



Bioinspired antifouling polymers

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Controlling biointerfacial phenomena is crucial to the success of many biomedical technologies. For applications in biosensing, diagnostics, and medical devices, precise control of interactions between material surfaces and the biological milieu is an important but elusive goal¹. Emerging strategies for manipulating the biological response to medical materials seek to take advantage of specific interactions between designed surfaces, biomolecules, and cells². Limiting nonspecific interaction of cells, proteins, and microorganisms with material surfaces is critical, since these interactions can prove highly problematic for device efficacy and safety. Thus, a central research focus continues to be the development of versatile, convenient, and cost-effective strategies for rendering surfaces resistant to fouling by proteins, cells, and bacteria.

A common method to reduce cellular and proteinaceous fouling is the immobilization of antifouling polymers on biomaterial surfaces (Fig. 1). Several polymer classes have been explored for this purpose, including polyacrylates³⁻⁷, oligosaccharides^{8,9}, polymer mimics of phospholipids¹⁰⁻¹², and poly(ethylene glycol) (PEG)¹³⁻¹⁷. Although the general physical and chemical properties that make surfaces antifouling are not known, Merrill¹⁸ as well as Whitesides and coworkers¹⁹ postulate that nonfouling surfaces should be electrically neutral, hydrophilic, and possess hydrogen bond acceptors but not hydrogen bond donors. Although exceptions to these rules have been observed^{20,21}, many polymers with antifouling properties possess most of these traits.

Two basic strategies exist for functionalizing material surfaces with antifouling polymers. The first approach, termed *graft-to*, consists of the adsorption to surfaces of presynthesized polymer chains end-functionalized with a chemical anchoring group (Fig. 1, top). Alternatively, *graft-from* approaches, in which a polymer is grown *in situ* from the surface via a surface-adsorbed initiation group, are generally capable of producing denser polymer layers (Fig. 1, bottom). Essential to both approaches, however, is the requirement of a robust mechanism for immobilizing the antifouling polymer onto metals, ceramics, polymers, and electronic materials. Numerous methods of anchoring polymers to surfaces have been proposed, and can be broadly classified as either *physisorptive* or *chemisorptive*.

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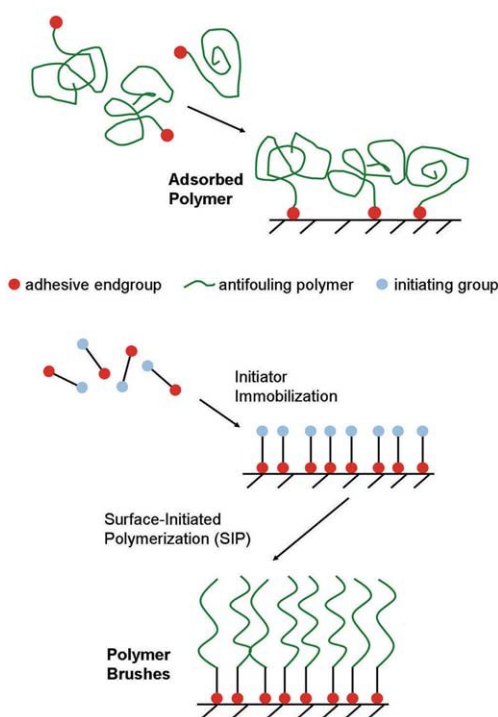


Fig. 1 'Graft-to' (top) and 'graft-from' (bottom) strategies for modification of surfaces with antifouling polymers.

Physisorption relies on relatively weak van der Waals and hydrophobic forces to tether polymers to a surface. Consequently, the polymers are not irreversibly bound to the surface and proteins may be exchanged with the polymer on the surface²². To provide greater stability, anchoring strategies involving the formation of more robust chemical bonds between the polymer and surface are deemed more desirable, as exemplified by thiol-Au^{23,24} or silane-metal oxide interactions²⁵. Most existing chemisorptive approaches for polymer immobilization, however, suffer from significant limitations, such as substrate chemical specificity, complicated and expensive protocols, and susceptibility to thermal or hydrolytic degradation^{26,27}.

A versatile, simple, and cost-effective method for functionalization of surfaces, therefore, would be of great value in designing antifouling biointerfaces, as well as more generally in the context of surface modification of materials. In this article, we review new experimental strategies that we have developed to exploit the natural adhesive characteristics of 'bio-glues' from one of nature's most notorious fouling organisms, the mussel. Mimics of mussel adhesive proteins are used in the form of chemical conjugates with antifouling polymers for conferring fouling resistance to surfaces.

Mussel adhesion

A number of organisms have adopted elegant solutions for robust attachment to wet surfaces. Although most synthetic adhesives do not perform well underwater, freshwater and saltwater species of mussels achieve opportunistic attachment to surfaces by way of a set of unique adhesive proteins²⁸. The adhesion apparatus consists of numerous protein tethers (byssal threads) attached at one end to the organism and by an adhesive pad at the other end to an object – rock, pier, ship hull, the shell of another mussel, etc. (Fig. 2A). The byssus itself is an acellular tissue secreted as a proteinaceous liquid precursor that rapidly hardens in a process that is rheologically similar to polymer injection molding. Byssal threads are secreted by glands in the mussel foot in a sequential manner and in many directions, so achieving mechanical stability in the presence of shear forces resulting from the movement of water²⁹.

The details of mussel adhesion have been best characterized in the common blue mussel, *Mytilus edulis*³⁰. In *M. edulis*, the core of the byssal threads are composed of collagen- and silk-like proteins, lending exceptional mechanical strength and resiliency to the threads^{31,32}. Located at the distal end of the byssal threads are adhesive pads containing the mussel adhesive proteins (MAPs)^{33,34}

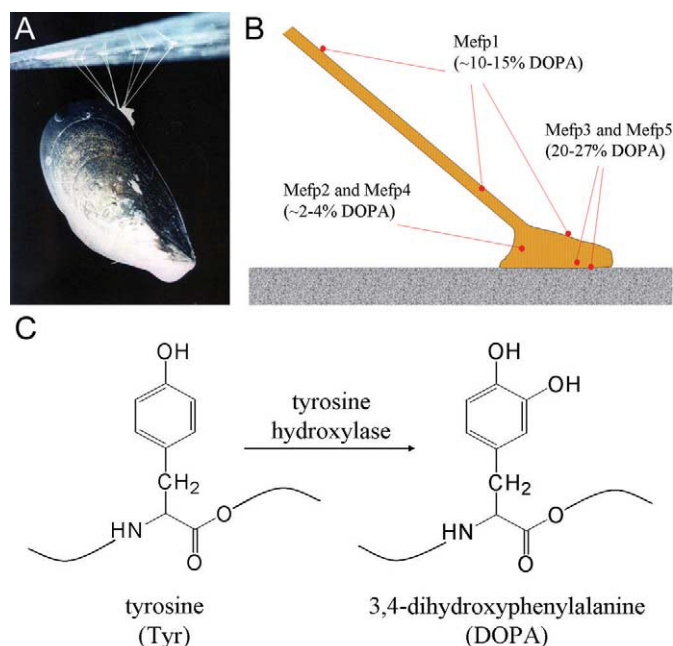


Fig. 2 (A) The common blue mussel, *M. edulis*, adheres to substrates via byssal threads and adhesive plaques³⁰, which (B) contain varying amounts of DOPA. (C) DOPA is produced by post-translational modification of Tyr.

(Fig. 2B), which have been the primary focus of biomimetic efforts related to adhesion. Detailed studies in *M. edulis* have led to the identification of at least five major adhesive foot proteins. The best characterized of these is *M. edulis* foot protein 1 (Mefp1), which is composed of 75–80 hexa- and decapeptide repeats in a linear tandem array^{35–38}. The sequence of the most common decapeptide is Ala-Lys-Pro-Ser-Tyr-DHP-Hyp-Thr-DOPA-Lys³⁹. Of particular note in this repeat motif are the many hydroxylated or dihydroxylated residues, i.e. *trans*-2,3-*cis*-3,4-dihydroxyproline (DHP), serine, threonine, tyrosine, and 3,4-dihydroxyphenylalanine (DOPA). DOPA is an unusual residue not found in many proteins outside of MAPs. Here, it is formed through enzymatic post-translational modification of tyrosine residues prior to secretion of the liquid protein precursor (Fig. 2C). Although Mefp1 has a high DOPA content, it appears unlikely that this protein plays a significant role in mussel-substrate adhesion, since it is mainly found as a coating on the byssal threads and adhesive pads^{40,41}. Within the bulk of the adhesive pad are located Mefp2 and Mefp4, two proteins that contain relatively low concentrations of DOPA^{41–43}. Finally, Mefp3^{44,45} and Mefp5⁴⁶ are found in higher relative abundance near the interface of the adhesive plaque with the substrata (Fig. 2B)^{47,48}. Of the known major adhesive proteins in the plaques, these two proteins have the highest DOPA content (21 mol% and 27 mol%, respectively). It is worth noting that a majority of the DOPA residues in Mefp5 are immediately adjacent to basic residues such as Lys.

The high concentration and wide distribution of DOPA within the byssus raise the possibility of multiple roles for this residue^{49–51}. The catechol side chain of DOPA is capable of many different types of chemical interactions and, furthermore, is particularly susceptible to oxidation under elevated pH conditions such as in the marine environment. The rich chemistry of catechols has made it difficult to clearly define the role of DOPA in MAPs. In spite of this, two defined roles appear to be emerging: cohesive and adhesive. The cohesive role primarily derives from reactions following the oxidation of DOPA to DOPA-quinone, while, at least on inorganic surfaces, there appears to be an adhesive role for unoxidized DOPA. Using experiments with model compounds as well as polymer mimics of MAPs, Yu *et al.*⁵¹ provided strong evidence that the unoxidized DOPA catechol is primarily responsible for adhesion to inorganic metal oxide surfaces, and that the crosslinking (and presumably

solidification) observed in MAPs is a result of reactions involving DOPA-quinone. Burzio and Waite⁵² have shown that radical coupling reactions lead to the formation of di-DOPA crosslinks, although a role for redox reactions involving transition metal ions has also been postulated^{53,54}. The main evidence for adhesive interactions involving DOPA lies in the experiments of Yu and Deming⁵⁵. They synthesized copolypeptides containing L-DOPA and L-Lys, which, upon oxidative crosslinking, were found to create moisture-resistant bonds with a variety of substrates including Al, steel, glass, and plastics with bond strengths that rival those formed by natural marine adhesive proteins.

MAP-mimetic polymers

Motivated by the prospect of capturing the exceptional properties of MAPs in synthetic adhesives, considerable effort has been devoted to the development of synthetic mimics of MAPs^{55–59}. Most work has focused on developing DOPA-containing adhesive polymers and hydrogels. As early as 1976, Yamamoto *et al.*⁶⁰ synthesized a DOPA homopolymer, and subsequently the first polyphenolic consensus decapeptide of Mefp1. The associated precursor form of this decapeptide containing two tyrosine residues has also been synthesized using genetic engineering technology and converted to the adhesive form using tyrosinase⁵⁷. Yu and Deming⁵⁵ synthesized unique copolypeptides containing L-DOPA and L-Lys, and *in situ* oxidative crosslinking with mushroom tyrosinase, Fe³⁺, H₂O₂, or IO₄⁻ was found to produce moisture-resistant bonds with a variety of substrate materials. This oxidative crosslinking strategy has recently been used by our laboratory to produce hydrogels from DOPA-conjugated bifunctional linear PEG and a tetrafunctional branched PEG⁵⁸. These gels, however, show minimal adhesion to inorganic surfaces, which is ascribed to the conversion of the DOPA catechol to its oxidized quinone form. In search of more benign gelation cues that do not sacrifice the adhesive character of DOPA functionalities, we have coupled DOPA to the ends of self-assembling triblock copolymers of PEG and poly(propylene oxide), or PPO, which undergo a sol-gel transition upon heating⁵⁹. Most recently, our group has prepared DOPA-containing hydrogels by copolymerization of *N*-methacrylated DOPA and PEG-diacrylate using ultraviolet irradiation⁶¹. Further discussion of MAP-inspired adhesive hydrogels will appear in a future communication.

MAP-mimetic polymers as antifouling coatings

The idea of using MAP-mimetic polymers for reducing or preventing fouling of surfaces is, at first thought, counterintuitive. How can the adhesive mechanism of one of nature's best fouling organisms be used to *prevent* fouling? The concept seems even less likely, given that a commercial extract of MAPs (Cell-Tak™, Becton-Dickinson) is used to encourage cell adhesion on tissue-culture labware⁶²⁻⁶⁴. The answer lies in the simple realization that MAP mimics make outstanding surface anchors for antifouling polymers. Catechols are well known for their affinity to oxide and hydroxide surfaces⁶⁵⁻⁶⁸, and there are several reports of catechols being used for anchoring small organic molecules and DNA onto oxide surfaces⁶⁹⁻⁷¹.

Our initial experimental efforts demonstrated the simplest manifestation of this concept. Using an antifouling polymer conjugated at one end to an adhesive moiety (amino acid or short peptide), surface modification is accomplished by simple adsorption of the modified polymer onto surfaces via the adhesive endgroup (Fig. 1, top). A typical example uses simple constructs of linear PEGs end-functionalized with 1-3 DOPA residues (**mPEG-DOPA₁₋₃**, Fig. 3) or an analog of the consensus decapeptide repeat sequence of Mefp1 (**mPEG-MAPD**, Fig. 3)⁷². These polymers adsorb to metal surfaces from solution, and the chemical composition of treated and untreated surfaces can be assessed with X-ray photoelectron spectroscopy (XPS) and time-of-flight secondary ion mass spectrometry (TOF-SIMS). For Au surfaces treated with **mPEG-DOPA₁**, the C1s XPS spectrum shows dramatic increases in the ether carbon component (286.0 eV) characteristic of PEG, while spectra from surfaces treated with **mPEG-OH** under identical conditions show no difference from unmodified Au. Positive-ion TOF-SIMS

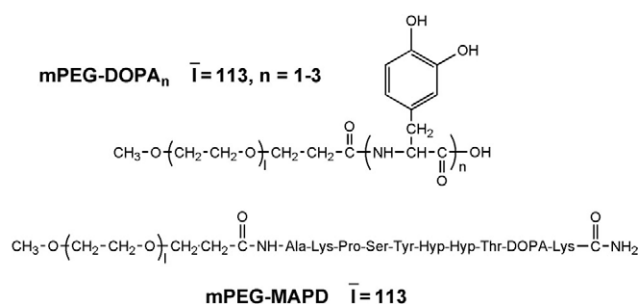


Fig. 3 Biomimetic antifouling polymers inspired by MAPs. The average number of ethylene glycol repeat units (l) for 5000 Da PEG is 113.

analysis shows substantial increases in the ion fragments $\text{C}_2\text{H}_3\text{O}^+$ and $\text{C}_2\text{H}_5\text{O}^+$ typical of PEG, indicating successful PEGylation of Au surfaces after treatment with **mPEG-DOPA₁**. Furthermore, in the high mass range, evidence of catecholic binding of Au is seen and a triplet repeat pattern representative of adsorbed PEG chains is readily observed (Fig. 4).

Cell attachment to Au surfaces treated with DOPA-containing PEGs was assessed by four-hour culture with fibroblasts. Fig. 5 shows an image of cell attachment to an Au substrate partially coated with **mPEG-MAPD**. Fibroblasts are observed to adhere and spread only on the region that remains unmodified by polymer (upper left), while the polymer-modified area is entirely cell-free (lower right). Further cell adhesion experiments on Au showed that a single DOPA amino acid was much less effective as a surface anchor for PEG compared with the decapeptide in **mPEG-MAPD**. Another material of great interest to the medical community is Ti, since its alloys are commonly employed in medical devices because of their excellent biocompatibility, corrosion resistance, and high strength⁷³. Unlike Au, however, interaction of polymers with the Ti surface will occur to an adventitious layer of native oxide. XPS analysis of Ti modified with **mPEG-DOPA₁₋₃** provides evidence of a potential mechanism for DOPA-Ti binding. Quantitative analysis of raw XPS spectra suggests the occurrence of catechol-Ti charge-transfer complexation events⁷⁴, as evidenced by increasing

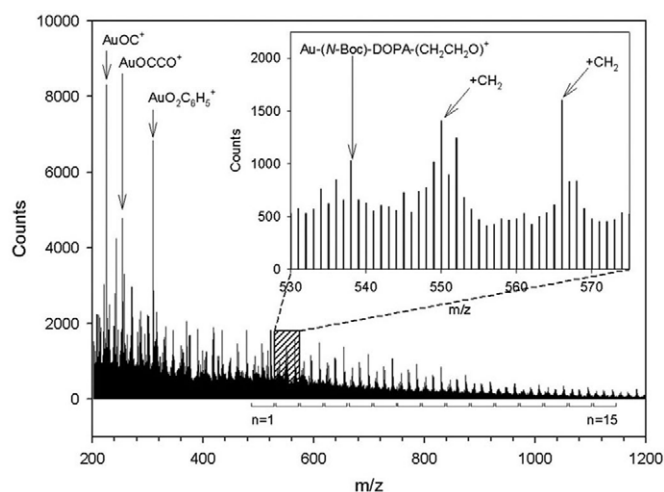


Fig. 4 The high-mass positive-ion TOF-SIMS spectrum of an Au substrate modified with **mPEG-DOPA₁**, showing Au-catechol fragments (AuOC^+ , AuOCCO^+ , and $\text{AuO}_2\text{C}_6\text{H}_5^+$). Au-DOPA-PEG fragments were identified by periodic triplets ($\Delta = 44$ a.m.u.) composed of sequential methyl and ether oxygen groups (see inset). (Adapted from⁷². © 2003 American Chemical Society.)

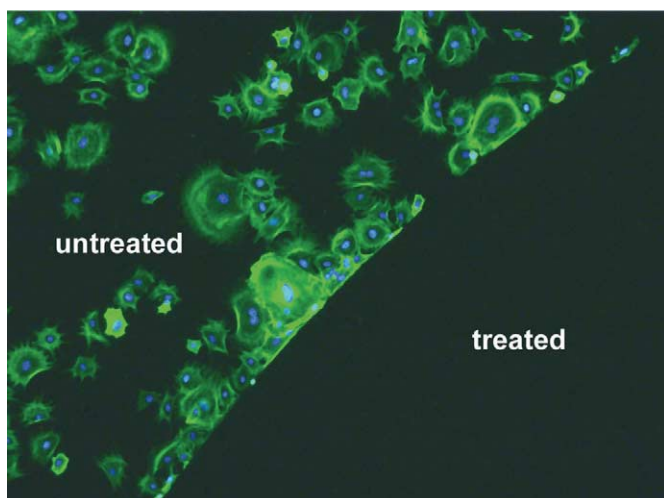


Fig. 5 Fluorescence microscopy image of fibroblast attachment after four hours to an Au substrate in which a circular portion of the surface was modified with **mPEG-MAPD** (treated). The remainder of the Au surface was unmodified (untreated). (Reprinted with permission from⁷². © 2003 American Chemical Society.)

depletion of surface hydroxyl groups on the substrates with longer DOPA peptides⁷⁵. Ti modified with PEG terminating in a single DOPA residue (**mPEG-DOPA₁**) possesses excellent short-term antifouling properties, similar to those observed on **mPEG-MAPD**-modified Ti (Fig. 6), while control polymers with a similar structure (**mPEG-Tyr** and **mPEG-Phe**) show no reduction in cell attachment.

Although indirect, the cell adhesion studies also provide a means of assessing MAP processing by the mussel, the relative contributions of DOPA and other residues in mussel adhesion, and the adhesive performance of DOPA-containing

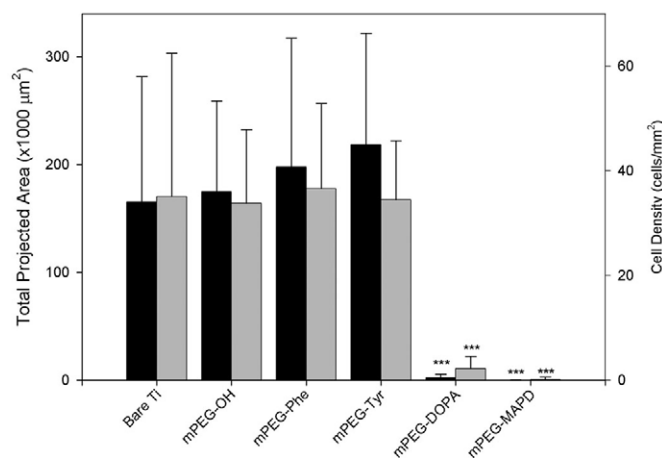


Fig. 6 Comparison of total projected area and density of cell attachment and spreading of 3T3 fibroblasts after four-hour culture on Ti and Ti modified with **mPEG-OH**, **mPEG-Phe**, **mPEG-Tyr**, **mPEG-DOPA**, and **mPEG-MAPD** (***: $p < 0.001$ versus bare Ti). (Reprinted with permission from⁷². © 2003 American Chemical Society.)

polymers on different substrate materials. It is interesting to note that cell attachment to Ti substrates treated with **mPEG-DOPA₁** is markedly lower than those treated with **mPEG-Tyr**. This is attributed to differences in adhesive ability of the catechol functionality of DOPA and the phenol side chain of Tyr, suggesting the importance of the post-translational modification of Tyr in adhesion. It is also clear that DOPA does not bind equally well to all surfaces – a single DOPA residue is sufficient for good anchorage of PEG onto Ti, but insufficient on Au, where only the decapeptide-terminated PEG performed well in cell-attachment assays. This result perhaps suggests that other amino acid residues play important adhesive roles on certain substrates. Given that mussels attach to a great variety of substrates^{76,77}, further detailed experiments to determine the strength of interactions between DOPA and a variety of substrates should be an important goal for the field.

Cell and protein resistance of DOPA-containing PEGs

Fundamental to studying the biological response to materials is the initial and immediate nonspecific adsorption of proteins at the interface, which ultimately leads to cell and bacterial attachment. Those surfaces that most effectively limit protein adsorption are least likely to support cell adhesion. Experimental observations from many laboratories^{75,78-81} make an overwhelming case for the dependence of protein resistance on antifouling polymer surface density, with high polymer surface densities providing better fouling resistance than low-density coatings. High surface densities can be achieved through manipulation of such parameters as polymer design (chain length, anchoring chemistry, and antifouling polymer composition) and processing. Thus, the classic structure-processing-properties paradigm of materials science applies in this case.

The effect of anchoring group composition on adsorbed PEG density and protein resistance has been studied in detail using **mPEG-DOPA₁₋₃**⁷⁵. Our investigation found that the mass of PEG adsorbed onto Ti is strongly correlated to the number of DOPA residues in the anchoring peptide (Fig. 7). Processing conditions are also important, as the highest polymer densities were achieved by adsorption of **mPEG-DOPA₃** under critical point conditions at elevated temperature and ionic strength⁸². Serum protein adsorption experiments reveal a clear trend between PEG surface density

and serum mass adsorbed (Fig. 8). This trend appears consistent with the results of other investigations using different nonfouling polymer systems and substrate materials⁷⁸, and further demonstrates the benefit of enhanced antifouling properties at high PEG surface density. A notable outcome of this study is that the DOPA-mediated PEGylation strategy is capable of generating PEG surface densities exceeding 'graft-to' systems used by other investigators⁷⁸⁻⁸⁰.

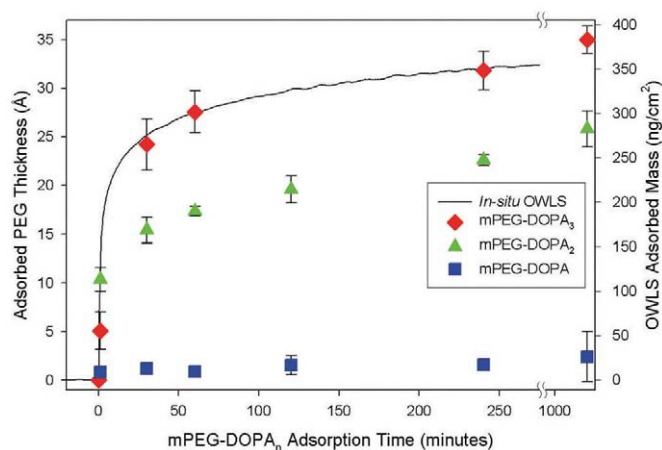


Fig. 7 Time-dependent adsorption of $m\text{PEG-DOPA}_n$ onto TiO_2 . PEG adlayer thickness was determined by ellipsometry (symbols). For $m\text{PEG-DOPA}_3$, the thickness strongly correlated to *in situ* mass adsorption obtained from optical waveguide lightmode spectroscopy (solid line). (Reprinted with permission from⁷⁵. © 2005 American Chemical Society.)

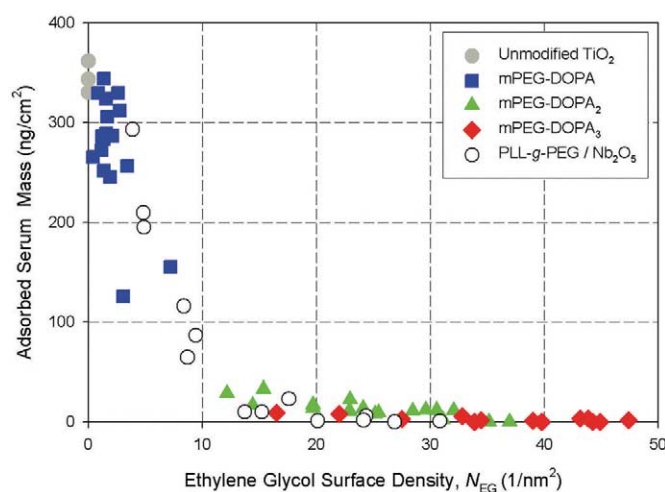


Fig. 8 Ethylene glycol surface density (N_{EG}) versus adsorbed serum thickness. N_{EG} was calculated from the mass per unit area of $m\text{PEG-DOPA}_n$ adsorbed⁷⁵. PLL-g-PEG/ Nb_2O_5 data was obtained from Pasche et al.⁷⁸. (Reprinted with permission from⁷⁵. © 2005 American Chemical Society.)

Peptoids: a new class of antifouling polymer

Although the use of PEG as an antifouling coating for biomaterial surfaces is well documented¹³⁻¹⁷, its long-term success *in vitro* and *in vivo* has been varied^{83,84}. Failure of PEG to confer fouling resistance over extended periods has been attributed to oxidative degradation and enzymatic cleavage of PEG chains⁸⁵. In an effort to develop more effective antifouling polymers, we synthesized a chimeric peptidomimetic polymer (**PMP1**) consisting of an *N*-substituted glycine (peptoid) oligomer coupled to a short functional peptide domain for surface adhesion (Fig. 9)⁸⁶. Peptoids are non-natural peptide mimics in which the side chain substitution occurs on the amide nitrogen rather than the α -carbon⁸⁷. The hydrophilic methoxyethyl side chain of **PMP1** was selected for its lack of hydrogen bond donor, ability to render the polymer water soluble, and for its resemblance to the repeat unit of PEG. In **PMP1**, we also introduced Lys residues into the peptide anchor in an effort to mimic the high Lys and DOPA content found in Mefp5, a protein implicated in mussel adhesion because of its location at the adhesive-substrate interface^{47,48}. We postulate that cationic Lys residues in the anchoring peptide may contribute long-range attractive electrostatic interactions^{78,81} that may supplement DOPA-mediated surface binding.

Both XPS and TOF-SIMS characterization confirms the adsorption of **PMP1** on Ti, and optical waveguide lightmode spectroscopy (OWLS) shows the **PMP1** adlayer to be highly resistant to serum protein fouling over short periods of time (Fig. 10). Fibroblast culture was used to determine the ability of **PMP1** to confer cell resistance to Ti surfaces for an

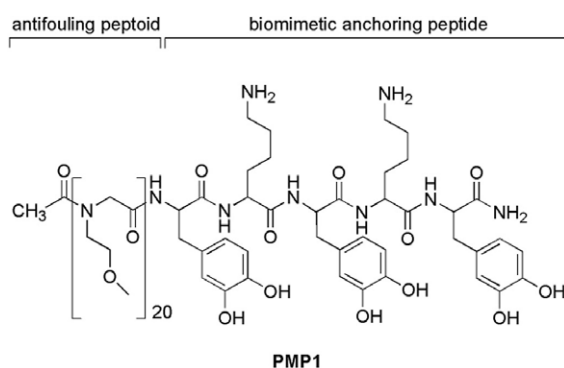


Fig. 9 Antifouling peptidomimetic polymer (**PMP1**). (Reprinted with permission from⁸⁶. © 2005 American Chemical Society.)

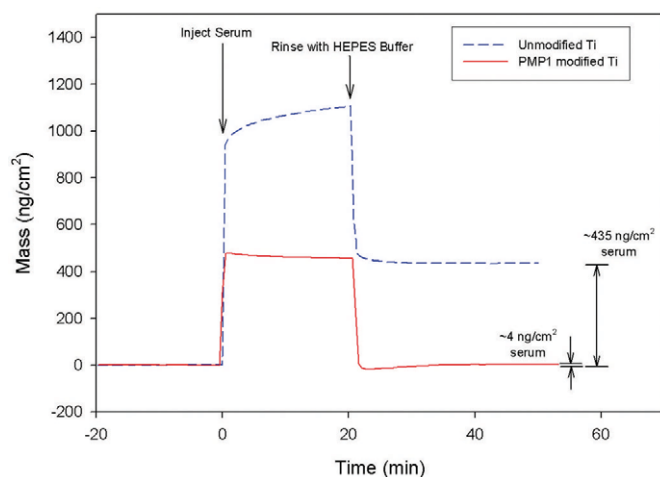


Fig. 10 PMP1-modified surfaces exhibit short-term resistance to serum protein adsorption. OWLS mass plots of serum protein adsorption on unmodified and PMP1-modified Ti. (Reprinted with permission from⁸⁶. © 2005 American Chemical Society.)

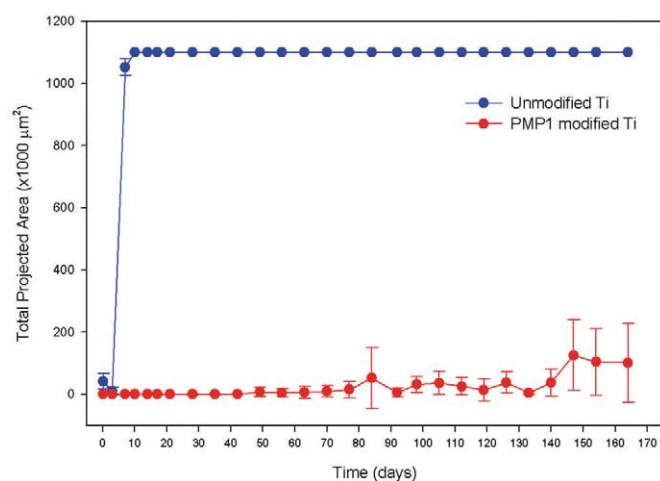


Fig. 11 PMP1-modified Ti surfaces exhibit long-term resistance to 3T3 fibroblast cell attachment. (Reprinted with permission from⁸⁶. © 2005 American Chemical Society.)

extended duration. PMP1-modified Ti surfaces show extremely low levels of cell attachment over five months (Fig. 11) in spite of twice-weekly challenges with new cells. Based on the low cell attachment, it is reasonable to infer that protein adsorption also remains low during this period.

Peptoids have several other important properties that make them attractive for use as antifouling polymers. Unlike natural peptides that are easily degraded by proteases found in the gut and bloodstream, peptoid enzymatic susceptibility is reduced by the attachment of the side chain to the amide nitrogen, leading to a protease-resistant backbone. Their peptide bonds are not cleavable because the misalignment of the side chains and carbonyl groups removes the bond from

the range of normal nucleophilic catalysts⁸⁸. This resistance to protease degradation, as well as their relatively low mass, reduces the likelihood of peptoids causing an immune response, suggesting that these biomimetic polymers may be useful for *in vivo* application⁸⁹. Furthermore, diverse peptoid sequences can be synthesized using literally hundreds of different natural and non-natural side chains^{90,91}, providing a useful platform for further molecular design of this new class of antifouling polymer.

Building antifouling surfaces from the bottom up

Increasing attention has been given in recent years to 'bottom-up' or 'graft-from' approaches, in which antifouling polymers are grown directly from surfaces with an adsorbed chemical species capable of initiating polymerization (Fig. 1, bottom)⁹². These approaches have the theoretical advantage of achieving thicker and higher-density layers of surface-bound polymer, owing to a high density of initiation sites and growing chain ends. The basic requirement for this approach is a bifunctional molecule containing an initiating functional group coupled to a moiety capable of physical or chemical adsorption to the surface of interest. We have developed a biomimetic example containing a catechol for adsorption to surfaces and 2-bromoamide for initiation of radical polymerization (Fig. 12). Adsorption of the initiator on Ti and subsequent atom transfer radical polymerization (ATRP) of oligo(ethylene glycol) methyl ether methacrylate

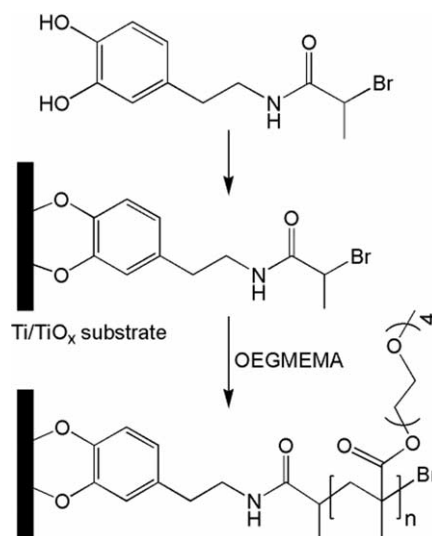


Fig. 12 Biomimetic initiator structure, surface anchoring, and ATRP of OEGMEMA.

(OEGMEMA) produces a brush-type grafted polymer⁹³. Quantitative XPS confirms the presence of the grafted poly(OEGMEMA), or POEGMEMA, layers according to the theoretical and observed carbon-to-oxygen ratios for the surface-tethered polymer. The absence of the Ti XPS signal for POEGMEMA-grafted surfaces, in conjunction with spectroscopic ellipsometry, demonstrates a dry POEGMEMA layer thickness of ~100 nm after 12 hours of ATRP polymerization. This grafted polymer thickness is many times greater than can be achieved by typical 'graft-to' methods. Biological response to the grafted POEGMEMA surfaces, assayed by four-hour fibroblast adhesion, shows a decrease in cell adhesion of >90% for POEGMEMA thicknesses of ~50 nm or more (Fig. 13).

This 'graft-from' approach is also compatible with established photolithographic methods to pattern surfaces for spatial control of biointeractions. Molecular

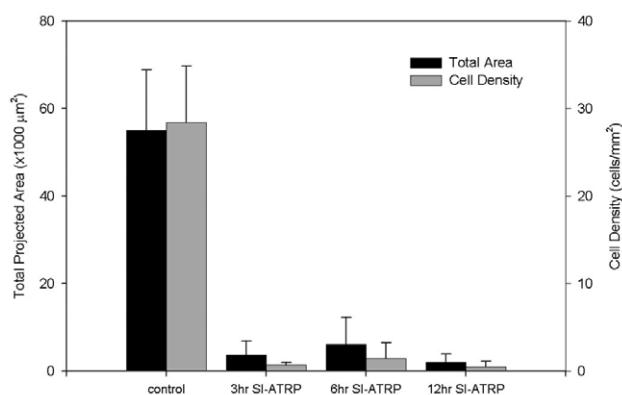


Fig. 13 Cell attachment data (four-hour culture) to a bare Ti/TiO_x substrate (control) and samples with grafted POEGMEMA layers.

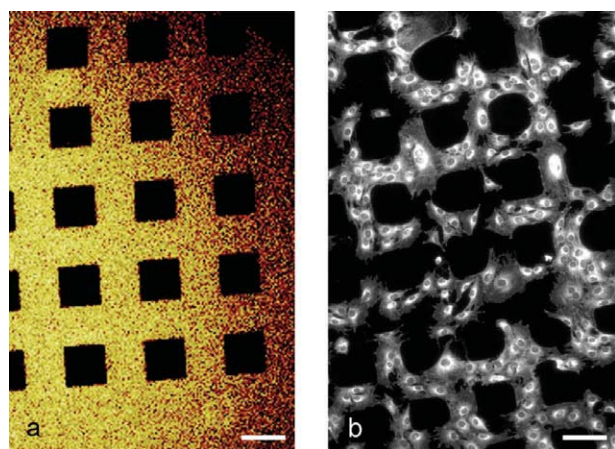


Fig. 14 (a) TOF-SIMS map of Ti⁺ signal ($m/z = 47.89$) collected from a patterned POEGMEMA thin film after 12-hour ATRP. (b) Fluorescence microscopy image of fibroblast attachment (four-hour culture) on the patterned POEGMEMA surface.

assembly/patterning by lift-off (MAPL)⁹⁴ was used to produce nonfouling regions within a cell-adhesive Ti field. Fig. 14 shows the TOF-SIMS chemical map of the patterned surface and the cell attachment to the patterned Ti surface. This type of bottom-up strategy coupled with simple patterning routines may be very useful in creating surfaces designed for diagnostic cell-based arrays or other devices where spatially controlled interactions are desired.

Summary and future directions

Strategies for preparing antifouling surfaces for biomedical applications continue to face several challenges: the development of simple and versatile methods for modifying a variety of materials; the identification of new polymers with improved antifouling performance, including long-term durability under *in vivo* conditions; and a more thorough understanding of the relationship between polymer chemical composition, architecture, surface density, and antifouling performance. As we have pointed out, biological inspiration represents a general starting point for addressing some of these challenges.

The adhesive proteins used by one of nature's most prolific fouling organisms have provided an unlikely source of inspiration for limiting fouling of material surfaces. The strong interfacial binding of DOPA represents a powerful, general platform for the robust surface modification of materials, particularly those whose performance is dictated by precise control of biointerfacial adsorption events. Identification of a single antifouling polymer strategy capable of universal success on all materials is an elusive goal. However, with further research and more sophisticated constructs, this may be possible. Finally, preliminary studies on peptoid-based peptidomimetic polymers suggest that further investigation of this new class of antifouling polymer is warranted. The chemical and structural versatility of peptoid synthesis offers a virtually unlimited parameter space within which to study the role of polymer chemical composition, molecular weight, and architecture, which should aid in achieving the full potential of these polymers in the future. **MT**

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REFERENCES

- Ratner, B. D., In *Titanium in Medicine: Material Science, Surface Science, Engineering, Biological Responses and Medical Applications*, Brunette, D. M., et al. (eds.), Springer, Heidelberg and Berlin (2000), 1
- Nath, N., et al., *Surf. Sci.* (2004) **570** (1), 98
- Montheard, J. P., et al., *J. Macromol. Sci. RMC* (1992) **C32**, 1
- Terada, S., et al., *J. Reconstr. Microsurg.* (1997) **13** (1), 9
- Tanaka, M., et al., *Colloids Surf., A* (2001) **193** (1-3), 145
- Tanaka, M., et al., *Colloids Surf., A* (2002) **203** (1-3), 195
- Tanaka, M., et al., *Biomacromolecules* (2002) **3** (1), 36
- Zhang, T. H., and Marchant, R. E., *Macromolecules* (1994) **27** (25), 7302
- Rueggsegger, M. A., and Marchant, R. E., *J. Biomed. Mater. Res.* (2001) **56** (2), 159
- Ishihara, K., et al., *Biomaterials* (1995) **16** (11), 873
- Willis, S. L., et al., *Biomaterials* (2001) **22** (24), 3261
- Lewis, A. L., et al., *Biomaterials* (2002) **23** (7), 1697
- Golander, C.-G., et al., In *Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications*, Harris, J. M., (ed.), Plenum Press, New York (1992), 221
- Harris, J. M., et al., *Poly(ethylene glycol): Chemistry and Biological Applications*, American Chemical Society, Washington, DC, (1997), 489
- Caldwell, K. D., In *Poly(ethylene glycol): Chemistry and Biological Applications*, Harris, J. M., and Zalipski, S., (eds.), American Chemical Society, Washington, DC (1997), 400
- Mrksich, M., and Whitesides, G. M., In *Poly(ethylene glycol): Chemistry and Biological Applications*, Harris, J. M., and Zalipski, S., (eds.), American Chemical Society, Washington, DC (1997), 361
- Zhang, F., et al., *J. Biomed. Mater. Res.* (2001) **56** (3), 324
- Merrill, E. W., *Ann. N.Y. Acad. Sci.* (1987) **516**, 196
- Ostuni, E., et al., *Langmuir* (2001) **17** (18), 5605
- Luk, Y.-Y., et al., *Langmuir* (2000) **16** (24), 9604
- Holland, N. B., et al., *Nature* (1998) **392**, 799
- Holmberg, K., et al., *Colloids Surf., A* (1997) **123-124**, 297
- Bain, C. D., and Whitesides, G. M., *Science* (1988) **240**, 62
- Laibinis, P. E., et al., *Science* (1989) **245**, 845
- Zhang, Y., et al., *Biomaterials* (2002) **22** (7), 1553
- Tarlow, M. J., and Newman, J. G., *Langmuir* (1992) **8** (5), 1398
- Schoenfish, M. H., and Pemberton, J. E., *J. Am. Chem. Soc.* (1998) **120** (18), 4502
- Waite, J. H., *CHEMTECH* (1987) **17**, 692
- Waite, J. H., *Integr. Comp. Biol.* (2002) **42** (6), 1172
- Waite, J. H., *Chem. Ind.* (1991) **17** (2), 607
- Qin, X. X., and Waite, J. H., *Proc. Natl. Acad. Sci. USA* (1998) **95** (18), 10517
- Qin, X.-X., et al., *J. Biol. Chem.* (1997) **272** (51), 32623
- Waite, J. H., and Tanzer, M. L., *Biochem. Biophys. Res. Commun.* (1980) **96** (4), 1554
- Waite, J. H., and Tanzer, M. L., *Science* (1981) **212**, 1038
- Olivieri, M. P., et al., *J. Adhes. Sci. Technol.* (1990) **4**, 197
- Fant, C., et al., *Biofouling* (2000) **16** (2-4), 119
- Ooka, A. A., and Garrell, R. L., *Biopolymers* (2000) **57** (2), 92
- Haemers, S., et al., *Biomacromolecules* (2003) **4** (3), 632
- Taylor, S. W., et al., *J. Am. Chem. Soc.* (1994) **116** (23), 10803
- Miki, D., et al., *Biol. Bull.* (1996) **190** (2), 213
- Rzepecki, L. M., et al., *Biol. Bull.* (1992) **183** (1), 123
- Inoue, K., et al., *Biol. Bull.* (1995) **189** (3), 370
- Weaver, J. L., Isolation, purification and partial characterization of a mussel byssal precursor protein, *Mytilus edulis* foot protein 4, Master's Thesis, University of Delaware, 1998
- Papov, V. V., et al., *J. Biol. Chem.* (1995) **270** (34), 20183
- Inoue, K., et al., *Eur. J. Biochem.* (1996) **239**, 172
- Waite, J. H., and Qin, X., *Biochemistry* (2001) **40** (9), 2887
- Floriolli, R. Y., et al., *Mar. Biotechnol.* (2000) **2** (4), 352
- Warner, S. C., and Waite, J. H., *Mar. Biol.* (1999) **134** (4), 729
- Waite, J. H., *Comp. Biochem. Physiol. B* (1990) **97** (1), 19
- Waite, J. H., *Biol. Bull.* (1992) **183** (1), 178
- Yu, M., et al., *J. Am. Chem. Soc.* (1999) **121** (24), 5825
- Burzio, L. A., and Waite, J. H., *Biochemistry* (2000) **39** (36), 11147
- Taylor, S. W., et al., *Inorg. Chem.* (1994) **33** (25), 5819
- Sever, M. J., et al., *Angew. Chem. Int. Ed.* (2004) **43** (4), 448
- Yu, M., and Deming, T. J., *Macromolecules* (1998) **31** (15), 4739
- Yamamoto, H., *Biotechnol. Gen. Eng. Rev.* (1996) **13**, 133
- Maugh, K. J., et al., Production of bioadhesive precursor protein analogs by genetically engineered organisms. US patent 5,242,808, (1993)
- Lee, B. P., et al., *Biomacromolecules* (2002) **3** (5), 1038
- Huang, K., et al., *Biomacromolecules* (2002) **3** (2), 397
- Yamamoto, H., and Hayakawa, T., *Macromolecules* (1976) **9** (3), 532
- Lee, B. P., et al., *J. Biomat. Sci. Polym. E* (2004) **15** (4), 449
- Arnoult, C., et al., *Proc. Natl. Acad. Sci. USA* (1996) **93** (23), 13004
- Schedlich, L. J., et al., *J. Biol. Chem.* (1998) **273** (29), 18347
- Shao, J.-Y., et al., *Proc. Natl. Acad. Sci. USA* (1998) **95** (12), 6797
- Connor, P. A., et al., *Langmuir* (1995) **11** (11), 4193
- Chen, L. X., et al., *J. Phys. Chem. B* (2002) **106** (34), 8539
- Rajh, T., et al., *J. Phys. Chem. B* (2002) **106** (41), 10543
- Chirdon, W. M., et al., *J. Biomed. Mater. Res. B* (2003) **66B** (2), 532
- Xu, C., et al., *J. Am. Chem. Soc.* (2004) **126** (32), 9938
- Rajh, T., et al., *Nano Lett.* (2004) **4** (6), 1017
- Rice, C. R., et al., *New J. Chem.* (2000) **24** (9), 651
- Dalsin, J. L., et al., *J. Am. Chem. Soc.* (2003) **125** (14), 4253
- Brunette, D. M., et al., *Titanium in Medicine*, Springer, New York (2001), 1019
- Rodriguez, R., et al., *J. Colloid Interface Sci.* (1996) **177** (1), 122
- Dalsin, J. L., et al., *Langmuir* (2005) **21** (2), 640
- Young, G. A., and Crisp, D. J., In *Adhesion* 6, Allen, K. W., (ed.) Elsevier, (1982), 279
- Crisp, D. J., et al., *J. Colloid Interface Sci.* (1981) **104** (1), 40
- Pasche, S., et al., *Langmuir* (2003) **19** (22), 9216
- Sofia, S. J., et al., *Macromolecules* (1998) **31** (15), 5059
- Malmsten, M., et al., *J. Colloid Interface Sci.* (1998) **202** (1), 507
- Kenausis, G. L., et al., *J. Phys. Chem. B* (2000) **104** (14), 3298
- Kingshott, P., et al., *Biomaterials* (2002) **23** (9), 2043
- Zhang, M. Q., et al., *Biomaterials* (1998) **19** (10), 953
- Branch, D. W., et al., *Biomaterials* (2001) **22** (10), 1035
- Han, S., et al., *Polymer* (1997) **38** (2), 317
- Statz, A. R., et al., *J. Am. Chem. Soc.* (2005) **127** (22), 7972
- Simon, R. J., et al., *Proc. Natl. Acad. Sci. USA* (1992) **89** (20), 9367
- Miller, S. M., et al., *Drug Dev. Res.* (1995) **35** (1), 20
- Patch, J. A., and Barron, A. E., *Curr. Opin. Chem. Biol.* (2002) **6** (6), 872
- Kirshenbaum, K., et al., *Proc. Natl. Acad. Sci. USA* (1998) **95** (8), 4303
- Zuckermann, R. N., et al., *J. Am. Chem. Soc.* (1992) **114** (26), 10646
- Ma, H. W., et al., *Adv. Mater.* (2004) **16** (4), 338
- Fan, X., et al., *Polym. Prepr.* (2005) **46**, 442
- Falconnet, D., et al., *Adv. Funct. Mater.* (2004) **14** (8), 749