forward for identifying those with the highest impact on the disease process. By combining sophisticated bioinformatics and confirmatory experiments, he showed that it is possible to examine networks of biological interactions in complex diseases and identify bottlenecks that are key to their pathogenesis. These approaches may allow us to reduce the number of potential therapeutic targets for addressing progression, thereby increasing the chances of success.

**What can we learn from studying MS tissues?** Dr. Philip De Jager (Harvard Medical School) showed how technology is being used in a large-scale study that uses tissue samples from people with Alzheimer’s disease, along with identified genetic links and other data, to drill down into biological pathways to bring new insights for treating the disease. He also discussed the possibilities for doing similar analyses to discover targets to stop progressive MS.

**Clinical Trials of Promising Therapies**

Pharmaceutical and biotechnology industry representatives including Biogen, F. Hoffmann-La Roche, Genentech, Genzyme, Novartis, Teva and Opexa Therapeutics presented findings related to compounds whose modes of action may address some of the targets important in progressive MS. There are trials going on right now testing new therapies and will provide needed information about progressive MS.

**What can we learn from clinical trials?** A clinical trial of ibudilast in primary and secondary progressive MS is being led by meeting co-chair Dr. Robert Fox (Cleveland Clinic - USA). He noted that no matter its outcomes, it is testing several types of imaging and biomarkers that will teach how to design faster and more efficient early-stage clinical trials in progressive MS.

**When does progression start?** Although there is no clear answer yet, we know that loss of brain tissue can occur from the earliest stage of MS. Attendees discussed the brain’s amazing capability of compensating for ongoing damage, suggesting that the disease, and progression, may start much earlier than when the first signs are noticed by an individual or a doctor.

**We need more tools.** Finding tools to detect and predict MS progression, and developing new testing models, are critical. These tools are being actively investigated by the Alliance through its pioneering research programs.

“This meeting has been an unprecedented opportunity for a critical reappraisal of the translational potential of current knowledge in progressive MS.”

– Meeting Co-Chair Dr. Marco Salvetti

Outcomes of the meeting will help Alliance members plan ongoing research priorities, and will be summarized in a white paper and published to share ideas with the larger scientific community. By bringing the world’s scientific knowledge and determination to the task of better understanding progression and therapeutic targets, we will accelerate the development of treatments that change the world for people with progressive MS. To stay updated on the work of the Alliance, visit progressivemsalliance.org.