

## A REVIEW ON ADVANCEMENT ON MIP (MOLECULAR IMPRINTED POLYMER) BASED SENSOR FOR DIAGNOSIS OF LUNG CANCER DETECTION

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### ABSTRACT

Cancer remains a severe disease characterized by abnormal cell proliferation that spreads throughout the body, making early diagnosis and targeted treatment absolutely critical for improving patient survival rates. Traditional diagnostic techniques, such as invasive tissue biopsies, alongside conventional targeting agents like natural antibodies and aptamers, often suffer from being laborious, expensive, and prone to physical degradation. To address these inherent limitations, molecularly imprinted polymers (MIPs) have emerged as highly stable, cost-effective "synthetic receptors" capable of recognizing targeted molecules with exceptional affinity and selectivity. This review meticulously details diverse synthesis strategies—including bulk, surface, and epitope imprinting—which provide the structural rationale behind these artificial antibodies and allow them to overcome mass transfer issues associated with complex biological macromolecules. Furthermore, it provides a comprehensive overview of the recent progress in utilizing MIPs for in vitro and in vivo cancer theragnostics. MIP-based biosensors demonstrate exceptional adaptability, successfully targeting and capturing a wide array of circulating cancer biomarkers, ranging from nucleic acids and proteins to uniquely shaped exosomes and whole cancer cells. Beyond diagnostics, MIPs facilitate the transition to advanced theragnostics by enabling highly localized, stimuli-responsive drug delivery. These smart nanocarriers release chemotherapeutics triggered by internal or external stimuli (such as pH, temperature, or magnetic fields) and integrate seamlessly with light-mediated treatments like photothermal and photodynamic therapies, thereby enhancing localized efficacy while minimizing off-target toxicity. They are also being explored for biological activity regulation, successfully acting as artificial enzyme inhibitors and aiding in immune checkpoint blockade therapies to reactivate T-cell immunity. Despite their immense promise, the clinical deployment of MIPs faces several hurdles, including the complex heterogeneity of tumor subtypes, a lack of standardized synthesis and evaluation protocols, and the critical need for deeper investigations into long-term in vivo toxicity, biological dispersion, and biodegradability. Taken together, the extensive topics discussed in this review aim to provide concise guidelines for overcoming these current bottlenecks, ultimately paving the way for the development of novel MIP-based systems that can diagnose cancer more precisely and promote highly successful, personalized treatments.

**KEYWORDS:** Molecular imprinted polymer (MIP), Lung cancer, Drug delivery.

## INTRODUCTION

Cancer, including severe malignancies like lung cancer, originates from malfunctions at the single-cell level that proliferate to destroy healthy tissues, ultimately threatening the patient's life. For these patients, the survival rate is heavily dependent on early diagnosis and the implementation of efficient treatments.<sup>[1]</sup>

Historically, the precise diagnosis of cancer has relied on the histological evaluation of tissues. However, these traditional tissue biopsies are often invasive, time-consuming, and laborious, which makes detecting cancer at its earliest stages incredibly difficult. Consequently, modern oncological research has shifted its focus toward the development of highly sensitive biosensors capable of monitoring cancer biomarkers in less invasive liquid biopsies. Because biomarkers often exist at extremely low concentrations during the early stages of cancer, detection systems must be exceptionally sensitive and specific to ensure successful diagnosis and treatment.<sup>[2]</sup>

While natural antibodies and aptamer-based targeting materials provide great specificity for detecting these biomarkers, they come with significant drawbacks: they are produced through long, laborious, and costly selection and screening processes. In stark contrast, Molecularly Imprinted Polymers (MIPs) offer a highly adaptable, cost-effective alternative that has shown incredible promise for sensitive and selective biomarker detection.

### Key advantages and mechanisms of MIPs include

- **Straightforward Synthesis:** MIPs only require a high-purity sample of the target molecule. They are created through the polymerization of specific functional monomers and crosslinking agents in the presence of this template. This molding process yields a highly specific, three-dimensional structure that is selectively complementary to the molecule of interest once the template is removed.<sup>[3]</sup>
- **Superior Stability and Shelf-Life:** Compared to biological antibodies or aptamers, these synthetic probes offer a significantly greater advantage in terms of stability, maintaining excellent structural integrity during prolonged storage. This allows the material to be adapted to a much broader range of clinical environments.
- **Customizable Affinity:** Post-imprinting modifications can be applied to custom-tailor the polymer. This not only increases the binding affinity between the target and the MIP but has also been shown to improve upon the sensitivity and detection range of traditional ELISA (enzyme-linked immunosorbent assay) systems.
- **Multifunctional Theragnostic Potential:** Beyond serving as exceptional detection probes and separation tools for complex biological samples, MIPs are now being harnessed for advanced therapeutic approaches. By imprinting a target on the surface of carrier nanoparticles, MIPs enable localized, controlled drug release, reducing toxic side effects by using only the exact amount of drug required.
- **Integration with Light Therapies:** MIPs can incorporate light-sensitive components to aggressively target cancer tissues while sparing healthy cells. When exposed to specific light wavelengths, these polymers can generate localized heat for photothermal therapy (PTT) or produce cytotoxic reactive oxygen species (ROS) for photodynamic therapy (PDT).

### MIP Synthesis Strategies for Sensor Development

The ultimate goal of molecular imprinting is to create synthetic receptors that exhibit a high degree of specificity and affinity toward a particular target molecule, allowing them to rival or replace biological receptors.<sup>[4]</sup> Selecting the appropriate synthesis method and reagents is crucial for producing a sensor with the required binding properties for cancer diagnostics.

### ❖ Essential Components of MIPs

The molecular imprinting process relies on the careful selection and interplay of three essential reagents:

- **Templates:** The template is the central blueprint that directs the organization of functional groups during polymerization. An ideal template must be chemically stable during the reaction, contain rich functional groups to form complexes with monomers, and ensure that binding does not interfere with the polymerization process.

While biological macromolecules (like whole proteins or cells) are commonly used, their complex structures and non-specific recognition sites have led to a shift toward synthetic receptors like glycans, oligosaccharides, aptamers, and epitopes.

- **Functional Monomers:** Monomers must possess functional groups capable of interacting with the chosen template through covalent or non-covalent interactions (such as hydrogen bonding, dipole, van der Waals, or  $\pi$ - $\pi$  interactions). The specific interaction between the template and the monomer during the pre-polymerization phase dictates the quality and quantity of the recognition units within the final MIP.
- **Cross-linkers:** Cross-linking agents immobilize the functional monomers around the template, generating a highly cross-linked, three-dimensional polymeric matrix. The amount and type of cross-linker strictly determine the mechanical stability, porosity, and the number of recognition sites of the MIP. An insufficient amount leads to mechanical instability, whereas an excessive amount can decrease the available recognition sites per unit mass.

### ❖ Imprinting Strategies

To manufacture MIPs suitable for capturing cancer biomarkers, researchers primarily utilize three distinct categories of molecular imprinting techniques.<sup>[5,6]</sup>

#### Bulk Imprinting

- **Mechanism:** This is the most traditional and straightforward approach. Template molecules, functional monomers, initiators, and crosslinkers are mixed in a solvent and completely polymerized into a solid mass.
- **Post-Treatment:** To expose the buried three-dimensional binding sites, the bulk polymer must undergo mechanical crushing, grinding, and sieving to obtain the desired particle size.
- **Advantages vs. Limitations:** While this method is low-cost, quick, and produces high-purity materials without complex instrumentation, the post-treatment steps are time-consuming and often yield particles with irregular sizes, shapes, and heterogeneous binding sites. Furthermore, the diffusion of large target molecules (like whole cells or proteins) to binding cavities buried deep inside the matrix is significantly hindered, which can lower sensor sensitivity.

#### Surface Imprinting

- **Mechanism:** To overcome the mass transfer limitations of bulk imprinting, surface imprinting places the template directly at or near the surface of the polymeric framework. This generally involves two steps: immobilizing the target template on a solid substrate surface, and then polymerizing a thin polymer layer around it.
- **Advantages:** This technique boasts a high surface-to-volume ratio, resulting in rapid template transfer, minimized diffusion distances, and reduced steric hindrance. This guarantees highly accessible binding sites and rapid biomarker recognition, making it exceptionally beneficial for capturing large (bio)macromolecules and circulating tumor cells.<sup>[7]</sup>

### Epitope Imprinting

- **Mechanism:** Utilizing whole proteins as templates can be difficult due to their numerous functionalities and high risk of denaturation during synthesis. Epitope imprinting refines the surface imprinting process by using only a specific, distinctive sequence of amino acids (the epitope) from the target protein as the template.
- **Advantages:** This greatly decreases the structural complexity of the imprinting process while still yielding an MIP capable of recognizing the whole protein in real biological samples. It offers improved applicability under diverse reaction conditions, a defined orientation for binding, and a much more abundant choice of viable templates.

### Advancements in MIP-Based Cancer Diagnosis

Tissue biopsy remains the most definitive method for cancer diagnosis, yet its invasive nature limits continuous monitoring and analysis to specific sample areas. Liquid biopsies utilizing MIPs present a non-invasive, highly sensitive alternative by detecting circulating biomarkers such as nucleic acids, proteins, exosomes, and whole cancer cells.<sup>[8,9]</sup>

#### ❖ Nucleic Acid Detection

Nucleic acids (DNA and RNA) released into the bloodstream after cell apoptosis serve as vital early-stage cancer markers.

- **MicroRNA Extraction:** Researchers successfully synthesized capture probes by polymerizing a layer of dopamine on silica nanoparticles to specifically extract microRNA-21 from glioblastoma cell lysates.
- **dsDNA Sensing:** A radiometric sensor utilized mercapto-propyl-trimethoxy-silane-capped Mn-doped ZnS quantum dots imprinted with malachite green. This system operates on a "turn on/turn off" phosphorescence resonance energy transfer mechanism, achieving a limit of detection (LOD) of 19.48 ng/mL for double-stranded DNA.
- **Gene Detection via Antibody Mimicry:** An electrochemical biosensor targeting the BRCA-1 gene utilized a glassy carbon electrode modified with gold nanoparticle-reduced graphene oxide and an MIP film (using rhodamine B as a template), yielding an ultra-low LOD of 2.53 fM.

#### ❖ Protein Biomarker Detection

Proteins are exceptional templates for MIPs due to their highly abundant functional sites.

- **HER2:** An MIP-based laser-scribed graphene sensing platform modified with gold nanostructures demonstrated an LOD of 0.43 ng/mL for human epidermal growth factor receptor 2 (HER2), a critical breast cancer marker.
- **Prostate-Specific Antigen (PSA) & CA-125:** Dual-modality impedimetric immunosensors and electrochemiluminescence sensors have successfully detected PSA at levels as low as 3.0 pg/mL. Similarly, screen-printed electrodes utilizing electropolymerized pyrrole achieved an LOD of 0.01 U/mL for CA-125, an ovarian cancer biomarker.

#### ❖ Exosome and Cell Detection

- **Exosomes:** The variable size and shape of exosomes complicate imprinting. Researchers address this by using "dull templates" (like silica nanoparticles matching the exosome's size) or by pairing MIPs with specific aptamers. For example, a fluorescence resonance energy transfer (FRET) system utilizing magnetic microparticles achieved an LOD of 2.43 million particles/mL.

- Whole Cells: Sialic acid (SA), overexpressed on cancer cell membranes, is a prime target. Thermo-responsive SA-imprinted hydrogels enable the selective capture and release of cancer cells from blood simply by adjusting the temperature to 37° C and 25° C , avoiding the denaturation issues common with traditional lectin-based methods.<sup>[10]</sup>

**Table 1: MIP-Based Cancer Biomarker Detection Capabilities.**

Biomarker Category	Target Biomarker	Detection Mechanism	Limit of Detection (LOD)
Nucleic Acid	BRCA-1 Gene	Electrochemical	2.53 fM
Nucleic Acid	dsDNA	Phosphorescence/Fluorescence	19.48 ng/mL
Protein	HER2	Electrochemical	0.43 ng/mL
Protein	CEA	Electrochemical / SERS	0.2589 pg/mL / 0.064 pg/mL
Protein	PSA	Electrochemiluminescence	3.0 pg/mL
Exosome	Exosomes	FRET Fluorescence	2.43 million particles/mL

### Advanced Theragnostic Modalities

Theragnostics combines targeted diagnostics with localized therapy. Because therapeutics can be encapsulated directly into the MIP network during its synthesis, the drug payload is protected from premature degradation until the polymer reaches the target site and is triggered to release it.

#### ❖ Combinatorial Light-Mediated Therapies

Single-mode therapies often face limitations, such as cancer cells developing resistance. MIPs are highly effective at delivering combinatorial treatments:

- Chemo-Photothermal Synergism: Heat generated by Photothermal Therapy (PTT) increases cell membrane penetrability, which dramatically enhances the cellular uptake of chemotherapeutic drugs released by the degrading MIP. For example, MIP-encapsulated doxorubicin (DOX) paired with graphene quantum dots allows for a slow, cumulative release of the drug over 3 hours when heated to 43°C via an 808 nm near-infrared laser.
- PTT paired with Immunotherapy: PTT can activate immune stimulation by generating heat within the tumor microenvironment. Human serum albumin-imprinted Fe<sub>3</sub>O<sub>4</sub> nanoparticles (Fe<sub>3</sub>O<sub>4</sub>@MIPs) target the SPARC protein (which is overexpressed in most tumor tissues). When irradiated, the localized heat triggers efficient immunogenic cell death, and when combined with a PD-L1 antibody, this method effectively inhibits primary tumor growth and metastasis.<sup>[11,12]</sup>

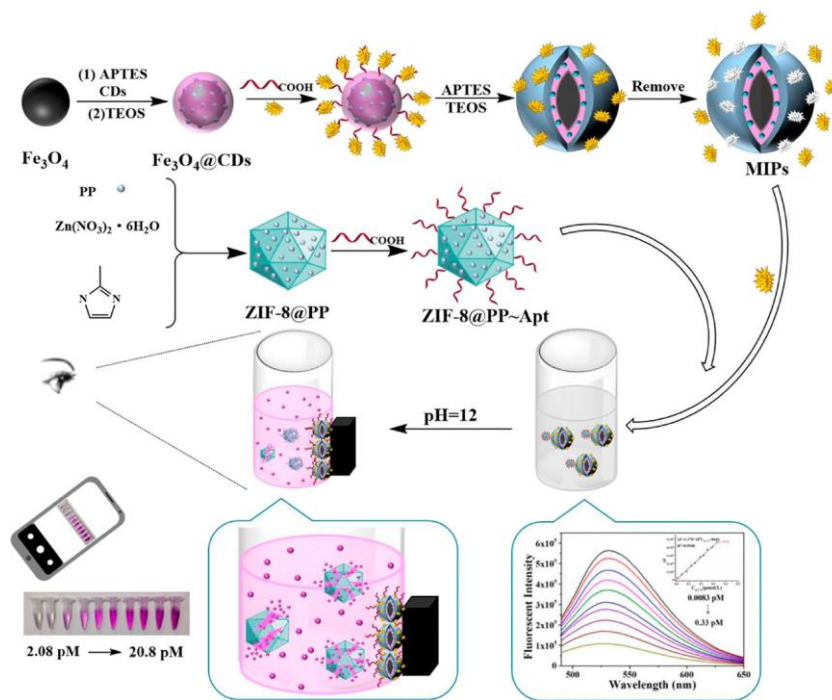


Figure 1: Schematic representation of the sensor construction and workflow with detection method of the virus.

❖ Synergistic Chemo-Photodynamic Therapy (PDT)

Traditional PDT relies on adequate oxygen to create toxic reactive oxygen species (ROS) via a type II reaction mechanism, but the rapid proliferation of neoplastic cells often creates a highly hypoxic (low-oxygen) tumor environment, hindering the treatment.

- To bypass this, researchers developed dual-template imprinted polymers with a core-shell structure combining DOX (chemotherapy) and chlorin e6 (a photosensitizer).
- Utilizing customized conjugated oligomers, these MIPs can generate cytotoxic ROS via an alternative type I reaction mechanism, successfully killing cancer cells even under severely hypoxic conditions (1%  $\text{O}_2$ ).<sup>[13]</sup>

Table 2: Overview of MIP-Based Specific Recognition for Cancer Therapy.

Therapeutic Strategy	Target / Template	Therapeutic Agent(s)	Targeted Cancer Type
Targeted Drug Delivery	Sialic Acid (SA)	Nitric Oxide (NO)	Hepatocellular carcinoma (HepG2)
Targeted Drug Delivery	N-terminal epitope of CD59	Doxorubicin (DOX)	Breast cancer (MCF-7)
Photothermal Therapy (PTT)	Sialic Acid (SA)	Polydopamine (PDA)	Breast (MCF-7) & Liver (HepG2)
PTT + Drug Delivery	Epitope of EGFR & DOX	PDA + DOX	Lung cancer (A549)
PTT + Immunotherapy	Human Serum Albumin	PDA + PD-L1 antibody	Breast cancer (4T1)
Photodynamic Therapy (PDT)	Sialic Acid (SA)	Photosensitizer (CB)	Prostate cancer (DU 145)

Advancements in MIP Sensors for Lung Cancer Diagnosis

The detection of lung cancer, particularly non-small cell lung cancer (NSCLC), relies heavily on identifying specific circulating biomarkers. MIPs are uniquely positioned to capture these diverse targets from complex biological fluids, providing a foundation for highly sensitive liquid biopsies.<sup>[15,16]</sup>

## 1. Ultra-Sensitive Detection of Carcinoembryonic Antigen (CEA)

Carcinoembryonic Antigen (CEA) is a highly prominent glycoprotein biomarker that is frequently overexpressed in several malignancies, including lung and gastrointestinal cancers. In clinical diagnostics, tracking CEA levels is vital for both early detection and monitoring a patient's response to therapy. Because CEA exists at extremely low concentrations in the early stages of cancer, traditional diagnostic assays often lack the necessary sensitivity. To bridge this gap, researchers have developed highly advanced, ultra-sensitive MIP platforms that drastically lower the limit of detection (LOD) using various signal transduction methods.

### A. Electrochemical Sensing Platforms

Electrochemical biosensors are highly favored in clinical diagnostics due to their high sensitivity, low cost, and simplicity.

- **Fabrication:** Lai et al. engineered an advanced electrochemical sensor by utilizing a glassy carbon electrode coated with highly conductive polythionine and gold nanoparticles (AuNPs).
- **Imprinting Mechanism:** Polydopamine (PDA) was utilized as the polymeric matrix, undergoing multiple electropolymerization cycles with CEA acting as the protein template.
- **Diagnostic Outcome:** By measuring the binding properties through differential pulse voltammetry (DPV), this highly conductive platform achieved a remarkable LOD of 0.2589 pg/mL, demonstrating extreme sensitivity for early-stage screening.

### B. Surface-Enhanced Raman Spectroscopy (SERS)

SERS is a powerful analytical technique that provides molecular fingerprint information, making it ideal for detecting trace amounts of biomarkers in complex fluids like whole blood.

**Fabrication:** Lin et al. pushed the boundaries of sensitivity by combining a SERS substrate with a surface-molecularly imprinted polymer (SMIP) capture method.<sup>[17]</sup>

- **Imprinting Mechanism:** The team encapsulated ethynylbenzene (EB) into dopamine on the surface of AuNPs. By combining these with an imprinted core-molecule-shell-molecule nanoparticle-coated surface, they optimized the sensor's internal standard to feature a "silent zone" at 2024  $\text{cm}^{-1}$ . This specific silent zone prevents interference from other biological molecules naturally present in human blood.
- **Diagnostic Outcome:** This innovative approach yielded an unprecedented, interference-free LOD of 0.064 pg/mL for CEA directly in real human blood samples.

### C. Orthogonal Double Recognition Immuno-Sandwich Assay

A significant challenge in detecting glycoproteins like CEA is the risk of "false positives" caused by the sensor accidentally binding to non-target proteins with similar structures.

- **Fabrication:** To solve this, Zhou et al. developed an orthogonal double recognition method that mimics a traditional immuno-sandwich assay but uses two entirely distinct MIPs instead of biological antibodies.
- **Imprinting Mechanism:** The first MIP was coated on a layer of gold nanoparticles explicitly designed to recognize the specific peptide epitope of CEA. The second MIP was coated over Raman-active silver nanoparticles engineered to capture the macro-structure of the CEA protein itself.
- **Diagnostic Outcome:** This dual-verification system successfully differentiated CEA from a wide variety of other

glycoproteins (like horseradish peroxidase and ribonuclease B) and non-glycoproteins (like bovine serum albumin), ensuring superior specificity alongside ultra-sensitive detection.

**Table 3: MIP Advancements in CEA Detection.**

Detection Methodology	Sensor Platform & Modifiers	MIP Matrix / Recognition Strategy	Limit of Detection (LOD)	Reference
Electrochemical Sensing	Glassy carbon electrode modified with polythionine and AuNPs	Electropolymerized polydopamine (PDA) / Whole protein template	0.2589 pg/mL	Lai et al.
Surface-Enhanced Raman Spectroscopy (SERS)	AuNPs core-shell nanoparticles with an internal standard	Ethynylbenzene encapsulated in dopamine / Surface imprinting (SMIP)	0.064 pg/mL	Lin et al.
Plasmonic Immunosandwich Assay	Dual substrates: AuNPs and Raman-active AgNPs	Orthogonal double recognition: Epitope-MIP + Whole protein-MIP	5.6 X 10 <sup>-14</sup> M	Zhou et al.

## 2. Targeting EGFR on Lung Cancer Cells (A549)

The Epidermal Growth Factor Receptor (EGFR) is a critical transmembrane protein that regulates cell proliferation and survival. In several malignancies, particularly in non-small cell lung cancer (such as the A549 cell line), EGFR is significantly overexpressed, making it an ideal target for both diagnostic tracking and highly localized therapeutic intervention.

To exploit this overexpression, researchers have engineered highly specialized, multi-functional molecularly imprinted polymers (MIPs) capable of actively recognizing and binding to lung cancer cells while simultaneously delivering a lethal therapeutic payload.<sup>[18,19]</sup>

### A. Nanoparticle Design and Synthesis

Liu et al. successfully designed a "capsule-like" MIP engineered specifically for targeted chemo-photothermal synergistic therapy against EGFR-overexpressing cancer cells.

- **The Core:** The foundation of the nanoparticle is a zeolitic imidazolate framework-8 (ZIF-8) that encapsulates the chemotherapeutic drug Doxorubicin (DOX).
- **The Imprinting Layer:** Polymerizable dopamine (DA) was utilized as both the functional monomer and the crosslinker to form the MIP shell. Dopamine was specifically chosen for its excellent biocompatibility, biodegradability, and inherent photothermal conversion ability.
- **The Template:** To ensure the sensor selectively targets the cancer cells, an epitope of the EGFR protein was used as the template molecule during the polymerization process.<sup>[20,21]</sup> The resulting synthesized complex is referred to as DOX@MIP (MD).

### B. High Selectivity and Target Recognition

The diagnostic and targeting power of these artificial antibodies relies heavily on their ability to distinguish between diseased and healthy tissues.

The DOX@MIP nanoparticles demonstrated highly specific targeting and binding to EGFR-over-expressing cancer cells, specifically A549 (lung cancer) and MDA-MB-468 (breast cancer) cell lines.

Crucially, these specialized MIPs successfully avoided binding to normal, healthy bronchial epithelial cells (16HBE), demonstrating the high specificity of the epitope imprinting strategy and ensuring minimal off-target toxicity.

### C. Theragnostic Mechanism of Action

Once the DOX@MIPs bind to the A549 lung cancer cells, they trigger a dual-action therapeutic response:

- **Photothermal Therapy (PTT):** Because the polydopamine shell acts as a photothermal agent, irradiating the targeted cells with a near-infrared (NIR) laser (808 nm) for just 10 minutes causes the localized temperature to rapidly increase to 44.2 °C. This localized hyperthermia achieves a photothermal conversion efficiency of 36.3%, effectively ablating the targeted cancer cells.
- **Chemotherapy Release:** Under normal physiological conditions, the MIP layer maintains a rigid, protective shape. However, once internalized into the uniquely acidic microenvironment of the tumor, the polymer matrix degrades, controllably releasing the DOX payload directly into the cancer cell.

### Extraction of Circulating microRNA (miR-21)

The detection of circulating nucleic acids—such as double-stranded DNA and ribonucleic acids (RNA)—has become a cornerstone of modern oncological diagnostics. Because cancer cells frequently release these genetic materials into the bloodstream following cell apoptosis, they serve as highly reliable biomarkers for early-stage cancer and tumor profiling. Among these, microRNAs (miRNAs) like miR-21 are heavily targeted due to their critical role in regulating gene expression and their abnormal upregulation in various malignancies, including lung cancer and glioblastoma.

However, extracting RNA from complex biological fluids is notoriously difficult because RNA is highly prone to rapid degradation, and traditional commercial extraction methods (like Trizol reagents) can be tedious and lack target-specific selectivity. To overcome this, researchers have successfully engineered molecularly imprinted polymers (MIPs) to act as highly stable, target-specific RNA capture probes.<sup>[22,23]</sup>

### A. Nanoparticle Probe Design and Synthesis

Hashemi-Moghaddam et al. pioneered a highly efficient MIP-based separation method specifically targeting microRNA-21 (miR-21).

- **The Substrate:** The researchers utilized silica nanoparticles as the foundational core for the capture probes, providing a high surface area-to-volume ratio ideal for mass transfer.
- **The Imprinting Matrix:** A layer of dopamine was polymerized directly onto the surface of the silica nanoparticles. Polydopamine (PDA) is highly favored in these biological applications due to its excellent biocompatibility and ability to form robust, stable matrices.
- **The Template:** The target miR-21 itself was utilized to mold the specific three-dimensional recognition cavities within the polydopamine shell.

### B. Extraction Efficiency and Diagnostic Outcome

The performance of these synthesized MIP probes was directly compared against non-imprinted polymers (NIPs) and standard commercial Trizol extraction reagents using real glioblastoma cell line lysates.

- **Target Selectivity:** The outcomes confirmed that the dopamine-based MIPs selectively and securely entrapped miR-21 directly from the complex cell lysate mixture.
- **Diagnostic Enhancement:** By selectively concentrating the target biomarker, the MIP extraction method led to a

significant, measurable upregulation of miR-21 expression in the final eluate.<sup>[24]</sup>

- This proves that MIPs can effectively replace or enhance traditional, non-specific RNA extraction protocols, isolating extremely fragile genetic markers with the precision required for early-stage liquid biopsies.

### **Critical Challenges and Future Perspectives**

Despite the remarkable potential of molecularly imprinted polymers (MIPs) in separating, purifying, and detecting targeted biomarkers, their application in cancer theragnostics is still considered to be in its infancy. Transitioning these artificial antibodies from the laboratory bench to real-world clinical practice for lung cancer diagnosis requires overcoming several formidable scientific and physiological hurdles.

### **The Complexity of Tumor Heterogeneity**

One of the primary challenges in deploying MIPs for cancer diagnostics is the intrinsic complexity and heterogeneity of cancer cell subtypes and tumor tissues.

- Depending on their specific subtype and stage of progression, lung cancer cells can express a vast and fluctuating array of surface antigens, glycoproteins, and other membrane biomolecules.
- This dynamic physiological landscape makes it exceptionally difficult to design a single MIP that can selectively recognize and bind its intended target without interference.

Overcoming this background noise in a complex biological environment (such as whole blood or serum) is a major limiting factor in the successful development of target-specific diagnostic biosensors and nanomedicines.<sup>[25]</sup>

### **Lack of Standardization in Synthesis and Evaluation**

The fabrication of highly specific MIPs is a delicate chemical process that currently lacks universal standardization.

- The successful synthesis of an MIP requires the painstaking optimization of numerous variable parameters, including the specific choice of functional monomers, template molecules, and cross-linkers.
- Currently, there is no universally standardized method for evaluating the binding affinity and selectivity of the resulting polymers.

Without an established baseline for these metrics, it remains incredibly challenging for researchers and clinicians to accurately compare the diagnostic precision, sensitivity, and clinical viability among different newly developed MIP-based sensors.<sup>[26]</sup>

### **In Vivo Safety, Toxicity, and Biodegradability**

While MIPs show excellent stability *in vitro*, their behavior inside the human body presents another layer of complexity that has not yet been fully mapped out.

There is a significant lack of adequate, long-term research regarding the prolonged toxicity and biodegradability of these synthetic nanocarriers.

The compatibility of these polymers with human biological systems, specifically regarding how well they disperse within biological fluids like the bloodstream without causing blockages or immune rejection, poses a massive challenge for practical *in vivo* implementation.<sup>[27]</sup>

### Future Perspectives and the Path Forward

To navigate these challenges and bring MIP-based lung cancer diagnostics into everyday clinical use, several strategic areas of research must be prioritized.

- Real Sample Validation: Future research and development efforts must move beyond controlled laboratory buffers and prioritize extensive testing using real clinical fluid samples (liquid biopsies) and *in vivo* animal models.<sup>[28,29]</sup>
- Advanced Material Engineering: Achieving highly effective and controlled therapeutic delivery will require the development of "smart" MIPs capable of targeting multiple biomarkers simultaneously and exhibiting responsiveness to multiple microenvironmental stimuli (such as combining pH and heat responses).
- Refined Chemistry: Future advancements will heavily rely on the discovery of new targeting ligands and the development of improved polymer coating techniques to enhance overall biocompatibility and reduce off-target toxicity.<sup>[30]</sup>

### CONCLUSION

The precise and early diagnosis of lung cancer is critical for patient survival, driving a necessary shift from invasive tissue biopsies toward non-invasive liquid biopsies. To overcome the high costs, complex screening, and poor stability associated with traditional biological antibodies, researchers have increasingly turned to Molecularly Imprinted Polymers (MIPs)—highly stable, cost-effective "artificial antibodies" customized through specialized molding techniques to recognize specific target molecules with exceptional affinity and selectivity. In the realm of lung cancer diagnostics, MIP-based biosensors have demonstrated remarkable sensitivity; for instance, integrating surface-imprinted polymers with Surface-Enhanced Raman Spectroscopy (SERS) achieved an unprecedented limit of detection of 0.064 pg/mL for the glycoprotein Carcinoembryonic Antigen (CEA) directly in real blood samples. Furthermore, MIPs have been successfully engineered to selectively capture tumor-derived exosomes, precisely extract circulating genetic markers like microRNA-21 (miR-21) from complex cell lysates, and directly target Epidermal Growth Factor Receptor (EGFR)-overexpressing A549 lung cancer cells while avoiding healthy tissue. Beyond diagnostics, these synthetic receptors facilitate the transition to "theragnostics" by acting as smart nanomedicines capable of encapsulating chemotherapeutic drugs, such as Doxorubicin, and releasing them specifically when triggered by the acidic tumor microenvironment. They also seamlessly integrate with advanced light-mediated treatments, enabling highly localized photothermal (PTT) and photodynamic therapies (PDT) that destroy cancer cells with minimal off-target toxicity to surrounding healthy tissue. Despite these groundbreaking advancements, the widespread clinical application of MIPs remains hindered by the intrinsic heterogeneity of lung cancer tumors, a lack of standardized synthesis and evaluation protocols, and the urgent need for comprehensive, long-term *in vivo* studies to assess the prolonged toxicity, biological dispersion, and biodegradability of these polymers before they can enter standard clinical practice.

### REFERENCES

1. Siegel, R. L., K. D. Miller, and A. Jemal. "Cancer statistics, 2019." *CA Cancer J Clin* 69 (2019): 7-34.
2. Labi, V., and M. Erlacher. "How cell death shapes cancer." *Cell Death Dis* 6 (2015): e1675.
3. Chen, X., J. Gole, A. Gore, Q. He, M. Lu, J. Min, Z. Yuan, X. Yang, Y. Jiang, T. Zhang, and C. Suo. "Non-invasive early detection of cancer four years before conventional diagnosis using a blood test." *Nat Commun* 11 (2020): 3475.
4. Fiala, C., and E. P. Diamandis. "Utility of circulating tumor DNA in cancer diagnostics with emphasis on early

- detection." *BMC Med* 16 (2018): 1-10.
5. Jeong, Y., and K. Na. "Synthesis of a gadolinium based-macrocyclic MRI contrast agent for effective cancer diagnosis." *Biomater Res* 22 (2018): 1-8.
  6. De Rubis, G., S. R. Krishnan, and M. Bebawy. "Liquid biopsies in cancer diagnosis, monitoring, and prognosis." *Trends Pharmacol Sci* 40 (2019): 172-86.
  7. Brown, N. A., and K. S. Elenitoba-Johnson. "Enabling precision oncology through precision diagnostics." *Annu Rev Pathol* 15 (2020): 97-121.
  8. Shanmugasundaram, K. B., J. Li, A. I. Sina, A. Wuethrich, and M. Trau. "Toward precision oncology: SERS microfluidic systems for multiplex biomarker analysis in liquid biopsy." *Mat Adv* 3 (2022): 1459-71.
  9. Lino, C., S. Barrias, R. Chaves, F. Adegas, P. Martins-Lopes, and J. R. Fernandes. "Biosensors as diagnostic tools in clinical applications." *Biochim Biophys Acta Rev Cancer* 1877 (2022): 188726.
  10. Lee, J. U., W. H. Kim, H. S. Lee, K. H. Park, and S. J. Sim. "Quantitative and specific detection of exosomal miRNAs for accurate diagnosis of breast cancer using a surface-enhanced Raman scattering sensor based on plasmonic head-flocked gold nanopillars." *Small* 15 (2019): 1804968.
  11. Jayanthi, V. S., A. B. Das, and U. Saxena. "Recent advances in biosensor development for the detection of cancer biomarkers." *Biosens Bioelectron* 91 (2017): 15-23.
  12. Haupt, K., P. X. Medina Rangel, and B. T. Bui. "Molecularly imprinted polymers: antibody mimics for bioimaging and therapy." *Chem Rev* 120 (2020): 9554-82.
  13. Ozcelikay, G., S. I. Kaya, E. Ozkan, A. Cetinkaya, E. M. Nemutlu, S. Kir, and S. A. Ozkan. "Sensor-based MIP technologies for targeted metabolomics analysis." *TrAC Trend Anal Chem* 146 (2022): 116487.
  14. Liu, Y., J. Li, H. Ou, D. Qi, B. Hu, Y. Xu, J. Hu, Y. Xiong, L. Xia, J. H. Huang, and X. Hu. "Identification of new aptamer BC-3 targeting RPS7 from rapid screening for bladder carcinoma." *Genes Dis* (2022).
  15. Wu, L., Y. Wang, X. Xu, Y. Liu, B. Lin, M. Zhang, J. Zhang, S. Wan, C. Yang, and W. Tan. "Aptamer-based detection of circulating targets for precision medicine." *Chem Rev* 121 (2021): 12035-105.
  16. Kim, D. H., J. M. Seo, K. J. Shin, and S. G. Yang. "Design and clinical developments of aptamer-drug conjugates for targeted cancer therapy." *Biomater Res* 25 (2021): 1-2.
  17. Lowdon, J. W., H. Dillen, P. Singla, M. Peeters, T. J. Cleij, B. van Grinsven, and K. Eersels. "MIPs for commercial application in low-cost sensors and assays-An overview of the current status quo." *Sens Actuators B Chem* 325 (2020): 128973.
  18. Mahmoudpour, M., M. Torbati, M. M. Mousavi, M. de la Guardia, and J. E. Dolatabadi. "Nanomaterial-based molecularly imprinted polymers for pesticides detection: Recent trends and future prospects." *TrAC Trend Anal Chem* 129 (2020): 115943.
  19. Dong, Q., M. Yang, Y. Wang, Y. Guan, W. Zhang, and Y. Zhang. "Peptide-crosslinked molecularly imprinted polymers for efficient separation of immunoglobulin G from human serum." *Biomater Sci* (2023).
  20. Wang, P., J. Liu, Y. Ma, X. Tian, Y. Li, X. Niu, J. Luo, and J. Pan. "Sequential assembly enabled surface precise imprinting on Janus nanosheets for highly specific separation of adenosine 5'-monophosphate." *Chem Eng J* 432 (2022): 134349.
  21. Sun, Y., Y. Luo, L. Sun, X. R. Wang, L. W. Chen, N. Zhang, Y. Wang, L. Y. Dong, H. Guo, and X. H. Wang. "Improving performance of cell imprinted PDMS by integrating boronate affinity and local post-imprinting modification for selective capture of circulating tumor cells from cancer patients." *Biosens Bioelectron* 223

- (2023): 115023.
22. Matsumoto, H., H. Sunayama, Y. Kitayama, E. Takano, and T. Takeuchi. "Site-specific post-imprinting modification of molecularly imprinted polymer nanocavities with a modifiable functional monomer for prostate cancer biomarker recognition." *Sci Technol Adv Mater* 20 (2019): 305-12.
  23. Smolinska-Kempisty, K., A. Guerreiro, F. Canfarotta, C. Cáceres, M. J. Whitcombe, and S. Piletsky. "A comparison of the performance of molecularly imprinted polymer nanoparticles for small molecule targets and antibodies in the ELISA format." *Sci Rep* 6 (2016): 37638.
  24. Wang, W., X. Wang, N. Cheng, Y. Luo, Y. Lin, W. Xu, and D. Du. "Recent advances in nanomaterials-based electrochemical (bio) sensors for pesticides detection." *TrAC Trend Anal Chem* 132 (2020): 116041.
  25. Tuwahu, C. A., C. C. Yeung, Y. W. Lam, and V. A. Roy. "The molecularly imprinted polymer essentials: curation of anticancer, ophthalmic, and projected gene therapy drug delivery systems." *J Control Release* 287 (2018): 24-34.
  26. Gu, Z., Y. Dong, S. Xu, L. Wang, and Z. Liu. "Molecularly imprinted polymer-based smart prodrug delivery system for specific targeting, prolonged retention, and tumor microenvironment-triggered release." *Angew Chem* 133 (2021): 2695-9.
  27. Wang, H. Y., P. P. Cao, Z. Y. He, X. W. He, W. Y. Li, Y. H. Li, and Y. K. Zhang. "Targeted imaging and targeted therapy of breast cancer cells via fluorescent double template-imprinted polymer coated silicon nanoparticles by an epitope approach." *Nanoscale* 11 (2019): 17018-30.
  28. Piletsky, S., F. Canfarotta, A. Poma, A. M. Bossi, and S. Piletsky. "Molecularly imprinted polymers for cell recognition." *Trends Biotechnol* 38 (2020): 368-87.
  29. Ali, M. M., S. Zhu, F. R. Amin, D. Hussain, Z. Du, and L. Hu. "Molecular imprinting of glycoproteins: From preparation to cancer theranostics." *Theranostics* 12 (2022): 2406.
  30. Yin, D., X. Li, Y. Ma, and Z. Liu. "Targeted cancer imaging and photothermal therapy via monosaccharide-imprinted gold nanorods." *Chem Commun* 53 (2017): 6716-9.