The Future of Microbiome-Based Therapeutics

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The 32nd United European Gastroenterology Week, held from 12th–15th October 2024 in Vienna, Austria, brought together over 11,500 participants from more than 115 countries to discuss groundbreaking developments in the diagnosis and treatment of digestive system diseases. This year's interdisciplinary sessions focused on innovative, non-invasive techniques for managing gastrointestinal conditions, alongside cutting-edge translational and basic research.

INTRODUCTION

The gut microbiome plays a critical role in maintaining health and mediating disease, as discussed by three leading researchers during a session entitled 'Future Microbiome Therapeutics' on microbiota-based therapies. Harry Sokol, Saint Antoine Hospital, Paris, France, explored bacterial consortia as a targeted approach to managing inflammatory bowel disease (IBD); while Rafael Valdes, University of Navarre, Pamplona, Spain, presented innovative bacteriophage therapies aimed at pathogenic gut bacteria. To conclude the presentations, Benjamin H. Mullish, Imperial College London, UK, shed light on the importance of gut microbial metabolites and their therapeutic potential.

BACTERIAL CONSORTIA: A TARGETED APPROACH

In his presentation, 'Bacterial Consortia', Sokol outlined innovative strategies for harnessing the gut microbiota to treat diseases such as IBD. He emphasised that the gut microbiota is a crucial player in the pathogenesis of IBD, making it a compelling therapeutic target. While traditional approaches like faecal microbiota transplantation (FMT) have demonstrated utility in acute conditions, their limitations have prompted researchers to develop more refined methods, including bacterial consortia.

Moving Beyond Faecal Microbiota Transplantation

Although FMT has proven effective in treating recurrent *Clostridioides difficile* (*C. diff*) infections, Sokol noted several challenges to its broader application, particularly in chronic diseases like IBD. A significant issue is the lack of standardisation as up to 50% of sequences identified in human stool cannot be mapped, and the functions of many identified genes remain unknown.[1] Additionally, a large proportion of gut metabolites, critical players in microbiome–host interactions, remain unidentified. This complexity, coupled with the variability in FMT efficacy, emphasises the need for well-defined, scalable microbiome-based therapies.

The Concept of Bacterial Consortia

Bacterial consortia represent a promising alternative to FMT as these carefully designed groups of bacteria are selected for their complementary functions and synergistic interactions. By assembling bacteria that collaborate metabolically or immunologically, consortia can achieve specific therapeutic effects. Sokol

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highlighted several examples, including a pioneering study that identified 17 bacterial strains capable of inducing regulatory T cells in mice, which are crucial for reducing inflammation in colitis models.[2] This research laid the foundation for clinical developments, including an ongoing Phase II trial that is testing a bacterial consortium for mild-to-moderate IBD.[3]

Another promising application of bacterial consortia is decolonising harmful bacteria, such as antibiotic-resistant *Enterobacteriaceae*, from the gut. Recent research demonstrated that an 18-strain consortium could successfully eliminate *Klebsiella pneumoniae* from the gut microbiota of mice by outcompeting it for resources, such as gluconate.[4] These findings suggest that bacterial consortia could provide an ecological solution to combat multidrug-resistant organisms, a pressing public health concern.

Defining the Next Generation of Microbiome-Based Therapies

Beyond small consortia, researchers are exploring the potential of highly defined, large-scale consortia that mimic the complexity of a healthy gut microbiota. In a groundbreaking study, scientists identified 119 bacterial strains that collectively represented a functional human microbiome.[5] When introduced into germ-free mice, this artificial microbiome restored key immune, metabolic, and bile acid functions, demonstrating its potential to replicate the benefits of a natural gut microbiota.[5]

At the other end of the spectrum, single-strain approaches also hold promise. For instance, *Faecalibacterium prausnitzii*, a bacterium known for its anti-inflammatory properties, is reduced in patients with IBD, and early-stage clinical trials have shown that administering this strain is safe and could lead to new treatments targeting specific microbial deficits.

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Challenges and Future Directions

While bacterial consortia offer exciting possibilities, Sokol described several hurdles that must be overcome, emphasising that ensuring safety is paramount, particularly in chronic disease settings as researchers must design bacterial formulations to avoid unintended interactions or persistence in unintended environments. Although regulatory frameworks for live biotherapeutics are evolving, they remain complex and challenging for developers. Additionally, understanding the nuances of microbiome–host interactions is crucial for optimising the efficacy of these therapies.

Looking ahead, Sokol describes how the ultimate goal is to develop a "super consortium" that recapitulates the functions of a healthy microbiota and can be tailored to treat diverse conditions, including IBD, cancer, and liver diseases.

BACTERIOPHAGES IN INFLAMMATORY BOWEL DISEASE

In his talk titled 'Bacteriophages', Valdes detailed an innovative approach to treating IBD by targeting specific pathogenic bacteria with bacteriophage therapy. He outlined the challenges of identifying shared IBD-associated microbiome signatures and the limitations of current treatments, which primarily target downstream adaptive immune responses rather than addressing the underlying bacterial contributors to the disease.

The Role of *Klebsiella pneumoniae* in Inflammatory Bowel Disease Pathogenesis

Using data from four diverse IBD cohorts totalling 537 samples, Valdes and his team identified a bacterial signature associated with Crohn's disease and ulcerative colitis.[6] The study's findings observed *Klebsiella pneumoniae* (KP2) as a key pathobiont enriched during IBD flare-ups and linked to a distinct profile of antibiotic resistance genes.

Germ-free mouse experiments were used to test the causal relationship between KP2 strains and IBD, showing that colonisation with KP2 strains resulted in reduced IL-10 production and elevated interferon-γ levels in splenic cells. These results confirmed the pro-inflammatory potential of these bacteria, thus providing a strong rationale for targeting KP2 strains as a therapeutic strategy.

Bacteriophages: Advancing to Human Trials

Valdes turned to bacteriophages as a precision tool to target IBD-associated KP2 strains. Bacteriophages have two unique advantages, their high host specificity, and their safety, as they do not infect human cells. However, they also present challenges, such as the potential for bacterial resistance and their interaction with the immune system, which can trigger strong immune responses.

To address these challenges, Valdes developed an iterative approach to isolate and combine bacteriophages that target KP2 strains while maintaining efficacy. Testing 18 different phage combinations, each containing three-to-five bacteriophages, demonstrated varying levels of efficiency. In preclinical mouse models, phage therapy successfully reduced intestinal inflammation by suppressing KP2 strains, as evidenced by improved histopathological scores and decreased pro-inflammatory cytokines.[6]

GUT MICROBIAL METABOLITES

In his talk, 'Microbial Metabolites in Engineered Probiotics', Mullish explored the profound significance of gut microbial metabolites and their therapeutic applications. Mullish's own research has

provided valuable insights into the role of microbial metabolites in combating infections like *C. diff* and multidrug-resistant organisms (MDRO). In a 2023 study, mice exposed to antibiotics or stool from healthy donors exhibited increased nutrient levels and decreased metabolites.[7] This reduction in metabolites following antibiotic treatment contributed to the rise of MDROs; however, supplementing mice with a mixture of metabolites led to a significant reduction in the colonisation of carbapenem-resistant *E. coli*, a key MDRO.

Similarly, FMT has shown promise in restoring metabolite balance as, after FMT, valerate levels were restored to those of healthy donors. Valerate was shown to inhibit the growth of *C. diff in vitro* in a dose-dependent manner.[8]

Bile Acids: A Double-Edged Sword

Mullish also discussed the impact of bile acids on gut health. In antibiotic-treated guts, there is a marked drop in bile salt hydrolase activity and an increase in stool taurocholic acid, a primary conjugated bile acid that promotes *C. diff* infection.[9] Whilst secondary bile acids like deoxycholic acid could potentially reduce *C. diff* colonisation, they pose risks such as increased colonic cancer rates, highlighting the complexity of using bile-metabolising enzymes or small molecules therapeutically.

Challenges in Therapeutic Applications

While the therapeutic potential of microbial metabolites is immense, Mullish outlined several challenges. One significant issue is the palatability of these compounds, as many metabolites, particularly short-chain fatty acids, have unpleasant smells and tastes that make them difficult to administer. Stability and volatility further complicate their use, as these compounds are often unstable and degrade rapidly. Another major obstacle lies in targeting and absorption; it is challenging to deliver metabolites precisely to their intended sites of action within the body. Ensuring proper dosing is equally problematic, as incorrect dosing can lead to toxicity or adverse effects. Responses to metabolites can also vary widely between individuals, adding another layer of complexity and, finally, the regulatory and intellectual property landscapes pose additional hurdles.

Engineered Bacteria: A Promising Solution

To overcome these obstacles, engineered bacteria offer a promising approach to restoring gut microbial metabolites. Probiotic strains such as *E. coli* Nissle and various *Bacteroides* species, which have established safety profiles, are particularly attractive for this purpose. These bacteria can be engineered using a range of techniques, from classical plasmid

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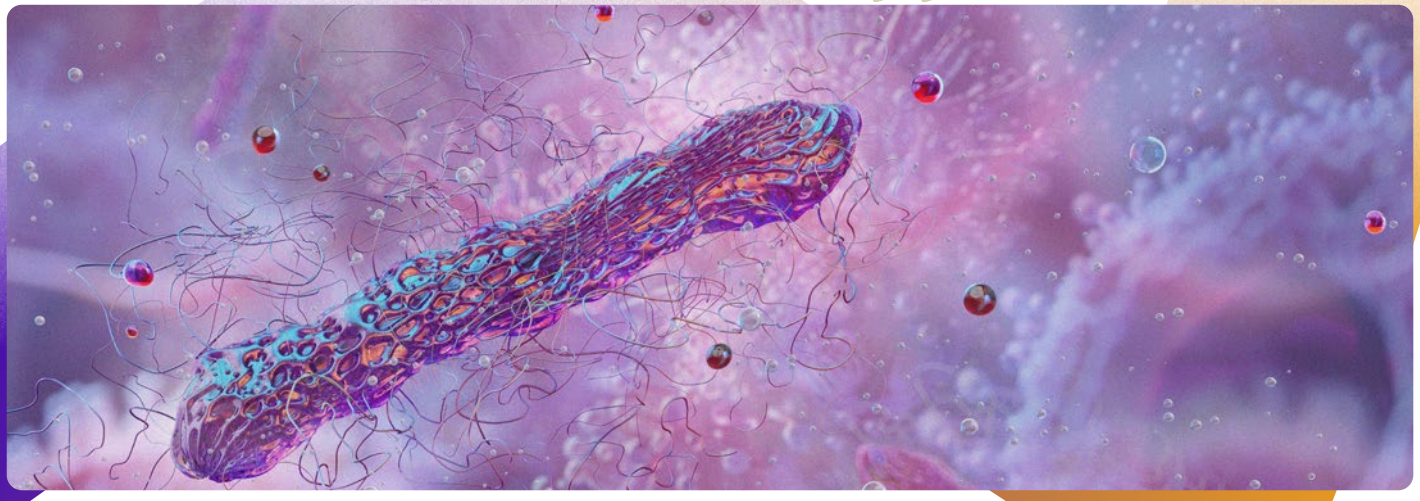

transfection to advanced methods like CRISPR-Cas systems, allowing precise modifications to the bacterial chromosome.

Despite promising results in animal studies, translating these findings to human practice is fraught with challenges. For example, SYNB1020, an engineered *E. coli* Nissle 1917 designed to convert ammonia into L-arginine, showed success in reducing systemic hyperammonaemia and improving survival in mouse models of urea cycle disorder and liver injury.[10] Phase I human trials indicated the treatment was well-tolerated and quickly reached a steady state; however, a subsequent Phase IB/II study was halted due to a lack of efficacy.

Future Perspectives

Mullish discussed potential future directions for engineered probiotics. One approach involves using native gut bacteria instead of traditional probiotic strains, as the former may colonise more effectively. Another notable development involves engineering bacteria not only to produce metabolites but also to sense them. In one study, *E. coli* was designed to detect gut sulphates, a marker of inflammation. Upon sensing these sulphates, the bacteria activated a base-editing system that produced a colourimetric signal, recorded the inflammatory episode in DNA, and released an immunomodulatory molecule to reduce inflammation.[11] This multifunctional system demonstrated the potential for bacteria to serve as both sensors and therapeutics.

CONCLUSION

The session provided a compelling overview of the cutting-edge developments in microbiota-based therapies, showcasing the convergence of scientific innovation and clinical application. From refining bacterial consortia for chronic disease to targeting specific pathogens with phages and leveraging engineered probiotics, these approaches offer promising avenues to restore gut health and combat disease.

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