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Genetically Engineered Probiotics: Design, Therapeutics, and Clinical Translation

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ABSTRACT

Genetically engineered probiotics aim to address transient colonization and the intra- and inter-subject variability that limit conventional probiotics. These strains utilize CRISPR/Cas editing, programmable gene circuits, and biosensors in chassis such as *E. coli* Nissle 1917 and *L. lactis*. This narrative review summarizes the current engineering toolkits and standards (e.g., SEVA), chassis selection criteria, biocontainment strategies, and translational requirements under CMC/GMP frameworks and discusses regulatory considerations for clinical translation. Representative examples include IL-10-secreting *L. lactis* and phenylalanine-metabolizing strains for PKU (SYNB1618/SYNB1934), which illustrate pharmacodynamic target engagement and short-term preclinical safety. We outline clinical advancements in predefined pharmacodynamics, durability of function, monitoring shedding and HGT, and genomic-microbiome-informed patient stratification. Systems modeling approaches (GEM/ABM) are discussed as tools to guide rational design. GEPs offer programmable "sense-and-respond" therapeutics, with successful clinical adoption depending on durable efficacy, long-term safety, and clearly defined regulatory pathways.
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INTRODUCTION

The global probiotics field has expanded substantially in recent years[1]. Concurrently, advances in microbiome science have highlighted how host-microbe interactions shape digestion, immunity, metabolism, and even neurobiology[2-4]. However, conventional probiotics, mainly bacteria such as *Lactobacillus* and *Bifidobacterium* and the yeast *Saccharomyces*, show inconsistent clinical efficacy. Variability in gut microbiome composition, immune tone, diet, and host genetics contribute to differences in colonization and therapeutic outcomes[5].

GEPs, a class of engineered live biotherapeutic products, are designed to address these limitations by integrating tractable microbial chassis with programmable genetic circuits and biosensing capabilities. Using CRISPR/Cas tools, including CRISPRi/a, modular gene circuits, and biosensors, GEPs can detect host or environmental cues and actuate context-dependent functions in situ[6-8].

This narrative review has three objectives. The first is to define design constraints at the host-microbiome

List of abbreviations
ABM: Agent-Based Model; **AI:** artificial intelligence; **CMC**: Chemistry, Manufacturing, and Controls; **CRISPR**: Clustered Regularly Interspaced Short Palindromic Repeats; **CRISPRi:** CRISPR interference; ***E. coli:*** *Escherichia coli*; **GEM**: Genome-Scale Metabolic Model; **GEP**: genetically engineered probiotics; **GMO**: genetically modified organism; **GMP**: Good Manufacturing Practice; **GWAS:** genome-wide association studies; **HGT:** horizontal gene transfer; **IBD:** inflammatory bowel disease; **IL:** interleukin; ***L. lactis*:** *Lactococcus lactis*; **PKU:** phenylketonuria; **RSV**: Respiratory Syncytial Virus; **SEVA**: Standard European Vector Architecture

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interface. The second is to synthesize core engineering toolchains, standardization, CRISPR/Cas (CRISPRi/a), gene circuits, biosensors, biocontainment, and chassis selection, within a unified framework. The third is to survey medical and industrial applications, including anti-inflammatory, anticancer, and antiviral indications, as well as supplements, natural products, and functional foods. Our review further delineates translational requirements, encompassing biosafety, regulatory affairs, ethical considerations, and GMP guidelines. Using preclinical and early human data (e.g., IL-10-producing *L. lactis*; SYNB1618/SYNB1934), it evaluates which toolchains and chassis most reliably enable controllable colonization, durable function, and on-target in vivo activity. Ultimately, it summarizes safety and regulatory criteria, strategies for biocontainment and mitigation of HGT, and product quality/traceability considerations pertinent to late-stage trials and real-world deployment.

DATA SOURCES, SEARCH STRATEGY, AND STUDY SELECTION

We conducted a structured narrative review of PubMed/MEDLINE, Web of Science, and Scopus from July 10 to August 1, 2025. Searches combined controlled vocabulary and free-text terms, including engineered probiotics/live biotherapeutics, CRISPR/ CRISPRi/a, gene circuits, biosensors, kill switches, and common chassis (e.g., *E. coli* Nissle 1917, *L. lactis*). Eligibility criteria focused on engineered-strain studies reporting preclinical or human outcomes. Reports addressing translational enablers, such as GMP/CMC, biosafety/biocontainment, and regulation/ethics, were also included. Non-engineered probiotics were considered only as comparators. Study selection involved title/abstract screening, targeted full-text review, and citation chasing. Key variables were charted and narratively synthesized using predefined thematic categories.

HOST GENETICS AND MICROBIOME INTERACTIONS

The gut microbiome is shaped not only by environmental exposures (e.g., diet or antibiotics) but also by host genetics. Twin studies and large GWAS show that several bacterial taxa are heritable and influenced by specific genetic variants[8,9]. A well-documented example is FUT2, which encodes an enzyme that secretes fucosylated glycans into the gut lumen. Individuals with nonfunctional FUT2 ("non-secretors") display distinct microbiota profiles, notably reduced *Bifidobacterium* abundance[10]. Likewise, polymorphisms affecting lactose metabolism are associated with differences in lactose-fermenting bacteria, including *Bifidobacterium* and *Lactococcus*[11]. Understanding the host-microbiome-genome axis enables the rational design of GEPs tailored to genetic background. For example, strains can be programmed to supply enzymes or metabolites that compensate for deficits in mucin secretion, immune regulation, or bile-acid metabolism[12,13]. This approach supports the vision of precision microbiome therapeutics, in which microbial interventions are aligned with host genomic profiles to maximize clinical benefit and minimize variability[2,7].

ENGINEERING PROBIOTICS: TOOLS AND STRATEGIES

Synthetic biology enables the design and control of living microorganisms, including probiotics, for both therapeutic and diagnostic purposes. Using modern molecular techniques, genetically engineered probiotics can be designed to respond to host and environmental signals, enabling programmable sensing, activation, and targeted, context-specific delivery.

CRISPR/Cas systems

The CRISPR-Cas9 system has become a central tool in microbial genome editing, enabling site-specific insertion, deletion, or modification of genes in probiotic strains. It has been used to introduce genetic payloads, such as therapeutic genes or metabolic pathways, into safe bacterial chassis, including *Lactobacillus reuteri*, *E. coli* Nissle 1917, and *Bacteroides thetaiotaomicron*[7,14]. Recent advances include CRISPRi and CRISPRa systems for transcriptional repression or activation, which allow for temporal control of gene expression without altering genomic sequences[15] (Fig. 1).

Synthetic gene circuits

Gene circuits, composed of promoters, repressors, and feedback loops, can be designed to produce complex dynamic behaviors such as logic gating, feedback inhibition, or pulse-like responses. These circuits enable engineered probiotics to make decisions in situ; for example, to secrete an anti-inflammatory cytokine only in the presence of a disease-associated biomarker[9]. These modular systems provide multi-layered control by combining biosensing with therapeutic molecule delivery.

Biosensors and environmental responsiveness

Engineered biosensors can detect host-derived signals (e.g., nitric oxide levels and inflammatory markers) as well as gut luminal cues (e.g., pH, oxygen availability, and bile acids). These signals are translated into specific gene expression responses. For instance, *E. coli* strains have been engineered to detect gastrointestinal bleeding

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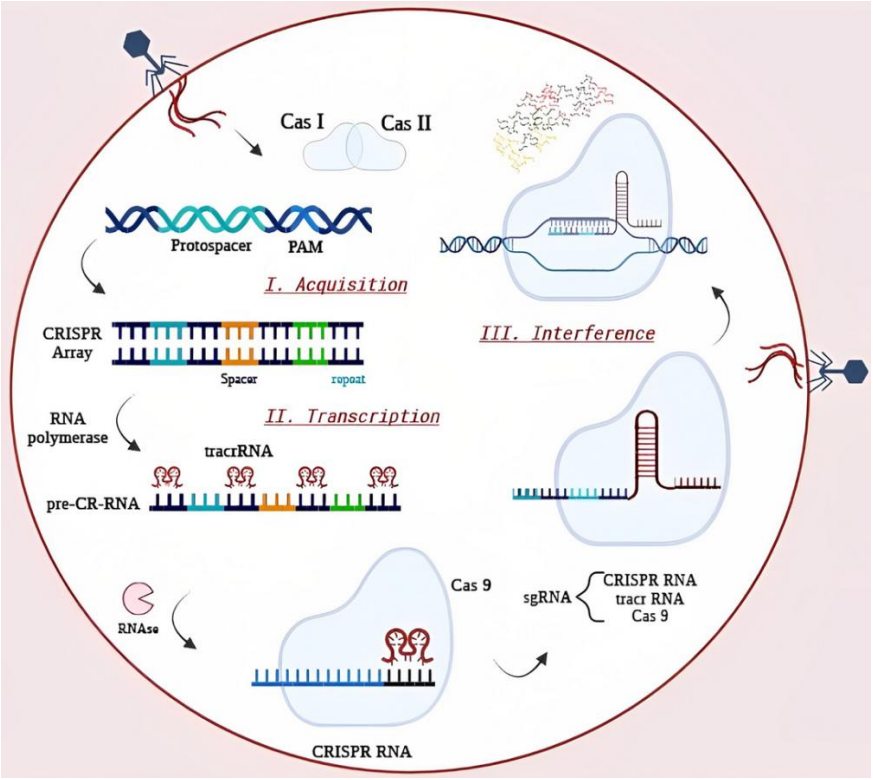

Fig. 1. Overview of the CRISPR-Cas system and its application in engineered probiotics. Acquisition: Cas1-–Cas2 capture invading DNA fragments (protospacers) next to a PAM and insert them into the CRISPR array. Transcription/processing: the array is transcribed into pre-crRNA, which associates with tracrRNA and is processed into mature crRNA. Interference: crRNA/sgRNA guides an effector nuclease (e.g., Cas9) to complementary target DNA for cleavage. This three-stage process underlies CRISPRi/a and enables precise genome control in probiotic chassis such as *E. coli* Nissle 1917 and *L. lactis*. Figure reproduced from reference 50 under the Creative Commons Attribution–NonCommercial–NoDerivatives 4.0 International License (CC BY-NC-ND 4.0)[16].

and express luciferase as a readout[17]. Such biosensors enable GEPs to localize their activity spatially and temporally within the host, potentially reducing systemic side effects.

Kill switches and containment systems

To mitigate biosafety concerns, synthetic kill-switch mechanisms have been designed to limit the survival and replication of engineered strains outside the host or beyond the target niche. These systems employ toxin–antitoxin modules or quorum-sensing genetic circuits to trigger cell death under specific conditions conditions. Such safeguards are important for the safe and effective clinical deployment of engineered probiotics[18].

Modular toolkits and standardization

The development of standardized parts and modular toolkits, such as SEVA (a system for plasmid vector assembly) and CIDAR MoClo (a modular cloning toolkit for genetic circuit construction), has greatly accelerated the design-build-test cycle in synthetic biology. These platforms enable rapid prototyping and high-throughput screening of candidate designs in probiotic strains[19]. Collectively, these technologies allow researchers to create “smart” probiotics that can sense, compute, and act within the human body in highly controlled ways. The convergence of synthetic biology, computational modeling, and systems microbiology is paving the way for next-generation microbiome-based therapeutics.

MEDICAL AND INDUSTRIAL APPLICATIONS

GEPs expand possibilities in clinical medicine and functional foods. Their programmable nature enables precise, localized, and responsive therapeutic actions that are not easily achieved with conventional drugs or probiotics. Herein, we discuss GEP applications in IBD, metabolic and genetic disorders, cancer immunotherapy, and functional foods.

IBD and autoimmunity

Chronic inflammatory conditions of the gastrointestinal system, such as Crohn’s disease and ulcerative colitis, are characterized by immune dysregulation and disruption of the mucosal barrier.

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Several GEPs have been engineered to secrete anti-inflammatory cytokines (e.g., IL-10) or neutralize inflammatory mediators, such as TNF-α, directly at the site of inflammation[12]. For example, engineered *L. lactis* strains producing IL-10 have demonstrated efficacy in murine models of colitis and have progressed to early-phase clinical trials[20].

Metabolic disorders

GEPs are being developed to assist in the management of metabolic disorders such as type 2 diabetes, obesity, and hypercholesterolemia. These engineered strains target bile acid pathways, increase glucagon-like peptide 1 (secretion, and regulate short-chain fatty acid synthesis, hereby improving insulin sensitivity and supporting energy homeostasis [21,22].

Inborn errors of metabolism: PKU

One of the most advanced clinical applications of GEPs targets PKU, a rare genetic disorder characterized by the toxic accumulation of phenylalanine. Synlogic Inc. (Massachusetts, USA) has developed an engineered *E. coli* Nissle strain, SYNB1618, which lowers systemic and gastrointestinal phenylalanine levels through the overexpression of degrading enzymes[8]. This therapeutic candidate has advanced through phase I/II clinical trials, representing a milestone in microbiome-based medicine.

Cancer immunotherapy

Emerging research has suggested that GEPs can serve as vectors for cancer immunotherapy, either by delivering tumor antigens, modulating immune checkpoints, or producing immunostimulatory molecules such as IL-12 within the tumor microenvironment.

Nutraceuticals and functional foods

GEPs are being incorporated into functional foods and nutraceuticals for daily health support. These probiotics include strains engineered to enhance vitamin biosynthesis (e.g., B12 and folate), produce prebiotics or antioxidants, and modulate gut-brain axis signaling to support mood and cognition[23]. Such applications are poised to transform the food industry toward evidence-based and precision nutrition.

ANTIVIRAL APPLICATIONS OF GEPS

Virology has long sought new strategies to fight viral infections, especially in the face of emerging pathogens, antiviral resistance, and the limitations of standard vaccines and therapies. Recently, a promising approach has merged synthetic biology and microbiome science using GEPs as antiviral agents. These modified bacteria can selectively suppress viral activity, modulate host immune responses, mucosal protection in the gut and respiratory tract, common portals of viral entry, and support microbiome stability. In addition to direct antiviral activity, GEPs help restore microbial balance, aiding recovery[24,25]. Several representative applications of GEPs in virology are depicted in Figure 2.

Gastrointestinal viruses

Rotavirus and norovirus are the leading causes of viral gastroenteritis. GEPs that produce virus-neutralizing proteins or present decoy antigens can reduce both infection severity and transmission. Engineered *L. lactis* has been reported to reduce rotavirus shedding by more than 90% in mouse models[26,27]. Oral therapeutic formulations harness the gut immune system to elicit systemic and mucosal immune responses, resulting in robust and persistent immunity[24].

Respiratory viruses

Intranasal or orally administered GEPs have the potential for protection against influenza, RSV, or even SARS-CoV-2. Strains engineered to produce nanobodies or ACE2 decoys are under evaluation for their ability to block viral entry at the respiratory mucosa. Researchers have also explored the expression of viral proteins, such as influenza hemagglutinin or rotavirus VP6, on the surface of *Lactobacillus* species to stimulate mucosal and systemic immunity[24].

HIV prevention

Topical or oral GEPs expressing HIV entry inhibitors (e.g., cyanovirin-N or CD4 mimics) are being developed as microbicides to prevent sexual transmission. Lactobacilli have been investigated as mucosal vaccine vectors to enhance immune responses at typical mucosal sites of infection. Several studies have investigated engineered lactobacilli that express HIV antigens as a way to target the virus at its main entry site, the mucosa. In animal models, oral administration of these recombinant strains, expressing HIV proteins such as MPE and Gag, and in some cases combined with adjuvants like IL-1β or Salmonella flagellin C, has been shown to strengthen both mucosal IgA and systemic serum IgG immune responses against HIV. These in vitro studies have further shown evidence of T cell recruitment using *L. plantarum* strains expressing a CCL3/HIV Gag fusion protein. However, no challenge studies in non-human primates or humans have been performed to determine the efficacy of the immune response[26].

Chronic viral infections

For persistent viral infections, engineered probiotics deliver CRISPR components or immunomodulators.

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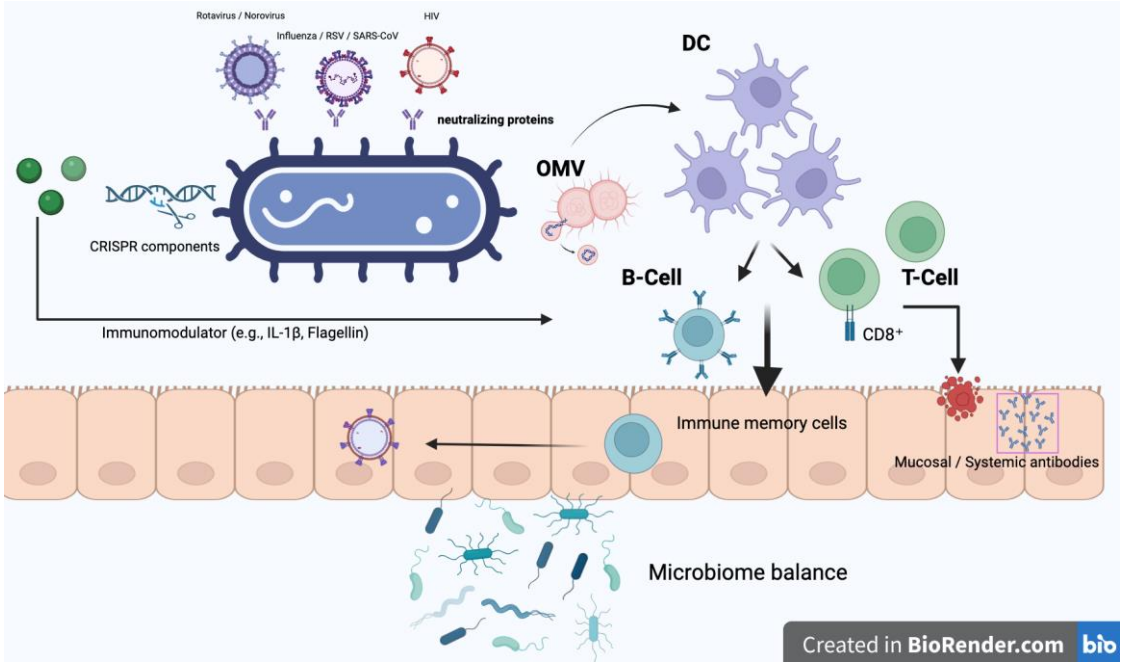

Fig. 2. Genetically engineered probiotics as antiviral agents. Engineered probiotic bacteria combat viral infections through multiple mechanisms. Surface-displayed neutralizing proteins (nanobodies, ACE2 decoys, and viral decoy antigens) block the entry of gastrointestinal viruses (rotavirus and norovirus), respiratory viruses (influenza, RSV, and SARS-CoV-2), and HIV. Outer membrane vesicles (OMVs) carrying viral antigens are released and taken up by dendritic cells (DCs), leading to the activation of B and T lymphocytes. This immune response induces mucosal (IgA) and systemic (IgG) antibodies, long-lived immune memory cells, and $CD8^+$ cytotoxic T cells capable of eliminating infected epithelial cells. For chronic infections, GEPs can deliver CRISPR components or immunomodulators (e.g., IL-1β and flagellin) to enhance local antiviral immunity. Beyond direct antiviral action, engineered probiotics also contribute to restoring microbiome balance, thereby supporting host recovery and resilience.

This approach enables localized, long-term treatment and reduces systemic side effects[28]. Building on this foundation, the therapeutic use of engineered probiotics and bacteria has evolved into a promising field, particularly in immunotherapy. Probiotics have demonstrated remarkable potential to reduce the risk and severity of various viral respiratory tract infections, as well as prevent bacterial and viral infections, including sepsis and gastroenteritis[24].

REGULATORY AFFAIRS, BIOSAFETY, AND ETHICAL CONCERNS

GEPs are subject to stringent regulatory oversight as they fall under the broader category of GMOs. Their application in human health raises complex questions about their safety, long-term stability, and potential ecological effects. Regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require comprehensive risk assessments, including studies on HGT, unintended host interactions, and environmental containment strategies[29,30]. However, biosafety remains a major concern, particularly regarding the persistence of engineered strains in the human gut, potential gene flow to pathogenic bacteria, and disruption of native gut microbiota. To address these risks, researchers have developed containment strategies such as kill switches, auxotrophic dependencies, and environmental sensor circuits that trigger self-destruction or deactivation under non-permissive conditions[18,31]. Furthermore, the use of genomically stable chassis and removal of mobile genetic elements reduces the risk of unintended HGT[32]. The clinical deployment of live engineered organisms in humans raises important ethical considerations, including informed consent, traceability, and long-term surveillance. Persistent colonization or unanticipated immune responses necessitate careful monitoring and transparency. Frameworks for post-market surveillance, traceable genetic signatures, and adaptive regulatory pathways are being explored to foster public trust and ensure safe implementation. Public perception also plays a pivotal role. Mistrust of GMOs, especially in food and health contexts, underscores the need for proactive risk communication, transparent labeling, and participatory decision-making[33,34]. Overall, the integration of GEPs into medicine and industry demands a new paradigm of biosafety and bioethics. This paradigm must account for the dynamic and

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programmable nature of these living therapeutics. As synthetic biology advances, regulatory and ethical frameworks must evolve in parallel to ensure responsible and equitable application.

SYSTEMS BIOLOGY AND COMPUTATIONAL MODELING IN GEP DESIGN

The development of GEPs increasingly relies on systems biology and computational modeling to guide rational strain design, predict host-microbiome interactions, and optimize therapeutic efficacy. Unlike traditional trial-and-error approaches, systems biology uses multi-omics data, such as genomics, transcriptomics, proteomics, and metabolomics, to build quantitative models of microbial behavior in complex ecosystems, such as the human gut[35]. GEMs are particularly useful in simulating the metabolic capabilities of engineered strains under varying physiological conditions. These simulative models allow researchers to predict nutrient utilization, metabolite production, and potential cross-feeding interactions between engineered probiotics and native gut microbiota[36]. For instance, constraint-based modeling techniques, such as flux balance analysis, have been used to assess how genetic modifications affect microbial fitness and metabolite output[37]. In addition, ABMs and host-microbiome interaction networks are being applied to explore dynamic, spatially resolved responses of GEPs within the host tissues, including inflammatory niches or tumor microenvironments. These computational frameworks facilitate the design of logic circuits or biosensors that respond appropriately to host-derived signals[38]. Recent advances in machine learning and AI-driven synthetic biology platforms are accelerating the design-build-test-learn process for GEPs. These tools facilitate the selection of optimal genetic designs, enable the prediction of off-target effects, and refine gene regulatory circuits to enhance safety and therapeutic performance[39]. Ultimately, integrating computational modeling with wet-lab engineering enables more precise, efficient, and scalable development of probiotic therapeutics tailored to host-specific contexts.

CLINICAL EVALUATION OF GEPS

Clinical evaluation of GEPs is accelerating, especially for treating metabolic and immune disorders. A leading example is *SYNB1618*, a live biotherapeutic developed by Synlogic Inc. for the treatment of PKU. This *E. coli* Nissle strain expresses enzymes that break down phenylalanine in the gut, showing safety and dose-dependent activity in phase I/II trials[8]. An improved version, *SYNB1934*, has entered phase II testing. For inflammatory diseases, engineered *L. lactis* strains delivering IL-10 have demonstrated biological activity and safety in early Crohn's disease studies[40]. Despite these promising early results, larger randomized controlled trials are needed to establish efficacy, optimal dosing, and long-term safety. However, current limitations include variability in host microbiome response, regulatory complexity, and challenges in maintaining the genetic stability of engineered strains during production and delivery.

FROM BENCH TO BEDSIDE: CHALLENGES AND FUTURE DIRECTIONS

GEPs have demonstrated proof of mechanism through context-responsive sensing and actuation in tractable microbial chassis, with early human studies reporting signals of target engagement[41]. Colonization efficacy and therapeutic effect size vary by microbiome composition, immune activity, diet, and host genetics. This variability highlights the need for pre-intervention diagnostics and microbiome/genomic stratification, rather than reliance on an empiric one-size-fits-all approach[19]. Human feasibility has been demonstrated in early studies; for example, engineered *E. coli* Nissle strains developed for PKU have provided quantifiable pharmacodynamic readouts. However, larger and longer randomized trials, benchmarked against standard-of-care and appropriate non-engineered comparators, are required to define the effect size and the durability of response[8]. Current regulatory frameworks focus on biocontainment performance, genetic traceability, post-market surveillance for live biotherapeutics, and harmonized CMC analytics[42]. These frameworks, however, were not designed to accommodate real-time programmability, dynamic control circuits, or multi-strain microbial consortia. Consequently, clinical adoption will depend on clear benefit-risk communication, transparent labeling, robust environmental containment strategies, privacy safeguards for multi-omics monitoring, and deeper integration of microbiome science into routine clinical practice[14]. Key strengths of GEPs include programmable genetic circuits, biosensors, early signals of target engagement in clinical studies, and the use of partially de-risked chassis such as *E. coli* Nissle and *L. lactis*. Limitations include small early-phase cohorts, short follow-up durations, limited quantification of microbial shedding, risks of HGT, long-term immunogenicity, and inconsistent durability of response across hosts[43]. Opportunities include the development of synthetic-ecology consortia, reduced-genome chassis with enhanced safety safeguards, and well-powered randomized trials incorporating longitudinal safety monitoring and prespecified pharmacodynamic endpoints[44]. Next steps should prioritize standardized

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Table 1. Summary of engineered probiotics for diagnosis and therapy[27]

Indication	Chassis (probiotic)	Model
Cancer	*E. coli* Nissle 1917	Mice, human
Colitis/ulcerative colitis	*E. coli* Nissle 1917	Mice
Hyperammonemia	*E. coli* Nissle 1917	Mice, humans, in vitro
PKU	*E. coli* Nissle 1917	Human
PKU	*Limosilactobacillus reuteri* 100-23C	Mice
IBD	*E. coli* NGF-1	Mice
IBD	Yeast strain BS016	Mice
Cholera	*L. lactis* CSL	Mice
Listeria infection	*Lactobacillus casei* ATCC 334	Mice
Obesity	*E. coli* Nissle 1917	Mice

shedding and genetic-stability endpoints, deployment of barcoded genetic traceability within GMP/CMC packages, and integration of multi-omics exposure-response modeling to support long-term safety registries[45]. Table 1 summarizes the engineering of candidate probiotic strains[28], and Tables 2 and 3 present exemplar animal and clinical studies[46].

CONCLUSION

Engineered probiotic strains provide a practical platform for programmable therapeutic activities within the human host. Early clinical studies have indicated on-target biological effects with acceptable short-term safety and tolerability. However, successful clinical use will require that these strains remain genetically stable and undergo thorough testing. In addition, they must incorporate safe containment measures, and researchers should monitor both bacterial shedding and the potential for HGT. Clinical trials should also account for differences among patients in their genetics and microbiome composition. Clear and harmonized regulatory guidance, together with post-marketing surveillance and traceability, will be essential for sustained deployment. Moreover, the integration of iterative strain engineering with systems-level computational modeling can streamline design decisions, reduce translational risk, and accelerate progress toward late-stage evaluation and implementation in healthcare settings.

Table 2. Examples of engineering probiotics in clinical trials[27]

Species	Engineered probiotic	Disease/ function	Research facility	Stage	Result	ClinicalTrials. gov ID
E. coli	SYNB1934, SYNB1618	PKU	Synlogic	Phase I	–	NCT04984525
E. coli	SYNB1618	PKU	Synlogic	Phase I/IIa	–	NCT03516487, NCT04534842
E. coli	SYNB8802	Enteric hyperoxaluria	Synlogic	Phase I	–	NCT04629170
E. coli	SYNB1891	Metastatic solid neoplasm/lymphoma	Synlogic	Phase I	–	NCT04167137
E. coli	SYNB1020	Cirrhosis/ hyperammonemia	Synlogic	Phase I/II	Terminated	NCT03447730
Bacteroides[*]	NB1000S	Enteric hyperoxaluria	Novome	Phase I/IIa	–	NCT04909723
L. lactis	AG013	Oral mucositis	Oragenics/Precigen ActoBio	Phase II	Terminated	NCT03234465
L. lactis	AG019	Type 1 diabetes	Precigen ActoBio	Phase I/II	–	NCT03751007
Bifidobacterium longum	bacTRL-IL-12	Solid tumors	IQVIA Pty Ltd.	Phase 1	–	NCT04025307

[*]Researchers did not list specific species.

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Table 3. Illustrative engineered probiotic microorganisms in animal models[29]

Disease target	Microbial strain	Model	Outcome
Cancer	*Bacteroides ovatus* D-6	Mice	Increased TNF-α–specific IgG and IgM
Intestinal inflammation	*Bacteroides ovatus* V975	Mice	Reduced symptoms in DSS-induced colitis (mouse model)
Clearance of infectious agents	*Bacteroides acidifaciens* JCM 10556(T)	Mice (gnotobiotic)	Increased gut IgA levels
IBD (also eczema, asthma, type II diabetes)	*Faecalibacterium prausnitzii*	Mice	Protective/ameliorative effects in colitis and related models
IBD	*L. lactis* (food-grade; IL-27)	Mice	Protection from T-cell transfer-induced enterocolitis via mucosal delivery of LL-IL-27
Oral mucositis	*L. lactis* sAGX0085	Hamster	Improved repair of intestinal/ epithelial damage during radio/chemotherapy-induced mucositis
Inflammatory diseases	*Streptococcus gordonii* (RFVP/IL-RA)	Mice (in vitro & in vivo evidence)	Demonstrated biological activity of RFVP/IL-RA; suitable for selective mucosal targeting
Inflammatory diseases (mainly IBD)	*L. lactis*	Mice	Moderate evidence across IBD animal models

DECLARATIONS

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Grammarly was used for language polishing, grammar correction, and improving clarity. It did not contribute to the study design, data collection, analysis, interpretation, scientific content, or the conclusions of the manuscript, and it was not used to generate new text or references. All edits were reviewed and approved by the authors, who take full responsibility for the final content.

Ethical approval

Not applicable.

Consent to participate

Not applicable

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

MB: conceptualization and writing original draft preparation; MM: conceptualization and investigation. NH: supervision, writing, and review & editing.

Data availability

All relevant data can be found within the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Supplementary Information

The online version does not contain supplementary material.

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