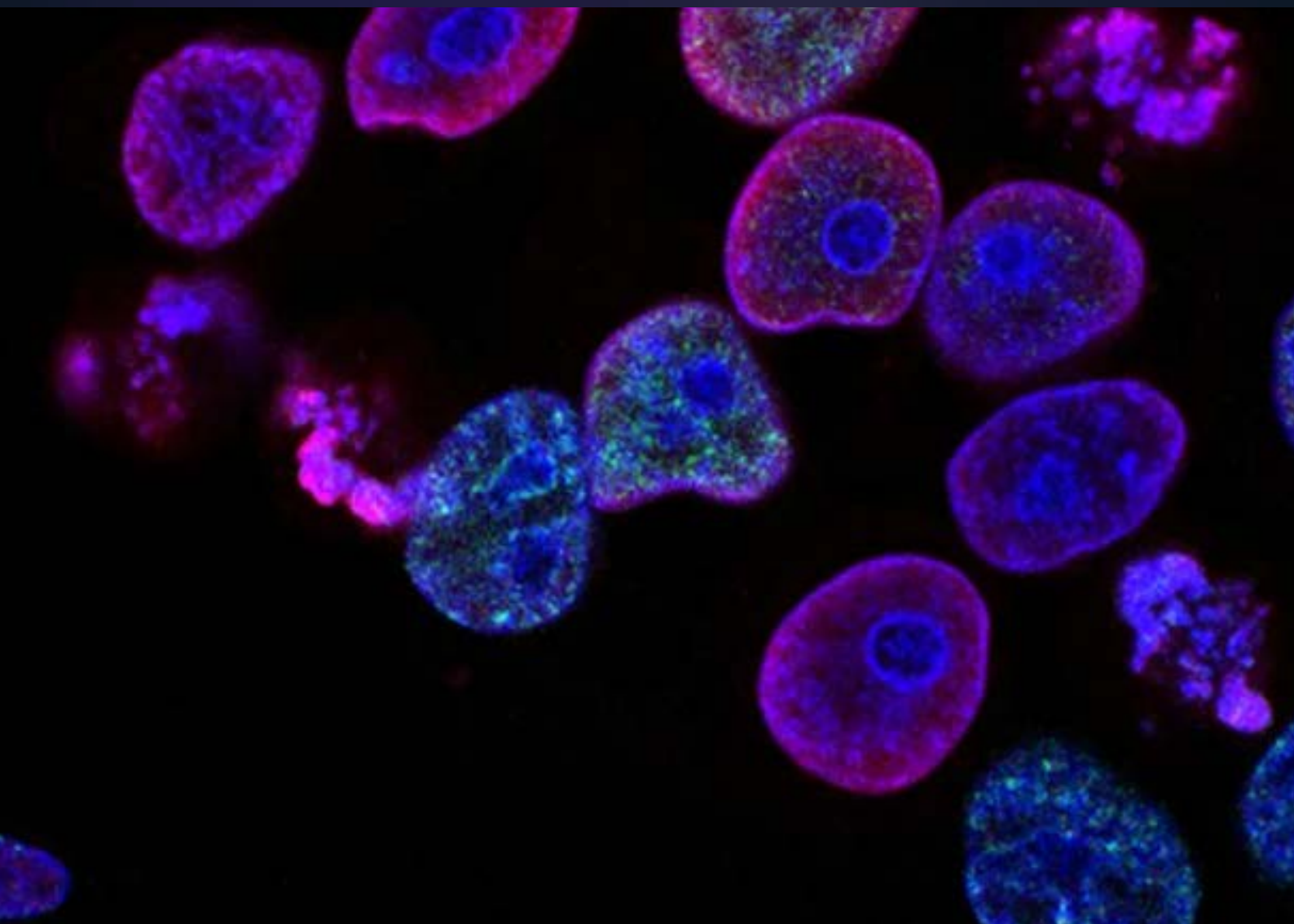
BEST PRACTICE EBOOK

Leveraging Microbiome Case Studies to Drive Microbiome-Based Therapeutics Development

Explore expert insights into harnessing the microbiome to drive therapeutic progress



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Introduction

The microbiome is the collection of all microbes, such as bacteria, fungi, viruses, and their genes, that naturally occur in the human body. The human microbiota plays an important role in human health and contributes to the metabolism of therapeutic drugs affecting their potency. Therefore, understanding drug-microbiome relationships are key to understanding patient responses and therapeutic success. Yet the microbiome is often overlooked and not always considered in drug development or clinical practice.

The microbiome is an emerging field that offers an opportunity to develop fundamentally new diagnostic markers and therapeutics. However, the current knowledge linking the microbiome to human disease is still being developed. For example, discerning a clear cause-and-effect relationship between microbiome change and specific diseases is complicated. Additionally, different patients have different microbiome compositions shaped by genetics, diet and lifestyles which complicates the development of therapeutics. Furthermore, regulatory agencies such as the FDA and EMA have limited experience with microbiome-targeted therapies, leading to a lack of standardisation protocols. To gain a better understanding of the microbiome, experts featured in this eBook present their latest case studies which demonstrate how an imbalance of microbiota can impact gut health and influence brain health.

This eBook explores microbiome case studies across a range of therapeutic areas, such as oncology and autoimmune diseases. The experts discuss challenges such as integrating and harmonising microbiome data, the importance of establishing a regulatory framework, and determining the impact that microbial players have on the manifestation of specific diseases. By adhering to best practices, researchers will be equipped with the tools necessary to drive progress in microbiome drug discovery, ultimately advancing therapeutic development and clinical applications.

Lucia Simmen
Digital Content Editor, Oxford Global

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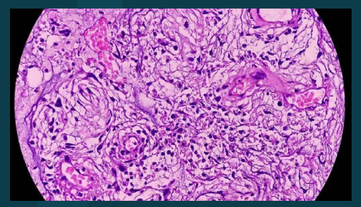


Key Summaries

Mona Bajaj – Elliott of **University College London (UCL)** discusses the crucial influence of diet, gut microbiota, and metabolites on both the immune system and brain health. She suggests that the challenge is to raise more awareness around the importance of diet and gut health. To promote a healthy microbiome, she suggests that the timing of butyrate into the early life is key: introducing butyrate via formula can lead to conditions such as asthma.

MONA BAJAJ – ELLIOTT
Associate Professor,
University College London (UCL)

Dr. Jonathan Blackburn of **Sengenics** explores how advances in antibody profiling, computational techniques, and multi-omics approaches also offer promising pathways to better understand microbiome-related diseases and therapeutic applications. Variability of data across different studies and the need for more reliable biomarkers in microbiome research are important challenges that Blackburn aims to address.

DR. JONATHAN BLACKBURN
Chief Scientific Officer,
Sengenics

Amedeo Amedei of the **University of Florence** gives nsights into how the gut microbiota influences the immune system. Key challenges include the diversity of microbial species and how imbalances (dysbiosis) can drive disease progression, influencing immune responses. He suggests that enhancing understanding of key microbial players, such as Prevotella and Bacteroides will allow scientists to better understand immune responses to tumours. He explains how targeting the microbiome for therapeutic approaches, offers potential for personalised treatments based on microbiota-immune interactions in specific diseases.

AMEDEO AMEDEI
Professor,
University of Florence

Lesley Hoyles of **Nottingham Trent University** explains how microbial metabolites in the gut interact with the brain. p-Cresol sulphate can have damaging effects on the blood-brain barrier (BBB), it can increase its permeability meaning that harmful substances can enter the brain. Hoyles proposes that inhibiting epidermal growth factor receptor (EGFR) with the drug erlotinib could prevent the damaging effects of p-Cresol sulphate on the BBB.

LESLEY HOYLES
Professor,
Nottingham Trent University

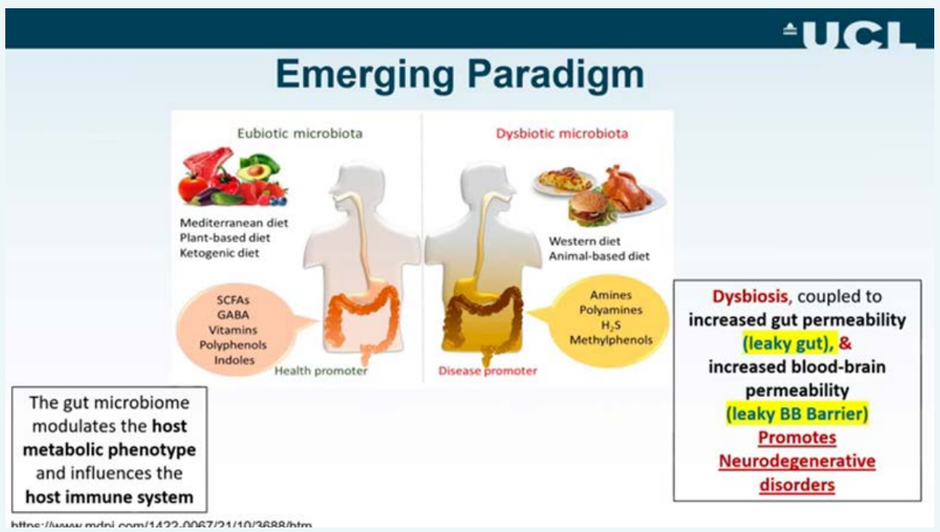
Chrysi Sergaki of the **Medicines and Healthcare Products Regulatory Agency (MHRA)** explains how standardising microbiome practices is challenging due to the large number of sectors and players involved. She explains how the use of reference reagents minimises bias, particularly in DNA extraction, sequencing, and bioinformatics analysis.

CHRYSI SERGAKI
Microbiome Group Leader,
Medicines & Healthcare products Regulatory Agency (MHRA)

Balancing Nutrition & Microbial Metabolites: Tackling Gut Health Challenges to Boost Immunity & Brain Function

Mona Bajaj-Elliott, Associate Professor, University College London focused on the impact of gut microbial metabolites on the gut immune system and gut-brain axis. She highlighted three key components in gastrointestinal health: nutrition, microbiota, and their communication with host physiology, particularly the immune system. The microbiome influences health through metabolites. Malnutrition remains a critical issue globally, contributing to both obesity and undernutrition, which affect gut health and immune functions.

The presentation discussed how gut microbiota and metabolites impact various diseases, including infections, inflammatory diseases, and cancer. For instance, diets like the Mediterranean diet promote beneficial metabolites, while processed, Western diets increase harmful metabolites. These can contribute to conditions like leaky gut and neurodegenerative diseases.

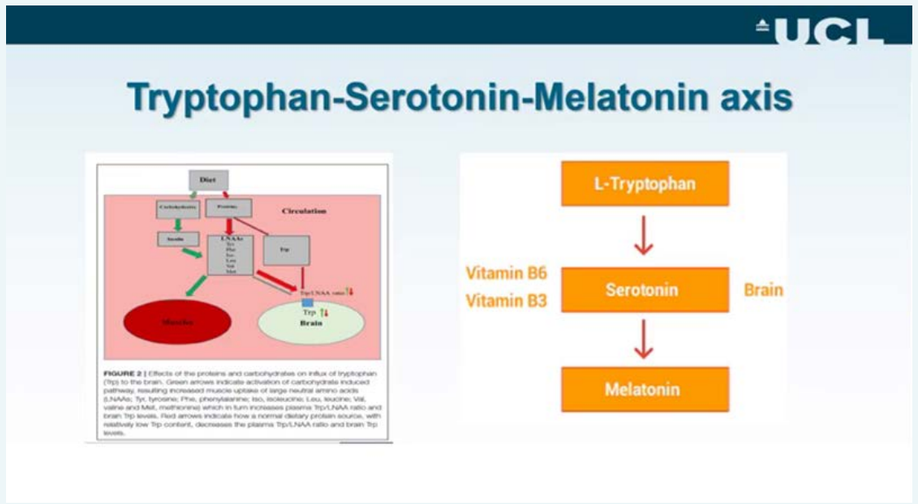


A notable study in cancer immunotherapy revealed that a fibre-rich diet improved melanoma patient outcomes compared to immunotherapy alone. However, probiotic supplementation worsened the outcomes: it weakened immune responses, counteracting the necessary immune activation for fighting cancer. Although probiotics are beneficial for inflammatory diseases they may suppress the immune system in a cancer environment. Therefore, it is essential to exercise caution when using them in certain conditions.

In early life, the timing of butyrate introduction in the microbiome is vital. Studies show that breastfeeding alone regulates early microbiome development, and the introduction of solid food, which increases butyrate-producing bacteria, occurs after several months. Introducing butyrate too early through formulas can disrupt immune education and lead to conditions like allergies and asthma.

Bajaj-Elliott also discussed gut-brain interactions, noting that leaky gut and compromised barriers (including the blood-brain barrier) are linked to neurodegenerative diseases. This emerging concern is exacerbated by findings, like microplastics in human brains, highlighting compromised bodily barriers as a growing health risk.

The role of tryptophan, an amino acid vital for gut-brain communication, was also discussed especially in the production of serotonin and melatonin. These hormones influence mood, sleep, and gut motility. The presentation concluded by discussing the role of microbial metabolites in regulating bacterial growth within the gut, with implications for conditions like antimicrobial resistance. Bajaj-Elliott emphasised the importance of nutrition in driving gut health and the need for more research into microbial metabolites' effects on human health and the microbiome.



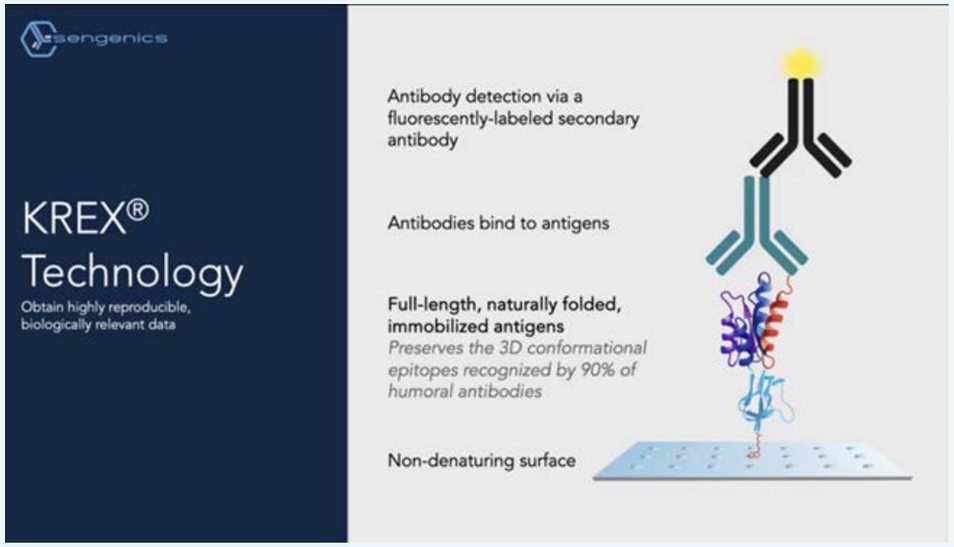
Overall, Bajaj-Elliott's presentation demonstrated the crucial influence of diet, gut microbiota, and metabolites on both the immune system and brain health. This intersectional approach has important implications for cancer, early childhood development, and neurodegenerative diseases.

Harnessing the Power of Antibody Profiling to Tackle Microbiota-Influenced Disease

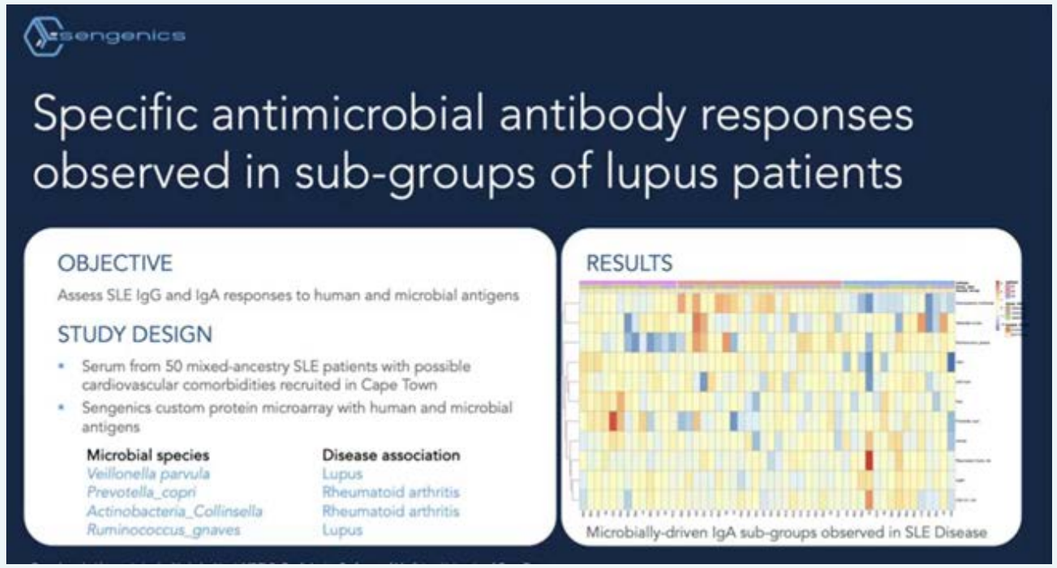
Dr. Jonathan Blackburn, Chief Scientific Officer at Sengenics, outlined best practices in studying the microbiome through his exploration of antibody repertoires and their significance in disease research, particularly as biomarkers.

Blackburn highlighted the importance of focusing on biomarkers in early disease detection. Good biomarkers should appear early in disease and be mechanistically linked to disease states. These characteristics are crucial because they allow researchers to detect disease before clinical symptoms manifest. He explained that antibodies are excellent biomarkers due to their specificity, stability, and ability to persist in peripheral fluids. This stability allows antibodies to be reliably measured and their association with diseases deciphered.

Furthermore, Blackburn advocated for the use of highly sensitive, multiplexed, and miniaturised assays, such as Sengenics' KREX™ technology, which preserves the folding and functionality of antigens. This technique ensures the discovery of biologically relevant antibodies and avoids false discoveries due to non-specific binding.



Blackburn then discussed customisation for microbiome and autoimmune studies. He introduced the utility of customised microbial antigen chips, which help identify disease-related microbial changes. Profiling antibody responses against specific microbial antigens can reveal links between the microbiome and diseases, particularly autoimmune conditions like lupus and Sjögren's syndrome. The idea of combining antibody profiling with microbial studies offers a powerful tool to distinguish between normal microbiota and disease-associated microbial strains. This could reveal triggers or markers of diseases like lupus and diabetes.



Furthermore, antibody profiling allows researchers to uncover disease subtypes, as demonstrated in his lupus study. This has practical applications, including more targeted treatments (e.g., patient selection for CAR T-cell therapies) and improving clinical trial designs. Antibody profiling can assist with patient stratification and disease subtyping.

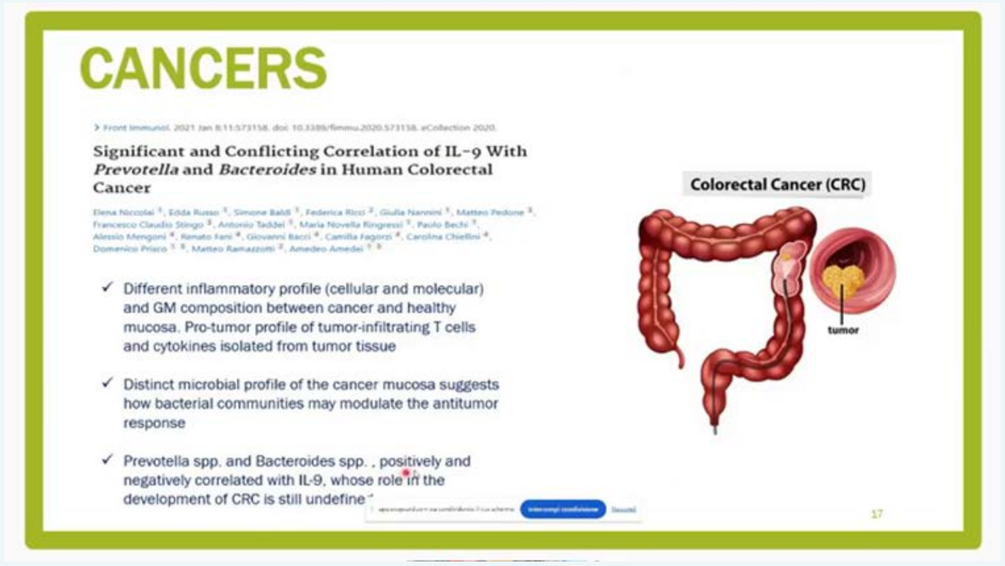
In summary, Blackburn suggested that robust and functional assays focusing on antibody repertoires and incorporating microbial antigens are vital for studying the microbiome's role in health. The ability to differentiate disease states at a molecular level, combined with the discovery of early, stable biomarkers, positions this technology as an advanced method in microbiome research.

Note: KREX™ technology for precision antibody profiling in now part of the SomaScan™ suite of solutions from Standard BioTools Inc.

From Autoimmunity To Cancer: Exploring Gut Dysbiosis Across Different Therapeutic Areas

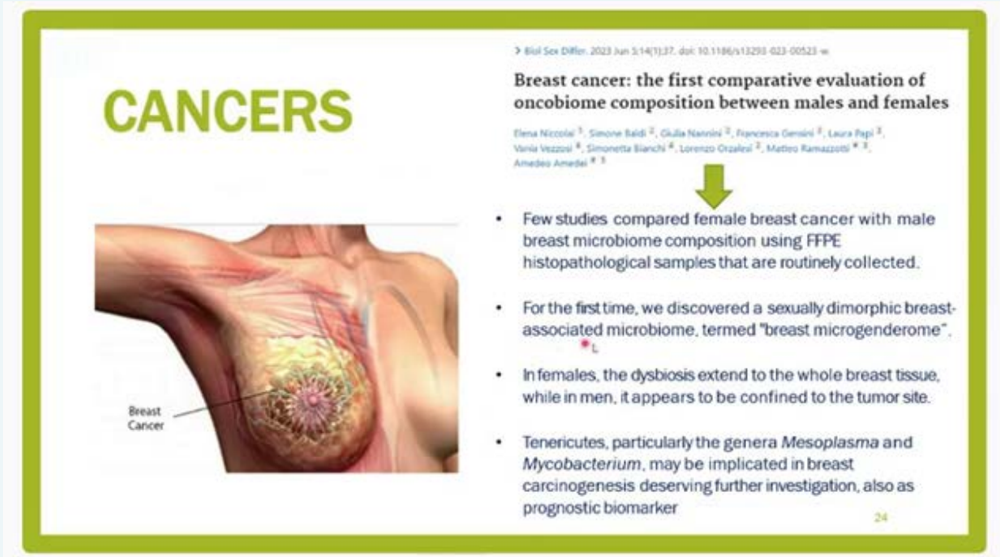
Amedeo Amedei, Professor of Immunology at the University of Florence focused on the role of the microbiome-immune axis in human diseases, ranging from autoimmune conditions to cancer. His presentation highlighted how the gut microbiota influences the immune system. When imbalanced the gut microbiota can lead to diseases like Crohn's disease, celiac disease, and cancer.

Amedei discussed studies showing how the microbiota composition and cytokine distribution differ between healthy and damaged tissues in Crohn's patients. These variations are linked to disease recurrence and inflammatory responses, particularly with certain microbial species like Mycoplasma.



He compared potential and atrophic celiac disease, noting differences in the gut microbiota and immune responses. This research revealed unique lipid metabolic profiles and immune cell behaviours between the two types, offering new insights into celiac disease progression.

Amedei's research also found important differences in the microbiota and immune responses between cancerous and healthy tissues. Notable microbial players, such as Prevotella and Bacteroides, were linked to pro-tumour immune responses. Amedei also examined gender differences in the breast cancer microbiome. His findings showed that women exhibited a dysbiosis across all breast tissue, while in men, the imbalance was confined to the tumour site. Certain bacteria, like Mycoplasma, were implicated in breast cancer development.



In conclusion, Amedei showed the significance of microbiota in disease development. He also highlighted potential therapeutic approaches targeting the microbiome.

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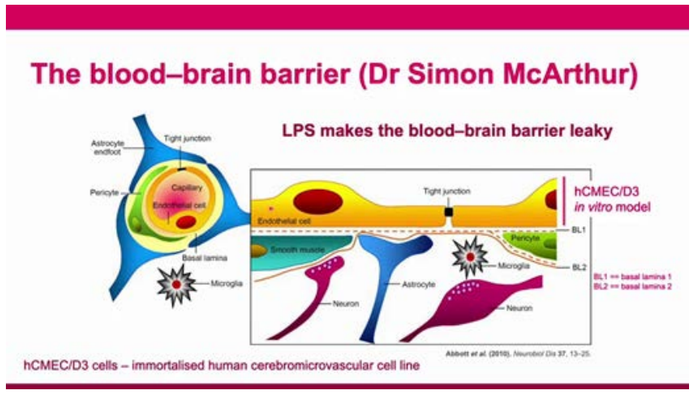
Combatting Blood-Brain Barrier Damage Through Microbial Metabolites and Targeted Therapies

Lesley Hoyles, Professor at Nottingham Trent University provided a general overview of how microbiome-associated metabolites influence the brain, focusing on the gut-brain axis. The talk explored how microbial metabolites from the gut, including short-chain fatty acids and lipopolysaccharides (LPS), interact with the blood-brain barrier (BBB).

The presentation discussed specific microbial metabolites, including short-chain fatty acids like acetate, propionate, and butyrate, and their protective effects on the BBB against inflammatory stimuli. Dietary methylamines, such as trimethylamine, were also studied, with trimethylamine oxide improving cognitive function in mice while trimethylamine caused damage to the BBB.



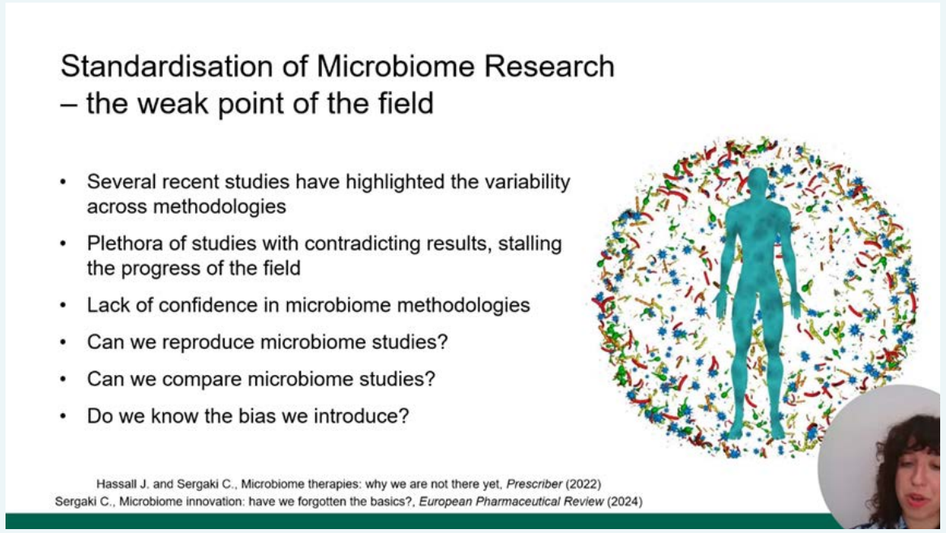
Hoyles' focus was on derivatives of p-Cresol, a metabolite produced by gut bacteria. In particular, she examined p-Cresol sulphate and p-Cresol glucuronide, two forms of the metabolite that behave differently in the body. p-Cresol sulphate is a toxin that accumulates in patients with chronic kidney disease and damages the BBB. Whereas p-Cresol glucuronide was found to have a protective effect on the BBB in the presence of inflammation. This was shown in both in vitro and mouse model studies. Hoyles described how p-Cresol glucuronide reduced the damage caused by LPS to tight junction proteins in the BBB.

Hoyles also discussed the detrimental effects of p-Cresol sulphate, which compromises the BBB via the epidermal growth factor receptor (EGFR) signalling pathway, leading to increased permeability. Her team found that inhibiting EGFR with the drug erlotinib could prevent the damaging effects of p-Cresol sulphate on the BBB. This discovery could be particularly relevant for chronic kidney disease patients, who often experience cognitive issues and BBB dysfunction.

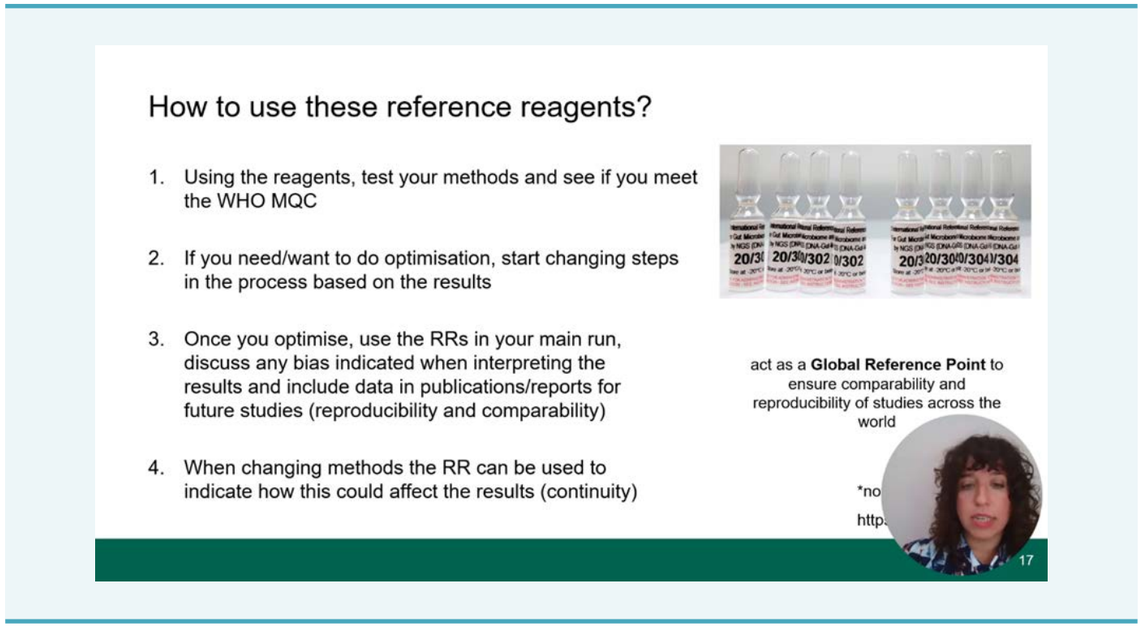
Hoyles concluded by acknowledging her collaborators. She expressed the need for further research to explore therapeutic options for protecting the BBB in disease contexts like chronic kidney disease.

Tackling the Lack of Standardisation Protocols Within Microbiome Using Bioinformatics and Reference Reagents

Chrysi Sergaki, Group Leader at Medicines and Healthcare Products Regulatory Agency (MHRA) outlined standardisation best practices in the microbiome field, she presented on the challenges and progress in this scientific area. She emphasised that while the microbiome has the potential to revolutionise public health, the field is hindered by variability in methodologies. This tends to result in inconsistent and contradictory research findings. Sergaki stressed the urgent need for biological standardisation to identify and address biases introduced during microbiome research, especially in DNA extraction, sequencing, and bioinformatics analysis.



Her team has developed reference reagents using 20 bacterial strains commonly found in the gut microbiome to harmonise and integrate various microbiome research steps. Initial studies revealed that different bioinformatics pipelines and DNA extraction kits produced vastly different results, with up to 42% of the data being inaccurate due to biases. Even in the best-case scenario, only 66% of the data is accurate, raising concerns about the reliability of microbiome research.



To address this, Sergaki's team has coordinated global studies involving laboratories across multiple sectors. These studies demonstrated the significant variability in microbiome research results, even when using the same reagents. Sergaki stressed that this variability diminishes progress in the field, and standards are essential to improve reproducibility and comparability between studies.

She also noted the critical need to discuss and understand the biological basis of these biases rather than relying on bioinformatics to "correct" data post-experiment. Sergaki concluded by outlining MHRA's ongoing efforts to develop reference standards for various microbiome environments (gut, respiratory, vaginal, etc.) and antibiotic resistance (AMR), urging the research community to prioritise addressing bias to advance the field.

Report Conclusion

Microbiome is a complex yet exciting field. These case studies show the diversity of the microbiome and how microbial data gives use important insights into a wide range of illnesses including cancer and autoimmune diseases. The presentations also explored the significant relationship between the gut microbiome and the brain and how this influences neurological behaviours. The speakers also touched on the potential of microbiome in personalised medicine: understanding and analysing a patient's microbiome composition can offer crucial insights into personalised treatments for infections and chronic diseases.

Collaboration and multi-disciplinary approaches are critical in advancing progress in this field. For instance, regulatory bodies are working alongside biotech companies, pharmaceutical manufacturers and academic institutions to facilitate drug discovery and drug development in the microbiome field. The speakers noted that a lack of standardisation has contributed to the accumulation of bias at various points in the pre-clinical and clinical phases. Furthermore, an increasing availability of comprehensive bioinformatic tools is important as this will allow scientists to extract useful information from multi-omics data. The industry experts also mentioned that while AI/ML and other computational methods are important to integrating and analysing complex microbiome data, the quality of the data they are trained on must be validated.

To connect with experts and thought leaders in the microbiome and immunotherapy field, join us at NextGen Omics & Spatial Biology US 2025 taking place 27 -28th March in Boston. This unmissable event gives you the opportunity to connect with experts working on using novel multi-omics technologies in the clinic and advancing biomarker profiling.