Understanding the role of immune dysregulation in MS

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Emily Warrender May 15, 2025

Despite significant progress in MS-related research, challenges remain. Dr Belinda Kaskow and Professor Allan G Kermode from the Perron Institute and The University of Western Australia explore the benefits of investigating the early stages of immune dysregulation in MS to enhance prevention strategies

In a landmark achievement for the global multiple sclerosis (MS) community, two MS researchers, Professor Stephen L. Hauser and Professor Alberto Ascherio, were recognised with the 2025 Breakthrough Prize in Life Sciences, often referred to as 'Oscars® of Science', for their pioneering work.

Professor Hauser was awarded for his groundbreaking contributions demonstrating the pivotal role of B cells in MS pathology and transforming treatment through B cell depletion therapies. (1) Professor Ascherio was honoured for his landmark epidemiological research demonstrating that Epstein-Barr Virus (EBV) infection is necessary for developing MS, (2) opening important pathways toward future prevention strategies.

While these advancements have significantly improved MS management, challenges remain in preventing disease progression and addressing underlying causes.

Bridging the gaps in MS treatment

Despite their benefits, current disease-modifying therapies primarily control inflammatory activity rather than fully preventing neurodegeneration. These treatments work best when initiated early. However, a critical knowledge gap remains around the immunological changes that precede a clinical MS diagnosis, limiting our ability to implement truly preventive interventions.

While transformative in MS care, B-cell depletion broadly suppresses immune responses, potentially compromising protective immunity and increasing infection risk. Furthermore, despite effective B cell depletion, many individuals experience worsening symptoms such as fatigue, cognitive dysfunction, and sensory disturbances as their treatment cycle nears completion. This highlights the need for therapies that promote sustained immune regulation and symptom control.

The need for early detection

Addressing these limitations requires a deeper understanding of the early biological events that precede clinical MS in order to intervene before irreversible damage occurs. Evidence increasingly suggests that disruptions to the balance between pro-inflammatory and regulatory immune pathways are central to MS pathogenesis.

Pro-inflammatory pathways activate immune cells against perceived threats, while regulatory pathways prevent excessive immune responses and maintain self-tolerance. In MS, this balance is disrupted, allowing immune cells to mistakenly target the central nervous system.

Research at the forefront:

The Perron Institute's approach The Perron Institute, in collaboration with the School of Biomedical Science at The University of Western Australia and the Personalised Medicine Centre at Murdoch University, is addressing these challenges by investigating the earliest stages of immune dysregulation in MS.

A central focus of this work is the role of killer immunoglobulin-like receptor (KIR) expressing immune cells, particularly KIR+ CD8+ T cells and natural killer (NK) cells. Traditionally known for their roles in immune surveillance, these cells are under investigation for their ability to modulate autoimmune responses in MS.

Supported by MS Australia, this research combines advanced immunophenotyping, high-resolution genotyping, and transcriptomic profiling to examine how KIR+ cells respond to high-efficacy therapies, such as B cell depletion. These studies aim to determine whether changes in KIR+ cell frequency or function could serve as biomarkers for disease progression or treatment response.

Preliminary findings suggest that KIR-related immune signatures vary between individuals and may contribute to both protective and pathogenic immune pathways in MS. This individual variability highlights the potential for personalised immunomodulation strategies tailored to a patient's unique immune profile, rather than relying solely on broad immunosuppression that treats all patients identically. These insights open the door to novel treatment strategies, including selective KIR modulation or blockade, that aim to rebalance immune function without compromising protective immunity.

Personalised medicine for MS: Addressing disease heterogeneity

The donor-specific immune responses observed in research directly reflect the broader challenge in MS treatment: the remarkable heterogeneity of the disease itself. The complexity and variability of MS across individuals make personalised treatment approaches not just beneficial but essential. MS 'endophenotypes', biologically distinct subgroups within the disease spectrum defined by immune, genetic, and clinical characteristics, are increasingly recognised as critical for patient stratification and targeted interventions. [(3)]

Building on these principles, Perron Institute researchers aim to define immunological endophenotypes in MS by integrating cellular, molecular, and clinical data. Understanding how specific immune profiles correlate with clinical outcomes can inform both early diagnosis and tailored therapeutic approaches.

Emerging research and clinical trials in MS

Researchers at the Perron Institute are involved in national and international clinical trials advancing MS understanding and care. Current studies include:

- The PLATYPUS trial investigating strategies for neuroprotection and remyelination (repairing damaged nerve coatings);
- Novel immunotherapy trials targeting specific immune pathways;
- Research on reproductive health and MS outcomes; and
- Studies into the role of viral infections, particularly EBV, in MS pathogenesis.

This diverse research portfolio reflects a commitment to advancing effective, personalised MS care that informs future public health initiatives.

Connecting research to the MS community

An essential aspect of the MS research program at the Perron Institute is its commitment to community engagement and patient-centred research. Initiatives such as the MS Consumer Advisory Group facilitate two-way communication between researchers and the MS community, ensuring that scientific priorities align with patient needs and experiences.

This collaborative model strengthens the translational impact of research and supports therapeutic advances that can be effectively implemented in public healthcare settings.

Policy implications and public health benefits

The research described has significant implications for public health policy:

- Early intervention programs:
  Immune profiling may inform screening and early intervention for high-risk individuals.
- Preventive strategies:
  The EBV-MS link suggests opportunities for vaccination or antiviral strategies as preventive public health measures.
- Healthcare resource allocation:
  Personalised care could improve cost-effectiveness by reducing treatment failures and preventing disability progression.
- Research funding priorities:
  Continued investment in early disease mechanisms and biomarker development would likely yield substantial returns in reduced disability and healthcare costs.

Towards a more personalised future in MS care

Advancing our understanding of early immune dysregulation, defining MS subtypes, and developing targeted therapies are critical steps towards more effective management of MS.

By combining cutting-edge immunological research with patient-centred approaches and supportive policy frameworks, we can deliver more precise, timely, and impactful interventions.

As the global MS research community continues to build on landmark discoveries, such as those recognised by the Breakthrough Prize, there is renewed hope for preventing MS, halting its progression, and improving the lives of people living with MS through coordinated research and healthcare initiatives.

1. Hauser, S.L., et al. B-cell depletion with rituximab in relapsing–remitting multiple sclerosis. New England Journal of Medicine. 2008.
2. Bjornevik, K., et al. Longitudinal analysis reveals a high prevalence of Epstein–Barr virus associated with multiple sclerosis. Science. 2022.
3. Gross, C.C., et al. Multiple sclerosis endophenotypes identified by high-dimensional blood signatures are associated with distinct disease trajectories. Nature Communications. 2024.

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