

Nanoscale

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Engineering Molecularly Imprinted Polymers for Receptor-Specific Cancer Therapeutics

Shreya Tiwari^a, Charles Luke Hutchinson^a, Pankaj Singla^a, Robert C. Rintoul^b, Timothy H. Witney^c, Nicholas W. Turner^d, Marloes Peeters^{a}*

^aDepartment of Chemical Engineering, University of Manchester, Nancy Rothwell Building, Manchester, M13 9QS, UK

^bDepartment of Oncology, University of Cambridge, Cambridge, CB2 0QQ, UK

^cSchool of Biomedical Engineering & Imaging Sciences, King's College London, London, SE1 7EH, UK

^dDepartment of Chemistry, School of Mathematical and Physical Sciences, University of Sheffield, Sheffield, S3 7HF, UK



*Corresponding author, marloes.peeters@manchester.ac.uk (Marloes Peeters)

1 Abstract

2 The therapeutic efficacy of cancer therapeutics is frequently limited by poor tumour
3 selectivity, systemic toxicity, and the emergence of drug resistance, underscoring the
4 need for advanced nanoscale drug delivery systems (DDSs) capable of precise
5 molecular targeting and controlled release. Molecularly imprinted polymers (MIPs)
6 have emerged as a promising class of synthetic nanocarriers that combine highly
7 selective and programmable molecular recognition with the robustness, tunability, and
8 scalability of polymeric materials. This review examines recent advances in the
9 nanoscale engineering of MIPs for receptor-guided precision cancer therapy, focusing
10 on how imprinting strategy, polymerisation methods, and nanostructure control govern
11 binding affinity, selectivity, and drug-release behaviour. Key advances in epitope
12 imprinting are highlighted to overcome the size, conformational complexity, and
13 stability challenges associated with whole-protein templates, enabling reproducible
14 targeting of cancer-associated receptors. Emerging stimuli-responsive, hybrid, and
15 multifunctional MIP architectures are discussed, illustrating how molecular recognition,
16 drug loading, and triggered release can be co-engineered within a single nanoscale
17 platform. Finally, the current challenges related to biocompatibility, reproducibility, and
18 translation towards manufacturable and regulatory-compliant systems are critically
19 assessed, outlining future directions for establishing MIPs as a viable class of next-
20 generation precision DDSs in oncology.

21 *Keywords: Molecularly imprinted polymers, Drug delivery systems, Cancer*
22 *therapeutics, Receptor-mediated targeting, Stimuli-responsive release, Synthetic*
23 *receptors, Epitope imprinting, Hybrid nanomaterials*



1. Introduction to drug delivery

Cancer is characterised by the uncontrolled growth and spread of abnormal cells in the body. According to Cancer Research UK (CRUK), an estimated 18.1 million new cancer cases were diagnosed worldwide in 2020, with approximately 10 million cancer-related deaths reported during the same year [1]. Over recent decades, substantial advances in cancer treatment have been achieved, partly due to a better understanding of cell biology and the tumour microenvironment. Current treatment modalities include chemotherapy, immunotherapy, radiotherapy, and surgery, with chemotherapy and chemoimmunotherapy being the main systemic approaches. Despite these advances, major challenges persist, including drug resistance, limited tumour specificity resulting in off-target effects, and treatment-related cytotoxicity. Moreover, patients who initially respond often relapse with recurrent disease [2]. In such cases, the treatment might then proceed with trying a different regimen of drugs or a combination of drugs, which would further increase the harmful effects but not significantly improve the patient's condition [3]. The fundamental mechanism of many chemotherapeutic agents is to target rapidly dividing cells, rendering them inherently toxic to healthy proliferating tissues such as bone marrow, gastrointestinal epithelium, and hair follicles [4]. Consequently, treatment failure is frequently associated not only with insufficient drug potency, but also with suboptimal drug delivery, poor pharmacokinetics, and lack of tumour-selective accumulation [5-7].

As an alternative, antibody-based therapies offer improved selectivity as both stand-alone therapeutics, co-factors or carriers. Antibodies are immunoglobulin proteins engineered to recognise tumour-associated antigens and, as such, can selectively target cancer cells for immune-mediated destruction. While antibodies offer high affinity, selectivity, and broad clinical applications, they do have some limitations, including immunogenicity, limited stability, susceptibility to enzymatic degradation, and complex, high-cost manufacturing and purification processes [8]. To address these drawbacks, a range of non-antibody platforms has been explored to perform the same functionality. These include nanobodies (engineered antibody fragments) [9], affibodies [10], and DARPins (synthetic proteins), as well as non-antibody scaffold drugs [11], and aptamers (single-stranded nucleic acids) [11]. These alternatives often offer better solubility, tissue penetration, stability, and comparatively lower production



1 costs than antibodies; however, each class is still associated with its own set of
2 challenges [12, 13].

3 The effectiveness of cancer treatment can be significantly improved by site-specific
4 drug release. To this end, drug delivery systems (DDSs) have been developed to
5 enhance the treatment efficiency and mitigate the harmful side effects of
6 chemotherapy. DDSs work by delivering high concentrations of chemotherapeutic
7 drugs to the tumours while limiting exposure to healthy tissues, thereby reducing
8 adverse effects and improving patient outcomes [14]. These systems commonly
9 employ nanoscale carriers capable of encapsulating or conjugating therapeutic agents
10 and enabling controlled, localised release. Nanocarriers offer several advantages over
11 conventional chemotherapy, including improved drug solubility, enhanced stability,
12 prolonged circulation time, and preferential tumour accumulation through the
13 enhanced permeability and retention (EPR) effect. Following tumour accumulation and
14 cellular uptake, efficient endosomal escape prevents intracellular degradation and
15 enables therapeutics to reach their intended intracellular targets, thereby enhancing
16 treatment efficacy [15].

17 A wide range of nanomaterials has been investigated for DDSs' design, including
18 polymers [16, 17], lipids [18, 19], and inorganic materials [20, 21]. Several
19 nanomedicines have achieved clinical translation, including Doxil® (liposomal
20 doxorubicin), Abraxane® (albumin-bound paclitaxel), Lupron Depot® (PLGA
21 microspheres for leuprolide), Oncaspar® (PEG-asparaginase), Zoladex®
22 (biodegradable goserelin implant), DepoDur™ (extended-release morphine in a
23 polymer-based system), and Eligard® (leuprolide acetate in ATRIGEL® polymer
24 matrix) [22] as discussed in **Table 1**. In parallel, nanobiomaterials have emerged as
25 an important class of nanocarriers engineered to interact with biological systems. Their
26 unique physicochemical properties, high surface area, and tunable surface chemistry
27 enable efficient loading of therapeutic agents and controlled interactions with cells and
28 tissues, making them versatile platforms for drug delivery, diagnostic and targeted
29 therapies [23, 24] .

30 Among the nanocarrier platforms, polymeric nanoparticles are of particular interest
31 due to their structural versatility and tunable physicochemical properties. Their high
32 surface-to-volume ratio enables efficient drug loading and functionalisation with
33 targeting ligands, while their degradability and mechanical flexibility allow for controlled
34 release and reduced systemic toxicity [25].



1 One emerging class of polymeric nanocarriers with significant promise for cancer drug
2 delivery is molecularly imprinted polymers (MIPs), particularly nanoMIPs (single-
3 particle MIPs with diameters of sub-250 nm). MIPs are synthetic materials engineered
4 with specific binding sites that are complementary in shape, size, and functional
5 groups to a target molecule, enabling selective recognition and rebinding. MIPs are
6 fully capable of selective molecular recognition, offering a robust alternative to
7 biological targeting ligands for drug delivery applications [26]. Their high chemical
8 stability, resistance to enzymatic degradation, and long shelf life make them
9 particularly attractive for use in physiologically demanding environments [27].
10 Importantly, advances over the past ten years have enabled MIPs to be engineered
11 into a nanopatform, nanoMIPs. nanoMIPs can be generated to recognise cancer-
12 relevant targets, including overexpressed cell-surface receptors and biomarkers,
13 peptide epitopes, and tumour-associated microenvironmental cues, enabling
14 preferential tumour localisation and controlled drug release [16, 28]. These attributes
15 position MIPs as a versatile and adaptable platform for developing DDSs.
16 This review focuses on the development of MIPs-based DDSs for cancer therapy,
17 emphasising cancer-specific recognition and controlled therapeutic administration. It
18 critically evaluates imprinting strategies, rational carrier design, and receptor-guided
19 approaches for precise drug delivery. In addition, key advances in MIPs-based
20 delivery architectures, including hybrid systems and combinational therapeutic
21 platforms, are discussed alongside biocompatibility considerations, scale-up
22 challenges, and translational barriers. Overall, this work aims to highlight the potential
23 of MIPs as next-generation nanocarriers for selective, safe, and effective DDSs.

24 **2. Design and engineering of MIPs for drug delivery**

25 MIPs are best described as synthetic molecular recognition materials that mimic the
26 selective binding properties of natural antibodies, achieved through templated
27 polymerisation. This interaction is best envisaged by the classical 'lock and key'
28 mechanism, where the polymer selectively binds with the molecule that was imprinted
29 within it during its formation [29], though naturally this is an analogy, and the reality of
30 recognition is far more complex, with an induced fit system commonly theorised. They
31 have found applications in a range of fields, including (bio)sensing, separations and
32 catalysis; however, since the inception of nanoMIPs design, they have emerged as
33 selective drug-carriers capable of providing targeting, high affinity/selectivity, stability,



1 and controlled release through their tailor-made binding cavities [28, 30]. Their
2 robustness, low immunogenicity, and tunable physicochemical properties can enable
3 the protection of loaded therapeutics while allowing for targeted delivery to tissues with
4 imprinted biomarkers or microenvironment conditions [28, 31, 32]. Recent advances
5 in MIPs-based DDSs design, including structural modifications, epitope imprinting,
6 stimuli responsiveness, and combinational therapies, have further enhanced their
7 potential in cancer therapy.

8 A general synthesis method for MIPs involves forming a pre-polymerisation complex
9 with the template and complementary monomers. Subsequently, the polymerisation is
10 carried out in the presence of an initiator and a crosslinker. Finally, the template
11 molecule is extracted from the polymer, leaving behind complementary cavities that
12 are specific to the template molecule, resulting in the production of a fixed, target-
13 specific binding site entrapped with a polymer matrix [33]. The nanoMIPs offer the
14 advantages of nanomaterials and can rival the affinity of natural receptors, in addition
15 to offering good biocompatibility [16, 34].

16 **2.1 Imprinting methods and polymerisation techniques**

17 Based on the molecular interactions involved in the formation of the pre-polymerisation
18 complex, the synthesis of MIPs can be categorised as covalent, non-covalent or semi-
19 covalent. In the covalent approach, reversible covalent bonds form between the
20 template and monomers during polymerisation and are later cleaved to remove the
21 template, generating homogeneous binding sites with reduced non-specific
22 interactions. However, this approach is limited by the difficulty of identifying suitable
23 reversible template-monomer systems and by slower binding kinetics associated with
24 covalent interactions, which can hinder equilibrium binding [35, 36]. When designing
25 a DDS, the key limitation of covalent imprinting is that only a few drugs with suitable
26 functional groups can be used, and covalent binding may reduce their therapeutic
27 activity [37].

28 The non-covalent approach, also known as the self-assembly method, involves non-
29 covalent interactions between the template and monomers prior to polymerisation,
30 including hydrogen bonds, hydrophobic interactions, ionic, electrostatic, and van der
31 Waals forces. This method is far more prevalent (>95% of examples) due to its
32 simplicity, flexibility and ease of template removal. Additionally, in terms of rebinding



1 kinetics, the non-covalent approach often gives better results. However, imprinting
2 efficiency can be sensitive to disruptions in template-monomer interactions [36, 38].
3 For example, a comparison for stigmasterol (a plant sterol with anti-inflammatory,
4 neuroprotective, and anti-tumour properties) showed that non-covalent imprinting is
5 synthetically simpler but yields lower-affinity MIPs due to unstable hydrogen bonds,
6 whereas covalent imprinting provides stronger binding, less cross-reactivity, and
7 higher imprinting efficiency [39]. Despite this, most MIPs-based DDSs favour the non-
8 covalent approach using acrylic monomers, often with minimal optimisation, as it
9 allows versatile and successful imprinting of a wide range of chemotherapeutic drugs
10 [37]. The semi-covalent approach combines covalent template attachment during
11 polymerisation with non-covalent rebinding, but its use remains limited due to
12 increased synthetic complexity [40, 41].

13 One of the primary advantages of MIPs is their versatility in forming different material
14 architectures, which has led to the development of multiple synthetic strategies. In bulk
15 imprinting, a mixture of template, monomers, and cross-linkers is polymerised to form
16 a monolithic polymer, which is subsequently ground into particles. Although
17 straightforward, this method often produces irregular, polydisperse particles with
18 partially inaccessible binding sites, reducing binding capacity and selectivity [42, 43].
19 Surface imprinting generates recognition sites at or near the surface of a support
20 material, improving site accessibility, mass transfer and binding kinetics, and is
21 particularly suitable for biomolecule imprinting [42, 44, 45]. However, it is limited to
22 applications beyond sensing and separations. These are but two strategies in a myriad
23 of methods that have been explored.

24 Solid-phase supported imprinting has recently emerged as an alternative strategy in
25 which the template is immobilised on a solid support during polymerisation. This
26 approach facilitates the synthesis of uniform nanoMIPs with improved binding-site
27 homogeneity, reduced template leaching and enhanced reproducibility, making it
28 particularly suited for drug-delivery applications [46].

29 Among the various polymerisation reactions used for synthesising MIPs, free radical
30 polymerisation (FRP) remains the most widely employed. FRP involves radical-
31 initiated chain-growth polymerisation of unsaturated monomers and is widely used due
32 to its simplicity, scalability, compatibility with a broad range of monomers and solvents,
33 and ability to proceed under mild conditions, including aqueous environments suitable
34 for biological targets [47-49]. Consequently, FRP is prevalent in the synthesis of solid-



1 phase nanoMIPs [46]. However, FRP provides limited control over polymer growth
2 which can lead to heterogeneous binding sites and branched polymer structures that
3 reduce affinity and selectivity [41, 50]. Controlled radical polymerisation (CRP)
4 techniques have therefore been developed to improve control over polymer
5 architecture and molecular weight, often resulting in more homogeneous networks and
6 more predictable drug-release behaviour [51]. However, FRP remains the dominant
7 approach due to its simpler procedure, broad applicability to a wide range of
8 monomers and templates, and ease of implementation without specialised catalysts
9 or chain-transfer agents [52].

10 **2.2 Rational design of MIPs**

11 During the pre-polymerisation stage, functional monomers associate with the template
12 through complementary non-covalent interactions, forming a template-monomer
13 complex, with monomer functionality, stoichiometry, and spatial arrangement
14 influencing the formation of recognition sites. Subsequently, polymerisation entraps
15 these complexes within a crosslinked polymer network, providing mechanical stability
16 and maintaining the integrity of the imprinted recognition cavities. As a result,
17 characterising the orientation and the strength of monomer-template interactions in
18 the pre-polymerisation has become a central strategy for informing rational MIPs
19 design [53]. However, the polymerisation process and cross-linking inevitably alter
20 local spatial arrangements, polarity, and accessibility of binding sites, meaning that
21 pre-polymerisation models capture important information but do not fully reproduce
22 the complexity of the final MIPs binding environment [41, 54].

23 The pre-polymerisation complex can be probed experimentally using techniques such
24 as UV-Vis or fluorescence spectroscopy, as well as Fourier-transform infrared (FTIR)
25 spectroscopy and Nuclear Magnetic Resonance (NMR), which provide qualitative and
26 semi-quantitative insight into monomer-template interactions [55, 56]. Post-
27 polymerisation techniques, including isothermal titration calorimetry (ITC) and surface
28 plasmon resonance (SPR), allow quantitative evaluation of binding affinities and
29 kinetics through association and dissociation constants [57, 58]. While these methods
30 provide valuable experimental validation, systematic screening of monomer-template
31 combinations can be time-consuming and resource-intensive [33].



1 Computational methods, therefore, play a complementary role to experimental
2 screening by providing a rapid, cost-effective means to predict and rank monomer-
3 template interactions prior to synthesis [59]. Modelling large and heterogeneous
4 systems, including polymers and proteins, remains computationally challenging [60].
5 Consequently, computational approaches typically focus on simplified
6 representations, such as epitopes rather than full proteins, and pre-polymerisation
7 complexes rather than fully formed MIPs structures [61].

8 Molecular docking is widely used to predict favourable binding geometries, identify
9 binding regions on the template, and rapidly screen large libraries of functional
10 monomers. This approach has been successfully applied to small-molecule drugs,
11 guiding the selection of functional monomers for high-affinity binding, as well as to
12 biomolecular targets such as bovine serum albumin (BSA) epitopes, where docking
13 helps identify key amino acid residues for targeted monomer interactions and rational
14 polymer design [62, 63]. Molecular dynamics (MD) simulations extend this analysis by
15 incorporating solvent effects, temperature and molecular motion, providing insight into
16 the stability and persistence of binding interactions [64]. MD studies in MIPs design
17 have highlighted the critical influence of solvent choice on complex stability and
18 binding-site formation [65]. By capturing conformational flexibility and dynamic
19 rearrangements, MD offers an important refinement step beyond static docking
20 predictions. Density Functional Theory (DFT) provides a complementary quantum-
21 mechanical description of specific interactions, enabling accurate calculation of
22 binding energies within pre-polymerisation complexes and facilitating quantitative
23 comparison of functional monomers, crosslinker monomers, and solvents [66, 67]. For
24 example, DFT analyses have been used to identify acrylic acid as an optimal functional
25 monomer, ethylene glycol dimethacrylate as an effective crosslinker monomer, and
26 toluene as a suitable porogenic solvent for developing a high-specificity imprinted
27 polymer, targeting the small-molecule drug oxybutynin [68]. Despite its accuracy, DFT
28 is not readily applicable to large-scale MIPs screening because of its unfavourable
29 computational scaling with system size [61]. Together, docking, MD and DFT form a
30 complementary computational framework for rational MIP design.

31 Experimental and computational approaches, therefore, provide complementary
32 advantages [61]. Analytical methods provide definitive insight into material
33 performance by using empirically determined parameters that reflect the system's true
34 behaviour, but they are typically labour-intensive and costly [56, 69]. Computational



1 modelling, whilst unable to provide definitive experimental validation, enables the high-
2 throughput exploration of theoretical design space, composition and synthesis
3 conditions [70]. Recent studies show that integrating *in silico* screening with rapid
4 experimental validation can establish more efficient design-build-test cycles for MIPs
5 development [71]. For example, multi-monomer docking strategies combined with
6 high-throughput fluorescence binding assays have been used to prioritise monomer
7 compositions for MIPs targeting SARS-CoV-2, showing strong agreement between
8 computational predictions and experimentally measured binding performance [72].
9 Addressing this central knowledge gap, the lack of a scalable, predictive framework
10 for rational MIPs design, therefore, requires hybrid, multi-fidelity approaches that
11 combine quantum accuracy with efficient exploration of high-dimensional design
12 spaces [73]. This challenge is particularly acute in the design of MIPs for drug delivery,
13 where trade-offs must be balanced between optimising the affinity of the materials for
14 specific receptors, enabling efficient drug incorporation into the polymer matrix, and
15 ensuring the biocompatibility of the final material.

16 Additional considerations further complicate the rational design of MIPs for drug
17 delivery. Template stability is a key factor, as peptides and biomolecules are prone to
18 degradation under some polymerisation conditions (e.g. elevated temperatures,
19 buffered solutions, ionic environments) [74]. Moreover, many drug-like templates and
20 inhibitors exhibit inherent instability or toxicity, thereby limiting their suitability for *in*
21 *vivo* applications. Crosslinkers influence affinity not only by stabilising the polymer
22 network but also by introducing additional binding-site interactions and modulating the
23 physicochemical properties of the pre-polymerisation complex, such as
24 hydrophobicity. The choice and amount of crosslinkers, therefore, represent a trade-
25 off between polymer stability and the flexibility needed to optimise binding site
26 formation [75, 76]. For example, in designing DDSs, lower degrees of crosslinking are
27 preferred, as it allows for more tunable and controlled drug release, with drug loading
28 capacity emerging as a key parameter [26]. Porogenic solvents further dictate MIP
29 morphology and pore structure, while also influencing the stability of non-covalent
30 template-monomer interactions during polymerisations [56, 77].

31 **2.3 Comparative advantages of MIPs in designing DDSs**

32 MIPs possess a unique combination of physicochemical and molecular recognition
33 properties, making them attractive candidates for biomedical applications, particularly



1 in the development of DDSs. Their high drug loading capacity, structural and chemical
2 stability, tunable crosslinking density, and strong affinity toward target molecules
3 enable efficient encapsulation, retention, and controlled release of drugs. Collectively,
4 these characteristics facilitate improved targeting of diseased sites and enhance the
5 potential of MIPs as advanced carriers for therapeutic delivery [26, 37, 78]. As
6 summarised in **Table 1** MIPs uniquely combine receptor-level molecular recognition
7 with the robustness and tunability of synthetic polymers, distinguishing them from
8 conventional drug delivery platforms.



Table 1 DDSs in cancer therapy: types, mechanisms and key advantages, endosomal escape strategies, preclinical and clinical evidence, targeting levels, and key attributes

DDS Type	Mechanism / Key Advantages	Endosomal Escape (EE) Role	Preclinical Evidence	Clinical / Commercial Examples	Targeting Level	Main Characteristics
Liposomes (PEGylated; pH-/thermo-sensitive)	Encapsulate hydrophilic/hydrophobic drugs; improve solubility and PK via PEGylation; stimuli-responsive release (pH, hyperthermia)	Critical for intracellular delivery; pH- and thermo-sensitive designs enhance cytosolic release	Functionalised liposomes, including immunoliposomes and pH-/thermosensitive types, improve DOX delivery [79]	Doxil®, Caelyx®, Myocet®, Onivyde®, Vyxeos®; LTLD in trials [80]	Passive (EPR) ± active (ligand-decorated)	Selectivity: medium to high; solubility: high; stability: medium to high
Albumin-bound nanoparticles	Solvent-free delivery of hydrophobic drugs via albumin pathway; altered biodistribution	EE not primary; uptake via caveolae transcytosis; some endosomal	Improved PK/efficacy vs. Cremophor-paclitaxel; caveolae-mediated	Abraxane® (nab-paclitaxel) [82]	Passive (EPR) + albumin pathway	Selectivity: medium; solubility: high; stability: high





		trafficking occurs	transport implicated [81]			
Polymeric nanoparticles/microparticles (PLGA, ATRIGEL®, micelles)	Controlled release; tunable degradation; high loading; improved PK/PD	Important when intracellular action required; proton-sponge/pH-responsive polymers can promote EE [83]	PLGA microspheres sustain leuprolide; PEG-PLA micelles (Genexol-PM) enhance paclitaxel delivery and efficacy [83]	Lupron Depot®, Eligard®, Genexol-PM [84]	Passive (EPR) ± active	Selectivity: medium; solubility: high; stability: high
PEGylated proteins/polymer conjugates	Increase half-life; reduce immunogenicity; improve PK	EE not central (systemic/extracellular enzymatic action)	PEG-asparaginase demonstrates improved PK and reduced immunogenicity vs. native enzyme [85]	Oncaspar® [86]	Systemic (non-targeted)	Selectivity: low; solubility: N/A; stability: high
Biodegradable implants	Localised, sustained release; improved compliance; reduced systemic toxicity	EE not applicable (local delivery)	Goserelin implants provide controlled hormonal suppression <i>in vivo</i> [87]	Zoladex® [88]	Local delivery	Selectivity: high; solubility: N/A; stability: high

Lipid nanoparticles (LNPs) for RNA	Ionizable lipids protect nucleic acids; optimised for EE via pH-triggered membrane interactions	EE is major barrier (<5% escape without design); ionizable/cationic lipids and EV-inspired strategies improve EE.	Structure–function evolution in ionizable lipids improves mRNA cytosolic release [89]	Multiple cancer mRNA nanovaccines in trials; no FDA-approved cancer LNP yet	Passive (EPR) ± Active (ligands)	Selectivity: medium to high; solubility: N/A; stability: medium to high
Inorganic nanoparticles (radio/thermotherapy)	Hafnium oxide (radioenhancer); iron oxide (magnetic hyperthermia)	EE not relevant (extracellular/physical modality).	Validated clinical use; tumour ablation/RT enhancement [90]	Hensify® (NBXR3), NanoTherm® [91, 92]	Physical targeting (field-driven)	Selectivity: medium; solubility: N/A; stability: high
Molecularly Imprinted Polymers (MIPs) / nanoMIPs	Synthetic epitope/receptor recognition; high stability; cost-effective; dual-template imprinting co-loads drug	Required for intracellular targets; pH-responsive monomers aid EE.	nanoMIPs targeting EGFR and ERα enable selective binding and functional inhibition; bispecific VEGF/DLL4 suppress MCF-7 tumours; dual-imprint EGFR+DOX systems achieve targeted delivery [16, 93]	Preclinical stage only [28]	Active (epitope/receptor)	Selectivity: high; Solubility: formulation-dependent; stability: high



1 One of the most significant advantages of MIPs is their selectivity towards target
2 molecules, arising from the formation of complementary cavities during
3 polymerisation, enabling MIPs to function as synthetic receptors with antibody-like
4 selectivity and enhanced robustness [94, 95]. This molecular specificity fundamentally
5 distinguishes MIPs from conventional polymeric nanocarriers, which typically rely on
6 non-specific interactions for drug loading and targeting. Additionally, MIPs exhibit
7 versatility in targeting different templates, uniquely enabling recognition of both small
8 molecules and macromolecules, capabilities that antibodies often cannot achieve [31,
9 96].

10 By imprinting peptides, proteins, or receptor-specific ligands, MIPs can be engineered
11 to selectively bind overexpressed receptors on cancer cells, facilitating receptor-
12 mediated targeting and enhanced cellular uptake. For instance, nanoMIPs imprinted
13 against a breast cancer marker have demonstrated antibody-comparable affinity while
14 facilitating the endocytosis and intracellular delivery of doxorubicin (DOX) in ER α -
15 overexpressing cancer cells [16]. In this way, MIPs can serve both to recognise target
16 cells and to retain the loaded drug within the polymer matrix, making them particularly
17 beneficial for the design of efficient DDSs. Additionally, this affinity-driven recognition
18 enables preferential binding and stable retention of therapeutic agents within the
19 polymer matrix, even in complex biological environments. This selectivity enhances
20 drug loading efficiency, reduces premature drug leakage, and promotes targeted drug
21 accumulation, thereby improving therapeutic efficacy and reducing systemic toxicity
22 [97]. Moreover, MIPs can be engineered to remain structurally stable under
23 physiological conditions (pH 7.4) while exhibiting pH-responsive behaviour in the
24 acidic tumour microenvironment (pH 6.5), which minimises premature drug loss during
25 systemic circulation [98].

26 A critical comparison with established targeting ligands further contextualises the roles
27 of MIPs in the design of DDSs. While monoclonal antibodies (mAbs) and antibody-
28 drug conjugates (ADCs) are widely used for active targeting due to their high affinity
29 and specificity, nanoMIPs have been shown to have K_D values in the nanomolar range.
30 For example, a comparative study using SPR and electrochemical impedance
31 spectroscopy (EIS) showed that nanoMIPs synthesised against the protein antigen
32 bovine haemoglobin reported binding affinities of 38 pM (EIS) and 3.1 pM (SPR), while
33 the corresponding polyclonal antibody exhibited affinities of 52 pM (EIS) and 49 nM
34 (SPR), demonstrating that nanoMIPs can rival antibody-based recognition in specific



1 systems [99]. Other studies have shown that MIPs enable precise detection of target
2 analytes at picomolar concentrations [100]. Moreover, mAbs are large protein
3 molecules (~150 kDa) protein molecules that exhibit limited tissue penetration [101]
4 and are susceptible to denaturation or enzymatic degradation, whereas MIPs are
5 synthetic polymeric materials with greater physicochemical stability and tunable
6 structural properties. However, unlike antibodies, whose pharmacokinetics and
7 biodistribution are well characterised, the *in vivo* fate and long-term clearance
8 mechanisms of MIPs remain less characterised. In this context, MIPs represent a
9 complementary class of synthetic recognition elements that combine receptor-level
10 molecular recognition with the robustness and design flexibility of synthetic polymers.
11 Unlike their biological counterparts, MIPs are stable over a broad range of pH,
12 temperature and chemical environments, allowing them to maintain structural integrity
13 during circulation and exposure to complex biological media. This stability enables
14 MIPs to protect encapsulated drugs from premature degradation following
15 administration, thereby preserving therapeutic activity until delivery to the target site
16 [102, 103]. Robustness is critical for DDSs that require site-specific action and precise
17 dosing, while also enabling the integration of stimuli-responsive features for controlled
18 drug release in response to physiological triggers [102, 103]. These properties of MIPs
19 also support formulation stability [37, 104, 105], a crucial consideration for clinical
20 translations of these systems. However, the rational design of biodegradable MIPs
21 offers a promising strategy to minimise systemic accumulation and facilitate safe
22 clearance, addressing growing concerns over the long-term persistence of non-
23 degradable nanocarriers [106]. Furthermore, MIPs adhere to the 3Rs by *replacing*
24 animal-derived antibodies, *reducing* the use of animals for immunisation, and *refining*
25 experimental design to minimise *in vivo* interventions [107].
26 The versatility of MIPs further extends to their synthesis and design. As briefly
27 discussed above, they can be prepared in various morphologies such as
28 nanoparticles, thin films, and bulk hydrogels, enabling their properties to be tailored to
29 specific applications. Key parameters such as particle size, crosslinking density, and
30 surface chemistry can be systematically tuned to optimise drug loading, release
31 behaviour, and biological interactions [108]. Multiple well-established synthesis
32 protocols exist, making their production relatively straightforward and reproducible [33,
33 109]. This reproducibility supports batch-to-batch consistency, which is critical for
34 pharmaceutical development and scale-up. Additionally, MIPs can be readily



1 integrated with other functional components, enabling the development of
2 multifunctional drug delivery platforms [106, 110, 111], as discussed later in this
3 review.

4 Cost-effectiveness represents another important advantage of MIPs. They are
5 typically synthesised from inexpensive monomers and crosslinkers using simple
6 polymerisation methods that do not require sophisticated equipment or complex
7 production conditions [112, 113]. For example, MIPs synthesised via solid-phase
8 synthesis for multiple templates exhibited picomolar-level affinity, acceptable cross-
9 reactivity, and retained binding performance after storage at room temperature for
10 extended periods [100]. These studies also highlight the mechanical and chemical
11 robustness of MIPs, which contributes to their long shelf life. MIPs can be stored in a
12 dried state without loss of functionality and can withstand harsh conditions, with
13 analytical characterisation confirming preservation of specificity and structural integrity
14 over several months. Additionally, preservation approaches such as lyophilisation and
15 autoclaving do not affect performance. [100, 114, 115]. For drug delivery applications,
16 MIPs are commonly synthesised using acrylate or (meth)acrylate-based functional
17 monomers and crosslinkers with favourable biocompatibility profiles; however,
18 comprehensive evaluation of their long-term toxicity and *in vivo* fate remains an
19 important area for future investigation [73, 108].

20 **3. Cancer receptors-guided targeted therapy**

21 **3.1 Targeting cancer receptors**

22 Tumours possessed distinct molecular and anatomical features that differentiate them
23 from normal, healthy tissue. Anatomical features of tumour biology include increased
24 blood vessel leakiness and branching, enabling systemic drug delivery to cancer cells
25 via the EPR effect, a passive mechanism for drug delivery [116, 117]. Cancer cells
26 often overexpress specific receptors or antigens on their surface, which support their
27 proliferation and survival [118]. Active targeting is a strategy often employed within
28 DDSs, which is achieved by specific recognition of targeted ligands to cancer-specific
29 cell surface receptors, followed by internalisation via receptor-mediated endocytosis
30 and subsequent release of the therapeutic to the cell [119, 120]. The advantages of
31 this approach include targeted drug delivery to the tumour site, reducing toxicity via
32 minimising exposure to healthy cells, enhanced efficacy, and the potential to bypass
33 certain multidrug resistance mechanisms [121, 122]. mAbs [123] and ADCs [124],



1 which have revolutionised cancer care and are a standard part of treatment for several
2 types of cancer, primarily work through this mechanism. Despite several ADCs
3 demonstrating clinical utility, approximately 90% of ADC candidates and compounds
4 fail in late-stage clinical trials, suggesting that alternatives are needed [125]. The
5 clinical implementation of MIP strategies, however, remains underexplored due to
6 tumour heterogeneity, complexity in the tumour microenvironment, and difficulties in
7 implementing large-scale strategies that facilitate the precise manufacturing of the
8 developed nanocarriers [126-129].

9 **3.1.1 Roles and types of receptors in targeted drug delivery**

10 Overexpressed cancer receptors range from growth factor receptors and nutrient
11 transporters (such as folate and transferrin receptors) to hormones, cell adhesion
12 molecules, cytokines, immune checkpoints, and developmental markers such as
13 Claudins, depending on the type of cancer [130, 131]. MIPs have been designed to
14 selectively target these receptors for cancer therapy, as summarised in **Table 2**. A
15 rapidly expanding area is the use of immune checkpoints to guide therapeutic
16 payloads into the tumour microenvironment (TME), aiming to overcome resistance to
17 checkpoint blockade inhibitors. Immune checkpoints are inhibitory receptors and
18 ligands that regulate T cell activation, maintain immune homeostasis, and prevent
19 autoimmunity. Common immune checkpoints include programmed death ligand 1
20 (PD-L1), programmed cell death protein 1 (PD-1) [132], cytotoxic T-lymphocyte-
21 associated protein 4 (CTLA-4), and lymphocyte activation gene 3 (LAG-3) [130].

22 In addition to immune checkpoints, several receptors are frequently overexpressed in
23 a wide range of cancer types, including folate receptors (FRs), lectins,
24 monosaccharides, growth factor receptors (e.g., vascular endothelial growth factor
25 (VEGF), epidermal growth factor receptor (EGFR), estrogen receptor (ER), and
26 human epithelial growth factor receptor (HER2)), biotin, and interleukins [131, 133-
27 135]. FRs are overexpressed in various cancers, including breast, ovarian, kidney,
28 lung, brain, and epithelial tumours, while being largely absent from normal cell
29 membranes [136]. MIPs have been engineered to recognise conformationally flexible
30 regions of FR α , enabling strong receptor-mediated binding that was minimally affected
31 by endogenous folate. When loaded with DOX or the photosensitizer methylene blue,
32 these nanoparticles exhibited predominant uptake via the caveolar endocytic pathway,
33 and *in vivo* studies confirmed preferential accumulation in HeLa tumour xenografts



1 [137]. In another study, paclitaxel-loaded, folate-functionalised MIPs were developed
2 to target folate receptor-positive MDA-MB-231 breast cancer cells, resulting in
3 markedly enhanced cytotoxicity, with an IC_{50} of 4.86 nM compared to 32.80 nM for
4 free paclitaxel [138].

5 Examples of lectins studied in oncology include galectins, which promote tumour
6 growth and immune evasion [139]; C-type lectins, which require Ca^{2+} for carbohydrate
7 binding and are often overexpressed on tumour-associated immune cells [140]; and
8 selectins, which mediate adhesion and metastasis [141]. Monosaccharides can be
9 exploited for targeted drug delivery by leveraging lectin overexpression, directing
10 nanocarriers to nutrient receptors, improving solubility, and enhancing uptake into
11 tumour-associated immune cells [142]. For instance, multi-responsive hydrophilic
12 “hairy” fluorescent MIPs imprinted with sialic acid (SA) have been developed for
13 receptor-targeted 5-fluorouracil (5-FU) delivery, enabling glutathione (GSH)-triggered
14 intracellular release, improved tumour penetration, and simultaneous bioimaging
15 [143]. Similarly, carbon dot-core MIPs developed to target glucuronic acid, a
16 substructure of hyaluronan overexpressed on cancer cells, allowed selective
17 recognition and imaging of human cervical cancer cells [144].

18 Growth factor receptors are prevalent in many cancers and associated with aggressive
19 phenotypes and receptor-mediated endocytosis, thus making them one of the most
20 popular targets for cancer drug delivery [53]. MIPs developed against VEGF
21 conjugated with quantum dots for fluorescence detection, selectively targeted VEGF-
22 overexpressing tumours in zebrafish xenografts, exhibiting high affinity (equilibrium
23 dissociation constant K_D of 1.56 nM) and minimal toxicity in embryos [145]. In another
24 recent study, bispecific MIPs engineered to target VEGF and Delta-like 4 (DLL4)
25 achieved selective tumour accumulation in MCF-7 mouse xenografts and 68-72%
26 tumour suppression [146]. Furthermore, EGFR-targeted nanoMIPs imprinted against
27 the receptor and DOX enabled selective cancer cell targeting, with a high K_D value of
28 3.6 nM for the receptor [93]. Additionally, dopamine-based EGFR-imprinted MIPs
29 demonstrated pH-responsive DOX release, enhancing delivery to receptor-
30 overexpressing cells [147]. In another example, MIPs targeting HER2 have been
31 shown to increase *in vivo* DOX accumulation, enhance tumour suppression, and
32 reduce off-target toxicity in ovarian cancer mouse models [148]. Similarly, MIPs
33 targeting $ER\alpha$, loaded with a fluorescent dye and DOX, exhibited preferential binding



1 to ER α (K_D =14.7 nM) in breast cancer cell models and delivered DOX to the nucleus
2 via receptor-driven uptake [16].

3 Biotin, a water-soluble vitamin, acts as a cellular growth promoter and is essential for
4 rapidly dividing cancer cells [134]. To exploit this, biotin-functionalized core-shell MIPs
5 were developed that specifically targeted MCF-7 breast cancer cells, demonstrated
6 enhanced adsorption and endocytosis-mediated uptake, enabled intracellular delivery
7 of DOX, and reduced MCF-7 cell viability from 90% to 60% [149]. Biotin-selective MIPs
8 have also been developed as adaptable scaffolds that bind biotinylated targeting
9 motifs, such as a CD44-specific aptamer, enabling precise recognition of cancer cells
10 [150]. Interleukin receptors, a type of cytokine, stimulate the growth and invasiveness
11 of various types of cancers, including ovarian, breast, malignant glioma, lung, colon,
12 bladder and pancreatic carcinoma [151]. Molecularly imprinted 'nanotraps' have been
13 developed to selectively bind and sequester IL-6, effectively lowering extracellular IL-6
14 levels in cell models and underscoring the potential of MIPs to modulate
15 pro-tumorigenic cytokines in cancer progression [152]. An overview of the various
16 receptors and cancer types is provided, along with examples that have been approved
17 by the FDA.

18
19 **Table 2** Overview of molecularly imprinted polymers developed for targeting cancer-
20 associated biomolecules, including receptors, carbohydrates, growth factors, vitamins,
21 cytokines, and immune checkpoints, with their functional roles

Receptor Family	Receptor Type	Example	Functional Role / Targeting Advantage	MIP Applications
Vitamin Transporter	Folate Receptor	FR α	Highly overexpressed in breast, ovarian, kidney, lung, and brain cancers; minimal in normal cells	MIPs targeting FR α loaded with DOX or methylene blue for HeLa xenografts [138]; paclitaxel-loaded folate-functionalized MIPs for MDA-MB-231 cells



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DOI: 10.1039/D6NR00511J
(IC₅₀ 4.86 nM vs 32.80 nM) [137]

Lectin Family	Lectin	Galectins	Promote tumour growth and immune evasion	Hairy fluorescent MIPs imprinted with SA for 5-FU delivery and imaging [143]
		C-type lectins	Requires Ca ²⁺ for carbohydrate binding; overexpressed on tumour-associated immune cells	Carbon dot-core MIPs targeting glucuronic acid for cervical cancer imaging [144]
		Selectins	Mediate adhesion and metastasis	MIPs for selectin-targeted delivery (conceptual)
Carbohydrate Target	Monosaccharide	Sialic acid	Enable receptor-mediated uptake via lectin overexpression; improve solubility and tumour penetration	Multi-responsive MIPs for SA (5-FU delivery) [143]
		Glucuronic acid	Target hyaluronan substructure overexpressed on cancer cells	Carbon dot-core MIPs for glucuronic acid imaging [144]
Growth Factor Receptor Family	Growth Factor Receptor	VEGF	Overexpressed in aggressive cancers such as glioblastomas; mediates endocytosis	VEGF-imprinted MIPs with quantum dots for zebrafish xenografts [99]; bispecific MIPs for VEGF & DLL4 (68-72% tumour suppression) [146]



		EGFR	Associated with aggressive phenotypes; receptor-mediated uptake	EGFR-imprinted nanoMIPs with DOX (K_D 3.6 nM) [101]; dopamine-based EGFR-imprinted MIPs for pH-responsive DOX release [147]
		HER2	Overexpressed in breast and ovarian cancers; mediates endocytosis	HER2-targeted MIPs for DOX delivery and tumour suppression [103]
		ER α	Hormone receptor; nuclear delivery via receptor-driven uptake	ER α -targeted MIPs with DOX and fluorescent dye (K_D 14.7 nM) [16]
Vitamin	Biotin	Biotin	Essential for rapidly dividing cancer cells; promotes growth	Biotin-functionalized core-shell MIPs for MCF-7 cells (DOX delivery, viability reduced from 90% to 60%) [149]; biotin-selective MIPs binding biotinylated CD44 aptamer [150]
Cytokine	Interleukin	IL-6	Stimulate growth and invasiveness in multiple cancers	Molecularly imprinted nanotraps for IL-6 sequestration, reducing extracellular IL-6 levels [152]
Immune Checkpoint	Immune Checkpoint	PD-L1	Guide therapeutic payloads into TME; overcome resistance to	Emerging concept: MIPs targeting PD-L1 for enhanced



checkpoint inhibitors

immunotherapy [132]

PD-1

Immune regulation: target for immunotherapy

Emerging concept: MIPs targeting PD-1 [132]

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DOI: 10.1039/D6NR00511J

1

2 **3.1.2 Receptor selection criteria and techniques**

3 The targeted receptors are not confined to a single tissue type; rather, they are often
 4 expressed at higher levels in specific regions of the body [153, 154]. Their distribution
 5 can be uneven across different tissues and may also vary in density within the same
 6 tissue [155, 156]. Therefore, an ideal receptor target for imprinting should exhibit a
 7 high tumour-to-normal tissue expression ratio to minimise on-target off-tumour effects
 8 during targeted delivery [157]. Subsequently, the targeted moieties must be accessible
 9 to the targeting agent, typically located on the cell surface and not obscured by other
 10 proteins or cellular complexes [158]. The recognition process is also influenced by the
 11 isoform diversity of the targeted molecule. Isoform-specific expression can alter
 12 epitope availability, ligand affinity, and downstream biological responses, thereby
 13 impacting targeting efficiency [158, 159]. Receptor targeting can promote
 14 internalisation of the nanocarriers, leading to intracellular drug release, but may also
 15 temporarily remove the receptor from the cell surface, thereby limiting the binding of
 16 additional drug-carrier complexes [158, 160]. Consequently, receptor internalisation is
 17 a critical parameter when selecting targets for sustained drug delivery. For example,
 18 a study investigated the targeting potential of MIPs toward both intracellular and
 19 extracellular EGFR epitopes and demonstrated that MIPs aimed at intracellular
 20 domains can sequester the receptor, inhibit its signalling, and reduce cancer cell
 21 viability [161]. Another factor that needs to be considered is the internalisation potential
 22 of the MIPs for drug release. The nanoparticles can enter cells through multiple
 23 endocytic mechanisms, generally via clathrin-mediated endocytosis. Other
 24 mechanisms include caveolae-mediated endocytosis and macropinocytosis, which
 25 are less frequent [162]. The dominance of a particular endocytic pathway can influence
 26 intracellular trafficking and therapeutic efficacy. For instance, MIPs imprinted against



1 EGFR have been reported to undergo endocytosis and subsequent accumulation in
2 the cytoplasm [93].
3 Computational techniques are often employed to select membrane proteins and
4 biomarkers for the design of targeted DDSs. ML is utilised to analyse multi-omics
5 datasets to identify protein mutations that drive tumour development and to assess
6 their effects on protein stability and function [163, 164]. Comprehensive bioinformatics
7 analyses of gene expression data from TCGA (The Cancer Genome Atlas), UALCAN
8 (The University of ALabama at Birmingham CANcer data analysis Portal), TNMplot
9 (Tumour, Normal, and Metastatic plot database), and LinkedOmics have been used
10 to identify membrane proteins as potential targets for breast cancer therapy [165]. In
11 addition, protein-protein interaction networks and cell-surface proteomics are used to
12 prioritise functionally central, accessible, and cancer-specific receptors [166, 167].
13 Structural prediction models such as AlphaFold2 and trRosetta can be applied to
14 model these proteins. AlphaFold2 offers accurate structural predictions for targets
15 lacking experimental data, thereby supporting structure-based drug design and virtual
16 screening [168, 169]. Studies have shown that predictions with high-confidence
17 regions are comparable to experimental structures and are valuable for computational
18 modelling, while low-confidence regions help define domain boundaries for protein
19 expression and functional studies [170]. At this stage, computational modelling
20 primarily serves as a screening and prioritisation tool for receptor selection.
21 Subsequently, molecular docking and simulation techniques are used to characterise
22 interactions between the proteins and the designed drugs [163]. Once the target has
23 been selected, polymer composition and monomer feed can be considered as
24 described above. Naturally, surface targets are difficult to obtain a whole free protein
25 without loss of secondary and tertiary structure, meaning that whole protein imprinting
26 is not suitable here – targeting a region of the protein is therefore required.

27 **3.2 Epitope imprinting**

28 **3.2.1 Epitope imprinting selection criteria**

29 Biological applications, such as drug delivery, require the imprinting of large
30 biomacromolecules, like proteins. However, there are some key challenges with using
31 these molecules as templates in molecular imprinting. First, high molecular weight can
32 hinder mass transfer and pose difficulties for the template to diffuse out after
33 polymerisation, though this is less of an issue with solid-phase imprinting. This



1 diffusion limitation also slows the rebinding of the target molecules to the MIPs. While
2 proteins and other biomolecules are more stable in aqueous solutions, certain
3 monomers used in molecular imprinting perform best with organic solvents, limiting
4 the choice of compatible monomers. Furthermore, proteins are heterogeneously
5 charged and have structurally similar regions, which can lead to cross-reactivity and
6 non-specific binding [31, 171]. As demonstrated by previous studies, MIPs
7 synthesised against a specific protein conformation exhibit the highest affinity for that
8 conformation during rebinding. Therefore, even minor structural changes in the protein
9 can reduce binding affinity [172]. These challenges are further exacerbated for
10 membrane proteins, whose native conformation is strongly dependent on the lipid
11 bilayer environment and is often disrupted upon removal from the membrane, leading
12 to loss of structural integrity and binding fidelity [173]. These limitations, alongside the
13 need to target membrane-bound polymers, led to the use of epitopes as templates for
14 molecular imprinting.

15 An epitope is a specific region of an antigen that is recognised by antibodies or other
16 targeting molecules [174]. These distinct protein segments act as antigenic
17 determinants, and their defined structural features enable them to represent the entire
18 protein in epitope-imprinting strategies. In such approaches, a short peptide fragment
19 or structural portion of the target protein serves as a substitute or partial template for
20 synthesising MIPs [175]. Compared to whole proteins, epitope templates are more
21 stable during imprinting and can be readily synthesised, even for rare targets. Since
22 epitope-imprinted sites mimic natural antibody recognition domains, they often provide
23 high binding specificity toward the target [74, 176].

24 Using a smaller molecule as a template overcomes structural and cost challenges of
25 larger proteins while maintaining binding to the full target. The reduced size also
26 restricts flexibility and the number of exposed functional groups, resulting in more
27 uniform imprint cavities [177]. Additionally, peptides are more stable than proteins
28 because they lack tertiary and quaternary structures and can be synthesised to be
29 soluble in a wider range of solvents, offering greater flexibility for MIP preparation.
30 Consequently, peptide-based epitope templates improve both the reproducibility and
31 the cost-effectiveness of MIP synthesis [178, 179], though in some cases, reduce the
32 affinity, likely due to steric hindrance.

33 An epitope can either be a linear sequence of amino acids located in the loops of a
34 protein or be discontinuous, where the amino acids are spatially close during protein



1 folding. Linear epitopes are generally preferred as templates in molecular imprinting
2 because they are easier to synthesise and present a well-defined, reproducible
3 structure, whereas discontinuous (conformational) epitopes are difficult to replicate
4 due to the challenge of reproducing their native three-dimensional spatial arrangement
5 [74, 177].

6 While linear epitopes offer practical advantages as templates for molecular imprinting,
7 concerns remain regarding whether recognition of a short linear peptide sequence can
8 translate to binding of the same region in the folded native protein. Factors such as
9 protein conformation and steric hindrance may limit epitope accessibility. However,
10 several studies have demonstrated that epitope-imprinted MIPs can successfully
11 recognise the corresponding full-length receptor in biological systems. For example,
12 nanoMIPs imprinted against short peptide epitopes derived from cancer receptors
13 have shown selective binding to receptor-expressing cells and receptor-mediated
14 endocytosis, indicating that recognition of the linear peptide template can translate to
15 interaction with the native membrane-bound protein [16]. In addition, conformational
16 epitopes can also be employed when more accurate protein recognition is required in
17 complex physiological environments. Unlike linear epitopes, conformational epitopes
18 consist of discontinuous amino acid residues that become spatially close after protein
19 folding, thereby better reflecting the protein's native three-dimensional structure.
20 Imprinting strategies based on such epitopes may therefore improve the specificity
21 and binding affinity of MIPs [180]. However, their practical application can be limited
22 by structural instability or susceptibility to degradation outside the native protein
23 environment, thereby hindering accurate imprinting. Furthermore, a direct validation
24 of MIP-protein recognition has been demonstrated using ELISA-type assays [181,
25 182]. For instance, MIP-based pseudo-ELISA assays developed for procalcitonin
26 detection achieved limits of detection of 3.8 ng mL⁻¹ in buffer and 4-6 ng mL⁻¹ in
27 plasma, demonstrating analytical performance comparable to its conventional
28 antibody-based ELISA assays [181].

29 The concept of epitope imprinting involves imprinting a portion of the protein, rather
30 than the entire molecule, offering a more economical and compatible alternative with
31 various monomers and solvents [179]. The concept of epitope imprinting was first
32 proposed by Rachkov *et al.*, who utilised a tetrapeptide derived from oxytocin instead
33 of the entire peptide in MIP synthesis to selectively bind oxytocin in an aqueous
34 environment [175]. Subsequently, a study by Tai *et al.* was the first to use an epitope



1 for protein recognition, employing a 15-mer peptide for imprinting to recognise the NS1
2 protein of dengue virus [183].

3 The selected epitope is typically a surface-based segment of the targeted protein that
4 enables specific binding. Often, C- or N-terminal epitopes are chosen as templates;
5 however, N-terminal is less favourable due to its higher susceptibility to post-
6 translational modifications, which can alter the structure of the peptide and interfere
7 with the imprinting [74]. Choosing a linear epitope has several advantages: it is cost-
8 effective, its binding sites are accessible on the protein surface, its position within the
9 protein simplifies selection, and it can be readily modified to meet synthesis
10 requirements [184].

11 Another important criterion in epitope selection is its length. While too-long peptides
12 can have complicated structures, peptides that are too short can lead to ineffective
13 imprinting and low binding affinity of the MIP [184]. One study demonstrated that
14 epitope length affects MIP performance, with a 14-amino-acid peptide exhibiting the
15 highest binding affinity. However, it was emphasised that factors beyond epitope
16 length and conformation significantly impact MIP performance [185]. Another
17 comprehensive study analysed the impact of epitope length by comparing three
18 epitopes with 9, 12 and 15 amino acids, derived from the C-terminal of human serum
19 albumin. The 12-mer peptide yielded the best imprinting factor, characterised by the
20 highest specificity and affinity, underscoring the importance of considering peptide
21 length during epitope selection [186]. Additionally, it has been observed that other
22 factors, including hydrophobicity and solvent compatibility, together with a peptide
23 length of less than 16 amino acids, are required for optimal MIP binding [187]. It is
24 acknowledged, though, that this is target-dependent, meaning there are no easy
25 selection criteria.

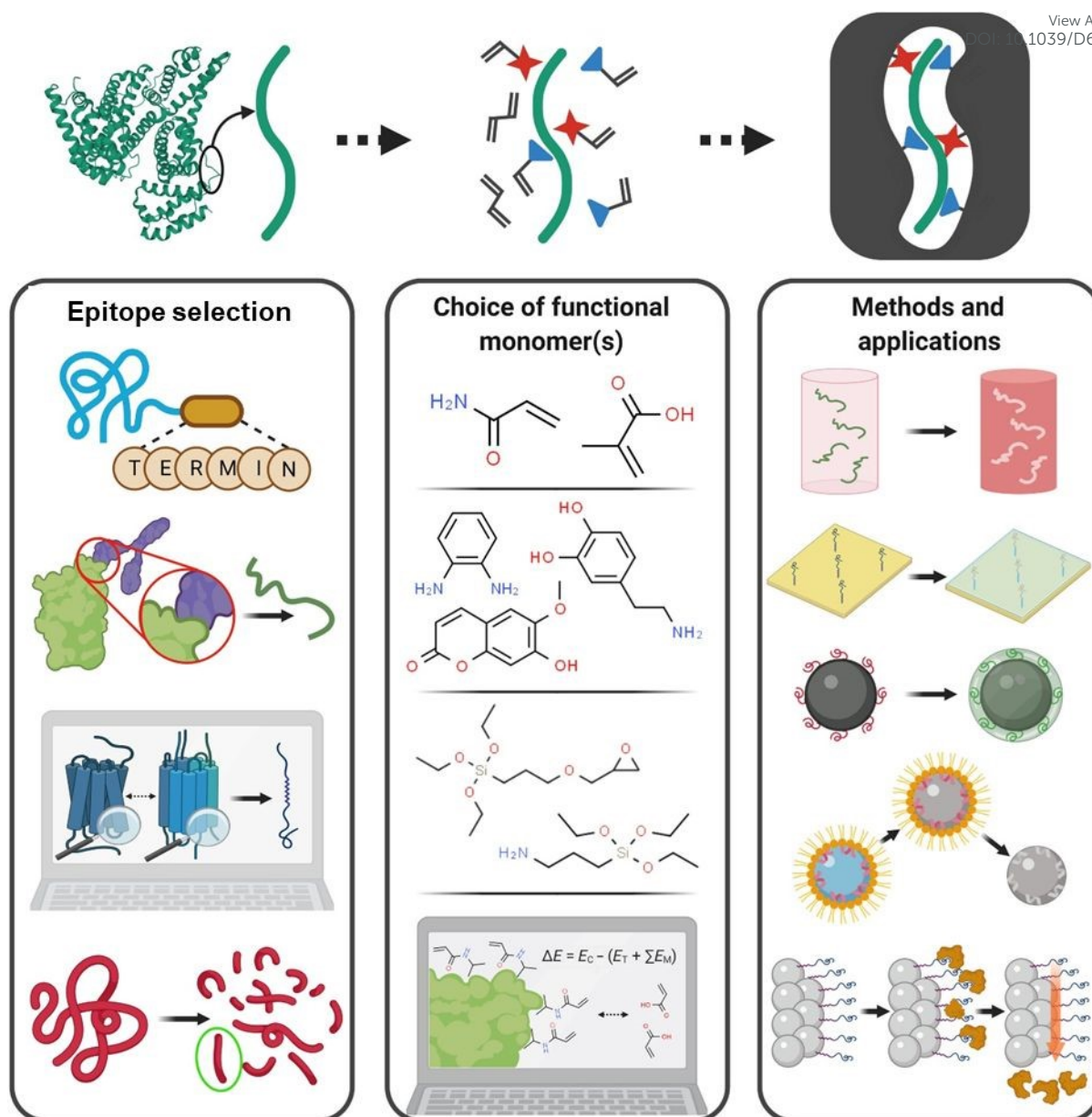
26 **3.2.2 Epitope Selection Techniques**

27 The process of selecting an epitope for an antibody synthesis is known as epitope
28 mapping [174]. Several methods exist for this; the most common is X-ray
29 crystallography of the antibody-antigen complex. Other approaches include NMR or
30 evaluating antibody binding to different protein fragments. However, these techniques
31 are often expensive and time-consuming. To address these limitations, *in silico*
32 methods such as machine learning and immunoinformatic tools are being used.
33 Factors commonly considered include selecting C- and N-terminal regions, peptide



1 lengths of 8-20 amino acids, and preference for surface-exposed regions [188]. An
2 identical approach can be used to select an epitope for molecular imprinting.
3 Commonly, the procedure for choosing an epitope for imprinting is based on the
4 above-discussed criteria. The epitope imprinting process is illustrated in **Figure 1**. The
5 C- or N-terminal of a protein with an appropriate peptide length is often chosen [189,
6 190]. Another common approach is to identify a region of the protein (or antigen) to
7 which the antibody binds and use that sequence as a template, or guidance from
8 biological epitope-paratope complexes. This strategy uses known, commercially
9 available antibodies to obtain the peptide sequence and to synthesise the artificial
10 antibodies as MIPs [66, 93]. This approach allows biologically validated recognition
11 motifs to be directly translated into synthetic imprinting systems.
12 Other chemical-based methods are also used for selecting the epitope. One such
13 approach involves immobilising the target protein on a solid support and then digesting
14 it enzymatically. This results in the selective retention of surface-accessible peptide
15 fragments, which can then be used directly as templates [191]. This concept was
16 employed using acetyl cholinesterase as the model protein, which was first imprinted
17 onto the polymer. After enzymatic digestion of the protein without removal from the
18 polymer, the remaining polymer-bound sequences are eluted and identified by mass
19 spectrometry. In this case, seven peptide sequences were identified, four of which
20 were consistent with the known literature epitopes [192].





1
2 **Figure 1** Major steps involved in the epitope imprinting process. Each step offers
3 multiple design options that must be carefully selected to optimise MIP performance
4 for the intended application. This Figure has been reproduced from ref [184] with
5 permission from the American Association for the Advancement of Science, 2026.

6 Another study employed a similar concept-based method, snapshot imprinting, for
7 biomarker discovery and epitope selection in complex systems. In this approach, MIPs
8 were synthesised in the presence of whole cells, enabling the polymers to 'record' the
9 exposed surface proteins. Subsequent trypsin digestion and mass spectrometric
10 analysis identified three senescence-specific proteins, which can be utilised for the
11 development of targeted personalised medicine for cellular ageing [193]. This strategy



1 demonstrates the potential of MIPs to identify biologically relevant epitopes directly
2 from complex biological environments.

3 A common strategy for epitope selection is based on computational or *in silico*
4 modelling. This approach has gained attention for its cost-effectiveness and ability to
5 reduce experimental burden. Both epitope templates and suitable functional
6 monomers can be selected computationally, reducing monomer and solvent
7 consumption and minimising waste generation [59, 188]. This method involves
8 screening monomer libraries to select those with the most favourable interactions and
9 identifying peptide epitopes that exhibit stable conformations. For example, MD
10 simulations have been used to analyse the stability of peptide segments derived from
11 neuron-specific enolase (NSE) and to identify regions that remain stable under
12 physiological conditions [194].

13 Bioinformatic resources such as the Immune Epitope Database and Analysis
14 Resource (IEDB) can also support epitope identification. The UniProt Knowledgebase
15 (UniProtKB) provides curated amino acid sequences of target proteins, while tools
16 available through the ExPASy portal can simulate enzymatic digestion to generate
17 peptide fragments with suitable length and orientation. The peptides can then be
18 analysed using BLAST to assess sequence specificity and surface relevance [179,
19 188]. In one study, BLAST analysis was used to identify biomarkers associated with
20 idiopathic pulmonary fibrosis, leading to the selection of two surface-accessible
21 epitopes. The resulting sensor successfully detected the epitopes in complex
22 biological media [195].

23 A related *in silico* strategy, termed fingerprint imprinting, integrates computational
24 proteomics with molecular imprinting for rational MIPs design. The target protein is
25 virtually cleaved into peptide fragments, screened against UniProtKB, and unique
26 peptides are synthesised as imprinting templates. This approach was demonstrated
27 using NT-proBNP, yielding MIPs with high selectivity and binding capacity [196]. By
28 combining experimental techniques and computational approaches, epitope selection
29 is becoming increasingly streamlined, reinforcing the role of epitope-based MIPs in
30 targeted drug delivery applications. Once selected, the epitope can be used as a free
31 (in solution) or fixed (solid-phase) template for imprinting with a degree of simplicity.



1 **4. MIP-Based Case Studies in Cancer Therapy**

2 As discussed in the previous sections, MIPs have several advantages that make them
3 suitable candidates for biomedical applications. They are suitable for drug delivery due
4 to their high loading capacity, high stability, control over crosslinking and, of course,
5 the high affinity, which makes it easier to target affected sites [197]. The first-ever
6 demonstration of MIPs for drug-delivery applications was reported in 1998. The
7 polymer composed of methacrylic acid (MAA) and ethylene glycol dimethacrylate
8 (EGDMA) could selectively distinguish theophylline from its structural analogue,
9 caffeine. Moreover, it exhibited a sustained release profile for theophylline,
10 demonstrating the potential of MIPs for controlled drug delivery applications [198].
11 Since then, the field has advanced remarkably, with MIPs-based DDSs evolving from
12 simple recognition polymers to nanoscale carriers for the controlled delivery of
13 anticancer, antibiotics, antivirals, anti-inflammatory, and several other drugs [197].

14 **4.1 Structural and Imprinting Design of MIP-Based DDSs**

15 A significant portion of drug delivery research focuses on cancer, owing to the
16 limitations of traditional chemotherapy. Accordingly, MIPs have been engineered to
17 address these challenges by enabling the controlled release of anticancer agents. The
18 mechanism of drug delivery with MIPs can be designed through different routes. One
19 common strategy involves engineering MIPs using tumour cell surface markers as
20 template molecules to achieve targeted delivery, allowing the nanocarriers to
21 recognise and bind specifically to cancer cells, as highlighted above [137, 199, 200].
22 Here, the developed MIPs are generically loaded with the carrier therapeutic. Another
23 technique involves creating cavities using the drug itself as the template. This
24 approach provides a high drug-loading capacity and facilitates controlled, prolonged
25 release by utilising the imprinted cavities as reservoirs for drug molecules, though it
26 does not provide targeting [201, 202]. In contrast to receptor-mediated endocytosis as
27 an internalisation method (as seen with surface marker templates), drug-imprinted
28 MIPs are generally internalised through non-specific or passive mechanisms, such as
29 adsorptive endocytosis or diffusion-driven uptake, and are primarily governed by
30 physicochemical properties, including particle size, surface charge, and
31 hydrophobicity [120, 203]. Additionally, stimuli-responsive release mechanisms, along



1 with combinational therapies, are employed to achieve controlled drug release, as
2 discussed in later sections.

3 Apart from the imprinting strategy, the structural architecture of MIPs-based
4 nanocarriers also plays a vital role in influencing their drug delivery performance.
5 Different structural configurations have been developed to optimise drug loading,
6 protection, and release profiles. Core-shell imprinting (coating the MIP around an inert
7 core) positions binding sites near the MIP surface, enabling faster target binding and
8 release while reducing mass-transfer resistance. Such behaviour has been
9 exemplified in photoluminescent core-shell nanocarriers, where gelatin quantum dots
10 coated with a methotrexate-imprinted MIP shell enabled selective drug recognition and
11 sustained release [204]. In another study, metal-organic framework (MOF)-based
12 MIPs were engineered as core-shell nanocarriers, integrating the high drug-loading
13 capacity of a Cu-MOF core with a DOX-imprinted polymer shell, resulting in pH-
14 responsive and sustained drug release under tumour-relevant conditions [205].
15 Magnetic cores are often used in targeted drug delivery to enable stimuli-responsive
16 drug release, as discussed in detail in later sections.

17 In addition to core-shell systems, capsule-like nanoparticles have also been developed
18 to achieve high drug loading and targeted delivery. For example, multi-responsive
19 fluorescent MIP nanocapsules meeting the 2R2SP (balancing drug retention and on-
20 site release, switching between stealthy and adhesive surface states, and enabling
21 deep tumour penetration beyond blood vessels) requirements demonstrated
22 prolonged circulation, targeted tumour accumulation, high loading capacity, rapid
23 intracellular release, and bioimaging potential owing to their SA-imprinted shell and
24 flexible semi-hollow structure [143]. Similarly, polydopamine-based capsule-like
25 nanoMIPs were developed for synergistic chemo-photothermal cancer therapy, where
26 EGFR served as the template and ZIF-8@DOX as the sacrificial core, enabling
27 targeted and controlled drug delivery along with pH- and NIR-responsive behaviour
28 [147]. Overall, these studies highlight that both the imprinting strategy and the
29 structural design of MIPs-based nanocarriers are critical for achieving targeted,
30 controlled, and stimuli-responsive drug delivery.

31 **4.2 Stimuli-Responsive DDSs**

32 Beyond the material composition and target, drug release from any nanoparticle-
33 based DDSs is also dependent on the stimuli that initiate it. This release can be either



1 internal (pH, redox potential, enzymes) or external stimuli-based (temperature, light,
2 magnetic field) [206]. One of the advantages of using MIPs as drug delivery vehicles
3 is that they can be tuned to release drugs across different delivery routes, as discussed
4 in **Table 3**.

5 The most used internal stimuli in DDSs are pH-based drug release, as the tumours
6 are known to exhibit an acidic pH compared to physiological pH [207]. For example,
7 boronate-affinity MIPs imprinted with 5'-Deoxy-5-fluorocytidine (DFCR) and SA
8 exhibited dual functionality, where acidic conditions enhanced tumour targeting via
9 strengthened boronate-SA interactions while weakening boronate-DFCR binding to
10 trigger drug release, enabling pH-responsive delivery [208]. Similarly, a pH-responsive
11 MIP carrier for capecitabine (CAPE) was prepared, where cleavage of borate ester
12 bonds under acidic tumour-like conditions triggered controlled drug release, leading to
13 effective inhibition of breast cancer cells [209]. Exploiting a different mechanism, pH-
14 responsive MIPs for 5-FU were developed for colorectal cancer, where protonation-
15 driven weakening of polymer-drug interactions enabled colon-specific release at pH
16 7.4. This minimised premature release of 5-FU and improved therapeutic efficiency
17 [210].

18 Other stimuli, such as redox responsiveness, have also been exploited for controlled
19 drug release by incorporating disulfide-containing crosslinkers, including N,N'-
20 bisacrylylcystamine (BACy) and bis(2-methacryloyloxyethyl) disulfide (DSDMA).
21 These designs leverage the elevated GSH levels in the tumour microenvironment,
22 where cleavage of disulfide bonds triggers drug release from the nanocarriers. As a
23 result, the drug remains stable under normal physiological conditions but is selectively
24 released within tumour tissues [211, 212]. Interestingly, these nanoMIPs exhibit lower
25 K_{DS} (μM) than solid-phase systems risking off-target binding. Similarly, organosilica-
26 based biodegradable MIPs have been engineered to respond to both pH and redox
27 stimuli, where the MIP shell enables selective cancer cell targeting, while disulfide
28 bond cleavage in the organosilica core induces the release of DOX and the
29 photosensitizer chlorin e6, facilitating combined chemotherapy and photodynamic
30 therapy [213].

31 Another approach combined pH-responsive release with external magnetic fields,
32 which disrupted hydrogen bonds between DOX and the MIPs, and included local
33 hyperthermia to enhance anticancer efficacy [214]. Core-shell magnetic MIPs have
34 been shown to achieve extended drug release of 5-FU for up to 200 h, compared to



1 57 h for non-imprinted controls [215]. Similarly, biodegradable MIPs crosslinked with
2 glucose were developed for targeted delivery of docetaxel, where magnetic properties
3 enabled both precise tumour localisation and controlled drug release [106]. Some
4 DDSs are also engineered for photo-responsive release. For instance, graphene
5 quantum dots-MIPs triggered the release of DOX upon 808 nm near-infrared (NIR)
6 light, weakening the interactions between the drug and the polymer matrix.
7 Additionally, the release kinetics partially followed a zero-order model, indicating
8 sustained and controlled drug release [216]. In another case, visible-light-responsive
9 MIPs bearing azobenzene undergo a conformational change from trans to cis with 400
10 nm blue light and revert to the trans conformation with 630 nm red light. These
11 reversible structural properties allowed controlled drug loading and release [217].
12 N-isopropylacrylamide (NIPAM) is frequently employed in the design of
13 thermoresponsive MIPs due to its lower critical solution temperature (LCST) of 32 °C,
14 which is close to human body temperature. Of note, NIPAM is also a common
15 monomer used in solid-phase imprinting to facilitate thermal polymerisation. Below the
16 LCST, the polymer exhibits hydrophilic behaviour, facilitating drug loading, whereas
17 above this temperature, it becomes hydrophobic, triggering drug release [218, 219].
18 Exploiting this property, a biocompatible thermoresponsive NIPAM-MIPs-based DDS
19 was developed by grafting the polymer onto konjac glucomannan, a natural
20 polysaccharide. This system was capable of selectively binding and releasing 5-FU in
21 response to temperature changes while exhibiting high selectivity and stability around
22 the LCST [220]. In another approach, Fe₃O₄ magnetic thermal seeds coated with
23 thermoresponsive MIPs were developed for methotrexate (MTX) delivery. Exposure
24 to an alternating current magnetic field (AMF) rapidly increased the MIP temperature,
25 triggering a release of up to 80% of the loaded drug due to the weakening of hydrogen
26 bonds [221].
27 Alongside other stimuli, enzyme-responsive MIPs have been developed, in which
28 specific, non-catalytic binding by template enzymes, such as lysozyme or α -
29 glucosidase, induces structural changes in chitosan-phthalate nanoparticles. This
30 triggered the selective disassembly of nanoparticles and on-demand drug release,
31 achieving approximately 90% compared to 11% in non-imprinted controls, driven by
32 enzyme-specific binding [222]. Thus, the combination of stimulus-responsiveness and

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- 1 selectivity in MIPs leads to the development of controlled-release systems that can
2 significantly enhance therapeutic effects while reducing systemic toxicity.

3 **Table 3** MIP-based stimuli-responsive drug delivery systems with fabrication method
4 and associated studies

Stimulus Type	Mechanism	Fabrication Approach	Studies
pH-responsive	Acidic tumour pH weakens polymer-drug interactions	Boronate-affinity imprinting; polymerisation with borate ester bonds	DFCR & SA MIPs [208]; CAPE MIPs [209]; 5-FU colon-specific MIPs [165]
Redox-responsive	Disulfide bond cleavage in a high-GSH environment	Incorporation of disulfide-containing crosslinkers (BACy, DSDMA)	BACy/DSDMA MIPs [211, 212]; organosilica MIPs for DOX + chlorin e6 [213]
Magnetic field	AMF disrupts hydrogen bonds & induces hyperthermia	Core-shell magnetic nanoparticles coated with imprinted polymer	DOX magnetic MIPs [169]; 5-FU magnetic MIPs [170]; glucose-crosslinked magnetic MIPs [64]
Light-responsive	NIR or visible light triggers structural changes	Integration of graphene quantum dots or azobenzene monomers	DOX release via NIR (808 nm) [216]; azobenzene-MIPs reversible with blue/red light [217]
Temperature-responsive	LCST-driven hydrophilic/hydrophobic switch	NIPAM-based polymer grafted on natural polysaccharide or magnetic seeds	NIPAM-MIPs on konjac glucomannan [220]; Fe ₃ O ₄ thermal seeds coated with MIPs [221]
Enzyme-responsive	Template enzyme binding induces	Chitosan-phthalate	Lysozyme/ α -glucosidase-



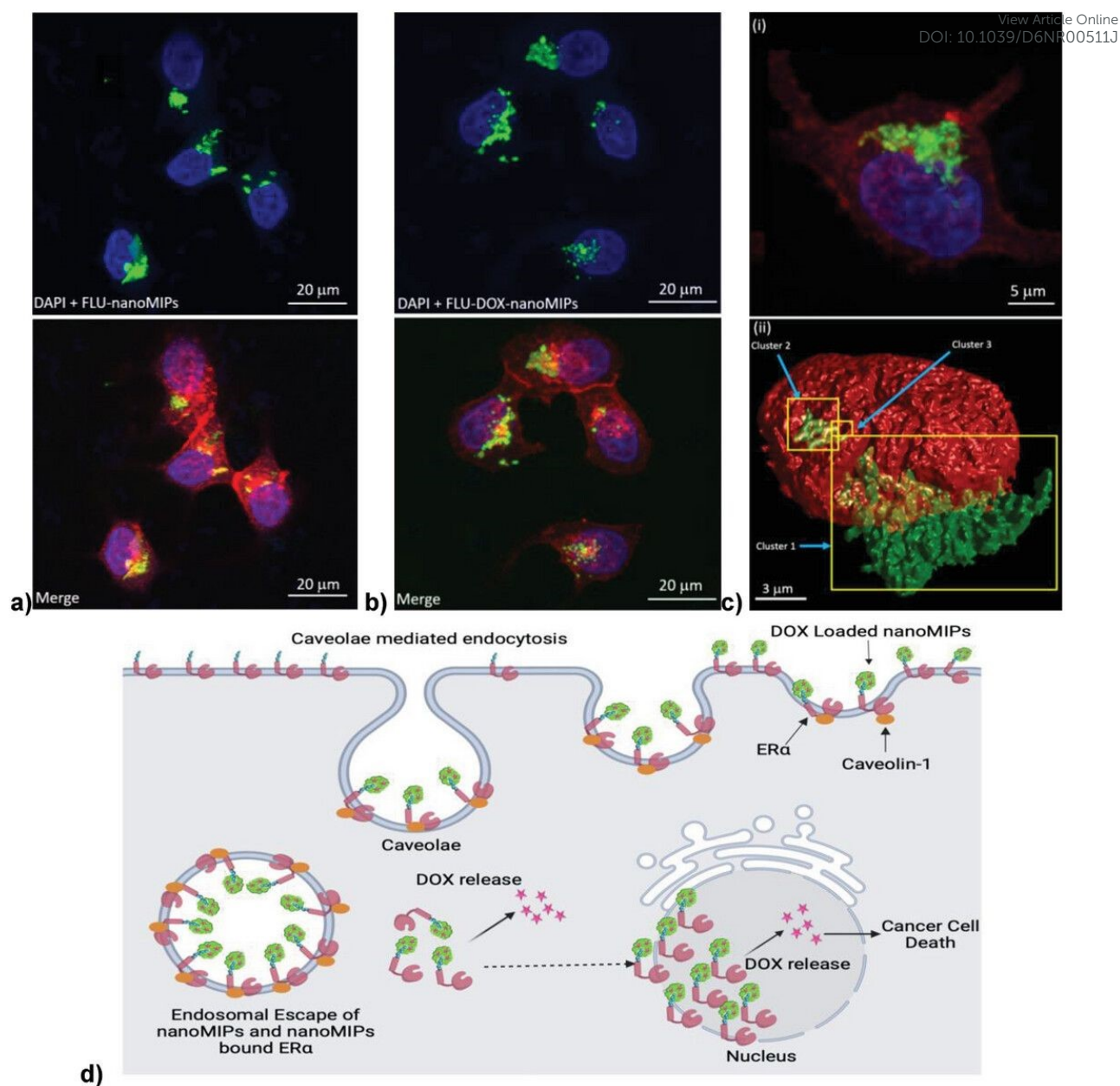
nanoparticle
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DOI: 10.1039/D6NR00511J

1 4.3 Hybrid MIPs and MIPs with Further Complexity

2 While traditional MIPs are valuable in nanomedicine due to their high selectivity, their
3 properties can be further enhanced by integrating them with complementary
4 nanoparticles, biological molecules, or inorganic functional components. Such hybrid
5 systems improve the selectivity, precision, stimuli-responsiveness, versatility, and
6 overall efficacy of the MIPs.

7 Within the framework of hybrid MIPs, double-imprinted polymers, or dual-template
8 MIPs, are prepared using multiple templates during polymerisation, enabling them to
9 simultaneously recognise, bind, load, detect, analyse, and separate multiple analytes
10 [223]. A specific form of double imprinting, mostly used in DDSs, involves using a
11 protein or epitope as a recognition template and a drug as the second imprint, which
12 remains loaded on the MIP. Canfarrota *et al.* employed an EGFR epitope alongside
13 DOX as templates. The resulting MIPs specifically targeted the cancer cells
14 overexpressing EGFR and simultaneously released DOX at the tumour site [93].
15 Another study on double imprinting, targeting Era and imprinted with DOX, resulted in
16 80% cytotoxicity in ER α -positive cancer cells. These nanoMIPs enabled receptor-
17 mediated endocytosis and nuclear drug delivery, as shown in **Figure 2** [16].





1
2 **Figure 2** Confocal laser scanning microscopy (CLSM, 63 \times) revealed efficient uptake
3 of a) fluorescent nanoMIPs (FLU-nanoMIPs) and b) drug-loaded variants (FLU-DOX-
4 nanoMIPs) by ER α -positive MCF-7 breast cancer cells after 24 h incubation at 37 $^{\circ}\text{C}$,
5 c) i) 3D reconstructions confirmed intracellular accumulation and partial nuclear
6 localisation, with green fluorescence (nanoMIPs) colocalising with blue-stained nuclei
7 (DAPI) and red-stained membranes (WGA-Alexa Fluor 594), ii) Yellow regions in the
8 3D render indicate nanoMIP clusters within the nucleus, suggesting receptor-mediated
9 endocytosis followed by nuclear translocation d) Schematic illustration of caveolae-
10 mediated uptake via ER α , followed by subsequent cytoplasmic trafficking and DOX



1 release in both the cytoplasm and nucleus, thereby enabling enhanced therapeutic
2 effects [16]

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3 Similar systems have integrated breast cancer cell membrane proteins with
4 chemotherapeutic agents to create fluorescent MIPs capable of effective tumour
5 suppression both *in vitro* and *in vivo* [224]. Overall, double imprinting is an emerging
6 and promising strategy in the field of drug delivery, though a broad set of questions
7 remains around the compromises in affinity and selectivity that arise from dual-target
8 imprinting (template-template interactions and compatibility) and capacity issues.
9 Despite this, continued research in this area is required as it holds great potential.

10 Inorganic moieties, such as magnetic nanoparticles, metal-organic frameworks, silica-
11 based nanoparticles, and quantum dots, can be integrated with MIPs to enhance their
12 drug-delivery functionality.

13 Conjugating with magnetic nanoparticles not only simplifies purification during
14 synthesis but also enables targeted delivery and helps mitigate rapid metabolism
15 associated with chemotherapeutics. For example, core-shell Fe₃O₄-MIPs systems for
16 6-mercaptopurine combined magnetic targeting and hyperthermia with selective
17 binding and controlled drug release, where the inorganic core enables stimuli-
18 responsive delivery and the organic MIPs shell provides high specificity and drug-
19 loading efficiency [225]. These magnetic nanoparticles are among the most used
20 functional conjugates in MIPs, enabling a wide range of versatile applications. In
21 another study, core-shell nanocarriers were constructed with a magnetic metal-
22 graphene oxide core and a dopamine-based MIP shell imprinted against CEA, a
23 cancer biomarker. This system exhibited dual targeting through magnetic guidance
24 and molecular recognition, along with pH-responsive drug release, leading to
25 improved anticancer efficacy [226]. Additional magnetic MIPs-based strategies have
26 been reported and are addressed elsewhere in this review.

27 Additionally, metallic components, such as metal-organic frameworks (MOFs), are
28 widely used in DDSs. MOFs are another class of hybrid materials characterised by
29 high surface areas and tunable porosity, making them excellent candidates for drug
30 delivery [227]. Integrating MOFs with MIPs combines the selective recognition of MIPs
31 with the high loading and controlled release capacity of MOFs. For example, a recent
32 study on Cu-MOF-based hollow MIPs reported exceptional DOX-loading efficiency
33 (81.1%) and pH responsiveness and showed strong cytotoxicity against MCF-7 cells



1 with an IC_{50} of $2 \mu\text{g mL}^{-1}$, whereas free DOX required higher concentrations to elicit
2 comparable effects [98]. Another study employing a zirconium-based MOF (UIO-66)
3 integrated with deep-eutectic solvent-assisted dual-templated MIPs against DOX and
4 phycocyanin demonstrated improved hydrophilicity, high drug-loading capacity, and
5 controlled drug release [228]. In addition to these, MOFs such as ZIF-8, MIL-101(Fe),
6 and UiO-66-NH₂ have also been employed in MIP-based DDSs, demonstrating high
7 drug-loading capacity, controlled release, and stimulus-responsive targeting [104].
8 Silica-based nanoparticles serve as functional scaffolds for MIPs-based targeted drug
9 delivery, offering mechanical stability and high payload capacity. Among these,
10 mesoporous silica nanoparticles are widely used as substrates for developing these
11 DDSs, providing high surface area, structured surfaces, mechanical robustness, and
12 biocompatibility [199, 229]. Additionally, siloxanes have been incorporated into MIPs
13 chemistry to enhance flexibility, durability, ease of functionalization, and imprinting
14 efficiency [104, 230, 231].
15 Another class of hybrid nanomaterials integrates quantum dots with MIPs, combining
16 selective molecular recognition with photoluminescence to enable simultaneous drug
17 delivery and bioimaging. For this purpose, carbon quantum dots [204], graphene
18 quantum dots [216, 232], and fluorescent silica nanoparticles (FSiO₂-NPs) [224, 233]
19 have been employed as functional cores. In a recent study, dual-template MIPs
20 developed against the HER2 peptide (overexpressed in several tumours) and DOX
21 utilised FSiO₂-NPs as the core for targeted DOX delivery, enabling both diagnostic
22 imaging and therapeutic functionality [233]. Similarly, a dual-imprinted DDS based on
23 FSiO₂-NP targeting the P32 membrane protein epitope enabled real-time cellular
24 tracking via intrinsic fluorescence, with confocal and dual-colour imaging confirming
25 DOX release and nuclear accumulation in cancer cells [224, 233].
26 Besides carbon and graphene quantum dots, other carbon-based materials, such as
27 graphene oxide (GO) and carbon nanotubes (CNTs), have also been combined with
28 MIPs for drug delivery applications. Both GO and CNTs are employed in the design of
29 DDSs due to their high surface area, ease of functionalization, strong drug-loading
30 capacity, π - π interactions, and structural stability [234]. For instance, a vinyl-
31 functionalized GO surface was coated with a curcumin-imprinted polymer, forming a
32 pH-responsive nanocomposite for selective binding and release of curcumin, with
33 enhanced drug loading via β -cyclodextrin inclusion [235]. Subsequently, CNTs
34 combined with POSS enhanced the imprinting efficiency of MIPs, improved the pore



1 structure and surface area, provided superior controlled *in vitro* release of gallic acid,
 2 and higher *in vivo* plasma concentrations, achieving a maximum AUC₀₋₉ of 544.73
 3 ng·h·mL⁻¹ compared to lower values for control MIPs [236]. In another study, liquid-
 4 crystalline MIPs-based nanocarriers were constructed on CNT supports via surface
 5 imprinting for the oral delivery of levofloxacin. The system achieved zero-order
 6 release, prolonged gastric retention, and markedly enhanced bioavailability,
 7 demonstrating the potential of MIPs-CNT hybrids for controlled drug delivery [237].
 8 Other functional materials, such as aptamers, have been integrated with MIPs to
 9 leverage their molecular recognition capabilities, primarily in sensing. Aptamer-MIPs
 10 hybrids have been employed in the detection of proteins, enzymes, genes, pathogens,
 11 and various other analytes, including pesticides, antibiotics, and explosives [238-240].
 12 Aptamers, which are single-stranded DNA or RNA molecules, have also gained
 13 attention in drug delivery, as they can modulate biological targets with high specificity
 14 and enable targeted delivery [241]. However, MIPs offer greater stability, improving
 15 affinity and are less susceptible to degradation [238]. Unlike base aptamers, those
 16 entrapped within a MIP scaffold can be exposed to high temperatures, DNAase,
 17 RNAase, pH 2-12 and organics without loss of action [242, 243]. Despite this potential,
 18 studies on aptamer-MIPs systems for drug delivery are scarce, and the field remains
 19 underexplored, presenting significant opportunities for future research.

20 4.4 Combination therapies

21 The effectiveness of cancer treatment can be enhanced by combining therapeutic
 22 strategies that act in a complementary manner to overcome multidrug resistance,
 23 minimise systemic toxicity, and achieve precise site-specific targeting. MIPs have
 24 emerged as a versatile platform not only for drug delivery but also for integration with
 25 other therapeutic modalities such as photothermal therapy (PTT), photodynamic
 26 therapy (PDT), magnetic hyperthermia, and imaging-guided theranostics, as
 27 summarised in **Table 4**.

28 **Table 4:** Combinational therapies based on MIPs strategies

Therapeutic Modality	Mechanism / Key Advantage	MIP Functionalization Strategy	Example / Evidence
Chemotherapy + PTT	Converts light to heat →	Incorporated photothermal	Iron-oxide core + DOX-imprinted +



	hyperthermia kills cancer cells; synergistic with chemo to reduce drug dose and regrowth	nanoparticles (e.g., Fe ₃ O ₄); used photothermal monomers, loaded photothermal agents	epitope-imprinted outer layer → NIR-triggered ablation [244]; Polydopamine/ZIF-8 nanocarriers for EGFR targeting [147]
PTT Sensitization	Overcomes heat tolerance by inhibiting HSP expression	Imprinted against metabolic enzymes (e.g., hexokinase) to induce tumour starvation	Hexokinase-epitope MIPs reduce glucose metabolism → enhance PTT [110]
Chemotherapy + PDT	Photosensitizer generates ROS under light → selective cell death	Embed photosensitizers in MOF or MIPs layer	Dual-gated MOF system with epitope-imprinted ZIF-8 and DNA gate for chemo + PDT [111]; black TiO ₂ MIP nanocomposites for 5-FU delivery + PTT + PDT [245]
Magnetic Hyperthermia	AMF triggers local heating → controlled drug release	Magnetic nanoparticle core + imprinted polymer shell	γ-Fe ₂ O ₃ @DOX-MIPs enable AMF-triggered DOX release [246]; Comparative study: MIPs vs nanogels for AMF-triggered release [247]
Immunotherapy / TME Modulation	Reprograms immunosuppressive microenvironment; enhances drug penetration	Tryptase-imprinted MIPs reduce stromal barriers PD-L1 peptide imprinting blocks PD-1/PD-L1 Sialic acid imprinting promotes TAM phagocytosis	Tryptase-targeting MIPs improve DOX/LIP penetration [248]; PD-L1-imprinted CaCO ₃ nanospheres + aptamer for immune checkpoint blockade [249]; Magnetic core + SA-imprinted shell

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DOI: 10.1039/D6NR00511J

1 PTT employs photothermal agents that convert absorbed light energy into localised
2 heat, raising the temperature of tumour tissues and inducing cancer cell death through
3 hyperthermia. When combined with chemotherapy, PTT can reduce the likelihood of
4 residual tumour regrowth while achieving comparable therapeutic effects with lower
5 chemotherapeutic doses [251]. MIPs can be functionalized for PTT by incorporating
6 photothermal nanoparticles as cores [244], using photothermal monomers [147], or
7 loading photothermal agents [53]. For example, a MIPs-based nanoplatform was
8 developed for combinational therapy with an iron-oxide nanoparticle core, an inner
9 DOX-imprinted layer, and an outer P32 epitope-imprinted layer. This system enabled
10 tumour-specific targeting, pH-responsive drug release, and NIR-triggered
11 photothermal ablation, demonstrating its potential for synergistic chemo-photothermal
12 therapy [244]. Similarly, nanocarriers combining imprinted polydopamine and ZIF-8
13 (zeolitic imidazolate framework-8) were developed against EGFR, for targeted
14 delivery, controlled DOX release, and effective tumour ablation, enabling a synergistic
15 chemo-photothermal therapeutic effect [147]. MIPs have also been employed to
16 overcome the heat tolerance of tumour cells, which arises from heat shock proteins
17 and limits the efficiency of PTT. For instance, MIPs imprinted against hexokinase
18 epitopes inhibited glucose metabolism to induce tumour starvation, thereby reducing
19 HSPs expression and sensitising tumours to hyperthermia, ultimately enhancing PTT
20 efficacy [110].

21 Another therapeutic technique, PDT, uses a photosensitising agent activated by light
22 to produce reactive oxygen species that selectively destroy target cells [252]. In a
23 recent study, a dual-gated, epitope-imprinted MOF system was developed for targeted
24 cancer therapy, dual-drug chemotherapy, and PDT. In this system, DNA bound to the
25 MOF served as the first gate and the carrier, while epitope-imprinted ZIF-8 films
26 formed a second gate, providing selectivity, protection of DNA from degradation, and
27 resistance to plasma phosphates. Embedded photosensitizers in the MOF enabled
28 PDT by generating cytotoxic singlet oxygen upon light irradiation, complementing the
29 chemotherapeutic drugs for synergistic treatment [111]. A multifunctional platform was
30 developed that combined drug delivery, PTT and PDT as MIPs-coated black titanium
31 dioxide nanocomposites. Here, the thermosensitive and pH-sensitive MIPs layer
32 allowed selective 5-FU loading and controlled release, while the black titanium dioxide



1 core served as both a photothermal agent, converting light into heat, and a
2 photodynamic agent, generating ROS under light irradiation [245].
3 As discussed above, MIPs are often functionalised with magnetic nanoparticle cores
4 for guided drug delivery, magnetic separation, and magnetic hyperthermia-assisted
5 chemotherapy. AMF have been used to trigger drug release from such magnetic MIPs.
6 For example, $\gamma\text{-Fe}_2\text{O}_3$ @DOX-MIPs with a poly(acrylamide) imprinted shell around
7 magnetic cores enabled precise DOX release under AMF, locally disrupting hydrogen
8 bonds at the polymer-drug interface without bulk heating, allowing spatially controlled
9 chemotherapy activation [246]. A comparative study evaluated magnetic nanogels and
10 magnetic MIPs for AMF-triggered DOX release. In nanogels, release was driven by
11 polymer conformation changes induced by local MNP heating, whereas in MIPs, it
12 resulted from the disruption of hydrogen bonds between DOX and the polymer. Under
13 AMF, MIPs released approximately 60% of DOX compared to 10% without AMF, while
14 nanogels released 45% versus 24%. Both systems showed efficient cellular uptake
15 and enhanced cytotoxicity in PC-3 cells, demonstrating the potential of localised
16 magnetic hyperthermia for targeted chemotherapy [247].
17 Beyond conventional drug delivery, MIPs can improve therapeutic outcomes by
18 reprogramming the immunosuppressive tumour microenvironment and enhancing
19 both drug penetration and bioavailability. Building on this concept, tryptase-targeting
20 MIPs were developed to modulate tumour-associated fibroblasts and promote intra-
21 tumoral delivery of doxorubicin liposomes (DOX/LIP). These nanoparticles bind
22 selectively to tryptase, exert inhibitory effects, and help reduce stromal barriers,
23 thereby facilitating deeper penetration of drugs [248]. In another study, a dual-targeting
24 system was developed by imprinting a PD-L1 peptide on a CaCO_3 nanosphere core,
25 followed by aptamer modification. The system specifically binds PD-L1, blocks PD-
26 1/PD-L1 interactions, reactivates T cells, and inhibits tumour growth, with a detection
27 limit as low as 0.003 mg/mL [249]. In a complementary strategy, a magnetic core was
28 combined with an SA-imprinted shell to engineer reprogrammed tumour-associated
29 macrophages (TAMs). Guided to the tumour by an external magnet, the nanoparticles
30 bound SA on cancer cells, tagged them for phagocytosis, and promoted M1
31 macrophage polarisation, which boosted TAM-mediated antitumor immunity without
32 affecting normal tissue [250]. Overall, these advances highlight the potential of MIPs
33 as multifunctional therapeutic platforms for more precise, effective, and synergistic
34 cancer therapy.



1 5. Challenges and translational potential

2 Biocompatibility is a critical consideration for nanomaterials, particularly for biomedical
3 applications such as drug delivery. A comprehensive *in vitro* study evaluating the
4 biocompatibility and cellular internalisation of MIPs across HaCaT (human
5 keratinocytes), MEFs (mouse fibroblasts), HT1080 (human fibrosarcoma), and
6 macrophages demonstrated minimal cytotoxicity, negligible macrophage activation,
7 and particle uptake that was dependent on surface chemistry and protein corona
8 formation [253]. Another study investigated the biodistribution, clearance, and
9 cytotoxicity of MIPs following intravenous and oral administration, showing that
10 nanoMIPs distributed to all major organs and were primarily eliminated as whole
11 particles via urine and faeces. At lower doses (100 µg/mL), minimal histological
12 alterations were observed, whereas higher doses (200 µg/mL) elicited mild
13 inflammatory responses and minor tissue changes, highlighting the importance of
14 dose-dependent safety assessment [254]. In the context of drug delivery, loaded MIPs
15 have demonstrated significantly higher therapeutic impact on targeted cancer cells
16 compared with normal cells. For example, pH/GSH-responsive CD73
17 epitope-imprinted MIPs exhibited less than 7% drug leakage over 96 h under
18 physiological conditions, while releasing more than 90% of the payload in tumour
19 microenvironment conditions. Moreover, their uptake was 4.5-fold higher in
20 CD73-overexpressing 4T1 cancer cells compared with CD73-low TC-1 cells [255]. In
21 another study, the safety of MIPs was evaluated using an MTT assay on HepG2 cells,
22 which showed that cell viability increased with increasing polymer concentration.
23 Specifically, survival increased from approximately 60% at 0.3 mg/L to 83% at 100
24 mg/L after 72 h, confirming the non-toxic nature of the carrier designed for docetaxel
25 delivery [106].

26 However, since clinical trials have not yet been conducted with MIPs and there are
27 limited literature studies evaluating the *in vivo* interactions of these materials in animal
28 models, our understanding of the biodistribution, (long-term) cytotoxicity and
29 clearance of MIPs for *in vivo* applications is underdeveloped. Standardised testing
30 procedures need to be implemented, as batch-to-batch variation can occur due to a
31 lack of control during polymerisation or variations in purification procedures, leading
32 to heterogeneity in functionalities, chemical composition, molecular weight, and
33 particle dimensions. Moreover, size, surface (and internal) chemistry, and mechanical



1 characteristics (unique to each MIPs) have a critical influence on biocompatibility [73].
2 Researchers can choose between designing a degradable MIPs-based system or
3 pursuing avenues in which the MIPs are cleared as intact particles. Both routes require
4 detailed studies on the degradation of MIPs under physiologically relevant conditions,
5 material stability, and investigation of potential leaching of monomers and other
6 chemicals. Critically, interpreting such biological outcomes is further complicated by
7 the fact that the final polymer composition often deviates from the feedstock
8 formulation; key physicochemical parameters, including particle mass, molecular
9 weight distribution, cross-linker density, and charge, strongly influence *in vivo*
10 behaviour yet remain difficult to measure and control accurately.

11 It has been reported that the biocompatibility of MIPs can be enhanced by carefully
12 selecting non-toxic monomers, crosslinkers, and initiators. For instance, naturally
13 derived biodegradable polymers, including protein-based polymers such as albumin,
14 gelatin, and collagen, as well as polysaccharides like chitosan, dextran, alginate,
15 hyaluronic acid, and cyclodextrins, can be utilised to produce MIPs [37]. Autoclaving
16 of MIPs without loss of functionality is possible due to the robustness of the material
17 and can help extend the shelf life of MIPs and minimise the risk of bacterial
18 contamination during storage [114]. To further reduce toxicity and improve systemic
19 circulation, the MIPs can also be coated with a hydrophilic, biocompatible coating,
20 such as polyethene glycol (PEG), which minimises opsonin adsorption, thereby
21 extending their blood circulation, reducing their toxicity, and improving their
22 performance [26].

23 While these strategies improve the biological performance of MIPs, translating them
24 from laboratory-scale synthesis to large-scale production introduces additional
25 challenges related to reproducibility, yield, and regulatory compliance. Current
26 synthesis procedures fail to reproducibly control polymerisation and lead to low yield,
27 which does not facilitate large-scale, reproducible MIPs manufacturing within the
28 complex regulatory health framework [256]. There are a few MIPs reactor designs
29 reported in literature, none of which are commercially available or widely implemented
30 within the community, likely because they still suffer from low yield and cumbersome
31 operation [257, 258].

32 Adaptation of platforms used for polymer synthesis in other research areas facilitates
33 *in situ* monitoring of critical polymerisation parameters (e.g. size, molecular weight)
34 and *in silico* and experimental screening of the polymer parameter space holds



1 promise for automating and scaling up synthesis [259, 260]. However, this requires a
2 significant shift to how MIPs are currently produced, especially for complex proteins
3 that are targeted in cancer drug delivery, with a need towards automating the full
4 process from rational design to optimise composition, to high-throughput production
5 and subsequent screening of specificity and selectivity for the target to link structural
6 properties and components to overall binding affinity [261].
7 Route of administration is another underexplored but critical consideration.
8 Intravenous delivery requires MIPs with excellent colloidal stability, controlled protein
9 corona formation, and efficient clearance to minimise long-term accumulation. Oral
10 delivery, by contrast, imposes additional constraints. Orally administered nanoMIPs
11 must protect the drug payload from the acidic gastric environment and digestive
12 enzymes, maintain structural stability across the gastrointestinal pH gradient, and
13 avoid premature drug release before reaching the absorption site [262]. Efficient
14 transport across the intestinal epithelium is also required, potentially via uptake by M
15 cells in Peyer's patches or enterocyte-mediated transcytosis [263]. In addition,
16 strategies to reduce hepatic first-pass metabolism, such as promoting lymphatic
17 uptake or surface functionalisation that enhances epithelial transport, may further
18 improve systemic bioavailability [262, 264]. However, the effectiveness of this
19 approach may be more feasible for small-molecule or small-peptide therapeutics, as
20 degradation by digestive enzymes in the gastrointestinal tract remains a significant
21 barrier for protein-based drugs within the MIPs structure [193]. These divergent
22 requirements underscore the need for application-specific MIPs design principles
23 rather than universal carrier architectures.

24 **6. Summary and future perspective**

25 MIPs have progressed from niche recognition materials to increasingly sophisticated
26 nanoplatfoms capable of selective targeting, controlled drug loading, and stimulus-
27 responsive release [26]. In the context of cancer drug delivery, MIPs offer a compelling
28 combination of molecular selectivity, chemical robustness, and synthetic flexibility that
29 distinguishes them from conventional polymeric carriers and biological target ligands.
30 As highlighted throughout this review, advances in imprinting strategies, epitope
31 selection, polymer chemistry, and hybrid material design have enabled MIPs to
32 achieve antibody-like affinities for cancer-relevant receptors while retaining superior
33 stability and lower production costs.



1 Recent studies demonstrate that MIPs can be engineered not only to recognise
2 overexpressed cancer receptors and microenvironmental cues but also to actively
3 participate in intracellular trafficking and controlled drug release [8]. Epitope imprinting
4 has emerged as a particularly powerful approach, enabling synthetic receptors to
5 recapitulate biologically validated binding motifs while avoiding the instability and
6 synthetic constraints associated with whole-protein templates. When combined with
7 nanoscale architectures, such as core-shell structures, hollow capsules, or hybrid
8 inorganic-organic composites, MIPs can integrate targeting, protection, and release
9 functions within a single platform. These attributes position MIPs as adaptable carriers
10 for precision drug delivery, including applications that require receptor-mediated
11 uptake, intracellular delivery, or combinational therapeutic strategies [265].
12 Experience with MIP-based sensing, assays, and separation technologies has
13 established several design principles that are highly informative for therapeutic MIPs,
14 though the transition is not a direct, one-to-one translation. In particular, diagnostic
15 and extraction applications have highlighted the importance of minimising non-specific
16 binding in complex media, maintaining binding-site accessibility through surface or
17 epitope imprinting, and using rational monomer-template selection and controlled
18 synthesis to improve selectivity and reproducibility. These lessons are directly relevant
19 to therapeutic MIPs because non-specific adsorption in complex media can
20 compromise receptor recognition, alter colloidal stability, and influence drug retention
21 and release. Commercial solid-phase extraction products, such as SupelMIP [266]
22 cartridges, further demonstrate that selective and robust imprinting can be translated
23 into real-world analytical workflows in complex matrices; however, these *in vitro*
24 systems do not need to address the additional constraints that define therapeutic
25 translation [267]. In contrast to diagnostic MIPs, drug-delivery nanoMIPs must also
26 satisfy stringent requirements relating to cytotoxicity, haemocompatibility, immune
27 interactions, biodistribution, degradation, clearance, and reproducible *in vivo*
28 performance. Accordingly, lessons from diagnostic and separation MIPs should be
29 viewed as transferable design principles rather than as direct evidence of therapeutic
30 readiness. Successful translation of therapeutic MIPs will therefore require that
31 molecular recognition be integrated from the outset with antifouling surface design,
32 pharmacokinetic control, and systematic *in vivo* validation.
33 Stimuli-responsive MIPs represent one of the most promising directions for future
34 development, particularly systems responsive to endogenous tumour characteristics



1 such as acidic pH, redox imbalance, or enzymatic activity [206, 218]. Even though
2 these systems align well with the intrinsic heterogeneity of TME, the TME is highly
3 complex and dynamic, characterised by abnormal vasculature, hypoxia, altered
4 extracellular matrix composition, immune suppression, and dynamic biochemical
5 concentrations [268]. Designing MIPs architecture that remains effective across this
6 heterogeneity, while maintaining predictable release kinetics and therapeutic
7 windows, remains a major scientific and engineering challenge [129, 269].

8 One potential strategy to address this challenge would be the development of
9 theranostics MIP-based nanoplatforms that integrate diagnostic and therapeutic
10 functionalities within a single system. DDSs are increasingly engineered with imaging
11 capabilities, such as fluorescent probes, magnetic resonance imaging (MRI) contrast
12 agents, nuclear imaging tracers for positron emission tomography (PET) and single-
13 photon emission computed tomography (SPECT) or surface-enhanced Raman
14 scattering (SERS) reporters, to enable tracking of nanoparticle biodistribution and
15 therapeutic response [270-272]. Incorporating analogous sensing or imaging elements
16 into MIPs could enable real-time analysis of local TME characteristics and modulate
17 the drug release kinetics accordingly. Such approaches may enhance treatment
18 robustness across heterogeneous tumours while supporting imaging-guided therapy
19 and improved patient stratification.

20 The integration of MIPs into combinational therapeutic platforms further expands their
21 potential impact. As reviewed here, MIPs have been successfully combined with
22 photothermal, photodynamic, magnetic, and immunomodulatory modalities, enabling
23 synergistic therapies that address drug resistance and enhance tumour eradication.
24 These multifunctional systems illustrate how molecular imprinting can be leveraged
25 not only for targeting and delivery but also for reprogramming tumour biology and the
26 surrounding microenvironment. Nonetheless, increasing system complexity must be
27 balanced against manufacturability and translational feasibility, particularly when
28 multiple functional components are incorporated into a single carrier.

29 Looking ahead, progress in MIPs-based drug delivery will depend on three converging
30 developments. First, advances in rational design—supported by computational
31 modelling, high-throughput screening, and machine learning—are expected to
32 accelerate the identification of optimal monomer compositions, imprinting strategies,
33 and release mechanisms. Second, innovations in reactor engineering and automated
34 synthesis will be essential to achieve reproducible, scalable manufacturing that meets



1 regulatory standards. Third, systematic *in vivo* studies, including pharmacokinetics,
2 biodistribution, immunogenicity, and long-term safety, are required to bridge the gap
3 between promising *in vitro* performance and clinical translation.

4 In the near term, the most likely entry point for MIPs into healthcare remains the
5 diagnostic space, where regulatory barriers are lower and performance requirements
6 differ from those of therapeutics. Success in diagnostics will play a critical role in
7 building confidence in the safety, reliability, and scalability of MIPs technologies. In the
8 long term, the continued integration of materials science, chemical engineering, and
9 biomedical insights has the potential to establish MIPs as a new class of synthetic,
10 precision-engineered drug delivery systems capable of addressing the complexity and
11 heterogeneity of cancer therapy.

12 **Author Contributions**

13 Shreya Tiwari: Writing - Original draft, Data curation, Formal analysis. Charles Luke
14 Hutchinson: Writing - Original draft, Data curation, Formal analysis. Pankaj Singla:
15 Writing - Original draft, Data curation, Formal analysis. Robert C. Rintoul: Writing -
16 Review and editing, Conceptualisation, Funding. Timothy H. Witney: Writing - Review
17 and editing, Conceptualisation, Funding. Nicholas W. Turner: Writing - Original draft,
18 Writing - Review and editing. Marloes Peeters: Conceptualisation, Supervision,
19 Funding, Writing - Review and editing.

20 **Conflicts of Interest**

21 The authors declare there are no conflicts of interest associated with this work.

22 **Acknowledgments**

23 The authors acknowledge financial support from MRC grant MR/Y008421/1 and
24 EPSRC grant EP/V056085/2.

25 **Declaration on Generative AI Use**

26 No AI tools were used in the preparation of this manuscript or the acquisition of data.

27 **Data Availability**



1 No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

View Article Online
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View Article Online
DOI: 10.1039/D6NR00511J

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

