Current Science
CS 5 (2), 2109-2118 (2025)
**Received 10 Feb** 2025 | **Revised 17 March** 2025 | **Accepted 10 April**. 2025 | **Online Available 30 April** 2025
**https://doi.org/ 10.52845/CS/2025-5-2-66**

**Current Science**
Current Science

**OPEN ACCESS** **ISSN(O)2795-8639**

**Research Article**

# Application of Phage-Based Biosensors in Disease Diagnosis and Food Safety Detection

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**Abstract:**
Phage-based biosensors, renowned for their exceptional specificity, sensitivity, and cost-effectiveness, have become a prominent research focus within the field of bio-sensing. This paper reviews recent advancements in the application of phage-based biosensors and their display technologies, with a particular emphasis on disease diagnosis and food safety detection. It assesses the practical efficacy of these biosensors in various application scenarios and elucidates the signal amlification mechanisms at play. Furthermore, the paper delves into the potential of microfluidics to enhance phage-based biosensors. The article concludes with a forward-looking perspective on the future development trends of phage-based biosensors, intending to provide valuable insights and inspiration for researchers in related fields.
**Keywords: phages; biosensors; disease diagnosis; food detection**

## Introduction

Infectious diseases account for approximately 15% of global mortality, with mortality rates reaching 23% in 2020 and 28.1% in 2021 due to novel coronaviruse12. Mainstream pathogen diagnostic methods include microbial culture techniques, polymerase chain reaction (PCR), and enzyme-linked immunosorbent assay (ELISA). Each of these methods has its own strengths, but they also have significant limitations3. Microbial culture is considered the gold standard for clinical diagnosis; however, it is time-consuming and has a limited ability to identify specific species. Polymerase chain reaction (PCR) can identify microorganisms with high sensitivity, but it is costly, technically complex, and susceptible to false positives4. Traditional enzyme-linked immunosorbent assay (ELISA) is highly accurate but has low sensitivity and requires a lengthy reaction time, which is not conducive to rapid detection. As modern lifestyles and socio-economic activities evolve, the transmission of pathogens has increased in number, speed, and scope, creating an urgent need for rapid, sensitive, and cost-effective detection methods. Among these, biosensors have garnered significant attention from researchers due to their advantages, including portability and rapid detection capabilities.

Over the past few decades, biosensing technologies have achieved significant breakthroughs in several key areas, including healthcare, food safety, environmental monitoring, industrial process control, public health, agriculture, pharmaceuticals, and defense5. These technologies have improved the convenience, timeliness, and cost-effectiveness of detection methods. As a result, biosensing technology has been rapidly developed and widely acknowledged across various application domains.

Most currently known biometric elements are sensitive to environmental changes, and extreme conditions can affect or even destroy their binding activity, thereby reducing the performance of the sensor6. Enhancing the stability and

environmental adaptability of biometric elements is crucial for the advancement of biosensor technology. Biometric elements are widely utilized to establish biosensing assays based on various transduction systems; however, assays that rely on biometric elements are often constrained by factors such as high costs, sensitivity to elevated temperatures, pH variability, and other specific requirements. Consequently, the pursuit of a low-cost and environmentally resilient biometric element is essential for the development of biosensors.

Based on their ability to specifically bind to host bacteria, researchers have begun to explore the use of phages as novel biorecognition elements. The appeal of such applications stems from the numerous advantages of phages: low cost, relatively straightforward preparation and purification processes, stability even under extreme conditions, and the capacity for functional groups to be immobilized on the sensor surface7. These benefits make phages ideal biorecognition elements for biosensors, which can be utilized for detection and monitoring across a wide range of applications8. The use of phages as biorecognition elements in the development of biosensors has emerged as a significant research focus in the field of biosensing.

## 1. Phage-Based Biosensors

### 1.1 Phage Display Technology

Phages are viruses that can specifically infect and replicate within bacteria, making them valuable tools for detecting host bacteria9. Research on phages has advanced to the point where they can be immobilized on various materials to enhance functionality, including antimicrobial activity, bacterial trapping, and the rapid assembly of nanostructures10.

Phage display technology establishes a physical link between peptides, proteins, and DNA. Discovered by George Smith in 1985, this technology involves fusing exogenous peptides into phage coat proteins, allowing the target protein to be displayed on the surface of recombinant phages11. Phage display technology employs an iterative screening process to selectively identify ligands with specific binding capabilities from a diverse library of displayed phages. In summary, phage display technology offers an efficient mechanism for screening and characterizing intermolecular interactions, enabling the analysis of peptides or proteins with targeted functions. It is capable of identifying and isolating target molecules from a vast array of molecular variants. As illustrated in Figure 1, through repeated screening of targets, molecules with desirable characteristics are progressively enriched and ultimately isolated from the phage display library.

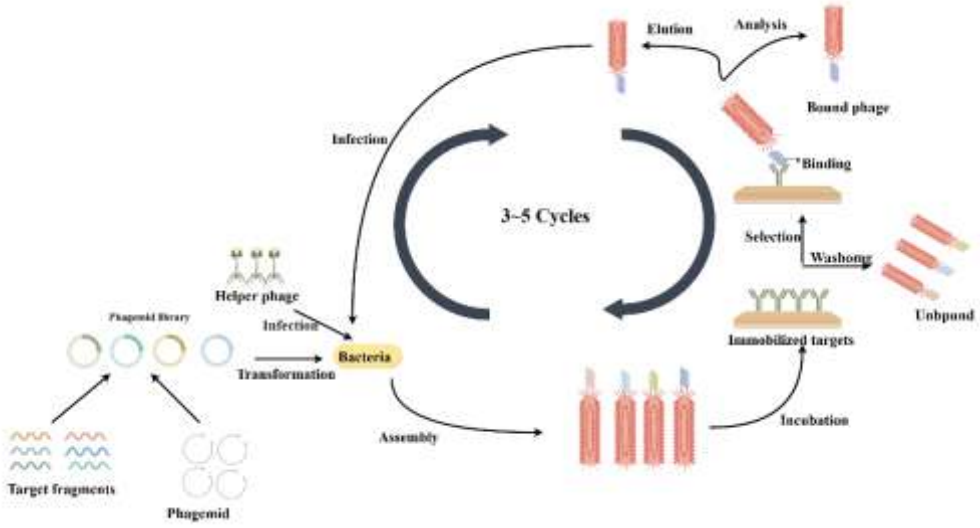


**Fig. 1: Phage Display Technique and Panning Process (By Figdraw)**

Phage display technology enables fusion proteins to retain their original spatial structure and

biological activity. Researchers can utilize this technology to screen proteins and peptides for specific binding to targets, and the selected molecules play a crucial role in medical diagnosis and therapy.

### 1.2 Phage and Phage Display Technology Applied to Biosensors

Characterized by low cost, high efficiency, and sensitivity, biosensors are widely used in medical diagnostics, environmental monitoring, and food safety testing. The specific detection of targets by biosensors depends on the biorecognition element, which interacts with the target molecules to convert the signals into acoustic, optical, and electrical forms for measuremen12, as shown in Figure 2. The surface properties of phage enable it to bind tightly to the sensor surface through functional groups, which, together with the phage's ability to recognize specific receptors on the surface of host bacteria, makes phage an ideal biorecognition element13. Phages can help sensors accurately detect and differentiate target bacteria, providing a highly sensitive and selective method for bacterial detection14. Phage-based biosensors are used in a variety of applications, including the detection and characterization of bacteria.

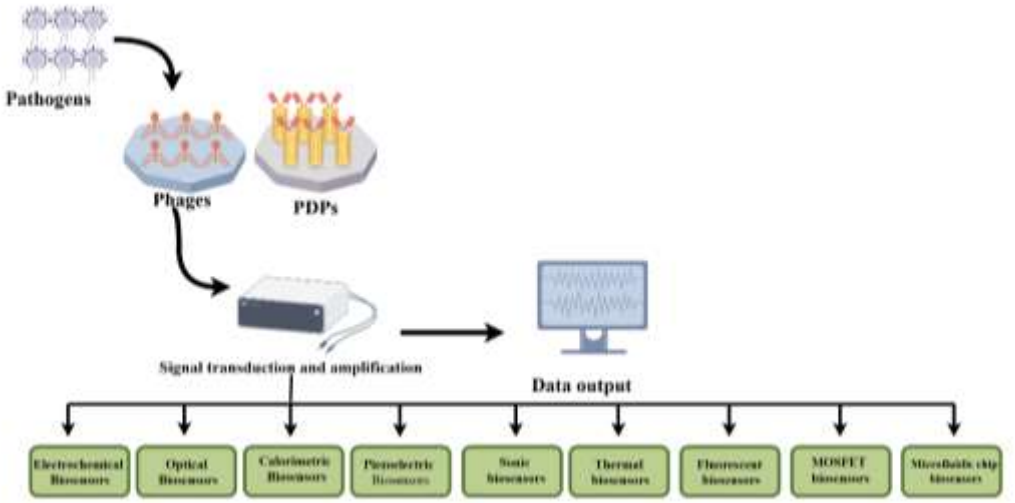


**Fig. 2 Phage biosensor pattern diagram (By Figdraw)**

Phages have naturally high specificity and the ability to rapidly lyse host bacteria, but these properties may also limit their application in biosensor technology. Yang et al15created a water-soluble bifunctional protein by fusing green fluorescent protein (GFP) with phage cell wall binding domain (CWBD) through genetic recombination technology. The broad-spectrum recognition of methicillin-resistant staphylococcus (MRSA) by the phage cell wall binding domain (CWBD) and the fluorescent properties of green fluorescent protein (GFP) were utilized as a fluorescent probe for targeted protein engineering. Immobilized phages have been used in a variety of biosensors, such as magnetoelastic surfaces and surface plasmon resonance16. With the increase in phage genomic data, this technology is expected to play a greater role in clinical diagnostics and therapeutics, demonstrating the potential of phage biosensor technology.

## 2. Applications of Phage-Based Biosensors

### 2.1 Phage-Based Biosensors for Disease Diagnosis

The application of biosensor technology in medical diagnostics is becoming increasingly diverse and significant. From the initial blood glucose monitors to the latest kits for detecting novel coronaviruses, biosensors have become an essential tool in disease diagnosis1718. Point-of-care testing (POCT) demands not only rapid results but also precise detection, which is propelling the advancement of highly sensitive and specific biosensing technologies19.

Peptides hold significant potential in the field of biosensors due to their ease of synthesis and

modulation, flexible design, and high specificity and affinity. These characteristics make them ideal materials for developing a new generation of biosensors20. Peptides screened using phage display technology are expected to play an increasingly important role in future biomedical research and clinical applications. Hyeon et al. 21 utilized phage display technology to identify peptides that can specifically bind to myoglobin, serving as recognition elements for biosensors. Electrochemical biosensors that employ myoglobin-binding peptides as biorecognition elements have emerged as powerful tools for the early diagnosis of myocardial infarction, owing to their exceptional sensitivity, specificity, and timeliness. The inherent high sensitivity, specificity, and ease of handling associated with electrochemical biosensors provide them with vast potential for application in multi-indicator detection platforms. The integration of electrochemical biosensor technology with phage display technology has resulted in significant advancements in the field of biomedical detection 22. Rafae et al. 23 applied this technology to screen for peptides that bind to breast cancer exosomes and proposed a streamlined exosome detection strategy that maintains high analytical performance, offering a cost-effective and innovative approach for disease diagnosis.

Phage-based biosensors have garnered significant attention from researchers due to their high potential in disease diagnosis. Rizzo et al. 24 utilized phage biochip technology to successfully differentiate between non-Alzheimer's disease (non-AD) and severe Alzheimer's disease (AD) cases through immunophage polymerase chain reaction (PI-PCR) detection on a miniaturized biochip. In another study, Juusti et al. 25 employed a dye-sensitized phage library to screen for phage conjugates associated with cancer metastasis, which proved statistically significant in distinguishing metastatic from non-metastatic cancers.

In summary, phage-based biosensor technology demonstrates significant potential in the field of disease diagnosis, particularly in enhancing the accuracy, timeliness, and convenience of diagnostic processes. With ongoing advancements and optimizations in this technology, it is anticipated that phage-based biosensors will assume an increasingly vital role in clinical diagnosis and disease monitoring.

### 2.2 Phage-Based Biosensors Applied to Food Safety Detection

Foodborne disease outbreaks pose a significant public health and food safety challenge. In this context, the development of efficient, accurate, and convenient methods for detecting foodborne pathogens has become a focal point of research. Traditional detection methods for foodborne pathogens rely on specific biochemical, serological, and nucleic acid-based techniques, which require skilled technicians and are often time-consuming and costly26. Most rapid tests fail to differentiate between dead and living cells, rendering them unsuitable for many foodborne pathogen assessments27. The U.S. Food and Drug Administration (FDA) has approved the use of bacteriophages as an aid in food processing to control the growth of critical bacteria such as Listeria monocytogenes, Salmonella, and Escherichia coli O157:H7 on food and food contact surfaces28. Certain phages, including T7-ALP, ΦV10 lux, and T7-NRGp5, have been developed for the detection of various E. coli strains across different food matrices29 31.

Biosensors offer several advantages over traditional analytical methods, including rapid response times, ease of operation, and cost-effectiveness. Denise Molinnus et al.32 developed an electrochemical impedance spectroscopy (EIS) biosensor capable of monitoring real-time changes in acetylin concentration during fermentation, serving as an indicator of beer maturity. This technology holds significant promise for food manufacturing and quality control, and it is anticipated to serve as a powerful complement to conventional detection methods. Zuqiang Jiang et al. 33 created a molecularly imprinted polymer (MIP) biosensor that outperforms traditional methods in terms of sensitivity and speed, providing new and efficient solutions for food safety detection.

The use of phage and phage display technologies, in conjunction with biosensors, for the detection of foodborne pathogens is being extensively investigated. Mannoor et al.34 immobilized phage display peptides on gold electrodes to detect foodborne pathogens using electrochemical methods. Pardoux et al. 35 employed phage display peptides as biorecognition elements for

the detection of specific foodborne pathogens through the surface plasmon resonance (SPR) technique. Morton et al. 36 utilized phage display peptides, screened via phage display technology, in combination with magnetic nanoparticles for the detection of foodborne pathogens. Garcia-Calvo et al. 37 identified and characterized a high-affinity peptide, based on which an indirect enzyme-linked immunosorbent assay (ELISA) was developed that meets the legal detection limit and can be applied to evaluate gluten-free diets. Chenxi Huang et al. 38 investigated phage-based magnetic relaxation switching (MRS) biosensors, which can detect Salmonella in food using bioorthogonal response signal amplification. Wang Shuai et al. 39introduced a novel dual-mode, dual-target biosensor that utilizes Tesla valve-assisted electrochemical and fluorescent signals for the simultaneous detection of foodborne pathogens. This approach reduces the false-positive rate through a dual-mode strategy and offers a new design concept for the rapid detection of multiple foodborne pathogens in the field.

To date, phage and phage display technology for screening peptides have been utilized to develop biosensors aimed at identifying various foodborne pathogenic microorganisms, including Escherichia coli O157:H7, Salmonella typhimurium, Listeria monocytogenes, and Bacillus anthracis40. A range of phage-based biosensors has been employed to detect different microbial pathogens in complex analytes or real samples. Ongoing studies conducted in laboratories demonstrate significant potential for the rapid detection of foodborne pathogens in the future.

## 3. Signal Amplification Mechanism of Phage-Based Biosensors

Signal amplification mechanisms enable biosensors to detect extremely low concentrations of target analytes, thereby increasing sensitivity and lowering the detection limits of these devices. The application of CRISPR/Cas (Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated proteins) systems in biosensors and bioimaging is rapidly emerging as a significant research focus. The precise nucleic acid targeting and cleavage capabilities of CRISPR/Cas systems can be seamlessly integrated with various nucleic acid-based signal amplification techniques, enhancing the performance of biosensor technologies that utilize CRISPR/Cas systems. The precision of the nucleic acid targeting and cleavage functions of the Cas system can be easily combined with a variety of nucleic acid-based signal amplification techniques to improve the performance of biosensor technologies based on the CRISPR/Cas system41 .The approach of the CRISPR/Cas system as a signal amplification mechanism can significantly improve the sensitivity and specificity of biosensing systems, broaden the range of detectable targets, and facilitate the use of diverse signal output modes42.

Phage display technology is a crucial component of signal amplification mechanisms. Recombinant phages can serve as biorecognition elements that bind to molecules captured by biosensors. The bound phage can enhance signal strength through its replication ability or catalyze signal generation from the substrate by attaching additional signal amplification components, such as enzyme tags 43. The M13 phage is a significant virus with characteristic structural features that can be widely utilized as a scaffold for manipulating signal transduction. The pIII coat protein at the end of the M13 phage is involved in the molecular recognition of specific target analytes through phage display technology, while the pVIII coat protein is responsible for amplifying signal transduction via its chemical and biological modifications 44.

In conclusion, phages serve as valuable tools for signal amplification mechanisms due to their inherent ability to replicate. Through modern bioengineering techniques, phages can be specifically designed and adapted to meet various biosensing requirements, significantly improving the sensitivity and detection capabilities of biosensors. The integration of diverse signal amplification strategies with electrochemical biosensors to boost sensitivity has become an essential trend. In the realm of phage-based electrochemical biosensors, multiple signal amplification strategies are employed to enhance the detection signal, minimize background noise, and improve overall detection performance. Therefore, selecting an appropriate signal amplification strategy is critical during the preparation of biosensors.

## 4. Application of Microfluidics in Phage-Based Biosensors

Microfluidics enables precise guidance, control, mixing, reaction, and detection of fluids by integrating micro-components such as microfluidic channels, micro-valves, micro-pumps, and sensors 4546. By simulating in vitro and in vivo conditions, microfluidics allows for rapid prediction of interactions between bioproducts and biological compounds, facilitating the study of the relationship between in vitro and in vivo environments47. Given its advantages, microfluidics has emerged as a powerful tool for high-throughput screening of high-purity and efficient antibodies. It has been widely applied in particle sorting, single-cell analysis, in vitro diagnostics, and high-throughput sequencing48 50.

The integration of microfluidics with phage display technology has garnered significant interest from researchers. Jonas et al.51 developed an acoustic microfluidic chip for automated phage isolation, offering an alternative to manual centrifugal separation. Jinpeng Wang et al. 52created a microfluidic-assisted phage display system that efficiently screens high-affinity peptides against a minimal number of target cells, minimizing cell loss. Raftery et al. 53proposed a microfluidic chip that markedly enhances phage-target mixing efficiency by employing electrohydrodynamic principles; however, the applicability of this chip for screening actual biological functions remains to be validated. Junxia Wang et al. 54developed a microfluidic system that facilitates monoclonal phage amplification and target binding by encapsulating a single phage and target within a water-in-oil droplet. Philpott et al. 55designed a magnetic field-driven microfluidic system to increase binding strength by introducing a substantial amount of non-target cellular background.

The integration of microfluidics, phage display, and biosensor technologies represents an innovative interdisciplinary research field. The complementary strengths of these three technologies provide new opportunities for advancements in biomedical research and diagnostics.

## 5. Summary

Biosensors are increasingly utilized in various fields, including healthcare, environmental monitoring, and food safety. However, their development and application face several challenges, such as the trade-off between sensitivity and selectivity, the need for real-time monitoring and detection, the demand for miniaturization and convenience, the complexities of multidisciplinary collaboration, and issues related to biocompatibility and reusability. When integrating phage technology with biosensing, it is essential to address not only the technical challenges associated with biosensors but also those specific to using phage as a recognition element. In summary, the research and application of phage-based biosensors are advancing in several innovative directions. The ongoing development of phage technology is also driving progress in biosensor technology, creating new possibilities and opportunities for applications across various fields. Through continuous technological innovation and interdisciplinary collaboration, the use of phage in biosensors is becoming increasingly extensive and sophisticated.

This paper discusses the application of phage-based biosensors in the fields of disease detection and food safety. By thoroughly analyzing existing literature and experimental data, it is evident that phage-based biosensors demonstrate exceptional sensitivity, specificity, and real-time monitoring capabilities during the detection process, efficiently identifying and monitoring target biomolecules. However, several challenges remain for the practical application of phage-based biosensors. Issues such as stability, reproducibility, and standardization must be addressed in current research. In light of these challenges, future research should focus on enhancing the overall performance of phage-based biosensors, particularly in terms of stability, reproducibility, and standardization. Additionally, researchers should explore the potential of phage-based biosensors across a broader range of applications to expand their utility and impact. As technology continues to advance, we have reason to believe that phage-based biosensors will play a pivotal role in various fields, providing innovative solutions for food safety, healthcare, and beyond. Through ongoing technological innovation and practical application, phage-based biosensors are expected to become an indispensable component of future detection technologies.

## Declarations

**Funding**

This work was supported by Scientific Research Project of Department of Education of Guangdong Province（Grant numbers ：2023ZDZX2057） and GuangDong Basic and Applied Basic Research Foundation（Grant numbers ：2023A1515140070).

**Competing Interests:** The authors declare that they have no conflict of interest.

**Ethical Approval:** Not applicable

**Consent to Participate:** Not applicable

**Consent to Publish:** Not applicable

**Authors Contributions:** Not applicable

**Availability of Data and Materials:** Not applicable

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