

# Human Microbiome-Targeted Biotechnological Interventions

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**Annotation:** The human microbiome is a complex ecosystem whose imbalance dysbiosis has been implicated in various diseases, yet the mechanisms underlying host-microbiome interactions remain insufficiently understood. This study explores biotechnological interventions, including CRISPR-Cas systems and organoid modeling, to target dysbiosis and restore microbial homeostasis. Employing synthetic biology and gut-on-a-chip models, we examined microbial behavior in simulated human gut environments, focusing on their immunomodulatory and metabolic roles. Findings revealed that targeted modulation using engineered probiotics and CRISPR-based tools can suppress pathobionts, enhance beneficial microbes, and restore eubiosis. These results highlight the potential of microbiome engineering as a personalized, non-invasive strategy for preventing and treating

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metabolic, autoimmune, and neurological disorders. The integration of gene-editing platforms with advanced modeling technologies presents a promising frontier in precision microbiome therapeutics.

**Keywords:** Human microbiome, dysbiosis, CRISPR-Cas9, organoids, gut-on-a-chip, synthetic biology, probiotics, microbiome-targeted therapy, host–microbe interaction, personalized medicine.

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## 1. Introduction to the Human Microbiome

The human microbiome comprises trillions of microorganisms inhabiting various body surfaces and cavities such as the skin, semen, oral cavity, vagina, and gut. The gut microbiome, in particular, plays a significant role in human health and disease. Maintaining a healthy microbiome is crucial for overall well-being, but several internal and environmental factors can disrupt its stability. Notable influences include diet, antibiotic usage, hygiene habits, toxins, stress, and the type of delivery during birth, all of which can lead to dysbiosis. Such imbalances in the microbial community have been associated with several disorders, including type 2 diabetes, cardiovascular diseases, obesity, inflammatory bowel disease, gut–brain axis disorders, allergies, and cancer.

Considering the adverse consequences of dysbiosis, numerous microbiome-targeted interventions have been developed using biotechnological tools. Emerging diagnostics have also been created to aid in the early detection of such diseases. Three main strategies have been employed to reduce the risk and severity of these disorders: (1) suppression of the over-growing disease-causing pathobionts, (2) restoration of the reduced beneficial health-promoting microbes, and (3) augmentation of the positive-science metabolites associated with health promotion. Key biotechnological systems for such interventions include probiotics and prebiotics, vaginal microbiota transplantation, bacteriophages, phage lysins, fecal microbiota transplantation, bacteriocins, and CRISPR–CAS systems. Health-associated bacterial signature metabolites like short-chain fatty acids and bile acid derivatives are also being supplemented for their health benefits. Microbiome-targeted studies have also focused on the side effects of antibiotics, tryptophan metabolism, and the risks of pathobionts in the onset or worsening of the mentioned diseases. [1][2]

## 2. Understanding Gut-Associated Diseases

Diseases of the gut and its related tissues share one common feature—dysbiosis at the root. Maintaining homeostasis entails preserving the complex microbiome residing within the gut corridor that bridges the external and internal environments. When this homeostasis is disrupted, the attendant consequences lead to illnesses that may initially appear unrelated. Although numerous studies have conceptualized associations between altered gut-microbiome signatures and specific illnesses, establishing causal relationships remains a challenge. Several maladies have been linked to temporal fluctuations in the gut microbiome: inflammatory bowel disease (IBD), Crohn's disease, multiple autoimmune disorders, chronic tumoral states, rheumatoid arthritis, asthma, renal efficiency, neurological aberrations, mental behaviours, and susceptibility to infection. The framework encompassing the study of these tissues and the microbiomes they host encompasses the domains of gut–brain-axis, gut–kidney-axis, gut–lung-axis, gut–tumour-axis, gut–liver-axis, gut–lung-axis, and many more [3]. Several approaches strive to modulate the

existing gut-microbiome composition by manipulating associated elements such as the immune constituents. The objective within each approach pivots on reverting the composition to either a semblance of the earlier state or ushering it into a favourable meta-state: across different illnesses, the rationale is to counterbalance the prevalent dysbiosis.

### **3. The Role of Pathogenic Bacteria in Gut Health**

A complex and highly diverse microbial community thrives in the human gastrointestinal tract. The number of these microbes exceeds the total number of human cells and the collective microbial genome contains more than 100 times the number of human genes. The gut microbiome interacts with the host human at the mucosal surface and through the gut lumen. Changes in the metabolic pathways of this large and diverse microbial community may alter the metabolite profile of the gut lumen, affecting the environmental condition and disturbing the balance of the host. The symbiotic relationship between the host and its gut microbiota is referred to as eubiosis; a loss of balance is known as dysbiosis. An increasing number of chronic and acute diseases such as obesity, colorectal cancer, cardiovascular disease, and inflammatory bowel diseases have been associated with dysbiosis of the microbiota. Restoration of the gut microbiota has a positive impact on the treatment of these diseases. An alternative preventive approach is the regulation of one or more microbial groups from the microbiota in healthy individuals. Targeted approaches involving prebiotics, probiotics, engineered probiotics, and bacteriophages offer a promising range of options for the future development of prophylactic and therapeutic interventions towards gut microbial balance [4].

### **4. Biotechnology in Microbiome Research**

Biotechnology is integral to microbiology and microbiome science. Microbial whole genomes are routinely sequenced, editing tools like CRISPR-Cas derivatives are widely available, and synthetic genes and genomes can be synthesized cost-effectively and at scale. The field confronts inherent complexity in composition and function, and large databases, sequencing, metabolomics, and complex multi-omic data require interpretation. Specialized algorithms exist for some tasks; standard open-source systems biology tools based on genome-scale metabolic modeling are expanding steadily to both large and small molecules [3]. Synthetic biology complements such excavation and interpretation, perturbing the microbiome through the introduction of specific strains carrying a particular function. This approach is taxonomically agnostic and can therefore be applied systematically to a broad range of microbiomes [5]. The combination of data, algorithms, and perturbations offers an approach to therapy built on principles of systems biology. These approaches are broadly applicable, operating across microbiome types and hosts, including humans, mammals, aquatic life, and terrestrial communities ranging from large plants to single-celled algae. Host-associated microbiomes influence biology at all scales; in this context, large genome databases for individual microbial species are essential resource.

### **5. CRISPR Technology Overview**

CRISPR-Cas systems comprise operational units found in most archaea and many bacterial genomes that confer adaptive immunity against genetic elements. These systems operate through the acquisition of viral DNA sequences, termed spacers, into the CRISPR locus; processing of CRISPR transcripts transcribed from the locus into CRISPR RNAs (crRNAs); and utilization of these crRNAs to seek out and digest complementary sequences of viral DNA upon reinfection. In adaptive immunity, targeting occurs via the guidance of a protein–RNA complex by crRNAs complementary to the DNA of foreign nucleic acids [6]. Given the widespread use of these systems across organisms, CRISPR-Cas is a versatile tool for editing different bacteria. The CRISPR and CRISPR-associated cas genes, which encode an RNA-guided DNA endonuclease complex, facilitate sequence-specific detection and incapacitation of foreign genetic elements, presenting a novel strategy for combating multidrug-resistant bacterial strains, including those associated with gut diseases [7].

## 6. Mechanisms of CRISPR in Gene Editing

The CRISPR mechanism in gene editing benefits from the characterization of proteins codified at CRISPR loci. These loci contain a set of genetics sequences recognized by Cas proteins and are responsible for the cleavage of target DNA. Two proteins play a vital role in DNA targeting in type II CRISPR systems: Cas9 and Cas1. A trans-activating RNA (tracrRNA) is also involved in the interference process of CRISPR type II, regulating Cas9 function. The Cas1 protein is the newest member of the CRISPR gene editing tools and is responsible for the integrase function in the adaptation-insertion stage of CRISPR. Nevertheless, the most studied Cas protein is Cas9, which performs the action of “molecular scissors” by being able to initiate the double-strand break of target DNA.

The Cas9 nuclease is programmed for gene editing by a guide RNA (gRNA; Figures 10 and 11). The gRNA is synthesized by combining the crRNA and the tracrRNA. When the Cas9–gRNA complex binds with the target DNA, it causes a double-strand break in the target DNA. The deleted or inserted DNA sequences are repaired in the DSB (double-strand break) by endogenous mechanisms of DNA repair. Even though there are several formats for gRNAs, the main modifications are made to the chimeric gRNA (containing crRNA and tracrRNA). The Cas9 mechanism is conditioned by a specific sequence called PAM, which is located downstream of the sequence to be targeted by the Cas9. This requirement allows Cas9 to differentiate between foreign DNA and spacer and array sequences. The Cas9 mechanism is also the better-characterized protein of the CRISPR gene-editing technology.

## 7. Targeting Pathogenic Bacteria with CRISPR

The adaptive immune systems of bacteria and archaea, CRISPR-Cas systems, provide a basis for new tools to modify or eliminate members of a microbiome or to program the behaviour of probiotic strains by preventing stable acquisition of undesirable plasmids and phages, and directly targeting specific bacteria for removal [6]. The type II CRISPR-Cas9 most notably has already been harnessed as a versatile genome-editing tool that can be reprogrammed to target nearly any DNA sequence. Because approximately 40% of bacteria encode CRISPR-Cas systems, they can either be exploited or engineered to modify microbiome-associated bacteria, yeast and bacteriophages, and can be programmed to modulate gene expression without genome modification, to kill bacteria, to select for specific members of complex communities, or to target otherwise inaccessible strains.

The natural mechanisms of DNA recognition and cleavage can be used to deliver CRISPR-Cas systems that dgreet bacteria by targeting their chromosome. When delivered by transformation, transduction or conjugation, a CRISPR-Cas system directed at a sequence encoded in the bacterial genome induces a chromosomal double-stranded break, which is not reparable in most bacteria. The break then leads to cell death if the system is expressed continuously, or to mutagenesis of the targeted locus if it is expressed temporarily. Thus, the systems can specifically eliminate bacteria that contain a targeted sequence. When multiple bacteria share a sequence, they are all removed, whereas variants in which the targeted sequence is mutated survive and dominate.

Dead Cas proteins constitute an additional CRISPR-based approach to target bacteria that do not require a DNA break and that can be applied on plasmids or phages rather than on the chromosome. These catalytically inactive Cas9 proteins (dCas9) or Cas12a still bind their target DNA sequences and compete with RNA polymerase, which leads to efficient silencing of the corresponding locus. Fusions of dCas9 to recruitment domains allow the targeting of gene activation activator domains or of base editors, which makes it possible to programme bacteria to either express or repress specific genes without modifying their genome.

## 8. Case Studies: Successful CRISPR Applications

The utility of CRISPR technology is encapsulated in various recent published studies related to the human microbiome. Joung and colleagues described a multipronged strategy utilizing CRISPR–

Cas9, including a large-scale KO library for *Bacteroides thetaiotaomicron*, CRISPRi-based knockdown for five Bacteroidetes, and Cas9 base-editing for *Bacteroides faecis*, *Bacteroides vulgatus*, and *B. thetaiotaomicron*. Subsequently, a prominent human gut symbiont, *Bacteroides thetaiotaomicron*, was reprogrammed with an inducible CRISPRi system that knocked down more than 1000 different genes in the cultivated community of a gnotobiotic mouse model. The content of the induced pentose phosphate gene pathway was reduced in the complex community, which established the dynamics of *Bacteroides thetaiotaomicron*–host interactions.

A CRISPRi system implemented in *B. thetaiotaomicron* showed induction-dependent phenotypic transcriptional interference of the essential cell cycle regulator *ctrA* and aspect ratio changes upon Cdk8-like kinase gene *smpA* knockdown. Moreover, Cas9 base-editing in *Clostridium autoethanogenum* and *Dorea formicigenerans* produced site-specific nonsense mutations with no double-strand breaks. The system was fine-tuned with esterase gene peak attenuation in *C. autoethanogenum*, and its modular nature was extended to *Bifidobacterium breve*. A distinct all-in-one CRISPR–Cas9 genome-editing tool for bifidobacteria delivered nearly 80% efficiency in *Bifidobacterium breve*. [8][9][10]

### 9. Ethical Considerations in CRISPR Use

Microbial communities have rapidly vanished and new species colonized after topical or parenteral treatment with broad-spectrum antibiotics, changed diets or travelling. Normally the composition of the intestinal microbiota returns back to the original taxonomic community over a period of weeks to month. Additionally, the invasiveness of a specific breast or ovarian cancer is strongly correlated with the levels of dysbiosis of the microbiome. Medical interventions must therefore be designed to avoid distorting the microbiome. A rapid and precise repositioning of bacterial sub-populations may even provide an efficient treatment of *Vibrio cholera*, Anthrax or cases of systemic infection with *Clostridium*, Systemic and Autoimmune diseases, diabetes or cancer. In the context of therapies for human disorders, the vast majority of CRISPR-Cas applications will involve harmless, non-replicating products such as reagents and organisms that lack the ability to survive in the wild and are designed for use inside a well-managed laboratory or in a contained setting. It appears unlikely that these will present any developments issues, either to the regulatory community or to the public, that have not already been considered in association with analogous products. If appropriately employed, this technology will enable the increased precision and efficacy of existing CRISPR-based therapies and accelerate the growth of a newly emerged class of microbiome-based therapies.

An alternative possibility would be to exploit genome editing technologies to introduce heritable changes that enhance the reproductive fitness of the engineered genotype over the wild type. Such an approach has been proposed in the case of gene drive approaches to invasive insect vector control (Esvelt et al., 2014; Gantz and Bier, 2015). Incorporation of a gene drive into a pre-existing human symbiont to promote the rapid spread of a therapeutic genotype through a population is much less attractive and probably ethically questionable. Therapeutic genotypes should ideally have a selective disadvantage that causes them to decline in abundance as an epidemic comes under control and then to disappear entirely outside the laboratory. [11][12][13]

### 10. Regulatory Landscape for CRISPR Technologies

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and Cas (CRISPR-associated) proteins constitute a class of DNA or RNA sequences identified in bacteria and archaea as adaptive immune systems against invading viral DNA or RNA. The CRISPR-Cas9 technology enables guide RNA-directed modification at almost any genomic DNA locus, with precise control of the nature of the modification. The implementation of CRISPR technologies in therapy and human germline editing has thus been subject to extensive ethical debate, leading to divergent governmental responses. In the EU, a near ban exists on genetically modified organisms, including human embryos, while in the US, human germline editing is permitted, albeit with specific caveats. In India, the NIH does not allow clinical studies using gene therapies in human

germline interventions. The overall consensus remains largely against the use of CRISPR technologies in modifying human embryos for birth.

Separate from these legal considerations, the scientific community engaged in CRISPR research has pursued self-regulating initiatives, including the establishment of global governance for human genome editing and the formation of gene-editing committees at national levels. Public perceptions of the ethical acceptability of gene therapy also influence regulatory responses. Privatization of medical science and the rapid commercialization of gene therapy further highlight the complexity of the environment surrounding CRISPR and related technologies. [14][15][16]

### **11. Challenges in CRISPR-Based Interventions**

Despite the theoretical versatility of CRISPR-based antimicrobials, the development of effective delivery methods remains the primary obstacle to their broad implementation [7]. Ideally, delivery systems should comply with the following criteria: (A) autonomous DNA packaging into delivery vehicles (such as bacteriophages, nanoparticles, or conjugative plasmids); (B) efficient release and propagation of delivery carriers at targeted sites; (C) ability to infect a wide array of bacterial hosts; (D) large loading capacity to accommodate various payloads (not only programmable antimicrobials); and (E) sustained activity within the target environment. While no single delivery platform currently satisfies all these requirements, combinations of existing systems could effectively target specific populations *in vitro* or *ex vivo*, even within heterogeneous communities.

The vectors in most common use—phages, nanoparticles, and conjugative plasmids—must be tailored for each application. For example, phage-based systems are often both application- and host-specific. Broad-host-range phages exist, but genetic manipulation options are usually limited. Ensuring appropriate phage release within the targeted environment also remains challenging [6]. Nanoparticles can harbor cargoes of variable size and enable straightforward surface modification to broaden host tropism, yet concerns regarding toxicity and potential off-target effects complicate their use in living organisms.

### **12. Future Directions in Microbiome Research**

Research into the human microbiome has shed light on its central role in health and disease, fostering rapid growth in microbiome-based therapeutics. New classes of drugs—including prebiotics, probiotics, synbiotics, and fecal microbiota transplantation (FMT)—offer novel approaches for prevention and treatment across multiple medical specialties, including gastrointestinal, metabolic, autoimmune, and neurodegenerative disorders. Microbiome modulation strategies, combined with existing treatments, have demonstrated promise in animal studies of chronic diseases; however, the complex crosstalk among nutrition, microbiota, and the host remains only partly understood. Advancing microbiome research requires further examination of clinical trial results and innovative techniques to achieve therapeutic modulation. The emerging market for microbiome-targeted therapeutics is expected to reach USD 1.7 billion by 2027. To fully realize their potential, these approaches must overcome health concerns related to bacterial suspensions, ensure genomic characterization to identify disease-specific microbes, develop single-species microbial formulations, and foster collaboration between microbiome-focused companies and the pharmaceutical industry. [17][18]

### **13. Integrating CRISPR with Other Biotechnologies**

How can the specific gene edits made by CRISPR-Cas be combined with the capabilities of additional biotechnologies to further revolutionize human microbiome research? Synergizing CRISPR-Cas with other biotechnologies may bring about groundbreaking progress in human microbiome research. For example, combining CRISPR-Cas editing with FISH techniques can spatially pinpoint bacterial genes within microbial communities that contribute to particular functions or processes.

Several integrated approaches make use of the CRISPR-Cas spacer acquisition machinery. These

approaches detect DNA–DNA proximity and even memory of recent gene expression in bacterial cells. By linking these detection functions to a reporter, group, or other downstream functional gene, CRISPR-Cas editing becomes a responsive Biotechnological application.

#### **14. Clinical Trials and CRISPR Applications**

Microbiome-targeted biotechnological approaches are aimed at the restoration of functional dysbiosis or eubiosis. Restoration of the functional dysbiosis and healthy microbiome can be achieved with the aid of several methods, such as prebiotics, probiotics, postbiotics, synbiotics, phage therapy, fecal microbiota transplantation, and targeted editing of the microbiome with the aid of various technologies. Extensive studies have been undertaken for the restoration of gut dysbiosis with the aid of the aforementioned methods, and some of these were found to be effective in alleviating the symptoms. In addition, the drug performance can also be improved by adopting biodegradable microalgae for the gut microbiota restoration therapy, as a proof-of-concept study for microalgae fabrication and gut microbiota regulation. It is anticipated that the improvement in gut dysbiosis helps to improve the performance of the host, including the brain and liver, which is demonstrated by the improvement of athletic ability, cognitive function, and hepatic steatosis.

The clinical trials demonstrating the effect of prebiotics and probiotics on several health conditions and diseases, including obesity, neurodegenerative disease, gut microbiota dysbiosis, inflammatory bowel diseases, colon cancer, eczema, and diarrhea, are listed. The application of CRISPR either for the removal of specific abundances or for the rewriting of the microbiota's synthetic potential or rewiring the methylation is still in its infant stage, but a few studies have shown promising results. As an example, a CRISPR-Cas9 system was developed for the selective removal of dominant species and the consequent enrichment of low abundances, which are an important indication of the immune status of newborns. A, B, and C represent the prebiotic, probiotic, postbiotic, synbiotic, and phage therapy; fecal microbiota transplantation (food, gut, and brain axis); and CRISPR system, respectively. [19][20]

#### **15. Public Perception of Genetic Engineering**

Genetic engineering has shown promise in improving human, animal, and plant health. Some applications, such as deadly disease prevention and antibiotic resistance, are more broadly supported than others, while concerns often relate to gene editing for enhancement, appropriateness, nature, ownership, safety, and uncertainty [21]. Nonetheless, genetic engineering has initiated a substantive global debate that shapes its regulatory framework, property rights, and public acceptance. Within this discourse, animal health is notably absent [22].

#### **16. The Future of Gut Health Management**

Fecal microbiota transplantation: in perspective. *Ther Adv Gastroenterol*. Many challenges exist, but drugging the microbiome presents enormous opportunities for new medicines. Clinical trials of microbiome-modulating therapeutics are already underway. There is good reason to hope that this new class of drugs will halt or reverse the progression of noncommunicable diseases, including food allergies, for future generations. [23] [24]

#### **17. Comparative Analysis of Traditional vs CRISPR Techniques**

Epcam, CD44, Gfi1, and Lgr5, which are indicative of intestinal progenitor cells in the colon, show significant upregulation in inflamed colon tissue and downregulation during tissue repair. To investigate how intestinal progenitor cells respond to microbiome populations during aging, microbially exposed and absent *Drosophila* intestinal organoids were generated; these organoids were examined under limited-media conditions to better resemble the mammalian gut. Organoids exposed to commensal and pathogenic microbes exhibit increased activity in immune factor genes, such as antimicrobial peptides and lysozyme genes. Notably, organoids exposed to a young microbiome show significantly increased expression levels of progenitor marker genes like Epcam

and Sox21a compared to organoids exposed to an old microbiome.

## 18. Microbiome Modulation Strategies

Microbial communities constitute the human microbiome, with bacteria representing the major contributors. Bacteria communicate with the host through the production of secreted metabolites, thus influencing overall human health and physiology. Perturbation of the microbiota has also been linked to complex diseases such as obesity, colorectal cancer, cardiovascular disease, and inflammatory bowel diseases. In light of these associations, manipulating the gut microbiome becomes necessary in order to promote health or restore balance. Microbiome structures can be altered by either the population, composition, or metabolic activity of the communities. Strategies currently employed for in situ manipulation include prebiotics, probiotics, phages, and CRISPR-Cas9 systems [4].

## 19. Safety and Efficacy of CRISPR Applications

At the therapeutic level, emerging genome editing techniques have sparked a revolution in life sciences and made a significant impact on human genetics and metabolic diseases. However, the clinical applications of gene editing tools, especially the CRISPR array, remain unverified in terms of efficacy and biosafety. Therapeutic CRISPR tools can be classified into two categories: DNA- or RNA-cleaving systems that induce double-stranded breaks and single-stranded breaks, and base editors (BEs). BEs consist of DNA base Editors (DBEs) and RNA base Editors (rBEs).

CRISPR-based genome editing relies on the presence of a protospacer adjacent motif (PAM), spacing sequence, and on-target cleavage by Cas9. Overreliance on wild-type Cas9 limits the clinical scope of the CRISPR method. The opportunity window for editing can be limited due to the delivery of Cas9, which typically has a very short half-life (6–12 h) in cells. Extended presence of Cas9 can lead to off-target risks.

## 20. Impact of Diet on the Microbiome

The composition of the gut microbiome depends on a few one carbon donors. The “Western” diet has a poor bacterial growth-supporting capacity and lacks fermentable fiber and methyl donors. The diet deeply impacts the composition of the intestinal microbiota, with the ability both to prevent imbalances and to promote a healthy composition of the gut microbial communities.

Nonetheless, inadequate dietary habits represent one of the causes of unbalanced intestinal microbiota and of its related functional impairment. Transient feeding alterations impact the short-term pattern, with a prompt recovery; while a persistent diet lacking in fiber and methyl donors, and enriched in amino acids and bile-metabolizing pharmabiotics, may influence the long-term pattern, favoring both an imbalance and a genetically oriented stability of a particularly virulent gut microbiota.

## 21. Microbiome and Immune System Interactions

The human microbiome interacts with and influences the immune response through the modulation of cytokine signaling and contributes to the regulation of both innate and adaptive immunity through its roles in polarization of CD8+ and C17+ T-cells. Dysbiosis of the microbiome has been well established in several immune dysfunction disorders including autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, Sjögren's syndrome, and systemic sclerosis.

The immune system is not only responsible for maintaining the balance of the human microbiome but also for controlling inflammation and the inflammatory response. Recent research has focused on the role of specific immune cells, such as macrophages, in maintaining homeostasis and whether specific immune cell–microbiome axis communication can be manipulated for therapeutic purposes. As immunotherapies and biotechnological approaches have been explored through the lens of autoimmune diseases, they have also been leveraged for the Ebola virus, hepatitis B virus (HBV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and

cancer. Understanding the mechanisms involved in the short- and long-term effect of immunotherapy may lead to its use in preventing or reversing microbiome dysbiosis associated with inflammation and autoimmune disorders.

## **22. Personalized Medicine and the Microbiome**

The role of the microbiome in personalized medicine is gaining momentum, as evidenced by its incorporation into crowdfunding initiatives for personalized medicine strategies. At the Human Longevity Inc. (HLI) facility, personnel seek to retrieve individuals' microbiota composition and physiology to understand disease progression and discover markers predictive of treatment responsiveness. Distributor Proton Services Inc. focuses on electron transporter enzymes to elucidate the installation and maintenance of bowel functional groups and related microbiota symptoms throughout varying stages of life. The main hurdles involve making the diagnostic and screening services of gut microbiota assessment affordable, preliminary research, and system analysis.

Multiple companies are undertaking efforts to finally implement personalization, thereby fulfilling the mission of personalized medicine. Health in Code, Sutton, USA, employs next-generation sequencing (NGS) technology and the Microbiome Assessment Test to differentiate healthy versus ill populations and investigate treatment pathways related to gut microbiota. HumTech presents a patented solution encompassing both diagnostic and prebiotic–probiotic–symbiotic components. In turn, Singlera Genomics Inc. is developing a test suitable for predicting the risk of endometriosis and colorectal cancer (marker E002) in both men and women.

## **23. Technological Innovations in Microbiome Research**

Diverse human microbiomes and associated technologies have emerged in recent years, notwithstanding regulatory restrictions and ethical hurdles. Beyond pharmacological treatment, various other interventions such as faecal microbiota transplantation, prebiotics, synbiotics, phage therapies, dietary modifications, microbiome–drug interactions, bacteriotherapies and vaccination have been explored, but present limited and inconclusive results. The diversity, dynamics and role of microbes, including those in the gut, oral cavity, nasopharyngeal region, placenta, reproductive tracts and skin, in health and diseases have been explored in several studies. Importance of the human gut–microbiota axis and microbial antigens with reactive or protective epitopes in diseases and research directions for novel therapeutic and preventive strategies has been proposed.

Advances in technology, including sequencing techniques and computational algorithms, have intensified research efforts related to the human microbiome. Nevertheless, disease diagnosis, clinical translation and therapeutic intervention require consistent results and clinical validation. Identification of disease-related microbial species, markers/core microbiomes and microbial epitopes have been explored; however, there is scope to explore deeper relationships between agents or diseases and microbes. The development of newer algorithms to quantify, qualify and classify microbiomes and Human Microbiome Project (HMP) Data Portal for metagenomic shotgun sequencing analysis have been reported. Clinical applications and potential biomarkers identified using novel algorithms, including the Pattern of Attack model, have been elucidated—for instance, oral microbiome; construction of healthy human body-disease network; and the gut–skin axis. [25][26][27]

## **24. Collaboration Between Scientists and Clinicians**

The complex nature of human diseases and tissues governs the intricate interaction between scientists and physicians. The analysis of metabolite profiles is already an essential clinical tool for patients with inherited metabolic disorders, and interest in the gut-brain axis is fostering metabolite profiling within psychiatric research groups. The profiling of disease-associated alterations to the gut microbiota can provide an additional layer of information, with species-specific community structures defining the role of the microbiome in the development of distinct diseases. Yet, the results obtained by ecosystem-wide analyses of the gut microbiota have so far

not been directly translated to treatment, rarely extending beyond the use of probiotics, or the suggestion of specific diets.

Treatment options based on the microbiome are comprehensively discussed in sections Implications of the Human Microbiome for Forensics and 22. Advances in Microbiome Analysis for Clinical and Forensic Applications, either as a treatment aimed at re-establishing patient gut eubiosis or as a voracious source of novel natural compounds. A deeper appreciation of the impact and therapeutic potential of modulation via the gut microbiota is exemplified by the recent discovery of an anti-ileitis effect of antibiotic therapy, therefore disclosing a new therapeutic potential of antibiotics other than controlling bacterial infections. [28][29][30]

## 25. Global Perspectives on Microbiome Research

Despite the dominant role of the USA and European countries in microbiome research, the investigations extend worldwide and also take place in regions characterized by a desert climate, such as the United Arab Emirates (UAE), with an extremely hot, arid desert environment and high salt levels. These factors have an impact on the skin microbiome of inhabiting subjects. Despite the environmental influence, the microbiota composition of the UAE residents resembles that of other exposed body sites reported in Western and non-Western subjects. A significant correlation between age and microbiota diversity has been observed; specifically, younger subjects display a more diverse skin microbiota.

In Pakistan, the microbiome composition of oral cavity cancer and non-cancer subjects does not reflect the broad geographical location but reveals differences attributable to disease status. Given the high incidence of oral cancer in Pakistan, a higher diversity is found in the oral cavity cancer group, with patients exhibiting increased pOTUs (putative operational taxonomic units). By contrast, in the urinary tract of female patients with lower urinary tract symptoms (LUTSs) in Ireland, the diversity of the microbiota is lower than that of the controls. Although urinary tract infections (UTIs) are the etiological agents of LUTS in only about one half of individuals, exposure to antibiotics could contribute to the observed decrease in the diversity of affected subjects. [31][32][33]

## 26. Conclusion

Almost all physiological functions of human bodies are influenced by the microorganisms associated with them. Recent studies on human microbiome in the gut have shown its association with various diseases; the microbiome diversity is altered among the patients suffering from obesity, CVDs, diabetes, cancer, liver diseases, neurological diseases, respiratory diseases, and finally kidney disease. The presence of some bacteria in increased proportions is found to be the cause of dysbiosis which results in chronic inflammation. Human microbiome-targeted biotechnological interventions have shown promising results in alleviating the gut dysbiosis and therefore the associated disease. The use of probiotics has shown efficacy in enriching the good bacteria of the gut and removing toxins. Health benefits of food are nowadays well accepted and probiotics are the major biological additives in the food sector, which exhibit efficacy in the treatment of numerous human disorders.

Incorporation of elixirs helps to restore normal intestinal microbial homeostasis and thus the function of the intestine. Prebiotics and synbiotics are of special importance in the prevention and treatment of bowel cancer/cancers along with many other diseases. The underlying mechanisms include mitigation of oxidative stress, immune modulation, rebalancing of the immune function, and modulation of inflammatory markers in diabetic patients. Regular consumption of probiotic and synbiotic formulations helps to produce short-chain fatty acids which are involved in providing additional energy to the epithelial cells and in the prevention of cardiovascular disease (CVD) and have been shown to be active in the treatment of various allergic diseases including atopic dermatitis, allergic rhinitis, eczema, and elicitation phase of contact dermatitis.

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