PATHWAYS
TO CURES
GLOBAL SUMMIT

Global Summit Reviews Advances and Opportunities for Strategic Collaborations to Speed Pathways to MS Cures

The first-ever Pathways to Cures Global Summit was held in New York City in early May 2023, convening nearly 200 participants from 15 countries. The goal was to review recent scientific advances in the Stop, Restore and End pathways, refine the Pathways roadmap, and develop a global strategy of collaboration and alignment of investments into areas of high opportunity to speed the development of MS cures.

Participants included leadership from MS advocacy organizations, researchers, doctors, government funders, pharmaceutical companies, supporters and people living with MS, and included many of the scientists and organizations who helped to write or endorse the published Pathways to Cures Roadmap. Sessions were organized by the Scientific Planning Committee[1] to include short presentations, panel discussions and audience input.

EXECUTIVE SUMMARY

Progress has been made in each of the Stop, Restore and End pathways. There remain hurdles to success, some of which will require larger and more sustained research efforts than any one MS organization can do alone.

Overarching Themes

- A strategic and global approach for curing MS is needed
- We must engage people with MS at every level of research to speed progress
- Discovering the biological underpinnings of MS at every stage is crucial to all three pathways and will inform how we describe and treat the disease
- Collaborations, Coordination, Communication and Commitment are critical to success
- Global collaboration will require a clear focus, the setting of priorities, and agreement on equitable rules of engagement
- Defined milestones and clear metrics to measure progress are essential
- Momentum will be built and sustained when we have both immediate priorities and longer-term goals

---

[1] The **Scientific Planning Committee** was chaired by Brenda Banwell, MD (United States), Alan Thompson, MD (United Kingdom) and Caroline Whitacre, PhD (United States) and included these members:
Bruce Bebo, PhD (United States); Jorge Correale, MD (Argentina); Ulrik Dalgas, PhD (Denmark); Philip De Jager, MD, PhD (United States); Anne Helme, PhD (Global); Anne-Katrin Pröbstel, MD (Switzerland); Kathy Smith, PhD (United States); Wee Yong, PhD (Canada); Paola Zaratin, PhD (Italy)

Next Steps

The Scientific Planning Committee co-chairs recommended these next steps to advance global collaboration:

- Define global priorities on critical topics, including:
    - Epstein-Barr virus
    - Biology-based terminology for defining different stages of MS
    - Biological mechanisms underlying the initiation of MS and ongoing disease
    - Strategies to overcome obstacles to data sharing
- Set timelines
- Review progress

Steps Underway

- A writing team will update and refine the Pathways to Cures Roadmap including recommendations for global collaboration. This will be submitted by Fall 2023 for publication to ensure wide dissemination.
- A global research strategy group involving executive and research leadership of MS advocacy organizations funding MS research has been formed to consider how to move ahead.
- A landscape analysis is underway to understand the global scope of MS research being conducted to help identify gaps and opportunities for future collaborations.

MORE DETAILS

National MS Society President and CEO Cynthia Zagieboylo opened the meeting by declaring, “MS has turned too many lives upside down and we’ve had enough!” She added that with a shared commitment and a global strategy, “We’ve never been in a better position to change the world for people with MS.”

Kathy Smith (KES Business Consulting, LLC, and a person living with MS) commented, “Every person living with MS dreams of a cure for their MS… In my dream I will know what medication works best for me. I won’t have to be my own experiment because my physician and I will have all the data. I’d like you to remember that you are making dreams come true.”

Following are brief summaries of panel discussions and participant feedback, which will form the basis of an update to the Pathways to Cures Roadmap and pave the way for global collaborations to speed cures for MS.

Global MS Research Landscape

Anne Helme, PhD, (Head of Research and Access at the Multiple Sclerosis International Federation, UK) discussed examples of international collaborative efforts within the MS field, noting that many organizations already agree on key themes related to stopping MS, restoring function, and ending the disease.

There was agreement that a strategic and global approach for curing MS is needed. Discussion included:

- putting people affected by MS at the heart of global research
- the need for a governance structure, a plan for prioritizing joint initiatives, and a way to balance funding of longer-term teams while allowing for innovation and investigator-initiated ideas
- the need to attract more talented investigators into the MS field
- the need to overcome obstacles to sharing resources including data, biospecimens and expertise
- opportunities for engaging people with MS more deeply in research and design and potentially as advocates for easing data sharing restrictions
- when solutions are discovered, there needs to be better dissemination and implementation, as well as engagement of policy makers to ensure access

Stopping MS

The Pathways to Cures Roadmap defines stopping MS as achieving a state of no new disease activity or injury to the central nervous system (CNS – the brain, spinal cord and optic nerve), no worsening of daily living or quality of life, and no change in disease manifestations.

Key goals of this pathway are **early detection**, which may enable earlier treatment to reduce CNS damage and improve a person's future disease course, and **precision medicine**, which means tailoring treatments to individuals for maximal benefit.

Session chair Anne-Katrin Pröbstel, MD (University Hospital Basel, Switzerland, and the International Women in MS) reviewed recent advances toward earlier detection of MS and precision medicine, along with invited panel speakers Naila Makhani, MD, PhD (Yale School of Medicine, US) and Amit Bar-Or, MD, FRCPC (University of Pennsylvania, US).

Dr. Pröbstel, panelists and meeting participants highlighted:

- the history of success in treating relapsing MS and the need for more and better therapies for progressive forms of MS and faster ways to detect benefit in progression trials
- there may be differences in the biology underlying relapses versus the biology of nerve tissue damage and progression, and types of inflammation outside and inside of the CNS
- growing evidence that comorbidities (MS plus other health conditions) and modifiable factors such as smoking and diet/gut microbiome can contribute to disease initiation and progression
- recognition of the MS "prodrome" – a time before MS is diagnosed when sometimes vague symptoms (such as mood disorders, fatigue) and CNS damage may occur – as a potential window for earlier detection
- recent success in delaying the first symptom of MS in people whose brain MRI showed MS-like lesions in the absence of symptoms (RIS, or Radiologically Isolated Syndrome) adds evidence of the protective power of early intervention

- a challenge of precision medicine is that MS is so different among people, and the operative mechanisms can differ at different stages of the disease

Key gaps and opportunities include:

- Better understanding of the underlying biology and evolution of MS will help us describe the stage an individual is in and the best treatment approach
- Work is underway by an international work group on developing a new framework for describing the courses of MS based on the underlying biology
- Clinical trials should be designed to contribute to our biological understanding of MS
- There is power in big data and long-term investments, including funding research infrastructure, and collaborative teams may be the best way to drive this kind of work
- There are increasing privacy protections around sharing data, resources, scans, and biological samples, and these regulatory constraints do not align with the wishes of people living with MS

Restore – Myelin Repair and Neuroprotection

The Pathways to Cures Roadmap defines the Restore pathway as reversing symptoms and recovering function to enable full participation in society. This pathway explores the opportunity to enhance **regeneration and remyelination**, as well as focus on strategies to **reverse symptoms** and improve quality of life.

Session Chair V. Wee Yong, PhD (University of Calgary, Canada) set the stage with an overview of prospects for repairing damage to the myelin coating on nerve fibers (axons) in the CNS. Panelist Gianvito Martino, MD (San Raffaele, Milan, Italy) described the history and prospects of using stem cell transplantation to treat progressive MS, including results of a recent clinical trial.

Dr. Yong, panelists and meeting participants highlighted:

- Recent research confirms the concept that repairing myelin protects the underlying axons and nerve cells and preserves CNS integrity
- Many processes are involved in myelin repair and its inhibition, and these offer opportunities to develop therapies that remove inhibitors or promote the maturation of young myelin-producing cells
- Transplanted stem cells appear to act by creating a beneficial microenvironment around MS lesions, rather than acting as replacement cells, and there are more lessons to learn in terms of the optimal cells and doses
- Myelin repair strategies will likely need to be combined with disease-modifying therapies that calm ongoing inflammation
- Repair of a very acute MS lesion will likely differ significantly from strategies to repair a long-established lesion

Key gaps and opportunities include:

- A need for better measures of whether myelin has been repaired in clinical trials, and ways to detect myelin damage in the cortex, the outer “gray matter” of the brain where nerve cells reside
- A need to better understand the mechanisms of repair and whether there is a way to manipulate signals to switch cells that are playing destructive roles into myelin-promoting roles
- More work is needed to understand how lifestyle factors such as exercise impact myelin and myelin repair

Restore – Functional Recovery

A separate session focused on another facet of the Restore pathway: recovering function through physical and cognitive rehabilitation, physical activity and exercise, and wellness approaches to improve quality of life.

Session Chair Ulrik Dalgas, PhD (Aarhus University, Denmark) described recent developments in the area of functional recovery with non-pharmacological approaches. He noted that there may be a window of opportunity earlier in the disease course to enhance the effectiveness of rehabilitation and exercise regimens. He also described the problem of sustainability – that most people don’t continue doing the exercises and lose benefits after studies are completed.

Panelist Lars Hvid, PhD (Aarhus University, Denmark) discussed results from studies focusing on exercise, cognitive function, and lifestyle. Many have shown some benefits for exercise, cognitive and memory rehabilitation, and some diets. But most studies have been small, of short duration, and often don’t include people who actually have the deficit the intervention is targeting. There is little diversity among participants, and published studies often don’t adequately describe the intervention so that others can verify the results.

Dr. Dalgas, panelists and meeting participants highlighted:

- Exercise has proven benefits and may be considered “medicine,” but more information is needed about proper dosing and who responds best to which approach
- Early rehabilitation and “pre-habilitation” that builds physical capacity and cognitive reserve may be protective against future decline
- Offering interventions virtually can increase access
- There are published guidelines for studying complex or combined rehabilitation approaches, which may offer better outcomes for daily living

Key gaps and opportunities include:

- Having rehabilitation and basic scientists work together may improve understanding of how physical activity, rehabilitation and lifestyle affect the brain and its circuitry, which would enable more targeted and precision approaches for individuals
- Better understanding of what motivates and sustains behavioral changes could inform programs that increase resilience and quality of life

- There's a need for better clinical and real-world outcome measures for functional recovery, and the possibility that wearable activity monitors could serve an increasing role for measuring function
- Rehabilitation, exercise and wellness trials need to be of adequate size and duration, and more inclusive of the diverse MS population, so that results can be implemented to clinical practice
- There is a growing appreciation that sleep impacts functioning and needs more attention
- Being overweight or obese can reduce function and cause other health issues; addressing this complex and chronic issue has not been adequately studied in MS

Ending MS

The Roadmap defines the End pathway as no new cases of disease – meaning preventing the disease so that no one ever hears the words, "You have MS." One goal is to prevent MS in the general population by limiting exposure to modifiable MS risk factors. Another is to identify its very beginnings to enable an intervention to prevent the typical symptoms and signs that lead to its diagnosis.

Session Chair Philip L. De Jager, MD, PhD (Columbia University Medical Center, New York City, US) described growing evidence that MS may be preventable. He noted key advances in identifying risk factors that increase a person's chances of getting MS, including mapping of over 234 gene variants and factors such as low vitamin D, smoking, and obesity, and more evidence that the Epstein-Barr virus (EBV) is a key trigger for MS.

Panelist Marco Salvetti, MD, PhD (Sapienza University of Rome, IT) discussed strategies related to EBV in particular. He noted that there are many variants of the virus, and evidence for interactions between the virus and genes associated with MS risk. In the short term, testing anti-viral medications may provide important information, while in the long term, considering an EBV vaccine presents possibilities and many questions about feasibility, timing and safety.

Panelist Kevin Deane, MD, PhD (University of Colorado Anschutz Medical, Aurora, US) described recent success in delaying the onset of rheumatoid arthritis (RA) in people with early signs and biomarkers of the disease. He noted that this was facilitated by agreement in the field on what terms to use for various pre-symptomatic and symptomatic stages of the disease. Their definition of prevention was to prevent an individual from moving to the "next worse stage."

Dr. De Jager, panelists and meeting participants highlighted:

- Growing evidence that MS starts well before symptoms emerge, and there may be ways to detect this pre-symptom phase or prodrome
- The emergence of blood and MRI biomarkers that can indicate early damage to the CNS and may be employed to screen at-risk individuals

- It isn’t yet clear that all MS risk factors have been identified, or the timing of their role in initiating MS, or whether currently known risk factors are relevant in members of underrepresented populations

Key gaps and opportunities include:

- There are lessons to be learned about delaying or preventing disease from other autoimmune and neurological disorders
- An early step could be to educate the public on modifiable risk factors such as vitamin D, nutrition, healthy weight, smoking and exposure to second-hand smoke
- It is critical to develop biology-based terminology for stages of MS; this work is underway by an international working group
- There is a need to determine other MS risk factors and risk factors for underrepresented populations
- Looking ahead, creating a risk “algorithm” that scores an individual’s probability of developing MS (such as genetics, exposure to known factors) could enable early intervention
- Understanding the underlying biology in the chain of events for how risk factors interact and drive the onset of MS would enhance both the Stop and End pathways
- There are existing cohorts and opportunities to find more first-degree family members and twins in whom only one has MS and they represent opportunities to study pre-symptomatic MS
- Epstein-Barr virus vaccines are in development, as are anti-viral medications; it will be important to consider whether and how to deploy these strategies aimed at preventing or treating MS
- The role of the gut microbiome in MS initiation and ongoing disease warrants further exploration

Enhancing Global Collaboration

Scientific Planning Committee members Kathy Smith and Jorge Correale, MD (Raul Carrea Institute for Neurological Research, Buenos Aires, Argentina) led sessions focusing on collaboration models from other fields and recommendations for enhancing global collaboration from Summit participants.

Suzana Petanceska, PhD (National Institute on Aging, National Institutes of Health (NIH), US) described a large initiative to propel research on Alzheimer’s disease, begun in 2011. Multi-billion-dollar funding has been invested in infrastructure, centers, and collaborations including a shared knowledge database platform, research tools and clinical trials. Pharmaceutical partners were engaged and provide funding for common needs such as biomarkers to detect the disease.

A large-scale collaboration in Europe is the Innovative Medicines Initiative, described by Nathalie Seigneuret, PharmD (Innovative Health Initiative, Belgium). This is a partnership of pharma and biotech companies, digital health companies, academic researchers, patients, regulators and doctors. They support collaborative research on fundamental questions to advance areas of high unmet needs across many medical conditions.

Summit participants engaged in several small-group discussions around global partnerships and collaboration. Some key themes and recommendations included:

- The importance of engaging people with MS at every level of research to speed progress
- Global collaboration will require a clear focus, the setting of priorities, and agreement on equitable rules of engagement
- It will be important to define milestones and clear metrics to measure progress
- Momentum will be built and sustained when we have both immediate priorities and long-term goals
- Collaborations should have value added and focus on projects that cannot be done by a single research group or a single funder
- Team science involving researchers from different regions can increase the diversity of study participants, bring in broader expertise, and offer mentoring opportunities to attract young researchers and researchers from other fields to MS
- Long-term collaborations need joint funding, infrastructure support, coordination, commitment, and strategies for sustainability

Next Steps

The Scientific Planning Committee co-chairs – Brenda Banwell, MD (Children's Hospital of Pennsylvania, Philadelphia, US), Alan Thompson, MD (University College London, UK) and Caroline Whitacre, PhD (The Ohio State University, Columbus, US) – recommended these next steps to advance global collaboration:

- Define global priorities on critical topics, including:
    - Epstein-Barr virus
    - Develop biology-based terminology for defining different stages of MS
    - Focus on biological mechanisms underlying the initiation of MS and ongoing disease
    - Explore strategies to overcome obstacles to data sharing

Steps Underway

- A writing team will update and refine the Pathways to Cures Roadmap including recommendations for global collaboration. This will be submitted by Fall 2023 for publication to ensure wide dissemination.
- A global strategy group involving executive and research leadership of leading MS funding organizations has been formed to consider how to move ahead.

Parting Thoughts

Closing the Summit, Cynthia Zagieboylo stated that MS organizations from Australia, Canada, Denmark, France, Germany, Italy, Spain, UK, US and MS International Federation, have come together to declare their collective and strong commitment to global collaboration to cure MS and agree to coordinate resources on high potential research to address knowledge gaps and avoid duplication to speed progress together.

“MS organizations exist because there are people with MS all over the world. With our shared passion and commitment and a global strategy, we will achieve cures.”