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Epitope Imprinting Approach to Monitor Diseases

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Abstract

Epitope sequences are unique combination of amino acids sequence positioned on exposed domains of proteins. Molecular imprinting is a promising technique for creating molecular receptors with recognition and binding sites that are chemically and sterically complementary in shape, size and functionality to the predetermined target molecules in synthetic polymer. This approach creates template-shaped cavities in polymer matrices with memory of template molecules to be used in molecular recognition. Imprinting whole protein denatures the tertiary and quaternary structures of protein in the polymer matrix and complexity and flexibility of its structure cannot be sustained in the polymer matrix. Epitope approach offers a way out of such snags. The epitope-imprinted film revealed high selectivity over the target protein and allow tolerance for even a single amino acid mismatch between the epitope and target protein. MIP sensors are ideal candidates for replacing biosensors as well as natural receptors in many sensing applications such as ELISA. In spite of advantages and burgeoning research in the field of MIPs, imprinting fraternity has not yet achieved commercial success. Substitution of antibodies used in diagnostic tools with synthetic analogues will cut down cost as well as time period for sample analysis. MIP sensing layers have proven to be highly economical and they have shown almost parallel feat as bio-sensing elements (antibody/antigen/enzyme) incorporated in ELISA. Rapid and accurate determination of disease biomarker proteins is vital for clinical diagnosis and medical abnormalities. Hence MIP-sensors of certain proteins will be useful in early diagnosis of diseased state.

Keywords: Molecularly imprinted polymer; MIP sensor; Epitope imprinting; Diagnostic tool; Disease biomarker

Introduction

Worldwide the ageing population and the increasing obesity epidemic are placing an increased burden on healthcare systems. The correct and timely diagnosis of a diseased state relies on accurate determination of disease biomarker. Whilst the current systems provide a range of possibilities, the rapid detection often requires use of sophisticated instruments and testing procedure via antibodies/antigens etc. Complex biological matrices often give rise to interferences that must be removed prior to analysis. This adds to the complexity of analysis, delays diagnosis and renders the approach inappropriate or unattainable in regional and lower income areas.

Evolution has provided biology with many intriguing examples of molecular recognition, including those involved in interactions between a ligand and a receptor (such as substrate and enzyme, antigen and antibody), and in transport and signal transduction processes. Studies of these molecules have been dependent on our ability to selectively capture these molecules from complex biological mixtures. Base-pair complementarity provides a robust and powerful tool for selectively isolating and purifying DNA and RNA molecules with desired sequences. This tool will remain instrumental in virtually all aspects of molecular biology research. Antibodies have been widely used for selective protein capture and thus are applied for industrial protein purification, basic biomedical research, and clinical diagnostics. However, antibodies exhibit characteristics that limit their applications. These proteins are large complex molecules that need to be stored carefully. As antibodies are produced by living cells, it is sometimes difficult to control their quality. An ideal molecular recognition agent should have high specificity and be composed of a stable, robust, non-biological material.

Molecular imprinting is one of few general, non-biological methods for creating molecular receptors and it has been proposed as a facilitator to create synthetic intelligent materials having the capability of mimicking biological recognition (Figure 1) [1]. Molecularly imprinted polymers (MIP)s are artificial analogues to aptamer (short oligo nucleotides or peptides complementary to target compounds of the same type), antibody, antigen, enzyme, and other bio-recognition elements. These are almost as selective as natural ones, such as antibodies, enzymes and histones; in fact they outperform natural receptors with low cost, long term stability and resistance to harsh environmental conditions. As an alternative to evolution by the natural selection process, fully synthetic MIPs have broken new ground with promising recognition capability, improved stability, reasonable cost and rapid manufacture. MIPs have advantages of high stability, ease of preparation, and low cost. In fact, a new era has begun by a synergistic merging of synthetic polymers (MIPs) with biomedicine replacing biosensors [2-4]. The main sensing feature of MIPs comprises selective recognition of target analyte because of the dedicated architecture of cavities embedded in the polymer matrix. Cieplak and Kutner state 'MIPs can recognize target analytes not only by their shape and size, because introducing a dedicated set of recognizing sites into the imprinted cavity increases both the affinity of the cavity for the analyte and its selectivity with respect to interferences' [5].

In spite of these advantages and burgeoning research in the field of MIPs, imprinting fraternity [5] still seeks answer of "When will inexpensive, user-friendly, sensitive, and selective (with respect to chosen analytes) devices capable of routine use in clinical analysis, such as for early disease diagnosis, be produced and appear on the market? And is it feasible to design MIPs with selectivity and affinity to an analyte as high as that of natural receptors, including enzymes, antibodies and histones?"

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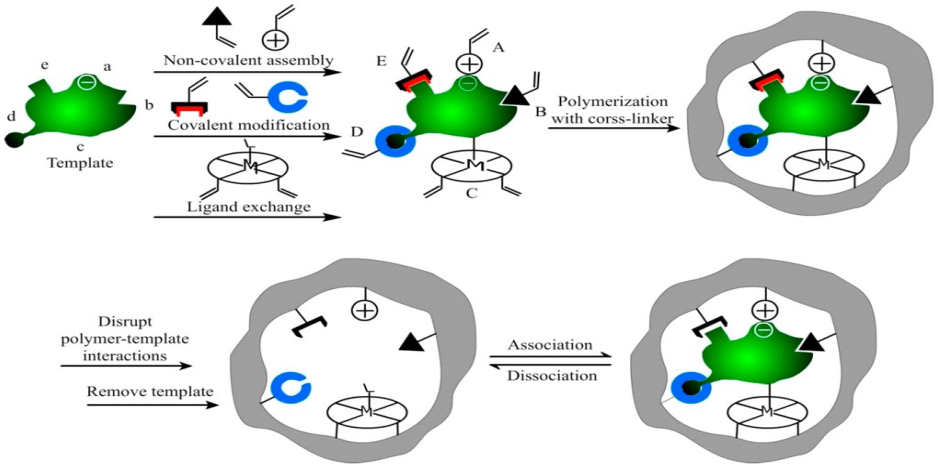

Figure 1: Schematic representation of different approaches for MIP synthesis [1].

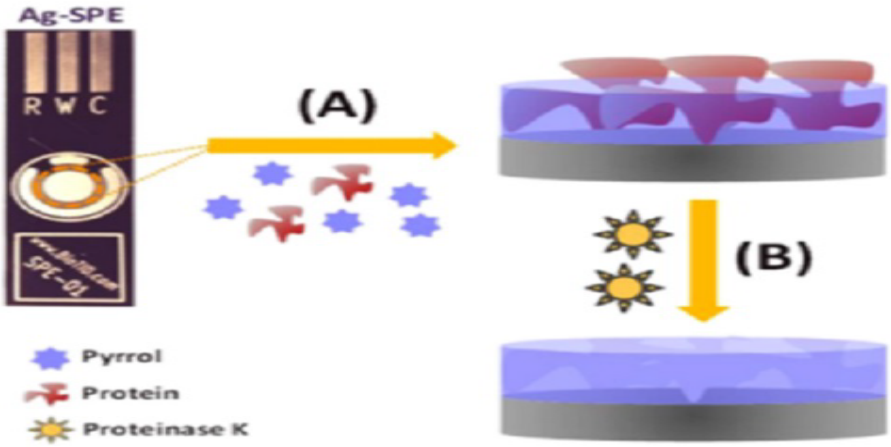

Figure 2: Schematic presentation of synthesis of Ag-SPE/PPy device [21].

Molecular imprinting has boundless opportunities to cater healthcare needs of society. Although it has traversed a long way from 1930s till date but still it has not achieved the success at commercial scale as well as at laboratory scale as compared to other technologies such as nanomaterial synthesis and fluorescent probe techniques. In order to stimulate the fast development of molecular imprinting, imprinting technique as a multidisciplinary field, it should develop rapidly along with the advances in polymer technology, nanotechnology, analytical chemistry, environmental science, biotechnology, etc.

Molecular imprinting was attempted in silica matrices in 1930's for the first time [6], since then continuous development of design, preparation, characterization and application of MIPs over recent years has reflected the gradual maturation of molecular imprinting technology. A large increase in number of articles, reviews [7-14] and monographs [15,16]. On molecular imprinting reflects its rapid development and inclusion to current trends and areas. Its applications range from purification and separation, chemo/biosensing, artificial antibodies, drug delivery, catalysis, and degradation attributable to their robust physical stability, straight forward preparation and cost-effective technology [17]. While extending this technology to bio-macromolecules, the structural complexity and the incongruity of peptide/protein targets with organic solvents that are generally used for imprinting seems difficult experimentally. Although Mosbach reported protein imprinting for the first time in 1985 [18] but this field has not yet progressed as expected and as other small molecules' imprinting is progressing [19]. This slow progress is mainly due to their large size, irreversible conformational change, many functional groups present in a single protein molecule, and most importantly problem in protein removal from polymeric matrices, and many more complications. Such obscurities have limited the choice of proteins to those ones with good conformational stability and robust properties facilitating selective and specific interactions. Hence protein imprinting still lags behind, but many attempts are being made to adopt various strategies which could overcome the barriers obstructing protein imprinting. An overview of such attempts is provided in the following section.

The protein, bovine haemoglobin was imprinted on an array of acrylamide based polymeric hydrogels for optimizing the piezoelectric sensor electrode surface [20]. In fact, this study was intended to investigate the intricacies of protein chemistry with that of monomers. A cancer biomarker, kininogen, a circulating plasma protein was imprinted for early diagnosis and prognosis of cancer (Figure 2) [21].

Another cancer biomarker, carcinogenic embryonic antigen protein, routinely used to follow up the progression of colon rectal cancer was

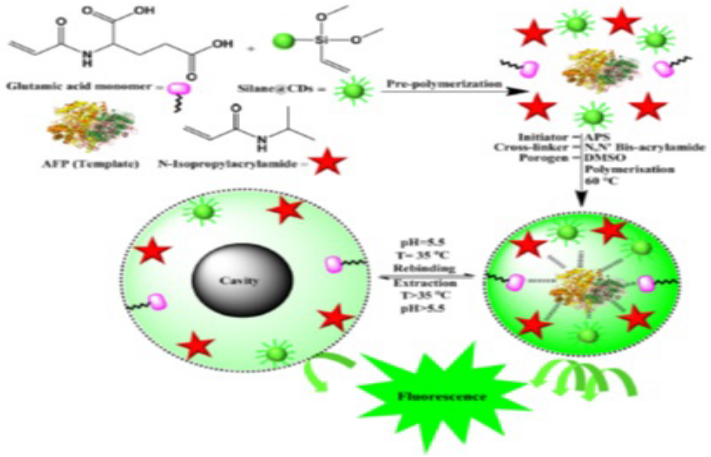

Figure 3: Synthesis of fluorescence, stimuli responsive imprinted polymer [22].

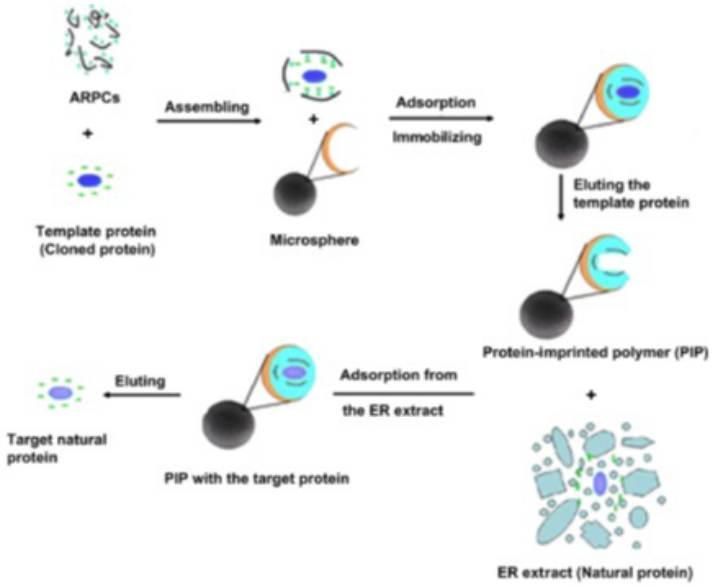

Figure 4: Strategy for synthesis of PIP [23].

imprinted in polypyrrole matrix on screen printed electrode [22]. Alpha-fetoprotein, a potential biomarker for hepatocellular carcinoma disease was imprinted in the polymeric matrix of three monomers-a temperature responsive monomer, N-isopropyl acrylamide, tyrosine derivative for pH-responsiveness and vinyl silane modified carbon dots as fluorphores (Figure 3) [22]. The imprinted matrix was successfully applied to 'real' samples. MIPs prepared in presence of a folded protein do not bind the same protein when unfolded or misfolded or even a mismatch of a single amino acid residue in the imprinted epitope/peptide/protein sequence.

Another approach for protein imprinting attempted is 'assistant recognition polymer chains' (ARPCs); template is selectively assembled with the recognition polymer chains to form a non-covalent complex, followed with adsorption of the assembled complex onto macroporous microspheres [23]. The adsorbed complexes were immobilized on microspheres via cross-linking polymerization of monomer and cross linker which immobilizes the ARPCs and form cross-linking network structure in the pore of macroporous microspheres after polymerization. On removing the template protein, synthesized imprinted polymer could be used for chromatographic isolation, as well as direct adsorption of the target protein (Figure 4) [23].

Epitope imprinting minimizes non-specific binding which seems to be a problem for protein or large macromolecule imprinting. On comparison of imprinting with whole protein molecule as template and imprinting of epitope sequence of protein, better result was obtained with latter approach (Figure 5) [24].

In 2006, Shea et al. imprinted C-terminus domains of three proteins, *viz.* cytochrome C, alcohol dehydrogenase and bovine serum albumin (BSA) [25]. These epitope sequences were first grafted on silica particles, subsequently exposed to the monomers solution and polymeric film around the grafted epitope sequences were fabricated. On extraction of these sequences, imprinted cavities for the chosen epitopes were generated and showed good binding for their respective protein molecules. Yang et al. reported the advantage of imprinting technology in harvesting the proteins albumin and immunoglobulin G from human serum [26]. Epitope approach was employed to imprint

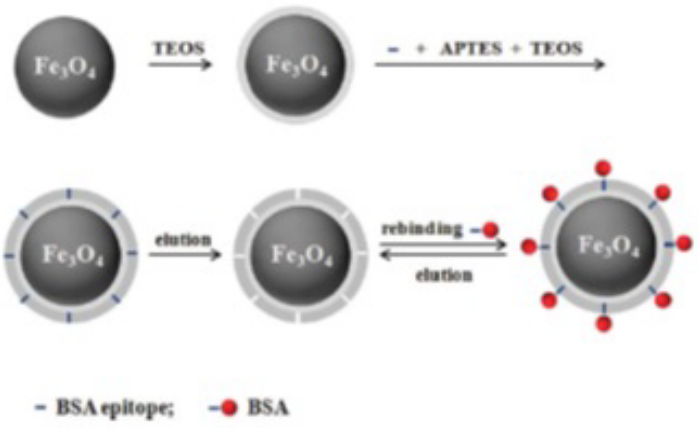

Figure 5: Synthesis route of Fe_3O_4@EMIPs by combining epitope imprinting and surface imprinting [24].

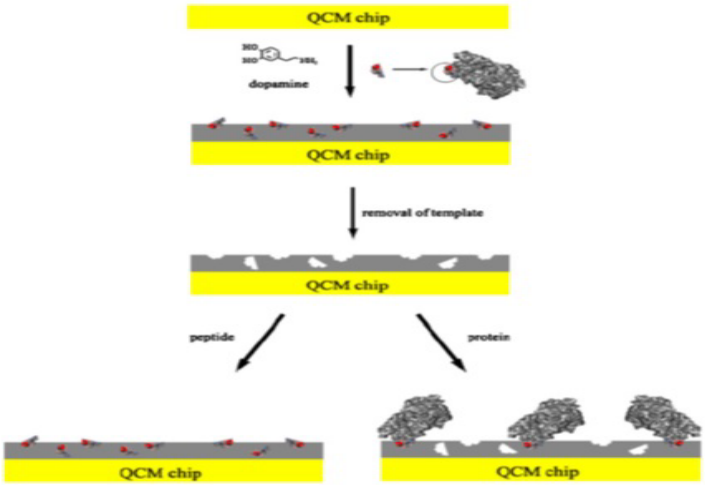

Figure 6: Schematic presentation of epitope imprinting of glycoprotein41 [27].

S. No.	Disease	Epitope sequence	Reference
1	Dengue	TELRYKTYGKAKM(Thr-Glu-Leu-Arg-Tyr-Ser-Trp-Lys-Thr-Trp-Gly-Lys-Ala-Lys-Met)	[28]
2	HIV-1	gp41 fragment 579–613 (RILA VERY LKDQ QLLG IWGC SGKL ICTT AVPW NAS)	[29]
3	Cardiac failure	EVATEGIR, LQESPRPTG	[30]
4	Alzheimer's disease	MVGGVV (Aß35-40), GGVVIA (Aß37-42), GGVVIA (Aß37-42), GLMVGGVV (Aß33-40), GLMVGGVVIA (Aß33-42)	[33]
5	Anthrax	epitopes of the anthrax protective antigen PA83.	[34]
6	Brain fever	KGLVDDADIC (lys-gly-leu-val-asp-asp-ala-asp-ile-cys)	[37]
7	Gastric, colorectal and liver cancers	K-2209 and K-1944(DQGHGHQ)	[43]

Table 1: Epitope approach for diagnosing and monitoring diseases.

these two proteins: three 11-mer peptides from C-terminal of human serum albumin (HSA) and immunoglobulin were used as template in the imprinting matrix of acrylamide-based monomers and grafted on quartz crystal microbalance (QCM) chips. These epitope imprinted QCM chips showed good efficiency in binding of HSA and IgG from blood serum, hence they were proposed as an alternative to monoclonal antibodies and protein A/G.

15-mer peptide from Japanese encephalitis virus was imprinted by employing a new crosslinking monomer which was able to distinguish oxytocin and vasopressin (Figure 6) [27]. Similar 15-mer epitope which is a consensus linear sequence present in NS1 protein of Japanese encephalitis virus and dengue virus both was imprinted for detection of dengue virus as an alternate early diagnostic tool (Table 1) [28]. Early diagnosis of such highly infectious and dreaded diseases is highly warranted for healthcare of society. Similarly, human immunodeficiency virus type 1 (HIV-1) was detected via HIV-1 glycoprotein 41 (gp 41) by imprinting its peptide fragment 579-613 [29]. Polydopamine was chosen as the imprinting matrix which was deposited on piezoelectric transducer QCM. Another clinical marker for assessing risk of heart failure, plasma B–type natriuretic peptide (BNP) was imprinted through its epitope sequence [30].

A peptide sequence (nonamer) from surface exposed C-terminus of cytochrome C was imprinted in an electrosynthesized polymeric network of scopoletin [31]. Histidine tagged C-terminal nonapeptide of HSA was imprinted in dopamine polymeric network over silica nanoparticles. MIP nanoparticles showed specific recognition toward the epitope as well as the HSA protein [31]. In a review on diagnostic

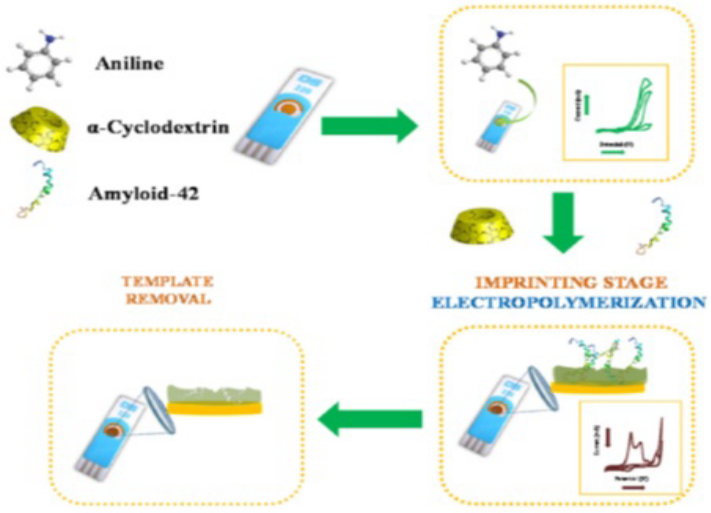

Figure 7: Schematic presentation of synthetic process of the BIOLAST film on the gold electrode of screen printed electrode [33].

strategies of Alzheimer's disease, authors concluded that epitope imprinting of key proteins are the most promising strategy for this disease. Diagnosis of Alzheimer's disease via imprinting was attempted by detecting the β amyloid peptides [32]. C-terminal epitope-imprinted polymers for Aβ142 were first identified through combinatorial library, and then it was used to synthesize MIPs for the β-amyloid isoforms under denaturing condition. The selective polymer was applied to serum for detecting these peptides in serum of patients. This attempt, the first at our best knowledge, shows that MIPs are promising new biosynthetic receptors with encouraging perspective in fundamental studies of peptide aggregation. Recently an electrochemical sensor for β amyloid peptides was fabricated by incorporating a polysaccharide component α-cyclodextrin and aniline as electropolymerizable component to sense foetal bovine serum (Figure 7) [33].

Protective antigen secreted on being infected with anthrax is chosen as biomarker of anthrax. Tai et al. synthesized the piezoelectric MIP sensor for this antigen through epitope imprinting on QCM electrode surface (Table 1). This epitope-imprinted QCM platform can be used for immunoassay of bacterial antigens [34]. Peptide imprinted MIP nanoparticles (NPs) were able to catalyse the conformational conversion of the recognized peptide and promote peptide structuration [35]. Experiments suggest that a chaperone kind of assisting to folding and refolding role could be anticipated from such MIP NPs. Such achievements of imprinting technology inches it toward inexpensive, user-friendly, sensitive, and selective devices capable of routine use in clinical analysis, for early disease diagnosis and design MIPs with selectivity and affinity to an analyte as high as that of natural receptors.

Even though protein imprinting remains elusive and challenging task to imprinting fraternity, but many successful attempts are reported today by employing epitope imprinting. Whatever are the limitations, imprinting technology is being developed to provide facile, cost-effective, time-effective diagnostic tools for detection of many critical diseases such as cancer [22,23], brain fever [36,37], Alzheimer's disease [33], Japanese encephalitis [28], dengue [28], HIV [29], cardiac failure [30] etc. to name a few (Table 1). As evinced by these studies, molecular imprinting when hyphenated with sensitive transducers yields viable alternate sensing technique.

Future Prospects

Most biomarkers for disease diagnosis and monitoring are peptides and proteins. As highlighted in literature, protein imprinting has evolved from 'bulk' imprinting to 'surface' imprinting to 'epitope' imprinting on surface. Now it's high time to exploit this sequential evolution of protein imprinting to solve 'real' life problems of society. Although MIPs are deeply researched to replace proteins in sensing applications as proteins are highly delicate and labile to slight changes in the surrounding media, but still a huge gap between general lab-scale use and industrial scale applications lies [5]. MIPs have continuously shown capability to replace ELISA kits with imprinted kits [38-40]. Substitution of antibodies used in diagnostic tools with synthetic analogues will cut down cost as well as time period for sample analysis [41]. MIPs are one of the best alternatives to replace biosensing elements from diagnostic tools, MIP sensing layers have proven to be highly economical and in terms of performance (sensitivity/selectivity), they have shown almost parallel feat as bio-sensing elements (antibody/antigen/enzyme) incorporated in ELISA and other tests for diagnosing the specific diseases [42,43]. Hence, the exemplary development shown by imprinting fraternity should be transferred to commercialization for routine clinical diagnostics.

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