Fighting Body Odor

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Plastic Antibodies for Cosmetics: Molecularly Imprinted Polymers Scavenge Precursors of Malodors

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Abstract: *Molecularly imprinted polymers (MIPs) are synthetic antibody mimics capable of specific molecular recognition. Advantageously, they are more stable, easy to tailor for a given application and less expensive than antibodies. These plastic antibodies are raising increasing interest and one relatively unexplored domain in which they could outplay these advantages particularly well is cosmetics. Here, we present the use of a MIP as an active ingredient of a cosmetic product, for suppressing body odors. In a dermo-cosmetic formulation, the MIP captures selectively the precursors of malodorous compounds, amidst a multitude of other molecules present in human sweat. These results pave the way to the fabrication of a novel generation of MIPs with improved selectivities in highly complex aqueous environments, and should be applicable to biotechnological and biomedical areas as well.*

Molecularly imprinted polymers (MIPs), often dubbed as "plastic antibodies", are synthetic antibody mimics.[1,2] Like antibodies, they are capable of specific molecular recognition for a target molecule but at the same time they are more stable, easy to tailor to a given application and less expensive. MIPs are synthesized by co-polymerizing functional and cross-linking monomers in the presence of a molecular template. The template can be the target molecule or a derivative thereof. Subsequent removal of the template leaves binding sites cavities complementary in shape, size and functional groups orientation in the polymer network which are able to rebind the template molecule with both high affinity and selectivity that are comparable to those of natural antibodies. These "plastic antibodies" are raising interest and several application areas have been identified such as affinity separation,[3] biosensing,[4] or even medical treatment.[5] For some of them, commercial products are already available.[6–8] Surprisingly, MIPs have been hardly explored in the vast market that represents the cosmetic industry. A few reports dealt with their applications for extraction/separation during the preparation and/or processing of active compounds,[9–11] and as a delivery system.[12] The work we present here (which was also the subject of a patent application[13]) describes the use of a molecularly imprinted polymer as an active principle in a cosmetic product. An active ingredient is defined as any component that has an effect on the skin for the treatment or prevention of a disorder. Inactive ingredients on the other hand are included to help deliver or stabilize the active ingredients, as well as to preserve the product and make it aesthetically pleasing.[14] We demonstrate the application on the example of a new deodorant principle. The idea is to prevent the formation of body odors without disturbing the fragile microbial equilibrium of the skin.[15] This is achieved by using a MIP as a specific scavenger agent to trap non-odorous precursors of malodors, thus preventing them from being transformed by skin bacteria into volatile malodorous compounds (Figure 1).

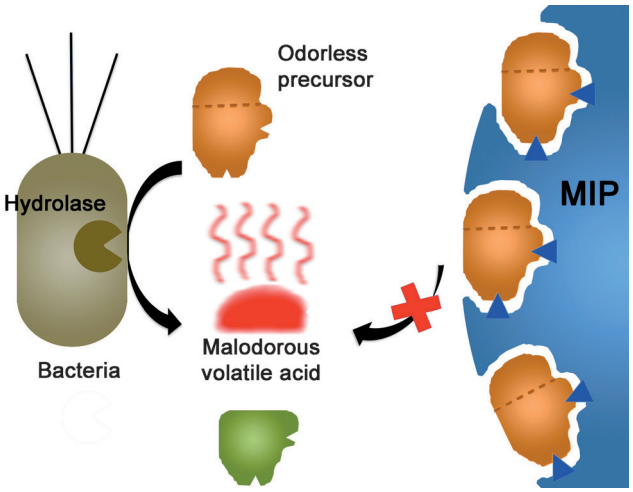

Figure 1. Schematic illustration of a MIP as the active ingredient in a cosmetic product to prevent body odor formation. By scavenging the odorless precursor, the MIP prevents its hydrolysis to a volatile malodorous acid by a bacterial enzyme.

The human axilla (armpit) is one of the predominant anatomical skin sites responsible for the formation of strong and unpleasant body odors.[16] The axillary region contains sebaceous glands and a large density of eccrine and apocrine sweat glands which secrete numerous classes of compounds like lipids, electrolytes (NH_4^+, Na^+, Cl^-), steroids, proteins, vitamins and various carboxylic acids. This availability of

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nutrients combined with the humid and semi-occluded environment of the armpit allows for dense bacterial colonization[15] reaching up to 1 million of cells per cm^2. The skin-resident bacteria are responsible for the generation of malodors as they transform the odorless natural sweat secretions into volatile malodorous molecules.[17–19] The main molecules causing the distinct pungency of underarm odors are thioalcohols and medium chain branched volatile fatty acids.[19] 3-Hydroxy-3-methyl-hexanoic acid (3H3MH) and (*E*)-3-methyl-2-hexenoic acid (3M2H) are the most abundant of these offenders[19–21] and are produced from their non-odorous glutamine conjugate precursors, cj3M2H and cj3H3MH, by the action of N_α-acylglutamine aminoacylase from *Corynebacteria spp*[15–21] commensal to the skin (Figure 2 A).

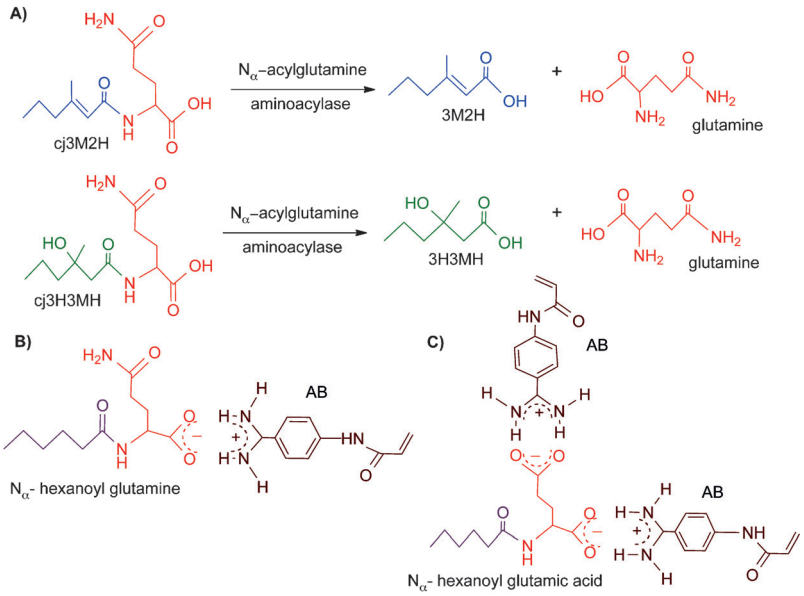

Figure 2. A) Formation of malodorous volatile fatty acids, (*E*)-3-methyl-2-hexenoic acid (3M2H) and 3-hydroxy-3-methyl-hexanoic acid (3H3MH) from their non-odorant glutamine conjugates by *Corynebacteria spp* in axillary sweat. Proposed complex formation between the templates B) N_α-hexanoyl glutamine and C) N_α-hexanoyl glutamic acid, with the monomer (4-acrylamidophenyl)(amino)methaniminium acetate (AB).

The understanding of the nature and biogenesis of axillary odors has been the focus of many scientific studies[16,19,20] and particular research has focused on the mechanisms of body odor formation so as to design deodorant systems to target specific bacteria, metabolic pathways or key enzymes. Most currently marketed anti-perspirants and deodorants contain, respectively aluminum salts and unspecific antibacterials, supplemented with odor-covering agents.[15,21,22] However, the extremely wide use of these products requires alternative solutions with regard to various problems (environmental, respect of skin ecosystem, etc.).[15,23] For this reason, an innovative approach based on a multi-target MIP was developed to capture the glutamine precursors of malodors before they are converted to the malodorous acids and eventually the acids themselves. Hence, the skin microbiota which helps to protect the body against harmful pathogens would not be disrupted. The main challenge was to synthesize MIPs with chemicals that would meet the criteria required by the cosmetic industry regarding topical skin application and to be able to use these materials to selectively capture target molecules in an extremely complex and unfavorable environment (mixture of sweat and cosmetic formulation). This is far from obvious despite many efforts in the past years to make MIPs recognize selectively target molecules in an aqueous environment and all the more in complex matrices.[1,24–26] Indeed, MIPs are conventionally synthesized in apolar and aprotic organic solvents, using commercial functional monomers which form weak non-covalent interactions with templates (association constant $K_a < 30\,M^{-1}$).[1] For the application targeted here, interactions involving high association constants are essential. Previously, in order to mimic the guanidinium group of arginine in antibodies which is known for its strong interaction with carboxylates and phosphates, Wulff and co-workers have synthesized the monomer, (*E*)-*N*,*N*′-diethyl-4-vinylbenzamidine (SI Figure S1),[27–29] which can form stoichiometric non-covalent complexes of $K_a > 10^3\,M^{-1}$ with various oxyanions like carboxylates, phosphonates and phosphates, in CD_3CN or CD_3Cl.[30] Their amidinium-based MIPs could mimic catalytic antibodies by hydrolyzing esters in a mixed buffer/acetonitrile system.[28,29] Likewise, MIPs based on urea monomers specially designed for stoichiometric oxyanions targeting ($K_{a(DMSO\text{-}d6)} \approx 9 \times 10^3\,M^{-1}$), were exploited for their selectivity in mixed organic solvent/buffer systems,[24,25] but not in 100% aqueous media. For our work, we synthesized an unsubstituted amidine monomer, (4-acrylamidophenyl)-(amino)methaniminium acetate (AB) (Supporting Information (SI) Figure S1), to be able to form a soluble complex in a polar solvent, in our case ethanol/water. The MIP based on this monomer was tailored for the selective capture of the targets in human sweat, deodorant formulation or their mixture.

Our first scavenging MIP was prepared by free radical polymerization using N_α-hexanoyl glutamine (SI Figure S1) as template, AB as functional monomer, ethylene glycol dimethacrylate as cross-linker, Perkadox 16 as initiator (compatible with cosmetics and skin care products, unlike most of the commonly-used azo initiators) and ethanol/water (4:1) as solvent. The monomer was synthesized similarly to our previous publication,[31] but as an acetate salt (SI Figure S2 (A-B-C) for ^1H NMR, ^{13}C NMR and mass spectra), to enable ready exchange with the template's carboxylate (Figure 2 B). N_α-hexanoyl glutamine (SI Figure S2 (D-E-F) for ^1H NMR, ^{13}C NMR and mass spectra) is a close structural analogue of the glutamine conjugates of the target molecules and was chosen as a generic template. The stoichiometry between AB and the template (Figure 2 B) was determined by ^1H NMR spectroscopy using the method of continuous variation (Job plot). A 1:1 stoichiometry with a high binding constant $\beta_{11} = K_{11}$ of $9.4 \times 10^3\,M^{-1}$ in CD_3OD/D_2O (4:1) was determined (SI Fig-

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ure S4 (A-B-C)), where K_{11} is equal to the association constant (K_a) of the 1:1 complex.

The binding behavior of the polymers was first investigated in the solvent of synthesis. Equilibrium binding assays showed a high binding capacity and specificity of the MIP towards N_α-hexanoyl glutamine, as evidenced by the quasi-total adsorption of the template by 10 mg of MIP and the higher binding of MIP as compared to the non-imprinted polymer (NIP) (SI Figure S5). The NIP is a control polymer and was prepared in the same way as the MIP but without the template (see SI for synthesis). The binding was then investigated in artificial sweat, a simplified model of human eccrine sweat, which is a solution containing the major constituents of human sweat, namely urea, lactic acid, albumin and sodium chloride. We observed no binding of our target conjugates to the MIP, which we mainly attributed to the high sodium chloride concentration, as its suppression from the artificial sweat composition restored more binding than the suppression of the other components.

In order to obtain binding in this environment and in the more challenging human sweat medium, we postulated that it would be beneficial to place a second amidinium function into the binding site, able to interact with the amide group of the glutamine conjugates, since this would provide a second strong anchoring point in the binding site. In fact, human sweat is composed of more than 60 different chemical constituants.[32] It contains in particular a large number of carboxylic acids, many of them at concentrations higher than those of our target molecules, for example lactic acid, pantothenic acid, nicotinic acid, and many amino acids (SI Table S1). These, in addition to other abundant molecules like urea, ammonia and NaCl may interact non-specifically with the amidinium groups present in the MIP, and thus interfere with target binding. It is therefore important that the interactions between the targets and the binding sites in the MIP be strong enough to allow efficient and specific binding in this very competitive environment. For this, we synthesized another template molecule, N_α-hexanoyl glutamic acid (Figure 2C; see also SI Figure S1 and Figure S2 (G-H-I) for ^{1}H NMR, ^{13}C NMR and mass spectra), which has two free carboxyl groups. Since amidiniums form stronger bonds with carboxylate than with amide groups, this should result in a more stable and favorably pre-organized 1:2 complex of template-AB (Figure 2C). ^{1}H NMR titration and Job plot performed in CD_3OD/D_2O (4:1) indeed revealed the coexistence of 1:2 and 1:1 complexes. The analysis of titration experiments supported the Job plot data and provided an overall binding constant $\beta_{12} > 10^7\,\text{M}^{-1}$ (SI Figure S4 (D-E-F)). The link between the overall binding constant and the association constants of the two equilibria is given by the following relationship: $\beta_{12} = K_{11}K_{12}$, where K_{11} and K_{12} represent the association constants of the 1:1 and 1:2 complex, respectively.

Accordingly, the MIP synthesized with N_α-hexanoyl glutamic acid showed high and specific binding in artificial sweat during equilibrium binding studies with 200 μM N_α-hexanoyl glutamine, 100 μM cj3M2H or cj3H3MH (SI Figure S6). This MIP has a diameter of ca. 600 nm, as inferred from the scanning electron microscope image (SI Figure S7) and is suitable for skin applications because their large size prevents their penetration into the skin.

The next step was to demonstrate whether this MIP could capture undesirable molecules in human sweat. Sweat (pH ≈6) was collected from the armpit of volunteers prone to develop armpit odors. The volunteers had not used any deodorant products three weeks prior to sweat collection. The sweat was immediately frozen to preserve the composition. It was found to contain $135 \pm 6.6\,\text{nmol mL}^{-1}$ ($37 \pm 1.8\,\mu\text{g mL}^{-1}$) of cj3H3MH, $16.7 \pm 1\,\text{nmol mL}^{-1}$ ($4.3 \pm 0.3\,\mu\text{g mL}^{-1}$) of cj3M2H and $2.68 \pm 0.14\,\text{nmol mL}^{-1}$ ($391 \pm 20\,\text{ng mL}^{-1}$) of 3H3MH, as determined by LC-MS/MS (SI Figure S8) and LC-ELSD-UV (SI Figure S9). Though the odorous acids are extremely volatile, the presence of 3H3MH could still be detected with LC-MS/MS, but not 3M2H. These values were deduced from standard calibration curves (peak area versus concentration) obtained from varying concentrations of the compounds (cj3H3MH, cj3M2H, 3H3MH) spiked in artificial sweat (SI Figure S8). To assess the binding performance of the MIP in human sweat, aliquots were incubated overnight with MIP and NIP at 20 °C. Human sweat alone, incubated in parallel served as a control. The supernatants were analyzed simultaneously for the presence of cj3H3MH, cj3M2H and 3H3MH. Figure 3 and (SI Figure S9) show that the MIP was efficient in human sweat, as it can capture the two conjugates

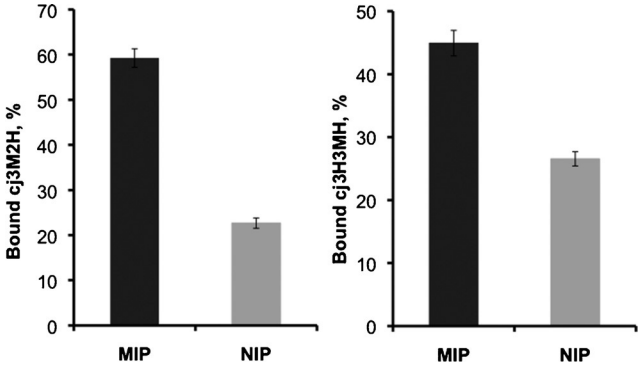

Figure 3. Capture of target conjugates in human sweat by 5 mg mL^{-1} of MIP and NIP at 20 °C. Amounts of cj3M2H and cj3H3MH in human sweat are 17 and 135 nmol mL^{-1}, respectively. Human sweat alone served as blank. Values represent the mean from two independent experiments with three repetitions of LC-MS/MS analyses for each case.

to a higher extent than the NIP. It can be observed that the NIP exhibits some significant non-specific binding. This is not surprising since the interaction between AB and N_α-hexanoyl glutamic acid ($\beta_{12} > 10^7\,\text{M}^{-1}$ in CD_3OD/D_2O (4:1)), as deduced from ^{1}H NMR titration data, is so strong that the randomly distributed amidinium groups can also bind to some extent the target molecules non-specifically. We should stress though that the binding to the NIP does not necessarily represent the non-specific part of the binding to the MIP. In fact, in the MIP most of the amidinium groups will be located in the specific binding sites and thus contribute to specific binding, whereas in the case of the NIP there are no imprinted sites and thus all

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amidinium groups are potentially available for non-specific binding.

Remarkably, despite the presence of numerous constituents with carboxylic acid groups (some in the mM range) (SI Table S1),[32] the MIP selectively captured the target molecules, hence proving the presence of high fidelity imprinted sites. Interestingly, the hydrolysis product 3H3MH was also captured by the MIP to some extent (not shown), which is a beneficial, though probably non-specific, side effect.

We now wanted to test the capture in human sweat of cj3M2H and cj3H3MH by the MIP incorporated in a dermocosmetic deodorant formulation (SI Table S2), which is important for real-life application. Equilibrium binding studies were performed, this time at body temperature (37 °C), in the deodorant formulation spiked with either 200 μM of cj3H3MH or 100 μM of cj3M2H. These values represent upper extremes in terms of concentration of the 2 conjugates in human sweat. Under these conditions, 4 mg of MIP showed high binding capacity as it could capture 63 % of cj3H3MH and 89 % of cj3M2H (Figure 4 (A-B)). The binding behavior towards the odorous acid 3H3MH could not be evaluated due to its high volatility at 37 °C.

Finally, to further simulate the conditions as in a real cosmetic application, the polymers were dispersed in the deodorant formulation and mixed with human sweat in a 1:1 (v/v) ratio. As shown in Figure 4 C, the MIP incorporated into the cosmetic formulation can specifically capture the glutamine conjugates in human sweat at 37 °C. The binding specificity of the two conjugates to the MIP in human sweat seems to be even better when mixed in the deodorant formulation (Figure 4 C and SI Figure S10) than in sweat alone (Figure 3). The lower non-specific binding may be due to the favorable environment created by the lipid components present in the formulation, or to the higher temperature (37 °C).

As an additional proof of specific binding to the imprinted sites of the MIP, a 1:1 mixture of artificial sweat and deodorant formulation was spiked with 200 μM of either cj3H3MH or a short chain carboxylic acid present in human sweat, hexanoic acid. Upon incubation with the polymers, a large difference in binding was observed between MIP and NIP with cj3H3MH, whereas with hexanoic acid, the binding was lower and virtually the same with MIP and NIP (SI Figure S11), which clearly indicates that the MIP binds specifically the target conjugate in this very complex environment. As expected, the MIP can also bind other COOH-containing molecules but via non-specific interactions.

In conclusion, we have developed a plastic antibody as the active ingredient of a cosmetic product, on the example of a new deodorant principle to suppress body odors. At the same time, we have demonstrated the feasibility of preparing highly selective molecularly imprinted binding sites for recognition in complex aqueous media, using a polymerizable amidinium monomer which can form stoichiometric interaction with a high binding constant for carboxyl groups. The judicious design of the template resulted in cavities bearing two amidinium functionalities favorably positioned in a precise spatial arrangement so as to selectively capture the precursors of malodorous compounds from human sweat.

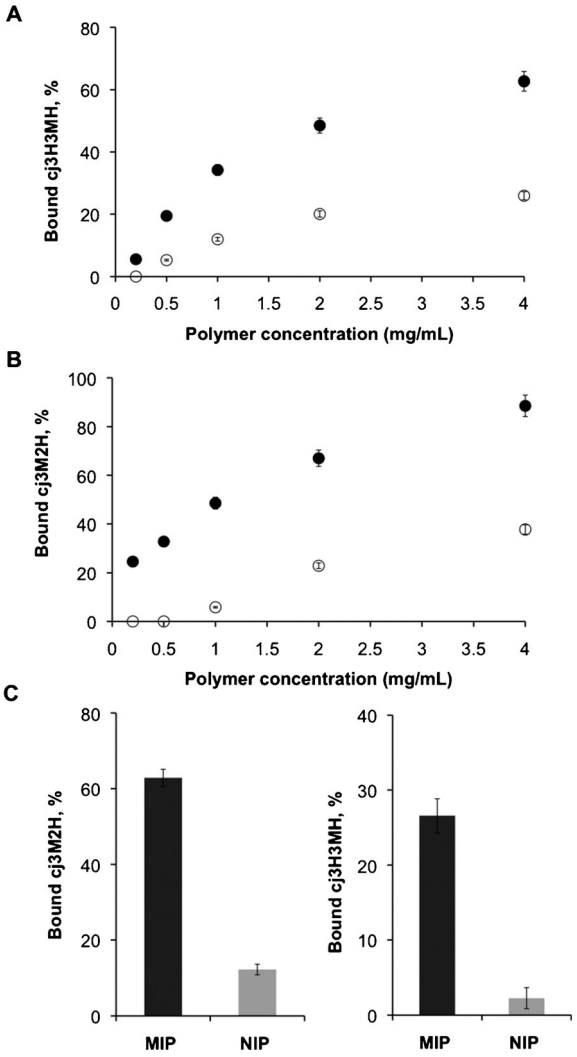

Figure 4. Equilibrium binding isotherms of MIP (filled circles) and NIP (empty circles) for spiked A) 200 μM cj3H3MH and B) 100 μM cj3M2H, in a deodorant formulation. C) Capture of target molecules by 10 mg mL^{-1} of MIP and NIP in a mixture of human sweat and deodorant formulation. Amounts of cj3M2H and cj3H3MH in human sweat were 17 and 135 nmol mL^{-1}, respectively. A mixture of human sweat and deodorant formulation served as blank. Incubation temperature was 37 °C. Values represent the mean from two independent experiments with three repetitions of LC-ELSD-UV analyses for each point.

This type of amidinium-based monomer would also find utility for the preparation of plastic antibodies for a wide range of carboxylate, phosphate, phosphonate and possibly sulfate-based biological molecules. The resulting MIPs could potentially be applied in other cosmetic areas and more generally in areas dealing with highly complex environments, where selective recognition is required like in sensing, bioanalysis, medical treatment and proteomic applications.

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Keywords: body odors · cosmetics · human sweat · molecularly imprinted polymer · stoichiometric monomer

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