Why increasing Akkermansia muciniphila can benefit your patient.

Presented by Elise Ryan
5 Minute Snap Shot

• Common factors influencing GIT disturbance and inflammatory markers.

• Explore the role that specific microbial strains have on regulating Akkermansia muciniphila.

• Discover the role Akkermansia muciniphila plays on mucin modulation.

• Learn the role Akkermansia muciniphila plays in gastrointestinal function, obesity, endotoxemia, glucose regulation, Type 2 diabetes and autism.

• Impact of B. longum BB536 and L. rhamnosus HN001 and the relation with Akkermansia muciniphila.
Microbiota

- **Microbiota** do not live in isolation, but rather inhabit an extremely complex and **synergistic environment**. Forming an **intricate co-existence**, they contribute to metabolic processes, protect against pathogens, influence the immune system and either directly or indirectly, **influence most of our physiological functions**.
GIT Disturbances

- Common factors that influence gastrointestinal integrity and function include:
  - Poor diet/ nutrition
  - Food intolerance
  - Pathogens
  - Stress
  - Medications

- Which may lead to:
  - Dysbiosis
  - Intestinal inflammation
  - Gut permeability
  - Local and systemic inflammation
  - Increased cytokine production
  - Opportunistic environment for pathogens to proliferate

Chronic systemic inflammation has been associated with the greatest pandemics of the modern era: obesity, type 2 diabetes and neurodegenerative disorders. The human gut provides a delicate environment in which inflammatory pathways are pivotal to maintain local and systemic homeostasis.

A. Muciniphia Metabolic Endotoxemia

- Akkermansia muciniphila, a mucin-degrading bacteria, is a member of the Verrucomicrobia phylum.

- A. muciniphila has been found to inhabit the gastrointestinal tracts of more than 90% of adult subjects analysed, and it constitutes 1 to 4% of the fecal microbiota.

- Present knowledge suggests that A. muciniphila is important in maintaining a healthy mucus layer in the human gut.

- In mouse studies, A. muciniphila played a causative role in lowering the body fat index, decreasing adipose tissue inflammation, improving glucose homeostasis, decreasing metabolic endotoxemia, increasing the number of goblet cells and increasing gut mucin integrity.


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A. Muciniphia Metabolic Endotoxemia

- **A. muciniphila** has been shown to **reduce high-fat-diet-induced endotoxemia**, which develops as a result of an **impaired gut barrier**.

- **A. muciniphila** has been demonstrated to **improve the metabolic profiles of type 2 diabetic mice**, to **restore mucus layer thickness**, and to **counteract high-fat-diet-induced lipopolysaccharide (LPS) endotoxemia**.

- **Tests in humans** have **shown** **A. muciniphila** is more abundant in the **normal glucose tolerance group** than in the **prediabetes group**, which suggests that it may be a marker of type-2 diabetes (T2DM).


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Mucin glycan foraging in the human gut microbiome

Louise E. Tallford*, Emmanuelle H. Crost†, Devon Kavanaugh‡ and Nathalie Juge* 

- The intestinal epithelium surface is covered by a layer of mucus which differs in terms of composition, organisation, and thickness along the GI tract. 
- In the colon, the mucus is divided into an outer layer which provides a nutrient-rich habitat for the microbiota and an inner layer firmly attached to the surface of the epithelium, and virtually free of bacteria. 
- **Mucins** are the main structural components of mucus and play an integral and multifaceted role in the interaction between microbes and epithelial surfaces. 
- In addition to their protective and lubricating activities, mucins facilitate microbial tropism through the presentation of glycans which may impact colonisation and act as a nutritional source for microorganisms. 
- It is thus believed that in healthy conditions mucosa-associated bacteria are not in direct contact with the epithelium but are restricted to the outer mucus layer.
Mucin – it’s role within the GIT

**Mucin glycan foraging in the human gut microbiome**

Louise E. Tailford *, Emmanuelle H. Crost *, Devon Kavanaugh * and Nathalie Juge *

- Interactions between the gut microbiota and mucus layer are dynamic systems that affect mucus barrier biology.

- The impact of *A. muciniphila* treatment on the thickness of the inner mucus layer. We demonstrated a 46% thinner mucus layer in HF-fed mice, and *A. muciniphila* treatment counteracted this decrease.

- The first mucin-degrading bacteria studied were pathogens and thus for a long period mucin degradation had been associated with pathogenicity.

- However, it is now clear that mucin degradation is part of a normal turn-over process starting a few months after birth.

- In mouse studies, *A. muciniphila* played a causative role in increasing the number of goblet cells, and increasing gut mucin integrity.
Mucin – Akkermansia muciniphila

Akkermansia muciniphila gen. nov., sp. nov., a human intestinal mucin-degrading bacterium

- Besides being able to degrade mucins, Akkermansia muciniphila was also found to simulate mucin production.

- Akkermansia muciniphila has not only the capacity to degrade mucins, but also to stimulate mucin synthesis, illustrative of an autocatalytic process.

- Akkermansia muciniphila was able to adhere to the epithelium and strengthen the intestinal barrier.

- Mucin also constitutes a carbon and energy source for intestinal microbiota.

- It has been estimated that 1% of colonic microbiota is able to degrade host mucin using enzymes (e.g. glycosidases and sulfatases) that can degrade the oligosaccharide chains.

- Despite the apparent low level of mucin degrading bacteria, these species provide nutrients for other resident bacteria, which can use the monosaccharides or amino acids released from mucin degradation.
• The gut symbiont *Akkermansia muciniphila* is positively correlated with a lean phenotype, reduced body weight gain, amelioration of metabolic responses and restoration of gut barrier function by modulation of mucus layer thickness.

• Reduced levels of *A. muciniphila* have also been found in biopsies of intestinal mucosa from IBD-patients in comparison to healthy controls.

• *Akkermansia muciniphila* was significantly higher in the healthy controls than in T2DM subjects.


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A. muciniphila T2DM

Examining the gut bacteriome, virome, and mycobiome in glucose metabolism disorders: Are we on the right track?

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- A. muciniphila treatment reversed high-fat diet-induced metabolic disorders, including fat-mass gain, metabolic endotoxemia, adipose tissue inflammation, and insulin resistance.

- A. muciniphila administration increased the intestinal levels of endocannabinoids that control inflammation, the gut barrier, and gut peptide secretion.

- Evidence demonstrates that gut microbiota influence whole-body metabolism by affecting the energy balance, gut permeability, serum lipopolysaccharides, metabolic endotoxemia, and metabolic inflammation that are associated with obesity and associated disorders.
Diabetes – gut dysbiosis

The abundance of *A. muciniphila* was 3,300-fold lower in leptin-deficient obese mice than in their lean littermates.

Also observed a 100-fold decrease of this bacterium in high-fat-(HF)-fed mice.

In T2D patients, gut dysbiosis is seemingly characterised by the growth of acidic pathobionts, further promoting the low-grade inflammation characterising T2D patients.

Prediabetes is characterised by commensal bacterial load depletion, possibly depicting the start of the dis-equilibrium for T2D.
B. Longum BB536 & L. rhamnosus HN001 increases A. muciniphila

- The aim of the present study was to investigate the effects of B. longum BB536 and L. rhamnosus HN001 on the gut microbiota composition.

- Twenty healthy Italian subjects, eight males and twelve females, received 4 Billion CFU of B. longum BB536 and 1 Billion CFU of L. rhamnosus HN001 dosage for one month.

- The beneficial impact that B. longum and L. rhamnosus strains had on intestinal homeostasis is underlined by the significant increase of Akkermansia muciniphila.
B. Longum BB536 & L. rhamnosus HN001 increases A. muciniphila

- **A. muciniphila** is closely related with human health and it is inversely associated with body fat mass and glucose intolerance.

- **A. muciniphila** seems to be involved in the maintenance of intestinal barrier functions and above all in prevention of intestinal inflammation, playing a pivotal role in the host’s overall health status.

- This highlights the importance for the use of B. longum BB536 and L. rhamnosus within the Multigen Biotic to help support the modulation gut microbiota, reduce intestinal inflammation, improve mucosal integrity, promote glucose homeostasis and reduce endotoxemia.

![Graph showing significant changes in gut bacterial species composition](image)
BB536 & HN001 Reduces Firmicutes and Obesity

- A **significant reduction of Firmicutes** was detected after one month of probiotic oral intake.

- This result is of importance since a **high abundance of Firmicutes has previously been related to obesity**, and with a reduction of Bacteroidetes, as obese individuals often show an unbalanced ratio of Firmicutes and Bacteroidetes in their intestinal microbiota.

- **Firmicutes phylum contains numerous bacterial species** with an increased ability to harvest energy from diet, leading to a **large increase in total body fat**.

- Further **reduction of Firmicutes** we observed after the end of probiotic administration was concomitant to a significant **reduction of Proteobacteria**, a bacterial phylum often involved in the onset and progression of gastrointestinal diseases.
B. Longum BB536 & L. rhamnosus HN001

- The anti-inflammatory effect B. longum and L. rhamnosus strains was further highlighted by the greater abundance of Blautia producta and Blautia wexlerae during the follow up period.

- Blautia spp, indeed, produce short-chain fatty acids, which act as main fuel for enterocytes, and anti-inflammatory compounds involved in the promotion of muscular activity and epithelial cell proliferation and in the enhancement of blood through the colonic vasculature.

- A reduction of potential harmful bacteria and an increase of beneficial ones may constitute an important probiotic feature of B. longum BB536 and L. rhamnosus HN001.
Low Abundances of A. muciniphila and Bifidobacterium spp. in Autism

Low Relative Abundances of the Mucolytic Bacterium
Akkermansia muciniphila and Bifidobacterium spp. in Feces of Children with Autism

Lv Wang,† Claus T. Christophersen, Michael J. Sorich, Jacobus P. Gerber, Manyu T. Angley, and Michael A. Conlon

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• Lower relative abundances of Bifidobacteria species and the mucolytic bacterium Akkermansia muciniphila were found in children with autism (ASD), the latter suggesting mucus barrier changes.

• A lower relative abundance of Bifidobacterium spp. in ASD participants compared to unrelated community controls with no family history of autism and sibling participants was observed.

• Abundance of A. muciniphila was decreased in ASD participants relative to that in unrelated community control participants and decreased in sibling participants relative to that in unrelated community control participants.
Low Abundances of A. muciniphila and Bifidobacterium spp. in Autism

Low Relative Abundances of the Mucolytic Bacterium
*Akkermansia muciniphila* and *Bifidobacterium* spp. in Feces of Children with Autism

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• A lower abundance of *A. muciniphila* in ASD children and their siblings may indicate a thinner GI mucus barrier in ASD children than in the unrelated community control participants.

• These results could represent indirect evidence of impaired gut permeability in children with ASD: a lower relative abundance of *A. muciniphila* may represent altered mucus turnover.

• The current Australian findings of depleted populations of *A. muciniphila* and *Bifidobacterium* spp. add to our knowledge of the changes in the GI tracts of ASD children.
Review

*Akkermansia muciniphila* and its role in regulating host functions

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**Fig. 2.** Schematic representation of the interaction of *Akkermansia* with the microbiota and its host. *A. muciniphila* may impact the resident microbiota by supplying growth factors released from mucin degradation. *A. muciniphila* interacts with its host by strengthening the intestinal barrier, or by modulating mucin turnover and immune responses.
HN001 Gestational Diabetes

Early pregnancy probiotic supplementation with *Lactobacillus rhamnosus* HN001 may reduce the prevalence of gestational diabetes mellitus: a randomised controlled trial
- First published online 3 April 2017

- The aim of the current study was to investigate whether the probiotic *L. rhamnosus* HN001 (HN001) taken by pregnant mothers from early pregnancy could reduce the prevalence of Gestational Diabetes Mellitus (GDM) by 26–28 weeks’ gestation.

- A double-blind, randomised, placebo-controlled parallel trial was conducted in New Zealand.

- A total of 184 (87%) women took HN001 and 189 (90%) women took placebo.

- Eligible women were enrolled into the study at 14–16 weeks’ gestation.
HN001 Gestational Diabetes

- Participating women were randomised to receive capsules containing either HN001 (6 × 10^9 colony-forming units or placebo (maize-derived maltodextrin, identical in appearance and smell to the probiotic) to be taken daily from enrolment throughout pregnancy and until 6 months post birth if still breast-feeding.

- Lifestyle factors such as changes in patterns of food consumption with economic development have led to the well-recognised and increasing problems of obesity and associated diseases, including gestational diabetes mellitus (GDM).

- Pre-pregnancy overweight and obesity have been shown to account for 46% of GDM, with excess weight gain during pregnancy, previous GDM or a family history of diabetes, polycystic ovary syndrome (PCOS), older age and higher parity also identified as risk factors.

- GDM itself increases the risk for preeclampsia, miscarriage, preterm birth, macrosomia, induction of labour and caesarean section.

- GDM also increases the risk for later maternal and child obesity and subsequent type 2 diabetes mellitus.
• The International Association of Diabetes and
Pregnancy Study Group (IADPSG) highlighted the
below recommendations for the study.

• Recommendations for **oral glucose tolerance test**
**(GTT)** **threshold glucose concentrations for the
diagnosis of GDM** (fasting plasma glucose ≥5·1
mmol/l or 1 h post 75 g glucose level ≥10 mmol/l
or at 2 h ≥8·5 mmol/l).

• **NZ guideline definitions for GDM** diagnosis specify
a higher baseline and 2 h glucose test threshold
(fasting plasma glucose ≥5·5 mmol/l or 2 h post 75
g glucose level ≥9 mmol/l)(1).
HN001 Reducing Gestational Diabetes

- The assessment for GDM was conducted at 24–30 weeks of pregnancy.

- The study highlights that only maternal age, BMI and having a history of GDM were significantly associated with GDM in this study.

- Within the older group, HN001 was associated with a 3-fold reduction in the prevalence of GDM compared with the prevalence among women in the placebo group.

- GDM did not re-occur in any of the HN001 participants who had a history of GDM.

- Among those with a history of GDM and for those without previous GDM, HN001 protected against a recurrence of GDM.

- Fasting mean blood glucose levels were significantly lower (P=0.001) in the HN001 group compared with that in the placebo group.

- The data within the study suggest that the probiotic HN001 at a dose of 6 x 10^9 cfu/d may lower the rate of GDM from 13.8 to 8.2 %, a 40 % reduction using the IADPSG guidelines or a 68 % reduction from 6.5 to 2.1 % using the NZ guidelines.

Early pregnancy probiotic supplementation with *Lactobacillus rhamnosus* HN001 may reduce the prevalence of gestational diabetes mellitus: a randomised controlled trial

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• The gut microbiota is profoundly altered during the three trimesters of pregnancy towards a less diverse state, with the most depleted microbial richness found in women with GDM.

• The study speculated that HN001 supplementation altered the composition and function of the gut microbiota in favour of improved insulin sensitivity and reduced inflammation in the host, which reduced the propensity towards GDM.

• Promoting good health in pregnancy through weight control programmes or diet has been largely ineffective, partly due to poor adherence with the interventions. Highlighting the need for a safe therapeutic tool to help reduce the risk of developing GDM.

• The lack of any deleterious effect on birth outcomes supports HN001 as a safe intervention to take from early pregnancy.
Take Home Message?

- What can you take home from this presentation?
- What do you think our challenges will be in the upcoming month?
- How can we support you?
- Any further feedback?
Upcoming Events

REFRAMING THE MITOCHONDRIA IN FUNCTIONAL MEDICINE
Evaluating current developments in mitochondrial science, going beyond ATP production.

18th September - 13th October 2017

Mitochondrial dysfunction is the underlying cause for many common chronic diseases that face modern society. These include diabetes, obesity, autoimmune disorders, neurodegenerative diseases, cognitive decline, cancer, cardiovascular disease, chronic infections, neurodevelopmental disorders, autism and Chronic Fatigue Syndrome. This webinar will expand your knowledge beyond the viewpoint that mitochondrial dysfunction causes health disturbance. Learn the biological role that mitochondria play beyond a strict biochemical perspective, to consequently understand their involvement in complex chronic illness.

For your understanding bring simple real life interventions to new concepts at the forefront of mitochondrial health. Learn how the complex connectivity between mitochondrial function and multi-system involvement can result in a common stress response. Join Dr Chrisabelle Yeoh, an active director of the Australian College of Nutritional and Environmental Medicine (ACNEM), as she delivers expert knowledge on the latest developments in mitochondrial health.

Concepts to be explored:
- The role of mitochondrial function in ancient bacteria.
- The mitochondria in human microorganisms: are they intimately linked?
- The role of the cell danger response.
- ATP in a danger signaling modulus.
- The pathways of deactivate metabolism in relation to cell danger response.
- Mitochondria as the first steps of innate immunity.

Learn:
- The role mitochondria play beyond ATP production.
- How to apply anti-inflammatory principles to initiate cell-shielding concepts.
- To apply anti-inflammatory principles with a focus on targeting the available pathways.
- To support with proven clinical diets for optimal mitochondrial function.
- To apply practical frameworks for dealing with chronic disease.

PRESENTERS

Dr Chrisabelle Yeoh
MBBS (Honours), MRCGP (UK), MSc (Nutrition)

Dr Michael Osideki
PhD, BSc (Chemical, Biotechnol) (Hons)

Emma Wishey

RESETTING THE ADDICTED BRAIN
FROM SOCIAL MEDIA AND FOOD TO ILLICIT DRUGS
NATIONWIDE WORKSHOP TOUR
Dates to be announced

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