Preface

Like a key in a lock, antibodies fit perfectly with their target antigens and are able to recognise and bind them with high affinity and selectivity. They have, therefore, found numerous applications in medicine, both for diagnostics and treatment, and in biotechnology. For example, enzyme-linked immunosorbent assays are widely used to detect and quantify small and large targets via a specific biological recognition mechanism. On the other hand, antibodies are also used to treat certain infections and other diseases, and have saved many lives. More recently, new cancer therapies have been developed based on antibodies. However, antibodies are not always perfect for these applications because they are unstable out of their native environment, may be degraded by proteases, and tend to be difficult to integrate into standard industrial fabrication processes. In addition, an antibody for the particular target of interest, in particular for small molecules, can sometimes be difficult to obtain. It has therefore been a long-term dream of researchers to be able to obtain such structures synthetically – creating tailor-made receptors for a given molecular target. One surprisingly simple way of achieving this is through the molecular imprinting of synthetic polymers.

Molecular imprinting is a process where interacting and cross-linking monomers are arranged around a molecular template, followed by polymerisation to form a cast-like shell. The template is usually the target molecule to be recognised by the synthetic antibody, or a derivative thereof. Initially, the monomers form a complex with the template through covalent or non-covalent interactions. After polymerisation and removal of the template, binding sites are exposed that are complementary to the target molecule in size, shape, and position of functional groups, which are held in place by the cross-linked polymer matrix. In essence, a molecular memory is imprinted in the polymer, which is now capable of selectively rebinding the target. Thus, molecularly imprinted polymers (MIPs) possess two of the most important features of biological antibodies – the ability to recognise and bind specific target molecules.

When these MIPs were first described in the 1970s and early 1980s by Wulff [1] and Mosbach [2], they were merely used as specific separation materials, for

example, for the chromatographic separation of enantiomers. It was not until 1993 and Mosbach's seminal paper in Nature [3] that the great potential of MIPs as synthetic antibody mimics was recognised. This resulted in a nearly exponential increase in the number of publications in the area, with several hundreds per annum over the recent years. There are a number of potential application areas that have been identified for MIPs, all based on their capability to specifically recognise molecular targets: affinity separation, chemical sensors and assays, directed synthesis and enzyme-like catalysis, and biomedical applications like drug delivery. To date, the main application area is analytical chemistry, and during the past decade, the only commercially available MIPs have been solid-phase extraction matrices for sample preparation and analyte pre-concentration, mainly for biomedical and food analyses. These are commercialised by the Swedish company *Biotage* and by the French *PolyIntell*. However, apart from separation, other promising commercial applications of MIPs are sensors and assay systems. Indeed, MIP-coated wipes for the detection of explosives are more recent products commercialised by the US company *Raptor*.

An exciting recent trend goes towards the use of MIPs for medical treatment, in particular for drug delivery. One example is the use of MIPs in contact lenses for drug delivery to the eye. In fact, there is a considerable need for more efficient delivery of ocular therapeutics. This can be achieved by using the molecular selectivity and affinity of an MIP to extend and control the residence time of drugs on the eye surface and thereby limiting drug loss by lacrimation, drainage, and non-productive absorption [4]. On the other hand, it is also conceivable to use MIPs for the removal of unwanted molecules from our body. While there have been no reports in the literature on real applications with living organisms, there are a few examples on the removal of toxic substances, for example bilirubin and metal ions, from biological fluids using extracorporeal devices [5], and the Israeli–US company *Semorex* lists an MIP for phosphate removal from the gastrointestinal system as one of their products.

In a similar direction, that is, using MIPs directly as drugs, goes the work by Cutivet et al. [6], who have developed water-compatible MIP microgels that strongly and selectively inhibit the protease trypsin, enzyme inhibitors being potential drug candidates. The inhibitory power of these MIPs was three orders of magnitude higher than that of small-molecule inhibitors like benzamidine. Very recently, Shea and colleagues [7] have made an exciting new contribution to the MIP field. They created molecular imprints for the cytotoxic peptide melittin, the main component of bee venom, in the surface of polymer nanoparticles, obtaining, as a result, an artificial antibody that could be used for the in vivo capture and neutralisation of melittin in mice. The authors for the first time demonstrated the possibility of in vivo application of the imprinted nanoparticles in mice. Normally, when mice are injected into the blood stream with a certain dose of melittin, they die within less than an hour due to the cytolytic activity of this peptide. However, when the MIP nanoparticles were injected shortly after the peptide, the survival time and rate of the mice increased considerably.

From a materials point of view, there is still much room of improvement for MIPs. Indeed, during the past 10 years, the development in the area has taken a few different directions aiming at making these improvements possible. For example, it has been suggested to apply controlled polymerisation techniques for MIP synthesis, in order to improve their inner morphology. Another trend is the combination of molecular imprinting and nanostructures, yielding materials with interesting additional properties. Examples are MIP photonic crystals, which can be used as optical sensors [8], or layers of surface-bound MIP nanofilaments, which allow us to tune the surface properties of a MIP film towards superhydrophobicity [9]. An important development is the systematic decrease of particle size, resulting in nanogels with sizes in the lower nanometre range [10], which seems to convey to MIP's properties closer to those of biological antibodies, such as a quasi solubility, very few, or even one, binding site per particle, and a more homogeneous affinity distribution, which can be even further improved by fractioning the particles by affinity chromatography [11]. Resmini and colleagues [12] have shown that these particles, when imprinted with a transition state analogue, can be efficient enzyme mimics. Others have worked on improving the compatibility of MIPs with aqueous solvents, by using monomers that interact more strongly with the molecular template [13]. The development of MIPs that can recognise proteins has also been a long-time dream of many researchers working in the area, which now seems to come true, an example being MIPs that very specifically recognise peptide epitopes of proteins [14].

It appears now that MIPs will finally find their own applications, rather than trying to do what antibodies already can do, and better. Industry is currently evaluating the potential application and commercial opportunities for MIPs. Companies need to investigate the selectivity for MIPs for their targets not in pure solvents but in the environment in which they are to be used, including complex ones like biological fluids. Criteria like the ready integration of molecular imprinting within existing industrial fabrication processes, yields, cost, and the competitiveness of MIPs with existing affinity materials also need to be examined. Certainly, a simple proof of principle will not be sufficient in this case. In the different chapters of this book, the reader will be able to learn about the latest developments in the area of molecular imprinting, about inspiring new concepts leading to considerable improvements of these materials, and also about many remaining challenges for their application in the Real World.

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