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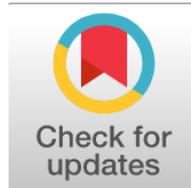
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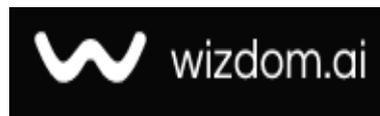How to submit to this journal (link)

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In Silico Comparative Evaluation of Biotechnology-Based Engineered Bacterial Therapeutic Platforms for Targeted Sensing, Controlled Payload Delivery, and Biocontainment : Evaluasi Komparatif In Silico terhadap Platform Terapi Bakteri Rekayasa Berbasis Bioteknologi untuk Deteksi Bertarget, Pengiriman Muatan Terkendali, dan Pengendalian Biologis

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Abstract

General Background Engineered bacterial therapeutics have emerged as programmable living systems capable of site-specific sensing and controlled therapeutic delivery. **Specific Background** Despite rapid advances in synthetic biology, there remains difficulty in selecting optimal platform architectures due to the lack of structured comparative evaluation tools. **Knowledge Gap** Existing literature lacks a decision-oriented framework that systematically compares engineered bacterial therapeutic platforms across integrated engineering and translational criteria. **Aims** This study aims to develop an in silico comparative evaluation model to assess representative therapeutic platforms based on specificity, payload control, biosafety, manufacturability, and translational readiness. **Results** The analysis identifies dual-input logic-gated biocontainment-enabled systems as the highest-ranked platform, followed by biomarker-responsive circuits, while constitutive and tumor-colonizing systems show lower balanced performance. **Novelty** The study introduces a weighted multi-criteria scoring framework that transforms descriptive knowledge into a structured decision-making tool for platform selection. **Implications** The proposed model provides a systematic basis for guiding design prioritization, optimization strategies, and future experimental validation in engineered bacterial therapeutics.

Keywords: Engineered Bacterial Therapeutics, Synthetic Biology, In Silico Evaluation, Gene Circuits, Biocontainment

Key Findings Highlights

1. Dual-input architectures achieve highest balance across evaluation criteria
2. Biomarker-responsive systems provide strong contextual activation with moderate complexity
3. Simpler and tumor-targeting designs show limitations in safety and control balance

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1. Introduction

 Engineered bacterial therapeutics also have a unique niche in the current bioengineering field as they are able to detect local signals, execute conditional logic and deliver therapeutic functions to the source sites of disease. In comparison to passive formulations, living bacterial systems are able to survive, evolve and be closed-loop biological machines. This functional structure describes their increasing applicability in the inflammatory disease, cancer, metabolic diseases, and mucosal medicine [1-4,11,14].

The lie of design challenge is not whether or not it is possible to alter the bacteria, but, which therapeutic design provides the most plausible combination of efficacy, controllability, safety and real world translation. The recent literature has developed at a tremendous pace in the areas of chassis selection, CRISPR-based editing, programmable circuits, materials-assisted delivery, and design-build-test-learn workflows [1,4,5,9,11-13]. Nonetheless, the discipline continues to lack an ordered comparative approach to classifying the types of platforms on integrative engineering and translational terms.

Numerous published reviews refer to engineered bacteria as a promising paradigm and fail to translate that information into a decision-oriented structure [2,3,10,12-15]. Consequently, conceptually elegant systems and deployable systems are frequently discussed at the same level even though they differ significantly in biosafety burden, complexity in manufacturing and clinical plausibility. This poses a practical research, supervisor and journal reviewer dilemma on what platform strategies truly should take priority.

In order to bridge this gap, the current work was redefined as an original in silico comparative study and not a narrative review. Rather than a descriptive summary of the field, the research stands up the archetypes of representative therapeutic platforms within the most recent literature and uses an explicit weighted evaluation paradigm to create new comparative outcomes. Its result is not then a ready review of existing literature, but a decision rule that brings forth new ranking and intuitive design trades. To ensure the support of the framework by the repetitive enabling technologies, the manuscript implies the explicit connection of the scoring logic with CRISPR-based editing, biomarker-reactive circuit design, and the DBTL optimization cycle (Figures 1-3).
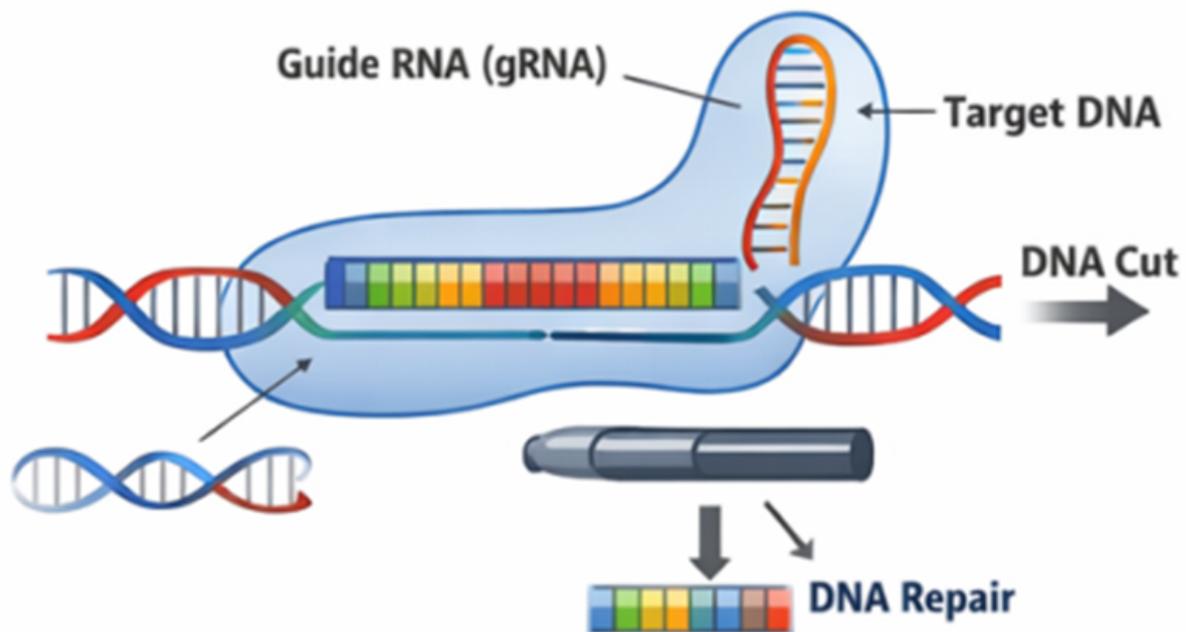

Figure 1.   *Figure 1. Conceptual representation of CRISPR-guided genome editing as an enabling tool for precise bacterial therapeutic engineering (adapted schematic).*
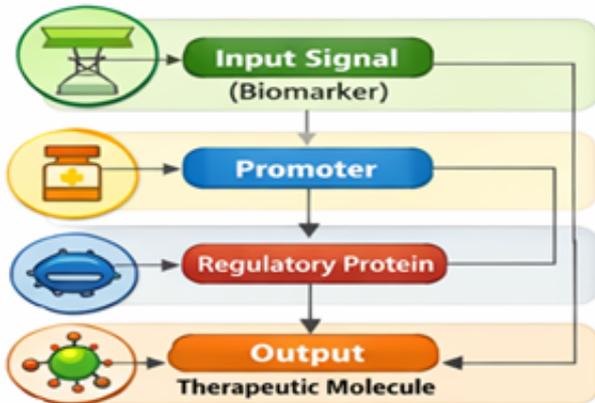
Figure 2. *Figure 2. Simplified biomarker-responsive gene-circuit architecture underlying conditional therapeutic output in higher-ranked platform designs (adapted schematic).*
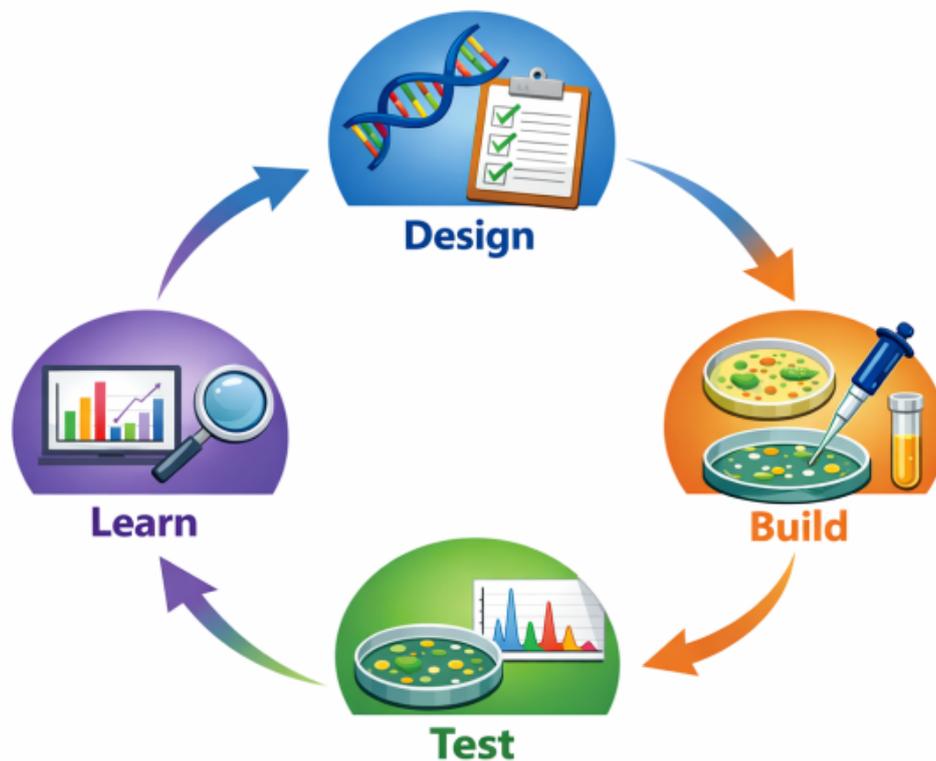
Figure 3. *Figure 3. Design-Build-Test-Learn (DBTL) cycle showing the iterative optimization logic that informs comparative therapeutic platform development (adapted schematic).*

Research question

What engineered bacterial therapeutic platform has the best balance of control in, target sensing, payload control, biosafety, manufacturability, as well as translational readiness?

Hypothesis

The hypothesis was that it would be found that multi-shape engineered bacterial systems uniting disease receptive

detecting, logic regulated framework and explicit biocontainment surpass simpler constitutive or doctorially regulated depictions in overall translationally significant execution.

2. Materials and Methods

2.1 Study design

The proposed study was an informed comparative in silico analysis of engineered bacterial therapeutic platforms. It did not purport new wet-laboratory readings or clinical experiences. It is unique in that it constructs and implements a formal system of scoring that is weighted, weighted criteria system, and comparative analysis across platforms based on the current published evidence [1-5,11-15].

2.2 Identification of the sources and platform of information.

The recurring archetypes of the therapeutic design in engineered bacterial medicine were defined based on recent peer-reviewed studies and reviews (2021-2026). Handicraft was laid more emphasis on literature that portrayed probiotic chassis, tumor-targeting bacteria, CRISPR-based editing, programmable gene circuits, DBTL optimization, materials-assisted stabilization, and biosafety restrictions [1-15]. It was not exhaustive systematic review, but representative abstraction of platforms to compare them.

2.3 Definition of evaluated platforms

The evaluated platforms consist of different environments and solutions, both virtual and real.

There were four archetypal platform platforms. P1 was a type of constitutive probiotic anti-inflammatory delivery system of the type based on a safe commensal chassis that had very little internal control logic. P2 Computational distillations showed a unique span of operation of biomarker-sensitive probiotic circuit that releases the payload in only a disease-related state during inflammatory processes. P3 was an example of tumor-colonizing bacterial platform whose therapeutic release is mediated by lysis or amplified locally. P4 was a 2-input logic controlled bacterial platform encompassing disease sensing and a specialized biocontainment or kill-switch layer. The structural form of these differences can be summarized as in Table 1, and Figure 2 shows the conditional control logic that divides responsive architectures and constitutive systems.

2.4 Evaluation framework

Eight criteria were used. There were five main criteria of direct engineering interest, target senience specificity, payload delivering ability, bio-safety and bearing durability, chassis-hostfulness, and translational preparedness. Three were secondary criteria: manufacturability, operational stability and regulatory plausibility. The scores were rated on a normalized ten-point scale on each criterion, with high scores equating to high perceived performance. The assigning of scores was based on explicit interpretation of literature-to-design and not based on extracting the numerical values of the scores in identical data sets as the endpoints reported in the source literature are not of homogenous type. The interpretation of Table 2 was taken in terms of both mechanistic control architecture (Figure 2), and the abstracted risk landscape (in Figure 6) [7,11-15].

2.5 Weighting model

Before scoring, weighted values of importance were used to avoid simple ranking by one desirable parameter. The specificity of target sensing, payload control, biosafety, and translational readiness had 0.18 of the total weight. Chassis-host compatibility had a weight of 0.12. Each of the manufacturing, operational stability, and regulatory plausibility possessed 0.08. The total weight equaled 1.00. The weighted score of each platform was obtained by adding the score weight of all criteria and thus the platform definitions of Table 1 are connected to the evaluative structure of Table 2.

2.6 Scoring procedure

The evaluations were done using rules-based rubric in each platform independently as compared to the framework. Constitutive expression systems were criticized to have a low control accuracy despite the simplicity in practice. Higher specificity and payload discipline were rewarded and lower complexity when it was plausibly lowering manufacturability or regulatory simplicity were punished in logic-gated systems. The credit of localization of tumor-colonizing systems on a spatial level was given but weighed heavily on biosafety and regulation burden. The scores were summed and ranked. This is an iterative synthetic-biological logic of design, build, test, and learn that is reflected by a rule-based procedure, instead of a single-pass comparison (Figure 3) [1,5,9,13].

2.7 Data analysis and interpretation

Data will be analyzed and interpreted using SPSS software.

Descriptive comparison, weighted ranking, criterion-level decomposition and trade-off interpretation were carried out. Since design decision support and not statistical inference through repeated measurements was the aim, no null-hypothesis test was used. In its place, comparative engineering meaning, internal consistency of scoring model and translational

implications of resulting rank order were emphasized. In this respect, Table 1 determines the compared therapeutic archetypes, Table 2 determines the logic of scoring, and Figures 1-3 and 6 determine the mechanistic context in which the scoring model is justified.

Platform	Core architecture	Main strength	Principal limitation
P1	Constitutive probiotic anti-inflammatory delivery	Simple chassis and practical manufacturability	Weak internal control and off-target activity risk
P2	Single-input biomarker-responsive probiotic circuit	Improved contextual activation and payload precision	Moderate circuit burden and dependence on signal reliability
P3	Tumor-colonizing lysis-amplified therapeutic platform	Strong local amplification in permissive tumor environments	Higher biosafety, ecological, and regulatory burden
P4	Dual-input logic-gated platform with biocontainment module	Best balance of precision, containment, and translational discipline	Highest design complexity and manufacturing challenge

Figure 4. Table 1. Definition of evaluated engineered bacterial therapeutic platforms.

Criterion	Type	Definition	Weight
Target sensing specificity	Primary	Ability to activate therapeutic action under disease-relevant cues while limiting unintended activation	0.18
Payload delivery control	Primary	Precision and conditional discipline of therapeutic release or function	0.18
Biosafety and containment robustness	Primary	Presence of control features reducing ecological escape, persistence, or uncontrolled growth	0.18
Chassis-host compatibility	Primary	Expected compatibility of the chassis with host physiology and acceptable colonization behavior	0.12
Translational readiness	Primary	Overall plausibility for progression toward reproducible preclinical and clinical development	0.18
Manufacturability	Secondary	Feasibility of strain construction, reproducibility, and process scalability	0.08
Operational stability	Secondary	Expected functional stability of the platform during deployment	0.08
Regulatory plausibility	Secondary	Relative simplicity of risk justification and regulatory acceptability	0.08

Figure 5. Table 2. Evaluation criteria and assigned weights.

3. Results

The weighted model gave a differentiated performance profile, and not a generic support of the entire engineered bacterial systems. The criterion-level scores and weighted totals are provided in table 3. The best overall score was obtained in P4 (7.75/10) and P2 (7.55/10) almost equally. P3 and P1 were following at 6.45 and 6.35, respectively. The relative positioning in Table 3 must be viewed alongside the schematic efficacy pattern in Figure 4 which graphically illustrates why the persistence of localized functioning may be more important than the intensity in instances where the translation balance is prioritized.
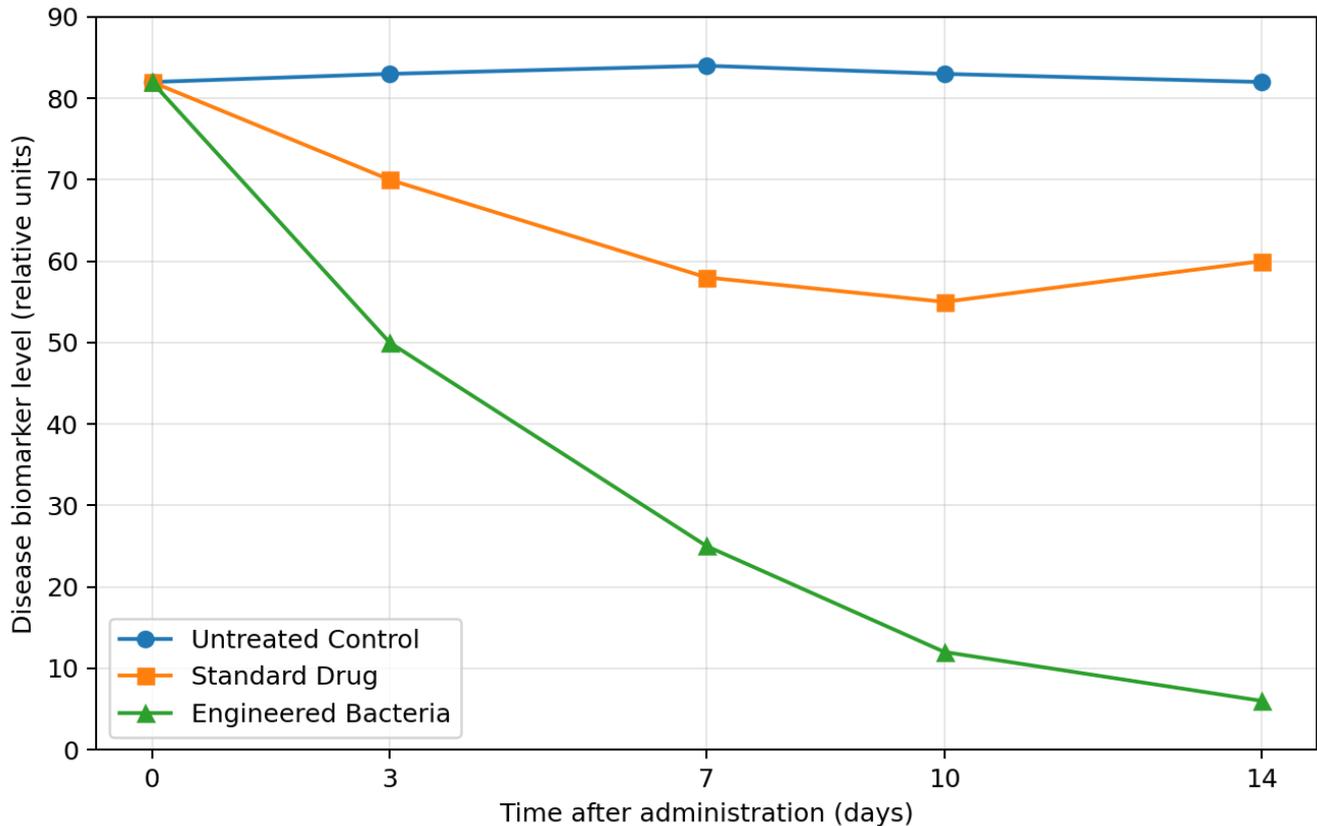
Figure 6. *Figure 4. Schematic efficacy pattern frequently reported in engineered bacterial therapeutic studies, highlighting sustained reduction relative to standard transient dosing.*

As indicated in the rank order, the difference in the platforms of a given field does not establish superiority of a particular platform based on raw therapeutic intensity. Architectures that used explicit control and containment discipline fared better than simpler or less gentlemanly architectures in being prioritized by the scoring model since translationally meaningful integration, but not isolated potency, prevailed. The only platform that continued to have high performance in respect to specificity, payload control, biosafety, and translational readiness is P4. This use of Figure 5, in that regard, offers a conceptual intermediation between the quantitative ranking in Table 3 and the functional persistence anticipated of viable engineered systems [11,13,14].

P2 was also successful as it maintained the probiotic benefit of host compatibility and added the contextual control. Its major weakness was that single-input activation was still subject to signal ambiguity, and failure to offer the same fault tolerance as a multi-condition logic gate. P3 had the advantage of the localization and good antitumor design rationale but biosafety penalties disqualified high priority. P1 was manufacturing attractive but was falling behind because of poor precision and little adaptive control [8,10,15].

Platform	Specificity	Control	Biosafety	Compatibility	Translation	Manufact.	Stability	Regulatory	Weighted total
P1	5	5	6	8	6	8	7	6	6.35
P2	8	8	7	8	8	7	7	7	7.55
P3	7	7	4	5	6	5	6	4	6.45
P4	9	9	8	7	8	5	8	6	7.75

Table 1. Table 3. Criterion-level scores and overall weighted performance.

3.1 Criterion-level interpretation

The most discriminating to the higher and lower platforms were specificity and payload control. P4 had the highest rating on the two variables due to the fact that dual-input logic minimises false activation and allows tighter therapeutic decision making. P2 was also highly rated due to the fact that biomarker-gated release is significantly superior to constitutive output. In comparison, P1 was punished due to poor context discrimination on continuous expression, whereas P3 was limited by the doubt of the stability of control in heterogeneous tumor environments. It is mechanistically plausible that these differences are produced by the responsive circuit architecture in Figure 2 [5,6,13].

3.2 Trade-off structure

The framework identified 3 major trade-offs. To begin with, sophistication of control enhances specificity at the expense of manufacturability. Second, locally aggressive treatment approaches may also increase local effectiveness and aggravate safety and control. Third, safe probiotic chassis only maintain a translational value when these are used in sufficient disciplined control modules. These trade-offs justify the reason why P4 and P2 became the most plausible architectures to be used in future development despite the fact that neither architecture was the simplest one. Figure 5 also makes it clear why sustained operation should be considered to be an advantage only as it is supported with reasonable control and containment [12-16].
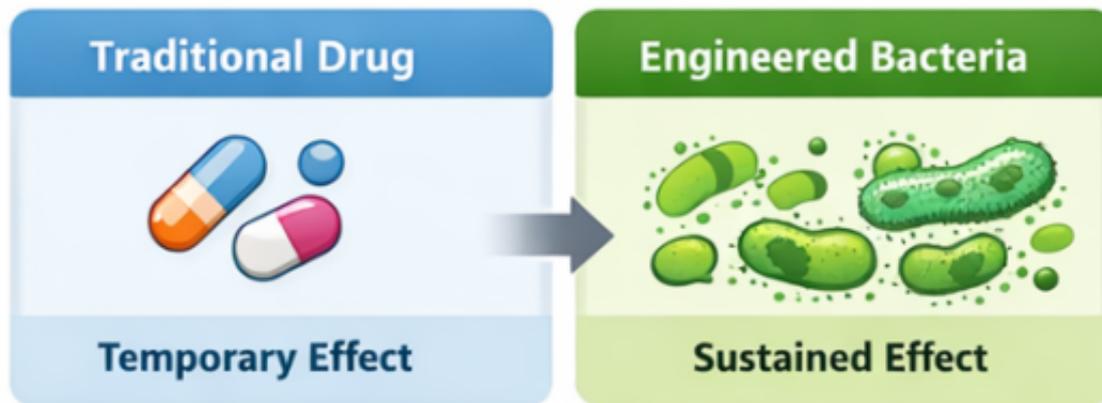

Figure 7.   *Figure 5. Conceptual contrast between transient conventional drug exposure and sustained localized function from viable engineered bacterial systems (adapted schematic).*

4. Discussion

The current research changes the discussion of descriptive enthusiasm to platform judgment of a structured nature. The originality is not the statement that engineered bacteria are a promising concept, which has been already proven, but the instance that platform credibility can be distinguished with the help of a clear multi-criteria framework. This is important since the discipline tends to confuse mechanistic ingenuity and translational maturity [1,11-15,17]. This framework of judgment is thus pegged on the scores of Table 3, and the facilitating/constraining schematics of Figures 1-6.

The top-ranked architecture was P4 which was a combination of disease sensing, logic gating and containment. It did not have the absolute superiority in individual features but was capable of high scores in the most clinically relevant dimensions. This implies in practical terms that next-generation bacterial therapeutic agents must be developed as less of a payload carrying system and more of a disciplined biological control system. The architectural problem is thus pharmacologic in nature preceding the engineering problem. It is best described by its architecture (shown in Figure 2): which is the responsive-control logic, and its development pathway would be more realistically described by the DBTL-discipline shown in Figure 3 [5,9,13,16].

P1 was the last, but it should not be understood as being irrelevant. Much simpler constitutive probiotic systems can still find application in low complexity systems, particularly where ease of manufacture and host compatibility are of greater value. Nevertheless, the findings suggest that constitutive output by itself is becoming inadequate in high-impact therapeutic statements. The systems in future have to explain not only what they provide, but when, where, and how they do it [1,2,6,12,18].

One of the major strengths of this study is the explicit honesty regarding the evidence structure. The paradigm does not make itself believe that it transforms the heterogeneous literature into the deceptive quantitative certitude. Rather it converts engineering reasoning that is informed by literature into a clear comparative instrument. Its only major weakness is that the scores are not measured experimentally and are merely modeled; hence, the scores not empirically validated should be used to design selection and prioritize experiments. Future testing should be conducted on the current ranking in the future with the help of standardized circuit datasets, preclinical benchmarking, and wet-lab validation. The enabling control technologies, persistence logic and barriers to erode translational credibility are visually represented by the current figure set: Figures 1-3 represent enabling control technologies, Figure 5 represents persistence logic and Figure 6 represents the barriers that can erode translational credibility [15-18].
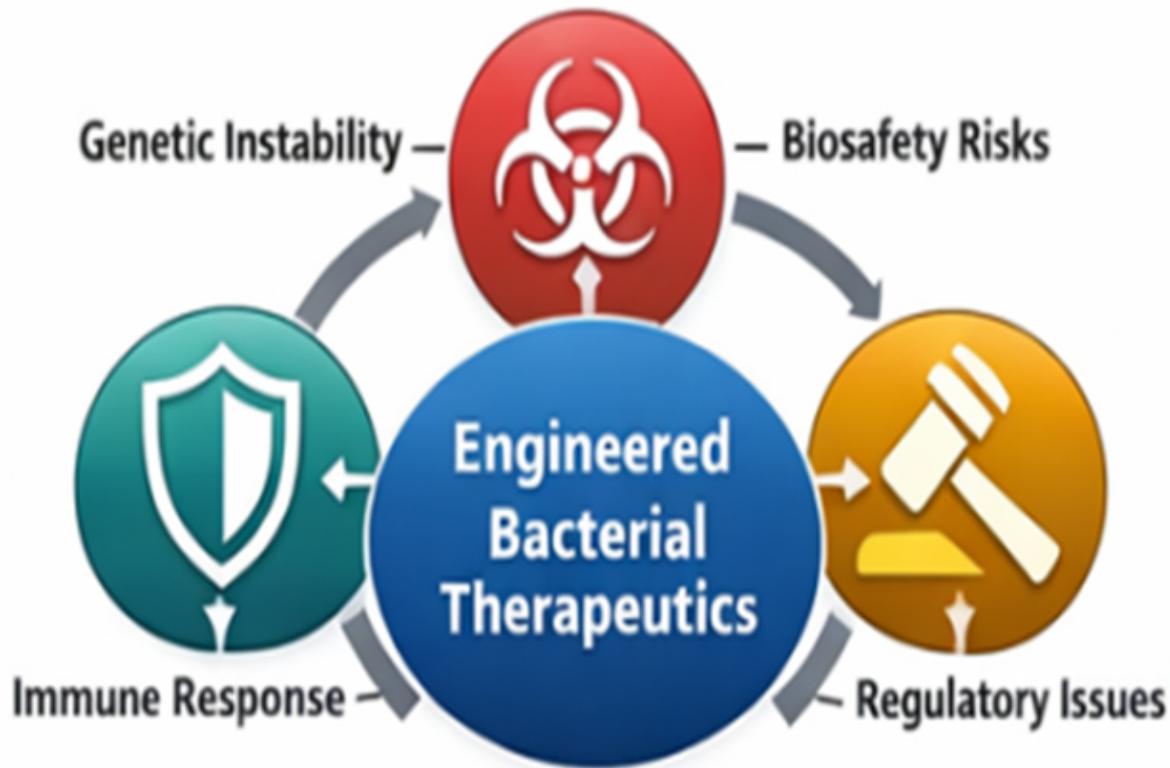
Figure 8. *Figure 6. Core translational barriers in engineered bacterial therapeutics, including genetic instability, biosafety risk, immune interaction, and regulatory burden (adapted schematic).*

5. Conclusion

This is an original in silico investigation that created and implemented a weighted comparative model of engineered bacterial therapeutics. The findings show that the most promising overall translational profile is obtained with dual-input logic-gated biosystems with sustained biocontainment, and biomarker-controllable probiotic systems are the most suitable next-generation compromise. The use of both constitutive and tumor-amplified platforms maintains a niche value, yet both remain weak in regard to balance between precision, safety and deployability. The paper thus justifies a strategic re-architecture of living therapeutics based on integrated control architecture as opposed to payload expression.

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