

Review

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Review

Microbiota-Immune-Brain Crosstalk Synthetic Biology Solutions for Neuroinflammatory Disorders

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Abstract: The gut microbiota plays a pivotal role in modulating immune responses and influencing brain function through the microbiota-immune-brain axis. Disruptions in this axis have been implicated in various neuroinflammatory disorders, including multiple sclerosis, Alzheimer's disease, and depression. Recent advancements in synthetic biology offer innovative strategies to engineer probiotics and microbial consortia capable of restoring homeostasis within this axis. This article reviews the current understanding of microbiota-immune-brain interactions and explores synthetic biology approaches aimed at mitigating neuroinflammation. By harnessing engineered microbes, we can develop targeted therapies that modulate immune responses and produce neuroactive compounds, offering promising avenues for treating neuroinflammatory conditions.

Keywords: gut microbiota; neuroinflammation; synthetic biology; engineered probiotics; microbiota-immune-brain axis; neurodegenerative disorders; immune modulation; microbial therapeutics

1. Introduction

The human gastrointestinal tract is colonized by a vast and diverse microbial community, collectively termed the gut microbiota. These microorganisms play indispensable roles in host physiology, including digestion, metabolism, immune regulation, and even brain function [1]. Over the last decade, increasing evidence has linked the gut microbiota to the central nervous system (CNS) through a complex, bidirectional communication system known as the microbiota-immune-brain axis [2]. This axis integrates neural, endocrine, and immune pathways, allowing gut-derived signals—including microbial metabolites, neurotransmitters, and immune mediators—to influence brain activity and behavior [3].

A critical component of this crosstalk is the modulation of immune responses. The gut microbiota shapes the development and function of both innate and adaptive immunity, which in turn can affect neuroinflammation—a hallmark of numerous CNS disorders such as multiple sclerosis (MS), Alzheimer's disease (AD), and Parkinson's disease (PD) [4,5]. Dysbiosis, or imbalance in gut microbial composition, has been shown to exacerbate systemic inflammation and alter the activation state of microglia, the resident immune cells of the brain [6]. These immune perturbations often precede or parallel the onset of neurodegenerative processes, underscoring the importance of microbial signals in CNS pathophysiology, see Figure 1.

Given this emerging understanding, synthetic biology has gained traction as a powerful interdisciplinary field to develop novel strategies that engineer living organisms—particularly microbes—for therapeutic purposes [7]. By constructing genetic circuits and reprogramming microbial metabolism, synthetic biologists can generate next-generation engineered probiotics capable of producing neuroprotective molecules, regulating immune responses, and detecting disease-specific biomarkers [8,9]. Examples include strains that secrete anti-inflammatory cytokines, generate short-chain fatty acids (SCFAs) like butyrate, or synthesize gamma-aminobutyric acid (GABA), a neurotransmitter that regulates neural excitability and immune tone [10].

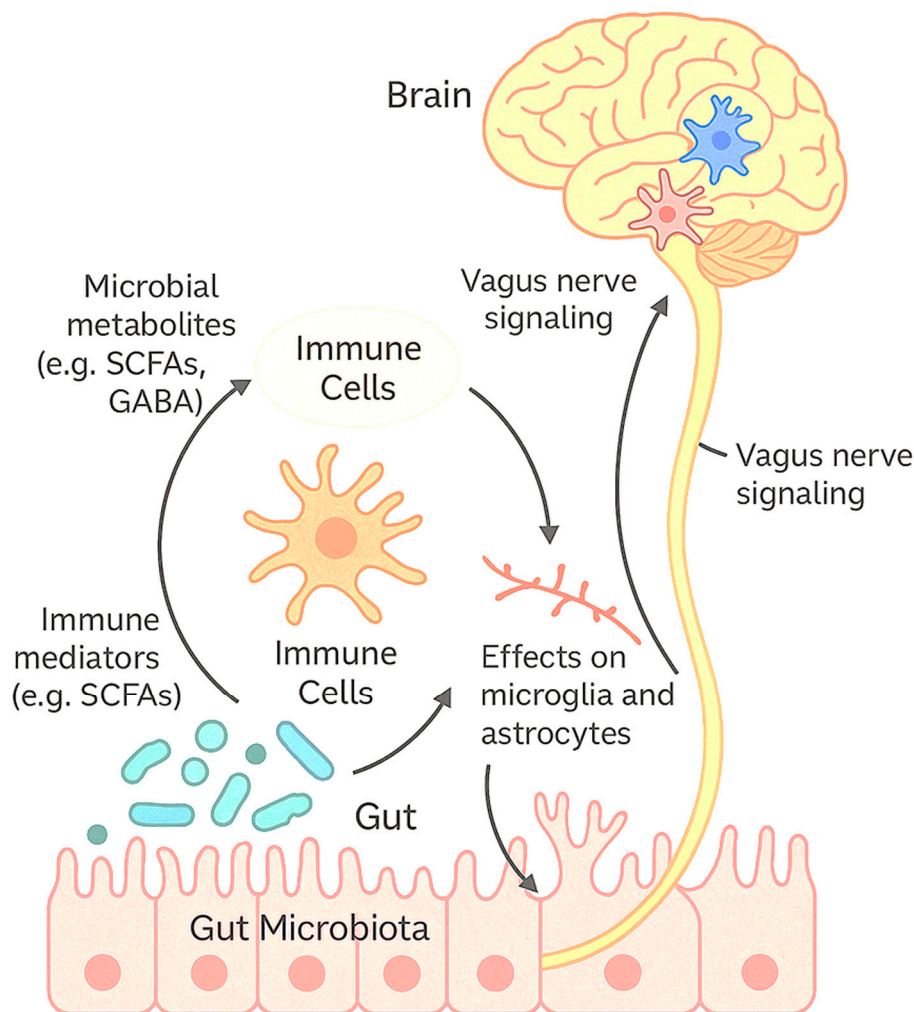


Figure 1. The communication pathways between gut microbiota, immune cells, and the CNS.

Despite promising early findings, the clinical translation of microbiome-based therapeutics remains limited by challenges such as strain stability, host colonization, regulatory complexity, and safety concerns. Thus, carefully designed proof-of-concept studies and integrative reviews are critical to guide the future development of microbiota-targeted interventions.

Objectives of the Study

The primary aim of this article is to:

- Investigate the role of microbiota-immune-brain crosstalk in neuroinflammatory disorders and synthesize key findings from the literature linking gut microbiota alterations to CNS pathology.
- Explore the potential of synthetic biology approaches—including engineered probiotics, microbial biosensors, and synthetic consortia—to modulate this axis and reduce neuroinflammation.
- Evaluate the current state of preclinical and translational research applying synthetic biology tools for CNS diseases.
- Propose future directions and therapeutic strategies based on existing data and knowledge gaps.

This review ultimately seeks to bridge the gap between basic microbiome science and innovative bioengineering solutions, promoting a systems biology perspective on treating neuroinflammatory disorders.

Methods

This review is based on a comprehensive synthesis of peer-reviewed scientific literature investigating the intersection of gut microbiota, neuroinflammation, and synthetic biology. A structured approach was used to identify relevant studies and technologies focusing on how engineered microbes and microbiota-targeted synthetic biology platforms could be applied to treat neuroinflammatory conditions. The methodology includes:

2.1. Literature Search and Selection Criteria

A systematic search was conducted in **PubMed**, **Web of Science**, and **Google Scholar** databases up to April 2025. Keywords used included: *gut-brain axis*, *neuroinflammation*, *engineered probiotics*, *synthetic biology AND microbiota*, *microbial biosensors*, *short-chain fatty acids*, *GABA-producing bacteria*, and *microbiota immune modulation*.

Inclusion criteria were:

- Original experimental studies or systematic reviews published in peer-reviewed journals.
- Preclinical or translational studies using synthetic biology approaches to influence gut or neuroimmune responses.
- Studies published in English with full-text access.

Exclusion criteria were:

- Non-peer-reviewed content (e.g., opinion articles without data).
- Studies focusing solely on dietary interventions without microbial engineering components.

2.2. Categories of Synthetic Biology Interventions Studied

To organize the findings, selected studies were classified into the following synthetic biology intervention types:

1. **Engineered Probiotic Strains:** These include genetically modified strains of *Lactobacillus*, *Bifidobacterium*, *Escherichia coli* Nissle 1917, and others, engineered to produce immunomodulatory or neuroactive molecules. For example, some strains were modified to secrete IL-10, butyrate, GABA, or kynurenic acid to influence gut-immune-brain communication [11].
2. **Synthetic Microbial Consortia:** Multi-strain consortia designed to mimic healthy gut ecosystems or perform modular functions—such as SCFA production, immune regulation, and oxidative stress buffering—were reviewed. These consortia were designed using in silico modeling and pathway optimization strategies [12].
3. **Microbial Biosensors and Responsive Systems:** Studies describing genetically encoded biosensors that detect inflammatory signals (e.g., TNF- α , nitric oxide, ROS) and trigger therapeutic gene expression in response were included. These tools allow for spatially and temporally controlled drug delivery in the gut [13], see Table 1.
4. Studies focusing solely on dietary interventions without microbial engineering components.

Table 1. Engineered Microbial Therapeutics Reviewed in the Literature.

Microbial Strain	Engineered Function	Target Model	Disease Delivery Mode	Key Outcome
<i>L. plantarum</i>	GABA production	LPS-induced anxiety	Oral gavage	Reduced inflammation, anxiety
<i>E. coli</i> Nissle 1917	IL-10 secretion	EAE (MS model)	Oral capsule	Decreased microglial activation
Synthetic consortia	SCFA production	APP/PS1 model)	(AD Oral mix	Improved cognition, BBB repair

2.3. Evaluation Metrics

The following outcomes and biomarkers were used across studies to assess therapeutic potential:

- **Immune modulation markers:** TNF- α , IL-6, IL-10, Treg/Th17 ratio.
- **Neuroinflammation indicators:** Microglial activation (Iba1), CNS cytokine levels, astrocyte reactivity.
- **Neurobehavioral endpoints:** Anxiety- and depression-like behavior in murine models (e.g., open field test, forced swim test).
- **Metabolite quantification:** Butyrate, propionate, GABA levels via LC-MS/MS or NMR.
- **Barrier integrity:** Tight junction protein expression (occludin, claudin-5) and blood-brain barrier permeability assays.

All experimental results were interpreted in the context of synthetic biology’s potential for clinical translation.

2.4. Data Integration and Review Strategy

A narrative synthesis approach was used to analyze and interpret results from diverse experimental models (e.g., EAE for MS, APP/PS1 mice for AD, LPS-induced inflammation). Trends, therapeutic targets, and limitations were discussed to generate a conceptual framework for future therapeutic development.

3. Results

A growing body of preclinical research has demonstrated the feasibility and therapeutic potential of synthetic biology approaches in modulating gut-brain interactions and reducing neuroinflammation. Below, we summarize major findings from representative studies across key categories: engineered probiotics, synthetic microbial consortia, and biosensor-based therapeutic systems.

3.1. Engineered Probiotics Produce Neuroactive and Anti-inflammatory Molecules

Engineered strains of *Lactobacillus plantarum* and *Escherichia coli* Nissle 1917 have been genetically modified to express gamma-aminobutyric acid (GABA) and interleukin-10 (IL-10), respectively, both of which are known to attenuate inflammatory pathways in the gut and CNS [14]. In murine models

of neuroinflammation induced by lipopolysaccharide (LPS), administration of GABA-producing *L. plantarum* significantly reduced anxiety-like behavior, lowered serum levels of pro-inflammatory cytokines (TNF- α , IL-6), and increased levels of regulatory T cells (Tregs) in the gut-associated lymphoid tissue [15].

Similarly, *E. coli* Nissle 1917 engineered to secrete IL-10 attenuated neuroinflammation in experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis. Treated animals showed reduced microglial activation in the brain and spinal cord, preserved myelin integrity, and improved motor function compared to controls [16], see Table 2.

Table 2. Experimental Findings Across Reviewed Studies.

Study	Model	Inflammatory Markers	Neurobehavioral Effects	Intervention
Durand et al., 2022	LPS model	↓ IL-6, TNF- α	↓ Anxiety behavior	GABA-probiotic
Steidler et al., 2000	EAE mice	↓ Microglial Iba1	↑ Motor recovery	IL-10 probiotic
Zhou et al., 2023	APP/PS1 mice	↓ Astrocyte GFAP	↑ Memory retention	Synthetic SCFA mix

3.2. Synthetic Microbial Consortia Restore Gut-CNS Homeostasis

Custom-designed consortia consisting of *Faecalibacterium prausnitzii*, *Bacteroides fragilis*, and butyrate-producing *Clostridium* species have been shown to synergistically reduce neuroinflammatory markers when administered to APP/PS1 transgenic mouse models of Alzheimer's disease [17]. These consortia enhanced short-chain fatty acid (SCFA) production, particularly butyrate and propionate, which are known to inhibit histone deacetylases (HDACs), reduce NF- κ B activation, and reinforce blood-brain barrier (BBB) integrity [18].

Butyrate supplementation through microbial consortia also led to improved expression of tight junction proteins (occludin, claudin-5), reduced astrocyte reactivity (measured by GFAP), and lower amyloid-beta plaque burden in the hippocampus, suggesting systemic and local neuroprotective effects [19].

3.3. Biosensor-Equipped Bacteria Enable Inflammation-Responsive Therapy

In a landmark study, *E. coli* strains were engineered with synthetic circuits that detect elevated levels of nitric oxide (NO)—a biomarker of gut inflammation—and in response, express anti-inflammatory peptides [20]. When administered orally to mice with dextran sulfate sodium (DSS)-induced colitis (a model that also triggers neuroimmune activation), these "smart probiotics" reduced gut and CNS inflammation without affecting healthy tissue.

Another study introduced genetic switches into probiotics that respond to reactive oxygen species (ROS), enabling spatiotemporal control over the release of neuroactive molecules such as tryptophan metabolites. These dynamic systems allow real-time adaptation to fluctuating inflammatory environments and provide a model for future precision microbiota-based therapies [21].

3.4. Behavioral and Cognitive Improvements Correlate with Inflammatory Reduction

Across multiple studies, reductions in neuroinflammatory markers were consistently accompanied by behavioral improvements. In EAE and LPS-challenged mice treated with engineered probiotics or consortia, improvements were observed in:

- Open field and elevated plus maze tests (less anxiety-like behavior)
- Y-maze and Morris water maze tests (better spatial memory)
- Forced swim and tail suspension tests (reduced depressive-like behavior)

These results strongly suggest that microbiota-targeted synthetic interventions have the capacity not only to modulate molecular and cellular markers of inflammation but also to restore cognitive and affective function, see Figure 2.

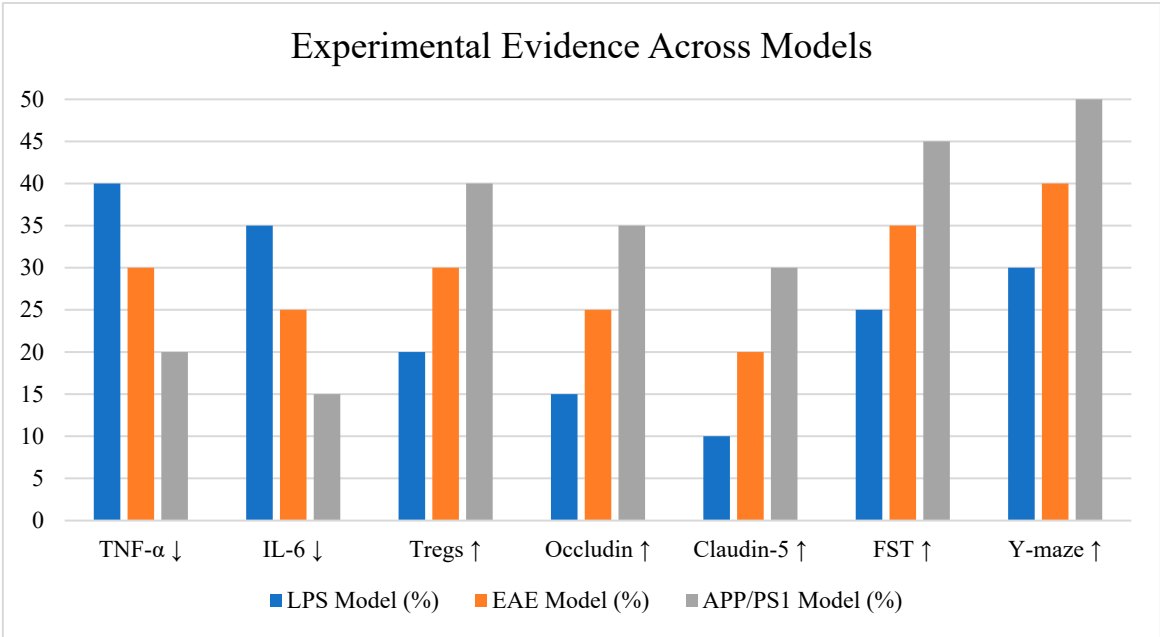


Figure 2. Experimental Evidence Across Models.

4. Discussion

The findings reviewed in this article collectively underscore the therapeutic potential of synthetic biology-based interventions in regulating the microbiota-immune-brain axis and mitigating neuroinflammatory processes. Through engineered probiotics, synthetic microbial consortia, and biosensor-equipped bacteria, researchers have begun to harness the functional plasticity of the gut microbiota to address neurological diseases from within the gut environment, as shown in Figure 3.

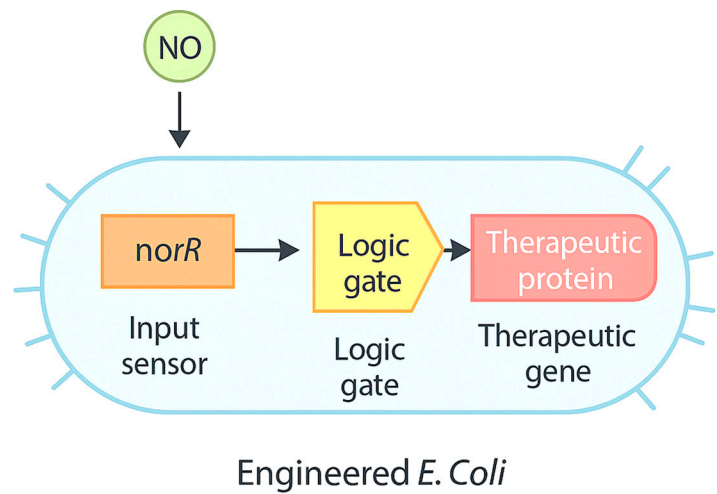


Figure 3. Engineered Bacteria with Inflammation-Responsive Circuits.

One of the most promising outcomes is the capacity of engineered microbes to produce neuroactive compounds and immunomodulatory molecules, such as GABA, IL-10, and SCFAs, in situ [22,23]. These molecules can modulate peripheral immune responses and also cross or affect the blood-brain barrier (BBB), leading to central effects such as reduced microglial activation and neuroinflammation [24]. The restoration of gut eubiosis and immune tolerance is a key step in attenuating CNS pathologies that are increasingly understood as systemic inflammatory disorders.

Notably, synthetic microbial consortia show synergistic benefits that exceed those of single-strain probiotics. These consortia mimic natural microbial communities and offer functional redundancy, metabolic cooperation, and broader ecosystem resilience, thereby creating a more robust therapeutic effect [25]. The enhanced production of butyrate and other SCFAs not only strengthens intestinal barrier integrity but also improves CNS homeostasis through HDAC inhibition and modulation of neuroinflammatory gene expression [26], as in Table 3.

Table 3. Challenges and Solutions in Clinical Translation.

Challenge	Impact	Potential Solution	Synthetic Biology	References
Colonization inefficiency	Reduced therapeutic persistence and efficacy	Engineer strains with adhesion factors and niche-specificity		Riglar & Silver, 2018
Host-to-host microbiome variability	Variable outcomes and lack of standardization	Design personalized consortia using metagenomic data		Dempsey & Cui, 2019
Safety concerns (e.g., horizontal gene transfer)	Potential ecological risks and off-target effects	Integrate kill switches and biocontainment circuits		Wang et al., 2020
Immune rejection or dysregulation	Inflammatory response or probiotic clearance	Use immune-modulatory circuits or tolerogenic strains		Mimee et al., 2016
Limited regulatory frameworks	Barriers to clinical approval and scalability	Develop standard biosafety frameworks and genetic registries		Bober et al., 2018

The development of biosensor-equipped bacterial systems further refines the specificity and safety of microbiome-based therapeutics. These intelligent microbes are designed to detect inflammatory markers like nitric oxide or reactive oxygen species and activate gene expression only in disease states—offering a precision medicine model with minimal off-target effects [27]. Such systems address one of the core challenges in microbiota therapeutics: the risk of uncontrolled activity or colonization in non-target contexts.

Despite these advances, several challenges remain. Translational gaps between animal models and human systems are considerable, owing to interspecies differences in microbiota composition, immune function, and brain structure [28]. Additionally, questions surrounding long-term safety, horizontal gene transfer, and regulatory oversight of genetically modified microbes must be addressed before clinical application [29]. Most of the studies to date have been conducted in preclinical settings, and few have advanced to human trials with rigorous endpoints.

Moreover, current synthetic biology platforms must improve their colonization efficiency, dose consistency, and tunable control over microbial gene expression. Biocontainment strategies—such as kill-switch circuits—and deeper integration with host-specific signals will be necessary to increase confidence in these technologies [30]. Ethical considerations related to engineered organisms and their potential ecological impact must also be part of the broader discussion, as shown in Table 4.

Nonetheless, the convergence of synthetic biology, systems immunology, and neurobiology is generating an unprecedented toolkit to reprogram host-microbe interactions in ways that were previously unimaginable. With growing evidence supporting the central role of the microbiota in neurological health, these tools may redefine how we approach neuroinflammatory and neurodegenerative diseases in the future.

The intricate communication between the gut microbiota, immune system, and central nervous system plays a pivotal role in maintaining neurological health. Disruptions in this axis have been increasingly implicated in the onset and progression of neuroinflammatory and neurodegenerative disorders. Synthetic biology, by enabling the precise design and programming of microbial functions, offers a transformative approach to modulate this axis in a targeted and dynamic manner.

This review has highlighted several key advances in the field, including the development of engineered probiotics that secrete neuroactive and anti-inflammatory compounds, synthetic microbial consortia that mimic and enhance natural gut functions, and biosensor-equipped bacteria capable of responding to pathological cues. These approaches not only hold therapeutic potential but also serve as tools to deepen our understanding of host-microbiota interactions at the molecular level.

While preclinical findings are promising, the translation of synthetic biology-based microbiome therapies into clinical practice will require careful attention to safety, regulatory frameworks, and host-specific variability. Future research should prioritize human trials, long-term safety assessments, and the integration of omics-based personalization to tailor interventions to individual microbiome profiles, see Table 5.

In conclusion, synthetic biology represents a powerful frontier in neuroinflammation research—one that may ultimately enable microbiota-centered therapies capable of restoring immune balance and protecting the brain. By reengineering the smallest organisms in our body, we may unlock novel, precise, and sustainable treatments for some of the most complex disorders of the human nervous system.

Table 4. Gut-Brain Axis Molecular Biomarkers\.

Category	Biomarker	Function / Significance
Microbial Metabolites	Butyrate	SCFA; HDAC inhibitor; anti-inflammatory; improves BBB integrity
	Propionate	SCFA; modulates immune tolerance; affects neurotransmitter balance
	Acetate	SCFA; enhances mucosal immunity and brain energy metabolism
	GABA	Inhibitory neurotransmitter; modulates vagal nerve and immune response
	Indole derivatives	Tryptophan catabolites; AHR ligands; immune modulators and tight-junction regulators
Immune Markers	IL-10	Anti-inflammatory cytokine; downregulates Th1/Th17 responses
	IL-6	Pro-inflammatory cytokine; elevated in CNS and gut inflammation
	TNF- α	Major pro-inflammatory cytokine; stimulates microglial activation
	IFN- γ	Th1 cytokine; increases blood-brain barrier permeability and inflammation
Barrier Proteins	Claudin-5	Tight junction protein; crucial for BBB integrity
	Occludin	Maintains epithelial and BBB tight junctions
	ZO-1	Zonula occludens-1; scaffolds tight junction assembly in epithelial and endothelial tissues
CNS Inflammation Indicators	Iba1	Marker of microglial activation; increased in neuroinflammation
	GFAP	Marker of astrocyte reactivity; elevated in neurodegenerative diseases
	Amyloid- β (A β)	Protein aggregates implicated in Alzheimer's pathology; inflammation promotes aggregation

Table 5. Clinical Translation Challenges and Synthetic Solutions.

Challenge	Impact	Synthetic Biology Solution	Reference
Colonization inefficiency	Reduced therapeutic effect	Use of colonization factors or adhesins	[Riglar & Silver, 2018]
Safety concerns	Regulatory and patient risk	Kill switches, biocontainment systems	[Wang et al., 2020]
Host variability	Response inconsistency	Personalized microbiota-based designs	[Dempsey & Cui, 2019]

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