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Review

# Revolutionizing medicine: Molecularly imprinted polymers as precision tools in cancer diagnosis and antibiotic detection

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## Abstract

Molecularly imprinted polymers (MIPs) are pivotal in medicine, mimicking biological receptors with enhanced specificity and affinity. Comprising templates, functional monomers, and cross-linkers, MIPs form stable three-dimensional polymer networks. Synthetic templates like glycan and aptamers improve efficiency, guiding the molecular imprinting process. Cross-linking determines MIPs' morphology and mechanical stability, with printable hydrogels offering biocompatibility and customizable properties, mimicking native extracellular matrix (ECM) microenvironments. Their versatility finds applications in tissue engineering, soft robotics, regenerative medicine, and wastewater treatment. In cancer research, MIPs excel in both detection and therapy. MIP-based detection systems exhibit superior sensitivity and selectivity for cancer biomarkers. They target nucleic acids, proteins, and exosomes, providing stability, sensitivity, and adaptability. In therapy, MIPs offer solutions to challenges like multidrug resistance, excelling in drug delivery, photodynamic therapy, photothermal therapy, and biological activity regulation. In microbiology, MIPs serve as adsorbents in solid-phase extraction (SPE), efficiently separating and enriching antibiotics during sample preparation. They contribute to bacterial identification, selectively capturing specific strains or species. MIPs aid in detecting antibiotic residues using fluorescent nanostructures and developing sensors for sulfadiazine detection in food samples. In summary, MIPs play a pivotal role in advancing medical technologies with enhanced sensitivity, selectivity, and versatility. Applications range from biomarker detection to innovative cancer therapies, making MIPs indispensable for the accurate determination and monitoring of diverse biological and environmental samples.

**Keywords:** Molecularly imprinted polymers (MIPs), Cancer diagnosis, Antibiotic detection, Biomedical applications

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# 1. Introduction

## 1.1. Formation

The development of molecularly imprinted polymers (MIPs) is a crucial step in the fabrication of materials designed to emulate the capabilities of biological receptors, placing significant importance on enhancing specificity and affinity. This complex procedure relies on three essential elements including functional monomers, templates, and cross-linkers. Templates play a central role in guiding the molecular imprinting process. They are instrumental in directing how functional groups within functional monomers are organized during polymerization. Ideal templates possess remarkable chemical stability and house functional groups that form effective bonds with functional monomers [1]. These bonds should endure throughout the polymerization process. Traditionally, templates were often derived from biological macromolecules like proteins or cells. However, the intricate nature of biological templates, their non-specific recognition sites, and limitations associated with polymerization methods have prompted the application of synthetic receptors involving aptamer, monosaccharide, oligosaccharide, and glycan. Synthetic templates play a critical function in enhancing the efficiency and accuracy of imprinting. Another crucial consideration in the formulation of MIP is the choice of functional monomers. The choice of these monomers is guided by the characteristics of the template, taking into account factors such as charge, size, and chemical identity. The monomers are carefully crafted with recognition units that engage with the template, establishing either covalent or non-covalent bonds. These interactions predominantly take place during the pre-polymerization phase, ultimately influencing the quality and quantity of recognition units present in the final MIP [2-4].

Following the effective engagement between functional monomers and the template, cross-linking agents are introduced. Their main function is to firmly bind the functional groups of the monomers to the template, leading to the formation of a sturdy three-dimensional polymeric network. This network serves to preserve the integrity of the binding sites, ensuring their stability even after the template molecule has been removed [5, 6] (Figure 1).

## 1.2. Crosslinking

Cross-linking assumes a crucial role in the imprinting process by aiding in the exact organization of functional monomers surrounding the template molecules. This leads to the formation of a highly cross-linked polymeric matrix, and upon template removal, it contributes significantly to refining the morphology and enhancing the mechanical stability of MIPs [7]. The selection and quantity of cross-linker monomers can affect the properties of MIPs during the polymerization process [8]. The amount of cross-linker monomers employed during polymerization can determine two main properties of MIPs including the number of recognition sites within MIPs and the mechanical stability. In this way, lower cross-linker monomers result in undesirable mechanical properties. In addition, a higher amount of cross-linker monomers can diminish the number of recognition sites per unit mass of MIPs [9, 10]. Therefore, optimization of the cross-linker-to-monomer ratio is a critical factor in obtaining optimal polymerization outcomes. Moreover, the choice of the crosslinking agent significantly influences the quality and yield of the final MIP post-polymerization. In addition to the selectivity and affinity for the target template, the porosity and mechanical properties can be affected by the meticulous pairing and arrangement of monomers [11].

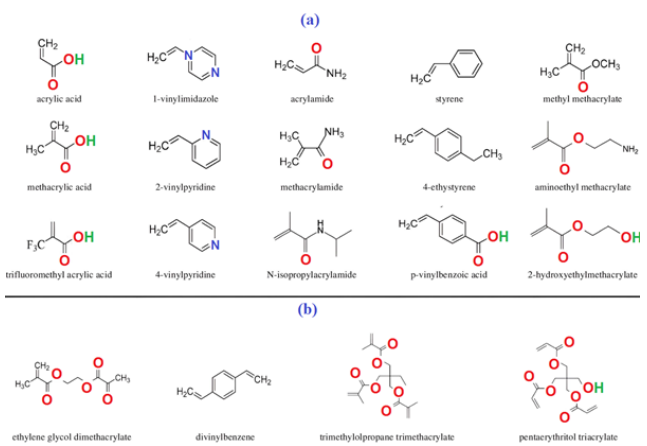


**Fig. 1.** Commonly applied functional monomers (a) and crosslinking monomers (b) in molecular imprinting process (Adopted with modification from [6]).

## 1.3. Printable Hydrogels

Printable hydrogels are 3D cross-linked polymer networks known for their remarkable water-absorbing and retaining capabilities, often exceeding 90%. These hydrogels are held together by a combination of interactions, including hydrogen bonds, electrostatic attractions, van der Waals interactions, hydrophobic forces, water-mediated hydrogen bonds, covalent cross-links, and various combinations thereof [12]. One of the key attributes of hydrogels is their suitability as soft material systems for emulating native extracellular matrix (ECM) microenvironments. Their biocompatibility, adjustable mechanical properties, and degradability make them ideal candidates [13, 14]. Moreover, hydrogels can easily integrate bioactive peptides including Ile-Lys-Val-Ala-Val (IKVAV), Arg-Gly-Asp (RGD), and Asp-Gly-Glu-Ala (DGEA), along with other biomolecular structures such as nucleic acids, glycans, fatty acids, and growth factors (brain-derived neurotrophic factor (BDNF), transforming growth factor-beta-1 (TGF-β1), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), and fibroblast growth factor-2 (FGF-2) [15, 16]. This enables the development of biomimetic supramolecular scaffolds [17]. Certain hydrogels demonstrate valuable shear-thinning and thixotropic properties, which enhance their suitability as materials for bioprinting [18]. Due to their adaptable characteristics and versatile manufacturing techniques, the application of printable hydrogels spans a broad spectrum in biomedical and engineering fields. These hydrogels find applications in various fields, such as tissue engineering, regenerative medicine, wastewater treatment, and soft robotics [19, 20].

Hydrogels frequently employed for 3D bioprinting originate from either natural or synthetic proteins involving collagen, fibrin, gelatin, spider silk, gelatin methacrylamide (produced by the reaction of methacrylic anhydride with gelatin), and ECM-derived proteins such as Matrigel matrix [11]. Additionally, self-assembling peptides and polysaccharides such as alginate, chitosan, gellan gum, agarose, κ-carrageenan, and methylcellulose are commonly employed in 3D bioprinting [11, 21]. The gelation process

of hydrogels significantly influences both cell viability and printing precision, and it can be broadly categorized into five common techniques: ionic, thermal, enzymatic, photo-crosslinking, and chemical crosslinking [22].

## 2. Anticancer applications

Cancer is a devastating disease originating from malignant cells that spreads within the body, causing damage to healthy tissues and, in many cases, resulting in fatal outcomes [23-26]. Early diagnosis and effective therapy by novel technology such as functionalized biomaterials and nanomaterials are crucial factors for increasing patient survival [27, 28]. Traditionally, cancer diagnosis relies on laborious and time-consuming histological tissue evaluation, often making early detection challenging [29-31]. MIPs are emerging as versatile biomaterials with multifaceted applications in the detection and treatment of cancer. MIP-based detection systems offer enhanced sensitivity and selectivity in identifying cancer biomarkers [32, 33]. In contrast to traditional methods relying on antibodies or aptamers, MIPs can be synthesized more efficiently and cost-effectively, with high specificity. These methods are performed by a molding process applying a template molecule, allowing customization and affinity enhancement through post-imprinting modifications. Due to their ability to identify specific molecules with a strong attraction and precise discrimination, hydrogels have been extensively studied as highly exceptionally promising biomaterials for theragnostic applications in cancer research [34, 35].

While numerous reviews primarily have focused on strategies for the diagnosis and therapy of cancer, the potential role of MIPs in the progress of these therapeutic issues has not been reviewed comprehensively. Therefore, this review conducts a thorough analysis of the recent developments in this field (Figure 2)[6].

### 2.1. MIPs-based cancer diagnosis

Tissue biopsies serve as the conventional, albeit invasive, method for cancer diagnosis, constrained to specific sample regions [36]. Liquid biopsies, detecting circulating cancer biomarkers, offer a non-invasive and cost-effective alternative [37]. An alternative approach involves the *in vivo* imaging of cancer biomarkers [38]. Sensors and imaging probes based on MIPs have proven effective in detecting a range of cancer biomarkers, encompassing cancer cells, exosomes, proteins, and nucleic acids [39]. These technologies combine stability, sensitivity, and adaptability to overcome the distinct detection challenges posed by different biomarkers [40]. For cancer diagnosis, nucleic acids, specifically ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), have conventionally functioned as important indicators. These molecules are commonly released into the bloodstream following cell apoptosis [41].

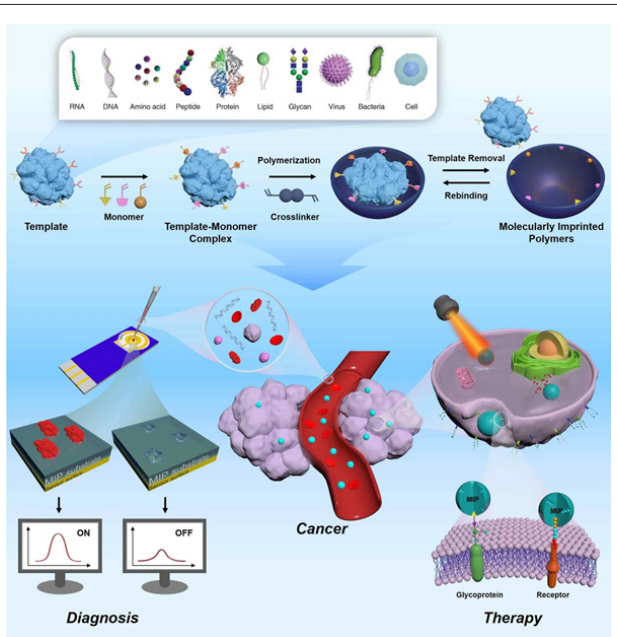


**Fig. 2.** Schematics show that MIPs are promising polymeric materials with versatile applications in cancer theragnostics and therapy (Extracted from [6]).


**Fig. 3.** The main steps for the discovery and application of new biomarkers (Adapted from [44]).

Arslan and colleagues have introduced a fluorescent sensor designed for the detection of double-stranded DNA (dsDNA), a common component in tumor exosomes with diagnostic significance. The sensor utilizes mercapto-propyl-trimethoxy-silane-capped Mn-doped ZnS quantum dots (QDs) that undergo imprinting through sol-gel polymerization. In this process, a polymeric network forms around the template, the cationic dye malachite green. The sensor operates in two modes including a 'turning off' mode and a 'turned on' mode. Under optimized conditions, the approach attains a limit of detection (LOD) of 19.48 ng/mL. Moreover, the sensor's performance in spiked urine samples validates its applicability to real-world samples [42]. Protein detection probes stand out as one of the extensively explored applications for MIPs [43]. It should be noted that there are five steps for the discovery and application of new biomarkers (Figure 3). In the case of cancer biomarkers, their remarkable bioavailability makes these highly dynamic molecules successful. Multiple studies underscore their potential in the diagnosis, prognosis, and monitoring of tumours [44].

Metal and metal oxide NPs have illustrated desirable properties for various applications in biomedicine [45, 46]. MIP-based electrochemical biosensors have obtained more attention owing to several benefits including simplicity, high sensitivity, and cost-effective properties [47-49]. In pursuit of these advantages, the application of a surface-enhanced Raman spectroscopy substrate with a surface-molecularly imprinted polymer (SMIP) is a useful method. This can be possible by the incorporation of ethynyl benzene into dopamine on the surface of gold nanoparticles (NPs), combined with an imprinted core-molecule-shell-molecule NP-coated surface. The biosensor's internal standard was fine-tuned, exhibiting a silent zone at 2024 $cm^{-1}$. Zhou et al. (2019) approached carcinoembryonic antigen detection differently by employing two types of MIPs in an immuno-sandwich assay. In their method, they utilized one MIP to cover the gold NP layer with glycan and used it for targeting

the peptide epitope. In another strategy, glycan-imprinted Raman-active silver NPs were applied to recognise and capture the peptide epitope. The dual recognition strategy, operating orthogonally, appeared to heighten the specific sensing mechanism. The efficacy of this approach was validated through testing with various proteins, including β-casein, bovine serum albumin, human apo-transferrin, horseradish peroxidase, and ribonuclease B [50].

Silica NPs in the dimer, trimer, and tetramer forms can be applied due to their high porosity properties for loading therapeutic agents [51]. Exosomes present a challenge in molecularly imprinted polymer MIP applications due to their irregular size and shape, often requiring the use of surrogate templates [52]. Zhu et al. (2020) tackled this by constructing an electrochemical detection platform for the analysis of exosome particle size distribution. They coated glassy carbon electrodes altered with gold NP-graphene oxide by 4-mercaptophenylboronic acid in a layer and employed silica NPs coated with horseradish peroxidase in various sizes (50, 100, and 150 nm) as templates. This approach enabled a successful and consistent analysis of simulated exosome size ratios. It's worth noting that the application of this method to biological samples was still pending [53].

An alternative strategy for addressing exosome surface irregularities involves combining MIPs integrated with specific antibodies and aptamers [54]. Mori et al. (2019) engineered a molecularly imprinted sensing platform designed for the detection of exosomes derived from prostate cancer. They utilized a histamine-tagged protein G-tagged protein G to anchor a CD9-targeting antibody to the gold sensor surface, as CD9 is abundant on exosome surfaces. After the immobilization of template exosomes from the PC3 prostate cancer cell line on the surface, methacryloyl disulfide groups were attached for post-imprinting modifications [55].

In the study carried out by Ma et al. (2021), a sialic acid (SA)-imprinted, temperature-responsive hydrogel layer has been developed for the discriminatory capture and release of cancer cells. The process involves imprinting the hydrogel with SA at 37°C, establishing switchable SA-recognition sites that strongly bind to SA at 37°C and weakly bind at a reduced temperature (e.g., 25°C). Due to the frequent overexpression of SA on cell membrane proteins or lipids, this hydrogel can selectively recognize cancer cells. The research confirmed the hydrogel's efficiency in capturing cancer cells from culture mediums and real blood samples. Furthermore, these captured cells can be non-invasively liberated by reducing the temperature. This method provided non-invasive processing, high capture efficiency, exceptional cell selectivity, and more stable and durable SA-imprinted sites when compared to natural antibodies or receptors [56].

## 2.2. MIPs-based cancer therapy

Cancer continues to pose a substantial global health challenge, characterized by limited treatment options and challenges such as multidrug resistance, tumor complexity, and non-specific drug targeting. Traditional therapies have drawbacks, including permanent genetic changes and off-target effects [57]. MIPs provide a solution by selectively targeting specific cancer-related proteins like saccharides and glycans, which are often overexpressed with cancer cells [58]. This unique characteristic of MIPs can be harnessed for drug delivery, photothermal therapy (PTT), photodynamic therapy (PDT) and biological activity regulation as standalone therapeutic agents, addressing the limitations of conventional treatments [58]. PTT is an emerging cancer treatment method that harnesses photothermal agents capable of absorbing specific light wavelengths. Upon exposure to this light, these agents generate heat, leading to localized cancer cell death. Photothermal nanoparticles have been verified to trigger an antitumor immune response and transform a "cold tumor" into a "hot tumor". PTT has garnered attention due to its advantages, including precision, non-invasiveness, and low toxicity, setting it apart from conventional treatment approaches [59]. In particular, near-infrared (NIR) light-mediated PTT has gained popularity for its ability to induce necrosis or apoptosis in cancer cells by producing localized hyperthermia [60].

In a study conducted by Ma et al., a novel approach was presented, utilizing human serum albumin (HSA)-imprinted polymer-coated $Fe_3O_4$ NPs ($Fe_3O_4$@MIPs) to enhance the delivery of photothermal nanoparticles for cancer therapy. $Fe_3O_4$@MIPs are engineered to tackle the issue of rapid elimination from the reticuloendothelial system. These nanoparticles are enveloped in a polymer imprinted with HSA and then stripped of the HSA template. The resultant $Fe_3O_4$@MIPs exhibited specific reabsorption of HSA, forming an albumin-rich protein corona in the bloodstream. This leads to reduced removal from the reticuloendothelial system in comparison to non-imprinted particles ($Fe_3O_4$@NIPs). Furthermore, the polydopamine-based molecularly imprinted polymer enhances the photothermal effect of $Fe_3O_4$ NPs. In vivo experiments showcase a significant increase in tumor accumulation with $Fe_3O_4$@MIPs, producing more heat upon laser irradiation and facilitating efficiently induced immunogenic cell death. The conjunction of $Fe_3O_4$@MIPs with a programmed cell death-ligand 1 (PD-L1) antibody curbs primary tumor growth and eliminates lung metastasis through immunological mechanisms [61].

In contrast to PTT, PDT emerges as another robust phototherapeutic strategy for cancer treatment by using light, a photosensitizer (PS), and oxygen to activate the PS, which then generates highly toxic reactive oxygen species (ROS) upon exposure to light. Two reaction mechanisms, known as type I and type II, produce ROS through electron/hydrogen transfer or energy transfer to molecular oxygen. PDT is highly regarded for its non-invasive nature, selective localized treatment, and minimal side effects, making it an attractive choice for anticancer therapy [62].

Lin and colleagues conducted a study centered on precision medicine applications in PDT utilizing luminescent nanocomposites known as MC540/MNPs@MIPs/UCNPs. In this study, green-emitting UCNPs ($LiYF_4$:$Yb^{3+}$/$Ho^{3+}$@$LiYF_4$:$Yb^{3+}$) were synthesized and loaded the photosensitizer MC540 on magnetic NPs (MNPs) were encapsulated within MIPs for targeting cancer cells. These nanocomposites enable cytotoxic PDT for precise tumour cell destruction by utilizing luminescence resonance energy transfer (LRET) from upconversion nanoparticles (UCNPs) to excite MC540. This catalyzes the generation of ROS, leading to cell toxicity. The research also exhibited the hindering of the PD-L1 which can further augment treatment by averting

PD-1/PD-L1 immune blockade during immunotherapy. Although the nanocomposites illustrated slight toxicity without illumination, surface modifications could be explored to mitigate these effects and enhance their utility for *in vivo* therapy (Figure 4)[63].

MIPs present innovative methods for biological activity regulation by precisely inhibiting or activating enzymes which can serve as anticancer drugs by modulating appropriate biological functions [64]. This strategy, distinguished by its high specificity and affinity, addresses the limitations of conventional inhibitors and antibodies. MIPs are emerging as a promising option for tailored enzyme regulation in various biological processes, with potential applications in drug development and therapy [65]. Trypsin, a well-studied matrix serine protease, plays a crucial role in diverse pathological processes, such as tumor invasion and metastasis. Suppression of trypsin activity is a promising approach for treating trypsin-dependent cell injuries [66].

Xu et al. (2021) produced highly specific and potent trypsin inhibitors using molecular imprinting techniques. They immobilized trypsin on the functionalized glass beads by IDA-$Cu^{2+}$ and created trypsin-imprinted NPs (MIP-trypsin) via solid-phase imprinting. MIP-trypsin featured an exposed immobilized active site and oriented binding sites on the surface, resulting in high selectivity toward trypsin. Quartz crystal microbalance sensors confirmed the MIP-trypsin selectivity, while in vitro assays demonstrated its inhibitory effect on trypsin (inhibition constant of 3.4 nM). Notably, MIP-trypsin protected human healthy liver cells (L-02) from trypsin-induced damage by inhibiting ECM lysis. These findings hold promise for targeted therapies against conditions involving abnormal trypsin activity, such as cancer metastasis [67].

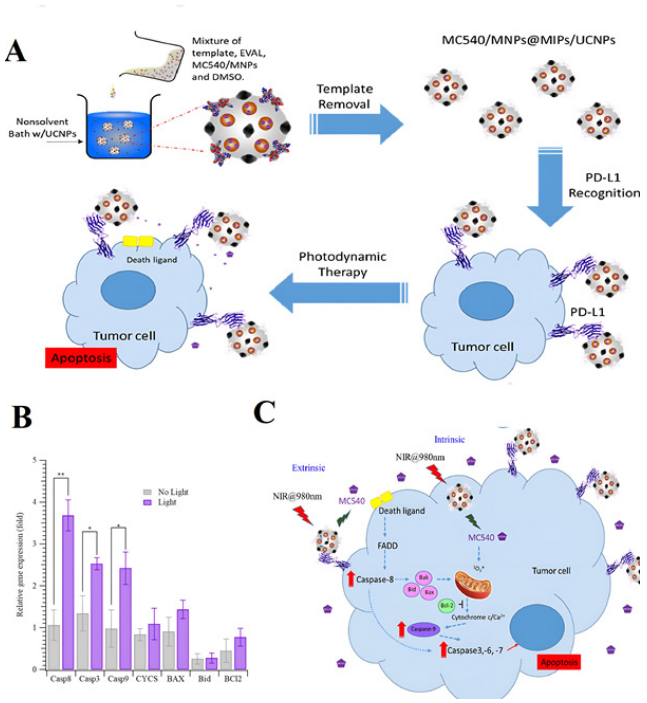


**Fig. 4.** (A) The study involves the synthesis and application of PD-L1 peptide-imprinted composite nanoparticles. (B) The analysis focuses on the relative gene expression. (C) The proposed pathway of cellular apoptosis, involving Casp3, Casp8, Casp9, and Bax, Bcl-2, Bid, somatic cytochrome c (CYCS), in HepG2 cells treated with MIPs under irradiation or without irradiation (Adopted from [63]).

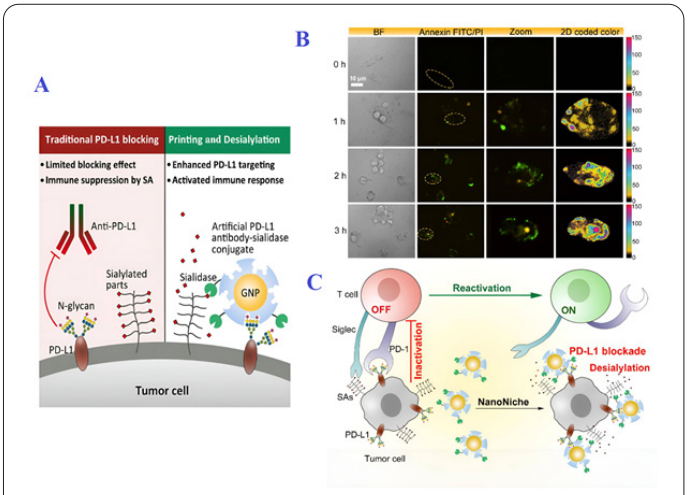


**Fig. 5.** Schematic images illustrating (A) Comparison of performance of molecularly imprinted using PD-L1 N-glycans as templates, with traditional PD-L1 blocking antibodies, (B) microscopy images reveal the T-cell-mediated eradication of tumor cells in MDA-MB-231 cells following incubation with 200 µL of NanoNiche at 0, 1, 2, and 3 hours post-treatment, (C) conceptual representation of T-cell reactivation facilitated by NanoNiche and its inhibitory effect on tumor cell growth (Adopted from [68]).

In the study carried out by Zhou et al. (2021), an innovative approach to inhibiting the PD-1/PD-L1 immune checkpoint is presented, to augment the reactivation of T-cells and thereby enhance their antitumor effects. The key component, termed "NanoNiche," is a molecularly imprinted nanostructure designed to specifically target N-linked glycans on PD-L1, thereby inhibiting the interaction between PD-L1 and PD-1, leading to T-cell reactivation. Furthermore, NanoNiche is conjugated with sialidase (Neuraminidase catalyse), an enzyme that cleaves SA from the tumor cell surface. The overexpression of sialoglycans on tumor cells can hinder immune cell infiltration by binding to Siglec receptors. NanoNiche's dual function—PD-L1 blockade and desialylation—works in tandem to enhance T-cell activity, ultimately leading to improved tumor cell killing. The methodology involves using gold NPs functionalized with boronic acid and $SiO_2$ imprinting layers to create NanoNiche. In cellular experiments, NanoNiche demonstrated specific binding to PD-L1, simultaneous SA degradation, and enhanced T-cell-mediated tumor-killing activity. This approach showed promising strategy for PD-L1 blockade therapy, offering a unique method for increasing treatment efficacy while reactivating T-cell immunity (Figure 5) [68].

## 3. Molecularly imprinted polymers in microbiology

The misuse and leftover traces of antibiotics pose a significant threat to both the environment and organisms [69]. Therefore, it has become crucial to be capable of precisely determining and monitoring the presence of antibiotics in various matrices. However, due to their low concentrations, diverse types, and complex compositions, it is often necessary to employ effective methods for recognition, separation, and enrichment before determining the presence of antibiotics [70]. MIPs have become a valuable asset in the field of analytical detection of antibiotics. MIPs are highly selective polymers that are prepared using molecular imprinting technology (MIT) [71].

This technology involves creating a template molecule

that mimics the structure of the target antibiotic followed by mixing the template molecule with functional monomers and cross-linkers to polymerization and form a three-dimensional network [72]. During this process, the template molecule is eliminated, leaving behind cavities or imprints that possess particular binding sites for the target antibiotic. One of the primary applications of MIPs in antibiotic analysis is as adsorbents in solid-phase extraction (SPE). SPE is a widely used technique for sample preparation, where MIPs are packed into a solid-phase cartridge or column. When a sample containing antibiotics is passed through the cartridge, the target antibiotics selectively bind to the imprinted sites on the MIPs, while other interfering compounds are washed away. This allows for efficient separation and enrichment of the antibiotics, enhancing their detection sensitivity [73]. Additionally, MIPs have also been utilized as identification elements in sensors for antibiotic recognition [71]. These sensors are designed to detect and quantify the presence of antibiotics in real time. The MIPs are integrated into the sensing platform, where they selectively bind to the target antibiotics. This binding event leads to a measurable signal change, which can be converted into a quantitative measurement of the antibiotic concentration [74]. In summary, the use of MIPs in antibiotic analysis has proven to be highly beneficial. Their ability to selectively recognize and bind to specific antibiotics allows for improved separation and enrichment techniques, leading to enhanced detection sensitivity. Furthermore, their integration into sensor platforms enables real-time monitoring of antibiotic presence. Overall, MIPs have an effective role in ensuring the accurate determination and monitoring of antibiotics in various environmental and biological samples.

Additionally, MIPs have been explored for bacterial identification in various strategies. One approach is to employ MIPs as selective recognition elements for specific bacterial strains or species. By imprinting the polymer with the target bacteria, MIPs can be designed to selectively bind to the target bacteria and differentiate them from other microorganisms. This can be useful in bacterial identification and detection applications. Moreover, MIPs can also be used for the extraction and enrichment of bacterial cells from complex samples, aiding in their identification and analysis [75].

### 3.1. MIPs for bacterial identification

MIPs have been applied as a tool for bacterial identification by imprinting the polymer with specific bacterial components, such as cell surface proteins or DNA sequences, MIPs can be used to selectively capture and identify bacteria in complex samples [76]. For instance, in a study conducted in 2020 by Bezdekova and colleagues [77], a new technique was developed to isolate *Staphylococcus aureus* from complex food samples using a method called molecular imprinting. Dopamine, a type of molecule, was used as a building block for creating a specific polymer layer that can bind to *S. aureus*. Fluorescence microscopy was used to detect the presence of the bacteria. The researchers investigated the optimal conditions for creating these polymer layers, as well as their ability to bind to *S. aureus*. The different steps of the process were combined into a single extraction method, where the polymer layer was attached to magnetic particles (referred to as magnetic MIPs). The researchers then used these magnetic MIPs to extract *S. aureus* from milk and rice samples. They also successfully tested the method on raw milk from cows with mastitis. With this new method, the researchers were able to detect bacteria in milk at a concentration of $1 \times 10^3$ colony-forming units per milliliter ($CFU \cdot ml^{-1}$), which is the limit set by European Union regulations for controlling microbial contamination in food [77, 78]. In a separate study, Yasmeen and colleagues (2021) formulated a chemosensor employing an electrochemical MIP for quick identification and quantification of the *E. coli* strain. The *E. coli* E2152 strain was effectively incorporated into a polymer through electrochemical polymerization. The functional monomer employed was 2-aminophenyl boronic acid and aniline served as the cross-linking monomer. Scanning electron microscopy (SEM) images revealed that the bacterial template was entirely encapsulated within the resulting MIP matrix in a single step, eliminating the need for additional complicated procedures. The three-step process employed to create MIP cavities proved successful. Subsequent SEM imaging verified the effectiveness of the template extraction process. Detection of the target *E. coli* E2152 strain was accomplished using an electrode coated with an MIP film, with a detection limit of up to 2.9 x 104 cells/mL [78].

In another study performed in 2023, the researchers developed a novel electrochemical sensing platform for detecting a toxin called vacuolating cytotoxin A (VacA) produced by the bacteria *Helicobacter pylori*. VacA is a virulence factor that has a prominent role in the pathogenesis of *H. pylori* and helps the bacteria establish it in the gastric cells of the host. The researchers developed a sensing platform by decorating silicon dioxide ($SiO_2$) nanoparticles on a screen-printed electrode. This platform acts as a receptor for the VacA protein. They created a molecularly imprinted polymer by polymerizing it directly on the screen-printed electrode using VacA antigen as a template. The functionality of the electrode was then researched using electrochemical techniques. Under carefully calibrated experimental parameters, the VacA-MIP/$SiO_2$@ screen-printed electrode demonstrated high sensitivity (0.304 mA $ng^{-1}$ $ml^{-1}$) and a very low limit of detection (0.01 ng $ml^{-1}$) within a linear range of 0.01-100 ng $ml^{-1}$. The researchers also investigated the influence of other potential interferents on the sensor's response and successfully determined the presence of VacA antigen [79]. In a 2023 study, researchers designed an electrochemical sensor for the detection of the specific bacterium *Listeria monocytogenes*. This sensor leverages platinum and screen-printed carbon electrodes that are customized with an MIP. The MIP bestows the sensor with the capability for selective detection of *L. monocytogenes*. The electrode modification involved a coating process including a layer of non-imprinted polypyrrole (NIP-Ppy) and a layer of *L. monocytogenes*-imprinted polypyrrole (MIP-Ppy). To eliminate the bacteria from the electrodes, they are subjected to incubation in various extraction solutions including trypsin, acetic acid, sulfuric acid, and L-lysine. The study seeks to determine the most efficient extraction solution, ensuring a sensor design that is both sensitive and reproducible. The efficacy of the MIP-Ppy and NIP-Ppy modified electrodes is assessed using pulsed amperometric detection (PAD). The most effective sensor is identified as the MIP-Ppy modified electrode with trypsin as the extraction solution. The

limit of detection (LOD) and limit of quantification (LOQ) for the sensor are established at 70 CFU/mL and 210 CFU/mL, respectively, with a linear range spanning from 300 to 6700 CFU/mL [80].

### 3.2. MIPs for antibiotics identification

This technique is also used against the evolution of antimicrobial resistance and to detect antibiotic residues. In a study, the researchers designed fluorescent nanostructures that can serve as sensing probes for detecting a specific antibiotic called ciprofloxacin. In detail, they synthesized a fluorescent metal-organic framework (MOF) called $NH_2$-MIL-53(Al) using a hydrothermal approach. They combined this MOF with MIPs to create a composite material that can selectively and specifically detect ciprofloxacin in water solutions. The use of MIPs is advantageous because it eliminates the need for pre-treatment of the sample. The creation of the MIP@NH2-MIL-53(Al) nanostructure was verified using various characterization techniques, including spectroscopy and microscopy. The resulting fluorescent composite demonstrates the potential for exceptionally sensitive and specific detection of ciprofloxacin in practical applications [81]. Furthermore, another study presented a new method for measuring the concentration of cloxacillin antibiotic in river and drinking water samples via a MIP as a selective sorbent for SPE (MISPE). The researchers synthesized several polymers using cloxacillin as a template and evaluated their binding characteristics through batch adsorption assays. They selected the most appropriate polymer for the determination of this antibiotic and combined it with high-performance liquid chromatography (HPLC) to analyse cloxacillin residues in water samples. The linearity of cloxacillin, a type of antibiotic, was evaluated by the MISPE methodology within the range of 0.05-1.5 µg/L. The recovery percentage, which measures the accuracy of the analysis, was found to be higher than 98% with a relative standard deviation (RSD) of less than 4%. The limits of detection and limits of quantification were determined to be 0.29 and 0.37 µg/L, respectively, for drinking water. For river water, the limits of detection and limits of quantification were found to be 0.8 and 0.98 µg/L, respectively. Thus, the suggested MISPE-HPLC methodology was effectively employed for the identification of cloxacillin in drinking and river water samples [82]. Another study describes a new type of sensor for detecting sulfadiazine (SDZ), a compound commonly found in food samples. The sensor is made using MIP, which involves creating a special membrane on an electrode. This membrane contains two templates, SDZ and propyl gallate, and is modified with nanocomposites called $CuInS_2$/ZnS. The sensor works by measuring the existing disparities between the MIP membrane and a non-imprinted polymer membrane at two different potentials (0.18 V and 0.92 V). By comparing these current differences, the sensor can determine the concentration of SDZ in a sample. This differential ratiometric method improves the reproducibility and stability of the sensor and reduces interference from other substances in the sample. The sensor was successfully used to detect SDZ in food samples, with a detection limit of 2.1 nM [83].

In a study in 2023, Zhang et al. developed a new fluorescence sensor that is highly sensitive and selective for detecting tetracycline antibiotics which pose a threat to both human health and the long-term growth of aquaculture and animal husbandry. The sensor is made up of nitrogen-doped carbon dots embedded in zinc-based metal-organic frameworks and incorporates a molecularly imprinted polymer (ZIF-8&N-CDs@MIP). The physical and chemical properties of the ZIF-8&N-CDs@MIP were analyzed using various techniques such as SEM, transmission electron microscopy (TEM), Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), Brunauer-Emmett-Teller (BET) analysis, and thermogravimetric analysis (TGA). Under optimal conditions, the sensor had a limit of detection of 0.045 µg mL−1 and was able to detect TC concentrations in the range of 0.1–4.0 µg/mL. The imprinted polymers used in the sensor demonstrated better selectivity for TC compared to non-imprinted polymers, and the quenching mechanism of the ZIF-8&N-CDs@MIP sensor was attributed to the inner filter effect. This study provides an effective and reliable method for specifically detecting TC and has been successfully applied to milk and egg samples with satisfactory recovery rates (80.67–95.22%) [84].

## 4. Conclusion

In conclusion, MIPs stand as pivotal tools in various scientific domains, showcasing their versatility and impact across different applications. In medicine, MIPs play a crucial role by mimicking biological receptors with enhanced specificity and affinity. The three components of MIPs–templates, functional monomers, and cross-linkers – come together to form stable three-dimensional polymer networks. The utilization of synthetic templates, such as glycan and aptamers, enhances the efficiency of the molecular imprinting process. In the realm of cancer research, MIPs shine in both detection and therapy. MIP-based detection systems demonstrate superior sensitivity and selectivity for cancer biomarkers, offering stability, sensitivity, and adaptability. In therapy, MIPs provide innovative solutions to challenges like multidrug resistance, excelling in drug delivery, PTT, photodynamic therapy, and the regulation of biological activity. Moving into microbiology, MIPs prove indispensable in the detection of antibiotics and the identification of bacteria. They serve as adsorbents in SPE, efficiently separating and enriching antibiotics during sample preparation. MIPs are tailored to recognize specific bacterial strains or species, contributing to bacterial identification. In the fight against antimicrobial resistance, MIPs play a vital role in monitoring antibiotic residues. In summary, MIPs emerge as versatile and indispensable tools, advancing medical technologies with enhanced sensitivity, selectivity, and adaptability. Their applications span from biomarker detection to innovative cancer therapies, making MIPs invaluable for accurate determination and monitoring across diverse biological and environmental samples.

## Abbreviations

BDNF: Brain-derived neurotrophic factor; TEM: Transmission electron microscopy; FTIR: Fourier-transform infrared spectroscopy; XRD: X-ray diffraction; BET: Brunauer-Emmett-Teller; SDZ: Sulfadiazine; TGA: Thermogravimetric analysis; SPE: Solid-phase extraction; CYCS: Somatic cytochrome c; DGEA: Asp-Gly-Glu-Ala; DNA: Deoxyribonucleic acid; dsDNA: Double-stranded DNA; SEM: Scanning electron microscopy; MOF: Metal-orga-

nic framework; ECM: Extracellular matrix; FGF-2: Fibroblast growth factor-2; HSA: Human serum albumin; IGF-1: Insulin-like growth factor-; IKVAV: Ile-Lys-Val-Ala-Val; LOD: Limit of detection; HPLC: High-performance liquid chromatograph; LRET: Luminescence resonance energy transfer; MIPs: Molecularly imprinted polymers; MNPs: Magnetic NPs; NIR: Near-infrared; NPs: Nanoparticles; PD-L1: Programmed cell death-ligand 1; PDT: Photodynamic therapy; PS: Photosensitizer; PTT: Photothermal therapy; QDs: Quantum dots; RGD: Arg-Gly-Asp; RNA: Ribonucleic acid; ROS: Reactive oxygen species; SA: Sialic acid; SMIP: Surface-molecularly imprinted polymer; SPE: Solid-phase extraction; TGF-β1: Transforming growth factor-beta-1; UCNPs: Upconversion nanoparticles; VEGF: Vascular endothelial growth factor; MIT: Molecular imprinting technology; MIP-trypsin: Trypsin-imprinted NPs; MISPE: MIP as a selective sorbent for SPE.

## Conflict of Interests
The author has no conflicts with any step of the article preparation.

## Consent for publications
The author read and approved the final manuscript for publication.

## Ethics approval and consent to participate
No human or animals were used in the present research.

## Informed Consent
The authors declare that no patients were used in this study.

## Availability of data and material
The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Authors' contributions
writing—original draft preparation: Sargol Aminnezhad and Mehran Alavi, conceptualization: Sargol Aminnezhad and Mehran Alavi, supervision and resources: Zhenchao Xu, review and editing: all authors. All authors have read and agreed to the published version of the manuscript.

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