

THE GUT-BRAIN AXIS IN MULTIPLE SCLEROSIS: UNRAVELING THE ROLE OF GUT MICROBIOTA

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INTRODUCTION

The gut microbiome is increasingly recognized as a key environmental factor in the pathobiology of multiple sclerosis (MS), with special emphasis on phyto-oestrogen-metabolizing gut bacteria, beneficial symbionts, and disease-promoting pathobionts.

MS is an autoimmune disease of the central nervous system (CNS) in which both genetic and environmental factors contribute to disease pathogenesis. Importantly, while genetic factors, primarily HLA class II alleles, account for

only 2-27% of disease risk, environmental factors contribute as much as 73-98%. Among these environmental determinants, the gut microbiome has emerged as one of the strongest factors linked to MS susceptibility, resistance, and progression. The gut microbiota can contribute to disease susceptibility and progression but can equally confer protection against disease development or worsening, making the microbiome a uniquely tractable target for both diagnostics and therapy.

GUT DYSBIOSIS IN PEOPLE WITH MULTIPLE SCLEROSIS

There are two independent MS microbiome cohorts published: the first is the “Mayo Clinic Rochester cohort” (Chen et al., 2016); the second is the “University of Iowa cohort” (Yadav et al., 2022). In both cohorts, beta-diversity ordination analyses demonstrated a statistically distinct gut microbial composition in MS subjects compared to healthy controls (HC). Beyond this overall compositional shift, targeted analysis of specific microbiota revealed a consistent pattern of depletion of particular bacterial genera in MS patients, most notably *Prevotella*, *Parabacteroides*, and *Adlercreutzia*. To place these findings in a broader context, MS microbiome studies from research groups across the globe were compared. The results of this comparison are shown in Table 1. Strikingly, the majority of these independent

studies reported depletion of one or more of these same three bacterial genera, underscoring the robustness and reproducibility of the dysbiosis signal across different populations, sequencing platforms, and study designs.

Certain bacteria, specifically *Prevotella* and *Sutterella*, were found to be enriched in MS patients receiving disease-modifying therapies (DMT). These observations suggest that effective MS treatment may partially restore the gut microbiota toward a healthier compositional state and further underscores the intimate relationship between gut microbial ecology and MS disease activity.

In summary, these human microbiome data from multiple cohorts worldwide provide compelling evidence that MS is associated with gut dysbiosis

Table 1: Alteration of *Prevotella*, *Parabacteroides*, and *Adlercreutzia*, reported in patients with MS across independent international studies

Study (Reference)	Bacteria depleted in MS vs. HC	Bacteria enriched after DMT
Chen et al., 2016	<i>Prevotella</i> , <i>Parabacteroides</i> , <i>Adlercreutzia</i>	-
Jangi et al., 2016	<i>Prevotella</i> , <i>Parabacteroides</i>	<i>Prevotella</i> , <i>Sutterella</i>
Miyake et al., 2015	<i>Prevotella</i> , <i>Parabacteroides</i>	-
Castillo-Alvarez et al., 2018	<i>Prevotella</i>	-
Cekanaviciute et al., 2017	<i>Prevotella</i> , <i>Parabacteroides</i>	-
Berer et al., 2017	<i>Adlercreutzia</i>	-
Cosorich et al., 2017	<i>Prevotella</i> (mucosal biopsies)	-

HC = healthy controls; DMT = disease-modifying therapy; “-” not reported.

characterized specifically by consistent depletion of *Prevotella*, *Parabacteroides*, and *Adlercreutzia* genera, and that restoration of some of these bacteria may accompany clinical benefit from

DMT. These findings laid the conceptual foundation for all subsequent mechanistic and translational work described here.

FROM BEDSIDE TO BENCH: *PREVOTELLA HISTICOLA* AS A BACTERIAL DRUG (BRUG)

Based on the fact that *Prevotella* species are depleted in stool of MS patients, a series of preclinical experiments were carried out to test the therapeutic hypothesis: if a bacterium consistently lacking in MS subjects is provided back to the host, can it ameliorate disease?

Using the experimental autoimmune encephalomyelitis (EAE) mouse model, the most widely employed preclinical model of MS, it was demonstrated that oral administration of *Prevotella histicola*, a human commensal bacterium, significantly suppressed EAE severity. The mechanism involved induction of immunoregulatory cells and restoration of both the intestinal epithelial barrier (gut barrier) and the blood-brain barrier (Mangalam et al., 2017). This dual barrier-protective effect is particularly relevant to MS pathophysiology, in which breakdown of both barriers is thought to

be an early step in CNS immune infiltration.

It was also examined whether *P. histicola* could synergize with approved MS drugs. Therefore, *Prevotella histicola* was tested in combination with Copaxone (glatiramer acetate) (Shahi et al., 2019) and with interferon-beta (Betaseron) (Shahi et al., 2020), two standard-of-care DMTs. While the combinations did not demonstrate synergy beyond either agent alone, a critical finding emerged: *P. histicola* as a single agent was as effective in suppressing EAE as Copaxone alone or Betaseron alone.

The term **BRUG** (beneficial bacteria as **drug**) was used to describe the concept of deploying human commensal bacteria as precision drug-like therapies. This term was recognized by the magazine *WIRED*, where it was featured as a

"Jargon Watch" entry in their November 2017 issue, reflecting broader interest in the therapeutic potential of commensal microorganisms.

In summary, these bedside-to-bench studies established that providing a human commensal bacterium that is deficient in MS subjects can ameliorate

disease in an animal model of MS, performing comparably to approved DMTs. This work provided the first direct proof-of-concept for the BRUG concept and supports the potential of *Prevotella histicola* and related organisms as microbiome-based therapeutics for MS.

GUT BACTERIA, PHYTO-OESTROGENS, AND THE MECHANISM OF MICROBIOME-MEDIATED IMMUNOMODULATION

Nutrient-based evolution and the microbiome

The fundamental question is: through what mechanism does the gut microbiota modulate MS? This question is framed within the context of nutrient-based evolution, arguing that the human microbiome exists largely because of its role in nutrient absorption and energy harvesting from food, a relationship refined over millions of years of co-evolution (Cady et al., 2020). In utero, the foetus harbours little or no microbiota. After birth, a simple microbiome is established, adapted to a milk-based diet. As infants transition from milk to solid foods, there is an enormous expansion of the gut microbiota, coinciding with physical elongation of the intestinal tract and the emergence of complex microbial communities capable of fermenting plant-based, indigestible polysaccharides to extract additional nutrients and energy. This evolutionary perspective places diet as the primary driver of microbiome composition, and the microbiome as the primary mediator of diet's immunological effects.

Three MS-depleted bacteria and their shared role in phyto-oestrogen metabolism

There is a striking shared characteristic of the three bacterial genera consistently depleted in MS: *Adlercreutzia*, *Parabacteroides*, and *Prevotella* are all

involved in the intestinal metabolism of phyto-oestrogens, plant-derived compounds that include isoflavones (found in soy products) and lignans (found in seeds, whole grains, and legumes). Humans lack the enzymatic machinery to metabolize these compounds directly; intestinal bacteria convert them into bioactive metabolites, principally S-equol and enterolactone, which share structural similarities with endogenous oestrogens.

This connection is biologically significant because oestrogens are known to be protective in MS (Gold and Voskuhl, 2009). Women with MS experience fewer relapses during pregnancy, a high-oestrogen state, and there are ongoing clinical trials of oestriol therapy in MS subjects. If MS patients are depleted of the bacteria required to generate oestrogen-like metabolites from dietary phyto-oestrogens, they may be functionally deficient in this protective pathway regardless of what they eat. To test this hypothesis rigorously there are three specific questions with regard to the EAE model:

- Do phyto-oestrogens have the ability to modulate disease in an animal model of MS?
- Are gut bacteria required for phyto-oestrogen-mediated disease protection?
- What is the mechanism of phyto-oestrogen-mediated immunomodulation?

Isoflavone diet protects against EAE across multiple mouse models

To address the first question, mice were randomized to either a phyto-oestrogen-free (PF) diet or an isoflavone-rich diet for six weeks prior to EAE induction. Mice on the PF diet developed a severe form of EAE, whereas those on the isoflavone diet showed significantly milder disease, a protective effect that was reproducible across three independent mouse strains: the C57BL/6 mice (standard chronic EAE model), the HLA-DR2 transgenic humanized model, and SJL mice (relapsing-remitting model). These data established unequivocally that dietary phyto-oestrogens have disease-protective properties in EAE (Jensen et al., 2021).

Gut bacteria are required for isoflavone-mediated disease protection

The isoflavone diet reshapes the gut microbiome in a pattern strikingly parallel to the difference between MS patients and healthy controls. Isoflavone-fed mice showed enrichment of *Parabacteroides* and *Adlercreutzia*, precisely the genera depleted in MS subjects, mirroring the microbiome of healthy controls (Jensen et al., 2021). Notably, *Prevotella* was not enriched, which was attributed to the fact that mice from Jackson Laboratory do not harbour *Prevotella* at baseline; the diet therefore could not expand a genus that was already absent. Conversely, mice on the phyto-oestrogen-free diet showed

enrichment of *Akkermansia muciniphila*, a species that had been reported by others to be elevated in MS subjects.

To formally demonstrate that gut bacteria mediate the protective effect, intestinal microbiota were depleted using an antibiotic cocktail. Antibiotic treatment abolished the disease-protective effect of the isoflavone diet. Mice on isoflavone diet but depleted of gut bacteria developed disease as severe as those on the PF diet. Crucially, when antibiotic-treated mice on the isoflavone diet were reconstituted by oral gavage with a combination of the phyto-oestrogen-metabolizing bacteria *Parabacteroides* and *Adlercreutzia*, disease protection was restored. By contrast, reconstitution of antibiotic-treated mice on the phyto-oestrogen-free diet with the same bacteria conferred no protection, establishing that both the appropriate diet and the bacteria are required simultaneously (Jensen et al., 2021).

In summary, the phyto-oestrogen experiments demonstrated that dietary isoflavones can protect against inflammatory disease in EAE, and that this protection is dependent on the presence of specific phyto-oestrogen-metabolizing gut bacteria. Since MS subjects are systematically depleted of exactly these bacteria, the data support a model in which MS-associated dysbiosis creates a functional phyto-oestrogen deficiency that contributes to the disease's pro-inflammatory milieu.

TRANSLATIONAL SIGNIFICANCE: DIET SWITCHING AS A THERAPEUTIC STRATEGY

To test the translational relevance of these findings, a clinically important question should be answered: if the gut microbiome of MS subjects resembles that of mice on a phyto-oestrogen-free diet, and the microbiome of healthy con-

trols resembles that of mice on an isoflavone-rich diet, then switching a patient from an inflammatory dietary pattern to an isoflavone-rich one should ameliorate disease, provided this can first be demonstrated in the animal model.

In a diet-switch EAE experiment, mice initially maintained on a phyto-oestrogen-free diet were switched to an isoflavone diet and four weeks later EAE was induced (Ghimire et al., 2022). In contrast, a parallel group was switched in the opposite direction (from isoflavone to phyto-oestrogen-free). Mice switched from the phyto-oestrogen-free to the isoflavone diet developed significantly milder EAE compared to those switched in the opposite direction. Microbiome analysis of these diet-switch animals revealed that the isoflavone diet caused expansion of

Bifidobacterium species, while the phyto-oestrogen-free diet promoted *Akkermansia*, a pattern that would become the foundation of the biomarker work described in the next section.

These data provide compelling evidence for the translational significance of phyto-oestrogen-rich diet and phyto-oestrogen-metabolizing bacteria as potential therapeutic strategies for MS patients, by demonstrating in an animal model that dietary correction, even after disease onset, can meaningfully reduce disease severity.

IDENTIFICATION OF A GUT MICROBIOTA-BASED BIOMARKER FOR MULTIPLE SCLEROSIS DISCOVERY IN THE EAE MODEL: THE *BIFIDOBACTERIUM*:*AKKERMANSIA* RATIO

The next question to be answered was whether a gut microbiota-based biomarker could be identified that is translatable to human MS. Using the EAE mouse model, three experimental groups were used: PBS-immunized controls, adjuvant-only controls (CFA + pertussis toxin), and CNS-antigen plus adjuvant-immunized mice (MOG₃₅₋₅₅ + CFA + pertussis toxin), of which only the last group develops EAE disease. Faecal and caecal microbiome samples were collected at baseline, day 7 (disease onset), and day 14 (peak disease).

Analysis revealed a clear and progressive trend: the ratio of *Bifidobacterium adolescentis* (BA) to *Akkermansia muciniphila* (AM), hereafter the BA:AM ratio, was higher in both control groups (PBS and adjuvant only) but significantly lower and declining in the EAE group in both the faecal and caecal compartments. Reanalysis of the diet-switch microbiome data from the phyto-oestrogen study corroborated this: the BA:AM ratio was higher in isoflavone-diet mice (the protective condition) compared to phyto-oestrogen-free-diet mice (the disease-promoting condition),

further strengthening the association of this ratio with inflammatory disease state (Ghimire et al., 2025).

Validation in human MS cohorts

Next, the BA:AM ratio in human subjects was validated. In the University of Iowa cohort, shotgun metagenomic sequencing was performed in 45 RRMS patients and 51 age- and sex-matched healthy controls. The BA:AM ratio, was significantly lower in MS patients compared to healthy controls ($p = 0.041$) (Ghimire et al., 2025).

This finding was then validated in the International Multiple Sclerosis Microbiome Study (iMSMS), the largest MS microbiome dataset currently available, comprising 576 MS subjects and 1,152 genetically unrelated household controls. The BA:AM ratio was again significantly lower in MS subjects ($p = 1 \times 10^{-5}$), confirming the finding across a completely independent cohort, different geography, and higher statistical power (Ghimire et al., 2025).

Importantly, the BA:AM ratio was not only a case-control discriminator but also correlated with disease severity: in

the iMSMS cohort, the ratio showed a significant negative correlation with EDSS score ($R = -0.13$, $p = 0.0041$) and with disease duration ($R = -0.14$, $p = 0.0023$), and a trend toward correlation with the MS Severity Score ($R = -0.075$, $p = 0.093$). Patients with greater disability and longer disease duration had lower BA:AM ratios, consistent with the hypothesis that dysbiosis tracks with, and may actively contribute to, disease progression rather than being a passive bystander (Ghimire et al., 2025).

Preliminary unpublished data further show that Parkinson's disease (PD)

subjects also exhibit a lower BA:AM ratio compared to healthy controls ($p = 0.0083$), raising the intriguing possibility that this ratio may represent a broader biomarker of neuroinflammatory and neurodegenerative disease (Ghimire et al., unpublished).

Taken together, these human microbiome studies from two independent MS cohorts, spanning hundreds of subjects, strongly suggest that the BA:AM ratio represents a robust, quantitative, stool-based biomarker of MS disease and severity.

FROM DISEASE MARKER TO PREDICTIVE BIOMARKER: A CAUSAL ROLE FOR MS-ENRICHED BACTERIA

Is the reduced BA:AM ratio merely a marker of established disease, or does it have predictive and causative significance? To identify the specific bacteria driving the microbiome differences between MS patients and healthy controls, topic modelling was applied (Fitzjerrrells et al., 2024) and co-occurrence network analysis to the shotgun metagenomic dataset. This analysis revealed that *Blautia* species were the dominant drivers of the MS-associated microbial community, whereas *Prevotella copri* drove the healthy control-associated community (Ghimire et al., 2025).

To test causality, a pseudo-germ-free mouse model was used: intestinal microbiota were depleted by antibiotic treatment, and mice were then colonized by oral gavage with one of three bacteria, (i) the HC-driving *Prevotella copri*, (ii) the MS-driving *Blautia wexlerae*, or (iii) a control human commensal (*Phocaeicola vulgatus*). All groups then received a common human faecal microbiota transplant to allow background community development, and microbiome composition was tracked at days 9, 13, 17, 22, and 27.

The results were striking as by day 27, mice initially colonized with the MS-driving *Blautia wexlerae* showed a significantly lower BA:AM ratio compared to those colonized with HC-driving *Prevotella copri* ($p = 2.2 \times 10^{-5}$). This reduction was temporally progressive, emerging as the microbial communities matured and the initial colonizer exerted its influence on community structure. Furthermore, the *Blautia*-colonized group went on to develop significantly more severe EAE after disease induction compared to the *Prevotella copri*-colonized group, and the magnitude of the BA:AM ratio reduction correlated directly with cumulative EAE disease scores ($R = -0.42$, $p = 0.025$).

Mechanistic investigation revealed that *Blautia wexlerae*-colonized mice also showed significantly elevated faecal lipocalin-2 and calprotectin, validated markers of gut inflammation, compared to both the *Prevotella copri*- and *Phocaeicola vulgatus*-colonized groups (Ghimire et al., 2025).

These studies provide compelling evidence that the enrichment of MS-

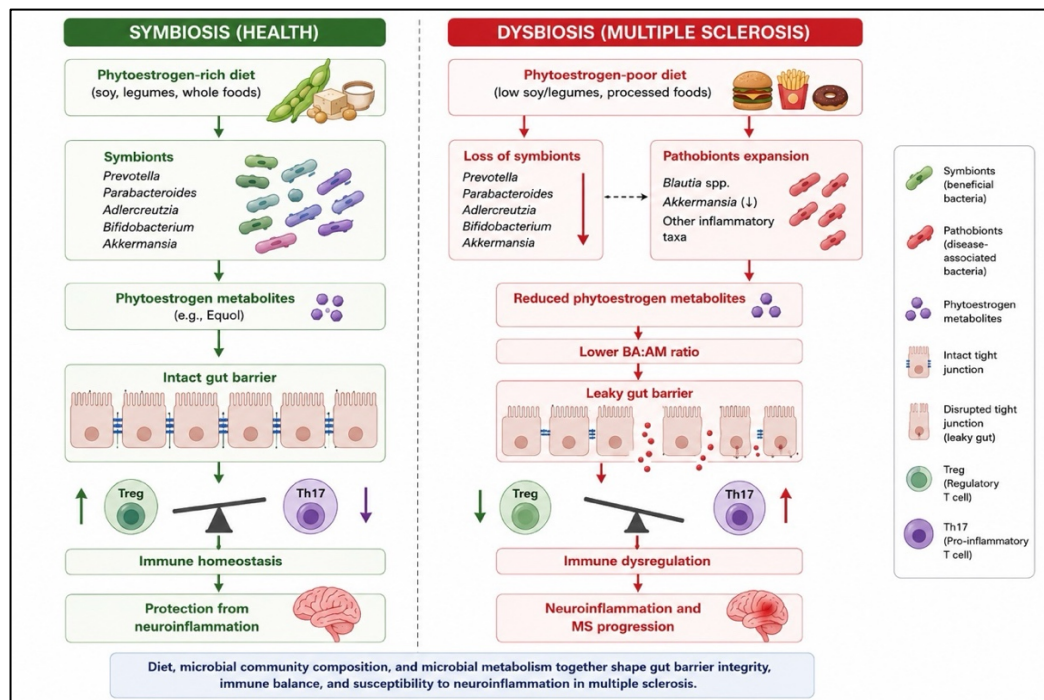


Figure 1: Diet-microbiome-immune interactions in health and disease (MS). Proposed model illustrating how a phyto-oestrogen-rich diet and beneficial gut bacteria promote production of immunoregulatory metabolites, maintain gut barrier integrity, and support immune homeostasis. In MS, depletion of phyto-oestrogen-metabolizing symbionts and enrichment of inflammatory pathobionts are associated with a lower BA:AM ratio, gut barrier dysfunction, immune dysregulation, and increased neuroinflammation.

associated bacteria such as *Blautia* species actively drives gut inflammation and promotes a lower BA:AM ratio, which in turn predicts greater disease severity in EAE. (Ghimire et al., 2025). Critically, this colonization experiment

establishes a causative rather than merely correlative role for gut microbiota in MS pathobiology, a mechanistic proof that moves the field beyond association studies toward actionable therapeutic and preventive targets.

CONCLUSIONS: FROM DYSBIOSIS TO CLINICAL TRANSLATION

With respect to gut dysbiosis in MS, this work and that of others have established that:

- (i) people with MS harbour a distinct gut microbiome characterized by depletion of multiple bacteria including phyto-oestrogen-metabolizing bacteria (*Prevotella*, *Parabacteroides*, *Adlercreutzia*);
- (ii) this dysbiosis has been mechanistically validated in animal models to

be functionally important, not merely associative;

- (iii) maximum disease protection requires both the correct diet and the appropriate bacteria acting in concert, neither alone is sufficient; and
- (iv) MS-associated dysbiosis is enriched for bacteria such as *Blautia* that promote gut inflammation and a lower *Bifidobacterium*:*Akkermansia* ratio.

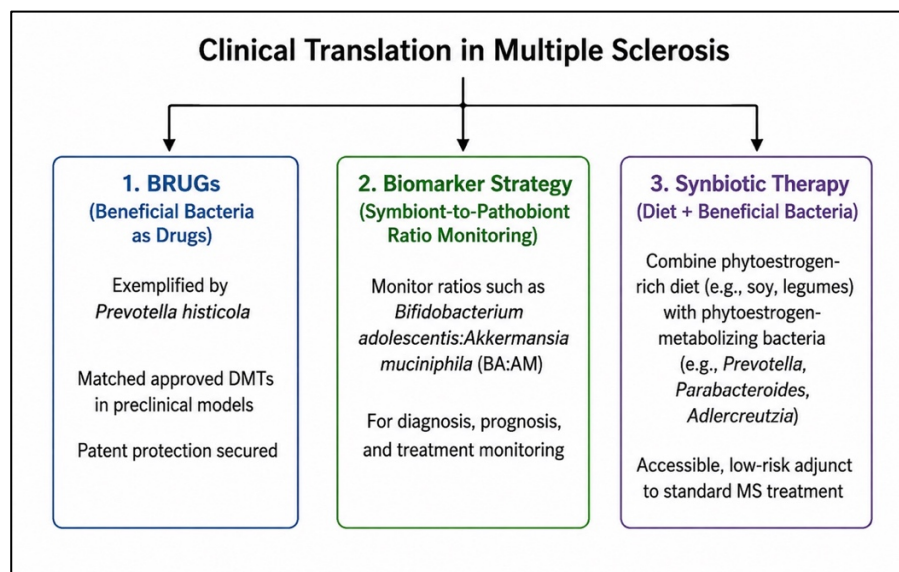


Figure 2. Microbiome-based strategies for clinical translation in MS.

Gut dysbiosis in MS provides opportunities for therapeutic and diagnostic development, including BRUGs (beneficial bacteria as drugs), symbiont-to-pathobiont ratios such as BA:AM as diagnostic/prognostic biomarkers, and synbiotic approaches combining phyto-oestrogen-rich diet with phyto-oestrogen-metabolizing bacteria.

With respect to biomarkers, the *Bifidobacterium adolescentis*:*Akkermansia muciniphila* (BA:AM) ratio has emerged from both animal and human studies as a promising diagnostic and prognostic gut microbiome biomarker for MS, validated in over 600 MS patients across two independent international cohorts and correlated with disability and disease duration (Figure 1).

With respect to clinical translation, the data collectively support three therapeutic strategies:

(i) BRUGs, beneficial bacteria as drugs, exemplified by *Prevotella histicola* which matched approved DMTs in preclinical models and for which patent protection has been secured;

(ii) symbiont-to-pathobiont ratio monitoring as a diagnostic and prognostic tool; and

(iii) synbiotic therapy, combining phyto-oestrogen-rich diet with phyto-oestrogen-metabolizing bacteria, as a potentially accessible and low-risk adjunct to standard MS treatment (Figure 2).

Future directions will focus on understanding the microbial functional pathways modulated during dysbiosis, including LPS biosynthesis, phyto-oestrogen metabolism, and short-chain fatty acid production, using multi-omic approaches, and on advancing the most promising candidates toward clinical trials in people with MS.

DISCLOSURE

The author declares the following patent interests relevant to the content of this presentation: (1) *Prevotella histicola* for treatment of autoimmune conditions

(Patent #US8617536B2, 2015); and (2) phyto-oestrogen combined with gut bacteria as treatment of disease (Patent #US20240091279, 2022)

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