

Review

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Review

Insights on the Management of Bacterial Infections and Quorum Sensing in the Context of Interkingdom Interactions

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Abstract

A key aspect of bacterial pathogenesis is the complex interplay between the host and the infecting pathogen. The many molecular pathways these organisms have developed to perform specific activities during host infections indicate that a systemic approach may be a promising avenue to explore. Investigating bacterial persistence in chronic infections reveals several multifactorial processes that highlight the complexity of this phenomena, including diverse metabolic pathways, stress responses, antibiotic resistance, and biofilm development, among others. As pathogens refine their infection strategies via a complex network of molecular structures, we assert that investigating the existence of quorum sensing (QS) signals in bacteria and their impact on interkingdom signaling, as well as the evolutionary emergence of quorum quenching (QQ) mechanisms that enzymatically degrade QS signals, or the mechanisms that disrupt QS systems through quorum sensing inhibitors (QSI) that competitively bind to QS molecule receptors on bacterial cell surfaces, is essential for elucidating how naturally evolved mechanisms may adapt to combat human infections.

Keywords: artificial receptors; interkingdom signaling; quorum sensing; synthetic biology; system biology; synthetic phage technology

1. Introduction

Upon examining bacterial persistence in chronic infections, one uncovers a multitude of multifactorial mechanisms that underscore the complexity of this phenomenon, encompassing various metabolic pathways, stress responses, antibiotic tolerance, and bio-film formation, among others. The interconnection among these multifactorial systems alludes to an old mechanism of cellular communication known as quorum sensing (QS). Bacteria use quorum sensing to regulate the gene expression that governs collective behaviors. Consequently, antibiotic tolerance correlates with biofilm development, which resulting from the activation of quorum sensing networks. This happens as a result of the elevated concentration of autoinducer molecules when reaching a certain cell density (see Figure 1). In recent decades, interest in these themes has surged, partly due to the quest for answers to a significant issue afflicting healthcare systems globally, namely the hunt for treatment options for illnesses caused by antibiotic-resistant microbes [1–3].

In this background, it is unsurprising that several strategies have been suggested to tackle the aforementioned issue. To our knowledge, the suggested solutions have not attained the expected results. We contend that numerous limitations in attaining the desired objectives, specifically in identifying effective treatments against microbial resistance, stem chiefly from the foundational assumptions inherent in the design of these investigations. This subject will be discussed in the first section.

In recent years, an approach for treating bacteria that to an extent was successful over a century ago has been reintroduced. Ironically, it was progressively forsaken with the advent of penicillin.

This review will concentrate on providing the most recent findings from research us-ing bacteriophages as a compelling method to combat bacterial diseases. Understanding the evolution of strategies that disrupt signaling networks associated with pathogen re-ceptors will provide insights into quorum sensing mechanisms, thereby enhancing our comprehension of receptor dynamics essential for developing novel antimicrobial thera-pies.

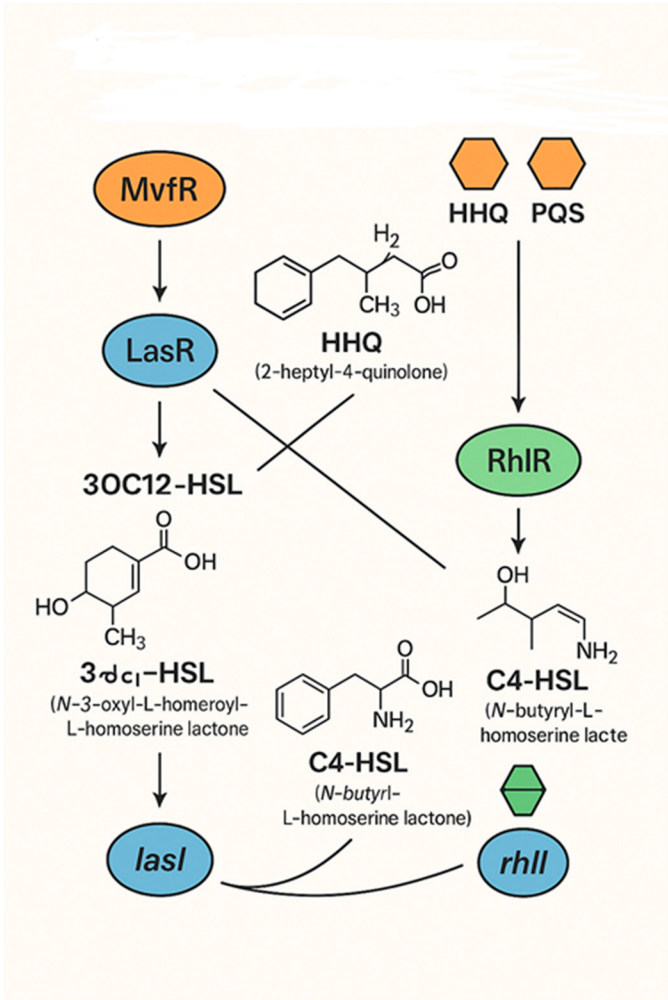


Figure 1. *Pseudomonas aeruginosa* QS Networks: A visual representation of the three quorum sensing networks in *P. aeruginosa*, highlighting their signaling molecules, regulatory hierarchy and molecular structures. This graphic was assisted by GenAI.

2. Biology the Way It Is and How It Could Be

Ecosystems consist of populations of various organisms, which may belong to distinct kingdoms. In this context, it may be said that interactions among microbes from various kingdoms have been facilitated by quorum sensing (QS).

These connections have evolved via both cooperative organisms and by pathogens. The intricate signaling networks present in single-celled organisms, both by cooperative organisms and by pathogens, have been enhanced by several stressors and survival threats, leading to the sophisticated molecular processes seen today.

Consequently, emphasizing the primary conclusions of the preceding paragraph necessitates a critical reassessment of the assumptions in biological research that, in various respects, overlook the continuous interplay of molecular interactions that have happened for millennia. Essentially, recognizing that several study designs on a subject as intricate as the one we are examining are hindered by many unknown variables, and that trial and error is not an effective approach to illuminate these overlooked aspects. Besides, a reductionist perspective on biological phenomena

fails to elucidate the molecular processes occurring continuously, some of which may be pertinent to addressing the intricate phenomenon of host-pathogen interaction.

At the end of the past century and into this new century, biology has bifurcated into two approaches, significantly influenced by advancements in the study of complex systems: systems biology and synthetic biology.

Nonetheless, it seems that the significant potential of both methodologies to provide innovative strategies for an enhanced comprehension of biology has not been completely actualized. It seems that in this quarter of the 21st century, the ramifications of seeing living organisms as complex systems—arguably the most complex in the universe—have not yet been completely understood. How can we use the concepts of dissipative and fractal systems in systems biology to comprehend the development of molecular network design?

This may also be employed within the context of synthetic biology. Consequently, we may inquire: what has been happening in these more than two decades of development in synthetic biology research? And we maintain that this indicates the direction taken by researchers mostly focused on the so-called “top-down” component of synthetic biology (although it is also possible that we can find some accents of this direction in research on the “bottom-up” component of synthetic biology).

The “top-down” strategy involves using established biological systems, such as bacteria or other cells, and use genetic engineering techniques to alter them for the introduction of novel functionalities or the synthesis of new molecules. Conversely, “bottom-up” methodologies seek to construct synthetic cells from the ground up, beginning with discrete molecules or components and integrating them into bigger nanostructures with innovative functionalities [4,5].

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Certainly, the research program centered around genes is mainly belonging to “top-down” synthetic biology. However, we are seeing that in recent years the “bottom-up” synthetic biology is also using the research program centered around genes to design and build artificial cells or protocells [6–10].

Although both approaches yield intriguing results, we contend that the bottom-up approach ought to prioritize comprehending the processes and functions arising from simpler systems to enhance the understanding of the development of biological mechanisms, processes, and functions from the ground up. The gene-centric research approach, is the legacy of the top-down synthetic biology. The significant potential for uncovering new knowledge and applications offered by the bottom-up method should guide the emergence of the third wave of synthetic biology, characterized by a more systemic rather than reductionist perspective [11].

3. Quorum Sensing, Interkingdom Interaction, Importance of Receptors

In all bacterial intercellular communication mechanisms, or quorum sensing (QS) mechanisms, two molecular types are crucial for initiating signaling events: signaling molecules, termed autoinducers (AI), and their corresponding receptors (Table 1 presents the most recognized receptors and their autoinducers).

Table 1. The table delineates each quorum sensing receptor, its corresponding autoinducers, and their principal roles across diverse bacterial species.

Receptor	Autoinducer Type	Bacterial Group	Signal Nature	Function Class
LuxS	AI-2	Gram-negative & Gram-positive	Diffusible metabolite	Signal synthesis (not a receptor)
LuxP	AI-2	Vibrio spp.	Periplasmic binding	Signal reception & transduction
LuxN	AI-1 (AHL)	Vibrio harveyi	Membrane-bound kinase	Sensor kinase
SdiA	AHL	Salmonella, E. coli	Cytoplasmic	LuxR-type (eavesdropper)
LasR	3OC12-HSL	P. aeruginosa	Cytoplasmic	LuxR-type transcriptional activator
EsaR	AHL	Pantoea stewartii	Cytoplasmic	LuxR-type transcriptional repressor
YenR	AHL	Yersinia enterocolitica	Cytoplasmic	LuxR-type activator
LamC	LamD	Lactobacillus plantarum	Two-peptide pheromone	Peptide-responsive transcription
PlcR	PapR7	Bacillus cereus group	Peptide signal	Transcriptional regulator
AgrC	AIP1	Staphylococcus aureus	Membrane-bound kinase	Sensor kinase (AIP receptor)
TraR	3OC8-HSL	A. tumefaciens	Cytoplasmic	LuxR-type activator

Concentrating on receptors, QS systems can be categorized into two classes: interspecies QS receptors and intraspecies QS receptors [12–14].

In interkingdom interactions, particularly between bacteria and eukaryotes, organisms from both kingdoms have developed the ability to recognize diverse chemicals, including quorum sensing signals, to modulate gene expression and behavior [15,16].

For instance, the QS signal molecule AHL influences mammalian host cells by engaging many signaling pathways, including calcium mobilization and the activation of Rho GTPases and MAPK, among others. Consequently, they regulate several functions and behaviors in host cells, including epithelial barrier integrity, differentiation, proliferation, apoptosis, and the synthesis of immune mediators, among others [17–19].

Quorum quenching has been identified in studies of several organisms, including bacteria, fungi, plants, and mammals, which inactivate AHL via enzymes [20,21]. In humans, a category of quorum quenching enzymes known as paraoxonases possesses the capability to degrade AHL [22–25].

This study emphasizes the promise of bacteriophages in developing treatments for pathogenic bacteria as alternatives to antibiotics; nevertheless, research on quorum sensing extends beyond these subjects.

Over the past two decades, research on QS systems has emerged as a significant priority within the science of microbiology.

Consequently, the progression of knowledge in QS systems originates from several domains. Besides pathogenic microbes, researchers have conducted research on quorum sensing systems in environmental, culinary, and industrial microorganisms, among others [26–28].

Nonetheless, despite the substantial number of academics engaged in QS systems across several domains and with diverse objectives, comprehension remains inadequate.

The various QS systems exhibit distinct communication methods. Although QS signaling molecules serve as a universal medium for inter-bacterial communication, the mechanisms by which receptors detect signals and initiate signal transduction differ significantly across various systems [29–33].

In this context, it is important to emphasize that one of the foremost themes in QS systems research is undoubtedly the pivotal role of receptors.

It appears that we have yet to fully define all the receptors within the quorum sensing systems of diverse bacteria. The receptor’s recognition of the mechanism of signal transduction of complex and diverse signaling chemicals from a specific host remains inadequately comprehended [34–39].

Finalizing, a recent study delineates numerous unresolved yet significant issues that may enhance the understanding of interkingdom connections mediated by quorum sensing systems Which specific biochemical pathways do quorum sensing molecules influence to alter eukaryotic metabolism and physiology? Which cell surface receptors or transcription factors are shared by QS-producing bacteria and QQ/QSI-producing eukaryotes that enable chemical communication between these entities? What regulatory mechanisms govern the modulation of viral replication methods by QS signals in relation to cell density and the host’s physiological condition? [40] (p. 9).

4. Bacteriophages as a Substitute for Antibiotics

A crucial facet of employing bacteriophages as a prospective replacement to antibiotics is their capacity to efficiently target and eliminate specific bacteria while sparing human cells from infection. Nonetheless, their elevated selectivity presents a challenge to the advancement of broad-spectrum products utilizing natural bacteriophages.

In recent years, synthetic biologists have transformed the area of phage research. Subsequent paragraphs will present some cutting-edge developments at the intersection of synthetic biology and phage engineering (Table 2).

Table 2. Synthetic biology is revolutionizing phage research. This table shows some cutting-edge developments where synthetic biology meets phage engineering. It was assisted by GenAI.

Application	Description
Phage Rebooting	Researchers have successfully assembled and rebooted <i>Pseudomonas aeruginosa</i> phages (e.g., JG024, DMS3) using yeast-based transformation cloning
Targeted Engineering	Synthetic biology enables precise modification of phage genomes to expand host range, evade bacterial defenses, or enhance lytic activity
Cell-Free Phage Synthesis	In vitro systems can now assemble and produce infective phages, allowing rapid prototyping and creation of large phage libraries
Therapeutic Customization	Engineered phages are being tailored to treat specific infections, especially those resistant to antibiotics, such as in cystic fibrosis patients

4.1. Phage Rebooting

Phage rebooting, alternatively referred to as phage genome rebooting or synthetic phage assembly, is an advanced approach in synthetic biology that facilitates the generation of infectious bacteriophage particles from their purified or synthetically engineered genomic DNA. Essentially, it resembles “booting up” a computer with its operating system from the ground up, but for phages..

Phage rebooting fundamentally entails transferring the genetic blueprint of a phage (its DNA genome) onto an appropriate host bacteria. The bacterial host subsequently “interprets” this DNA, expresses the phage genes, replicates the phage genome, and finally constructs new, infectious phage particles capable of infecting and lysing additional bacteria [41,42].

Historically, the engineering of phages has predominantly depended on homologous recombination. This entails co-infecting a bacterial host with a wild-type phage plus a modified DNA construct, such as a plasmid, that contains the intended genetic alterations. Recombination subsequently transpires within the host, resulting in an altered phage. This approach possesses multiple limitations: 1) Inefficiency; 2) Restricted changes; 3) Reliance on Wild-Type Phage; 4) Certain bacteria exhibit resistance to DNA transformation, complicating phage engineering [43,44].

Conversely, the benefits of Phage Rebooting include: a) Precise Engineering enabling meticulous and comprehensive alterations to the phage genome; b) Synthetic phages exhibiting novel characteristics; c) Mitigation of native host constraints; d) Diminished screening requirements relative to homologous recombination; e) Expedited development of phage therapy; f) Generation of extensive libraries of engineered phages [45–47].

In summary, phage rebooting is a synthetic biology approach enabling scientists to construct and reactivate bacteriophages from their genomic DNA, frequently outside their native hosts. Consider it as the digital modification of a phage's blueprint, subsequently manifesting it within a novel bacterial chassis.

4.2. Targeted Engineering

In synthetic biology, “targeted engineering” in phage research refers to the deliberate and precise modification of bacteriophage genomes and components to bestow new, enhanced, or entirely novel functionalities. This surpasses traditional genetic modification by utilizing systematic engineering techniques to develop phages with desired attributes, specifically for therapeutic, diagnostic, and biotechnological applications. It involves the precise design and modification of bacteriophage genomes to impart new or improved capabilities. This surpasses random modifications by the application of advanced techniques including gene synthesis, genome editing technologies (CRISPR-Cas systems, ZFNs, TALENs), directed evolution, and modular phage engineering (BioBricks and genetic circuits).

Essentially, targeted engineering in phage research involves transitioning from the utilization of naturally existing phages to the creation of them as advanced biological machines. This transition is essential for realizing the complete potential of phages, especially in addressing the global issue of antibiotic resistance [48–51].

4.3. Cell-Free Phage Synthesis

It employs cell-free transcription–translation (TXTL) systems—essentially, the molecular apparatus of cells (such as ribosomes, enzymes, and tRNAs) that have been removed and reconstituted in vitro—to express phage genomes and construct functional phage particles. Cell-free phage synthesis is an innovative method enabling researchers to generate infective bacteriophages entirely in vitro, eliminating the necessity for living bacterial hosts. This methodology is transforming phage engineering and medicinal advancement (see Figure 2).

This method possesses numerous benefits [52,53]:

1. Living hosts are unnecessary, mitigating host toxicity and simplifying biosafety issues.
2. It facilitates rapid prototyping, expediting the evaluation of created phage variants.
3. High-throughput compatibility facilitates the generation of extensive phage libraries (e.g., 7.5 million variations).
4. Exacting genome regulation facilitating modular construction and modification of phage genomes.
5. Capable of being tailored for individualized phage therapy and synthetic biology applications.

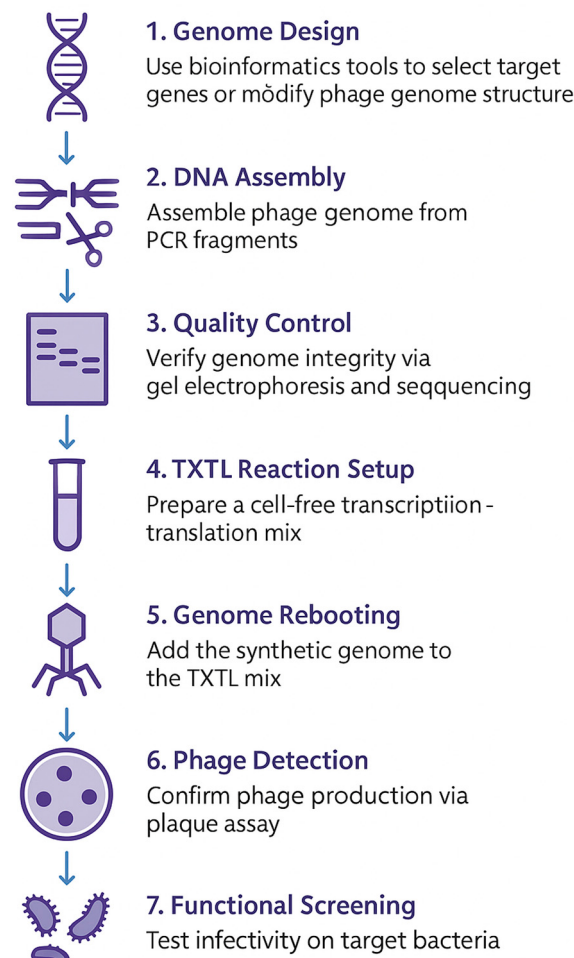


Figure 2. A detailed graphic representation of the sequential workflow for cell-free phage synthesis. Graphic assisted by GenAI.

4.3.1. Phage Engineering by In Vitro Gene Expression and Selection

Traditional *in vivo* phage engineering approaches, such as homologous recombination and lysogenization-based techniques, entail the introduction of specific genetic modifications into the phage genome during its replication within a living bacterial cell. This is frequently predicated on natural or artificial recombination mechanisms (e.g., λ Red recombination) or the incorporation of temperate phages into the host genome. Nonetheless, *in vivo* techniques are constrained by host viability and metabolic processes, and they need considerable time investment. The processes of bacterial culture, transformation, infection, and screening are time-consuming, often requiring days or weeks. Moreover, designing phages with genes capable of lethally or significantly inhibiting the bacterial host prior to adequate engineering is challenging. Phages that replicate most effectively within the host are preferentially selected, regardless of their therapeutic or functional attributes. Bacterial contamination and endotoxins present intrinsic obstacles to large-scale *in vivo* phage synthesis for therapeutic applications [54–59].

Recently, “Phage Engineering via In Vitro Gene Expression and Selection” has been established. This technology enables scientists to synthesize and enhance bacteriophages *in vitro*, independent of live cells. This is essential as it expedites the phage engineering process and enhances its precision. PHEIGES is a groundbreaking methodology in phage engineering, characterized by its transition from *in vivo* (in-cell) techniques to entirely *in vitro* (in-test-tube) processes for phage production and selection. This ostensibly straightforward modification provides a multitude of advantages that address the significant constraints of conventional phage engineering. PHEIGES markedly decreases the duration necessary for the design, construction, and testing of engineered phages, reducing it

from days or weeks to frequently a mere day. The swift iteration cycle is essential in domains like phage therapy, where prompt adaptation to advancing bacterial resistance is vital. The in vitro environment facilitates highly parallel studies, permitting the concurrent testing and selection of extensive libraries of phage variants.

Moreover, PHEIGES facilitates a direct correlation between the genetic alteration (genotype) and the resultant function (phenotype) of the phage. Phages self-assemble from genetic material in a cell-free system, with only those that assemble correctly and possess the intended function being “selected.”

This addresses the issues of genetic bottlenecks and biases that may occur during in vivo replication. Besides, PHEIGES eliminates host-cell compatibility constraints, facilitating the engineering and examination of phages that are challenging or unfeasible to control using conventional techniques, particularly those with atypical replication cycles or toxic components.

In summary, PHEIGES is a cell-free method for phage genome engineering, synthesis, and selection based on T7. It allows for the direct selection of engineered and mutant phages without compartmentalization (see Figure 3) [60].

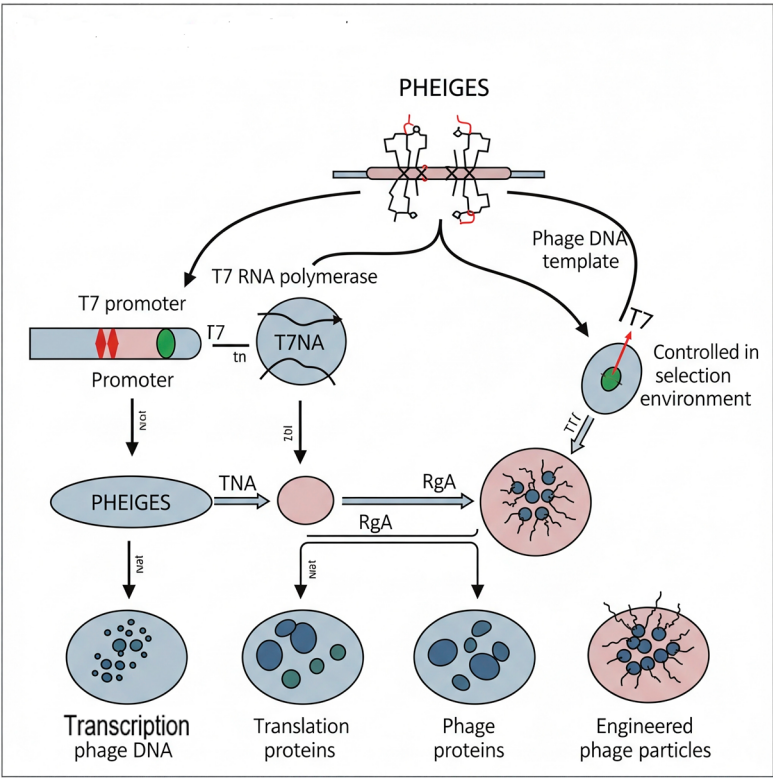


Figure 3. The graphic aims to visually communicate that PHEIGES provides a powerful, versatile, and accelerated platform for manipulating and discovering phages with desired properties, all within a controlled, cell-free environment. PHEIGES supports rapid genome assembly, expression in TXTL, and high-throughput selection. Graphic assisted by GenAI.

5. Artificial Receptors

With the growing recognition of bacteriophages as innovative antimicrobials and prospective diagnostic tools, there is an intensified interest in elucidating the processes of their interactions with bacterial hosts. The initial phase of a bacteriophage infection involves the identification of specific entities on the bacterial cell surface, facilitated by their phage receptor binding proteins (RBPs). They are situated on their tail structures to engage with specific receptors on the surfaces of bacterial cells. This physical contact is essential for phage attachment and subsequent infection, serving as a critical determinant of the phage’s host range [61–66].

In the past twenty years, synthetic biologists have utilized physical components and principles from natural receptors to create synthetic receptors. These technologies employ tailored sense-and-respond systems that connect a cell’s interactions with extracellular and intracellular signals to user-specified reactions.

Synthetic biology has utilized many receptor types to modify cells capable of detecting and responding to particular signals. Certain receptors are frequently incorporated into synthetic circuits to develop sense-and-respond systems, medicinal devices, or environmental biosensors. Receptors serve a pivotal function in synthetic biology as the sensory regulators of created systems. Synthetic organisms, whether bacteria, yeast, or mammalian cells, are permitted to identify certain environmental, cellular, or chemical signals and thereafter initiate a predetermined reaction (see Table 3) [67–75].

Table 3. Here are some key examples of natural receptors repurposed for synthetic use and synthetic receptors, grouped by their origin and function. Assisted by GenAI.

Natural Receptors Repurposed for Synthetic Use		
Receptor Type	Example	Function in Synthetic Systems
GPCRs	Human β 2-adrenergic receptor	Used in mammalian cell biosensors for drug screening or signal sensing
Histidine Kinase Receptors	EnvZ/OmpR system from <i>E. coli</i>	Enables osmolarity sensing and synthetic signal transduction
Toll-like Receptors	TLR4	Engineered to detect bacterial LPS in immune cell therapies

Synthetic or Engineered Receptors		
Receptor Type	Example	Application
MESA (Modular Extracellular Sensor Architecture)	Custom ligand-binding domains	Controls gene expression in response to extracellular cues 1
SynNotch Receptors	Synthetic Notch-based receptors	Enables programmable cell-cell communication and logic gating
Chimeric Antigen Receptors (CARs)	CAR-T cells targeting CD19	Used in cancer immunotherapy to direct T cells to tumor antigens

6. Conclusions

Recent revelations regarding phage-host interactions are creating opportunities to combat antibiotic resistance. Cell-free expression systems are emerging as a potential platform for the generation and engineering of bacteriophages. This method enables researchers to swiftly alter phage genomes and express them in vitro, facilitating the prototyping of phages for biotechnological, medical, or diagnostic purposes [76].

Synthetic phages are artificially manufactured bacteriophages, viruses that target and eliminate bacteria, created to address the shortcomings of wild phages in the treatment of bacterial illnesses. These alterations frequently entail modifying the phage’s receptor-binding proteins (RBPs), which are crucial for identifying and adhering to specific receptors on bacterial cell surfaces. By altering RNA-binding proteins (RBPs), researchers can expand the host range of phages, enhancing their

efficacy against a broader spectrum of bacterial strains or specifically targeting strains resistant to natural phages [77–80].

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