Analytical applications of biomimetic recognition elements — an update

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Selection of the recognition element responsible for molecular recognition is critical in the development of analytical methods, particularly for the design of chemical sensors. Traditionally, biological receptors such as antibodies, enzymes, nucleic acids, or receptor proteins have been successfully applied to this aim. In fact, their use has allowed the detection of target analytes at very low concentrations with superb selectivity even in complex matrices [1]. However, since the 1970s, a plethora of biomimetic recognition elements has emerged as an alternative to their natural counterparts for diagnostics, research, and therapeutic applications [2, 3]. Aptamers, recombinant antibodies, molecularly imprinted polymers, nanozymes, peptides, peptide nucleic acids (PNAs), locked nucleic acids (LNAs), protein scaffolds, and DNAzymes are some of the biomimetic elements finding increasing application in analytical chemistry. Furthermore, recent EU policies and legislation promote “the development of non-animal based models and methods that allow advancing in fundamental, applied and translational research to preserve human and animal health as well as the environment” [4].

In this regard, the production of recombinant antibodies (rAbs) has allowed the development of immunoassays and immunosensors without the need of animal immunization [5]. The use of rAbs involves amplification of the antibody genes from the host (immunized or naïve) or in vitro synthesis, followed by PCR amplification, cloning into an adequate vector, and rAb expression. They can be produced in different

formats and the most widely applied ones include the scFv and Fab fragments as well as single domain antibodies (sdAbs) obtained from heavy-chain antibodies from camelids (VHH), also known as nanobodies, or from sharks, referred to as variable new antigen receptor (VNAR) single domain antibodies [6]. Recombinant antibodies can be produced in unlimited amounts at a relatively low cost. They can be engineered to tune their selectivity or to include different functionalities depending on the final application. Moreover, the small size of sdAbs facilitates their interaction with epitopes inaccessible to conventional antibodies. They show good solubility, heat and physicochemical stability, affinity, and ease of cloning [7]. Therefore, they can be a useful alternative or, in certain applications, a complementary strategy to natural Abs. Actually, several vendors have already included them in their product portfolio [3].

The last decade has witnessed significant advances in the area of aptamer technology. These single-stranded DNA (ssDNA) or RNA molecules possess a well-defined 3D structure that binds with high affinity to their “complementary” species. The latter include low molecular weight molecules, biomolecules (proteins, lipids, etc.), and cells (viruses, bacteria). Aptamers can be prepared by chemical or enzymatic methods and, as such, can be considered chemical or biological receptors [8]. The introduction of new SELEX strategies has allowed the selection of high-affinity aptamer sequences against a large variety of targets [7, 9]. Aptamers present advantages over traditional antibodies including a reproducible synthesis, high stability, longer shelf life, and the ability to recover their original conformation after denaturation. In addition, they can be chemically modified with functional groups to adapt their structure to specific purposes. Nevertheless, aptamers can undergo degradation in biological fluids and any change in the solution conditions can modify their tertiary structure, potentially affecting negatively their affinity for the target species. Compared to antibodies, aptamers may be advantageous in point of care devices (POCT) as they are stable at higher temperatures and need

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not to be kept cold to remain functional [10]. Their application has also expanded to the field of handheld electrochemical sensors for clinical diagnostics, food analysis, and environmental monitoring [10].

The application of MIPs in the analytical field has increased exponentially since the early 1970s with the discovery of the covalent and non-covalent imprinting approaches [11]. These tailor-made materials are prepared in the presence of a target molecule (template) covalently bonded to or non-covalently interacting with the functional monomer(s). After polymerization, removal of the template leaves behind cavities complementary in size, shape, and orientation of its functional groups to the template molecule, potentially allowing rebinding of the target even from complex samples. Obtaining MIPs is simpler and more cost effective than producing natural antibodies. Moreover, they do not require special storage conditions, showing excellent chemical and thermal stability and good recognition properties in organic solvents where their natural counterparts do not work and, in principle, can be prepared for nearly any target. The use of MIPs as solid-phase extraction sorbents is widespread and there are several companies that commercialize these materials for analyte preconcentration [12]. They have also been applied successfully as carriers for sustained/controlled release of active principles, micro-/nanoreactors for catalysis, traps for environmental remediation, sensor elements, and, more recently, for bioimaging and therapy in nanomedicine [12]. However, there are still improvements that should be introduced to overcome some of the current limitations for the broad application and marketing of MIPs such as the non-homogeneous population of binding sites, non-specific binding, template removal, biocompatibility, and biodegradability for in vivo applications. Peptides selected from combinatorial or phage display libraries, or designed in silico, have also been used as alternatives to natural antibodies, especially for sensor development, although to a much lower extent than rAbs, aptamers, and MIPs [13].

The term nanozyme was coined back in 2004 and nowadays a plethora of metal and metal oxide nanoparticles, as well as metal-organic frameworks, have shown to exhibit enzyme-like properties. Advantages of these nanomaterials over the natural receptors include higher catalytic stability, ease of modification, lower manufacturing cost, and easy surface modification for a tailored design according to the final application [14]. They can mimic oxidoreductase or hydrolase enzymatic activities and have found applications in the fields of biosensing and immunoassays. This promising field is still in its infancy and must overcome many challenges.

Last but not least, computational chemistry and bioinformatics are some of the tools gaining attention for the rational design of recognition elements with the desired affinity, selectivity or solubility for specific targets, and selected analytical applications [15].

This topical collection of articles provides an insight into the recent advances and future prospects of biomimetic

recognition elements in analytical chemistry. It collects contributions to the fields of rAbs, DNA origami structures, molecular beacons, carbon-based enzyme mimics, and MIPs with application to the development of sensors, diagnostics, and analytical separations. We would like to thank all the authors for their excellent work, the reviewers for their careful revision and constructive criticism, and the *Analytical and Bioanalytical Chemistry* editorial team for their highly professional and valuable cooperation.

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